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23-24 May 2020

Guest Editors: ESMO Breast Cancer Virtual Meeting 2020 Scientific Committee

Japanese Society of Medical Oncology JSMO

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ESMO Breast Cancer Virtual Meeting 2020

23-24 May 2020

Guest Editors: ESMO Breast Cancer Virtual Meeting 2020 Scientific Committee

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Organisation

ESMO Head Office
Via Ginevra 4
6900 Lugano
Switzerland

Tel. +41 (0)91 973 19 00
Fax +41 (0)91 973 19 18
E-mail meetings@esmo.org
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1O Neratinib + capecitabine vs lapatinib + capecitabine in HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Exploratory biomarker analyses from phase III NALA trial

C. Saura[1], A. Vivancos[2], J. Matito[3], H. Wildiers[4], A.M. Brufsky[5], M. Oliveira[6], S. Waters[7], S.A. Hurvitz[8], B. Moy[9], S-B. Kim[10], W.J. Gradishar[11], G.S. Queiroz[12], E. Cronemberger[13], J. Bebchuk[14], K. Keyvanjah[15], A.S. Lalani[16], L.D. Eli[17], S. Delaloge[18]

[1]SOLTI Breast Cancer Research Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [5]Hematology/Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [6]Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Medical Oncology, Velindre Cancer Centre, Cardiff, UK; [8]Hematology/Oncology Clinical Research Unit, University of California at Los Angeles, Los Angeles, CA, USA; [9]Medical Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [10]Medical Oncology, University of Ulsan College of Medicine, Seoul, Republic of Korea; [11]Medical Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [12]Medical Oncology, Hospital Araújo Jorge, Goiânia, Brazil; [13]Medical Oncology, Centro Regional Integrado de Oncologia, Fortaleza, Brazil; [14]Biostatistics, Puma Biotechnology Inc., Los Angeles, CA, USA; [15]Clinical Science and Clinical Pharmacology, Puma Biotechnology Inc., Los Angeles, CA, USA; [16]Translational Medicine, Puma Biotechnology Inc., Los Angeles, CA, USA; [17]Translational Medicine and Diagnostics, Puma Biotechnology Inc., Los Angeles, CA, USA; [18]Medical Oncology, Institut Gustave Roussy, Villejuif, France

Background: The irreversible pan-HER tyrosine kinase inhibitor neratinib had a significant progression-free survival (PFS) benefit in NALA (NCT01808573), a randomized, phase 3 trial comparing neratinib + capecitabine (1500 mg, N+C) vs lapatinib + capecitabine (2000 mg, L+C) in 621 patients (pts) with HER2+ (either IHC3+ or IHC2+/FISH+) metastatic breast cancer (MBC) who received ≥2 prior HER2-directed regimens in the metastatic setting. Here we explore biomarker (PIK3CA or ERBB2 mutations, HER2 protein expression) associations with PFS changes.

Methods: PIK3CA and ERBB2 mutations were evaluated by next-generation sequencing on either primary (67.4%, 283/420) or metastatic/lymph node samples (32.6%, 137/420) and confirmed by ddPCR pending tissue availability. HER2 protein expression was evaluated by central IHC, H-score, and HERmark. Hazard ratios (95% CI) for subgroups were estimated using unstratified Cox proportional hazards model.

Results: PIK3CA and ERBB2 mutations were detected at incidences of 35.0% (148/420) and 6.2% (26/420), respectively. PIK3CA mutations were associated with decreased PFS (wt vs mut: HR=0.81; 95% CI 0.64–1.02; p=0.077). ERBB2 mutation trended with better PFS, but sample size was limited (wt vs mut: HR=1.68, CI 0.97–3.29, p=0.086). Higher HER2 protein expression was prognostic of increased PFS when treatment arms were grouped (IHC3+ vs 2+: HR=0.67, CI 0.54–0.82, p<0.001; H-score above vs below median HR=0.77, CI 0.63–0.92, p=0.005; HERmark positive vs equivocal or negative HR=0.71, CI 0.52–0.98, p=0.006). Pts whose tumors had higher HER2 protein expression evaluated by any of the three methods appeared to have derived consistent benefit from N+C vs L+C (HER2 IHC3+: HR=0.64, CI 0.51–0.81, p<0.001; H-score ≥median (240): HR=0.54, CI 0.41–0.72, p<0.001; HERmark positive: HR=0.65, CI 0.50– 0.84, p<0.001).

Conclusions: PIK3CA mutations associate with decreased PFS for pts enrolled in the NALA trial. Higher HER2 protein expression associates with increased PFS in the overall study population, and a greater benefit from N+C vs. L+C.

Clinical trial identification: NCT01808573.

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2O ERBB3 mRNA expression in breast cancer (BC): A SOLTI biomarker discovery analysis

T. Pascual[1], M. Oliveira[2], E.M. Ciruelos[3], M. Bellet Ezquerra[2], C. Saura[2], J. Gavila Gregori[4], S. Pernas Simon[5], M. Muñoz[6], M.J. Vidal[6], M. Margeli Vila[7], J.M. Cejalvo[8], B. González-Farré[9], M. Espinosa-Bravo[10], J.M. Ferrero-Cafiero[11], P. Villagrasa[11], A. Prat[6]

[1]Genetics Department, UNC Lineberger Comprehensive Cancer Center - University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department Medical Oncology, Vall d' Hebron University Hospital; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Department Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain; [4]Medical Oncology, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain; [5]Department Medical Oncology, Institut Catala d' Oncologia, Hospitalet de Llobregat, Spain; [6]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Translational Genomics and Targeted Therapeutics Group (IDIBAPS), Barcelona, Spain; [7]Medical Oncology, ICO - Institut Català d' Oncologia Badalona (Hospital Universitario Germans Trias i Pujol), Badalona, Spain; [8]Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [9]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [10]Breast Cancer Surgical Unit, Vall d' Hebron University Hospital, Barcelona, Spain; [11]Department Scientific, SOLTI Breast Cancer Research Group, Barcelona, Spain

Background: Recently, HER3 has received attention as new anti-HER3 antibody-drug conjugates (e.g. U3-1402) are showing activity in BC. The most common method to determine HER3 expression is immunohistochemistry (IHC)-based assays. However, technical limitations exist when using IHC, such as different sensitivities of the antibodies and its subjectivity in scoring and cut-off determination. To overcome those limitations, we developed an mRNA-based ERBB3 expression assay using FFPE BC tissues and the Nanostring nCounter platform.

Methods: 1,580 FFPE primary BC samples representing all IHC-based subtypes, nCounter-based PAM50 subtypes, and ERBB3 expression were analyzed. Results were compared to an independent cohort, METABRIC dataset, which includes 1,943 BC samples analyzed by the Illumina HT 12 IDATS platform.

Results: Among 1,580 samples, 65% were hormonal receptor positive (HR+) and 18% were HER2+. IHC subtype distribution was as follows: 52% HR+/HER2-, 14% HER2+/HR+, 5% HER2+/HR- and 29% triple-negative (TNBC). PAM50 distribution was: 28% Luminal A, 20% Luminal B, 14% HER2-enriched, 29% Basal-like and 9% Normal-like. The range of ERBB3 mRNA expression had an 18.6-fold difference (i.e. from the lowest to the highest ERBB3 value) and the inter-quartile range was 1.5 (in log2), which equals to a difference in expression of 2.9-fold. Overall, HR+/HER2- or PAM50 Luminal A/B subtypes showed the highest expression compared to the other subtypes. The table shows the proportion in our dataset and METABRIC using quartiles and correlation coefficients (CC). Interestingly, the CC of the proportions between the 2 datasets were very similar.

Table 2O: Comparison of the distribution of tumor samples according to ERBB3 mRNA expression in our in-house (IH) nCounter-based dataset versus METABRIC (MB) dataset. Proportions (%) of tumor samples within each quartile (Q) based on IHC subtype and correlation coefficients between both datasets.

	1st Q IH/MB	2nd Q IH/MB	3rd Q IH/MB	4st Q IH/MB	Correlation coefficients
HR+/HER2-	14.3/11.6	24.4/22.3	28.9/29.5	32.4/36.6	0.99
HR+/HER2+	46.3/28.4	28.8/31.1	21.6/28.9	3.3/10.8	0.78
HR-/HER2+	17.0/21.1	31.2/25.8	25.7/24.9	26.1/28.8	0.72
TNBC	65.2/48.4	19.5/28.8	9.8/17.5	5.6/5.3	0.94

Conclusions: High ERBB3 mRNA gene expression is observed across all subtypes of BC, although it predominates in HR+/HER2- disease. The assay using FFPE tissues is feasible and reliable. The predictive value of this biomarker will be prospectively tested in the upcoming SOLTI-1805 TOT-HER3 window trial using the U3-1402 anti-HER3 antibody-drug conjugate.

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3O Mutation analysis of circulating tumour DNA from baseline and study discontinuation samples in SANDPIPER, a phase III study of taselisib or placebo with fulvestrant in oestrogen receptor-positive, human epidermal growth factor receptor 2-negative, PIK3CA-mutant advanced breast cancer

W. Jacot[1], H.M. Savage[2], S. Dent[3], J. Cortés[4], Y-H. Im[5], V.C. Dieras[6], N. Harbeck[7], I.E. Krop[8], J. Chen[2], E. Sokol[9], F. Schimmoller[10], J. Hsu[10], M. De Laurentiis[11], T.R. Wilson[2]

[1]Medical Oncology, Institut du Cancer de Montpellier (ICM) Val d'Aurelle, Montpellier, France; [2]Oncology Biomarker Development, Genentech, Inc., South San Francisco, CA, USA; [3]Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; [4]Breast Cancer and Gynecological Tumors (IOB Institute of Oncology) and Breast Cancer Research Program (Vall d'Hebron Institute of Oncology), IOB Institute of Oncology, Quiron Group & Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; [5]Division of Hematology/Oncology, Samsung Medical Center, Seoul, Republic of Korea; [6]Clinical Research (Institut Curie) and Medical Oncology (Centre Eugène Marquis), Institut Curie & Centre Eugène Marquis, Paris, France; [7]Gynecology and Obstetrics, Brustzentrum der Universität München (LMU), Munich, Germany; [8]Breast Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [9]Cancer Genomics, Foundation Medicine, Inc., Cambridge MA, USA; [10]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA; [11]Experimental Clinical Oncology of Senology, IRCCS Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy

Background: Activating mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and AKT1 oncogenes, and mutations in the PTEN tumour suppressor gene, occur in 40—50% of oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). We assessed phosphatidylinositol 3-kinase (PI3K) pathway mutations in circulating tumour DNA (ctDNA) from responding patients in SANDPIPER (NCT02340221), a phase III study of taselisib (PI3K inhibitor) or placebo with fulvestrant in ER-positive, HER2-negative, PIK3CA-mutant locally advanced or metastatic BC.

Methods: Baseline and study discontinuation ctDNA samples were analyzed from 99 patients in SANDPIPER who had baseline tumour PI3KCA mutations (cobas® PIK3CA Mutation Test, Roche Molecular Systems) and had experienced a response or an extended progression-free survival with tumour shrinkage. Samples were assessed by next-generation sequencing (FoundationOne® Liquid assay, Foundation Medicine) using a proprietary analysis pipeline.

Results: 85/99 paired samples were evaluable for ctDNA sequencing, with 54 (63.5%) and 85 (100%) PIK3CA mutation-positive by baseline plasma and tissue, respectively. Of the 85 mutations newly detected at study discontinuation (i.e. absent at baseline), the most common were ESR1 (21), TP53 (10), PIK3CA (8), PTEN (8), and ERBB2 (5). Activating AKT1 and loss of function PTEN mutations were identified in the taselisib arm only.

Conclusions: Detection of AKT1 and PTEN mutations in the PI3K pathway within this population suggests possible resistance mechanisms following treatment with PI3K inhibitors. The recent approval of alpelisib in hormone-receptor (HR)-positive, PIK3CA-mutant BC, in addition to the development of novel AKT inhibitors in HR-positive, HER2-negative BC, highlight the importance of understanding changes in the PI3K pathway following treatment with inhibitors.

Clinical trial identification: GO29058/NCT02340221; 24 Jun 2018.

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Dent: Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. Hoffmann-La Roche Ltd; Honoraria (self), Research grant/Funding (self): Novartis Canada. J. Cortés: Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses, Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. 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Schimmoller: Shareholder/Stockholder/Stock options, Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. Hoffmann-La Roche Ltd; Full/Part-time employment: Genentech, Inc.; Shareholder/Stockholder/Stock options, Patent or intellectual property interests: Exelixis; Shareholder/Stockholder/Stock options: Teva. J. Hsu: Shareholder/Stockholder/Stock options, Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. Hoffmann-La Roche Ltd; Full/Part-time employment: Genentech, Inc. M. De Laurentiis: Honoraria (self), Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. Hoffmann-La Roche Ltd; Honoraria (self): Pfizer; Honoraria (self): Novartis; Honoraria (self): Celgene; Honoraria (self): AstraZeneca; Honoraria (self): Eisai; Honoraria (self): Eli Lilly; Honoraria (self): Amgen; Honoraria (self): MSD. T.R. Wilson: Shareholder/Stockholder/Stock options, Non-remunerated activity/ies, Support for third-party writing assistance for this abstract: F. Hoffmann-La Roche Ltd; Full/Part-time employment: Genentech, Inc.

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4P Independent validation of the PAM50-based chemoendocrine score (CES) as pathologic complete response (pCR) and disease-free survival (DFS) predictor in hormone receptor (HR)+/HER2+ breast cancer (BC)

T. Pascual[1], A. Fernandez-Martinez[1], M. Tanioka[1], M.V. Dieci[2], S. Pernas Simon[3], J. Gavila Gregori[4], V. Guarneri[5], J. Cortés[6], P. Villagrasa[7], M.J. Vidal[8], B. Adamo[8], M. Muñoz[8], G. Griguolo[9], A. Llombart Cussac[10], M. Oliveira[11], L. Paré[7], L.A. Carey[12], C.M. Perou[13], A. Prat[8]

[1]Genetics Department, UNC Lineberger Comprehensive Cancer Center - University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Medical Oncology 2 Department, Istituto Oncologico Veneto IRCCS, Padua, Italy; [3]Department Medical Oncology, Institut Catala d' Oncologia, Hospitalet de Llobregat, Spain; [4]Medical Oncology Department, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain; [5]Department of Surgery, Oncology and Gastroenterology, Istituto Oncologico Veneto IRCCS, Padua, Italy; [6]Department Medical Oncology, IOB Institute of Oncology, Quiron Group, Barcelona, Spain; [7]Department Scientific, SOLTI Breast Cancer Research Group, Barcelona, Spain; [8]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Translational Genomics and Targeted Therapeutics Group (IDIBAPS), Barcelona, Spain; [9]Medical Oncology Department, IOV - Istituto Oncologico Veneto IRCCS, Padua, Italy; [10]Medical Oncology, Hospital Universitario Arnau de Vilanova, Universidad Catolica, Valencia, Spain; [11]Department Medical Oncology, Vall d' Hebron University Hospital; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Medicine - Hematology/Oncology Division, UNC - The University of North Carolina at Chapel Hill - School of Medicine, Chapel Hill, NC, USA; [13]Genetics Department, UNC Lineberger Comprehensive Cancer Center - University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: HR+/HER2+ BC is heterogeneous and there is a need to identify predictive biomarkers. We previously reported the ability of the PAM50-based CES to predict chemoendocrine sensitivity in HR+/HER2-negative BC beyond intrinsic subtype and risk of relapse (ROR) (Prat.CCR.2017). Here we evaluate the association of CES with pCR and DFS following different anti-HER2 combinations in HR+/HER2+ BC.

Methods: Intrinsic subtype and clinicopathologic data were obtained from 8 independent studies for a total of 485 HR+/HER2+ early BC. Patients (pts) were treated with anti-HER2 therapy either with endocrine therapy (PAMELA and PER-ELISA) or with chemotherapy (CHERLOB, OptiHER, LPT109096, ICO, HCB, PER-ELISA and CALGB 40601 [Alliance]). CES was evaluated as a continuous variable and categorically (CES-E [endocrine-sensitive], CES-U [uncertain] and CES-C [chemosensitive]) using previously reported cutoffs. We first performed statistical analyses in each dataset individually, and then all 8 combined. Multivariable analyses were used to test the association of the CES score with pCR and DFS.

Results: In the combined cohort, CES-E, CES-U and CES-C were identified in 16%, 22% and 62% of the pts, respectively. CES (continuous variable) was associated with higher pCR rates independent of clinical characteristics, treatment type, intrinsic subtype and study (adjusted Odd Ratio [OR]=0.42; p = 0.02). In the PER-ELISA trial, CES was also found associated with response (decrease in ki67) following 2 weeks of letrozole alone (OR=29.1, p 0.01). 295 pts (CHERLOB, ICO, HCB and CALGB40601) were analyzed for DFS with a median follow-up of 66 months (IQR 37-82). The adjusted DFS hazard ratio of the CES (continuous variable) was 0.13 ($p < 0.01$) independent of pCR, clinical characteristics, ROR and intrinsic subtype. In pts without pCR, disease recurrence occurred in 4% of CES-E, 19% of CES-U and 34% of CES-C pts ($p < 0.01$).

Conclusions: In HR+/HER+ BC, CES shows clinical validity for predicting chemoendocrine sensitivity in combination with anti-HER2 targeted therapies and is a good prognostic factor beyond intrinsic subtype and clinicopathologic characteristics.

Clinical trial identification: CALGB-40601: NCT00770809; Per-ELISA: NCT02411344; SOLTI-PAMELA: NCT01973660; SOLTI-Opti-HER:NCT01669239; LPT109096: NCT00524303; CHERLOB: NCT00429299.

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5P Circulating tumour DNA (ctDNA) dynamics using a standardized multigene panel in advanced breast cancer patients (pts) treated with CDK4/6 inhibitors (CDK4/6i)

O. Martínez-Sáez[1], T. Pascual[1], F. Brasó-Maristany[2], N. Chic[1], B. González-Farré[3], E. Sanfeliu[3], A. Rodríguez[1], D. Martínez[2], P. Galván[2], A. Rodriguez Hernandez[1], F. Schettini[2], B. Conte[2], M.J. Vidal[1], B. Adamo[1], M. Muñoz[1], R. Moreno[1], E.M. Ciruelos[4], I. Faull[5], J. Odegaard[6], A. Prat[1]

[1]Department Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; [2]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain; [3]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [4]Department Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain; [5]Medical Affairs & Business Development, Guardant Health, Barcelona, Spain; [6]Clinical Development, Guardant Health, Redwood City, CA, USA

Background: Changes in ctDNA levels may predict response to a variety of drugs, including CDK4/6i; however, the best assay and method are still to be defined.

Methods: This is a prospective single-center study in hormone receptor-positive/HER2-negative advanced breast cancer pts treated with CDK4/6i and endocrine therapy (ET). Paired plasma samples were collected at cycle 1 day 1 (C1) and cycle 2 day 1 (C2). Somatic alterations and variant allele fraction (VAF) were assessed using the 74-gene Guardant360 assay (Guardant Health). A VAF ratio (VAFR) was calculated for each alteration with a VAF of $\geq 0.4\%$ at C1 or C2. Molecular response was defined for each patient as the mean of all VAFRs (mVAFR). Pts with VAFs $< 0.4\%$ at C1 and C2 were considered to have low-shedding tumors. Progression free survival (PFS) hazard ratios (HR) were calculated using a univariate Cox model. PAM50 subtypes and tumor infiltrating lymphocytes (TILs) were determined in a subset.

Results: 48 pts treated with ET and palbociclib (89%) or ribociclib (11%) were analyzed with a median follow-up of 12.0 months (IQR 6.7-14.6). Clinical characteristics: 65% had visceral disease, 48% were treated as 1st-line, 35% as 2nd-line, 57% used fulvestrant and 33% an aromatase inhibitor. PAM50 subtype distribution (n=27): Luminal A (n=9), Luminal B (n=10), HER2-enriched (n=4), Normal (n=3) and Basal-like (n=1). ctDNA was detected in 96% of pts. mVAFR < 0.3 (high-ctDNA responders) (n=12) and low-shedding tumors (n=13) correlated with significantly improved PFS (HR=0.39, p=0.025), especially when compared to pts with ctDNA mVAFR > 1 (HR=0.27, p=0.010, n=12). Within PAM50 tested tumors, non-Luminal (n=5) were low-ctDNA responders (mVAFR > 0.3) (n=3) or low-shedding (n=2); Luminal A or B were high-ctDNA responders (n=8), low-ctDNA responders (n=7) and low-shedding (n=4). TILs were increased in low relative to high-ctDNA responders (mean 3.3% vs 1.8%).

Conclusions: ctDNA dynamics are an early surrogate of CDK4/6i + ET efficacy. The clinical utility of this biomarker should be tested in prospective clinical trials in which pts with unfavorable ctDNA responses are randomized to alternative treatment strategies.

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6P Circulating tumour cells (CTCs) as biomarkers of resistance to the CDK4/6 inhibitor (CDK4/6i) palbociclib (P) in patients (pts) with ER+/HER2-negative advanced breast cancer (ABC)

F. Galardi[1], C. Biagioni[2], F. De Luca[1], G. Curigliano[3], A.M. Minisini[4], M. Bonechi[1], E. Moretti[5], E. Risi[6], I. Migliaccio[7], A. McCartney[5], M. Benelli[8], D. Romagnoli[8], V. Conti[9], L. Biganzoli[5], A. Di Leo[10], L. Malorni[2]

[1]Sandro Pitigliani Translational Research Unit, Nuovo Ospedale di Prato Santo Stefano - Azienda Usl Toscana Centro, Prato, Italy; [2]"Sandro Pitigliani" Medical Oncology Department, Bioinformatics Unit, Nuovo Ospedale di Prato Santo Stefano - Azienda Usl Toscana Centro, Prato, Italy; [3]Early Drug Development for Innovative Therapies Division, University of Milan, Istituto Europeo di Oncologia, Milan, Italy; [4]Oncology Department, "Azienda Sanitaria Universitaria del Friuli Centrale", Udine, Italy; [5]"Sandro Pitigliani" Medical Oncology Department, Nuovo Ospedale di Prato Santo Stefano - Azienda Usl Toscana Centro, Prato, Italy; [6]"Sandro Pitigliani" Medical Oncology Department, Nuovo Ospedale di Prato, Prato, Italy; [7]"Sandro Pitigliani" Translational Research Unit, Ospedale di Prato Sandro Pitigliani Med. Oncology Unit, Prato, Italy; [8]Bioinformatics Unit, Nuovo Ospedale di Prato Santo Stefano - Azienda Usl Toscana Centro, Prato, Italy; [9]Laboratory of Neurobiology Child Neurology Unit, Children's Hospital A. Meyer, Florence, Italy; [10]Medical Oncology Department, Nuovo Ospedale di Prato, Prato, Italy

Background: Resistance to CDK4/6i is inevitable. CTC count is prognostic in ABC, but its role in pts treated with CDK4/6i is not well defined. Genetic loss of RB1 is a known yet infrequent marker of CDK4/6i resistance. We assessed the prognostic role of CTC count and gene-expression (GE) levels of RB1 in CTCs in pts receiving P.

Methods: The TREnd trial (NCT02549430) randomized pts with endocrine resistant ABC to either P alone or P plus the endocrine therapy received in the prior line of treatment. In TREnd, blood samples were prospectively collected in CellSave® tubes before starting P (T0), after the first cycle (T1) and at disease progression (T2). CTCs were isolated and counted by CellSearch® System (CS) using CellSearch™ Epithelial Cell kit. Samples with ≥5CTCs were sorted by DEPArray system® (DA). RNA extraction and retro-transcription for GE experiments were performed by Cell Lysis Two-Step RT-qPCR. RB1 and GAPDH GE levels were measured by ddPCR, with a multiplex assay with a sensitivity of 30-10 pg of cDNA, set up on three different cell lines sensitive and resistant to P.

Results: 46 pts were suitable for CTC analysis. CTC count at T0 did not show significant prognostic value in terms of progression free survival (PFS). However, pts with at least 1 detectable CTC at T1 (n=26) had a worse PFS than those with 0 CTCs (n=16) (p=0.02). Similar results were observed with a cut-off of 5 CTCs (p=0.04). At T1, 7 out of 39 pts had an increase of at least 3 CTCs which proved prognostic (p=0.01). Pts with ≥5CTCs at T2 (n=6/23) who received chemotherapy as post-study treatment had a shorter time to treatment failure (p=0.02). DA sorting was conducted on 20/46 pts and GE data for RB1 were obtained from 19 pts. CTCs showed heterogeneous RB1 expression. Pts with detectable expression of RB1 in at least one time-point had better, but not significant, outcomes than those with undetectable levels.

Conclusions: Persistence or an increase in CTCs after one cycle of P may identify pts with worse outcome. High CTC counts at disease progression on P may indicate poor post-treatment prognosis. Measuring RB1 GE levels on CTCs by ddPCR is feasible, but its clinical significance is yet unclear.

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7P Prognostic value of the immune infiltration score in early breast cancer patients receiving dual HER2 blockade with trastuzumab and pertuzumab: An exploratory analysis of a randomized clinical trial

G. Wan, F. Cao, X. Cai, X. Yu, Z. Zuo, Y. Song, T. Xu, Y. Li, Y. Yu, X. Wang, X. Wang

Oncology, Hubei University of Medicine, Shiyan, China

Background: Although the survival benefit of dual epidermal growth factor receptor 2 (HER2) blockade with trastuzumab and pertuzumab was definitely demonstrated in HER2-amplified early breast cancer, sufficient biomarkers are urgently required to explain the heterogeneous response to dual HER-2 blockade therapy. The prognostic significance of immune infiltration in TRYPHAENA trial was investigated to tailor treatment in current analysis.

Methods: Among the 225 HER2-amplified early breast cancer patients randomly assigned to trastuzumab/pertuzumab concurrently or sequentially with standard chemotherapy as neoadjuvant therapy in TRYPHAENA trial, 162 patients with available gene expression profile and complete follow-up data were enrolled. The normalized gene expression matrix (GSE109710) based on the NanoString nCounter array was downloaded from Gene Expression Omnibus database and further used to estimate the immune infiltration score (IIS) for each patient by the Immune Cell Abundance Identifier tool. A cut-off of IIS to stratify patients was determined by the R-based survminer package. Multivariable Cox proportional event-free survival (EFS) hazard ratios were preformed.

Results: Among the 162 women included in the analysis (median [range] age, 49.0 [27-81] years), the pathologic complete response (pCR) rate was 50.0% (21/42) in patients with a high IIS (>0.628) and 66.7% (80/120) in patients with a low SII (≤0.628). At a median follow-up of 4.7 years, the multivariable-adjusted hazard ratio for EFS was 2.933 (95%CI, 1.223-7.033) for the high IIS and 0.356 (95%CI, 0.127-0.999) in patients who achieved pCR, respectively.

Table 7P: Cox regression for EFS

Variable	Univariate analysis		Multivariable analysis	
	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
Age (≥50 vs <50 y)	1.628(0.747-3.545)	0.220	1.779(0.760-4.165)	0.184
Histology grade (G3 vs G1/G2)	0.855(0.563-1.300)	0.464	1.019(0.633-1.641)	0.938
Hormone receptor (positive vs negative)	0.918(0.426-1.982)	0.828	0.920(0.369-2.296)	0.859
Clinical stage (III vs II)	2.207(0.975-4.995)	0.058	1.278(0.820-1.991)	0.279
pCR (yes vs no)	0.408(0.187-0.889)	0.024	0.356(0.127-0.999)	0.050
IIS (high vs low)	2.812(1.300-6.084)	0.009	2.933(1.223-7.033)	0.016

Conclusions: Our analysis demonstrates an independent prognostic value of IIS in patients receiving trastuzumab/pertuzumab-based neoadjuvant chemotherapy.

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8P Characterization of immune microenvironment before and following anti-HER2 neoadjuvant therapy (NAT)

G. Griguolo[1], G. Serna[2], T. Pascual[3], R. Fasani[2], N. Chic[4], L. Paré[5], S. Pernas[6], M. Muñoz[4], M. Oliveira[7], M. Vidal[4], A. Llombart Cussac[8], J. Cortés[9], P. Galván[4], B. Bermejo[10], N. Martínez[11], R. López[12], S. Morales[13], P. Villagrasa[5], A. Prat[14], P. Nuciforo[2]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [2]Molecular Oncology Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Hospital Clinic/IDIBAPS, SOLTI Breast Cancer Research Group, Barcelona, Spain, Department of Genetics - University of North Carolina, Chapel Hill, NC, USA; [4]Medical Oncology, Hospital Clinic/IDIBAPS, Barcelona, Spain; [5]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [6]Medical Oncology, Institut Catala d'Oncologia, Hospitalet de Llobregat, Spain; [7]Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]Medical Oncology, Hospital Universitario Arnau de Vilanova, Universidad Catolica, Valencia, Spain; [9]IOB Institute of Oncology, Quironsalud Group, Madrid & Barcelona, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Medical Oncology, Hospital Clínico Universitario de Valencia / INCLIVA / CIBERONC, Valencia, Spain; [11]Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain; [12]Medical Oncology, Hospital Clínico Universitario de Santiago / CIBERONC, Santiago de Compostela, Spain; [13]Breast Cancer Unit, Hospital Universitario Arnau de Vilanova, Lleida, Spain; [14]Medical Oncology, Hospital Clinic/IDIBAPS, SOLTI Breast Cancer Research Group, Barcelona, Spain

Background: Despite its recognized role in breast cancer (BC), the complexity of immune microenvironment remains largely unexplored. Multiplex immunohistochemistry (mIHC) holds opportunity to more comprehensively assess BC immunity, potentially providing information to improve immunotherapy.

Methods: In the neoadjuvant phase II SOLTI-1114 PAMELA trial (NCT01973660), 151 HER2+ BC patients received lapatinib and trastuzumab, plus hormonal therapy if HR+. Baseline (BSL, n=66) and day-15 (D15, n=54) biopsies from 76 patients were analyzed using a custom mIHC 6-plex panel, including immune subtyping (CD3, CD4, CD8, FOXP3), localization (keratin for tumor mask), and activity (Ki67 for proliferation). Immune cell density (cells/mm^2) and localization were determined by digital image analysis and classified in: intratumor (A), proximal peritumor (B - < 10um; C - 10 to 30um from tumor) and distal peritumor stroma (D). Intrinsic subtyping was determined at the same timepoints using the PAM50 predictor (nCounter).

Results: Both at BSL and D15, no significant difference in immune subpopulation densities was observed according to PAM50 subtype. At both timepoints, fraction of proliferating (Ki67+) immune cells (all subpopulations) differed significantly according to subtype (basal-like tumors showing the highest and luminal tumors showing the lowest fraction of proliferating cells, p varying from <0.001 to 0.031). Tumors achieving a pCR showed numerically higher densities of CD3+, CD8+ and FOXP3+ cells. Association with pCR was stronger at D15 and for immune cells intratumor/more proximal to tumor (Table). Overall, at D15, tumors achieving pCR showed higher CD3+ density (p=0.03) and higher ratio in Ki67+CD8+/Ki67+FOXP3+ (p=0.03).

Table 8P: Odds ratios (95% CI) for pCR for 1000 cells/mm2 increases in immune cell density according to subpopulation, timepoint, and localization

Timepoint		Baseline				Day 15			
Localization		A	B	C	D	A	B	C	D
Immune cell subpopulation	CD3+	1.37 (0.97-1.94)	1.31 (0.95-1.81)	1.35 (0.93-1.96)	1.02 (0.48-2.17)	1.38 (1.04-1.82)	1.25 (1.01-1.55)	1.31 (0.98-1.73)	1.79 (0.87-3.65)
	CD8+	1.51 (0.66-3.50)	1.33 (0.74-2.40)	1.39 (0.69-2.83)	1.00 (0.26-3.76)	1.61 (1.09-2.39)	1.42 (1.01-2.00)	1.59 (0.97-2.61)	2.87 (0.73-11.29)
	FOXP3+	1.12 (0.92-1.36)	1.28 (0.88-1.87)	1.43 (0.82-2.48)	0.26 (0.01-7.13)	1.10 (0.99-1.23)	1.19 (1.01-1.41)	1.31 (0.99-1.73)	4.61 (0.32-66.13)

Conclusions: In early HER2+ BC, immune cells show differential proliferation patterns according to tumor biology. Number of immune cells spatially interacting with tumor after priming by anti-HER2 therapy was associated with pCR.

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9P The histopathologic profile of pregnancy associated breast cancer; a particularly aggressive breast cancer subtype. Analysis of the Dutch National Registry

B. Suelmann[1], E. van der Wall[2], C. van Dooijweert[3], S. Linn[4], P. van Diest[3]

[1]Medical Oncology, UMC-University Medical Center Utrecht, Utrecht, Netherlands; [2]Cancer Center, UMC-University Medical Center Utrecht, Utrecht, Netherlands; [3]Pathology, UMC - University Medical Center Utrecht, Utrecht, Netherlands; [4]Medical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands

Background: Breast cancer is the most common type of malignancy in pregnant women and it occurs in 1-4 per 10,000 pregnancies. The incidence of pregnancy associated breast cancer (PABC), accounting for up to 3.8% of all breast cancers, is expected to rise, especially in developed countries. Whether these cancers arise before or during pregnancy, and whether they are stimulated by the high hormonal environment of pregnancy, is currently unknown. This study assesses the histopathological profile of PABC in a large Dutch population-based cohort.

Methods: We identified 744 patients with PABC (defined as breast cancer diagnosed during or within six months after pregnancy), between 1988 and 2019, in the nationwide Dutch Pathology Registry (PALGA). An age-matched PALGA cohort of unselected breast cancer patients (≤ 45 years), diagnosed between 2013 and 2016, was used as a control (n=4,314). Histopathologic features of both cohorts were compared.

Results: Mean age at diagnosis of PABC patients was 34.5 years and most breast cancers were diagnosed during pregnancy (70.7%). As compared to age-matched controls, PABC patients had tumors of higher Bloom-Richardson grade (grade I: 1.2% vs. 17.9%, grade II: 14.7% vs. 35.3%, grade III: 71.9% vs. 31.1%). Furthermore, estrogen (ER) and progesterone-receptor (PR) expression was more often reported as negative (ER: 45.0% vs. 20.2%, PR: 48.8% vs. 29.4%), while a higher percentage of PABC patients was reported as overexpressing HER2 (22.0% vs. 15.1%). The most observed subtype in PABC was triple-negative breast cancer; 34.1% compared to 15.1%, and luminal subtypes represented only 17.2% v.s. 60.6% in the non-PABC cases. There were no differences in grade or hormone receptor-status between pregnant -and postpartum-PABC patients.

Conclusions: This study, based on a large population-based cohort of 744 PABC patients, underlines a different, more aggressive histopathologic profile compared to age-matched breast cancer patients ≤ 45 years. RNA-and DNA sequencing of breast tumors will be conducted to unravel the genetic background and find opportunities for prevention and optimal treatment (more targeted and less toxic).

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10P Prediction of the 21-gene recurrence score by a non-genomic approach in stage I estrogen receptor-positive, HER2-negative breast cancer

F. Le Du[1], F. Takeo[1], M. Park[2], K.R. Hess[2], D. Liu[2], R. Jackson[1], C. Mylander[3], M. Rosman[3], A. Raghavendra[1], L. Tafra[3], N.T. Ueno[1]

[1]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Fortney Breast Center, Anne Arundel Medical Center, Annapolis, MD, USA

Background: The recurrence score (RS), which is derived from the results of an assay of 21 genes, predicts the likelihood of recurrence in patients with breast cancer, thus potentially helping clinicians decide when to recommend chemotherapy. However, non-genomic clinicopathologic prognostic markers may also be able to distinguish patients with low, intermediate, and high risk of recurrence without the added cost of genetic testing.

Methods: We developed a novel non-genomic tool called predicted RS (pRS) and investigated the relationship between RS and pRS among patients with stage I estrogen receptor-positive, human epidermal growth factor receptor 2-negative (HER2) breast cancer. We reviewed the records of 1055 patients at The University of Texas MD Anderson Cancer Center with estrogen receptor-positive, HER2-negative stage I breast cancer who had RS results available. We used multivariable linear regression to develop pRS in this population. We then validated our models in a cohort of 242 patients from Anne Arundel Medical Center with the same characteristics.

Results: The pRS model is pRS = 26.089 − 0.071ER − 0.092PR + 0.132Ki67 + 1.08I[HG=II] + 7.129I[HG=III] where I is an indicator function. The pRS had a Pearson correlation coefficient of 0.7352 with RS in our validation cohort ($p < 0.0001$). Two (1.2%) of the 170 patients with low/intermediate RS (RS ≤25) were classified into the high pRS group (P-value <0.0001). None of the patients with a pRS >30 were considered low/intermediate risk (RS ≤ 25) as defined in the TAILORx trial.

Table 10P: Correlation between recurrence score (RS) and predicted RS (pRS) in the Anne Arundel Medical Center validation cohort using two risk categories*

pRS	RS		
	High	Low	Total
High	24 (92%)	2 (8%)	26
Low/intermediate Missing data	15 (8%) 6	168 (92%) 27	183 33
Total	45	197	242

*10P: High: RS > 25; low/intermediate: RS ≤ 25.

Conclusions: pRS accurately identified patients who had an RS >25 and thus were at high risk for recurrence. These patients could therefore be prescribed chemotherapy without first undergoing genetic testing.

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11P BioItaLEE: Comparative biomarker analysis of liquid biopsies and paired tissue samples of patients treated with ribociclib and letrozole as first-line therapy for advanced breast cancer (aBC)

G. Bianchini[1], M. De Laurentiis[2], G. Arpino[3], A. Zambelli[4], F. Puglisi[5], L. Del Mastro[6], M.A. Colleoni[7], F. Montemurro[8], G.V. Bianchi[9], I. Paris[10], G. Allegrini[11], L. Amaducci[12], M.E. Cazzaniga[13], M. Orditura[14], C. Zamagni[15], S. Bianchetti[16], D. Castelletti[16], M. Benelli[17], M. Callari[18], L. Malorni[19]

[1]Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; [2]Division of Breast Medical Oncology, IRCCS Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [3]Dipartimento di Clinica Medica e Chirurgia, Università Federico II, Naples, Italy; [4]U.S.C Oncologia, Presidio Ospedaliero Papa Giovanni XXIII, Bergamo, Italy; [5]Dipartimento di Oncologia Medica, S.O.C. Oncologia Medica e Prevenzione Oncologica, Centro di Riferimento Oncologico (CRO), IRCCS, Aviano, Italy; [6]U.O.S.D. Breast Unit, I.R.C.C.S. Ospedale Policlinico San Martino, Genoa, Italy; [7]International Breast Cancer Study Group, Division of Medical Senology, Istituto Europeo di Oncologia, IRCCS, Milan, Italy; [8]Multidisciplinary Outpatient Oncology Clinic, Istituto di Candiolo - FPO - IRCCS, Candiolo, Italy; [9]Department of Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy; [10]Department of Woman and Child Sciences, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy; [11]U.O.C. di Oncologia Medica, Presidio Ospedaliero Livorno, Livorno, Italy; [12]U.O. Oncologia, P.O. Ospedale degli Infermi, Romagna, Italy; [13]Medical Oncology Department, Phase I Research Centre, University of Milan Bicocca, Monza, Italy; [14]U.O.C. Oncologia Medica e Ematologia; Department of Internal and Experimental Medicine, A.O.U. Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; [15]Medical Oncology, S.S.D. Oncologia Medica Addarii, Policlinico Sant'Orsola-Malpighi, Bologna, Italy; [16]Department of Oncology, Novartis Farma Italy, Origgio, Italy; [17]Dipartimento di Oncologia e Unità di Bioinformatica, Ospedale di Prato, Azienda USL Toscana Centro, Prato, Italy; [18]Cancer Research, Department of Oncology, University of Cambridge, Li Ka Shing Centre, Cambridge, UK; [19]Dipartimento di Oncologia e Unità di Ricerca Traslazionale "Sandro Pitigliani", Ospedale di Prato Sandro Pitigliani Med. Oncology Unit, Prato, Italy

Background: BIOITALEE aims to study circulating tumor DNA (ctDNA) alterations, their evolution and association with clinical outcome in patients (pts) receiving ribociclib+letrozole as 1st-line treatment for aBC. Here we report the analysis of baseline liquid biopsy (LB) and tumor tissue samples (TS), and their comparison.

Methods: 287 postmenopausal pts with HR+, HER2− aBC were enrolled in 47 Italian centers. 271 pts were suitable for Next Generation Sequencing (NGS) on LB and 144 had a paired TS valid for NGS. LBs and TSs were analyzed by a Custom panel (average coverage 23000x). LBs were also analyzed by Oncomine Pan-Cancer Assay (Thermo Fisher Scientific). The agreement was determined by Cohen's kappa statistic (K) and McNemar test (p).

Results: Of the 144 paired TSs, 116 (80.5%) were collected in the 6 months preceding study entry. In custom panel analysis, 72.9% TS and 44.4% LB, exhibited at least one alteration. The concordance was moderate (K=0.51, CI: 0.44-0.58, p<1e-4) mostly due to negative findings in LB. For PIK3CA, 21.5% of pts had TS+/LB- and discordant cases showed significantly lower allele frequencies (AFs) (Wilcoxon p<1e-4). The concordance for the 3 most frequently altered genes is detailed below:

Table 11P

Gene	LB (%)	TS (%)	K	p
PIK3CA	20.1	40.3	0.48	<0.0001
TP53	16.0	24.3	0.44	0.019
PTEN	4.2	7.6	0.56	0.125

25 distinct PIK3CA variants with different AFs were observed, suggesting both clonal and subclonal alterations. For LB, the concordance between Custom and Oncomine panel was good (K=0.70, CI: 0.64-0.76) (for PIK3CA, K=0.79, CI: 0.70-0.88).

Conclusions: In our study, mutations were more frequently found in TS rather than LB, supporting the strategy of querying the tissue to complement ctDNA results. The ultra-deep NGS of TS in this study, enabled improved comparison between TS and LB. LB+ findings with TS- results were infrequent. Discordancy in PIK3CA status is associated with lower AFs in TS, likely due to subclonal events. Further analyses are ongoing and will be presented.

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Zambelli: Advisory/Consultancy: Novartis; Advisory/Consultancy: Roche; Advisory/Consultancy: AstraZeneca; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Lilly; Advisory/Consultancy: Biogen; Advisory/Consultancy: Genomic Health. F. Puglisi: Research grant/Funding (institution): AstraZeneca; Research grant/Funding (institution): Eisai; Research grant/Funding (institution): Roche; Advisory/Consultancy: Novartis; Advisory/Consultancy: MSD; Advisory/Consultancy: Eli Lilly; Advisory/Consultancy: Roche; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: Eisai. L. Del Mastro: Honoraria (self): Roche; Honoraria (self): Pfizer; Honoraria (self): Ipsen; Honoraria (self): Eli Lilly; Honoraria (self): Novartis; Honoraria (self): Takeda; Honoraria (self): MSD; Honoraria (self): Genomic Health; Non-remunerated activity/ies: Celgene; Honoraria (self): Seattle Genetics. M.A. Colleoni: Advisory/Consultancy: AstraZeneca; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: Pfizer; Honoraria (self): Novartis; Advisory/Consultancy: OBI Pharma; Advisory/Consultancy: Puma Biotechnology; Advisory/Consultancy: Celldex. F. Montemurro: Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Roche; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis; Speaker Bureau/Expert testimony: Pfizer; Advisory/Consultancy: Pierre Fabre; Speaker Bureau/Expert testimony: Daiichi Sankyo. G.V. Bianchi: Advisory/Consultancy: Novartis; Speaker Bureau/Expert testimony: Eli Lilly. C. Zamagni: Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses, Non-remunerated activity/ies: Roche; Advisory/Consultancy, Research grant/Funding (institution): Eisai; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses, Non-remunerated activity/ies: Novartis; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Non-remunerated activity/ies: AstraZeneca; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses, Non-remunerated activity/ies: Pfizer; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: PharmaMar; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Celgene; Advisory/Consultancy, Research grant/Funding (institution): Lilly; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Amgen; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Tesaro; Honoraria (self), Advisory/Consultancy: QuintikesIMS; Research grant/Funding (institution), Travel/Accommodation/Expenses: Pierre Fabre; Research grant/Funding (institution), Travel/Accommodation/Expenses: Istituto Gentili; Research grant/Funding (institution): Takeda; Research grant/Funding (institution): Teva; Research grant/Funding (institution): Medivation; Research grant/Funding (institution): AbbVie; Research grant/Funding (institution): Array BioPharma; Research grant/Funding (institution): Morphotek; Research grant/Funding (institution): Synthon, Seattle Genetics. 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12P Gene expression profiling in early breast cancer treated with neoadjuvant ribociclib plus letrozole (R+L) versus chemotherapy (CT): A correlative analysis of the SOLTI-1402/CORALLEEN phase II trial

N. Chic[1], B. González-Farré[2], L. Paré[3], T. Pascual[3], C. Saura[4], C. Hernando Melia[5], M. Muñoz[6], P. Fernandez[7], D. Martínez[8], E. Sanfeliu[2], F. Brasó-Maristany[9], X. González-Farré[10], M. Oliveira[11], M. Gil-Gil[12], P. Celiz[3], E.M. Ciruelos[13], P. Villagrasa[14], J. Gavila Gregori[15], A. Prat[16]

[1]Medical Oncology, Hospital Clinic, Barcelona, Spain; [2]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [3]Department Scientific, SOLTI Breast Cancer Research Group, Barcelona, Spain; [4]Department Medical Oncology, Vall d`Hebron University Hospital Institut d'Oncologia, Barcelona, Spain; [5]Valencia, Hospital Clinico Universitario de Valencia, Valencia, Spain; [6]Department Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; [7]Department of Pathology, Hospital Germans Trias i Pujol, Badalona, Spain; [8]Department Scientific, Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; [9]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain; [10]Department Medical Oncology, Hospital General de Catalunya, San Cugat Del Valles, Spain; [11]Department Medical Oncology, Vall d' Hebron University Hospital; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Department Medical Oncology, Institut Catala d' Oncologia, L'Hospitalet de Llobregat, Spain; [13]Department Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain; [14]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [15]Department Medical Oncology, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain; [16]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain

Background: In the CORALLEEN trial, R+L achieved similar response rates to multiagent CT. We present a comprehensive gene expression analysis done before, during, and after therapy to fully characterize the biology behind the primary results of the trial.

Methods: CORALLEEN was a randomized study in postmenopausal women with stage I-IIIA hormone receptor positive (HR+)/HER2-negative Luminal B breast cancer by PAM50. Patients (pts) received either 6 cycles of R+L or 4 cycles of AC followed by 12 doses of paclitaxel. Primary endpoint was rate of PAM50 Risk of Relapse (ROR) low disease at surgery. Baseline, week 2, and surgical specimens were collected. Expression of 770 genes and 31 signatures were determined using the Breast360™ nCounter-based codeset. Response was defined as ROR-low disease at surgery, relative/absolute changes in ROR between baseline/week 2 and surgery, RCB-0/I or levels of Ki67 at surgery. To identify genes associated with response, a significance of microarrays (SAM) analysis with a false discovery rate (FDR) <5% was performed.

Results: A total 297/318 (93.4%) samples were available. No genes or signatures at baseline, or week 2, were found to be associated with response at surgery in each arm. At week 2, 146 (14.6%) genes or signatures were found significantly up-regulated (n=47) and down-regulated (n=99) in the R+L arm compared to CT. R+L induced higher expression of genes related to DNA damage repair and immune activation (e.g. TP53, RAD52, GZMM and CD19) and lower expression of cell-cycle and hormone-related genes (e.g. PGR, CDK1 and MKI67). At surgery, 102 (10.2%) genes or signatures were found significantly up-regulated (n=4) and down-regulated (n=98) in the R+L arm compared to CT. R+L induced higher downregulation of estrogen- and proliferation-related genes and signatures (e.g. PGR, ER signaling, and MKI67).

Conclusions: No genes were able to predict response. Compared to CT, R+L induced higher downregulation of proliferation-related genes and signatures at week 2 and surgery. These results support the strategy to use the neoadjuvant setting to select patients who achieve a large molecular downstaging following CDK4/6 inhibition.

Legal entity responsible for the study: SOLTI Breast Cancer Research Group.

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13P HER2 low testing in breast cancer: How to optimize detection

F. Cecchi[1], D. Carrolle[1], M. Gustavson[1], S. Sridhar[1], M. de los Reyes[1], S. Thyparambil[2], A. Bhalkikar[2], W-L. Liao[2], S. Coats[1], T. Hembrough[1]

[1]Translational Medicine Department, AstraZeneca USA, Gaithersburg, MD, USA; [2]Translational Medicine Department, MProbe, Gaithersburg, MD, USA

Background: 15-20% of breast cancers are HER2 over-expressing (IHC 3+), or over-amplified (IHC2+/ISH+) while 45% have lower levels of HER2 expression (IHC 2+/ISH- or IHC 1+); there are currently no approved HER2-targeted therapies for patients with low levels of HER2 expression. Measuring HER2 expression levels is critical in the management of patients with breast cancer yet IHC results are often confounded by multiple variables, including fixative conditions (pre-analytical) and staining procedures (analytical). In addition, results are often difficult to interpret since a number of cases show only moderate overexpression of the protein and the analysis of the IHC staining are subject to interobserver variability (post-analytical). Therefore, more sensitive and objective assays are needed to better identify patients who may benefit from anti-HER2therapies including those patients with lower levels of HER2. To address this gap, we evaluated non-antibody-based methods to quantify targets from FFPE tissue and liquid biopsy.

Methods: Here, we have analyzed 107 breast carcinomas for ERBB2 RNA and protein expression using, QRT-PCR (Fluidigm) and SRM-MS (mProbe) and compared between patients with HER2 expression levels of IHC 0(34.6%), 1+(15.9%), 2+(27.1 %) or 3+(22.4%) (ANOVA).

Results: ERBB2 RNA and protein expression were progressively increased according to HER2 IHC grouping (i.e. lowest concentration in HER2 0 samples, highest in HER2 3+ samples). ERBB2 RNA and protein levels were significantly elevated in 2+ vs. 0 samples (2-fold increase, $p < 0.05$). No significant trend was observed in 2+ vs. 1+ and in 1+ vs. 0. Moreover, no correlation was seen between plasma and tissue ERBB2 RNA expression or IHC status. In this work, SRM-MS revealed a 100-fold difference in HER2 expression between the HER2 IHC 0 versus IHC 3+ tumor tissue samples. PCR-based methods were not reliable enough to detect a similar range of expression.

Conclusions: These results are encouraging and favor SRM-MS profiling as a more sensitive method to detect HER2 protein levels from tumor tissue samples. Future studies will include comparative analysis of SRM-MS versus other methods to detect HER2 expression and require confirmation on a larger series of tumors, notably for the tissue samples expressing lower levels of HER2 (0, 1+ and 2+).

Legal entity responsible for the study: Translational Medicine.

Funding: AstraZeneca.

Disclosure: F. Cecchi, D. Carrolle, M. Gustavson, S. Sridhar, M. de los Reyes, S. Thyparambil, A. Bhalkikar, W-L. Liao, S. Coats, T. Hembrough: Full/Part-time employment, Employee of AstraZeneca.

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14P Evolution of cytotoxic and regulatory T cells in blood and in tissue after neoadjuvant treatment in breast carcinoma

N. Palazón Carrión[1], C. Jiménez Cortegana[2], M.L. Sánchez León[1], F. Henao Carrasco[1], E. Nogales Fernandez[1], V. Sánchez Margalet[2], L. de la Cruz Merino[1]

[1]Clinical Oncology Department, Hospital Universitario Virgen Macarena, Seville, Spain; [2]Medical Biochemistry and Molecular Biology and Immunology, Hospital Universitario Virgen Macarena, Seville, Spain

Background: There are more pathological complete responses (pCR) after neoadjuvant treatment in breast cancer with predominance of tumor infiltrating lymphocytes (TILs). The objective is to analyze immunosuppressive (regulatory T) and cytotoxic (CD8+ T) TILs before and after neoadjuvant treatment and the pathological response achieved in breast carcinoma.

Methods: Translational study of 50 breast carcinoma patients with neoadjuvant treatment. Measurement of cytotoxic CD8 + and regulatory T lymphocytes (CD25H or FOXP3 +) was performed in peripheral blood (before, during and after treatment), and before (biopsy) and after (surgical specimens) neoadjuvant in tumor tissue. The pathological response was assessed according to Miller & Payne (M&P: G1: minimal changes, G2: <30%, G3: 30-90%, G4:> 90%, G5: pCR). Peripheral blood lymphocytes were measured by flow cytometry (cells/microliter) and lymphocytes from tissue

were measured by immunohistochemistry using the Ladoire classification (G0: 0 cells in 5f/20x, G1: 1-5, G2: 5-15, G3: > 15).

Results: Peripheral blood CD8+ T lymphocytes decreased significantly after treatment in patients with a <30% tumor response (M&P grade 1-2), median of 239 cells/ul in cycle 1 (C1) vs 133 cells/ul in C6, p 0.041. However, they remained constant (200-300 cells/ul) in 30-90% tumor response (M&P grade 3-4) and in pCR (M&P grade 5). Median CD8+ T lymphocytes in M&P grades 1-2 vs 5 were 184 vs 258 cells/ul (p 0.044) in C4, 180 vs 276 cells/ul (p 0.023) in C5 and 133 vs 285 cells/ul (p 0.012) in C6. The percentage of CD8+ T from tissue in M&P grade 5 is focused on Ladoire grade 3, while M&P grade 1-2 highlights a lower gradation of CD8+ T (Ladoire grade 0-2). There are high levels of FOXP3+ from tissue both before and after treatment in M&P grade 1-2. However, a low FOXP3+ percentage is expressed in M&P grade 5, and even that percentage decreases drastically in Ladoire grade 2-3 after treatment. The peripheral blood regulatory T (CD25H) cells descrease in M&P grade 3-4 and do not vary in M&P grade 1.

Conclusions: There is a significant descent of CD8+ T cells in non-pCR patients, while remaining elevated in pCR. There are more FOXP3+ T cells in non-pCR. CD8+ T and regulatory T cells are potential predictive biomarkers in breast carcinoma.

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15P The CelTIL score as an early predictor of anti-tumour response following neoadjuvant therapy (NAT): A SOLTI biomarker analysis

B. González-Farré[1], P. Nuciforo[2], L. Pare Brunet[3], J. Cortés[4], A. Llombart Cussac[5], J. Gavila Gregori[6], E. Sanfeliu[1], N. Chic[7], M. Vidal[7], B. Adamo[7], M. Muñoz[7], P. Galván[8], D. Martínez[8], P. Villagrasa[3], T. Pascual[7], A. Prat[7]

[1]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [2]Molecular Oncology Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [4]Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [5]Medical Oncology, Hospital Universitario Arnau de Vilanova, Valencia, Spain; [6]Medical Oncology, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain; [7]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [8]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain

Background: Tumor cellularity and tumor-infiltrating lymphocyte score (CelTIL) measured at day (D) 15 following anti-HER2 therapy was found associated with pathologic complete response (pCR) (Nuciforo. Ann Oncol 2018). Here, we explored the dynamics of CelTIL across 3 trials to determine its value as an early read-out of NAT efficacy.

Methods: Samples and clinical information from 369 patients (pts) across 3 trials (CORALLEEN, PAMELA and NEOERIBULIN) were explored. In CORALLEEN, 106 pts with Luminal B/HER2- breast cancer (BC) were randomized to 6 months of letrozole + ribociclib (LTZ+RIB) or AC x 4 + paclitaxel x 12. In PAMELA, 151 pts with HER2+ BC were treated with lapatinib + trastuzumab (hormonal therapy if hormone receptor [HR]-positive) for 18 weeks. In NEOERIBULIN, 101 HR+/HER2- and 73 triple-negative pts were treated with eribulin x 4. In each trial, TILs and tumor cellularity were determined at baseline and at D15 (PAMELA and CORALLEEN) or D21 (NEOERIBULIN) of treatment. CelTIL is calculated following this formula: $-0.8 \times$ tumor cellularity (%) $+1.3 \times$ TILs (%). Changes in CelTIL between baseline and D15/21 samples and associations with response (RCB) were explored.

Results: In CORALLEEN, LTZ+RIB (n=49) or one dose of AC (n=47) did not show a significant change in CelTIL (mean -7.9; p=0.14 and +2.2; p=0.62). In NEOERIBULIN (n=132), eribulin significantly increased CelTIL in all pts (MD +10.0; p=0.03), both in HR+ (mean difference +4.8) and HR- (MD +11.1) BC. CelTIL changes were found significantly associated with both pCR and RCB0/1, independently of HR status. In PAMELA (n=141), NAT significantly increased CelTIL in all pts (MD +31.4; p<0.01), both in HR+ (MD +32.2) and HR- (MD +40.4) BC. CelTIL changes were found significantly associated with pCR and RCB0/1, independently of HR status. Finally, difference in CelTIL (D15-baseline) was found significantly associated with RCB0/1 (odds ratio=1.02, p<0.001) independently of trial and HR status.

Conclusions: Early and absolute changes in CelTIL following NAT are associated with tumor shrinkage at surgery. This biomarker could be used as an early read-out of drug activity and these data should help estimate power and sample size for future trials.

Legal entity responsible for the study: SOLTI Breast Cancer Research Group.

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17P Dysregulation of immune checkpoint proteins in newly diagnosed early breast cancer patients

B. Rapoport[1], A. Theron[1], H. Steel[1], S. Nayler[2], C. Benn[3], N. Hlatswayo[1], L. Kwofie[1], L. Heyman[4], T. Smit[5], L. Jooste[5], F. Moosa[5], R. Anderson[1]

[1]Department of Immunology, University of Pretoria Faculty of Health Sciences, Pretoria, South Africa; [2]Laboratory, Drs Gritzman & Thatcher Inc Laboratories & Wits Donald Gordon Medical Centre, Randburg, South Africa; [3]Surgery, Head of Netcare Breast Care Centre, Johannesburg, South Africa; [4]Medical Oncology, The Medical Oncology Centre of Rosebank, Johannesburg, South Africa; [5]Pharmacy Department, The Medical Oncology Centre of Rosebank, Johannesburg, South Africa

Background: Checkpoint proteins regulate the immune system. Breast cancer (BC) cells exploit the up-regulation or down-regulation of these proteins to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (ICM) can be measured in human plasma, however their biological and clinical significance remains essentially unknown. The aim of the present analysis was to measure the levels of pre-treatment ICM in newly- diagnosed BC patients (pts) and compare them to healthy controls.

Methods: Soluble forms of ICM, as well as cytokines and chemokines, were measured using Multiplex® bead array and ELISA technologies. Plasma samples from 98 BC pts and 45 healthy controls were analyzed for each protein. Data was prospectively obtained. Measured levels were compared between BC pts and healthy controls using a non-parametric test (Mann-Whitney).

Results: Soluble stimulatory molecules GITR (p<0.000002), GITRL (p< 0.007), CD27 (p< 0.002), CD28 (p<0.003), CD40 (p< 0.003), CD80 (p< 0.009), ICOS (p< 0.0006), as well as inhibitory molecules PD-L1 (p< 0.0000001), CTLA-4 (p< 0.005), TIM-3 (p< 0.00006), HVEM (p< 0.00002) TLR-2 (p< 0.05), levels were significantly lower in early BC pts compared to healthy controls. When analyzed according to BC characteristics (TNBC vs. non-TNBC, tumor size, stage, nodal status and age) no significant difference was detected between the soluble levels of these ICM between the different subsets. Additionally, serum levels of CXCL5 (p< 0.000001), CCL23 (p< 0.04), IL-16 (p< 0.00005), interferon-α (p< 0.03) and IL1-RA (p< 0.03) were significantly lower compared to healthy controls. Serum CX3CL1 or fractalkine (p< 0.024465) was significantly higher compared with healthy controls.

Conclusions: We identified low levels of both the stimulatory and inhibitory immune checkpoint molecules in newly diagnosed, non-metastatic BC pts compared to healthy controls. These results indicate that early BC is associated with a down-regulation of both soluble stimulatory and inhibitory immune-checkpoint pathways. Newly diagnosed early BC pts have a generalized immune-suppression independent of subtype and stage, which, to our knowledge, is the first study to describe soluble immune checkpoints in early BC pts.

Legal entity responsible for the study: Department of Immunology, University of Pretoria, South-Africa.

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18P Inter-tumour heterogeneity in breast cancers: The dynamic evolution of cancer genome during the metastatic process

C. Fumagalli[1], A. Ranghiero[1], S. Gandini[2], F. Corso[2], S. Taormina[1], E. De Camilli[1], G. Viale[3], M. Barberis[1], E. Guerini Rocco[3]

[1]Division of Pathology, IEO, European Institute of Oncology, IRCCS, Milan, Italy; [2]Department of Experimental Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy; [3]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Background: How the breast cancer genome evolves during malignant progression has been highly debated. To gain insight into the landscape of genomic aberrations occurring in breast cancers from the onset to metastasis, we compared the molecular profile of matched primary and relapsed tumors, focusing on the additional alterations developed in metastases.

Methods: The study population included a mono-institutional cohort of 128 patients with breast cancers (n=72 Luminal B - LUM, n=56 Triple-negative - TN) and with at least one recurrence in a timeframe of 17 years. 289 samples, comprising primary tumors (P) and matched metastases (M), were subjected to a comprehensive genomic profile using Next-Generation Sequencing (NGS) panels (FoundationeOne Dx or Oncomine Comprehensive Cancer Assay v.3). Genomic data were available for 106 P and 82 M that reached the NGS quality parameters.

Results: The most recurrent genomic alterations were TP53 mutations (P=49%, M=49%), PIK3CA mutations (P=33%, M=30%) and MYC copy number gain (P=25%, M=23%). TP53, PIK3R1, and NF1 aberrations were more frequently identified in TN breast cancer whereas ESR1 mutations and CCND1, FGF3, FGF19, and FGFR1 copy number gains in LUM cases (p-value < 0.05). The total number of P alterations, TP53 mutations, and MYC amplification were significantly and independently associated with a shorter time to relapse (p-value < 0.05). Considering matched P and M samples, we found a molecular subtype change in 10 of 128 (7.8%) cases. 55.8% of driver alterations were shared between P and matched M, including the most frequently mutated genes. In 27/61 (44.3%) cases 65 driver alterations were detected in M only, including 20 alterations classified as level1-level4 by OncoKB ranking and affecting mostly ESR1 (n=8) and PIK3CA (n=8) genes.

Conclusions: Prognostic biomarkers associated with time to relapse could be identified in primary tumors. A core of driver alterations was shared between P and M samples but novel and clinically relevant alterations could be identified in M only.

Legal entity responsible for the study: Giuseppe Viale.

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19P PIK3CA mutations in HER2-positive early breast cancer patients enrolled in the adjuvant randomized short-HER study

V. Guarneri[1], M.V. Dieci[1], G. Bisagni[2], A.A. Brandes[3], A. Frassoldati[4], L. Cavanna[5], A. Musolino[6], F. Giotta[7], A. Rimanti[8], O. Garrone[9], E. Bertone[10], K. Cagossi[11], O. Nanni[12], F. Piacentini[13], E. Orvieto[14], M. Curtarello[15], N. Chic[16], R. D'Amico[17], A. Prat[18], P.F. Conte[1]

[1]Medical Oncology 2, University of Padua, Veneto Institute of Oncology IOV — IRCCS, Padua, Italy; [2]Department of Oncology and Advanced Technologies, Oncology Unit, Azienda USL-IRCCS, Reggio Emilia, Italy; [3]Medical Oncology, Azienda Unità Sanitaria Locale di Bologna-IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy; [4]Oncology, Azienda Ospedaliera di Ferrara St. Anna, Ferrara, Italy; [5]Oncology Department, Azienda Ospedaliera Piacenza, Piacenza, Italy; [6]Medical Oncology, Azienda Ospedaliera di Parma, Parma, Italy; [7]Medical Oncology, Istituto Oncologico Bari, Bari, Italy; [8]Medical Oncology, Azienda Ospedaliera di Mantova, Mantova, Italy; [9]Medical Oncology, Azienda Ospedaliera St. Croce e Carle, Cuneo, Italy; [10]Medical Oncology, Sant'Anna Hosptital, Turin, Italy; [11]Breast Unit Ausl Modena, Ramazzini Hospital, Carpi, Italy; [12]Istituto Tumori della Romagna I.R.S.T., Meldola, Italy; [13]Oncology Department, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy; [14]Pathology Unit, Ulss 5 Polesana, Rovigo, Italy; [15]Immunology and Molecular Oncology, Veneto Institute of Oncology IRCCS, Padua, Italy; [16]Medical Oncology, Hospital Clinic, Barcelona, Spain; [17]Department of Medical and Surgical Sciences for Children & Adults, University of Modena, Modena, Italy; [18]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain

Background: PIK3CA gene mutations are a source of heterogeneity in HER2-positive breast cancer, with potential impact on prognosis and treatment sensitivity. We explored the frequency, association with clinicopathological features and prognostic impact of PIK3CA mutations in the randomized adjuvant ShortHER trial.

Methods: The ShortHER trial randomized 1254 patients with HER2-positive early breast cancer to 9 weeks or 1 year of adjuvant trastuzumab combined with chemotherapy. Non-inferiority of the short arm was not demonstrated with the frequentist approach. PIK3CA hot-spot mutations in exon 9 (E542K, E545K-A-G, Q546E-K) and exon 20 (M1043I, H1047R-L-Y, G1049R-S) were analysed by using Pyrosequencing method on DNA extracted from centralized FFPE tumor samples.

Results: A mutation of the PIK3CA gene was detected in 21.7% of the 803 genotyped patients (n=174 mutated; n=629 wild type). Mutations in exon 9 and 20 occurred in 78 (9.7%) and 95 (11.8%) cases, respectively. PIK3CA mutation occurred more frequently in hormone receptor-positive vs hormone-receptor negative cases (23.5% vs 17.4%, p=0.057) and in post-menopausal vs premenopausal patients (23.8% vs 17.7%, p=0.050). No association with stage, age, grade, TILs and treatment arm was observed. At a median follow up of 7.8 years, 5-yr DFS rates were 90.6% for PIK3CA mutated and 86.2% for PIK3CA wild-type patients (HR 0.84, 95% CI 0.56-1.27, p=0.417). PIK3CA mutation showed a favorable prognostic impact in the subgroup of patients owing to the PAM50 HER2-enriched subtype (n=232): 5-yr DFS 91.8% vs 76.1% for PIK3CA mutated and wild-type patients (log-rank p=0.049; HR 0.46 95% CI 0.21-1.02). There was no significant difference in DFS according to PIK3CA mutation in subgroups defined by hormone receptor status: HR 0.87 (95% CI 0.39-1.95, p=0.734) for hormone receptor-negative and HR 0.84 (95% CI 0.52-1.36, p=0.471) for hormone receptor-positive.

Conclusions: Within the HER2-enriched molecular subtype, PIK3CA mutated patients showed better DFS as compared to PIK3CA wild-type patients. These results highlight the need to integrate multiple biomarkers in order to dissect the heterogeneity of HER2-positive breast cancer.

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21P Germline and somatic variants in DNA DMAGE repair (DDR) genes in patients with untreated, early-stage triple negative breast cancers (TNBC)

J.K. Litton[1], L. Zhao[2], J. White[1], B. Arun[3], E. Ravenberg[1], X. Song[2], J. Zhang[4], S. Moulder[1]

[1]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Breast Medical Oncology and Clinical Cancer Genetics, The MD Anderson Cancer Center, Houston, TX, USA; [4]Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Mutations in DDR genes, most notably BRCA1/2 and have been predictive to respond to PARP inhibitors and other DNA-damaging systemic therapies. However, the reports of detected germline and somatic variants in other DDR-related genes in early-stage, untreated breast cancers is limited. Here we report variants identified in multiple DDR-related genes in patients with untreated TNBC and association with pathologic complete response (pCR).

Methods: Pretreatment core biopsies were obtained from 193 patients with early-stage (I-III) TNBC enrolled on the ARTEMIS trial (NCT02276443). DNA was extracted from blood for germline as well as from tumor samples for somatic testing and underwent whole exome sequencing and RNAseq. Enrichment of gene alterations were compared using a Fisher exact test in patients (pts) with and without pCR. Whole exome sequencing was performed and pair-end sequencing reads in FASTQ format were generated and aligned to the hg19 human reference genome. Platypus was used to call germline mutations on DDR genes. MuTect was used to identify somatic point mutations, and Pindel was used to identify somatic insertions and deletions. A series of post-calling filtering were applied for somatic mutations.

Results: Overall DDR variants were identified in 42% (82/193) of the patients and 110 total variants identified (Table). Almost all of were somatic (101/110). Out of 21 genes considered, 16 had an identifiedvariant in at least 1 patient. Somatic + germline mutations in BRCA was associated with an increase in pCR (p=0.03). Although filtering against known databases were completed to exclude polymorphisms as much as possible, some of these findings may still be consistent with variants of uncertain significance.

Table 21P

Gene	No. of germline variants	No. of somatic variants	No. frameshit	No. missense	No. other variant type
ATM	0	4	1	3	
ATR	0	3		2	1
BRCA1	2	14	8	5	3
BRCA2	1	7	5	3	
BRIP1	1	2	1	2	
CHEK2	0	1		1	
FANCA	3	5	2	6	
FANCD2	0	3	1	1	1
FANCE	0	2	1	1	
FANCF	0	1		1	
FANCM	0	20	15	2	3
NBN	1	6	3	4	
PALB2	0	2	1	1	
PTEN	0	12	6	1	5
RAD50	0	19	16	2	1
Rad51D	1	0			1

Conclusions: Both germline and somatic variants in DDR-related genes were identified in patients with early-stage, untreated TNBC. Further somatic variant analysis and response to neoadjuvant chemotherapy will be reported.

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23P Clinical, pathological and gene expression features of HER2-low breast cancer

F. Schettini[1], N. Chic[2], F. Brasó-Maristany[1], L. Paré[3], T. Pascual[4], B. Conte[5], O. Martínez-Sáez[6], B. Adamo[6], M. Vidal[2], A. Fernandez-Martinez[7], B. González-Farré[8], E. Sanfeliu[8], G. Perrone[9], P. Villagrasa[3], J. Gavila Gregori[10], C.H. Barrios[11], A. Lluch[12], M. Martin Jimenez[13], S. De Placido[14], A. Prat[15]

[1]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain; [2]Medical Oncology, Hospital Clinic, Barcelona, Spain; [3]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [4]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA; [5]Medical Oncology Department, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy; [6]Department Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; [7]Genetics Department, UNC Lineberger Comprehensive Cancer Center - University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [8]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [9]Pathology Department, Campus Bio-Medico University, Rome, Italy; [10]Medical Oncology, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain; [11]Medical Oncology, Centro de Pesquisa Clínica Hospital São Lucas da PUCRS, Porto Alegre, Brazil; [12]Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [13]Department Servicio de Oncologia Médica, Hospital General Universitario Gregorio Marañon, Madrid, Spain; [14]Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [15]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain

Background: Novel antibody-drug conjugates against HER2 are showing high activity in clinically HER2-negative (cHER2-) breast cancer (BC) with low HER2 expression. However, the clinical and molecular features of cHER2-/HER2-low BC are yet to be elucidated.

Methods: We collected retrospective data from 8 multicenter cHER2- BC datasets, including 4 clinical trials. HER2 status in each study was determined using standard FDA-approved antibodies and ISH-techniques and classified according to the ASCO/CAP guidelines. For this study, tumors were regrouped in HER2 0 (0 score) and HER2-low (1+ or 2+ with ISH-negativity). The following variables were compared between the 2 groups in all patients and according to hormone receptor (HR) status: age, grade, ki67, histotype, tumor size, HR, HER2 and nodal status. nCounter-based PAM50 subtypes distribution and the expression of the 50 PAM50 genes, including ERBB2, were also compared.

Results: A total of 3,136 patients with cHER2- disease (57.4% HER2-low and 42.6% HER2 0) were evaluated. Overall, 888 (28.3%) tumor samples came from metastatic sites. No statistically significant differences were found regarding clinicopathological variables between HER2-low and HER2 0. Within HR-positive (+) disease (n=2,497), 63.2% and 36.8% of tumors were HER2-low and HER2 0, respectively. Subtype distribution was similar across HR+/HER2-low and HR+/HER2 0. A total of 45/50 PAM50 genes were found differentially expressed between HR+/HER2-low and HR+/HER2 0 (False Discovery Rate [FDR]<5%). High expression of luminal (e.g. ESR1 and FOXA1) and ERBB2, and low expression of proliferation-related genes (e.g. MKI67) was found in HER2-low compared to HER2 0. Within triple negative BC (TNBC) (n=622), 34.2% were HER2-low and 65.8% were HER2 0. Subtype distribution was similar across TNBC/HER2-low and TNBC/HER2 0. No PAM50 gene was found differentially expressed between TNBC/HER2-low and TNBC/HER2 0 (FDR≥5%). Finally, ERBB2 mRNA levels were higher in HER2-low/HR+ tumors than HER2-low/TNBC (p<0.001).

Conclusions: HER2-low disease within clinically HER2- BC is frequent. However, significant differences exist according to HR status. Compared to HER2-low/TNBC, HER2-low/HR+ disease is a more distinct biological entity and has higher ERBB2 expression.

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24P The influence of metabolic syndrome on the risk of breast cancer: A study analysing nationwide data from the Korean National Health Insurance Service

K-T. Hwang

Surgery, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

Background: To investigate the influence of metabolic syndrome and its components on the risk of breast cancer.

Methods: Retrospective nationwide cohort study analyzing data of 13,377,349 women older than 19 years who were enrolled between 2009 and 2014 from the Korean National Health Insurance Service was performed. Cox proportional hazards model was used to calculate hazard ratio (HR) and 95% confidence interval (CI) of breast cancer risk according to metabolic syndrome and its components.

Results: The presence of metabolic syndrome decreased the risk of all breast cancer types in all subjects (HR: 0.954; 95% CI: 0.939-0.970). In women with age ≤ 50 years, metabolic syndrome decreased the risk of all breast cancer types, with similar findings for all subject groups (HR: 0.915; 95% CI: 0.892-0.939). In women with age >50 years, metabolic syndrome increased the risk of all breast cancer types (HR: 1.146; 95% CI: 1.123-1.170), especially in age groups of more than 55 years. The effect of metabolic syndrome was more prominent as age subgroups became older, especially in postmenopausal women. In women with age > 50 years, HRs increased as the number of metabolic syndrome components increased, while HRs decreased as the number of metabolic syndrome components increased in women with age ≤ 50 years.

Conclusions: The presence of metabolic syndrome increased the risk of breast cancers in postmenopausal women, but decreased the risk in premenopausal women. The effect of metabolic syndrome was more prominent as age subgroups became older, especially in postmenopausal women. Every metabolic syndrome component played similar roles on the risk of breast cancer. Their effects became stronger when the number of components increased.

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25P Breast cancers with heterogeneous HER2 amplification show a diverse distribution of 'driver' and 'passenger' somatic mutations and copy number variations

M.R. Van Bockstal[1], M.C. Agahozo[2], R. van Marion[2], P.N. Atmodimedjo[2], H.F.B.M. Sleddens[2], W.N.M. Dinjens[2], L.L. Visser[3], E. Lips[4], J. Wesseling[5], C.H.M. van Deurzen[6]

[1]Pathologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [2]Pathology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Division of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; [4]Division of Molecular Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands; [5]Divisions of Diagnostic Oncology & Molecular Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands; [6]Pathology, Erasmus University Medical Center, Rotterdam, Netherlands

Background: Invasive breast cancers with HER2 gene amplification are associated with poor outcome. Heterogeneous HER2 amplification has been observed in up to 41% of breast cancers, depending upon its definition. Carcinogenesis is driven by intra-tumour heterogeneity. Molecular diversity enables cancer cells to circumvent specific targeted treatment. In this study, we compared the genetic differences between admixed HER2-positive and HER2-negative breast cancer components. This in-depth analysis investigated the heterogeneity in their somatic mutational landscape.

Methods: Formalin-fixed, paraffin-embedded tissue of 10 breast carcinomas with at least one HER2-negative and at least one HER2-positive component was micro-dissected. Each component was subjected to targeted next-generation sequencing using a 53-gene panel. Somatic mutations and copy number variations were investigated.

Results: We identified 3 splice site alterations, 32 missense variants, 12 deletions, 9 insertions, and 7 nonsense variants in 26 different genes, which are (likely) pathogenic. Overall, these molecular anomalies were heterogeneously distributed among the different tumour components. The HER2-negative tumour components did not yield common alternative drivers. One patient had a CCND1 copy number gain limited to a HER2-negative tumour component. Two patients had an 8q24 gain in at least one cancer component, resulting in increased copy numbers of the MYC and PVT1 genes. Two patients had an FGFR1 copy number gain in at least one tumour component. One patient had an EGFR copy number gain in a HER2-negative DCIS component, resulting in EGFR protein overexpression.

Conclusions: This series of 10 heterogeneously HER2-amplified breast tumours demonstrates that not all breast cancer cells require HER2 as a driver of tumour growth. Several other molecular anomalies are able to act as alternative or collaborative drivers. This study illustrates that breast carcinogenesis is characterized by a diverse and heterogeneous molecular landscape, of which some genetic anomalies drive cancer progression, and others are mere 'passenger' molecular aberrations.

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28P Europe-side external quality assessment (EQA) of RNA based testing of ER, PR, HER2 and Ki67 in invasive breast cancer

R. Erber[1], A. Hartmann[1], P. Fasching[2], R. Stöhr[1], M.W. Beckmann[2], M. Zentgraf[1], M. Ruebner[2], H. Huebner[2], J. Fischer[3], E. Guerini Rocco[4], G. Viale[4], A. Cayre[5], F. Penault-Llorca[5], T. Caniego Casa[6], J. Palacios Calvo[6], P. Jank[7], C. Denkert[7], L. Khoury[8], T. Mairinger[8], F. Ferrazzi[9]

[1]Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; [2]Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany; [3]Qualitätssicherungs-Initiative Pathologie QuIP GmbH, Qualitätssicherungs-Initiative Pathologie QuIP GmbH, Berlin, Germany; [4]Department of Pathology and Laboratory Medicine, European Institute of Oncology IRCCS and University of Milan, Milan, Italy; [5]Department of Biopathology, Centre Jean Perrin, Clermont-Ferrand, France; [6]Servicio de Anatomía Patológica, Hospital Universitario Ramón y Cajal, Madrid, Spain; [7]Institute of Pathology, Uniklinikum Giessen und Marburg, Marburg, Germany; [8]MVZ Helios Hospital Emil von Behring GmbH, MVZ Helios Hospital Emil von Behring GmbH, Berlin, Germany; [9]Institute of Pathology, Department of Nephropathology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany

Background: Invasive breast cancer (IBC) subtypes, which are subject to different treatments, are identified in clinical routine by expression of estrogen receptor (ER), progesterone receptor (PR), Ki-67 and HER2 status by immunohistochemistry (IHC) and/or in situ hybridization (ISH). Yet, IHC evaluation might be hampered by (pre-) analytical errors and optimal cut-offs are still under discussion. Gene expression assays may offer a reliable way to measure mRNA expression of these four markers (ESR1, PGR, ERBB2 and MKI67). Here, we investigated the correlation of the commercially available "four-marker" Xpert® Breast Cancer STRAT4 (CE-IVD) mRNA assay with the gold standard (IHC/ISH) in different pathologic laboratories across Europe.

Methods: Ten pre-therapy breast core biopsies with IBC [six ER+/PR+ with varying Ki-67, two HER2+, two triple negative IBC diagnosed in the coordinating center (CC)] with sufficient formalin fixed paraffin embedded tissue were evaluated. IHC/ISH data for ER, PR, HER2 and Ki-67 were extracted from the original pathology report. For each case, STRAT4 (ESR1, PGR, ERBB2 and MKI67 mRNA assay) was performed in the CC and STRAT4 results matched IHC subtyping. Five European pathology laboratories participated in the harmonization study. Each site received one H&E stained slide and one unstained slide for STRAT4 testing. Binary mRNA results of each marker (positive vs. negative) were compared with the gold standard IHC/CISH of the CC. 80% of all results tested at each site had to be in agreement with the gold standard to pass the EQA.

Results: All centers passed the EQA study. Sensitivity, specificity and accuracy of ESR1 and ERBB2 mRNA were 100% for all ten samples. Instead, PGR mRNA was falsely reported as negative for one case (case #2) by two sites and MKI67 was falsely negative for two cases (case #2 by four sites, #10 by one site). Case #2 was a pleomorphic invasive lobular BC with heterogeneous PR (IHC staining 10%) and Ki-67 IHC (up to 30%), whereas case #10 displayed homogenous Ki-67 IHC.

Conclusions: The results of our study showed that STRAT4 might offer a reliable alternative for the evaluation of ER, PR, HER2 and Ki-67 in IBC. However, prognostic and predictive value of STRAT4 should be further validated in clinical cohorts.

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29P Key cancer gene expression features of hereditary breast cancer in the Kazakh population

N. Omarbayeva[1], D. Kaidarova[2], A. Abdrakhmanova[3], G. Zhunussova[4], S. Abdikerim[4], L. Djansugurova[4]

[1]Breast Cancer Department, Kazakh Research Institute of Oncology & Radiology, Almaty, Kazakhstan; [2]Administrative, Kazakh Research Institute of Oncology & Radiology, Almaty, Kazakhstan; [3]Oncology Department, Kazakh Research Institute of Oncology and Radiology, Almaty, Kazakhstan; [4]Genetic Laboratory, Institute of General Genetics and Cytology, Almaty, Kazakhstan

Background: Breast cancer (BC) shows a high incidence both in Kazakhstan and around the world, among the diseased the proportion of young women in the last 10 years is increasing, some women have a burdened family history. Approximately 20-30% of cases of hereditary breast cancer are caused by presence of BRCA1 and BRCA2 genes defects. Also, there are additional genes which can increase the risk of BC and they are still under study.

Methods: The study included 235 unrelated patients from Kazakh population(the average age 34.25 ± 4.56) with BC. Genomic DNA was obtained from peripheral blood and sequencing was performed using TruSight Cancer Kit on the MiSeq platform. Studio Variant was used to annotate and interpret genetic variants. 26 (11,1%) patients had a maternal family history of BC, 21 (80.8%) of them had first- degree relatives diagnosed with BC at different age.

Results: Bioinformatics analysis of NGS data identified 23,915 variants in 83 genes, 8030 evaluated as missense variants, 13212 as synonymous nucleotide substitutions, 753 variants in the 3′-untranslated region (3′-NTO) , 1221 variants in the 5′-untranslated region (5′-NTO), 35 variants leading to a shift of the reading frame (deletion /

insertion), nonsense (stop codon variants) - 17, variants in the acceptor splicing site - 7, variant splicing donor site - 2, inframe deletion /insertion-10, variants that violate start codons- 3, as well as 622 intron variants / variants in non-coding regions. Pathogenic mutations in the genes BRCA1 (24 variants (37.5%) and BRCA2 (18 (28.1%) were most often found. Also, 22 additional pathogenic variants were identified in the non-for BRCA genes (APC, ATM, BLM, CHEK2, PALB2, TP53, ERCC2, FANCA, FANCM, NBN, PMS1, PMS2, SDHB and XPA). A hereditary history was recorded in 29.1% and 27.8% of representatives of the group with pathogenic mutations in the BRCA1 and BRCA2, respectively, higher compared to the group of patients without pathogenic mutations and to the group of patients with mutations in the BRCA-negative genes.

Conclusions: NGS showed frequent and novel germline mutations in BRCA1/2 and non-BRCA genes. After final statistic data processing, diagnostic and prevention tools for key genes will be developed and included in the National guidelines of Republic of Kazakhstan.

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30P In search of a bone metastasis (BM) gene signature in circulating tumour cells (CTCs) from stage IV breast cancer (BC) patients

S. D'Oronzo[1], D. Lovero[1], R. Palmirotta[1], P. Cafforio[1], J. Brown[2], S. Wood[3], M. Cives[4], M.G. Tucci[5], L.S. Stucci[5], R.E. Coleman[6], F. Silvestris[5]

[1]Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy; [2]Oncology and Metabolism, Weston Park Hospital Cancer Research Centre, Sheffield, UK; [3]Oncology and Metabolism, University of Sheffield, Sheffield, UK; [4]Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy; [5]Biomedical Sciences and Human Oncology, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy; [6]Department of Oncology and Metabolism, Weston Park Hospital Cancer Research Centre, Sheffield, UK

Background: Common sites of distant metastases from BC include the skeleton and a number of studies have long attempted to identify a specific osteotropism signature to select patients for preventive therapeutic options. Here, we evaluated the expression of a gene panel potentially involved in BM onset in CTCs from metastatic BC patients and found a putative correlation of such a gene profile with sites of distant relapse.

Methods: Following approval by local Ethics Committee and written informed consent, CTCs were isolated from 39 stage IV BC patients, either treatment naïve or in progressive disease, through immunomagnetic pre-enrichment with autoMACS Separator® and sorting by DEPArray®. A panel of 136 genes involved in BC progression and BM development was derived from literature data to assess their expression levels in CTCs by RNAseq. The panel was first verified on subclones of the MDA-MB231 BC cell line with different organotropism (P0:parental population; P7:osteotropic subclone; LM:subclone with lung tropism) and then validated in CTCs from patients grouped in relation to their metastatic sites, namely (a) BM-only, (b) Other, (c) BM and Other, at the time of collection.

Results: The median number of recovered CTCs was 56 (range 9—106). No correlation was found between CTC number and BC histopathological features. The transcriptome heatmap of unsupervised hierarchical clustering of BC cell lines, based on normalized read counts, clustered distinct profiles in relation to their tissue tropism. The feasibility of this approach was then validated on CTCs and 31 differentially expressed genes (DEGs) were revealed between CTCs from (a) and (b) groups. By Gene Ontology evaluation of these DEGs, we found that most of them were enriched with greater statistical significance in different biological processes enrolled in bone tissue development and morphogenesis.

Conclusions: CTCs isolated from BC patients with different sites of metastases harbor distinct GEP that can be successfully evaluated by our assay. Prospective investigation is desirable to assess the prognostic role of identified DEGs in earlier BC stages.

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31P BRCA1/2 gene mutation detection in 2686 Chinese clinical samples based on NGS HANDLE technology

F. Zhang[1], B. Jin[2], L. Zhang[3], A. Zhang[3], H. Ge[4], M. Mueser[4], L. Ruan[3]

[1]NGS Data Analysis and Interpretation, AmoyDx Medical Institute, Xiamen, China; [2]Bioinformatics, Amoy Diagnostics Co., Ltd., Xiamen, China; [3]New Technology Platform, Amoy Diagnostics Co., Ltd., Xiamen, China; [4]International Market, Amoy Diagnostics Co., Ltd., Xiamen, China

Background: BRCA1 and BRCA2 are tumor suppressor genes that play an important role in prevention, monitoring, and use of targeted therapy in cancer. The mutation types include single-nucleotide variation (SNV), small insertions and deletions (InDel) and copy number variations (CNV). Traditional methods for SNV and InDel detection are multiplex polymerase chain reaction (PCR) plus Sanger sequencing or Next Generation Sequencing (NGS). For CNV detection, the gold standard method is Multiplex Ligation-dependent Probe Amplification (MLPA). A new NGS method based on Halo-shape ANnealing and Defer-Ligation Enrichment (HANDLE) technology developed by AmoyDx can detect all mutation types within one reaction tube, and a turn-around time of 5 h for library preparation with hands-on time of 1 hour.

Methods: There were 2686 Chinese samples (2563 whole blood samples and 123 FFPE tissue samples) detected in AmoyDx Medical Institute, including 1357 breast, 754 ovarian, and 575 other samples (prostate, pancreatic, patients of unknown cancer types and family members of cancer patients). All samples were tested following the instructions of the AmoyDx BRCA1 and BRCA2 gene mutation detection kit combined with the automatic AmoyDx NGS Data Analysis System (ANDAS). The MLPA method was used for confirmation of CNV results of whole blood samples.

Results: In total, there were 476 samples detected with a pathogenic or likely pathogenic BRCA mutation. The mutation rate was 17.7% for all samples, 12.2% in breast and 26.4% in ovarian cancer samples. There were 11 samples with multiple breast cancer types or combined breast cancer and other cancer types, 6 of which were detected with pathogenic or likely pathogenic mutations. There were 20 out of 476 (4.2%) samples that demonstrated pathogenic or likely pathogenic BRCA CNVs by MLPA. 18 (90%) of these mutations were from BRCA1 gene, and 19 (95%) of them were concordant with the BRCA mutation detection according to the AmoyDx NGS test kit based on HANDLE technology.

Conclusions: BRCA1/2 gene mutations were detected in multiple cancer types. CNVs of BRCA1 were much more frequent than CNVs of BRCA2 in Chinese cancer patients. Testing of BRCA 1/2 by NGS based on HANDLE technology is a valid and fast solution for detection of BRCA1/2 mutations.

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32P The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict efficacy of CDK 4/6 inhibitors in women with hormone receptor-positive/HER2-negative advanced breast cancer

E. Zattarin[1], C. Fabbroni[1], F. Ligorio[1], F. Nichetti[1], R. Lobefaro[1], L. Rivoltini[2], G. Capri[1], G.V. Bianchi[1], F.G.M. De Braud[1], C. Vernieri[1]

[1]Medical Oncology & Haemathology Department, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy; [2]Unit of Immunotherapy of Human Tumors, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: Preclinical evidence indicates that cyclin-dependent kinase (CDK) 4/6 inhibitors stimulate antitumor immunity, which may contribute to their anticancer activity. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) reflect systemic inflammation and immune system functional status, and could be associated with CDK 4/6 inhibitor efficacy in patients (pts) with hormone receptor-positive advanced breast cancer (HR+ aBC).

Methods: We performed a retrospective, monocentric study to investigate the association between NLR or PLR, as measured at baseline and after the first three treatment cycles, and progression free survival (PFS) in HR+ aBC pts treated with CDK 4/6 inhibitors in combination with endocrine therapies (ETs). The thresholds for NLR and PLR were defined using the maximally selected rank statistics. The impact of these parameters on PFS was evaluated at univariate and multivariable analysis by using Cox proportional hazard model.

Results: A total of 162 pts treated with palbociclib (n=142), ribociclib (n=16) or abemaciclib (n=3) plus ETs between January 2017 and December 2019 at our Institution were included. NLR and PLR at baseline were not associated with PFS. Conversely, high NLR (>3) and high PLR (>323.6) after three treatment cycles were associated with significantly lower PFS (p=0.011 and p=0.013, respectively). Multivariable analysis confirmed an independent association between high NLR or PLR and lower PFS (aHR 3.66, 95% CI 1.44-9.33, p=0.007 and aHR 2.79, 95% CI 1.36-5.70, p=0.005, respectively). Another factor associated with worse PFS was the presence of liver metastases (aHR 3.02, 95% CI 1.53-6.00, p=0.003).

Conclusions: This is the first study to show a significant association between high NLR or PLR values, as measured during CDK 4/6 inhibitor treatment, and lower PFS in HR+ aBC pts. Our results suggest that the NLR and PLR could be used as precocious biomarkers of treatment efficacy. A multicenter observational study to confirm these data in a larger cohort of pts is ongoing.

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33P Immune analysis of lymph nodes in relation to the presence or absence of tumour infiltrating lymphocytes in triple negative breast cancers

A. Quintana[1], V. Peg[2], T. Moline[3], A. Prat[4], L. Paré[5], P. Galván[5], G. Villacampa[6], R. Dientsmann[6], J. Perez[7], E. Muñoz[8], M. Martí[9], J. Blanco-Heredia[10], C. Dos Anjos[10], M. Vazquez[11], L. de Mattos[10], J. Cortés[12]

[1]Breast Cancer Unit, Vall d'Hebron University Hospital, Barcelona, Spain; [2]Pathology Department, Vall d'Hebron University Hospital, Universidad Autónoma de Barcelona, Spanish Biomedical Research Network Centre in Oncology (CIBERONC) (Madrid), Barcelona, Spain; [3]Pathology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Translational Genomics and Targeted Therapeutics Group (IDIBAPS), Barcelona, Spain; [5]Translational Genomics and Targeted Therapeutics Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [6]Oncology Data Science (ODysSey Group), Vall d'Hebron University Hospital, Barcelona, Spain; [7]Medical Oncology Department, IOB Institute of Oncology, Quironsalud Group, Barcelona, Spain; [8]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [9]Cell Immunology Laboratory, Universidad Autónoma de Barcelona, Bellaterra, Spain; [10]IrsiCaixa, Hospital Universitari Trias i Pujol, Badalona, Spain; [11]Genome Bioinformatics, Barcelona Supercomputing Center, Barcelona, Spain; [12]Vall d'Hebron Institute of Oncology (VHIO), IOB Institute of Oncology Madrid & Barcelona, Quironsalud Group, Barcelona, Spain

Background: Triple negative breast cancer (TNBC) is a subtype of breast cancer with poor survival. Tumor-Infiltrating Lymphocytes (TILs) have been identified as a potential biomarker in TNBC. However, some tumors lack of TILs completely. This could be explained by the confinement of lymphocytes in the nearby lymph nodes (LN). This project aims to identify immune checkpoints that could be retaining those lymphocytes. We also analyzed other immune biomarkers in LN and tumor; and performed mutation, neoantigen analysis and gene expression profiling in tumor.

Methods: We identified 102 TNBC patients with localized tumors and no metastasis (T1c-T2N0M0), that did not receive neoadjuvant treatment, and had tumor and LN available in paraffin blocks. We scored TILs as indicated in the latest published guidelines (2017), and included only patients with >=50% (high TILs) or =<5% (low TILs). Total n was 35 patients, 15 high and 20 low. We measured CTLA-4, PD-1, PD-L1, PD-L2 and OX-40 by immunohistochemistry, and the expression of 50 immune genes by the nCounter platform in tumor and LN. We performed Whole Exome Sequencing (WES) and the Breast Cancer 360TM (BC360) panel (770 genes) in tumor.

Results: CTLA-4 is significantly more expressed in LN of low TIL (p=0.01, median 4% vs. 7%), PD-L1 in tumor cells of high TILs, PD-L2 in germinal centers of high TILs, and OX-40 in tumor, LN and GC of low TILs. Gene expression panel showed that CD274, CD273 and VEGF are significantly more expressed in low TILs tumors. In LN, only CD68 and CD8 were significantly more expressed in high TILs. Despite non-significant median mutation load (p=0.76) by WES analysis, we found significant neoantigen load (p=0.027) in low TILs. BC360 panel showed significant expression of stromal signatures in low TILs.

Conclusions: Low TIL tumors demonstrate higher neoantigen load, but incapable of recruiting T cells at the tumor. On the contrary, high TILs, with less neoantigens, have more antigen presentation (CD68) and T cell proliferation in LN. These suggest another mechanism of avoiding immune infiltration. We observed higher CTLA-4 expression in LN of low TILs, indicating a potential first brake for lymphocyte migration to the tumor. PD-L1 could be a secondary brake at the tumor site.

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34P Comprehensive clinical and molecular portraits of grade 3 ER+ HER- breast cancer

K. Wang[1], S. Franch-Expósito[2], L. Li[3], T. Xiang[4], J. Wu[3], G. Ren[4]

[1]Department of the Endocrine and Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China; [2]Gastrointestinal and Pancreatic Oncology Team, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Fudan University, Shanghai, China; [4]Key Laboratory of Molecular Oncology and Epigenetics, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: Estrogen receptor-positive, and human epidermal growth factor receptor 2-negative (ER+HER2-) breast cancer account for 60～70% of all breast cancer patients, whose grade III cases are rare but respond poorly to endocrine therapy. We systematically analyzed clinical and multi-omics data to find a potential avenue for personalizing therapy for them.

Methods: SEER database (n=25,629) and another two Chinese cohorts (WCCCG (n=546); FUSCC (n=348)) were used to assess the association between different subtypes (grade III vs. I/II ER+HER2-) and clinicopathological and survival significance. The remaining three multi-omics cohorts came from TCGA (n=88), METABRIC (n=404) and MSKCC (n=272), and we analyzed multi-omics data to describe the molecular features of grade III ER+HER2- cases.

Results: Grade III ER+HER2- cases harbored higher proportions of large tumor size (>5cm), lymph nodes metastasis, chemotherapy rate and luminal B subtype than I/II cases, where inferior survival outcomes were also observed. We detected increased mutation prevalence of TP53, CSMD3 and TTN in grade III cases with enrichments of mutation signatures linked to DNA repair deficiency. DNA methylation (HM450) data and methylation specific PCR indicated that cg18629132 located in promoter of MKI67 was hypermethylated in grade I/II cases and normal tissue, but hypomethylated in grade III cases, who harbored higher expression of mRNA MKI67. GISTIC2.0 identified 42 and 20 focal copy number variation events in non-metastatic and metastatic grade III cases, respectively, either CDKN1B on 12p12.3 or MDM2 on 12q15 amplification event has an independent prognostic effect on grade III cases. For transcriptional profiling between PAM 50 defined luminal and non-luminal grade III cases, the differential expressions of mRNAs were enriched in IL-17 and estrogen signaling pathways. Recursive partitioning analysis (RPA) used to construct a decision tree with two genes (non-luminal: GATA3+/GATA3- and AGR+), where this classifier was validated in our IHC-based WCCCG cohort.

Conclusions: Grade III ER+HER2- tumors have distinct clinical and molecular characteristics compared to grade I/II tumors, particularly with respect to non-luminal subgroup, and we should tailor and escalate therapies for them.

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35P The role of interplay between microRNA-133a and Mre11 in breast cancer

L.C. Kao, F-M. Chen

Breast Surgery, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan

Background: In Taiwan, breast cancer has been rapidly jumped to the first place in the incidence of women-specific malignancies. It will be urgent to discover some critical biomarkers predicting patient prognosis and outcome in Taiwan. Because Taiwanese breast cancer has a relatively lower incidence and earlier onset than Western population, the subset of clinical biomarkers and treatments applied in Western population may not be suitable for all Taiwanese population.

Methods: Recently microRNAs (miRNAs) were found to be frequently deregulated in breast cancer, and some specific miRNAs were found to be associated with the DNA damage response (DDR). We measured miR-133a, both circulating and intra-tumor levels, to identify the relationship among miR-133a, HER2, and sruvival. We also detected the protein level of Mre11, one of double-strand break repair protein complex, to fingure out the correlation with miR-133a.

Results: Our preliminary results showed that circulating miR-133a levels of breast cancer patients are significantly higher than those of health subjects by using the receiver operating characteristic (ROC) curve (p=0.001). Both circulating and intra-tumor miR-133a levels were inversely correlated with the HER2 status (p=0.015 and 0.011), suggesting that Her2 modulate the expression of miR-133a. The Kaplen-Meier survival curve further showed that high circulating miR-133a can increase the overall survival rate of patients who didn't receive chemotherapy, implicating that miR-133a might also modulate the response of chemotherapy, which has been linking to DNA repair ability. We found that ectopic miR-133a overexpression suppressed the protein levels of Mre11 but did not impact its mRNA levels.

Conclusions: In this project, we aim to disclose the interplay of miR-133a with Her2 and Mre11 in breast cancer development. Furthermore, we will establish the minimally invasive screen platform to improve early detection, prognosis, and follow up of breast cancer. We believe that the accomplishment of this project will not only provide better understanding of the carcinogenesis of breast cancer but also a pre-screening tool to facilitate decisions about which individuals to be recommended for further diagnostic tests or treatments.

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36P Molecular subtypes in Tunisian breast cancer

M. Frikha[1], S. Zouari[1], N. Fourati[1], M. Kallel[1], F. Elloumi[1], M. Bahri[1], W. Siala[1], T. Boudawara[2], A. Khanfir[3], W. Mnejja[1], J. Daoud[1]

[1]Radiation Oncology, Hopital Habib Bourguiba - Sfax University, Sfax, Tunisia; [2]Anatomopathology, Hopital Habib Bourguiba - Sfax University, Sfax, Tunisia; [3]Medical Oncology, Hopital Habib Bourguiba - Sfax University, Sfax, Tunisia

Background: The aim of this study is to report the particularities of breast cancer molecular subtypes and their correlations with the clinicopathological characteristics in a large cohort of South Tunisia.

Methods: We analyzed 617 breast cancer cases collected at Habib Bourgiba Hospital of Sfax between 2016 and 2019. Clinicopathological features were studied. Molecular subtypes were determined based on four parameters: human epidermal growth factor receptor 2 (HER2), proliferation index (Ki 67), estrogen and progesterone receptors. Five subgroups were reported: luminal A, luminal B HER2 positive, luminal B HER2 negative, triple negative and HER positive. Chi-squared test was performed to evaluate the correlation between pathology and molecular subtype classifications.

Results: Hormone receptor (ER and or RP) were positive in 80.8% and 35.3% of cases were HER positive. Luminal B HER2 negative was the most frequent molecular subtype (30%) followed by luminal B HER2 positive (27.4%), luminal A (12.9%), triple negative (11.6%) and HER positive (7.3%). Seventy eight percent of T4 stage was in luminal B (p=0.03). Histological grade was lower with Luminal A (20.8 %, p < 0.001) with more negative lymph nodes status (49.4%, p=0.01).Triple negative were significantly associated with high histological grade (80%, p <0.001) and tended to significance for HER2 positive (66%, p=0.07).

Conclusions: Our data demonstrated that the luminal B subtype was the most frequent subtype in South Tunisian population; however, the proportion of luminal A subtype was less than reported in other studies. Moreover, HER2 positive breast cancer subtype occurred at a high incidence. According to this molecular profile, we suggest that breast cancer in our region seems to be aggressive tumor that needs more systematic treatment intensification.

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37P A pooled analysis of the clinical utility of genomic signatures in young women with breast cancer

A.S. Ferrigno[1], C. De la Garza-Ramos[1], M. Lambertini[2], R. Barragan-Carrillo[3], H.A. Azim Jr[1], C. Villarreal-Garza[4]

[1]Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, San Pedro Garza Garcia, Mexico; [2]Breast Unit, IRCCS Ospedale Policlinico San Martino, and Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Genoa, Italy; [3]Department of Oncology, National Institute of Medical Sciences and Nutrition, Mexico City, Mexico; [4]Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, San Pedro Garza Garcia, Tlalpan. D.F., Mexico

Background: Risk stratification by genomic signatures has been shown to improve prognostication and guide treatment decisions among patients with hormone-receptor positive tumors. However, their role in young women breast cancer (YWBC) has witnessed some controversy.

Methods: A systematic search was performed in the MEDLINE, EMBASE and CENTRAL databases for studies that evaluated the use of commercially available genomic signatures OncotypeDx, Mammaprint, Endopredict, Breast Cancer Index, Genomic Grade Index and Prosigna in YWBC (i.e. patients aged ≤40 years at diagnosis). Eligible studies were those that included YWBC and disclosed the number of patients per risk category. The Fisher's test for independence was used to assess differences between age groups.

Results: Out of 752,935 women that underwent genomic testing, the minority (3.7%) were YWBC. 742,671 were tested with OncotypeDx, 10,053 with MammaPrint and 211 with Endopredict. Analysis of this age-group was not available for the other tests. Compared to older patients, YWBC were more likely to be subjected to genomic testing (33% vs 29%, p=0.02) and had a higher proportion of intermediate- to high-risk tumors when classified by OncotypeDx (61% vs 50%, p<0.01), MammaPrint (65% vs 38%, p<0.01), and Endopredict (68% vs 49%, p=0.06). Only three studies specifically exploring the prognostic value of genomic tests in YWBC were found, all using OncotypeDx. In patients with genomic low-risk, 6-year distant recurrence-free survival was 92%, while 5-year overall survival and breast cancer specific survival were nearly 100%. Nonetheless, YWBC were more likely to receive chemotherapy than older patients when classified as low- (24 vs 3%, p<0.01) or intermediate- (57 vs 32%, p<0.01) risk.

Conclusions: Only a small proportion of YWBC were included in genomic signature studies, with approximately one third classified as low-risk. Although the prognostic value of genomic tests for young women is currently available only for OncotypeDx, data support that patients with low genomic-risk have an excellent prognosis. Hence, genomic tests could be a useful tool for identifying young patients in which chemotherapy omission is appropriate.

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38P Morphological heterogeneity in ductal carcinoma in situ of the breast

C. Stanciu Pop[1], M-C. Nollevaux[1], M. Berlière[2], F. Duhoux[3], M.R. Van Bockstal[4]

[1]Pathology, CHU UCL Namur - Site Godinne, Yvoir, Belgium; [2]Surgery, Cliniques Universitaires Saint Luc, Belgium, Belgium; [3]Medical Oncology, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium; [4]Pathologie, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium

Background: Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous disease in terms of morphology and genetics. Tumor architecture and cellular morphology classify DCIS into subgroups to guide clinical management. This leaves a large portion of histopathological features (HPF) uncharacterized. This study explored the extent of heterogeneity of nuclear atypia, DCIS architecture, necrosis, calcifications, stromal architecture and stromal inflammation between biopsies and their subsequent resection specimen in DCIS.

Methods: The percentage of ducts containing a particular HPF was assessed on the biopsy slide and 3 slides of the resection specimen. A histoscore was determined to allow assessment of histopathological heterogeneity. For instance, the histoscore for nuclear grade was calculated as follows: (% grade 1 nuclei) + (% grade 2 nuclei)*2 + (% grade 3 nuclei)*3, with a score ranging from 100-300. Heterogeneity was arbitrarily defined as a mean histoscore with a standard deviation > 10% of the maximum histoscore. Statistical analysis comprised the Friedman test, post hoc Wilcoxon tests with Bonferroni corrections and Spearman's correlation tests.

Results: Fifty-one DCIS biopsies were correlated with their subsequent resection specimen: 24 cases of 51 (47%) showed heterogeneity for nuclear atypia, 25/51 (49%) for tumoral architecture, 23/51 (45%) for calcifications, 29/51 (57%) for necrosis, 22 /51 (43%) for myxoid stromal architecture, and 21/51 (41%) for stromal inflammation. Heterogeneity was not associated with patient age, DCIS size or type of surgery except for one weak association (p=0,048) between heterogeneity in stromal inflammation and DCIS size. No relationship between heterogeneity in nuclear atypia and heterogeneity in other HPF was found. All HPF in the biopsy correlated significantly with the HPF in the resection specimen, except for necrosis (p=0,004).

Conclusions: DCIS lesions present a heterogeneous histoscore for each HPF (41%-57%). All HPF determined in the biopsy correlated well with the surgical specimen, except for necrosis. We therefore conclude that overall morphological heterogeneity in DCIS has only a limited impact, and that biopsies of pure DCIS are generally representative for the entire DCIS lesion.

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39P Role of early circulating tumour cell (CTC) monitoring for prediction of clinical outcome in patients with HER-2 negative metastatic breast cancer receiving first-line treatment with bevacizumab and paclitaxel

I. Álvarez-López[1], E. González[2], L.M. Manso[3], J.L. Alonso[4], J.J. Cruz-Hernández[5], V. Carañana Ballerini[6], I. Gallegos[7], M. Quindós Varela[8], J.J. Illaramendi[9], E. Vicente[10], A.I. Ballesteros Garcia[11], F. Ayala de la Pena[12], A. Perelló[13], J. Vidal[6], A. Llombart Cussac[6]

[1]Medical Oncology, Hospital Universitario Donostia-Biodonostia, San Sebastian, Spain; [2]Medical Oncology, Hospital Universitario Virgen de las Nieves, Granada, Spain; [3]Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Medical Oncology, Hospital Clinico Universitario Virgen de la Arrixaca, El Palmar, Spain; [5]Department of Medical Oncology, Hospital Universitario de Salamanca, Salamanca, Spain; [6]Medical Oncology, Hospital Arnau de Vilanova, Valencia, Spain; [7]Medical Oncology, Hospital General Segovia, Segovia, Spain; [8]Medical Oncology, Hospitalario Universitario A Coruña, A Coruña, Spain; [9]Medical Oncology, Hospital de Navarra, Pamplona, Spain; [10]Medical Oncology, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain; [11]Medical Oncology, Hospital Universitario de La Princesa, Madrid, Spain; [12]Medical Oncology, Hospital General Universitario Morales Meseguer, Murcia, Spain; [13]Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, Spain

Background: Circulating tumor cells (CTC) are associated with clinical outcome in metastatic breast cancer (MBC). We explored the ability of early CTC monitoring (after 2 cycles) for predicting clinical benefit (CB), overall response rate (ORR) and outcome in terms of progression-free survival (PFS) and overall survival (OS) in patients (pts) with HER-2 negative MBC receiving first-line treatment with bevacizumab and paclitaxel.

Methods: Multicenter prospective observational study. Centralized CTC determination was performed at baseline (C0) and after cycle 2 (C2) using CellSearch. A cutoff of 5 CTCs/7.5ml was used to stratify pts into treatment-sensitive (<5 CTCs) and resistant (≥5 CTCs). The optimal CTC level cutoff for predicting CB and PFS was assessed using ROC curves.

Results: 111 pts were enrolled: median age: 54 years; ECOG 0/1: 50.5/39.6%; triple-negative: 29%; metastatic sites (median): 3; metastases location: liver (62%), bone (58%), lung (40%). The clinical benefit rate (CBR), ORR, and median PFS for the whole cohort were 65%, 41%, and 16.6 months, respectively. With a median follow-up of 17.5 months, the median OS was not achieved. At C0, 43/87 (49%) and 44/87 (50.6%) pts presented with <5 and ≥5 CTCs, respectively. The CTC level after C2 was in 73/85 (86%) and 12/85 (14%) pts <5 and ≥5, respectively. Among pts with CTCs ≥5 at C0, 78% had <5 CTCs after C2. The CTC level after C2 was predictive for CBR (73% vs 59%, p=0,046), ORR (48% vs 17%, p=0.043), and PFS (17 vs. 5 months, p=0.026). Median OS was 13 months in pts with ≥5 CTCs after C2 and it was not achieved in pts with <5 CTCs (p <0.001). A cutoff point of 1 CTC after C2 yielded 65% sensitivity and 61% specificity for prediction of PFS (p=0.021). Pts with 0 CTC achieved a significantly longer PFS vs. those with at least 1 CTC after 2 cycles (22.6 vs. 8.1 months; p=0.005). Grade 3-4 toxicity rate (39%) was not significantly different according to CTCs after 2 cycles (p =0.531).

Conclusions: CTC monitoring after 2 cycles of first-line bevacizumab-paclitaxel treatment may predict tumor response and clinical outcome in terms of PFS and OS in HER-2 negative MBC.

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40P Analysis of clinical pathological association with somatic mutations through next-generation sequencing

S. Jung

Breast Surgery, Kosin Univeristy Gospel Hospital, Busan, Republic of Korea

Background: The next generation sequencing technology has the advantages of high speed, high throughput and high accuracy. Because of these advantages, it is used in various cancer fields. Several gene pannels have been applied to breast cancer to assess risk and determine treatment direction accordingly. The purpose of this study was to improve the prognosis and future treatment of patients with breast cancer by applying NGS.

Methods: From January 2018 to December 2018, we studied patients who underwent surgery at Kosin University Gospel Hospital. The study patients were from stage 1 to stage 3 of breast cancer. Patients who were not able to undergo surgery or who had more than stage 4 patients were excluded. This study included patients who underwent Neo-systemic therapy(NST). NGS was performed postoperatively. And in patients who underwent NST, NGS proceeded to pre-chemotherapy specimens.

Results: The expression of somatic mutations varies with the type of breast cancer. In all type of breast cancers, TP53 was 26%, PIK3CA was 24%, and ERBB2 was 8%. In luminal type, PIK3CA was 32%, GATA 13% and TP53 12%. In the HER2 type, TP53 was 35%, ERBB2 was 23%, and PIK3CA was 17%. TNBC had 44% TP53, 13% PIK3CA, and 4% GAS6. In most cases, two or more mutations were combined.

Table 40P

Characteristic	Status	No NST(110)	
Age	(mean, range)	54.29(35-86)	
T stage	T1 or 1mic	69	62.7%
	T2	37	33.6%
	T3	4	3.6%
N stage	N0	89	80.9%
	N1	17	15.4%
	N2	2	1.8%
	N3	2	1.8%
Grade	G1	23	20.9%
	G2	54	49.0%
	G3	31	28.1%
	unknown	2	1.8%
ER	positive	75	68.1%
	negative	35	31.8%
PR	positive	72	65.4%
	negative	38	34.5%
HER2	positive	20	18.1%
	negative	90	81.8%
Ki67	<10	44	10.0%
	10-20	23	20.9%
	>20	43	39.0%

Conclusions: Different types of somatic mutations have been observed, depending on the subtype of breast cancer. Each type exhibited a different mutation distribution. Some treatments for mutations are being developed, and we expect to be effectively applied through NGS. The limitations of this study did not determine how these various mutations correlate with the prognosis of breast cancer. Long term follow up is needed in the future.

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41P A window-of-opportunity study with atezolizumab and the oncolityc virus pelareorep in early breast cancer (REO-027, AWARE-1)

L. Manso[1], P. Villagrasa[2], N. Chic[3], J.M. Cejalvo[4], Y. Izarzugaza[5], B. Cantos[6], S. Blanch[7], M. Juan[8], B. González-Farré[9], R. Laeufle[10], G. Nuovo[11], G. Wilkinson[12], M. Coffey[13], A. González[8], D. Martínez[14], L. Paré[2], F. Salvador[2], X. González-Farré[15], A. Prat[16], J. Gavila Gregori[17]

[1]Breast and Gynecologic Cancer Unit, Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [3]Medical Oncology, Hospital Clinic, Barcelona, Spain; [4]Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [5]Medical Oncology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [6]Medical Oncology, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [7]Medical Oncology, Instituto Valenciano de Oncología, Valencia, Spain; [8]Servei d'Immunologia, Hospital Clinic de Barcelona, Barcelona, Spain; [9]Pathology, Hospital Clinic of Barcelona, Barcelona, Spain; [10]Oncology, Oncolytics Biotech Inc, Calgary, AB, Canada; [11]Phylogeny Medical Lab, Ohio State University Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, Powell Ohio, OH, USA; [12]Translational Medicine, Oncolytics Biotech Inc., Calgary, AB, Canada; [13]Oncology, Oncolytics Biotech Inc., Calgary, AB, Canada; [14]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain; [15]Department Medical Oncology, Hospital General de Catalunya, San Cugat del Valles, Spain; [16]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [17]Medical Oncology, IVO - Fundación Instituto Valenciano de Oncología, Valencia, Spain

Background: A previous phase 2 study in metastatic breast cancer compared treatment with intravenously delivered oncolytic reovirus, pelareorep (pela), in combination with paclitaxel (PTX) versus PTX alone. This study demonstrated a statistically significant improvement in overall survival (OS), without differences in objective response or progression-free survival. We hypothesized that the OS benefit from pela + PTX may be attributed to an adaptive immune response triggered by pela. To test this hypothesis, and examine if pela can mediate the priming of an anti-tumor immune response, we designed a study called AWARE-1 (A window-of-opportunity study of pela in Early Breast Cancer), which is currently enrolling and for which initial translational research results are presented.

Methods: AWARE-1 is evaluating the safety and effect of pela ± atezolizumab on the tumor microenvironment (TME) in 38 women with early breast cancer. Patients are treated with pela on days 1, 2, 8, and 9, while atezolizumab is administered on day 3. Tumor biopsies are collected at diagnosis, day 3, and day ~21. The primary endpoint of the study is CelTIL score, a metric for quantifying the changes in tumor cellularity and infiltration of TILs, where an increase in CelTIL is associated with a favorable response to treatment. Tumor tissue was examined for pela replication, and changes to the TME were assessed by immunohistochemistry and TCR-seq. Peripheral blood was also examined by TCR-seq.

Results: Analysis of CelTIL show an increase in four of the six patients to date. Productive viral replication in day 3 and day ~21 biopsies was very high, as measured by in situ detection of viral capsid protein in tumor cells. Immunohistochemistry analysis revealed an increase in CD8+ T cells and upregulation of PDL1 on day 3 and day 21 biopsies for all patients. TCR-seq from blood showed that levels of T cell clonality correlate with changes in the TME and CelTIL.

Conclusions: Overall, the degree of viral replication was consistent with changes in CelTIL and changes within the TME. Preliminary data from the first six patients in AWARE-1 demonstrate pela-mediated priming of an adaptive immune response.

Clinical trial identification: NCT04102618.

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42P Expression of WNT, Hedgehog and NOTCH signaling pathways in HER-2 overexpressed and triple negative subtypes of breast cancer with high and low content of cancer stem cells

S. Demidov[1], S. Sazonov[2], A. Brilliant[3], Y. Brilliant[3]

[1]Department of Breast Surgery, City Clinical Hospital N40, Ekaterinburg, Russian Federation; [2]Histology, Cytology and Embryology, Ural State Medical University, Ekaterinburg, Russian Federation; [3]Department of Pathomorphology, Institute of Medical Cell Technologies, Ekaterinburg, Russian Federation

Background: There are three main cascades - WNT, Hedgehog and NOTCH, occur in cancer stem cells during the cancerogenesis. However, the conducted studies indicate the existence of other signaling mechanisms of regulation - NF-kB and PI3K signaling pathways. In our work, we investigated the expression of NF-kB, PI3K, PTEN molecules, as well as WNT, Hedgehog, NOTCH in cells of triple negative and HER-2 overexpressed breast cancer with high and low content of cancer stem cells (positive and negative ALDH1A1 expression).

Methods: We studied a material of 110 cases of invasive breast cancer. To determine the stem cells in the tumor population, the presence of ALDH1A1 protein in cancer cells was investigated. In all cases, expression of estrogen, progesterone receptors, as well as expression of HER-2 and Ki-67 protein was studied by immunohistochemistry to determine a subtype of breast cancer. The expression of signaling pathways molecules PI3K, NF-kB, PTEN, WNT, Notch, Hedgehog was also determined by immunohistochemical method.

Results: The results are shown in the table:

Table 42P: Groups with high/low expression of ALDH1A1

	NF-kB	PI3K	PTEN	NOTCH	WNT	HH
Triple negative	100%/ 100%	100%/ 98%	33%/ 20%	11%/ 27%	11%/ 33%	0%/ 14%
HER-2 overexpressed	100%/ 100%	100%/ 100%	9%/11%	36%/ 30%	36%/ 29%	0%/7%

Conclusions: It was found, that cancer cells of all cases of triple negative and HER-2 overexpressed subtypes expressed NF-kB, PI3K signaling pathways molecules. Activation of Notch and WNT signaling pathways was more common for cells of HER-2 overexpressed subtype than Triple-negative subtype ($p<0.05$) in the group with high level of ALDH1A1, while in the group with low level of ALDH1A1, expression of NOTCH and WNT in cancer cells of both subtypes was not significantly different ($p>0.05$). We did not found any activity of Hedgehog (HH) signaling pathway in the group with high level of ALDH1A1, while in the group of low level of ALDH1A1 expression of HH signaling was positive in some cases, and besides, it was higher in cancer cells of Triple negative subtype than HER-2 overexpressed subtype ($p<0.05$).

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43P PDL1 protein expression is a prognostic factor in triple negative breast cancer

J. Yue[1], P. Yuan[1], A. Zhu[2], N. Hu[3], X. Wang[1], W. Wang[4], Z. Wang[5]

[1]Department of VIP Medical Services, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2]Department of Breast Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [3]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [4]Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [5]Department of Pathology, Beijing Hospital, National Center of Gerontology, Beijing, China

Background: Programmed death-liangd-1(PDL1) is a molecule involved in immune evasion in breast cancer. In the phase III clinical trial of impassion 130, the PDL1 expression is a predictive biomarker for the metastatic triple-negative breast cancer therapy. To determine PD1/PDL1 expression in early stage of triple-negative breast cancer, and to analyze the relationship between their expression and prognosis.

Methods: Immunohistochemistry (IHC) was performed on paraffin-embedded tumor samples. Logistic regression was used to analyze the associations between PDL1 protein expression and long-term prognosis. Kaplan-Meier plot and log-rank test were used to compare disease-free survival (DFS) between groups. A cox proportional hazards model was used to calculate the adjusted hazard ratio (HR) with 95% confidential interval (95%CI).

Results: 205 triple-negative patients were enrolled in this study from 1 June 2009 to 31 Oct 2015. Patients had a representative tumor specimen (formalin-fixed, paraffin-embedded archival) for testing of PDL1 expression. We collected the clinicopathological characteristics of the patients. The median follow-up time was 66.9 months. The 5-year DFS rate was 86.1% (95% CI 81.4%-90.8%) and the 5-years OS rate was 93.6% (95% CI 91.0%-97.6%). In the univariate analysis, we found that lymph nodes, Ki67 index and PDL1 expression were associated with DFS and OS; however, in the multivariate analysis, patients with PDL1 expression showed significantly more favorable prognosis in DFS (HR 2.875, 95%CI 1.216-6.796, p=0.016) and improve the OS compared with the PDL1 negative group (HR 3.157, 95%CI 0.844-11.809, p=0.088).

Conclusions: PDL1 protein expression is a predictive biomarker of good prognostic factor for survival in triple-negative breast cancer patients.

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44P Obesity is associated with a late-stage diagnosis in triple-negative breast cancer

A. Aranda-Gutierrez[1], A.S. Ferrigno[1], M. Moncada-Madrazo[1], A. Gomez-Picos[1], C. De la Garza-Ramos[1], F. Mesa-Chavez[1], H. Diaz-Perez[1], S. Cardona[1], R. Ortiz-Lopez[2], C. Villarreal-Garza[1]

[1]Breast Cancer Center, Hospital Zambrano Hellion Tecnológico de Monterrey, San Pedro Garza Garcia, Mexico; [2]Escuela de Medicina y Ciencias de la Salud, Tecnologico de Monterrey, Monterrey, Mexico

Background: Approximately one third of breast cancer (BC) patients are obese, a fact that has been associated with an increased frequency of aggressive clinicopathological features and worse disease outcomes. The aim of this study was to evaluate if obesity plays a selective role in disease stage according to molecular subtype.

Methods: Medical records of women diagnosed with BC between January 2013 and December 2015 in a center located in Monterrey, Mexico were retrospectively reviewed. The patients were grouped by body mass index (BMI; obese: $\geq$30 kg/m^2 and non-obese: $<$30 kg/m^2) and clinical stage (early-stage: 0-II and late-stage: III-IV). Associations between the variables were examined using Fisher's exact test of independence. The significance level was set at $p < 0.05$.

Results: A total of 821 patients were diagnosed with BC, of which 363 were excluded since information about disease stage was missing. Median age was 51 years (range: 29-88), with 14% classified as young. The predominant molecular subtype was luminal-A (55%), followed by triple-negative (23%), and luminal-B and HER2+ (11% each). Most patients presented with early-stage disease (56%). Overall, obesity was not associated with disease stage. However, when stratified by molecular subtype, obesity was associated with diagnosis at a late-stage among women with triple-negative disease (55% vs 35%, p=0.0495). None of the other molecular subtypes demonstrated an association between stage and BMI.

Conclusions: In this cohort, obesity was only associated with a late-stage diagnosis in women with triple-negative disease. Although obesity and related comorbidities have been associated with unfavorable characteristics in triple-negative tumors, the molecular factors involved have not been elucidated. Current evidence indicates that increased availability of steroid hormones, insulin-like growth factors, adipokines and inflammatory cytokines could all play an important role in the aggressiveness of these tumors. Major limitations are present in this study, mainly its retrospective nature, limited number of patients and lack of information regarding clinical outcomes. Future research is needed to confirm these findings and analyze their clinical relevance.

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45P Characterizing the impact of pathogenic BRCA mutations on tissue-specific gene expression and pre-mRNA splicing

P. Bak-Gordon

Cell Biology Unit, IMM-Instituto de Medicina Molecular, Lisbon, Portugal

Background: It is well established that the regulation of pre-mRNA splicing is highly tissue specific. However, whether breast cancer-predisposing splicing defects observed in blood cells also occur in other cell types, namely in stem cells from which tumors are likely to originate, remains to be established. The aim of this study was to characterize BRCA1/2 mRNAs expressed in different primary cell types derived from normal individuals and heterozygous carriers of the pathogenic Portuguese BRCA2 c.156_157insAlu founder mutation that leads to an in-frame skipping of exon 3.

Methods: Upon informed consent, we collected and cultured primary human fibroblasts and isolated peripheral blood mononuclear cells (PBMCs) from whole blood of 6 donors with and without the Portuguese founder mutation. For understanding BRCA1/2 transcriptomic differences between proliferating and terminally differentiated cells, we used a sendai virus-based approach to reprogram human fibroblasts into induced pluripotent stem cells (iPSCs). RNA was extracted and analyzed using a nanoliter-sized droplet technology paired with digital PCR (ddPCR) that allows for high-throughput, absolute nucleic acid quantitation and detection of alternative mRNA processing events.

Results: We found mRNA isoforms generated by alternative splicing of normal BRCA2 transcripts, including skipping of exon 3, in all cell types analyzed. However, the proportion of exon 3 skipping was higher in cells carrying the c.156_157insAlu mutation. Remarkably, we detected significantly higher levels of BRCA2 transcripts in iPSCs compared to PBMCs and fibroblasts, in both normal and mutant cells.

Conclusions: Our results indicate that the Portuguese BRCA2 founder mutation induces quantitative rather than qualitative differences in mRNA splicing. Moreover, we observed upregulation of BRCA1/2 gene expression upon reprogramming of fibroblasts to iPSCS. This result is consistent with previous findings suggesting that BRCA genes are more expressed in stem cells compared to differentiated cells.

Legal entity responsible for the study: Carmo-Fonseca Lab at Instituto de Medicina Molecular João Lobo Antunes.

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46P Tumour infiltrating lymphocytes in breast cancer: High levels of CD3, CD8 cells and Immunoscore® are associated with pathological CR in patients receiving neo-adjuvant chemotherapy

B.L. Rapoport[1], J. Galon[2], S. Nayler[3], B. Mlecnik[4], A. Fugon[4], C.A. Benn[5], M. Martel[4], T. Cronje[6], T. Smit[7], F. Moosa[7], L. Jooste[7], R. Anderson[1]

[1]Department of Immunology, University or Pretoria Faculty of Health Sciences, Pretoria, South Africa; [2]Cordeliers Research Center, INSERM Team 15, Laboratory of Integrative Cancer Immunology, Paris, France; [3]Laboratory, Drs Gritzman & Thatcher Inc Laboratories & Wits Donald Gordon Medical Centre, Randburg, South Africa; [4]Luminy Biotech Enterprises 163 Ave de Luminy, HalioDx, Marseille, France; [5]Surgery, Head of Netcare Breast Care Centre, Johannesburg, South Africa; [6]Department of Statistics Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa; [7]Pharmacy Department, The Medical Oncology Centre of Rosebank, Johannesburg, South Africa

Background: The presence of high levels of tumor infiltrating lymphocytes (TILs) has been associated with better prognosis in early triple-negative breast cancer (TNBC). The Immunoscore® (IS) is a prognostic tool, which categorizes the densities of spatially positioned CD3 and CD8 cells in both invasive margins (IM) and the center of the tumor (CT), yielding a five-tiered classification (0–4). High IS values have been reported to predict improved outcomes in colorectal cancer patients (pts).

Methods: We performed the IS in 103 breast cancer (BC) pts who previously received neo-adjuvant anthracycline and taxane +/- trastuzumab based chemotherapy TNBC=53, Luminal=32, HER2+=18. Pre-treatment tumor samples were immune-stained for CD3 and CD8 T-cell markers. Quantitative analysis of the immune cells was carried out using a computer-assisted image analysis in different tumor locations.

Results: The pathological complete response (pCR) rate of the entire cohort was 44%. On univariate analysis, factors associated with higher pCR included primary tumor size ($p<0.005$), nodal status ($p<0.069$), ER ($p<0.000$), PR ($p<0.000$), molecular subtype (TNBC=62%, HER2+=50% and Luminal A+B=9%, $p<0.000$), Ki67 (>40=56% vs 15-39=40% vs <15=0%, $p<0.000$) and Stage ($p<0.028$). A high density of CD3 (> than 800mm^2) and CD8 (> than 400mm^2) positive T-cells in the CT was associated with higher pCR (CD3 CT: 60% vs 25%, p=0.000 and CD8 CT: 64% vs 27%, p=0.000). Analysis of CD3 (> than 1400mm$^{2)}$ (CD3 IM: 63% vs 19%, p=0.00) and CD8 in the IM (> than 500mm^2) was also significant for an association with pCR (CD8 IM:63% vs 15%, p=0.000). High IS (3+4= 63%) vs intermediate (2=35%) vs low (0+1=24%) was significantly associated with

pCR (p=0.006). In a logistic regression model Ki-67 (p<0.005) and IS (p<0.021) and molecular subtype (p<0.010) retained significance. DFS: At 3 years 94% of IS high pts did not relapse compared to 80% IS intermediate or low pts (p<0.07).

Conclusions: This study shows a significant prognostic and potentially predictive role for the IS in BC pts, particularly in TNBC. This study shows a significant prognostic and potentially predictive role for the IS in BC pts, particularly in TNBC.

Legal entity responsible for the study: The Rosebank Clinical and Translational Research Unit.

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47P Androgen receptor expression and survival in triple negative breast cancer

L. Moyano[1], J.L. Soto[1], M.L. Garmendia[2]

[1]Pathology, Instituto Nacional del Cancer, Santiago, Chile; [2]Epidemiology, Institute of Nutrition and Food Technology, Universidad de Chile, Santiago, Chile

Background: Triple negative breast cancer (TNBC) is characterized by aggressive behaviour, with high morbimortality. Androgen Receptors (AR) have a role in the activation of cellular proliferation, migration and invasiveness. The AR are expressed in 7-75% of TNBC. This study evaluates the relationship between positive AR with clinical data, relapse and overall survival.

Methods: All TNBC cases from the Pathology Service of Instituto Nacional del Cáncer were studied between 2015 to 2019 (n=69). Eligible patients (n=32) had at least 18 months of follow-up, ending at the 31/01/2020 or death. From clinical files and biopsy reports, age, TNM, treatment, relapse and Ki67 were extracted. Date and cause of death were obtained from death certificates. AR status was determined by immunohistochemistry and defined as AR-positive (>1%) or AR-negative (0%). The Kaplan-Meier method was used to estimate survival rates. Crude and adjusted Hazards Ratios (HR) were estimated by proportional Cox regression model.

Results: At diagnosis the average age was 54.6 years (DE:14.7), tumor size 3.9 cm (DE:2.2), 59.4% had positive lymph nodes, positive skin 18.8% and 87.5% without metastasis. Stage I - II 53.1%, Stage III - IV 46.9%. 37.5% received lumpectomy, 50% mastectomy. Neoadjuvant chemotherapy 44%, 59.4% adjuvant or palliative, and 50% radiotherapy. Average follow-up was 38.9 months (DE:15.7). 50% relapsed in an average of 14.9 months (DE:10.9) and 28% died (months to death 32.1 (DE:7.9)). 56.3% had AR+. There was no difference between AR+ and AR- regarding size nor Ki67 expression. There was an increased rate of death with AR+ (33.3% vs 21.4%) and metastasis (16.7% vs 7.1%), but that was not significant. In adjusted Cox regression models, AR+ showed higher risk of relapse (HR:3.54 IC95%:0.65,19.3, p=0.144) and mortality (HR:3.85 IC95%:0.82,18.1, p=0.088).

Conclusions: This study confirmed a high mortality in TNBC. Expression of AR-positive appears to be correlated with increased recurrence and mortality. AR-positive could be a prognostic and predictive marker. TNBC AR-positive patients could potentially apply to anti-androgen targeted therapy. More prospective studies with larger samples size and longer follow-up are required.

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48P Association of a genomic index of sensitivity to endocrine therapy with disease-free survival in breast cancer

P. Singh[1], I. Bedrosian[1], M.J. Ha[2], Y. Shen[2], L. Du[3], R. Gould[3], F. Symmans[4]

[1]Breast Surgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [3]Translational Molecular Pathology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [4]Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Background: The sensitivity to endocrine therapy (SET2,3) index measures transcriptional activity of genes related to the estrogen and progesterone receptors (ER, PR) adjusted for baseline prognostic index (cT, cN, RNA4). Higher SET2,3 predicts greater intrinsic tumoral sensitivity to endocrine therapy (ET). SET2,3 was prognostic in patients receiving chemotherapy (CT) and ET. In this study, we measured SET2,3 performed using a new clinical assay platform, QGP, in a prospective registry study to compare SET2,3 with disease-free survival (DFS).

Methods: This was a single institution, prospective registry study of women ≥ 18 years newly diagnosed from 2011-2016 with Stage I-III hormone-receptor positive (HR+), Her2-negative invasive breast cancer treated with adjuvant ET with or without neoadjuvant or adjuvant CT. SET2,3 is continuous and has a pre-defined cutpoint that defined high vs low score in the setting of chemo-endocrine treatment. Kaplan-Meier method was used to estimate the DFS distributions. Log-rank test and multivariable Cox proportional hazards models were performed to associate DFS with SET2,3 and other clinical factors.

Results: The population included 278 subjects with median age 56 (25-84) and follow-up 70 months (65-72). Most had clinical stage T2 (57.6%), N0 (65.8%). SET2,3 was performed on the clinical QGP platform in 256 samples with 59.4% high and 40.6% low score. 5-year DFS in the overall cohort was 90.8% (95% CI 87.3-94.5). In the high SET2,3 group, 5-year DFS was 95.3% (95% CI 92.0-99.1) and in the low SET2,3 group, 85.7% (95% CI 79.0-92.9). SET2,3 was significantly asscociated with DFS in the overall cohort (p=0.0005) and in patients receiving both CT and ET (p=0.013). There was a trend toward significant association of SET2,3 and DFS (p=0.079) in a subset of 96 patients who received ET only. A multivariable model including receipt of CT, neoadjuvant treatment, and SET2,3 demonstrated SET2,3 to be the only independent predictor of DFS (HR 0.51, 95% CI 0.27-0.96, p=0.037).

Conclusions: SET2,3 was independently predictive of DFS in this registry study of HR+/Her2-negative breast cancers using a clinical-grade QGP assay. Future studies incorporating SET2,3 as a prognostic factor in clinical decision-making are indicated.

Legal entity responsible for the study: Fraser Symmans, MD.

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Disclosure: F. Symmans: Licensing/Royalties, Co-inventor on a patent application regarding the SET index: United States Patent and Trademark Office; Advisory/Consultancy, Unpaid scientific advisor: Delphi Diagnostics; Shareholder/Stockholder/Stock options, Co-founder shares of Delphi Diagnostics (that licensed the IP from MDACC): Delphi Diagnostics. All other authors have declared no conflicts of interest.

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49P BRCA mutation testing rates among breast cancer patients meeting testing criteria: A single-centre experience

M. Boianu, N. Daaboul, G. Speranza, C. Prady, S. Soldera, S. Martel

Medical Oncology and Hematology, Hopital Charles - Le Moyne, Greenfield Park, QC, Canada

Background: Genetic counselling and testing are recommended for selected patients with breast cancer (BC). We aimed to asses genetic counselling referral rates in an academic center of patients with BC that fulfilled clinical criteria and/or family history for BRCA status testing.

Methods: In this retrospective study, all patients diagnosed with breast cancer at the Integrated Cancer Care Centre of Charles-Le Moyne Hospital between January 1st and December 31st 2017 were included. The clinical characteristics and family history from the patient's charts were reviewed in order to determine if genetic counselling was indicated according to the NCCN Version 2.2015 of "Clinical practice guidelines in oncology. Genetic/Familial High-Risk Assessment: breast and ovarian" and to assess if the patients were subsequently referred. The main objective was to determine the proportion of patients with BRCA status testing criteria referred for genetic counselling in an academic center.

Results: 266 patients diagnosed with BC were included. 81 (30.4%) patients met one or more criteria for BRCA status testing. Among those, 48 (59.2%) were referred for genetic counselling and 33 (40.8%) were not. Among the patients not referred, 11 (33.3%) met clinical criteria and 22 (66.6%) met family history criteria. The family history criteria most often overlooked was of two or more BC diagnoses in close family (15 patients), followed by BC diagnosis of a relative under the age of 50 (4 patients). The clinical criteria of BC diagnosis equal or under the age of 45 was most often missed (6 patients), followed by triple negative BC at age equal or under 60 years in 2 patients. There were also 25 patients which had genetic testing but who did not appear to meet referral criteria (34% of patient of all patients referred).

Conclusions: A lower than expected genetic counselling referral rate of patients meeting criteria for BRCA status testing was observed. A significant number of patients were also referred without meeting testing criteria. These findings support the need to raise awareness and better inform clinicians treating breast cancer patients in order to improve the rates of genetic counselling and testing.

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50P Cardiosafe nano-formulation of doxorubicin allows coadministration with trastuzumab in neoadjuvant setting improving antitumor efficacy and preventing trastuzumab-mediated cardiotoxicity in HER2 + murine model of breast cancer

S. Mazzucchelli[1], F. Andreata[1], A. Bonizzi[1], M. Sevieri[1], M. Truffi[1], L. Sitia[1], R. Ottria[1], F. Silva[1], P.F. Zerbi[1], D. Prosperi[2], F. Corsi[1]

[1]Department of Biomedical and Clinical Sciences "L. Sacco", Università degli Studi di Milano, Milan, Italy; [2]Department of Biotechnology and Biosciences, Università degli studi di Milano- Bicocca, Milan, Italy

Background: The mainstay of neoadjuvant chemotherapy for HER2-positive breast cancer (BC) is the combination of highly cytotoxic drugs such as doxorubicin (DOX) and the anti-HER2 therapy with Trastuzumab (TZ), which allows a pathological complete response in up to 50% of patients. Unfortunally, their co-administration is strongly limited by intrinsic cardiotoxicity, therefore only a sequential administration of DOX and TZ is allowed in clinical practice. However, the concurrent use of DOX and TZ has been demonstrated to be more useful both for responder and non-responder patients representing an unmet clinical need in BC oncology. Nanomedicine could fix this issue developing smart drug delivery systems specifically targeted toward BC cells, which display limited off-target toxicity. Here, we propose nanoformulation of DOX in H-Ferritin-nanocages (HFn-DOX), exploiting its capability to increase doxorubicin (DOX) anticancer efficacy while reducing its cardiotoxicity.

Methods: A murine model of HER2+ BC has been treated twice a week for 2 weeks and half with placebo, TZ alone (5 mg/Kg), DOX or HFn-DOX (1 mg/Kg), DOX+TZ and HFn-DOX+TZ. Tumors have been evaluated for size, apoptosis grade, Granzyme release, angiogenesis, Tumor Infiltrating Leucocytes enumeration, amount of Cancer-Associated Fibroblasts, DOX and DOXol content, TZ accumulation and penetration using different approaches such as immunohistochemistry, western blot, flow cytometry, immunofluorescence and mass spectrometry. Cardiotoxicity has been evaluated by morphological analysis of cardiac tissue by transmission electron microscopy. TZ accumulation has been assessed also in heart lysates by western blot.

Results: The coadministration of HFn-DOX with TZ displays increased antitumor potential combined with a cardio protective effect against TZ-induced mitochondrial cardiotoxicity, which is attributable to its capability to reduce TZ accumulation in heart improving in the meantime its penetration in tumour.

Conclusions: HFn-DOX could be a valuable strategy to allow safe co-administration of DOX and TZ exploitable for clinical application.

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51P Evolution of low HER2 expressions between primary and metastatic breast cancer

P. Tarantino[1], E. Nicolò[1], P. Zagami[1], F. Giugliano[1], P. Trillo A[1], A. Marra[1], D. Trapani[1], S. Morganti[1], L. Mazzarella[2], C. Criscitiello[2], A. Esposito[2], G. Curigliano[1]

[1]Early Drug Development for Innovative Therapies Division, University of Milan, Istituto Europeo di Oncologia, Milan, Italy; [2]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy

Background: About half of luminal and triple negative breast cancers (TNBC) show low HER2 expressions. These HER2-low breast cancers (BC), with a HER2 IHC score of 1+ or 2+ with negative ISH, are emerging as a new druggable entity, related to the development of novel anti-HER2 antibody-drug conjugates. Little data is available on the evolution of low HER2 expressions between early and metastatic BC (mBC).

Methods: We retrospectively reviewed clinical-pathological data of mBC patients consecutively referred to our New Drugs Division (from Jan2014 to Dec2019), for whom both primary tumor and a metastatic biopsy (performed at any time) were characterized. We divided HER2-negative cases by ASCO/CAP 2018 guidelines into an IHC 0 subgroup and a HER2-low subgroup (1+ and 2+/ISH-negative). χ2-test was used for comparisons between categorical parameters.

Results: 267 patients were included in the analysis (64% HR+/HER2-neg, 19% HER2+, 17% TNBC at diagnosis). Among primary tumors, 42% showed low HER2 expression, with a higher rate in the luminal-like BC population compared to TNBC (60% vs 39%, p=0.04). There was a significant enrichment for HER2-low cases in mBC compared with primary lesions (50% vs 42%, p=0.02). Late-relapsers (DFS $\geq$ median) showed a higher relative increase compared to early relapsers (DFS $<$ median) (+35% vs +0%), with a similar trend in both luminal-like and TNBC. Overall, the increase in HER2 expression between primary and mBC was mainly driven by IHC 0 cases shifting to HER2 low, with a decrease from 39% IHC 0 cases on primary to 32% on metastatic (p=0.12). More details on HER2 expression evolution are provided in the table.

Table 51P: Evolution of HER2 IHC expression on primary vs mBC

	Primary	Equal score on biopsy	Increased score on biopsy	Decreased score on biopsy
HER2 IHC 0	104/267 (39%)	53%	47%	NA
HER2-low (IHC 1+, 2+/ISH-)	113/267 (42%)	40%	20%	40%
HER2-positive	50/267 (19%)	48%	12%	40%

Conclusions: Low HER2 expressions are more common among luminal-like cancers than TNBC, and appear enriched in mBC compared with primary tumours, enlarging the cohort of advanced patients eligible for trials of novel anti-HER2 compounds. Validation on larger populations is warranted.

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52P Characterising clinicopathological and biological parameters predictive of outcome for patients diagnosed with invasive lobular carcinoma

P. Simpson[1], A. McCart Reed[1], J. Kutasovic[1], C. Coorey[1], L. Kuo[1], H. Nguyen[1], W. Pei[1], J. Ong[1], A. Sokolova[1], E. Evans[2], A. Porter[2], S. Lakhani[1]

[1]UQ Centre for Clinical Research, University of Queensland, Brisbane, Australia; [2]Wesley Breast Clinic, The Wesley Hospital, Brisbane, Australia

Background: Invasive lobular carcinoma (ILC) is the second most commonly diagnosed histological subtype of breast cancer, comprising up to 15% of all cases. Considerable data suggest there are fundamental clinical and biological differences between ILC and the more commonly diagnosed invasive carcinoma no special type. We sought to characterise clinical, pathological and biological parameters that could predict prognosis in ILC that would aid in the understanding of tumour subtype and in the management of patients diagnosed with this subtype of disease.

Methods: Patient cohorts were assembled from the Royal Brisbane and Women's Hospital and Wesley Hospital, Brisbane, Australia. Clinical and pathology data were obtained from medical records and re-review of radiology (mammography and ultrasound) and pathology features. Clinical follow up data were collected from the Queensland Cancer Registry. Tissue microarrays were constructed from resected specimens in the form of formalin-fixed, paraffin-embedded tumour tissue. Immunohistochemistry (IHC) was performed for a series of putative novel biomarkers predictive of prognosis that were identified during the development of LobSig, a novel gene signature with prognostic potential in ILC.

Results: Features of known prognostic nature in ILC were evident in this cohort (i.e. tumour size, grade and lymph node status). By mammography, most ILC were classified as localised, spiculated lesions (124/260, 48%), while 30% showed no detectable abnormality. ILC were classified by ultrasound as localised (80%) or diffuse (20%) lesions. ILC not detected by mammography were more likely to be patients $<$50 years and/or with dense parenchyma in the surrounding breast tissue. In both mammography and ultrasound, localised lesions had a significantly better breast cancer specific survival (BCSS) relative to diffuse lesions (p$<$0.05). Preliminary IHC data indicate the expression of ARGLU, FBXL3 and RNF135 might be associated with BCSS in ILC (p$<$0.05, Log rank (Mantel-Cox) test).

Conclusions: We illustrate some novel clinicopathological and biological features that contribute to the understanding of ILC as a tumour entity and may aid in the management of patients in the future.

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53P Role of immune biomarkers in evaluating predictive and prognostic value in advanced stage HER2 positive breast cancer

S. Pasricha[1], D. Bansal[1], A. Jajodia[2], K.D. Choudhary[3], G. Gupta[1], A. Sharma[1], A. Sharma[4], G. Durga[1], M. Kamboj[1], A. Kumar[1], S.J. Bothra[5], M.K. Chllamma[6], V.P.B. Koyyala[5], A. Russo[7], D.C. Doval[4], A. Mehta[1]

[1]Pathology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [2]Radiology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [3]Medical Oncology Department, International Oncology Services Pvt Ltd (IOSPL), New Delhi, India; [4]Research, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [5]Medical Oncology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [6]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [7]Medical Oncology, University of Palermo, Palermo, Italy

Background: Few studies have evaluated the prognostic role of immune biomarkers in HER2 positive Breast cancer (HPBC) patients irrespective of clinical stage. There is paucity of studies evaluating their predictive and prognostic value in advanced stage HPBC subjected to upfront systemic therapy.

Methods: A total 57 advanced stage HPBC patients, who received upfront NACT and antiHER2 therapy were evaluated for immune cell (CD8+ T-cells and FOXP3+ Treg) infiltration (per mm2) in tumor microenvironment (TME) and peritumoral stroma (PTS). The PDL1 expression score (SP263) was evaluated in tumor cells (TPS), immune cells (ICS) and as combined positive score (CPS). PD-L1: TPS, ICS and CPS of $>$ 1% were considered positive. These parameters were correlated with response to systemic therapy and prognosis: responders(R)/non-responders(NR).

Results: Out of 57 patients, 25 were concomitantly hormone positive. Patients were classified as NR (n=24) and R (n=33). There was no significant association of PDL-1 positivity with treatment response (TPS: p=0.489; ICS: p=0.910 and CPS: p=0.977). Increased CD8+ T cell infiltration significantly correlated with treatment response (p=0.013) in TME as well as in PTS (p=0.013). FOXP3+ Treg infiltration did not significantly correlate with treatment response in both TME (p=0.569) and PTS (p=0.412). Ratio of CD8+Tcells/FOXP3+ Treg infiltration significantly correlated with treatment response in both TME (p=0.05) and PTS (p=0.045). In the R category, within the TME, increased CD8+Tcells were statistically associated with positive PDL-1 (TPS:p=0.017; CPS:p=0.015) and similar findings in PTS (TPS:p=0.017; CPS:p=0.015).

Conclusions: We found statistical significant association of treatment response with CD8+Tcells infiltration and ratio of CD8+ Tcells/FOXP3+ Treg infiltration in both TME and PTS in advanced stage Her-2 Positive Breast cancers.

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54P Establishment and characterization of luminal A breast PDX models from patients with acquired resistance to CDK 4/6 inhibitors

M.J. Wick, J. Flores, A. Moriarty, M. Beeram, K. Papadopoulos

Nonclinical, South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA

Background: CDK 4/6 inhibitors have been recently approved in combination with letrozole in hormone receptor-positive breast cancer. Although this combination therapy has been found effective in some patients, resistance often develops. To aid in developing new therapies for palbociclib-resistant breast cancer and better understand resistance mechanisms, we established two PDX models from patients with luminal A breast cancer at time of progression, following acquired resistance to palbociclib therapy. Two models, designated ST3932 and ST4378, were developed in athymic nude mice and characterized for receptor expression, genomic alterations, and in vivo drug sensitivity.

Methods: ST3932 was established from a biopsy taken from a 62-year-old woman pretreated with various therapies including tamoxifen, fulvestrant/palbociclib, and paclitaxel. ST4378 was established from fluid taken from a 66-year-old woman pretreated with various therapies including letrozole/radiation, docetaxel/cyclophosphamide, and letrozole/palbociclib. The resulting models were passaged and challenged with palbociclib and other CDK4/6i to confirm resistance. Receptor expression was determined immunohistochemically. Genomic analysis, including WES and RNAseq, were performed to characterize models and identify mechanisms of resistance. For in vivo studies, endpoints included tumor volume and time from treatment initiation with %T/C values and tumor regression reported at study completion.

Results: The ST3932 and ST4378 models retained ER expression over tested passages with similar histology compared with an archival clinical sample. Sequencing identified several conserved variants; however, none have been currently identified as known mechanisms for palbociclib resistance. Both models demonstrated resistance to palbociclib with %T/C values $>$90%; however, ST3932 reported moderate sensitivity to both ribociclib and abemaciclib (%T/C$\sim$50%).

Conclusions: We have established and characterized two palbociclib-resistant breast PDX models, designated ST3932 and ST4378, which can be utilized as a valuable tool in better understanding CDK4/6i resistance and in developing novel therapies for CDK4/6i-resistant patients.

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55P Role of radiomics for predicting immunophenotypes in male breast cancer

V.P.B. Koyyala[1], A. Jajodia[2], S. Pasricha[3], A. Gupta[4], A. Chaturvedi[2], A. Rao[2], R. Tripathi[5], M. Kamboj[3], M.E. Mayerhoefer[6], D. Leithner[7], H. Prosch[6], M.K. Chllamma[8], M. La Mantia[9], A. Russo[10], D.C. Doval[1], A. Mehta[3]

[1]Medical Oncology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [2]Radiology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [3]Pathology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [4]Centre for Computational Biology, Indraprastha Institute of Information Technology, New Delhi, India; [5]Research Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [6]Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria; [7]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [9]Medical Oncology, University of Palermo, Palermo, Italy; [10]Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy

Background: Male breast cancers (MBCs) are rare and account for 1% of all breast cancers. Radiomics is evolving as tool for precision medicine in various cancers, in particular breast cancer. This paper aims to establish the benefit of using radiomics data derived from PET images in the categorization of breast cancer immunophenotype in male population.

Methods: One radiologist having 6 years experience manually drew the region of interest on the tumor for purposes of segmentation and textural analysis. The segmented tumor was validated independently by two radiologists having 30 years of experience each. 851 radiomics features were extracted from the available imaging (PET-CT; Total n = 18) using slicer 3D software and Pyradiomics. Feature selection was done by taking union of the features which had Pearson correlation $>$ 0.5 with p53 and Ki-67. Models were trained to predict the biomarkers using leave one out cross validation and different algorithms for different biomarkers.

Results: All cases were hormonal receptor positive, Estrogen receptor (ER) expression range was 80-100%, and progesterone receptor (PR) expression range was 0-100%. p53 was overexpresssed in 16% cases (n=3), while low heterogenous expression was seen in 84% (n=15). Ki-67 was high ($>$14%) in 33.3% (n=6), and low in 66.6% (n=12). The various other markers namely cyclin D1 , GCDFP15 , Bcl2 , and AR were not utilized for radiomic model building in view of skewness of expression in above cases. Using nearest shrunken centroids model for evaluation of p53 in the subset population we were able to achieve an accuracy of 75%. The Kappa score was 0.30 and area under the curve was 0.75. Using same model in the subset population of Ki-67 we were able to achieve an accuracy of 81%. The Kappa score was 0.58 and area under the curve was 0.80.

Conclusions: Radiomic features could be useful in deciphering male breast cancer immunophenotypes and serve as potential imaging biomarkers. This modality can potentially address tumoral heterogenity that may be missed on a single biopsy from the most feasible site. Also, imaging biomarkers can be used as a real time estrimate of the dynamics of biomarker expression in an individual patient.

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57P Benefit of CDK4/6 inhibitors beyond PIK3CA mutations in metastatic breast cancer patients

P. Tolosa Ortega[1], J.M. Cejalvo[2], S. Moragon Terencio[2], L. Carril-Ajuria[1], B. Bermejo[2], Á. Ruiz[1], C. Hernando Melia[3], A. Sánchez-Torre[1], M.T. Martínez[2], M. Herrera[1], V. Gambardella[2], L. Lema[1], D. Roda[2], E. Bernal[1], P. Rentero-Garrido[2], A. Lluch[2], E.M. Ciruelos[1], A. Cervantes[2], L. Manso[4]

[1]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [3]Hospital Clinico Universitario de Valencia, Valencia, Spain; [4]Breast and Gynecologic Cancer Unit, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: CDK4/6 inhibitors (CDK4/6i) in combination with hormone therapy is the standard treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer (mBC). Resistance mechanisms are unknown and constitute an unmet medical need. In PALOMA-3 trial the PIK3CA mutations (PIK3CA mut) were not associated with resistance to palbociclib (p=0.34). The aim is to assess the role of PIK3CA mut in routine clinical practice as a mechanism of resistance to CDK4/6i in patients with luminal mBC.

Methods: We conducted a retrospective and bi-centric study, between Hospital Clínico Universitario de Valencia and Hospital Universitario '12 de Octubre, to evaluate the impact of PIK3CA mut on CDK4/6i treatment in patients with HR+/HER2- mBC. The relationship between PIK3CA mutational status and progression-free survival (PFS) was analyzed by Cox's proportional hazards model and the log rank test. With the aim of homogenizing the sample, patients treated in the first line were also analyzed separately.

Results: All patients (n=92) were diagnosed with a luminal mBC. Forty patients (43.5%) presented PIK3CA mut and 52 (56.5%) were wild type (WT). The median PFS was 12.0 months (95% CI 9.3-14.6). No significant difference in PFS was found based on PIK3CA mutational status (10.9 months in PIK3CA mut, 95% CI 7.9-14.0; vs 12.7 months in PIK3CA WT, 95% CI 8.6-16.8) HR 1.05 p=0.84 (logrank test). The incidence of PIK3CA mutations were higher among patients treated at first line for $\leq$ 6 months (46.67%), however only 26.92% of long-term responders presented PIK3CA mutations. This effect was not identified at second line.

Table 57P: Patient baseline characteristics

n(%)	PIK3CA mut (40)	PIK3CA WT (52)
Median age (years)	51.9	48.92
Menopausal status		
Premenopausal	24 (60.0 %)	27 (51.9 %)
Postmenopausal	16 (40.0 %)	25 (48.0 %)
Visceral met		
No	24 (60.0%)	29 (55.8%)
Yes	16 (40.0 %)	23 (44.2 %)
CDK4/6i		
Palbociclib	29 (72.5 %)	38 (73.0 %)
Ribociclib	9 (22.5 %)	12 (23.1 %)
Abemaciclib	2 (5.0 %)	2 (3.8 %)
Line of therapy		
1st Line	14 (35.0 %)	27 (51.9%)
2nd or more lines	26 (65.0 %)	25 (48.1%)

Conclusions: The presence of PIK3CA mutations was not associated with resistance to CDK4/6 inhibitors in terms of PFS. Nevertheless, the frequency of PIK3CA mutations was lower in patients with extended benefit (more than 6 months) at first line of treatment. Future studies to explore the impact of triplet combination therapy (PIK3CA and CDK4/6i plus endocrine treatment) are needed.

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58P Detection of PIK3CA mutations in plasma ctDNA by Crystal Digital PCR for the selection of alpelisib treatment in routine clinical practice in advanced breast cancer patients

T. de La Motte Rouge[1], F. Le Du[1], J. Corne[2], F. Godey[2], H. Bourien[1], A. Brunot[1], L. Crouzet[1], C. Perrin[1], C. Lefeuvre-Plesse[1], V.C. Dieras[1], V. Quillien[2]

[1]Medical Oncology, Centre Eugene - Marquis, Rennes, France; [2]Biology, Centre Eugène Marquis, Rennes, France

Background: Alpelisib (a PI3Kα-specific inhibitor) has demonstrated clinical benefit in combination with fulvestrant and is approved for PIK3CA-mutated, ER +,HER- metastatic breast cancer (MBC) patients who relapsed after aromatase inhibitor (Andre F et al, NEJM, 2019). The PI3CA status may be determined either in tumour biopsy and/or cell-free DNA (cfDNA) (Andre F et al, NEJM, 2019). In our center we use a multiplex digital droplet PCR assay (ddPCR) for the detection of circulating PIK3CA mutations.

Methods: MBC ER+/HER2− patients were tested at the time of disease progression. cfDNA was extracted from 5 mL of plasma with a QIAamp circulating nucleic acid kit and quantified using a fluorometer-based quantification. Our ddPCR assay allows the detection and quantification of 26 mutations located in exons 4, 7, 9 and 20, with a high sensitivity and specificity, using a three-colour detection system (Stilla Technologies).

Results: Thus far, 116 patients have been tested. They had previously received a median of two lines of treatment (min-max: 0-14) in the metastatic setting. Plasma cfDNA concentrations ranged from 4 to 897 ng/ml (median: 16 ng/ml). Forty-seven patients (40%) harboured at least one mutation; among them, 8 (6.9%) patients had 2 PIK3CA mutations and 2 (1.7%) patients had 3 PIK3CA mutations. H1047R, E545K, H1047L, E542K, Q546K, C420R and N345K mutations were identified in, respectively, 19 (16.4%), 16 (13.8%), 9 (7.8%), 6 (5.2%), 4 (3.4%), 3 (2.6%) and 2 (1.7%) patients. The median number of mutant copies per ml of plasma was 128 (min—max: 1—41953) and the median allele frequency was 2% (min—max: 0.01%—59.12%). PIK3CA-mutated patients had significantly higher levels of cfDNA (mean = 80.4ng/ml for mutated patients, mean = 28.8ng/ml for non-mutated patients, p<0.0001). The mutation detection rate was higher for patients with visceral metastases (47.3%) compared from those with non-visceral metastases (27.5%).

Conclusions: The ddPCR assay is a very sensitive, rapid, and cost-effective technique for the selection of alpelisib treatment in routine clinical practice. We plan to compare these results to those obtained from matched tumour biopsies.

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59P Primary tumour and circulating tumour cell (CTC) copy number alterations (CNAs) in triple negative breast cancer (TNBC) patients (pts) treated with neoadjuvant chemotherapy (NAC)

S. Di Cosimo[1], M. Silvestri[1], M. Dugo[1], M. Vismara[1], C. Reduzzi[1], G. Pruneri[2], S. Folli[3], V. Cappelletti[1], M.G. Daidone[4]

[1]Applied Research and Technological Development, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy; [2]Dipartimento di Patologia Diagnostica e Laboratorio, Fondazione IRCCS Istituto Nazionale Tumori (INT) Milan, Milan, Italy; [3]Breast Cancer Unit, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy; [4]Applied Research and Technical Development, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

Background: Approximately 60% of pts with early-stage TNBC who undergo NAC without attaining pathologic complete response (pCR) will eventually relapse. Here we assessed the relationship between primary tumor (t-CNAs) and CTC-CNAs and clinical outcome in TNBC pts at the time of initial diagnosis and following NAC.

Methods: CNA analysis was performed by the targeted NGS IonAmpliSeq Comprehensive Cancer Panel on pre-NAC tumor specimens, and low-pass whole genome sequencing on CTCs enriched by the marker-independent Parsortix approach and selected through the DEPArray system. t- and CTC-CNAs were tested for association, and compared to the publically available TCGA-BRCA dataset.

Results: Starting from a case study of 19 pts, we successfully analyzed up to 58 CNA events per pt (median 47, range 31-58) in 16 pre-NAC tumor specimens from 4 and 12 women with stage I-III TNBC achieving or not pCR. Global genomic gain of chromosomes 8, 6 and 17 occurred in 7%, 6%, and 5% of cases; loss of chromosomes 1, 2 and 9 in 12%, 8% and 2% of cases. Overall DAXX (69%), MYC (62%) and SOX11 (56%) were the most commonly altered genes. MSH2 and PRDM1 amplifications were found exclusively in pts attaining pCR (4/4 vs 0/12). Loss of PAX3 occurred in tumor samples of all patients with pCR and in 1 case with residual disease at surgery (4/4 vs 1/12). MSH2 and PRDM1 gains and PAX3 loss were found in 28%, 28% and 23% respectively of the TCGA-BRCA dataset, largely comprising of naïve pts. None of these CNAs significantly correlated with overall survival (Hazard Ratio [HR] 1.2, 95%CI 0.47-3.2; HR 1.7, 95%CI 0.65-4.2, and HR 2.1, 95%CI 0.6-6.4, for MSH2, PRDM1 and PAX3, respectively), suggesting their potential to reflect NAC response. A total of 18 CTCs

were retrieved from 4 patients at the time of first relapse (min-max CTC number per patient 2—8). A common feature of all these CTCs was the absence of PAX3 deletion.

Conclusions: In TNBC t- and CTC-CNAs may represent genomic markers of poor response to NAC that are possibly maintained during metastatic dissemination. Further investigations are required to assess their potential to identify pts at high risk of recurrence for whom alternative therapies and more frequent monitoring are advised.

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60P Prognosis and survival of single hormone receptor positive breast cancer comparing to double HR positive and triple-negative breast cancers

K. Oualla, L. Nouiakh, O. Zouiten, L. Amaadour, Z. Benbrahim, S. Arifi, N. Mellas

Medical Oncology, CHU - University Hospital of Hassan II, Fez, Morocco

Background: Positive estrogen and progesterone receptors (ER, PR) breast cancers (BC) require endocrine therapy and were associated to favorable outcomes. Hormone receptors (HR) status is considered a crucial predictive factor. The ER−PR+ group is reported to be only 1—5% of all BCs and remains poorly understood and was associated to poor outcomes The aim of this study was to compare the clinical outcomes of patients with single HR positive BC to those with ER+PR+ tumors and TNBC.

Methods: It is a retrospective study including 700 women with invasive Her2 negative breast carcinoma were included. Patients were stratified according to ER and PR expression as double HR+ (ER + PR+), single HR+ (ER + PR- and ER-PR+) and triple negative HR-negative (HR-, ER-PR-) We reviewed the clinicopathologic characteristics of patients, including biologic factors, such as ER, PR, and Ki-67 Survival was analysed using the Kaplan-Meier method. Hazard ratios were estimated using a Cox regression for OS in a multivariate analysis.

Results: 700 patients with negative Her2 disease were included, 421 (60.1%) were ER + and PR +, 111 (15.8%) cases were single HR+ tumors, of which 48 (43.2%) ER-PR+ and 63 (56.7%) were ER + PR- Single HR+ tumors were grade III in 45%, KI67 were > 20% in 70%, T3 in 23% and T4 in 35% and metastatic in 25% of cases. The multivariate analysis revealed that patients with ER + PR- tumors were associated with shorter survival compared with ER + PR+ tumors, with a hazard ratio of 3.69 for overall survival (OS). Patients with ER-PR+ tumors had higher risk of death compared with ER + PR+ tumor, with a hazard ratio of 6.23 for OS. While OS of ER- PR+ patient was statistically non different from the one of triple negative breast cancer.

Conclusions: Single HR+ tumors without HER2 overexpression (ER + PR-or ER-PR +) were associated with more aggressive clinic-pathological features and poorer survival than ER + PR + tumors, and had comparable poor survival to triple-negative breast cancer.

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62P XRCC1 (Arg194Trp), Palb2 T1100T (3300T>G), HMMR (V353A), TNF (aG308A) polymorphisms as diagnostic markers of breast cancer in the Kyrgyz ethnic group

A. Semetei kyzy[1], E. Makimbetov[2], J. Isakova[3]

[1]General Medicine, International School of Medicine-International University of Kyrgyzstan (IUK), Bishkek, Kyrgyzstan; [2]Oncology, Kyrgyz Russian Slavic University, Bishkek, Kyrgyzstan; [3]Molecular Biology, Research Institute of Molecular Biology and Medicine, Bishkek, Kyrgyzstan

Background: Breast cancer is identified as a leading cancer in Kyrgyz females. Poor diagnostic approaches lead to high rate of advanced breast cancer cases and consequently to high mortality rate. Genetic testing is a promising method of prevention and early diagnosis of breast cancer.

Methods: This was a case-control study of 201 women of the Kyrgyz ethnic group with a morphologically verified breast cancer (N=99) and 102 controls age-matched with BC cases. The mean age of the patients was 48 years (minimum 24, maximum 74, STD=9.83). The genotyping was performed by using restriction fragment length polymorphism assay. The extraction of DNA was carried out from venous blood.

Results: Genotype CT of the HMMR V353A polymorphism is associated with low risk of breast cancer in the Kyrgyz females (OR=0,481, 95%CI 0,272 − 0,850, p=0,011). Combination of the allele 194Trp (XRCC1 Arg194Trp) and genotype CT (HMMR V353A) (OR=0,302, [95% CI 0,128-0,713], p=0,005), combination of genotypes CT (HMMR V353A) //TT (Palb2 T1100T (3300T>G) (OR=0,459, 95% CI [0,259-0,814], p=0,007), combination of genotypes CT (HMMR V353A) //GG (TNF aG3080A) (OR=0,546, 95% CI [0,298-0,999], p=0,048) are also associated with low risk of breast cancer in the Kyrgyz ethnic group. Furthermore, the allele 194Trp is associated with late age of onset of breast cancer when comparing to 194Arg allele of XRCC1 gene (p=0,017). Allele 194Trp significantly more often occurs in postmenopausal women (p=0,005) and in women with high BMI (>25) (p=0,003).

Conclusions: These results may contribute to further genetic research aimed at identifying genes associated with breast cancer in the Kyrgyz population.

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63P Study of single nucleotide polymorphism of thymocyte selection associated high mobility group box 3 and fibroblast growth factor receptor 2 genes in breast cancer patients

A.M. Alhanafy[1], M. Hammoudah[2], A. Dawood[2], M. Abouelenin[2]

[1]Clinical Oncology and Nuclear Medicine Department Menoufia University - Faculty of Medicine, Shebeen El-Kom, Egypt; [2]Medical Biochemistry and Molecular Biology, Menoufia University - Faculty of Medicine, Shebeen El-Kom, Egypt

Background: Breast cancer is one of the most common malignancies in women worldwide. The development and progression of breast cancer is very complicated process and involves both genetic and epigenetic factors. Genetic variation of both thymocyte selection associated high mobility group box family member 3 (TOX3) and fibroblast growth factor receptor 2 (FGFR2) genes is a newly-described risk factor for breast cancer.

Methods: Eighty participants were enrolled in this study; 40 women with breast cancer and 40 age- matched healthy controls. Detection of (TOX3) rs12443621 and (FGFR2) rs2981582 SNPs was done for all the included subjects using Taq Man Allelic Discrimination assay technique by real time PCR. For patients, all clinical and pathological data, chemotherapy toxicity and survival were studied and analyzed in relation with (TOX3) and (FGFR2) SNPs.

Results: A statistically significant difference was observed between cases and controls regarding the frequency of rs122443621 in TOX3 gene with GG genotype (45% in patients compared to 25% in controls) (P=0.04) and rs2981582 of FGFR2 gene polymorphisms AA genotype (42.5% in patients compared to 17.5% in controls) (P=0.02). There was a significant statistical difference among different genotypes of TOX3 rs122443621 regarding molecular subtypes& TNM stage. There was a significant statistical difference among different genotypes of TOX3 (rs12443621) as 58.3 % of patients with GG genotype developed toxicity grade (G) II & III compared to 15.4% of AG while AA genotype developed only GI (P=0.02) , for FGFR2 (rs2981582) G II&III toxicity was 53.8 % in patients with AA genotype while GA and GG developed lower incidence of toxicity (11.1% and 9.1% respectively) (P=0.03). Regarding survival, the mean progression free survival (PFS) 20.59 months with 95% CI (19.42 − 21.76) months, during this follow up duration there was a non significant statistical difference either among different genotypes of TOX3 (rs12443621) or FGFR2 (rs2981582) (P>0.05).

Conclusions: TOX3 rs122443621 and FGFR2 rs2981582 SNPs are associated with an increased risk for breast cancer, advanced stages, molecular subtype of the disease and with chemotherapy toxicity.

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64P Comprehensive genomic analysis of primary triple negative breast cancer prior to neoadjuvant chemotherapy

M. Drobniene[1], R. Sabaliauskaite[2], E. Zurauskas[3], R. Meskauskas[3], B. Brasiuniene[1], S. Jarmalaite[4]

[1]Department of Medical Oncology, National Cancer Institute, Vilnius, Lithuania; [2]Laboratory of Genetic Diagnostics, National Cancer Institute, Vilnius, Lithuania; [3]Pathology, National Center of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [4]Administration Department, National Cancer Institute, Vilnius, Lithuania

Background: Triple negative breast cancer immunohistochemically defined by negative estrogen receptor (ER), progesterone receptor (PR) and HER2 expression, is highly heterogenous. As there is a lack of routine targeted therapies, chemotherapy in neoadjuvant setting remains a standard of treatment. Genomic alterations are extensively investigated to determine the drivers of tumor evolution, new treatment targets and to identify the ways of resistance to therapies.

Methods: 28 patients with stage II – III triple negative breast cancer were assigned to receive neoadjuvant chemotherapy with paclitaxel (80mg/m^2) and carboplatin (AUC 1.5-2) 12 cycles weekly followed by 4 cycles of AC (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 3-weekly). Hybrid capture-based next-generation sequencing was performed by using FoundationOne®CDx test on DNA from formalin-fixed paraffin-embedded (FFPE) primary tumor tissue obtained prior to the treatment.

Results: The median age of 28 patients was 52 years (ranged 32 to 72 years). One or more mutations were found in all cases. The number of detected gene mutations was an average 5.4 (range 1 to 14 per case). The most frequent somatic mutations were TP53 92.9% (26 of 28), PIK3CA 28.6% (8 of 28), RAD21 21.4% (6 of 28), PTEN and MYC 17.9% (5 of 28), NSD3 14.3% (4 of 28), NF1, FGFR2, CCNE1, AKT2 and ZNF703 10.7% (3 of 28). Germline BRCA1 mutation was found in 2 cases, while germline BRCA2 mutation - in 1 case.

Conclusions: Comprehensive genomic profiling of primary triple negative breast cancer identifies potentially actionable mutations in a large set of tumors and might be clinically important for treatment individualization.

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65P Investigating the molecular connection between hormone receptor status and ploidy management in breast cancer

S. Nath

Basic Research and Molecular Biology Department, Saroj Gupta Cancer Centre & Research Institute, Kolkata, India

Background: Management of breast cancer banks upon hormone receptor (HR) status, whose absence is associated with features like poor prognosis and aneuploidy. A newly identified protein, CUEDC2 was found maintaining HR level by promoting its degradation, while its moonlighting job is detected in ploidy maintenance during mitosis. The HR members (ER/PR) function as transcription factors. However, their involvement in transregulation of mitotic checkpoint protein(s) is largely unexplored. We hypothesize that HR controls mitosis and maintains ploidy by employing its transregulatory activity, while upregulated CUEDC2, as seen in several cancer types, rendering HR reduction, promotes mitotic deregulation and aneuploidy in HR-negative breast cancer.

Methods: Expression analyses were performed by real-time PCR, immunohistochemistry, and/or Western blot. Plasmid or siRNA constructs were transfected with lipofectamine reagent. The phosphorylation of CUEDC2 was blocked by Cdk1 blocker, RO3306 or site directed mutagenesis. Mitotic synchronization was made with nocodazole treatment. Mitotic progression was examined by immunofluorescence of Ser10-phosphorylated-Histone3. Cellular ploidy was examined by fluorescence in situ hybridization.

Results: The data revealed high expression of mitotic-checkpoint proteins in HR+ve tumors, compared to HR-ve cases, in both primary tumors as well as in cell lines, where ectopic ER-α induced their endogenous levels. Concurrently, HR-ve lines showed abnormal mitotic progression post release from mitotic arrest. Further, CUEDC2 showed higher expression in HR-ve breast malignancies, compared to HR+ve cases, in both primary tumors and cell lines. Additionally, mitotic ubiquitin ligase and Ser110-phosphorylated-CUEDC2 were found crucial in ER-α regulation. Finally, promotion of mitotic deregulation and aneuploidy, upon CUEDC2 upregulation, were rescued by ectopic ER-α.

Conclusions: We found a novel molecular connection between hormone receptor and ploidy maintenance in breast cancer. Furthermore, upregulated CUEDC2, at this crossroad, deregulates this balance, promoting aneuploidy in HR-ve breast malignancies.

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66P Impact of EPClin on adjuvant therapeutic decision-making and comparison of EPClin to PREDICT tool

H. Bourien[1], V. Quillien[1], F. Godey[1], C. Perrin[2], F. Le Du[1], A. Brunot[2], L. Crouzet[2], T. de La Motte Rouge[1], V. Dieras[1], C. Lefeuvre-Plesse[1]

[1]Oncology, Centre Eugene - Marquis, Rennes, France; [2]Medical Oncology, Centre Eugene - Marquis, Rennes, France

Background: Despite molecular classification, patients with luminal early breast cancers have different clinical outcomes. In order to select whose patients would be more benefit from adjuvant chemotherapy, despite clinico-pathological features, genomic signatures help clinician to decide which adjuvant treatment is the most appropriate. EndoPredict is one of them.

Methods: Since November 2016, for patients treated in Brittany's institutions, we proposed EndoPredict assay for unclear cases of adjuvant treatment. For patients treated in our Comprehensive Cancer Center, we retrospectively reported decision of adjuvant treatment before and after EndoPredict assay and compare to PREDICT's tool scores.

Results: From November 2016 to July 2018, 274 breast cancer tumors were analyzed with EndoPredict assays. 131 patients were treated in Rennes, and presented in multidisciplinary breast tumor board before and after EndoPredict assay. Before EndoPredict results, clinicians, recommend chemotherapy for 37 patients (28%). 91 patients (70%) were classified as EndoPredict high risk. Finally, 76 (58%) received chemotherapy. PREDICT tool recommend chemotherapy for 7 patients (5%).

Conclusions: Although genomic tests were developed in order to de-escalate adjuvant treatment, in our Comprehensive Cancer Center, the use of EndoPredict assay lead to an increase of 30% of prescription of chemotherapy.

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67P Digital analysis of distant and cancer-associated adipocytes in breast cancer

E. Isnaldi[1], F. Richard[1], M. De Schepper[1], D. Vincent[2], S. Leduc[1], M. Maetens[1], T. Geukens[1], G. Floris[3], G. Rouas[2], F. Rothé[2], F. Cardoso[4], M. Piccart[5], C. Sotiriou[2], G. Zoppoli[6], E. Biganzoli[7], D. Larsimont[8], C. Desmedt[1]

[1]Department of Oncology - Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium; [2]Laboratoire JC Heuson de Recherche Translationnelle en Cancérologie Mammaire, Institut Jules Bordet, Bruxelles, Belgium; [3]Department of Imaging & Pathology, Translational Cell and Tissue Research Unit, UZ Leuven, Leuven, Belgium; [4]Breast Unit, Champalimaud Foundation Cancer Center, Lisbon, Portugal; [5]Department of Oncology, Institut Jules Bordet, Brussels, Belgium; [6]Department of Internal Medicine, University of Genoa-DIMI, Genoa, Italy; [7]Department of Clinical Sciences and Community Health & DSRC, University of Milan, Campus Cascina Rosa, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [8]Department of Pathology, Institut Jules Bordet, Brussels, Belgium

Background: Adipocytes and cancer-associated adipocytes (CAAs) are under-investigated cells from the tumour microenvironment. Different image analysis software exist for counting and measuring these cells, however, it is unclear which is the best for breast cancer (BC) samples. The objectives are: (1) to identify the best software for counting and measuring distant adipocytes and CAAs, and, (2) to apply the identified software for comparing distant adipocytes and CAAs in a series of BC.

Methods: Firstly, we compared adipocyte counts, diameters and areas on three BC test slides using HALO®, Adiposoft, and AdipoCount. Secondly, we analysed a series of 10 BC samples with HALO®. For each patient, we analysed ∼ 500 distant adipocytes and ∼ 500 CAAs. Distant adipocytes were defined as at least two mm away from cancer cells, whereas CAAs were defined as the three first lines of adipocytes close to the invasive front.

Results: All three methods performed equally good with regard to area and diameter measurement (all estimated concordance correlation coefficient values > 0.97 and

Table 67P

Test Image	Software	Sensitivity	Specificity
Slide 1	HALO Adiposoft AdipoCount	97% 92% 87%	97.96% 60% 26.53%
Slide 2	HALO Adiposoft AdipoCount	97.27% 25.69% 97.22%	100% 63.93% 40.68%
Slide 3	HALO Adiposoft AdipoCount	99% 92.16% 98.99%	100% 37.70% 48.08%
Overall	HALO Adiposoft AdipoCount	97.75% 69.21% 94.46%	99.36% 53.88% 38.75%

> 0.96, respectively). HALO® clearly outperformed the other two methods with regard to adipocyte counting, reaching higher sensitivity and specificity (Table). When applying this software to the BC samples, CAAs presented smaller areas (median fold-change: 2.4, IQR: 2.13 − 2.63) and diameters (median fold-change: 1.6, IQR: 1.51 − 1.66) compared to distant adipocytes (p<.001, p<.001, respectively). Both CAAs size and distant adipocytes size were associated with BMI as continuous (rho = 0.8 p = .008; rho = 0.73 p= .029, respectively) and as categorical variable (Kendall's tau = 0.60 p = .038, Kendall's tau = 0.55, p = .062, respectively).

Conclusions: Quantifying adipocytes in BC sections is feasible by digital software analysis. This study is the first digital analysis that demonstrates a clear reduction in size between CAAs and distant adipocytes supporting the concept of an interaction between CAAs and cancer cells.

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68P Deciphering the interplay between nuclear RNA export factors and long non-coding RNAs in breast cancer metabolism

C. Klec[1], D. Schwarzenbacher[1], B. Gottschalk[2], R. Margit[1], F. Prinz[1], T. Bauernhofer[1], H. Stoeger[1], W.F. Graier[2], M. Pichler[1]

[1]Oncology, Medical University of Graz, Graz, Austria; [2]Molecular Biology and Biochemistry, Gottfried Schatz Research Center, Graz, Austria

Background: As cancer cells strongly rely on glycolysis, targeting cancer cell glucose metabolism could be a suitable approach to find novel therapeutic targets. The role of RNA export factors and long non-coding RNAs (lncRNAs) in cancer cell metabolism have not been fully uncovered yet. Therefore, we comprehensively examined the interplay between the RNA export factor paraspeckle-associated protein 1 (PAP1) and the lncRNA NEAT1 in triple negative breast cancer cell metabolism.

Methods: In order to uncover PAP1-associated genes, RNA sequencing was performed. After identifying a correlation with NEAT1, cellular growth and apoptosis assays were conducted. Mitochondrial morphology was visualized after cellular staining with MitoTracker® on a confocal microscope. Key metabolic pathways such as mitochondrial respiration and glycolysis were measured with the Seahorse XF Analyzer.

Results: In a preceding study, we established the RNA export factor PAP1 as mediator of breast carcinogenesis - regulating cell growth by apoptosis induction. These findings motivated us to further investigate this topic. RNA sequencing data identified a significant correlation between PAP1 and the BC-related lncRNA NEAT1. Strikingly, we could elaborate PAP1 as transcriptional regulator of NEAT1 and mediator of NEAT1-dependent paraspeckle formation. These data were corroborated by the finding, that silencing NEAT1 phenocopies PAP1 silencing in terms of cellular growth and apoptosis induction. As mitochondria are crucially involved in apoptotic processes, glucose metabolism and ATP production, we examined the effect of PAP1 and NEAT1 silencing on mitochondrial morphology and function. Reducing the expression of either one of these genes changes mitochondrial shape to a more spherical, apoptotic phenotype and significantly decreases mitochondrial respiration and ATP production.

Conclusions: In this study, we could elaborate PAP1 as novel regulator of NEAT1 in breast carcinogenesis. Furthermore, our data point towards a crucial involvement of PAP1 and NEAT1 in cancer cell metabolism — an interesting finding justifying a more detailed investigation on the role of RNA export factors and lncRNAs in cancer metabolism.

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69P TGFBI promoter methylation validation as an epigenetic biomarker for trastuzumab resistance in HER2+ breast cancer patients cohort

H. Pla[1], Á. Díaz-Lagares[2], A. Hernandez[1], G. Oliveras[3], F. Pérez-Bueno[3], M. Esteller[4], T. Puig[5], S. Palomeras[5], G. Viñas[1]

[1]Medical Oncology Department, Catalan Institute of Oncology (ICO), Dr. Josep Trueta Hospital, Girona, Spain; [2]Translational Oncology Department, Health Research Institute of Santiago (IDIS), University Clinical Hospital of Santiago (CHUS), CIBERONC, Santiago de Compostela, Spain; [3]Pathology Department, Dr. Josep Trueta Hospital and Catalan Institute of Health (ICS), Girona, Spain; [4]Cancer Epigenetics, Josep Carreras Leukaemia Research Institute (IJC), Badalona, Spain; [5]Department of Medical Science, TargetsLab, University of Girona, Girona, Spain

Background: The identification of potential biomarkers capable of detecting, predicting or monitoring treatment response is currently one of the main objectives in oncology. Our research group had previously identified the epigenetic inactivation of Transforming Growth Factor β-Induced (TGFBI) in different trastuzumab resistance HER2-positive breast cancer (HER2+ BC) cell models. In the present work, our objective was to validate the TGFBI promoter methylation in a cohort of HER2+ BC patients before and after neoadjuvant treatment.

Methods: The study cohort included 24 patients with HER2+ early BC treated with neoadjuvant anthracycline-taxane-based chemotherapy plus trastuzumab, of which 20 patients presented partial or no response and 4 patients complete treatment response. TGFBI methylation was analyzed in formalin-fixed paraffin-embedded (FFPE) biopsy (pre-treatment) and tumor samples (post-treatment) from each patient. All the DNA samples were analyzed using bisulfite pyrosequencing. The correlation between TGFBI methylation and clinical-histopathological characteristics has been analyzed and characteristic curves (ROC) were used to assess the predictive capacity of TGFBI as a marker.

Results: Similar TGFBI promoter hypermethylation levels were observed in pre-treatment samples from patients with complete response to trastuzumab and from the non-responders. In contrast, non-responsive patients showed significantly higher methylation levels in post-treatment (30.26%±3.52) than pre-treatment samples (6.08%±1.51). In particular, significant TGFBI hypermethylation after trastuzumab (80%) compared to the pre-treatment samples was observed in non-responsive patients with pre- and post- treatment paired samples. Importantly, the ROC curve analysis showed an area under the curve (AUC) of 0.9502 (95% CI: 0.8716 to 1.029). No significant association between TGFBI methylation levels before and after treatment and their clinical-histopathological characteristics was identified.

Conclusions: These preliminary results provide a basis for further studies to validate TGFBI hypermethylation as a potential epigenetic monitoring biomarker for trastuzumab resistance in HER2+ BC patients.

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70P Genetic polymorphisms of ESR1 are associated with hormone resistance to aromatase inhibitors therapy in patients with metastatic luminal breast cancer (MLBC)

T. Tarasenko[1], L.A. Syvak[1], N.O. Verovkina[1], S. Lyalkin[2]

[1]Chemotherapy Department, National Cancer Institute of the Ministry of Health of Ukraine, Kiev, Ukraine; [2]Chemotherapy of Solid Tumours, National Cancer Institute of the Ministry of Health of Ukraine, Kiev, Ukraine

Background: The endocrine therapy (ET) has established itself as the basis for drug treatment in MLBC due to its high efficiency and low toxicity. Aromatase inhibitors (AI) are initial therapy in the most cases. However, a third of them have a progression of the disease due to primary or acquired resistance.The role of ESR1 mutations is actively discussed as an early and practically achievable (especially when repeat biopsies are impossible) marker for predicting the development of insensitivity to standard ET.

Methods: Treatment results of 53 patients with MLBC, who received first-line ET with nonsteroidal AI - letrozole (2.5 mg daily) or anastrozole (1 mg daily) were analyzed. We provided the baseline and post-treatment molecular genetic testing of ESR1 in peripheral blood. ESR1 (A-351G, T-397C) polymorphism was detected by analysis of DNA restriction fragment length polymorphism. The treatment response assessed according to RECIST 1.1. In a year of treatment all patients were divided into 2 groups depending on the progression of the disease. The first group included 19 patients with progression earlier than one year after AI and in the second was 34 patients without progression in one year of AI.

Results: We identified that ESR1 gene heterozygous variant A/G351 occured in 51,7 % and T/C397 in 68,8 %. Analysis of associations between genetic variants ESR1 A-351G and ESR1 T-397C showed significant relationship between themselves ($p < 0.05$). It has been established that the presence of polymorphic genotypes ESR1 A-351G (odds ratio (OR) 2.81 [95% CI = 1.16 −6.82], p=0.05) and ESR1 T-397C (OR 3.33 [95% CI =1.00 − 11.90], p=0.05) was associated with early disease progression (up to 1 year). There was no statistically significant association of the polymorphisms ESR1 (A-351G, T-397C) gene with receptor status (ER%, progesterone receptor %) and Ki-67% ($p < 0.05$).

Conclusions: Further research is required to provide evidence of the ESR1 gene polymorphisms (A-351G, T-397C) as an additional risk factor of early resistance to AI in patients with MLBC.

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71P Role of radiomics in predicting molecular phenotypes of female breast cancer

A. Jajodia[1], A. Gupta[2], A. Mehta[3], A. Chaturvedi[1], A. Rao[1], G. Gupta[4], D.C. Doval[5], A. Bp[5], P. Medisetty[6], S. Bommera[7], V.P.B. Koyyala[5], S. Pasricha[3], M.E. Mayerhoefer[8], H. Prosch[8], M.K. Chllamma[9], M. la Mantia[10], A. Russo[10]

[1]Radiology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [2]Center for Computational Biology, Indraprastha Institute of Information Technology, New Delhi, India; [3]Pathology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [4]Research Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [5]Medical Oncology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [6]Anaesthesia, BSAH - Dr. Baba Saheb Ambedkar Medical College and Hospital, Rohini, India; [7]Radiotherapy, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [8]Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria; [9]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [10]Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy

Background: Radiomics is a promising tool for imaging biomarker discovery in the era of precision medicine. This paper aims to establish the benefit of using multi-modality radiomics data from PET and MR images in the categorization of breast cancer molecular phenotype.

Methods: One radiologist having 6 years of experience manually drew the region of interest on the tumor for purposes of segmentation and textural analysis. The segmented tumor was validated independently by two radiologists having 30 years of experience each. A total of 851 radiomics features were extracted from the available imaging (Total n = 63; PET-CT 25/MRI 38) using slicer 3D software and Pyradiomics. Harmonization was achieved in the different imaging modalities and hence the removal of batch effect was done with the help of the combat-a R package. Feature selection was done by taking the union of the features which had Pearson correlation >3 with any of the biomarker ER, PR or Her2neu, or > 2.5 with BRCA. Models were trained to predict the biomarkers using leave one out cross-validation and different algorithms for different biomarkers.

Results: Using KNN (K- Nearest neighbor) model in the subset population of ER (22 positives and 41 negatives) we were able to achieve an accuracy of 80%. The Kappa score was 0.45 and the area under the curve (AUC) was 0.72. Using the KNN model in the subset population of PR (18 positives and 45 negatives) we were able to achieve an accuracy of 82%. The Kappa score was 0.43 and AUC was 0.70. Using KNN (K-Nearest neighbor) model in the subset population of ER (22 positive and 41 negatives) we were able to achieve an accuracy of 80%. The Kappa score was 0.45 and the area under the curve (AUC) was 0.72. Using the KNN model in the subset population of PR (18 positive and 45 negatives) we were able to achieve an accuracy of 82%. The Kappa score was 0.43 and AUC was 0.70.

Conclusions: Radiomic features on imaging could be useful in deciphering breast cancer phenotypes and serve as potential imaging biomarkers. This modality can potentially address tumoral heterogeneity that may be missed on a single biopsy from the most feasible site. Also, imaging biomarkers can be used as a real-time estimate of the dynamics of biomarker expression in an individual patient.

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72P Non-mass like enhancement patterns on MR mammography and their pathological correlation

A. Parashar[1], A. Jajodia[1], A. Chaturvedi[1], A. Rao[1], A. Mehta[2], D.C. Doval[3], A. Bp[3], P. Medisetty[4], V.P.B. Koyyala[3], S. Pasricha[2], M. la Mantia[5], M.K. Chllamma[6], D. Leithner[7], M.E. Mayerhoefer[7], A. Russo[5], H. Prosch[8]

[1]Radiology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [2]Pathology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [3]Medical Oncology Department, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [4]Anaesthesia, BSAH - Dr. Baba Saheb Ambedkar Medical College and Hospital, Rohini, India; [5]Medical Oncology, University of Palermo, Palermo, Italy; [6]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [7]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

Background: Non-mass enhancing breast lesions pose a diagnostic dilemma and a clinical challenge that are encountered commonly in clinical practice. Suspicion of breast cancer makes it an important entity for a radiologist and medical oncologist.

Methods: All patients with clinical suspicion of Breast disease were included in the study. MRI reveals MR-BIRADS 4 and 5 non mass enhancing lesions and further underwent biopsy/post MRM/BCS/lumpectomy in our hospital. After inclusion/exclusion criteria clinically meaningful 128 non-mass lesions were assessed further for distribution pattern, internal enhancement pattern and kinetics.

Results: 128 non-mass lesions were analyzed in n= 127 patients. 83 lesions were malignant and MR-BIRADS 5 category dominated (66/128, 51.5 %). Most common pattern of distribution/internal enhancement/curve type were segmental (47, 36.72%), clumped (64, 50%) and washout curve type (99, 77.34%) respectively. Regarding association with malignancy, odds ratio of lesions with segmental/regional/multiple regional distribution pattern was 13.5 (95% CI= 5.6-32.5), clumped/clustered ring internal enhancement pattern was 43.07 (95% CI= 14.3-129.6) and washout curve type was 17.8 (95% CI= 6.0-52.3). The sensitivity of the washout curve type for diagnosis of malignancy was 93.9%. The specificity of clumped/clustered ring internal enhancement pattern was 88.9%.

Conclusions: Segmental/regional/multiple regional distribution patterns, clumped/clustered ring internal enhancement pattern and washout curve type was the most powerful indicator for malignant pathology in non-mass enhancing lesions. The study envisaged the unmet need for consensus on the characterization of non-mass enhancing lesions in most of the previously done studies.

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73P microRNA expression profiles of single hormone receptor-positive breast cancers

M. Kunc[1], M. Popeda[2], A. Szalkowska[3], M. Niemira[3], A. Lacko[4], B.S. Radecka[5,14], M. Braun[6], J. Pikiel[7], M. Litwiniuk[8], K. Pogoda[9], A. Szwajkosz[10], E. Izycka-Swieszewska[11], A.J. Zaczek[12], W. Biernat[1], E. Senkus-Konefka[13]

[1]Department of Pathomorphology, Medical University of Gdansk, Gdańsk, Poland; [2]Laboratory of Translational Oncology, Intercollegiate Faculty of Biotechnology, Medical University of Gdansk, Gdansk, Poland; [3]Clinical Research Centre, Medical University of Bialystok, Bialystok, Poland; [4]Department of Oncology, Wroclaw Medical University, Wroclaw, Poland; [5]Institute of Medical Sciences, University of Opole, Opole, Poland; [6]Department of Pathology, Medical University of Lodz, Lodz, Poland; [7]Department of Oncology, Szpital Morski, Gdynia, Poland; [8]Department of Oncology, Wielkopolskie Centrum Onkologii-Greater Poland Cancer Centre, Poznan, Poland; [9]Department of Breast Cancer and Reconstructive Surgery, The Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland; [10]Department of Oncology, Beskid Oncology Center, Bielsko-Biała, Poland; [11]Department of Pathology & Neuropathology, Medical University of Gdansk, Gdansk, Poland; [12]Laboratory of Translational Oncology, Intercollegiate Faculty of Biotechnology, Medical University of Gdansk, Gdańsk, Poland; [13]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; [14]Department of Clinical Oncology, Tadeusz Koszarowski Cancer Centre, Opole, Poland

Background: The molecular landscape of single hormone receptor-positive breast cancers — ER(+)/PgR(-) and ER(-)/PgR(+), remains vague. Clinically, endocrine sensitivity and prognosis of these tumors are believed to be intermediate between ER(+)/PgR(+) and double-negative cancers. MicroRNAs (miRNAs) emerge as important players in breast cancer biology and may serve as potential therapeutic targets. In the current study, we aimed to compare the miRNA expression profiles of these cancers.

Methods: The group consisted of 32 breast cancer patients with thoroughly characterized status of ER and PgR expression [14 ER(+)/PgR(-) and 18 ER(-)/PR(+) cases]. The expression of 829 miRNAs was evaluated with nCounter Human v3 miRNA Expression Assay (NanoString). miRNAs differentiating between ER/PgR phenotypes were selected based on fold change, and the differences were estimated with Student's t-Test or Two Way ANOVA (considering also the HER2 status). The results were validated using the TCGA dataset.

Results: A trend of higher expression of miRNAs associated with ER-positivity (miR-149, miR-375, miR-26b, miR-425, miR-29c, miR-200a, miR-191, miR-144) was observed in the ER(+)/PgR(-) group. In contrast, ER(-)/PgR(+) cases tended to express higher levels of miR-92a-3p, miR-155-5p, miR-18a-5p, miR-222-3p, characteristic for triple-negative cancers. The last two miRNAs are known to directly down-regulate ER expression. Yet, due to the limited number of cases in our cohort, no differences between miRNAs expression in ER(+)/PgR(-) and ER(-)/PgR(+) breast tumors remained significant after correction for multiple comparisons. Four miRNAs validated in the TCGA dataset (miR-1180, miR-223, miR-30d, miR-99a) were down-regulated in HER2-overexpressed/amplified tumors of both ER/PgR phenotypes.

Conclusions: Our data support the role of miRNAs in the pathogenesis of ER(-)/PgR(+) breast tumors. Interestingly, the miRNA profiles of the single hormone receptor-positive breast cancers are mainly associated with the HER2 status. The high expression of miR-1180 in HER2-negative cases has not been reported before.

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74P Clinical value of HER3/ErbB3 serum level determination in patients with breast cancer qualified for neoadjuvant chemotherapy

B. Kotowicz[1], P. Winter[2], M. Fuksiewicz[1], A.I. Jagiello-Gruszfeld[2], Z. Nowecki[2], M.M. Kowalska[1]

[1]Laboratory of Tumours Markers, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [2]Breast Cancer and Reconstructive Surgery Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: Human epidermal growth factor receptor 3 (HER3) is a member of family of receptor tyrosine kinases, including EGFR, HER2 and HER4. HER3 is thought to function as a signaling protein promoting tumorigenesis, proliferation, migration and metastasis. Overexpression in tumors has been associated with worse clinical outcomes. HER3 serum level was shown to corelate with disease progression. The aim of this study is to assess clinical value of HER3 serum level determination in patients with breast cancer qualified for neoadjuvant chemotherapy.

Methods: 57 patients with confirmed breast cancer before treatment were qualified for the study, aged 31-77 (median 53 years), including 28 premenopausal and 29 postmenopausal. The control group consisted of 26 healthy women aged 16-80. Clinical and pathological features were determined in a selected group of patients with breast cancer who subsequently underwent preoperative chemotherapy, i.e. tumor size (T), lymph node status (N), presence of distant metastases (M), estrogen receptor status (ER) and progesterone (PgR), HER2 receptors and Ki 67 proliferative index. The blood serum of the examined patients and healthy women was determined by the enzyme-linked ELISA method in doublets of the HER3 biomarker concentration. Mann-Whitney test and ROC curve analysis were used for statistical calculations.

Results: Significant differences between HER3 concentrations in breast cancer patients and in the control group were shown as preliminary results of the study ($p = 0.035$). In the examined group of patients, no differences in HER3 levels were found depending on the menopausal status. In the ROC curve analysis in patients vs healthy women, the diagnostic sensitivity for HER3 was AUC (area under curve) 0.652; $p = 0.023$. Considering the clinical-pathological features, no significant correlation was found between biomarker concentration and tumor size (T), lymph node status (N), receptor status and Ki67 index.

Conclusions: Based on the preliminary results of the study, a relatively high diagnostic sensitivity of ErB3 / HER3 concentrations was demonstrated, which shows its potential usefulness in breast cancer patients. The research is continuing.

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75P Clinical and pathological feature of primary lung cancer in patients with primary breast cancer

T. Zeng, W. Li, Y. Yi

Department of Oncology, Jiangsu Province Hospital - The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: With increased survival in breast cancer, resulting from advances in treatment, patients incur the possibility of subsequent primary malignancies, especially lung cancer. The aim of this study was to assess the frequency of lung cancer following breast cancer diagnosis, the associations between breast cancer and lung cancer, the pathological features of double primary cancer, and the status of epidermal growth factor receptor (EGFR) mutations in second primary lung cancer.

Methods: A review of medical charts at the Jiangsu Province Hospital (Jiangsu, China) revealed 8048 patients with pathologically confirmed breast cancer between January 2008 and December 2018. Clinical information, including pathology and immunohistochemistry of cancer tissues, EGFR status, date of GGO detection, and cancer stage, was collected. Statistical analysis was performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

Results: Of the 8048 patients, 55 (0.7%) were diagnosed with a second primary lung cancer, which accounted for approximately 13.6% of the pulmonary ground-glass opacity (GGO) detected. The incidence was higher than in the general female population (standardized incidence ratio 1.4 [95% confidence interval (CI): 1.25-1.55]). Patients who experienced a second primary lung cancer exhibited a significantly higher rate of EGFR mutation (78.6%) than those with lung adenocarcinoma alone, with most exhibiting low-grade malignancy, older age, estrogen receptor negativity, low Ki67, and no lymph node metastasis.

Conclusions: Breast cancer patients, especially those with low-grade malignancy, were at high risk for developing primary lung cancer. For isolated GGO in patients with high-risk factors, clinicians should insist on close follow-up. Furthermore, EGFR may play an important role in primary lung adenocarcinomas and breast cancer.

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76P Retrospective study about the prevalence of (TILs) tumour infiltrating lymphocytes in non-metastatic triple negative breast cancer patients and its prognostic value

A.M. Kamal, H.A. Elghazaly, M.M. El-Mahdy, A.M. Adel, N.M. Abdel-Kader

Clinical Oncology, Mataria Teaching Hospital, Cairo, Egypt

Background: Among breast carcinomas, TNBC comprises a distinct disease entity with a unique microenvironment of TILs ,To clarify the biological and prognostic function of TILs, which is a host factor in tumor microenvironment, we focused on effector $CD8^+$ T cells in our study as marker for TILs , CD8+ TILs represent a vital component of the local anti-cancer immune response.

Methods: We were evaluating the prevalence of CD8+ as a marker for TILs in the parrafin wax block of pre-treatment biopsies of 30 triple negative breast cancer patients ,and its prognostic value by correlating it with OS and DFS.

Results: Our study showed that All our patients (100%) were positive for CD8+, with a minimum range of 1% and a maximum range of 60 %, most of the patients (20 patients) had CD8 % between (10% to 20 %). high levels of CD8 + TILs are good prognostic indicators in TNBC. our study showed that there were associations of CD8+ TILs infiltrate status with longer progression free survival and better overall survival in triple-negative breast cancer, but were not statistically significant probably due to our small sample size. Our study showed no correlation between CD8+ level and some clinical-pathological variables (tumor size, nodal status, tumor stage, menopausal status, age, family history). Our findings as well as other studies demonstrate that quantification of CD8 + TILs is feasible using routine immunohistochemical techniques.

Conclusions: TNBC is the subtype that is most frequently associated with TILs, but only a minority of TNBCs demonstrate a high number of TILs, suggesting that IM therapy could be necessary to promote immunorecognition and increase the adaptive immune infiltrate to levels adequate for a survival benefit in the majority of patients with this BC subtype. Patients with high levels of TILs at the time of diagnosis might benefit from the use of drugs that can enhance antitumoral immune responses.

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79P Liquid biopsy-based detection of PIK3Ca mutations in HR positive metastastic breast cancer patients

C. Suppan[1], Q. Zhou[2], R. Graf[2], V. Klocker[1], A. Terbuch[1], N. Dandachi[1], E. Heitzer[2], M. Balic[3]

[1]Division of Oncology, LKH-Univ. Klinikum Graz, Graz, Austria; [2]Institute of Human Genetics, Medical University of Graz, Graz, Austria; [3]Department of Internal Medicine, LKH-Univ.Klinikum Graz - Universitätsklinik für Innere Medizin, Graz, Austria

Background: The treatment of hormone receptor positive metastatic breast cancer patients has changed dramatically over the last few years and combination strategies attempting to overcome resistance of the disease are gaining importance. After introducing CDK 4/6 inhibitors in the treatment one of the subsequent strategies is definitely targeting PI3 kinase pathway. Several drugs have been tested, but only recently, SOLAR1 phase III trial demonstrated the benefit of addition of alpelisib to fulvestrant, with acceptable tolerability. With this trial the importance of liquid biopsy testing was postulated.

Methods: Cell-free DNA from plasma from 23 patients with metastatic hormone receptor positive was screened for PIK3CAhotspot mutations. To this end a SimSen-seq assay (simple, multiplexed, PCR-based barcoding of DNA for sensitive mutation detection using sequencing) covering the 11 most frequent PIK3CA mutations (Table) was designed. Using Seraseq® ctDNA Reference Materials with various variant allele frequencies (VAFs) the assay enabled a detection of PIK3CA H1047R, down to a VAF of 0.125%, while the mutation could not be detected in the wild type sample. Nevertheless, since in a set of healthy controls, background noise was observed during assay validation, only samples with VAFs >1% were considered as positive.

Results: Out of 23 tested patients, a PIK3CA mutation with a VAF >1% could be detected in 14 patients (60.9%). Ten patients were identified with H1047R mutation and 2 patients were E542K positive. In one patient, we were able to identify co-ocurrence of both mutations. VAF ranged from to 1.1% to 49.9% with an average of 8.2%. It is of note though, that presences of PIC3Ca mutations below the detection limit cannot be excluded.

Conclusions: SimSen-seq based detection of PIK3CA mutations from plasma selected for alpelisib treatment has shown promising results and warrants further validation in a larger cohort of candidate patients. FDA recommendation is to initially carry out the mutation testing in ctDNA and if the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in tumour tissue. Tissue analysis is currently ongoing.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EARLY BREAST CANCER: ADJUVANT THERAPY

80O Patient (pt) preference and satisfaction with the subcutaneous fixed-dose combination of pertuzumab (P) and trastuzumab (H) in pts with HER2-positive early breast cancer (HER2+ eBC): Interim analysis of the open-label, randomised cross-over PHranceSCa study

J. O'Shaughnessy[1], S.P. Sousa[2], J. Cruz[3], L.J. Fallowfield[4], P. Auvinen[5], C. Pulido[6], A. Cvetanovic[7], S. Wilks[8], L. Ribeiro[9], M. Burotto[10], D. Klingbiel[11], D. Messeri[11], A. Alexandrou[12], P. Trask[13], J. Fredriksson[11], L. Stamatovic[14]

[1]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [2]Department of Medical Oncology, Portuguese Oncology Institute of Porto, Porto, Portugal; [3]Hospital Universitario de Canarias, La Laguna, Medical Oncology, Santa Cruz De Tenerife, Spain; [4]Brighton and Sussex Medical School, Sussex Health Outcomes Research & Education in Cancer, Falmer, UK; [5]Cancer Center, Kuopio University Hospital, Kuopio, Finland; [6]Centro de Oncologia, Hospital Da Luz Lisboa, Lisbon, Portugal; [7]Medical Faculty, Nis and Clinical Centre, Nis, Serbia; [8]Texas Oncology, San Antonio, TX, USA; [9]Centro Hospitalar Universitário Lisboa Norte, Hospital Santa Maria (CHULN/HSM), Lisbon, Portugal; [10]Bradford Hill, Clinical Research Center, Santiago, Chile; [11]F. Hoffman-La Roche Ltd, Global Product Development, Basel, Switzerland; [12]Roche Products Ltd, Product Development Safety, Welwyn Garden City, UK; [13]Genentech Inc, Patient Centered Outcomes Research - Oncology, San Francisco, CA, USA; [14]Clinic for Medical Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Background: A subcutaneous fixed-dose combination of P + H (PH FDC SC) may offer pts less invasive, faster administration vs intravenous P + H (PH IV). PHranceSCa is an open-label, randomised cross-over study evaluating pt preference and satisfaction with PH FDC SC vs PH IV.

Methods: Pts with histologically confirmed, HER2+ eBC who completed neoadjuvant therapy with P + H + chemotherapy and had surgery are enrolled and 1:1 randomised to Group A: 3 cycles of PH IV every 3 weeks (q3w) (P: 840 mg loading dose, 420 mg maintenance; H: 8 mg/kg loading; 6 mg/kg maintenance) then 3 cycles of PH FDC SC q3w (loading: 1200 mg P, 600 mg H; maintenance: 600 mg P, 600 mg H); or Group B: 3 cycles of PH FDC SC q3w then 3 cycles of PH IV q3w. Pts then choose PH FDC SC or PH IV to complete anti-HER2 therapy (up to 18 cycles). The primary objective is to evaluate patient preference for PH FDC SC.

Results: At clinical cut-off (19-08-19), 118 patients were randomised (Group A, n = 56; Group B, n = 62). All were female; median age was 49 years. 42/51 pts (82%; 95% CI 69—92%) who completed the cross-over therapy preferred PH FDC SC. Main reasons for PH FDC SC preference were "less time in clinic" (n = 38) and "more comfortable therapy administration" (n = 22). 46/51 (90%) pts were "very satisfied" or "satisfied" with PH FDC SC vs 34/51 (67%) with PH IV. 84% pts chose PH FDC SC to complete their therapy. 81/116 pts had ≥1 adverse event (AE), 1 had a serious AE (PH IV; pyrexia) and 5 had a Grade 3 AE (PH FDC SC, n = 3: ejection fraction [EF] decrease, diarrhoea, device-related infection; PH IV, n = 2: EF decrease, lymphopenia); there were no deaths and no AEs led to study discontinuation. 16/116 (13.8%) pts had diarrhoea, mainly low grade. Systemic administration-related reaction rates were 2/116 (1.7%) for PH FDC SC and 3/116 (2.6%) for PH IV. 21/116 (18.1%) pts had local injection site reactions; there were no local infusion-related reactions.

Conclusions: In the PHranceSCa interim analysis, 82% (95% CI 69—92%) of pts preferred PH FDC SC. PH FDC SC was generally well tolerated; the safety profile was consistent with PH IV and no new safety signals were seen.

Clinical trial identification: NCT03674112.

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82P A multinational study of real-world treatment patterns among patients with early stage HR+/HER2- breast cancer (BC)

C. Criscitiello[1], D. Spurden[2], A. Rider[3], R. Williams[3], M. Corsaro[4], J. Pike[5], E.H. Law[6]

[1]Early Drug Development for Innovative Therapies Division, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]Patient & Health Impact, Pfizer Ltd, Walton Oaks, UK; [3]Disease Specific Programme, Adelphi Real World, Bollington, UK; [4]Global Medical Affairs, Pfizer Italia s.r.l., Milan, Italy; [5]Statistics & Data Analytics, Adelphi Real World, Bollington, UK; [6]Global Health Economics & Outcomes Research (Oncology), Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA

Background: This study aimed to describe surgical, neoadjuvant, and adjuvant treatment patterns among patients diagnosed with early-stage HR+/HER2- BC.

Methods: Data from a multinational (France [FR], Germany ([DE], Italy [IT], Japan [JP], Spain [ES], United Kingdom [UK], and United States [US]) sample of patients with stage I-III HR+/HER2- BC who received at least one treatment in the adjuvant setting were analysed. Surgery, chemotherapy, and endocrine (aromatase inhibitor or tamoxifen) treatment patterns in neoadjuvant and first adjuvant settings were summarized overall, by country, and age at initiation of first adjuvant treatment (≤50 and >50 years).

Results: A total of 2,447 patients were included in this analysis. Neoadjuvant therapy was given in 18% patients. Of these, 89% of regimens included chemotherapy (66% taxane, 66% anthracycline) and 52% included endocrine treatment (34% aromatase inhibitor, 12% tamoxifen). More than half of all patients (55%) received only one surgery (41% mastectomy, 38% lumpectomy). In the adjuvant setting, 1,261 (52%) patients received chemotherapy (36% anthracycline, 33% taxane). DE had lowest rate of adjuvant chemotherapy (38%) and IT the highest (68%). Overall, adjuvant endocrine therapy was prescribed in 1,509 (62%) patients, with the highest rate observed in DE (74%) and lowest rate in the UK (53%) and JP (54%). Among first adjuvant endocrine treatments, 19% and 38% of patients aged ≤50 at initiation received an aromatase inhibitor or tamoxifen, respectively. In patients aged >50 at initiation, aromatase inhibitor and tamoxifen use in endocrine therapy was 52% and 10%, respectively. Overall, rates of aromatase inhibitor use ranged from 33% (JP, DE, UK) to 48% (IT); tamoxifen use ranged from 8% (IT) to 32% (DE).

Conclusions: This study describes real-world treatment patterns among patients with HR+/HER2- early stage BC across seven countries. Chemotherapy use is generally high in the neoadjuvant setting but varies in the adjuvant setting across countries. Approximately 50-75% of patients received adjuvant endocrine therapy, indicating a potential treatment gap among this HR+ patient population.

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83P Impact of treatment duration of extended adjuvant therapy with neratinib in early stage HER2+ HR+ breast cancer after trastuzumab-based therapy on patient outcomes

M. Martin Jimenez[1], M.I. Gnant[2], B. Ejlertsen[3], J.L. Mansi[4], M. Ruiz-Borrego[5], E.H. Jakobsen[6], C.K. Osborne[7], R. Birhiray[8], B. Zhang[9], A. Wong[10], B. Moy[11], F.A. Holmes[12]

[1]Department Servicio de Oncologia Médica, Hospital General Universitario Gregorio Marañon, Madrid, Spain; [2]Department of Surgery and Comprehensive Cancer Center, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria; [3]Clinical Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [4]Oncology, Guy's and St. Thomas' Hospital NHS Trust, London, UK; [5]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain; [6]Oncology, Vejle Hospital Sygehus Lillebaelt, Vejle Sygehus, Vejle, Denmark; [7]Oncology, Texas Oncology, Dallas, TX, USA; [8]Oncology, Hematology/Oncology of Indiana, Indianapolis, IN, USA; [9]Statistics, PUMA Biotechnology, San Francisco, USA; [10]Clinical Science and Pharmacology, PUMA Biotechnology, San Francisco, USA; [11]Medical Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [12]Breast Medical Oncology, Texas Oncology, Fort Worth, TX, USA

Background: ExteNET, an international, randomized, placebo-controlled phase III trial, showed that extended adjuvant neratinib given for 12 months after trastuzumab-based adjuvant therapy significantly improved 2-year (HR=0.50, p=0.003) and 5-year (HR=0.58, p=0.002) invasive disease-free survival (iDFS) in early-stage HER2+ and hormone-receptor positive (HR+) breast cancer. We explored the impact of treatment duration on outcomes in the ITT population and in the subgroup of patients (pts) with HR+ disease who started neratinib <1 year after prior trastuzumab (EU label population).

Methods: Pts with early-stage HER2+ breast cancer received oral neratinib 240 mg/day or placebo for 12 months (or until disease recurrence or unacceptable toxicity) after trastuzumab-based adjuvant therapy. Pts who received neratinib for ≤3 or ≥11 months (including those who had recurrence prior to 11 months) were compared with the ITT placebo group. iDFS (primary endpoint) and secondary endpoints (DCIS, DDFS, time to distant recurrence, and 5-year CNS recurrence) were analyzed using Kaplan-Meier methods and Cox proportional-hazards models adjusted for prognostic factors. Data cut-off: March 1, 2017.

Results: There were 2840 pts in the ITT population and 1334 patients who were HR+, <1-year. The table shows iDFS findings for HR+, <1-year pts and stratified by treatment duration (≤3, ≥11 months). Greater benefit was seen in pts who stayed on treatment for ≥11 months when compared to pts who received ≤3 months of treatment. Similar findings were seen for secondary endpoints.

Table 83P

Duration	N		5-year iDFS rate, %			
	Neratinib	Placebo	Neratinib	Placebo	Difference	HR (95% CI)
EU label population	670	664	90.8	85.7	+ 5.1%	0.58 (0.41-0.82)
≤3 months	201	664	85.9	85.7	+ 0.2%	0.88 (0.51-1.42)
≥11 months	402	664	93.1	85.7	+ 7.4%	0.44 (0.28-0.68)

Conclusions: These exploratory data suggest that pts who received a longer duration of treatment with neratinib (≥11 months) derived greater benefit compared to those who stopped treatment early (≤3 months). Patients who receive recommended duration of treatment with neratinib of 12 months may have improved outcomes when compared to patients who discontinue early (within 3 months).

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Legal entity responsible for the study: PUMA Biotechnology.

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84P Actual 5-year survival of dose-dense sequential adjuvant chemotherapy in early breast cancer (BC) patients treated in the post-trastuzumab era: A pooled analysis of 3 clinical trials

E. Aravantinou Fatorou, G-A. Koliou, F. Zagouri, L. Kostadima, H. Gogas, D. Pectasides, I. Binas, A. Koutras, G. Aravantinos, A. Psyrri, G.L. Lazaridis, D. Bafaloukos, E. Saloustros, C. Karanikiotis, I.B. Bombolaki, E. Razis, A. Koumarianou, P. Papakostas, P. Kosmidis, G. Fountzilas

Oncology, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece

Background: The addition of trastuzumab (T) in dose-dense (dd) sequential (s) chemotherapy (CT) has been found to improve the outcome of patients (pts) with HER2(+) BC. We aimed to evaluate the 5-year survival benefit of dds-CT in pts treated in the post-trastuzumab era.

Methods: We analyzed 3,026 pts diagnosed with operable BC between 2005 and 2013, treated with dds-CT within one randomized and two observational HeCOG trials. Pts with HER2(+) disease had received T for 1 year. Hormonal and radiation therapy were administered, as indicated.The primary endpoints were disease-free survival (DFS) and overall survival (OS).

Results: In total, 59.7% of pts had Hormone receptor (HR)(+)/HER2(-)(luminal) tumors, 25.5% had HER2(+) disease, and 14.5% had triple-negative breast cancer (TNBC). T was administered in 95.5% of pts with HER2(+) disease. At a median follow-up of 7.4 years, the 5-year DFS rate of pts with HER2(+) and luminal tumors was 88%, respectively, as compared to 83% for those with TNBC. The 5-year OS rate was 93% for pts with HER2(+) disease, 92% for luminal and 87% for TNBC. Pts with luminal disease had the greatest 5-year DFS rates both among women with positive and negative nodes (86% and 95%, respectively), followed by pts with HER2(+) BC (83% and 94%, respectively) and TNBC (76% and 89%, respectively).The 5-year OS rate of pts with HER2(+) and luminal disease was 91%, respectively among pts with positive nodes and 97%, respectively in pts with node-negative BC. The 5-year OS rate of TNBC pts with node-negative disease was 92%.

Conclusions: Trastuzumab is a part of one of success stories in Oncology, as its use dramatically improved the prognosis of HER2(+) pts. In this study, the outcomes of pts with HER2(+) BC were similar to those with luminal tumors, while TNBC remained the most unfavorable group.

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85P Racial differences in predictive value of 21-gene recurrence score assay: A population-based study using the SEER database

J. Jung[1], H. Kim[2], K-T. Hwang[3]

[1]Surgery, Seoul Medical Center, Seoul, Republic of Korea; [2]Radiation Oncology, Boramae Medical Center, Seoul, Republic of Korea; [3]Surgery, Boramae Medical Center, Seoul, Republic of Korea

Background: The 21-gene recurrence score (RS) assay is included in treatment guidelines for predicting adjuvant chemotherapy benefit for early-stage breast cancer patients with hormone-receptor (HR) positive disease. However, there has been no consideration regarding racial difference of that predictive value, although the assay had developed based on mainly Western women. This study aimed to demonstrate the racial differences in the predictive values of 21-gene RS assay.

Methods: T1-2N0 HR-positive breast cancer patients who had results of 21-gene RS were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Breast cancer-specific mortality (BCSM) was compared between patients who had adjuvant chemotherapy (the "CTx group") and who did not (the "no CTx group") to estimate predictive value of the assay. That comparison was repeated within each racial group (Whites, Blacks, other races).

Results: The SEER database included 89,402 T1-2N0 HR-positive breast cancer patients who had results of 21-gene RS. Among them, 13,193 patients had RS 26-100, which includes 10,697 Whites, 1,282 Blacks, and 1,144 other races respectively. Adjuvant chemotherapy was given to 8,364 (63.4%) patients. Adjusted hazard ratio for BCSM in the CTx group (relative to the no CTx group) was 0.732 (95% confidence interval[CI]: 0.587—0.915) in Whites, 0.695 (95% CI: 0.396-1.217) in Blacks, and 1.422 (95% CI: 0.580-3.487) in other races respectively. No subgroup in non-White women showed predictive value of the 21-gene assay within patients with RS 26-100 except Black women with grade 3 disease.

Conclusions: The predictive value of the 21-gene RS assay assessing adjuvant chemotherapy benefit was validated in White women based on the SEER database, although that predictive value was not warranted in non-White women.

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86P Patients (pts) preference for different administration methods of trastuzumab (T) in pts with HER2+ early breast cancer (BC) treated within the GAIN-2 trial

M. Reinisch[1], M. Untch[2], T. Reimer[3], R.J.C. Mahlberg[4], M. Aydogdu[5], T. Hitschold[6], C. Jackisch[7], F. Marmé[8], H-J. Lück[9], E. Ladda[10], S. Schmatloch[11], M. Schmidt[12], P. Klare[13], B.V. Sinn[14], E. Stickeler[15], S. Seiler[16], J. Rey[16], N. Klutinus[17], V. Möbus[18], S. Loibl[16]

[1]Breast Unit, Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany; [2]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin Buch, Berlin, Germany; [3]Universitätsfrauenklinik, Klinikum Südstadt Rostock, Rostock, Germany; [4]Innere Medizin I, Klinikum Mutterhaus der Borromäerinnen, Trier, Germany; [5]Klinik für Gynäkologie, Klinikum Bremen-Mitte, Bremen, Germany; [6]Frauenklinik, KLinikum Worms, Worms, Germany; [7]Gynäkologie und Geburtshilfe, Sana Klinikum Offenbach GmbH, Offenbach am Main, Germany; [8]Gynecologic Oncology, UMM - Universitaetsklinikum Mannheim - Medizinische Fakultaet, Mannheim, Germany; [9]Private Practice, Gynäkologisch-Onkologische Praxis, Hannover, Germany; [10]Private Practice, Onkologische Praxis Neumarkt, Neumarkt, Germany; [11]Brustzentrum, Elisabeth Krankenhaus Kassel, Kassel, Germany; [12]Gynaecology, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany; [13]Krebsheilkunde für Frauen, Praxisklinik Berlin, Berlin, Germany; [14]Institut für Pathologie, Charité - Universitätsmedizin Berlin, Berlin, Germany; [15]Department of Gynecology and Obstetrics, Universitaetsklinikum Aachen (UKA), Aachen, Germany; [16]Department Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [17]Frauenheilkunde, HELIOS Klinikum Pforzheim, Pforzheim, Germany; [18]Medizinische Klinik II, Abtlg.Hämatologie/Onkologie, Universitätsklinikum Frankfurt, Frankfurt, Germany

Background: The Hannah trial proofed equivalent efficacy of T (600mg q3w) for subcutaneous (sc) injection into the thigh versus (vs) intravenous (iv) administration in early BC. This trial allowed sc injection only into the thigh. The aim of this analysis was to evaluate pts preference for different routes of administration of T.

Methods: Within the GAIN-2 trial a prospective, multicenter, randomized phase II T sc substudy was performed. HER2+ BC pts who have received T iv simultaneously to (neo) adjuvant chemotherapy were randomized (1:1) to receive postoperatively T 600mg sc either into the thigh or abdominal wall (AW). Co-primary endpoint was pts preference for previous iv administration vs sc injection (thigh/AW) and pharmacokinetic profiles of T sc (thigh/AW). Safety, compliance and factors influencing the preferences were also analyzed. Pts preference was assessed by patient interviews (PINT) before randomization (PINT1) and after 8 cycles of T sc (PINT2). A modified intention-to-treat (mITT) analysis was conducted for randomized pts with at least one dose of T sc.

Results: 219 pts represented the mITT set (thigh 110; AW 109). Baseline characteristics were well balanced between the treatment groups. 182 pts (83.1%) replied to PINT2. Of them overall 83.5% (95% CI 78.1, 88.9) preferred administration of T sc (thigh 80.6% [95% CI 72.6, 88.7]; AW 86.5% [95% CI 79.4, 93.6], p=0.322). 23 pts (thigh 15; AW 8) had no preference. The expected preferences given in PINT1 (iv/no preference vs sc) showed a significant influence on the preference of the application site given in PINT2 (univariate analysis; OR 1.12 [95% CI 1.03-1.21]; p=0.007). No increased toxicity was observed and the study compliance was comparable (thigh vs AW). T sc injections were generally described as acceptable by the majority of patients.

Conclusions: We confirmed, as previously demonstrated in the PrefHer study (Pivot et al. 2014), that the sc regimen is preferred over iv regimen by pts. There were no safety signals or differences in compliance regarding the different areas of sc injection. Due to higher bioavailability (Möbus et al. 2017) thigh remains the preferred site of injection.

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87P Patient-reported and cancer-specific health-related quality of life among patients with early stage HR+/HER2- breast cancer (BC)

C. Criscitiello[1], D. Spurden[2], A. Rider[3], R. Williams[3], M. Corsaro[4], J. Pike[5], E.H. Law[6]

[1]Early Drug Development for Innovative Therapies Division, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]Patient & Health Impact, Pfizer Ltd, Walton Oaks, UK; [3]Disease Specific Programme, Adelphi Real World, Bollington, UK; [4]Global Medical Affairs, Pfizer Italia s.r.l., Milan, Italy; [5]Statistics & Data Analytics, Adelphi Real World, Bollington, UK; [6]Global Health Economics & Outcomes Research (Oncology), Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA

Background: To describe and characterize cancer-specific health-related quality of life (HRQOL) among patients diagnosed with early stage HR+/HER2- BC.

Methods: A multinational (France, Germany, Italy, Japan, Spain, UK and US) survey of patients diagnosed with stage I-III HR+/HER2- BC was conducted from June to October 2019. Patients were identified by their consulting physician and invited to complete a pen and paper questionnaire. Patients completed the General and Breast version of the cancer-specific Functional Assessment of Cancer Therapy (FACT-G and -B) questionnaires. Mean FACT-G and FACT-B scores (overall and specific subscales) were calculated and compared by disease status (active adjuvant treatment vs. surveillance vs. recurrence) at the time of questionnaire completion using Mann-Whitney and Chi-Squared tests.

Results: 1,152 patients completed HRQOL questionnaires (mean age 59 years, treatment status at diagnosis: 76% active adjuvant treatment, 21% surveillance and 3% recurrence). Mean [standard deviation] FACT-G scores (62.2 [16.0]) for the recurrence group were significantly lower than mean scores for disease-free patients in active adjuvant treatment (72.8 [18.3]) or surveillance (71.3 [16.0]) groups. Mean FACT-B scores were also significantly lower for the recurrence group (86.4 [19.5]) compared to active adjuvant treatment (99.4 [22.5]) and surveillance groups (97.7 [19.7]). FACT subscale scores for physical, emotional and functional well-being were also the lowest among the recurrence group (all p-values <0.05).

Conclusions: Group-level differences in cancer-specific HRQOL were statistically significant, with disease-free patients in active adjuvant treatment or surveillance groups reporting higher HRQOL and well-being than patients in the recurrence group. These findings demonstrate the high burden of disease on HRQOL with recurrence among patients with early stage HR+/HER2- BC.

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88P Latent class analysis (LCA) to identify and describe clinically relevant subgroups in a multinational study of patients with HR+/HER2- early breast cancer (eBC)

A. Rider[1], D. Spurden[2], R. Williams[1], M. Corsaro[3], J. Pike[4], E.H. Law[5], C. Criscitiello[6]

[1]Disease Specific Programme, Adelphi Real World, Bollington, UK; [2]Patient & Health Impact, Pfizer Ltd, Walton Oaks, UK; [3]Global Medical Affairs, Pfizer Italia s.r.l., Milan, Italy; [4]Statistics & Data Analytics, Adelphi Real World, Bollington, UK; [5]Global Health Economics & Outcomes Research (Oncology), Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [6]Early Drug Development for Innovative Therapies Division, IEO, European Institute of Oncology IRCCS, Milan, Italy

Background: To identify and describe clinically meaningful subgroups based on clinical and pathologic disease characteristics during primary diagnosis and treatment of HR+/HER2- eBC.

Methods: Data was analyzed from a multinational (France, Germany, Italy, Japan, Spain, United Kingdom, United States) sample of patients with an initial diagnosis of stage I-III HR+/HER2- BC who were disease-free or in recurrence. LCA was used to cluster patients based on tumour size, nodal status, progesterone receptor status, and histological grade. Kruskal-Wallis and Chi-Squared tested differences across clusters by patient characteristics, treatment, and current disease status (disease-free vs. recurrent disease).

Results: From 1,512 eligible patients, four distinct clusters were identified potentially corresponding to levels of risk for disease-recurrence: Lowest (38%), Moderate (52%), Highest (6%), and Uncertain risk (4%). Risk groups differed by mean age (55 [Highest] to 62 years [Lowest]); node positive status: Lowest (4%), Moderate (47%), Uncertain (33%), Highest (69%); tumour size >5cm: Lowest (0%), Moderate (2%), Uncertain (87%), Highest (67%); and histological grade 2/3 at diagnosis: Lowest (31% / 7%), Moderate (70% / 25%), Uncertain (83% / 2%), Highest (0% / 99%). Stage II and III disease at diagnosis differed by cluster: Highest (21% and 77%), Uncertain (35% and 61%), Moderate (63% and 23%) and Lowest (30% and 4%). Use of neoadjuvant and adjuvant chemotherapy also varied; most common for Highest Risk (93% and 71%, respectively), least for Lowest Risk (79% and 23%, respectively). Highest and Uncertain risk groups were most likely to experience disease recurrence compared to Moderate and Lowest groups. All p-values $\leq$0.0001.

Conclusions: Patient clusters based on key disease characteristics at initial diagnosis of eBC were identified across 7 countries and may represent clinically relevant subpopulations. Clusters exhibiting the most advanced disease characteristics (Highest and Uncertain) corresponded well to stage II and III disease classification. Future research is required to confirm the predictive validity of these risk groups.

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89P Tamoxifen versus aromatase inhibitors as adjuvant therapy in premenopausal women with hormone receptor-positive breast cancer: Effects on sexuality and the female reproductive system

A. Skolariki[1], A. Boutis[1], E.K. Kosmidis[2]

[1]First Department of Medical Oncology, Theagenio Cancer Hospital, Thessaloniki, Greece; [2]Laboratory of Physiology, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: The objective of this cross-sectional study is to compare the prevalence of sexual dysfunction in premenopausal women with breast cancer in Greece, who receive adjuvant endocrine therapy with either tamoxifen or aromatase inhibitors (AI), with or without ovarian function suppression (OFS). A second endpoint is to investigate and compare the incidence of genitourinary symptoms and conditions.

Methods: A questionnaire was distributed on hardcopy and through an online platform from November 2018 to March 2019, to Greek-speaking women of 18 years of age or older, who had been receiving adjuvant endocrine therapy for breast cancer for at least three months and were deemed premenopausal/perimenopausal at diagnosis. The questionnaire included investigator-generated items regarding demographics, sexual and gynecologic history, as well as validated instruments for sexual functioning and urogenital tract disorders (FSFI, QLQ-BR23, UDI-6 and PFIQ-7).

Results: Of the 108 received responses, 70 were considered eligible for analysis. Most participants were currently on treatment with tamoxifen/OFS (N=35). Women on AI/OFS reported great deterioration of their sex life compared to women on tamoxifen with OFS (p=0.001). Sexual dysfunction was evident in 74% (N=49) of our participants, as defined by the cutoff value of 26 for the FSFI total score (median: 17.45, IQR=26.18). In particular, women on AI/OFS had significantly lower scores compared to those on tamoxifen with (20.8, 95%CI [14.58;22.67] vs 8.8, 95%CI [4.86;13.60], p=0.040) and without OFS (19.95, 95%CI [13;22.91] vs 8.8, 95%CI [4.86;13.60], p=0.039). Sexual enjoyment of women on AI/OFS was significantly affected compared to women on tamoxifen with or without OFS (p=0.019 and p=0.020, respectively). No differences in vaginal atrophy symptoms or gynecologic conditions were detected.

Conclusions: Sexual dysfunction is highly prevalent in premenopausal women on endocrine therapy, especially in those treated with aromatase inhibitors and ovarian function suppression. Health professionals should promote discussions with their patients in order to decide the optimal treatment choice.

Legal entity responsible for the study: Aristotle University of Thessaloniki, Thessaloniki, Greece Theagenio Cancer Hospital, Thessaloniki, Greece.

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90P Patient-reported outcomes among patients with HR+/HER2- early breast cancer: A systematic literature review

E.M. Salvo[1], J. Cueto[2], E.H. Law[3], C. Aniceto Da Silva[1], C. Cameron[4], I.A. Samjoo[1]

[1]Value & Evidence Division, Eversana, Burlington, ON, Canada; [2]Health Economics & Outcomes Research, Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [3]Global Health Economics & Outcomes Research (Oncology), Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [4]Value & Evidence Division, Eversana, Nova Scotia, NS, Canada

Background: This study reviewed published literature of patient-reported outcomes (PROs) associated with different treatment phases for patients with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) early breast cancer (BC).

Methods: A systematic literature review was conducted according to PRISMA guidelines to identify studies evaluating PROs among patients aged $\geq$18 years and diagnosed with HR+/HER2- eBC. Ovid MEDLINE, Embase, and Cochrane Evidence Based Medicine databases were searched between 2005 to 2019. Reported PRO measurements were summarized and categorized based on association with treatment (neoadjuvant, adjuvant, surgery), remission (or disease-free), and recurrence.

Results: Of 3,622 records evaluated, 10 studies reported PROs for HR+/HER2- eBC patients. Of these, 8 studies reported on cancer-specific health-related quality of life (HRQOL), 3 on general anxiety, and 5 on decisional conflict. Study treatments in the neoadjuvant setting included endocrine and targeted therapies. In the adjuvant/remission setting, studies investigated the use of either prognostic tests or hydrotherapy. Baseline and on-treatment HRQOL were available among patients receiving neoadjuvant therapy (4 studies) using the Functional Assessment of Cancer Therapy (General, Breast, and Endocrine Subscale modules) and European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ) C30 and -BR23 questionnaires. In the adjuvant setting (5 studies), baseline and post-administration of prognostic tests using general anxiety (State-Trait Anxiety Inventory) and/or decision conflict (Decision Conflict Scale) were measured. One study of hydrotherapy used the EORTC QLQ-BR23 to measure HRQOL during remission. No studies evaluated the relationship between PROs and disease recurrence.

Conclusions: Current literature indicates that PROs are either measured prior to surgery, during adjuvant therapy, or during remission with a lack of studies evaluating

PROs with disease recurrence. Future research is needed to fully articulate the disease- and treatment-related experiences across the patient journey in HR+/HER2- eBC.

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91P Gene expression profiling in localised luminal N+ breast cancer: Efficacy and utility of 50 gene expression platform in adjuvant treatment decision making

P. Tolosa Ortega[1], A. Sánchez-Torre[1], L. Carril-Ajuria[1], M. Herrera[1], Á. Ruiz[1], E. Bernal[1], L. Lema[1], L. Manso[1], E.M. Ciruelos[2]

[1]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Department Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain

Background: Gene expression profiles (GEP) represents a relevant tool to evaluate the best adjuvant approach for localised luminal breast cancer (BC) patients. Several platforms have been already validated for menopausal N0 patients, but the use among pre-menopausal, N+ population still needs further validation. The results obtained with Mammaprint® has suggested the possibility to adopt GEP to drive treatment decisions also in N+ population. Nevertheless, Prosigna™ is not yet prospectively validated to assess risk and personalise treatment in these patients.

Methods: To evaluate the impact in adjuvant treatment decision of Prosigna™ among BC patients diagnosed with N1a disease, a retrospective analysis was performed in our institution. Between November 2015 and November 2019, 56 patients (P) were finally selected and analysed as they met all the inclusion criteria, clinical characteristics are shown in the table. The objectives of the study were to evaluate the role of Prosigna in the decision-making process, and to identify, among all the parameters used to obtain the risk of recurrence (ROR) score, such as group of risk, intrinsic subtype and probability of relapse at 10 years, the parameter which mostly affected treatment decision.

Results: All the 56 P included would have been candidate to receive chemotherapy (CT) according to clinical practice. Using Prosigna™, it was possible to stratify risk and personalize the treatment by avoiding chemotherapy in in 29 P (51,8%). After a median follow-up of 18 months [range 3-43] no relapses were detected.

Table 91P

	All (n 56)	Luminal A n 42 (75%)	Luminal B n 12 (21,4%)	HER2-E n 1 (1,8%)	Basal-like n 1 (1,8%)
Menopausal status					
Premenopausal	15 (27%)	13 (31%)	1 (8%)	1 (100%)	0 (0%)
Postmenopausal	41 (73%)	29 (69%)	11 (92%)	0 (0%)	1 (100%)
Tumor size-cm:					
<1 1 to 1	5 (9%)	4 (9%)	0 (0%)	0 (0%)	1 (100%)
9 >1	28 (50%)	23 (55%)	5 (42%)	0 (0%)	0 (0%)
9 to 5	23 (41%)	15 (36%)	7 (58%)	1 (100%)	0 (0%)
Tumor grade:					
G 1	14 (25%)	13 (61%)	1 (8%)	0 (0%)	0 (0%)
G 2	37 (66%)	29 (69%)	8 (67%)	0 (0%)	0 (0%)
G 3	5 (9%)	0 (0%)	3 (25%)	1 (100%)	1 (100%)
Lymph-nodes:					
1	36 (64%)	26 (62%)	8 (37%)	1 (100%)	1 (100%)
2-3	20 (36%)	16 (48%)	4 (33%)	0 (0%)	0 (0%)
Ki-67-%:					
<=20	44 (79%)	35 (83%)	7 (58%)	1 (100%)	1 (100%)
>20	12 (21%)	7 (17%)	5 (42%)	0 (0%)	0 (0%)

Conclusions: GEP has improved precision medicine for BC and Prosigna™ showed ability to induce changes in decision making in up to 51,8% of N+ tumours. Further validation of its role in N+ disease will be evaluated in prospective ongoing trials.

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93P Clinical and genetic predictions of early-onset cardiac toxicity in adjuvant chemotherapy for breast cancer

B. Liu[1], X. Guan[1], Y. Wang[2], X. Sun[3], Z. Yi[1], W. Wang[1], L. Li[1], J. Zhai[1], H. Li[4], F. Ma[1]

[1]Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Comprehensive Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Medical Oncology, Cancer Hospital of Huanxing, Beijing, China; [4]Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Background: Although cardiotoxicity has been widely concerned, clinical factors are often insufficient to accurately predict early-onset cardiac toxicity with low cumulative dose of chemotherapy drugs. Our research is to identify clinical and genetic variants associated with early-onset cardiac toxicity in breast cancer and to establish an ideal predictive risk model.

Methods: A total of 388 recruited patients completed routine blood, liver and kidney function, D-dimer, troponin T, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Electrocardiogram (ECG) and Echocardiography (UCG) tests before and after adjuvant chemotherapy. Twenty-five single nucleotide polymorphisms (SNPs) were tested. Univariable and multivariable analyses were performed to identify independent risk factors. The accuracy and discriminative ability of the predictive models, which included genetic and clinical risk factors, were determined by the area under the receiver operating characteristic (ROC) curve (AUC) and calibration plots.

Results: A total of 277 adjuvant chemotherapy-related cardiac toxicity events were recorded in 180 patients (46.4%), including an abnormal ECG (37.4%), an abnormal UCG (9.3%), an elevated NT-proBNP (5.7%), and elevated myocardial enzymes (0.3%). Anthracycline-containing chemotherapy ([OR]= 1.698; 95% CI: 1.118-2.579; P=0.013) and the SLC28A3 (rs885004) GG genotype ([OR]=2.073; 95% CI: 1.207-3.560; P=0.008) were found to be associated with overall cardiac toxicity. The predictive risk model consisted of the anthracycline-containing chemotherapy, pathology and genotype of SLC28A3 (rs885004). The ROC of the new model was 0.604 (0.548-0.660), p=0.000. A good calibration was also shown in the calibration plot.

Conclusions: Early-onset cardiac toxicity is quite common in the real world. A prediction model combining SNPs and clinical risk factors might be able to assess the risks of early-onset cardiac toxicity.

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Legal entity responsible for the study: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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Disclosure: All authors have declared no conflicts of interest.

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94P Integration of clinicopathological and genomic data and adjuvant treatment decisions in premenopausal women with recurrence scores between 16 and 25

M.E. Alsendi, M. Lucas, W.M.Z. Darwish, M. Higgins, C. Kelly

Medical Oncology, The Mater Misericordiae University Hospital, Dublin, Ireland

Background: Data from the TAILORx trial show a three way interaction between age, chemotherapy and recurrence score (RS). By integrating clinical risk and genomic information women under 50 years with high risk cancers and recurrence scores(RS) between 16 and 25 may derive an absolute benefit from chemotherapy (CT) of between 6-9%. This benefit may be due to CT-induced menopause. The addition of ovarian suppression (OS) to endocrine therapy (ET) in premenopausal women at high risk of breast cancer (BC) recurrence is better than ET alone (SOFT/TEXT). It is has been proposed that ET/OS may be a rational option for premenopausal patients with clinically high risk breast cancer BC and a RS between 16-25 or a clinically low risk BC with a RS between 21-25. The predicted risk of distant recurrence for these patients is 14.7% (+/-3.1%) and 11.4% (+/-3.9%) respectively. The objective of our study was to determine the proportion of premenopausal patients (pts) with a RS between16-25 and a clinically high or low risk BC.

Methods: We extracted the following on all pts with ER-positive, HER2-negative, node negative BC who had OncotypeDx testing as part of routine care between 2013-9; RS, age, menopausal status, tumour size, grade, adjuvant treatment. We classified pts as low or high clinical risk (CR) using the MINDACT criteria.

Results: 325 patients had OncotypeDx testing between 2013-9. Of these 55 were < 50 years (17%) and were premenopausal at diagnosis. Of these 7 (13%) had a RS between 16-25 and a high CR BC and 3 (1%) had a RS between 21-25 and low CR BC. ET alone was given to 41 (73%) and 15 (27%) received CT and ET. Three (1%) patients received ET/OS.

Conclusions: Using integrated clinicopathological and genomic data, we found that almost 15% of our premenopausal pts had a RS between 16-25 and a high clinical risk BC or a RS between 21-25 and a low clinical risk BC. These patients have a predicted risk of distant recurrence of between 11-15% and therefore an additional therapy to

reduce their risk is warranted. Most of these women received tamoxifen only, under a third received CT and only 1% received ET with OS. The recent data from TAILORx and the SOFT/TEXT trials would support a discussion about the addition of OS as a way to further reduce risk.

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95TiP Gruppo Italiano Mammella (GIM) 10 — CONSENT: A phase III randomized study comparing concurrent versus sequential administration of adjuvant chemotherapy (CT) and aromatase inhibitors (AIs) in post-menopausal patients (pts) with hormone receptor-positive (HR+) early breast cancer (EBC)

M. Lambertini[1], V. Guarneri[2], E.R. Caremoli[3], A. Rocca[4], F. Montemurro[5], M. De Laurentiis[6], M. Giordano[7], S. De Placido[8], G. Bisagni[9], O. Garrone[10], A. Ferzi[11], F. Giovanardi[12], F. Cognetti[13], L. Amaducci[14], A. Bernardo[15], L. Livi[16], C. Bighin[1], F. Poggio[17], A. Ballestrero[18], L. Del Mastro[19]

[1]Breast Unit, IRCCS Ospedale Policlinico San Martino - University of Genoa, Genoa, Italy; [2]Department of Surgery, Oncology and Gastroenterology, Istituto Oncologico Veneto IRCCS, Padua, Italy; [3]Medical Oncology, ASST Papa Giovanni XXIII, Bergamo, Italy; [4]Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [5]Multidisciplinary Outpatient Oncology Clinic, Istituto di Candiolo - FPO - IRCCS, Candiolo, Italy; [6]Medical Oncology, Istituto Nazionale Tumori "Fondazione G. Pascale", Naples, Italy; [7]Medical Oncology, Ospedale Sant'Anna, Como, Italy; [8]Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [9]Department of Oncology and Advanced Technologies, Oncology Unit, Azienda USL-IRCCS, Reggio Emilia, Italy; [10]Medical Oncology, Azienda Ospedaliera St. Croce e Carle, Cuneo, Italy; [11]Medical Oncology, Ospedale Civile, Legnano, Italy; [12]Medical Oncology, IRCCS AUSL Reggio Emilia, Guastalla, Italy; [13]Medical Oncology, Istituto Nazionale Tumori Regina Elena, Rome, Italy; [14]Medical Oncology, Presidio Ospedaliero di Faenza, Faenza, Italy; [15]Medical Oncology, Fondazione S. Maugeri IRCCS, Pavia, Italy; [16]Radiotherapy Department, AUC Careggi, Florence, Italy; [17]IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy; [18]Department of Internal Medicine, Università degli Studi di Genoa and Ospedale Policlinico San Martino IRCCS, Genoa, Italy; [19]Internal Medicine Department, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

Background: In pts with HR+ EBC who are candidates to receive adjuvant CT, endocrine therapy (ET) is currently administered following CT completion. This recommendation is based on preclinical and clinical data suggesting a potential negative interaction between tamoxifen and CT when given concomitantly. However, there is no evidence to support this recommendation with the use of modern CT regimens containing taxanes or when AIs are given as adjuvant ET. Therefore, the optimal timing for integrating modern adjuvant CT and ET with AIs has not been defined yet.

Trial design: GIM 10 — CONSENT is an ongoing prospective, two-arm randomized, multicenter, open-label, phase III trial in postmenopausal pts with surgically removed HR+ EBC who are candidates to adjuvant CT. Pts with HER2+ BC are eligible only if scheduled to receive adjuvant trastuzumab. Pts are randomized 1:1 to receive ET with an AI following completion of CT (sequential arm) or concurrently with CT (concurrent arm). The choice of CT regimen is at physician discretion; anastrozole, letrozole or exemestane are given for at least 5 years. Primary study endpoint is disease-free survival (DFS). Invasive DFS, distant DFS, distant relapse-free survival, overall survival and toxicity are secondary endpoints. Tumor collection is performed in pts defined at clinical intermediate risk (stage I-II HR+ G2) for future translational studies aiming to analyze their genomic, epigenetic and proteomic landscape. After final amendment, study hypothesis is that concurrent administration of CT and ET will be associated with a 25% relative reduction in the hazard of recurrence, with a 9.4% absolute increase in 10-year DFS. For a type I error level of .05 (two sided) and 80% power, 500 pts per arm are required to observe 350 events presumably after 5.5 years of follow-up. The study is ongoing at 55 GIM centers. Accrual was completed in June 2019 with 1,014 randomized pts; follow-up is currently ongoing.

Clinical trial identification: 2013-001629-23; NCT02918084.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EARLY BREAST CANCER: NEOADJUVANT THERAPY

96O Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2+ breast cancer: Subgroup analysis from KATHERINE

S. Loibl[1], C-S. Huang[2], M.S. Mano[3], T.P. Mamounas[4], C.E. Geyer[5], M. Untch[6], G. von Minckwitz[7], J-C. Thery[8], I. Schwaner[9], S. Limentani[10], N. Loman[11], K. Lübbe[12], J.C. Chang[13], T. Hatschek[14], D. Tesarowski[15], T. Boulet[16], C. Wiese[17], C. Song[15], N. Wolmark[18]

[1]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [2]Department of Surgery, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Oncology Department, Hospital Sirio Libanes, Sao Paulo, Brazil; [4]Department of Surgery, University of Central Florida, Orlando, FL, USA; [5]Internal Medicine, Houston Methodist Cancer Center, Houston, TX, USA; [6]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany; [7]German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [8]Medical Oncology, Centre Henri Becquerel, Cancer Center, Rouen, France; [9]Hematology/Medical Oncology, Onkologische Schwerpunktpraxis Kurfürstendamm, Berlin, Germany; [10]Cancer Institute, Novant Health, Charlotte, NC, USA; [11]Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden; [12]Gynecological Oncology, Diakovere Henriette Stift Hannover, Hannover, Germany; [13]Cancer Center, Houston Methodist Hospital, Houston, TX, USA; [14]Department of Oncology-Pathology, Karolinska University Hospital, Solna, Sweden; [15]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA; [16]Biometrics, F. Hoffmann-La Roche, Basel, Switzerland; [17]Product Development Safety, F. Hoffmann-La Roche AG, Basel, Switzerland; [18]Medical Affairs, NSABP Foundation and University of Pittsburgh, Pittsburgh, PA, USA

Background: In the phase 3 KATHERINE study (NCT01772472) adjuvant T-DM1 reduced the risk of invasive disease recurrence or death by 50% compared to adjuvant T in pts with residual invasive breast cancer after neoadjuvant chemotherapy plus HER2-targeted therapy. Here we present subgroup analyses: adjuvant radiotherapy (ART) vs no-ART; hormone receptor (HR)+ vs HR−/unknown disease; and HER2− status on retesting of a surgical specimen.

Methods: Pts were randomized to 14 q3w cycles of adjuvant T-DM1 (3.6 mg/kg) or T (6 mg/kg) with ART and hormonal therapy (HT) administered per local standards. Efficacy is reported according to tumor HR status; and safety according to HT received. The primary endpoint was invasive disease-free survival (IDFS). HER2 status was centrally assessed on available paired pre-neoadjuvant and surgical samples.

Results: Most pts received ART (82%) and/or HT (71%). IDFS benefit was consistent regardless of ART or HR status (Table). There were more grade ≥3 AEs (27.4% vs 16.2%) and serious AEs (13.2% vs 10.3%) with T-DM1 in the ART vs no-ART group. There were similar rates of grade ≥3 AEs (24.9% vs 26.0%) and serious AEs (12.2% vs 12.9%) with T-DM1 in the no-HT and HT groups. Of 845 pts with paired pre-neoadjuvant biopsy and surgical HER2 status data, 70 (8.3%) had residual disease which was considered HER2− (ie, HER2− or IHC 0-1+/ISH unk) on retesting. In this group, there have been no IDFS events among pts randomized to T-DM1 (n=28), and 11 events in pts randomized to T (n=42).

Table 96O

	3-yr IDFS (95% CI)	Unstratified hazard ratio (95%CI)
T ART	77.4% (73.8−83.9)	0.50 (0.38−0.66)
T-DM1 ART	88.3% (85.5−91.0)	
T no-ART	75.5% (67.6−83.5)	0.50 (0.27−0.93)
T-DM1 no-ART	88.2% (82.2−94.2)	
T HR+	80.7% (77.2−84.3)	0.48 (0.35−0.67)
T-DM1 HR+	90.7% (88.1−93.4)	
T HR−/unknown	66.6% (59.5−73.6)	0.50 (0.33−0.74)
T-DM1 HR−/unknown	82.1% (76.7−87.5)	

Conclusions: No new safety signals were observed with concomitant ART or HT. Exploratory HER2 analysis of paired specimens, suggests that T-DM1 should not be withheld in pts with HER2− residual disease at surgery. Thus HER2 retesting of residual disease may be unnecessary in this population.

Clinical trial identification: NCT01772472.

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C-S. Huang: Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Amgen; Advisory/Consultancy, Research grant/Funding (institution): Eli Lilly; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Speaker Bureau/Expert testimony, Research grant/Funding (institution): Novartis; Research grant/Funding (institution): EirGenix; Research grant/Funding (institution): OBI Pharma; Research grant/Funding (institution), Travel/Accommodation/Expenses: AstraZeneca; Research grant/Funding (institution): MSD; Research grant/Funding (institution): Daiichi Sankyo. M.S. Mano: Honoraria (self), Honoraria (institution), Travel/Accommodation/Expenses: Roche; Honoraria (self), Advisory/Consultancy: Novartis; Honoraria (self), Advisory/Consultancy: Lilly-Imlcone; Honoraria (self): Oncologia Brasil; Advisory/Consultancy: Amgen; Honoraria (self): DASA; Advisory/Consultancy, Travel/Accommodation/Expenses: Pfizer; Advisory/Consultancy: AstraZeneca; Shareholder/Stockholder/Stock options: Biotoscana; Shareholder/Stockholder/Stock options: Hypera; Shareholder/Stockholder/Stock options: Fleury. T.P. Mamounas: Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Genentech/Roche; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Exact Sciences (Genomic Health); Advisory/Consultancy: Merck; Advisory/Consultancy: Daiichi Sankyo; Advisory/Consultancy: Biotheranostics. C.E. Geyer: Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses, Non-remunerated activity/ies, Medical writing and uncompensated advisory boards: Genentech/Roche; Advisory/Consultancy, Travel/Accommodation/Expenses, Non-remunerated activity/ies, Uncompensated consulting and advisory board: Daiichi-Sankyo; Advisory/Consultancy, Travel/Accommodation/Expenses, Uncompensated advisory board: AstraZeneca; Advisory/Consultancy, Non-remunerated activity/ies, Uncompensated advisory board: Seattle Genetics; Non-remunerated activity/ies, Medical writing: AbbVie; Advisory/Consultancy, Non-remunerated activity/ies, Uncompensated consulting: Athenex. M. Untch: Advisory/Consultancy, all fees to the employer/institution: AbbVie; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: AstraZeneca; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Celgene; Advisory/Consultancy, all fees to the employer/institution: Daiichi Sankyo; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Amgen; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Lilly; Advisory/Consultancy, all fees to the employer/institution: MSD Merck; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Mundipharma; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Myriad Genetics; Advisory/Consultancy, all fees to the employer/institution: Odonate; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Pfizer; Advisory/Consultancy, all fees to the employer/institution: Puma Biotechnology; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Roche Pharma; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Sanofi Aventis; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Novartis; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Pierre Fabre; Honoraria (institution), Advisory/Consultancy, all fees to the employer/institution: Clovis. 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Loman: Honoraria (institution): Roche; Honoraria (institution): Pierre Fabre; Honoraria (institution): AstraZeneca; Honoraria (institution): MSD. K. Lübbe: Advisory/Consultancy: Roche; Advisory/Consultancy: Lilly; Advisory/Consultancy: Novartis; Advisory/Consultancy: Pfizer. J.C. Chang: Advisory/Consultancy: Lilly USA; Advisory/Consultancy: Genentech; Advisory/Consultancy: Celgene. T. Hatschek: Honoraria (self), Advisory/Consultancy: Roche Sweden; Honoraria (self), Advisory/Consultancy: Pfizer Sweden; Honoraria (self), Advisory/Consultancy: Pierre Fabre; Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Research grant/Funding (institution): Pfizer. D. Tesarowski: Full/Part-time employment: Genentech. T. Boulet: Full/Part-time employment: F. Hoffmann-La Roche. C. Wiese: Shareholder/Stockholder/Stock options, Full/Part-time employment: F. Hoffmann-La Roche. C. Song: Shareholder/Stockholder/Stock options, Full/Part-time employment: F. Hoffmann-La Roche. 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97O PREDIX HER2 trial: Event-free survival and pathologic complete response in clinical subgroups and stromal TILs levels

T. Hatschek[1], A. Andersson[2], J. Bjöhle[3], A. Bosch[4], L. Carlsson[5], A.C. Dreifaldt[6], Z. Einbeigi[7], E. Elinder[8], H. Fredholm[9], E. Isaksson-Friman[10], M. Hellström[11], H. Johansson[11], T. Lekberg[12], H. Lindman[13], I. Zerdes[14], T. Foukakis[15], J. Hartman[16], Y. Brandberg[17], J. Bergh[18]

[1]Oncology, Karolinska Solna - Karolinska Universitetssjukhuset, Solna, Sweden; [2]Oncology, Norrlands University Hospital, Umeå, Sweden; [3]Oncology, Karolinska University Hospital, Solna, Sweden; [4]Oncology, Lund University, Lund, Sweden; [5]Oncology, Länssjukhuset Sundsvall, Sundsvall, Sweden; [6]Oncology, Örebro University Hospital, Örebro, Sweden; [7]Oncology, Sahlgrenska University Hospital, Göteborg, Sweden; [8]Oncology, Södersjukhuset, Stockholm, Sweden; [9]Surgery, Karolinska University Hospital, Solna, Sweden; [10]Oncology, Capio St Görans Hospital, Stockholm, Sweden; [11]Clinical Trials Unit, Karolinska University Hospital, Stockholm, Sweden; [12]Oncology, Karolinska University Hospital, Stockholm, Sweden; [13]Oncology, University Hospital Uppsala Akademiska Sjukhuset, Uppsala, Sweden; [14]Oncology-Pathology Department, Nya Karolinska Solna, Godsmottagning, Solna, Sweden; [15]Oncology, Karolinska Universitetssjukhuset - Radiumhemmet, Solna, Sweden; [16]Pathology, Södersjukhuset, Stockholm, Sweden; [17]Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [18]Oncology-Pathology Department, Karolinska Institutet - Bioclinicum, Solna, Sweden

Background: Neoadjuvant treatment with Trastuzumab-emtansine was associated with similar rates of pathological complete remission (pCR) as standard therapy with docetaxel, trastuzumab and pertuzumab in the PREDIX HER2 trial. Here, results of event-free survival (EFS), and pCR rates in key clinical-pathological subgroups and biomarkers including the abundance of stromal tumor infiltrating lymphocytes (TILs) are presented.

Methods: PREDIX HER2 is a randomized, multicenter, open-label, phase 2 study involving 9 Swedish sites. Patients with HER2 positive breast cancer, verified by ISH, T >20 mm and/or verified lymph node metastases were randomized to six three-weekly courses of either docetaxel, trastuzumab SC and pertuzumab (group A), or trastuzumab emtansine (T-DM1, group B). Switch of treatment to the opposite arm was allowed in case of lack of response or severe toxicity. Radiological evaluation included 18F-FDG PET/CT. Patients in both groups received adjuvant chemotherapy with epirubicin and cyclophosphamide. TILs were evaluated using standard methodology, median 10%.

Results: In total 197 pts. were evaluable, 99 in group A, and 98 in group B. pCR (ypT0/is ypN0) was achieved in 90 pts, 45.7%, with no significant difference between the two treatment groups. pCR rates were lower in the group of patients with hormone receptor (HR)—positive compared with HR-negative tumors but similar in both treatment groups. pCR rates did not differ between the two treatments in subgroups defined by age, menopausal status, tumor grade, T size, node status, HR-status, HER2 status and Ki67. Progressive disease was observed in 3 pts. (3%) during treatment with T-DM1, none in group A. After a median follow-up of 2.4 years 13 EFS events occurred, with no significant differences between the treatment groups. The presence of ≥10% TILs predicted pCR significantly (p=0.009), similar in both treatment groups. We also found that a decrease of SUVmax by more than 80% was highly predictive of pCR. HRQoL was significantly better in pts. receiving T-DM1.

Conclusions: Our data suggest that neoadjuvant T-DM1 may be as effective as standard neoadjuvant treatment in all clinical subgroups evaluated. Both TILs and PET/CT showed potential to predict pCR.

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98O The immunomodulatory (IM) signature enhances prediction of pathologic complete response (pCR) to neoadjuvant therapy (NAT) in triple negative breast cancers (TNBC) with moderate stromal tumour infiltrating lymphocytes (sTIL)

N. Abuhadra[1], R. Sun[2], J.K. Litton[1], G. Rauch[3], A.M. Thompson[4], B. Lim[1], B. Adrada[3], E. Mittendorf[5], S. Damodaran[6], R. Pitpitan[3], B. Arun[7], J. White[1], E. Ravenberg[1], L. Santiago[3], A. Sahin[8], R. Murthy[6], N.T. Ueno[1], N. Ibrahim[1], S. Moulder[1], L. Huo[8]

[1]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Biostatistics, MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Breast Surgical Oncology, Baylor College of Medicine, Houston, TX, USA; [5]Surgery, Brigham and Women's Hospital, Boston, MA, USA; [6]Breast Medical Oncology, The MD Anderson Cancer Center, Houston, TX, USA; [7]Breast Medical Oncology and Clinical Cancer Genetics, The MD Anderson Cancer Center, Houston, TX, USA; [8]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: In TNBC, the IM signature is highly enriched in immune cell markers and signaling which likely represents gene expression from both the tumor cells and infiltrating lymphocytes. High sTIL is independently associated with improved pCR rates in TNBC. The association between the IM subtype and sTIL in predicting pCR is not known.

Methods: Pretreatment core biopsies from 181 patients with early-stage TNBC enrolled on the ARTEMIS trial (NCT02276443) were evaluated for sTIL by H&E and Vanderbilt subtype using Affymetrix arrays and TNBCtype. sTIL was graded as low (<10%), moderate (10-30%) and high (>30%) using cut-points previously established to correlate with pCR. We calculated a point estimate and 95% confidence interval for the probability that a subject with given IM and TIL status will achieve pCR.

Results: The IM subtype was identified in fewer TNBCs with low or moderate sTIL (4 and 27%, respectively) than in those with high sTIL (62%, p<0.05). Independently, IM subtype and high sTIL subgroups achieved pCR at similar rates (62% and 76% respectively). We observed the largest difference in pCR rates between IM and non-IM subtype patients in the Moderate sTIL group. (58% vs 33%, p=0.051).

Table 98O: sTIL and pCR rates according to IM status

IM				
sTIL Group	N	# pCR	%pCR	CI
Low	3	1	33	(0.01-0.91)
Moderate	24	14	58	(0.37-0.78)
High	13	10	77	(0.46-0.95)
Total	40	25	62	
Other Subtypes				
sTIL Group	N	# pCR	%pCR	CI
Low	67	21	31	(0.21-0.44)
Moderate	66	22	33	(0.22-0.46)
High	8	6	75	(0.35-0.97)
Total	141	49	34	

Conclusions: High TIL and IM subtype are associated with similar rates of pCR and the addition of the IM signature to sTIL high or sTIL low TNBCs did not impact prediction of pCR. In patients with moderate TIL, the IM subtype was associated with higher rates of pCR (58%) as compared to other subtypes (33%). Larger numbers of patients are needed to confirm the predictive value of the IM signature in TIL moderate TNBC.

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99P Association of gut microbiome diversity and composition with pathological complete response (pCR) after neoadjuvant chemotherapy in triple negative breast cancer

G. Vernaci[1], E. Cumerlato[1], G. Griguolo[1], D. Massa[1], A. Menichetti[1], F. Miglietta[1], G. Tasca[2], E. Savarino[1], P.F. Conte[1], V. Guarneri[1], M.V. Dieci[1]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [2]Medical Oncology Unit 2, IOV - Istituto Oncologico Veneto IRCCS, Padua, Italy

Background: The human gut microbiome has been shown to influence the efficacy of anticancer therapies. Little is known regarding the role of gut microbiome in triple negative breast cancer patients receiving neoadjuvant chemotherapy.

Methods: In this pilot prospective study, we characterized the gut microbiome of 18 triple negative breast cancer patients undergoing neoadjuvant chemotherapy. All patients received anthracycline and taxane-based chemotherapy, including carboplatin in 16 patients. Pre-treatment fecal samples were analyzed by 16S RNA sequencing. Shannon index was used to evaluate alpha-diversity. Differentially abundant bacterial OTUs between groups were determined using Linear Discriminant Analysis (LDA) Effect Size (LEfSe).

Results: Patients characteristics were as follows: premenopausal 44%, ductal infiltrating carcinoma 100%, histologic G3 100%, cN+ 67%, cT>2cm 89%. No significant association between Shannon diversity index and baseline characteristics was shown. As expected, the most abundant taxa at the phylum level were Bacteroidetes and Firmicutes. Ten patients achieved a pCR. The Shannon diversity index was significantly higher in pCR vs non-pCR patients: median 5.057 (95% CI 4.923-5.339) vs 4.639 (95% CI 4.427-4.913), p=0.016. At the genus level, Alistipes and Ruminococcaceae UCG-002 were significantly enriched in pCR vs non-pCR patients (LDA score >3.0, $p<0.05$).

Conclusions: The results of this pilot study show preliminary insights into the potential implications of gut microbiome in neoadjuvant chemotherapy efficacy for triple negative breast cancer. Patients recruitment is ongoing, updated results will be presented including association between intestinal microbiome and tumor immune microenvironment.

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101P Predictors of 18F-fluorodeoxyglucose (F) positron-emission tomography (PET)-driven disease detection in patients (pts) with HER2[+] early breast cancer (EBC). A substudy of the PHERGain trial

A. Llombart Cussac[1], A. Prat[2], J.M. Pérez-García[3], J. Mateos[4], T. Pascual[2], S. Escrivà-De-Romani[5], A. Stradella[6], M. Ruiz-Borrego[7], B. Bermejo De Las Heras[8], M. Keyaerts[9], M. Sampayo-Cordero[10], A. Malfettone[10], R. Cortés[11], P. Galván[12], J. Cortés[13], G. Gebhart[9]

[1]Medical Oncology, Hospital Universitario Arnau de Vilanova, Universidad Catolica, Valencia; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and, Barcelona, Spain; [2]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [3]Medical Oncology, IOB, Institute of Oncology, QuironSalud Group, Madrid and Barcelona; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; [4]Medical Oncology, IEC, Barcelona, Spain; [5]Medical Oncology, Hospital Universitari Vall d' Hebrón, Barcelona, Spain; [6]Medical Oncology, ICO l'Hospitalet, Barcelona, Spain; [7]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain; [8]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain; [9]Medical Oncology, Institute Jules Bordet, Brussels, Belgium; [10]Scientific Department, Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; [11]Business Development, Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; [12]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain; [13]Medical Oncology, IOB, Institute of Oncology, QuironSalud Group, Madrid and Barcelona; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: PHERGain (NCT03161353) is assessing the early metabolic response by F-PET to neoadjuvant chemotherapy-free treatment with trastuzumab and pertuzumab and the opportunity of chemotherapy de-escalation with a response-adapted strategy in pts with HER2[+] EBC. In this substudy, clinical and molecular predictors of disease detection using F-PET were evaluated.

Methods: PHERGain inclusion criteria required a breast lesion with a SUVmax ≥1.5xSUVmean liver+2SD by F-PET (PERCIST). A total of 512 pts with HER2[+] EBC were screened and 75 (14.7%) were PET[-]. Association between SUVmax and clinicopathological features was analyzed in all screened pts. Moreover, evaluation of stromal tumor-infiltrating lymphocytes (TIL) and gene expression data by PAM50 classifier and Vantage 3D Cancer Metabolism Panel was conducted on a selected cohort of 21 PET[-] and 21 PET[+] matched pts.

Results: Median age of the entire screened population was 52 years, 41.8% had node [+] disease, and 68.4% had hormone receptor (HR)[+] status. Median tumor size by magnetic resonance imaging was 30 mm (range 9−157). Median SUVmax was 7.3 (range 1−39). In an unadjusted analysis of all screened pts, SUVmax was associated with tumor size, lymph node involvement, HR status, HER2 expression levels, Ki67 index, and histological grade ($p<0.05$). PET[-] tumors had lower tumor size, histological grade, and lymph node involvement than PET[+] tumors. Although no difference in TIL counts was found among selected PET[-]/[+] cases, PET[-] tumors showed a decreased risk of recurrence and lower proportion of HER2-enriched subtype by PAM50 than PET[+] tumors ($p<0.05$). In PET[-] pts genes involved in glucose metabolism (DLAT, IDH2, LDHA, PGK1, PGLS, and TPI1), hypoxia signaling (HIF1A), and carbon metabolism (SLC7A5, SLC16A3) resulted under expressed, whereas genes involved in the mTOR pathway (AKT2) and growth factor receptor (FLT3) were over expressed compared with PET[+] pts (false discovery rate $q<0.05$).

Conclusions: Taking into account the clinical and biological heterogeneity of HER2[+] disease, these results may need to be considered for an appropriate selection of PET [+] pts in HER2[+] EBC.

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J.M. Pérez-García: Advisory/Consultancy, Travel/Accommodation/Expenses: Roche; Advisory/Consultancy: Lilly. S. Escrivà-De-Romani: Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Pierre-Fabre; Speaker Bureau/Expert testimony: Eisai; Research grant/Funding (institution): Synthon; Travel/Accommodation/Expenses: Daiichi Sankyo. A. Stradella: Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Roche; Speaker Bureau/Expert testimony: Eisai; Travel/Accommodation/Expenses: Pfizer. M. Ruiz-Borrego: Speaker Bureau/Expert testimony: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony: Pfizer; Advisory/Consultancy: MSD; Speaker Bureau/Expert testimony: Lilly; Speaker Bureau/Expert testimony: AstraZeneca. B. Bermejo De Las Heras: Advisory/Consultancy, Speaker Bureau/Expert testimony: Genentech; Advisory/Consultancy: MSD; Travel/Accommodation/Expenses: Pfizer. M. Keyaerts: Research grant/Funding (self): Camel-IDS; Research grant/Funding (self): Bayer; Licensing/Royalties: Nanobody imaging and therapy. M. Sampayo-Cordero: Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (self), Travel/Accommodation/Expenses: MedSIR; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (self), Travel/Accommodation/Expenses: Syntax for Science; Honoraria (self), Advisory/Consultancy: Nestlé; Speaker Bureau/Expert testimony, Research grant/Funding (self), Travel/Accommodation/Expenses: Roche. A. Malfettone: Full/Part-time employment: MedSIR. R. Cortés: Full/Part-time employment: MedSIR. J. Cortés: Honoraria (institution), Advisory/Consultancy, Research grant/Funding (institution): Roche; Honoraria (institution), Advisory/Consultancy: Celgene; Advisory/Consultancy: Cellestia; Advisory/Consultancy, Research grant/Funding (institution): AstraZeneca; Advisory/Consultancy: Biothera Pharmaceutical; Advisory/Consultancy: Merus; Advisory/Consultancy: Seattle Genetics; Honoraria (self), Advisory/Consultancy: Daiichi Sankyo; Advisory/Consultancy: Erytech; Research grant/Funding (institution): Ariad pharmaceuticals/Baxalta GMBH/Servier Affaires/Bayer healthcare; Advisory/Consultancy: F.Hoffman-La Roche/Guardanth health/Pfizer/Piqur Therapeutics/Puma C/Queen Mary University of London; Honoraria (self), Advisory/Consultancy: Lilly; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Merck Sharp & Dohme; Advisory/Consultancy: Athenex/Polyphor/Servier/Bioasis/Clovis Oncology/Leuko/Gsk; Shareholder/Stockholder/Stock options: MedSIR; Honoraria (self): Novartis; Honoraria (self), Research grant/Funding (institution): Eisai. 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102P Predictive models associated with the presence of pathological complete response following neoadjuvant chemotherapy for breast cancer

Y. Xie

Breast Surgery, West China Medical Center of Sichuan University, Chengdu, China

Background: Studies have shown that breast cancer (BC) patients whose tumors show pathological complete response (pCR) present better outcomes than patients whose tumors show residual disease (RD) at surgery after neoadjuvant chemotherapy (NAC). This study aimed to construct predictive models associated with the presence of pCR after NAC to establish guidelines for medical therapies.

Methods: The gene expression profiles and clinicopathological data of 614 (training set) and 408 (validation set) patients with BC who received NAC were analyzed. Weighted gene co-expression network analysis (WGCNA), Logistic regression analyses, and decision tree analyses were performed to construct predictive models within the R environment.

Results: In training set, pCR was associated with N stage, AJCC stage, HER2, tumor subtype, nuclear grade, estrogen receptor, and progesterone receptor. When we introduced these clinical parameters to logistic analysis, the sensitivity and specificity of predicting pCR in validation set were as low as 67.43% and 66.32%, respectively. Though the false prediction rate was just 20% using decision tree model in validation set, only 1.01% patients were correctly predicted as pCR. In order to construct a more precise predictive model, WGCNA was performed and identified a yellow module that constitutes upregulated cell proliferation genes and a blue module that enriched in metabolite pathways were highly associated with pCR in the training set. Logistic analysis model base on critical genes in yellow and blue modules obtained relatively high sensitivity (78.79%) and specificity (72.24%) in validation set. Decision tree model base on critical genes in yellow and blue modules also obtained relatively high accuracy rates to predict pCR after machine learning, with a sensitivity of 48.94% and a specificity of 86.55% in the validation set.

Conclusions: Logistic regression analysis model and decision tree model, which derived from the key genes of co-expression modules identified by WGCNA, can predict chemotherapy responses in BC more precise than models just derived from clinicopathological parameters and can contribute in developing personalized medicines.

Legal entity responsible for the study: Zhenggui Du.

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103P Loss of HER2 after neoadjuvant treatment of HER2+ early breast cancer

S. Morales, A. Gasol Cudos, A. Rodriguez Galindo, A. Velasco, C. Canosa Morales, D.-R. Sánchez Guzmán, J. Melé Olivé

Breast Cancer Unit, Hospital Universitario Arnau de Vilanova, Lleida, Spain

Background: Changes in the expression of HER2 receptors on tumor samples before and after neoadjuvant chemotherapy (NACT) and surgery have been correlated with bad prognostic therefore is important to know the magnitude of this feature and its correlation with other known prognostic factors used.

Methods: We analyzed the loss of expression of HER2 in a retrospective cohort of 121 HER2 positive patients with residual tumor and correlate with clinical-pathological variables. The median age was 56 years (29-89), initial tumor size was 41(10 to 100) and 68 (56%) had initial node involvement. 81 patients (67%) had positive hormone receptors, the median Ki67 index was 40% (5-95) and the expression of HER2 by immunohistochemistry was +2 in 51 (42%) and +3 in 70 (58%).

Results: A total of 33 patients (27%) had a total loss of HER2 expression (HER2 negative), 19 (15%) had a loss of HER2 expression (HER2 +1 by IHQ) and 69 patients did not present. We found a worse disease free survival (DFS) in patients with total loss of HER2 expression with a median DFS of 91 months (63 — 120) compared to 175 (152 — 198,long rank p:0,013). Only initial expression of HER2 (HER +2 vs HER+3) had correlation with total loss of HER2 (47% vs 12%) and this group had the worst prognosis with a DFS of 58 months (40 — 76). The previous treatment with trastuzumab and pertuzumab was associated with total loss of HER2 expresion. 31 of 93 patients that received trastuzumab had total loss of expression of HER2 compared to only 2 of 28, and 16 of 32 that received trastuzumab and pertuzumab presented a higher loss of expression of HER2compared to 17 of 89 (19%).

Conclusions: The loss of expression of HER2 is a significant predictor of worse DFS, especially in patients with HER2 +2 in the initial diagnoses.This group of patients have the lowest DFS with only 58 months. Initial treatment with trastuzumab and pertuzumab conditions a greater loss of HER2 expression (50%) and especially in cases with initial HER2 +2 with 70% with total loss of expression. We will need to find some new treatment strategy for this group of patients with loss of HER2 expression, especially if they have a low expression of HER2 in the initial diagnosis.

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104P Cost and healthcare resource utilization (HCRU) for patients receiving neoadjuvant therapy for early-stage triple-negative breast cancer (ESTNBC)

W.C. Rhodes[1], S. Gautam[1], A. Haiderali[2], M. Huang[2], J. Sieluk[2], K.E. Skinner[1], L.S. Schwartzberg[3]

[1]Outcomes Science & Services, Concerto HealthAI, Memphis, TN, USA; [2]Center for Observational and Real-World Evidence, MSD - Merck Sharp & Dohme, North Wales, PA, USA; [3]Oncology Department, West Cancer Center, Germantown, TN, USA

Background: The available economic evidence base for ESTNBC is limited. This study evaluated costs and HCRU for patients receiving neoadjuvant treatment for ESTNBC.

Methods: This was a retrospective observational study of patients with ESTNBC from US community oncology practices. Patients were required to be adult females diagnosed with stage II-IIIB ESTNBC between 3/2008 and 3/2016 with definitive surgery following neoadjuvant systemic therapy, with or without adjuvant therapy. Cost and HCRU were evaluated descriptively from neoadjuvant treatment initiation until surgery (Time 1) and surgery until the earliest of first recurrence, death, or end of record (Time 2).

Results: Of 308 eligible patients, 236 received neoadjuvant but not adjuvant treatment (Neo) and 72 received neoadjuvant and adjuvant treatment (Neo+Adj). Mean monthly cost for Neo was $14,466 for Time 1 with infused or injected supportive care (antiemetics, anti-neutropenia, anti-anemia) [ISC] ($5,305) and systemic anticancer therapy [SAT] ($4,464) respectively as primary cost drivers. Monthly cost was $12,989 for Neo+Adj, with ISC ($4,320) and SAT ($3,538) as the highest cost components. Time 2 mean monthly cost was $1,120 for Neo, with hospitalization [HOS] ($636) followed by ED visits ($214) as the key costs. For Neo+Adj, mean monthly cost was $3,167, with HOS ($1,851) and SAT ($513) as key cost drivers for Time 2. HCRU was highest in Time 1 for Neo and Neo+Adj. The table reports HCRU by category for Time 1 and 2.

Table 104P: Mean number of events per month per incident patient, Mean (SD)

	Time 1		Time 2	
	Neo (N=236)	Neo+Adj (N=72)	Neo (N=236)	Neo+Adj (N=72)
Hospitalization	0.25 (0.098)	0.31 (0.234)	0.06 (0.098)	0.12 (0.127)
ED Visits	0.24 (0.124)	0.30 (0.078)	0.06 (0.055)	0.07 (0.086)
Infused or Injected Supportive Care	1.49 (1.328)	2.18 (1.924)	0.02 (0.007)	0.37 (0.438)
Office Visit	2.41 (1.359)	2.96 (1.221)	0.29 (0.328)	0.58 (0.788)

Conclusions: The results of the present study demonstrate the economic and resource burden of ESTNBC, particularly during the time from neoadjuvant treatment initiation until surgery.

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105P Lower-dose apatinib combined with nanoparticle albumin-bound paclitaxel and carboplatin as a neoadjuvant regimen for triple negative breast cancer: A prospective, single-arm, phase II study

Y. Yin[1], W. Li[1], X. Zha[2], J. Wang[2]

[1]Oncology Department, Jiangsu Province Hospital - The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; [2]Department of Breast Diseases, Jiangsu Province Hospital - The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Apatinib is an orally administered small-molecular receptor tyrosine kinase inhibitor (TKI) with potential antiangiogenic and antineoplastic activities. This study was conducted to assess efficacy and safety of lower-dose apatinib combined with nanoparticle albumin-bound paclitaxel (nab-p) and carboplatin as a neoadjuvant regimen for triple negative breast cancer (TNBC).

Methods: This single arm study enrolled patients with operable TNBC. Patients received apatinib (250mg, po, d1-21), nab-p (260mg/m^2, ivgtt, d1) concurrently with carboplatin (AUC=5-6, ivgtt, d1) for 6 cycles, each 21-day cycle, followed by surgery. The primary endpoint was pathological complete response (pCR) rates, defined as no invasive or noninvasive tumor residuals in both breast and axillary lymph nodes (ypT0 ypN0), or no invasive tumor residuals in the breast, and no invasive or noninvasive tumor residuals in the axillary lymph nodes (ypT0/is ypN0). Secondary endpoints included objective response rate (ORR), disease free survival (DFS), overall survival (OS), and toxicity.

Results: 18 female patients with a median age of 45 years (20-62 years) were enrolled from Sep. 22, 2018 to Dec. 24, 2019. All the 18 pts completed neoadjuvant chemotherapy followed by surgery, however, only 1 patient did not provide enough data for efficacy evaluation. Rates of ypT0 ypN0 and ypT0/is ypN0 were 35.2% (6/17) and 41.2% (7/17), respectively. ORR was 94.1% (16/17). DFS and OS had not been evaluated since short time follow-up. 8 pts experienced apatinib-related dose discontinuation during treatment. Carboplatin induced myelosuppression was the main reason of chemotherapy delay. The most common grade 3/4 treatment-related adverse events (AEs) were thrombocytopenia (11/18), anaemia (10/18), neutropenia (7/18) and hypertension (3/18). Adverse events were well controlled after drug discontinuation and dose adjustment. No treatment-related death was occurred.

Conclusions: This neoadjuvant regimen, apatinib combined with nab-p and carboplatin, exhibited acceptable efficacy and manageable toxicity in neoadjuvant treatment of TNBC pts. Long-time follow-up are still needed.

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Legal entity responsible for the study: The authors.

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107P Preservation of ovarian function with goserelin in young breast cancer patients: Does it hamper the effect of neoadjuvant chemotherapy?

S.Y. Wang, S. Wang

Breast Surgery, Peking University People's Hospital, Beijing, China

Background: Goserelin, a gonadotropin-releasing hormone agonist (GnRHa), has been widely used concurrently with chemotherapy to protect ovarian function for young breast cancer patients. However, potential negative interaction between the two treatments is a matter of concern due to few conclusive data on the oncological safety, especially for patients with positive hormone receptor. The aim of this study was to determine the impact of concurrent use of goserelin with neoadjuvant chemotherapy on pathological complete response (pCR).

Methods: Breast cancer patients aged between 18 and 45 years with clinical stage II to III from December 2015 and December 2019 were assigned without interference to receive either neoadjuvant chemotherapy with goserelin (goserelin group) or without goserelin (chemotherapy group) as their own selection. Primary end point was pCR rate and secondary end point was objective response rate (ORR), including clinical complete response (CR) and partial response (PR) in the breast based on magnetic resonance imaging.

Results: A total of 95 patients (23 in goserelin group and 72 in chemotherapy group) were eligible and could be assessed. At baseline, more childless, hormone receptors negative patients with strong fertility desire who received regimen containing cyclophosphamide, tended to select goserelin for ovarian function preservation before neoadjuvant chemotherapy. The main outcome showed no difference in pCR rate, being 30.4% in goserelin group versus 25.0% in chemotherapy group (P =0.606). And ORR was consistent with pCR rate (86.9% in goserelin group and 84.7% in chemotherapy group, P =1.000). Additionally, for patients with positive hormone receptor, pCR rate and ORR did not differ significantly between the two groups as well, although numerically higher in goserelin group (pCR, 37.5% vs. 18.0%, P =0.427; ORR, 87.5% vs. 84.0%, P =1.000).

Conclusions: Preservation of ovarian function using goserelin can be safely considered for young breast cancer patients with clinical stage II to III regardless of hormone receptor status in terms of oncologic outcomes. Further studies are needed to assess the long-term outcomes of concurrent administration of GnRHa with neoadjuvant chemotherapy.

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109P Role of MRI and histopathological classification in pre-treatment identification of non-responders to neoadjuvant chemotherapy in breast cancer

B. Vertakova Krakovska[1], L. Vanovcanova[2], V. Lehotska[2], I. Waczulikova[3], K. Gocarova[1]

[1]1st Oncology Department, Commenius University- Medical Faculty, Oncological Institute of St. Elizabeth-Onkologický ústav sv. Alžbety, s.r.o., Bratislava, Slovak Republic; [2]2nd Radiology Department, St. Elizabeht Cancer Institute, Commenius University, Medical Faculty, Bratislava, Slovak Republic; [3]Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics, Comenius University in Bratislava, Bratislava, Slovak Republic

Background: The selection of breast cancer (BC) patients to neoadjuvant chemotherapy (NAC) is subject to indication criteria. The most used tool to evaluate the response to NAC is the determination of the pathological complete response (pCR= residual cancer burden RCB 0). However, some tumors do not respond to NAC despite their histopathological parameters (HP). This study is proposed to identify the non-responders to NAC according to pretreatment MRI signs and molecular subtypes.

Methods: In the retrospective study (01/2014 – 06/2019), 181 patients (median 50y), with locally advanced BC, underwent pretreatment biopsy and MRI. The patients were classified as luminal A, luminal B HER2neg, luminal B HER2+, HER2+, triple negative, and treated with NAC (doxorubicin and/or taxane regimen). The prediction of response: pCR or incomplete response (pRD pathological residual disease; pNR pathological no response) was based on MRI signs and HP. Analysis of the predictive performance was performed using StatsDirect 3.2.7.

Results: Prediction based on the HP outperformed prediction based on MRI in all but the subgroups of Triple negat (23, 38.33%) and Luminal B HER2negat (20, 33.33%), which represented the largest groups of 60 posttreatment nonresponders despite pretreatment prediction. Logistic regression model was built to involve all mutual associations among patients' characteristics. The final model ($p<0.001$) was composed of age(y) (OR= 1.06, p=0.0005), MRI signs (ADC coef OR= 0.16, p=0.049, absence of restriction of diffusion OR=16.39, p=0.026, pattern of lesion OR= 8.63, p=0.040, ring enhancement OR= 2.87, p=0.039), ER (%) (OR= 1.77 per each 10%, p=0.001), HER2negat (OR= 0.39, p=0.028), with sensitivity 88.64%, specificity 55.32%, with area under ROC curve = 80.5% and 79.9% correctly classified cases at cut-off probability of 0.6.

Conclusions: Nonresponding is significantly connected with triple negative and luminal B HER2 negative status as well as with higher age, HER2 negativity, and ER positivity. MRI plays a substantial role in the identification of nonresponders in both mentioned groups and helps to classify these patients more precisely especially in ambiguous cases.

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110P Primary endocrine therapy of breast cancer: Is there a good radiological technique to define pathological response?

J.I. Lopez Velazco[1], M. Otaño[1], L. Larburu[1], A. Lahuerta[1], K. Elorriaga[1], V. Segur[1], J.C. Irizabal[1], A. Martinez[1], L. Jáuregui[1], J.A. Alberro[1], L. Álvarez[1], I. Etxabe[1], M. Huarte[1], M.M. Caffarel[2], A. Urruticoechea Ribate[1]

[1]Oncología, Onkologiko Donostia - Kutxa Fundaziona, Donostia, Spain; [2]Cáncer de Mama, Instituto de Investigación Sanitaria Biodonostia, Donostia, Spain

Background: Neoadjuvant Endocrine Therapy (NET) of breast cancer has been used to increase the number of patients amenable to conservative surgery. The preoperative assessment of tumor size after this therapy is used to determine response grade and help surgical decision. In this setting we do not have many information about which radiological technique, ultrasound (US) o magnetic resonance (MRI) correlates best with pathological size (PS). The aims of this study are to determine which radiological technique MRI or US correlates best with PS.

Methods: Retrospective study of patients with estrogen receptor (ER) positive/HER2 negative resectable breast cancer, treated with NET with an aromatase inhibitor for at least 4 months previous to surgery. Radiological assessment: MRI and US at diagnosis and previous to surgery. Radiological response evaluated by RECIST 1.1 Pathological specimens: Formalin fixed paraffin embedded biopsy at diagnosis and surgical specimens.

Results: N=102. Baseline characteristics: table below. Radiological response (complete response (CR), partial response (PR), stable disease (ED) and progressive disease (PD)): *By MRI: 25 CR, 43 PR, 27 ED and 1 PD *By US: 15 CR, 56 PR, 19 ED and 2 PD. Mean tumour size before surgery and after surgery by PS, in millimeters (mm): MRI 11.78; US 9.61; PS 20.24 Correlations between the size estimated by MRI and US before surgery versus (vs) PS: MRI (r=0.3903) p= <0.0001 (95% CI, 0.203 to 0.549); US (r=0.3898) p=0.0001 (95% CI, 0.197 to 0.553). Size at diagnosis by MRI and US vs PS [20.24 mean (0-80range)] in mm: MRI 23.94 (10-90) vs PS correlation (r=0.5982) p= <0.0001 (95% CI, 0.448 to 0.715); US 18.52 (8-50) vs PS correlation (r=0.5026) p=0.0001 (95% CI, 0.3326 to 0.6410).

Table 110P

Age, years (range)	68/47-93
Tumour [MRI/US] % T1 T2 T3	43/64 55/36 2/0
Node % N0 N1 N2	86 13 1
Grade % I II II	74 23 3
Type % Ductal Lobular Other	83 10 7
% stained cell, mean (range) - Ki67 - Estrogen receptor	20.43 (3-60) 93.48 (20-100)

Conclusions: 1.MRI and US after NET and previous to surgery underestimate pathological tumor size. 2. MRI at diagnosis correlates best with pathological size than MRI previous to surgery. 3. There is a need to find other biomarkers to predict tumor response in NET.

Legal entity responsible for the study: The authors.

Funding: Onkologikoa.

Disclosure: All authors have declared no conflicts of interest.

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111P Evaluating the protective effect of metformine on cancer: A retrospective cohort analysis

N. Honoré[1], A. Van Der Elst[1], D. D'Augusto[2], E. Seront[3]

[1]Oncology Department, UCLouvain Brussels Woluwe, Brussels, Belgium; [2]Pathology, Jolimont Group, La Louvière, Belgium; [3]Oncology Department, Centre Hospitalier Jolimont-Lobbes, Haine Saint Paul, Belgium

Background: The phosphoinositol-3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway is excessively activated in around 50% of breast cancer (BC). Metformin regulates negatively mTOR through AMPK-activation. The role of metformin in BC is unclear. We retrospectively analyzed the efficacy of metformin-chemotherapy association in a cohort of BC patients and explored mTOR-related proteins expression.

Methods: Patients treated for BC separated in Jolimont hospital between December 2017 and June 2019 were included in this retrospective analysis and were stratified in non-metformine (group A) and in metformin-treated group (group B). We first compared the tumor characteristics within these groups. For those who received neoadjuvant chemotherapy (excluding HER2) patients, we compared the tumor shrinkage with chemotherapy in these groups. We also correlated the expression of p-AMPK, p-AKT, p-S6RP a with treatment efficacy (good responders were defined as ^{3}75% of response rate on chemotherapy).

Results: Two hundred fifty-four BC patients were included: 219 in group A and 30 in group B. Compared to group A, group B presented more Luminal A-B types (67 vs 78%; P=0.02) and a lower median baseline tumor size (20.2 vs 31mm, P=0.07). Among patients who received neoadjuvant chemotherapy (30 patients from group A, 7 from group B), the percentage of reduction in tumor size was higher in group B (95% vs 75%, P=0.01) compared to group A. 35 patients were evaluable for protein expression; p-AMPK and PTEN were highly expressed in good responders compared to poor responders in both groups A and B, suggesting the implication of the mTOR pathway in good responders.

Conclusions: Patients with metformin treatment appear to have less aggressive tumors. The association of metformin and chemotherapy results in a higher response rate than chemotherapy alone. Regardless the use of metformin, mTOR inhibition could enhance chemotherapy efficacy.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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112TiP SOLTI-1710 PROMETEO II: Palbociclib in combination with letrozole in patients with hormone receptor-positive (HR+)/HER2-negative residual disease after standard neoadjuvant chemotherapy (NAC)

E.M. Ciruelos[1], X. González-Farré[2], A. Perelló[3], E. Alba[4], P. Palacios-Ozores[5], J. Salvador-Bofil[6], M. Merino[7], P. Villagrasa[8], P. Celiz[8], T. Pascual[8], A. Prat[9], S. Pernas Simon[10]

[1]Department Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; [2]Department Medical Oncology, Hospital General de Catalunya, San Cugat Del Valles, Spain; [3]Department Medical Oncology, Hospital Universitari Son Espases, Palma de Mallorca, Spain; [4]Department Medical Oncology, Hospital Virgen de la Victoria, Málaga, Spain; [5]Department Medical Oncology, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain; [6]Department Medical Oncology, Hospital Virgen del Rocío, Seville, Spain; [7]Department Medical Oncology, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain; [8]Department Scientific, SOLTI Breast Cancer Research Group, Barcelona, Spain; [9]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [10]Department Medical Oncology, Institut Catala d' Oncologia, Hospitalet de Llobregat, Spain

Background: Despite the improvement in the treatment of early-stage breast cancer (BC) with chemotherapy, many patients have residual disease with a higher risk of metastatic recurrence and poorer outcome than those who achieve a pathological complete response (pCR), particularly in highly proliferative tumors. In HR+ BC, the pCR rates after NAC are around 10-15%. Additional therapeutic strategies to eradicate these residual tumor cells are needed. The combination of cyclin-dependent kinase inhibitors with first or second-line endocrine therapy are options for metastatic BC and its role in the early-setting is being evaluated in several studies. Posttreatment Ki67 levels provide prognostic information for patients with HR+ BC and residual disease, but the prospective validation of this biomarker is necessary. We hypothesize that palbociclib plus letrozole offers antiproliferative benefit in the pre-surgery setting for patients with residual disease and high risk of recurrence.

Trial design: SOLTI1710 PROMETEO II is a prospective single-arm window of opportunity trial in HR+/HER2-negative operable BC patients with residual disease after NAC designed to evaluate the biological effect of palbociclib plus letrozole and to identify biomarkers for better patient selection. Patients must have histologically confirmed HR+/ HER2-negative tumors and locally assessed baseline Ki-67 $>$ 10%, have completed $\geq$80% total dose of an anthracycline/taxane-based NAC; and residual disease $\geq$ 1 cm by magnetic resonance imaging and Ki67% $\geq$ 10% after NAC. Patients will be administered palbociclib at a dose of 125 mg/day, 3 weeks on/1 week off and letrozole 2.5 mg/day continuously, one cycle of treatment. After the neoadjuvant treatment, patients will undergo surgery. Tumor tissue and blood samples will be collected for correlative translational studies. The primary endpoint is the Complete Cell Cycle Arrest (CCCA) determined by Ki67$<$2.7%, centrally assessed at surgery. Secondary endpoints include rate of RCB 0/1 and pCR after neoadjuvant treatment and adverse events. Recruitment of the planned 20 patients is ongoing in 8 sites across Spain.

Clinical trial identification: NCT04130152.

Legal entity responsible for the study: SOLTI Breast Cancer Research Group.

Funding: Pfizer.

Disclosure: E.M. Ciruelos: Advisory/Consultancy, Travel/Accommodation/Expenses: Roche; Advisory/Consultancy: Lilly; Advisory/Consultancy: Novartis; Advisory/Consultancy: Pfizer. X. González-Farré: Travel/Accommodation/Expenses: Roche; Travel/Accommodation/Expenses: Eisai. P. Villagrasa: Speaker Bureau/Expert testimony: NanoString. A. Prat: Advisory/Consultancy, Research grant/Funding (institution): Novartis; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Lilly; Advisory/Consultancy: NanoString; Advisory/Consultancy, Research grant/Funding (institution): Amgen; Advisory/Consultancy, Research grant/Funding (institution): Roche; Advisory/Consultancy: Oncolytics; Advisory/Consultancy: Daiichi Sankyo; Advisory/Consultancy: Puma; Advisory/Consultancy: BMS. S. Pernas Simon: Travel/Accommodation/Expenses: Roche; Advisory/Consultancy: Poliphor. All other authors have declared no conflicts of interest.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EARLY BREAST CANCER: SURGERY AND RADIOTHERAPY

113P Impact of local recurrence on disease-specific survival in breast cancer patients who underwent breast-conserving surgery

D.G. Tiezzi[1], L. de Mattos[2], L.F. Orlandini[1], F.J. Candido Dos Reis[1], H.H. Carrara[1], O.M. Rueda[3], C. Caldas[3], J.M.D. Andrade[1]

[1]Breast Disease Division, Ribeirão Preto Medical School, Ribeirao Preto, Brazil; [2]Irsi-Caixa, Hospital Universitari Trias i Pujol, Badalona, Spain; [3]Oncology Department, Cancer Research UK & University of Cambridge UK, Cambridge, UK

Background: Breast-conserving surgery (BCS) is the current standard treatment for early stage breast cancer (EBC) patients. Although, long-term randomized trials have demonstrated its safety in terms of overall survival, those studies did not consider breast cancer as a heterogenous disease. Recent evidence has demonstrated distinct local recurrence (LR) rates across breast cancer subtypes.

Methods: We retrospectively analyzed clinical files from 1,748 non-metastatic invasive breast cancer patients from Jan 2000 to Mar 2015 in order to characterize the impact of ipsilateral LR after BCS in disease-specific survival (HC cohort). Additionally, publicly available data from METABRIC cohort was used for clinical and molecular / mutational profile analyses. LR was considered as the first recurrence event.

Results: A total of 804 and 1,146 EBC patients were subjected to BCS in HC and METABRIC cohorts, respectively. We observed 55 LR (6.8%) in the HC cohort. In METABRIC, the LR ratio was 10.6% (122 cases). Patients with LR were divided into two groups according to the time of the event: early or late local recurrence (ELR and LLR, respectively) groups whether the event occurred within or after 5 years of surgical treatment. Multivariate regression including patients from both cohorts demonstrated LR has a significant impact on disease-specific survival (HR= 2.1), especially in ELR events (HR= 4.0). The significant risk factors for ELR are triple-negative breast cancer (TNBC), age, pathological stage III and HER2 expression. In the METABRIC cohort, the incidence of ELR is higher in iClusters 5 and 10 (17.9% and 16.7%, respectively). There was no ELR among 75 patients with iCluster 6 or 7 tumors (p= 0.01). The prevalence of TP53 and SYNE1 somatic mutations was significantly more prevalent in ELR tumors (p= 0.003 and p= 0.03, respectively).

Conclusions: Local recurrence after BCS is highly associated with a decrease in disease-specific survival, especially among ELR patients. There is a subset of younger patients (< 54 yo) with TNBC or HER2-enriched tumors (iC10 and iC5) and TP53 somatic mutation with higher risk of ELR after BCS. These patients deserve closer surveillance and would benefit from strategies to battle ELR.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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114P Non-metastatic metaplastic breast cancer; clinicopathological characteristics and treatment outcomes: A single institution experience

A.A. Erjan, A. Dayyat

Radiation Oncology, KHCC - King Hussein Cancer Center, Amman, Jordan

Background: Metaplastic breast cancer (MpBC) is a rare heterogenous aggressive subtype of breast cancer. Data addressing this entity is lacking. We reviewed the clinicopathologic characteristics and outcomes of non-metastatic MpBC patients at our center.

Methods: Women with stage I-III MpBC were reviewed from our database from 2000-2018. Locoregional failure-free survival (LRFFS), overall-survival (OS) and distant metastases-free survival (DMFS) were estimated using Kaplan-Meier method. Log-rank tests and Cox proportional-hazards models were conducted to study associations of various variables with these endpoints.

Results: 81 patients with pathologically proven MpBC were eligible. Median age at diagnosis was 48 years. 88% had pathologic grade III. 65% were node negative. 68% were triple negative, and 7.4% were HER2-neu positive. Mastectomy was the most common surgical approach (66.7%). Free margins were achieved in the entire cohort, however, 17.3% had close margin (<2mm). 94% received chemotherapy, 75.3% received radiotherapy, 23.5% received hormonal therapy and 6.2% received Trastuzumab. With a median follow-up of 53 months, 15 patients (18.5%) recurred locoregionally and 28 patients (34.6%) relapsed distally. 5-year OS, LRFFS and DMFS were 68.23%, 77.31% and 64.27%, respectively. Several variables were associated with survival endpoints on univariate analysis. However, on multivariate analysis: adjuvant radiotherapy provided better OS, (HR 0.2, 95% CI, 0.06-0.65, p=0.008), nodal involvement correlated with worse OS (HR 4.8, 95% CI, 1.3-17.6, p=0.012) and margins >=2mm correlated with improved DMFS, (HR 0.34, 95% CI, 0.14-0.81, p=0.016). There was no survival difference with respect to tumor size, triple negativity, and morphologic subtype.

Conclusions: MpBC carries worse prognosis compared to invasive ductal carcinoma. To our knowledge, these results are the first to show that close margin is linked to worse DMFS. This is likely explained by the presence of sarcomatous component and should raise the question for obtaining wider surgical margins in this entity. Further prospective data are warranted to validate our finding.

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115P Factors associated with mastectomy in women with small residual tumour after neoadjuvant chemotherapy for breast cancer

E. Bernell[1], A. Duinmeijer[2], R. Altena[2], T. Foukakis[2], H. Fredholm[3]

[1]Medicine Program, Uppsala University, Uppsala, Sweden; [2]Oncology Pathology and Theme Cancer, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [3]Molecular Medicine and Surgery, Breast Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Background: Mastectomy is the most common type of surgery after neoadjuvant chemotherapy (NACT). We aimed to characterize the factors associated with mastectomy even after good response to NACT.

Methods: Women treated with NACT in Stockholm between 2007-2017 (N=1463) were identified in the Swedish National Quality Register for Breast Cancer. Logistic regression analyses were used to identify factors associated with mastectomy in women with small residual tumor, defined as ypT≤20 mm in the mastectomy specimen. The ratio between tumor volume (including all foci and cancer in situ) and excised breast volume was calculated in order to describe the tumor-affected proportion on a randomly selected subset of women having a mastectomy (n=136).

Results: A total of 1041 women (71.2%) underwent mastectomy and 422 (28.8%) breast conserving surgery (BCS). In the mastectomy group, 551 (52.9%) had a residual invasive tumor extent of ≤20 mm. Factors independently associated with having a mastectomy and ypT≤20 mm after NACT were diagnosis in the earlier study periods [2007-2010 (OR 11.09, 95% CI 6.42-19.16, p<.001) and 2011-2014 (OR 2.92, 95% CI 2.10-4.07, p<.001)], younger age [age <40 (OR 2.08, 95% CI 1.39-3.13, p<.001) and age 40-49 (OR 1.61, 95% CI 1.12-2.32, p=.011)], large tumor size at diagnosis [cT3 (OR 4.25, 95% CI 2.47-7.31, p<.001) and cT4 (OR 7.42, 95% CI 2.25-24.52, p=.001)], pretreatment biopsy being PR negative (OR 1.55, 95% CI 1.04-2.31, p=.032) or HER2 positive (OR 1.51, 95% CI 1.10-2.06, p=.011). After a median follow-up time of 3.5 years, local relapse rate was 3.3% (14/422), 3.8% (21/551) and 5.7% (28/490) in the BCS, mastectomy with ypT≤20 mm and mastectomy with ypT>20 mm groups respectively (p=.158). Only 10.3% (14/136) of women who had undergone mastectomy had >10% of breast volume consisting of tumor.

Conclusions: In this population-based study, mastectomy after NACT was commonly used even in women with good tumor response, especially in younger women and tumours with certain high-risk features. However, a strong trend of more BCS is seen in the more recent years of the study period without compromising local disease control.

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116P Is young age an independent adverse prognostic factor in carcinoma breast? A single institute retrospective comparative study from South India

A. K P

Surgical Oncology, RCC - Regional Cancer Centre, Thiruvananthapuram, India

Background: The incidence of breast cancer is as low as 0.50% in females younger than 40 years old. Young age in patients with breast cancers is thought to be associated with poor prognosis, but the reason is not well defined. Adverse pathological features like more TNBC and Her2 positivity as well as a lack of reliable screening methods in young women leads to the poor prognosis in this group of patients. This study aimed to analyse the prognostic value of age in patients with carcinoma breast.

Methods: Patients with nonmetastatic carcinoma breast who had registered in our hospital during the year 2012 were selected for the study. Treatment details were retrospectively collected and survival data till 31st July 2019 was obtained via telephonic interview. Patients were grouped into two based on their age at diagnosis (less than or equal to 40, and more than 40). The Kaplan Meier method was employed for survival analysis. Survival comparison was done using the log-rank test. Cox proportional hazards regression analysis was done for assessing the risk.

Results: Out of 1611 curatively treated patients with carcinoma breast, 281 (17.44%) were young breast cancer patients (equal to or less than 40 years). The median follow up period was 82 months. Median age of diagnosis was 51.3 years. Young patients presented larger tumour size, but nodal stage and composite stage were not different. They had more TNBC status, 35% vs 24%, p=0.001. The young patient group had a decrease in 5-year OS but it was statistically nonsignificant (75.9% vs 82.5%, p=0.179), and a marginally significant decrease in DFS (67.9% vs 73.3%, p=0.056). Patient with nodal yield more than 10 was found to have significant benefit in OS compared to lower nodal count (86% vs 77%, p=0.038). In Cox regression analysis T, N status, Her2neu status and nodal yield were found to be the independent risk factors affecting overall survival.

Conclusions: The proportion of young breast cancer is very high in the Indian population. Age is not an independent risk factor for worse prognosis. T and N stage, Her2neu status and adequacy of nodal clearance are the most important independent risk factors determining the 5-year OS.

Legal entity responsible for the study: Director, RCC.

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117P Pregnancy-associated breast cancer (PABC): Demographics and outcome analysis from a lower and middle income country (LMIC)

J. Bajpai[1], S. Dandekar[2], V. Simha[3], T. Shylasree[4], R. Sarin[5], V. Bansal[6], J. Ghosh[2], S. Rath[2], N. Nair[4], S. Gulia[2], A. Patil[7], S. Gupta[2]

[1]Medical Oncology Department, Tata Memorial Hospital - Tata Memorial Centre, Mumbai, India; [2]Medical Oncology, Tata Memorial Centre, Mumbai, India; [3]Medical Oncology, Tata Memorial Centre, Chandigarh, India; [4]Surgical Oncology, Tata Memorial Centre, Mumbai, India; [5]Radiation Oncology, Tata Memorial Centre, Mumbai, India; [6]Medical Oncology, Wadia Hospital, Mumbai, India; [7]Biostatician, Tata Memorial Centre, Mumbai, India

Background: PABC is defined as breast cancer diagnosed during pregnancy or one year post-partum. It poses a unique challenge to safeguard oncologic outcome and fetal safety. This is an unmet need especially in LMICs and merits exploration.

Methods: A prospective and retrospective registry study of PABC was carried out from May 2013-Feb 2020 at Tata Memorial Center in India.

Results: There were 100 patients with a median age of 31 (20-42) years; 33 diagnosed during pregnancy while 67 postpartum; 79 had delayed diagnosis. 23 had family history, 1 was positive for BRCA mutation (185DelAG). Of these, 96% had IDC grade III tumours, 50 were triple-negative and 35 were Her2-positive. 84 patients received anthracyclines and taxanes; grade III/IV complications occurred as: 12 febrile-neutropenias, 3 mucositis, 1 hypersensitivity. Of 72 non-metastatic patients, 52 received neoadjuvant-chemotherapy, 28 underwent breast-conservations and 4 had pathological complete remission. Of the total, 33 patients were diagnosed during pregnancy (14-first, 12 -second, 7-third trimester). There were 16 medical terminations (MTP) (5 metastatic), 15 full term, and 2 premature deliveries with average birth -weight of 2.48kg (1.7-4kg). One neonate had hydrouretronephrosis and another two required ventilator support due to prematurity. Trastuzumab, tamoxifen and radiotherapy were administered post-delivery. 65 patients were diagnosed postpartum. There were 2 MTPs (1 metastatic), 15 full term, 1 premature delivery with average birth weight of 2.9kg (1.7-4kg). There was no congenital abnormality but two infants succumbed at 18 days (unknown cause) and 6 months after birth (severe diarrhea). Of the rest, all 78 (17/33 and 61/65) babies are alive with normal milestones. At median follow up of 18 (11-25) months, 2 years overall and event free survival in early (100%, 92%), locally advanced (76%, 54%) and metastatic breast cancer is (77%,32%), p values of 0.019 and 0.001.

Conclusions: PABC is associated with delayed, advanced presentation and aggressive biology. Outcomes deteriorated as stage is advanced. However, stage-matched outcomes are comparable if adequately treated. International collaboration and consensus are highly warranted to optimize outcomes.

Legal entity responsible for the study: Jyoti Bajpai, Tata Memorial Centre.

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118P Should DIBH (deep inspiration breath-hold) be the standard of care in LBC (left breast cancer)?

M.G. Garcia Alvarez[1], C. Peraza Fernandez[1], C. Rodrigues[2], M. Mateos Dominguez[1], M. Montijano Linde[1], I. Marrone[1], L. Tinoco Gil[1], E. López Ramirez[3]

[1]Radiotherapy, GenesisCare, H. San Francisco de Asís, Madrid, Spain; [2]Radiotherapy, Genesiscare, Windsor, UK; [3]Radiotherapy, GenesisCare, Madrid, Spain

Background: Radiotherapy is the most effective treatment to eradicate the residual locoregional disease after breast cancer surgery with significative survival improvements after 15 years post diagnostic. For women receiving left-breast radiotherapy (DIBH) is used to further mitigate mortality and morbidity due to late cardiac toxicity, with a demonstrated linear relationship with Mean Heart Dose (MHD). The risk increases 7.4% per Gy, starting within the first 5 years and continuing into the third decade after radiotherapy. The aim of this study was to evaluate the effect of DIBH irradiation on MHD, V16, V8, V4 and mean, maximum and D10% left anterior descending coronary artery (LADCA) dose.

Methods: 75 patients with left breast cancer (LBC), after radical mastectomy or conservative surgery, that were able to maintain voluntary DIBH $\geq$ 20 seconds, were irradiated with this cardiac sparring approach. All patients received hypofractionated radiotherapy (total dose of 40.05Gy / 2.67Gy per fraction) with 58 receiving a concomitant boost (total dose of 48Gy / 3.2Gy per fraction) and 9 patients having axillary nodes irradiated. The target volume was delineated on CT in DIBH and Free Breathing (FB) according to the ESTRO consensus guideline and heart according to the CT-based atlas by Feng et al. Tangent-based intensity modulated radiation therapy (n: 71) or VMAT (n: 4) plans were developed for both datasets. Patient set-up and tracking in FB/DIBH was monitored by Surface Guided Radiation Therapy (VisionRT, London, UK), after daily validation by cone beam CT matching.

Results: DIBH reduces significantly MHD, V16, V8, V4 and mean, maximum and D10% LAD dose compared to FB ($p = 0.001$). This difference is irrespective of breast PTV volume (797$\pm$367.6 cm3) or boost PTV volume (75.3 $\pm$ 30.3cm3). DIBH average MHD was 1.20 Gy (0.87-1.62) and average LADCA Dmean of 4.95 Gy (2.79-9.14) with respectively in FB 3.18 Gy (2.47-4.26) and 20.20Gy (12.29.-25.40).

Conclusions: DIBH in LBC does lead to a significant reduction in heart and LADCA doses by increasing the distance between target and heart. These reductions could contribute to increase cardiovascular health of LBC. These findings apply to all patients and further studies will indicate to which subgroups the benefits are more pronounced.

Legal entity responsible for the study: GenesisCare Spain.

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Disclosure: All authors have declared no conflicts of interest.

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120P Synchronous breast cancers with dissimilar radiological appearances

S. Gnaneswaran[1], A. Palmer[1], E. Millar[2]

[1]Medical Imaging, BreastScreen NSW South Eastern Sydney Illawarra, Kogarah, Australia; [2]Anatomical Pathology, NSW Health Pathology, Kogarah, Australia

Background: To discuss the incidence and characteristics of synchronous breast cancers in a cohort of screening patients who had radiologically dissimilar lesions.

Methods: We performed a retrospective study in screening patients over a 10 year period who underwent biopsies of at least two synchronous lesions, one of which had been classified as having a benign/equivocal radiological appearance (with the other being radiologically suspicious for malignancy). The cohort was separated into two groups based on whether the benign-appearing lesion was proven to be a cancer (Group A) or benign (Group B). Patient and tumour factors were then reviewed.

Results: There were 29,643 patients who attended a screening assessment clinic at our institution between 1st July 2009 to 30th June 2019. Twenty (0.07%) had synchronous breast lesions with dissimilar imaging appearances. Seven (35%) of these were in Group A where there were 15 cancers diagnosed. There were 15 benign lesions and 29 cancers diagnosed amongst the 13 patients in Group B. Of the 5 benign-appearing cancers diagnosed in Group A, 2 (40%) were of favourable histology (mucinous or papillary). There were two (40%) invasive ductal carcinomas NOS, one of which was high grade. The majority (60%) of benign lesions within Group B were fibroadenomas. Of the radiologically suspicious cancers between the two groups, 43% were high grade in Group A. This compared to 3% in Group B. In all cases (100%) within Group A the benign-appearing cancer was located in the same breast as the radiologically suspicious cancer. In comparison, in Group B, 54% of the radiologically dissimilar lesions were in the same breast. There was no difference in age between the groups. None of the patients in Group A had a family history of breast cancer, whilst 3 (23%) in Group B had close relatives who had been diagnosed.

Conclusions: Synchronous breast cancers with dissimilar imaging appearances are a rare occurrence in screening patients. Regardless, those who have radiologically dissimilar lesions should be viewed with a high index of suspicion, particularly as the benign-appearing lesion proved to be malignant in 35% of cases in our cohort. When the benign-appearing lesion was a cancer the second radiologically suspicious cancer was also more likely to be high grade.

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Disclosure: All authors have declared no conflicts of interest.

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121P Can axillary surgery be avoided in patients with breast pathologic complete response after neoadjuvant systemic therapy? A real-world study in China

R. Chen, Y. Li, S. Li, Q. Zhu, X. Shi, X. Zha, J. Wang

Breast Surgery, Jiangsu Province Hospital - The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Some breast cancer patients can achieve pathologic complete response (pCR) for breast and/or axillary lymph node after neoadjuvant systemic therapy (NST). If the breast achieved pCR confirmed by extensive biopsy, the necessity of breast surgery has been questioned. Whereas, the appropriate management of the axilla in breast pCR patients is rarely studied. This cohort study was designed to retrospectively evaluate the status of axillary lymph nodes in relation to breast pCR and identify patients who may be eligible for omission of axillary surgery.

Methods: This study in a single institution concluded operable breast patients who received NST followed by standard breast and nodal surgery from 2015 to 2019. The rates of axillary pCR (ypN0) were compared between patients who did or did not achieve breast pCR (ypT0/is).

Results: Among 258 patients, 70 (27.1%) patients achieved ypT0/is, and there was no statistical difference according to patients' age, menopausal status, clinical tumor size and lymph node status when compared with non-ypT0/is patients. Patients with HER2-positive and triple-negative (TN) subtypes have a higher incidence of ypT0/is than patients with luminal subtype ($P<0.001$). Overall, the rate of ypN0 in ypT0/is group was higher than in non-ypT0/is group (87.1% vs 34.6%, $P<0.0001$). For cN0 (clinically assessed negative lymph node before NST) patients, although there was no difference of ypN0 rates between ypT0/is group and non-ypT0/is group (100% vs. 85.7%, $P=0.1534$), the high value of ypN0 rate in ypT0/is group (100%) provided evidence of axillary surgery omission. In addition, for cN+ (clinically assessed positive lymph node before NST) patients, the ypT0/is group population was more likely to achieve ypN0 than non-ypT0/is population (82.7% vs 22.9%, $P<0.0001$). Moreover, more cN+ patients achieved ypN0 in ypT0 group than in ypTis group (94.3% vs 58.8%, $P= 0.0034$), and the high rate number (94.3%) also indicated possibility of axillary surgery omission.

Conclusions: Evidence supported that, for cN0 patients who achieved ypT0/is, and cN+ patients who achieved ypT0, axillary surgery may be omitted.

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122P A comparison of margin involvement and re-excision rates with the use of 'Klinitray' versus standard suture specimen orientation in wide local excision surgery for breast cancer

T. Clarke[1], K. Edwards[2], J. Piper[2]

[1]General Surgery Department, York District Hospital, York, UK; [2]Breast Department, York District Hospital, York, UK

Background: The National Institute for Health and Care Excellence (NICE) guidelines recommend breast conservation surgery (BCS) as the mainstay of treatment for breast cancer. The Association of Breast Surgery (ABS) advises a 1mm clear radial margin after BCS for early invasive breast cancer and in situ carcinoma of the breast. Margin involvement varies across the UK, with national rates around 14.8% following ABS guidelines. We report on the use of clinical equipment 'KliniTray' to orientate tissue specimen intra-operatively in wide local excision (WLE) surgery, allowing more accurate anatomical positioning by the surgeon, compared to standard orientation with sutures only. We considered the rate of margin involvement and further need for surgery.

Methods: A retrospective study was conducted at the York District Hospital looking at patients from 4th September – 4th December 2018 who underwent WLE surgery for breast cancer with standard orientation of tissue specimen, and patients from 4th September – 4th December 2019 after the introduction of 'KliniTray'.

Results: A total of 105 patients were included. We accept margins >1mm as clear for both invasive and DCIS. The rate of margin involvement reduced from 23.1% to 17.5% after the introduction of KliniTray ($p>0.05$) with a reduction in the need for further surgery from 18.5% to 7.5% ($p>0.05$).

Conclusions: 'KliniTray' reduces the rate of margin involvement and thus further need for surgery and its use should be considered in other hospitals performing BCS. Future studies with a larger sample size should be conducted to determine whether this is statistically significant.

Legal entity responsible for the study: York District Hospital.

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123P Cosmetic outcome after vacuum-assisted excision is good and independent of the amount of resected tissue

E. Van De Voort, T. Klem, G. Struik, A. Ghandi, R. Sinke

Surgery, SFVG - St Franciscus Gasthuis, Rotterdam, Netherlands

Background: A better cosmetic outcome after vacuum-assisted excision is suggested in previous studies, but it has, to the best of our knowledge, never been formally evaluated nor demonstrated. While, providing more insight in patient reported outcomes is especially important for treatment decision making of this non-malignant disease. Therefore, we aimed to evaluate patient reported cosmetic outcome and the contributing variables after vacuum-assisted excision.

Methods: In this cross-sectional study, patients who underwent vacuum assisted excision were invited to complete the cosmetic subscale of the Dutch Breast Cancer Treatment Outcome Scale (BCTOS-cs). For each patient, the mean cosmetic outcome was calculated and cosmetic outcome was dichotomized as either good or suboptimal. All clinically relevant variables were independently tested for the impact on cosmetic outcome. Variables that were possibly associated with cosmetic outcome (univariate $p<0.2$) were included in a multivariable regression analysis.

Results: The BCTOS-cs was completed by 46 of 64 (73.4%) contacted patients. Mean cosmetic outcome was 1.5 (good) and was not related to the number of resected cores and weight of the specimen ($r=0.248$, $p=0.093$ and $r=0.221$, $p=0.131$ respectively). Cosmetic outcome was not significantly different between tumors ≥3cm and <3cm (respectively mean 1.74 ± 0.66 vs. 1.53 ± 0.45, $p=0.36$). The absence of follow-up complications was the only significant factor associated with a better mean cosmetic outcome score ($\beta= 0.367$, SE=0.152, $p=0.02$) and with the dichotomized cosmetic outcome (OR=13.5, 95% CI 1.13-162.0, $p=0.04$) in the multiple regression analyses.

Conclusions: It was already known that vacuum-assisted excision of benign lesions is safe and effective and now this study confirms that the patient reported cosmetic outcome after vacuum-assisted excision is good and independent of tumor size and resected specimen. The absence of complications was the only factor that contributed to a better cosmetic outcome. All recurrent lesions occurred in tumors < 3cm and no

severe complications occurred in lesions > 3cm. Thus, vacuum-assisted excision could also be beneficial in patients with larger (> 3cm) benign breast tumors.

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Disclosure: All authors have declared no conflicts of interest.

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125P Prognostic factors in phyllodes tumours (PT) of the breast: A single-institution cohort

E. Di Liso[1], M. Bottosso[1], V. Tsvetkova[2], M. Lo Mele[3], M.V. Dieci[4], C. Falci[4], G. Faggioni[5], G. Tasca[5], C.A. Giorgi[4], T. Giarratano[4], E. Mioranza[4], A.P. Dei Tos[6], V. Guarneri[7], P.F. Conte[4]

[1]Medical Oncology 2, Istituto Oncologico Veneto, Padua, Italy; [2]Department of Pathology and Diagnostics, University and Hospital Trust of Verona, University of Study of Verona, Verona, Italy; [3]Department of Medicine, Surgical Pathology Unit, University of Study of Padua, Padua, Italy; [4]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy; [5]Medical Oncology 2, IOV - Istituto Oncologico Veneto IRCCS, Padua, Italy; [6]Department of Medicine, University of Padua, School of Medicine, Padua, Italy; [7]Department of Surgery, Oncology and Gastroenterology, Istituto Oncologico Veneto IRCCS, Padua, Italy

Background: PT are rare fibroepithelial tumors accounting for < 1% of all breast tumors. We assessed clinicopathological features and their prognostic effect in a single-institution patients cohort.

Methods: Patients diagnosed with PT between 2001 and 2008 at our Institution were identified. Clinical, surgical and pathological features were collected. Phyllodes-related relapse (PRR) was defined as locoregional or distant recurrence (contralateral excluded).

Results: 115 patients with benign, 30 with borderline and 21 with malignant PT were identified. Features associated with malignant PT were: younger age, larger T size, higher mitotic count, marked cytologic atypia, stromal overgrowth, stromal hypercellularity, necrosis and heterologous differentiation (all $p<0.01$). The majority of malignant PT patients received mastectomy (63.2% vs 3% of benign/borderline, $p<0.001$) and had negative surgical margins (83.3%). 4-yr cumulative PRR incidence was 7% for benign/borderline and 21.3% for malignant PT ($p=0.107$). In the entire cohort, marked cellular atypia and heterologous differentiation were associated with worse PRR-free survival (HR 14.10, $p=0.036$ for marked vs mild atypia; HR 4.21, $p=0.031$ for heterologous differentiation present vs absent). For patients with benign PT larger tumor size was associated with worse PRR-free survival (HR 9.67, $p=0.013$ for T>5cm vs T<2cm,). Positive margins were a poor prognostic factor for malignant PT patients (HR 16.61, $p=0.025$). Overall, 4 patients died because of PT: 3 patients with malignant and 1 with borderline PT.

Conclusions: Patients with malignant PT had increased rates of PRR and phyllodes-related death. Cellular atypia and heterologous differentiation were poor prognostic factors in the entire cohort; large tumor size and positive margins were associated with increased risk of PRR in benign and malignant PT, respectively.

Legal entity responsible for the study: The authors.

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126TiP Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (SAKK 23/16 / IBCSG 57-18 / ABCSG-53 / GBG 101 - TAXIS): A multicenter randomized phase III trial

W.P. Weber[1], G. Henke[2], K. Ribi[3], S. Hayoz[4], S. Seiler[5], C. Maddox[6], T. Ruhstaller[7], D. Zwahlen[8], S. Muenst[9], M. Ackerknecht[10], F. Fitzal[11], Z.T. Matrai[12], M. Újhelyi[12], C. Kurzeder[13], L. Lelièvre[14], C.J. Tausch[15], J. Heil[16], M. Knauer[17]

[1]Breast Surgery, University Hospital Basel, Basel, Switzerland; [2]Radiation Oncology, University Hospital St. Gallen, St. Gallen, Switzerland; [3]7SAKK Coordinating Center, Switzerland, SAKK Coordinating Center, Bern, Switzerland; [4]IBCSG Coordinating Center, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland; [5]SAKK Coordinating Center, Bern, Switzerland; [6]SAKK Coordinating Center, Switzerland, ETOP - European Thoracic Oncology Platform, Bern, Switzerland; [7]Breast Center Eastern, Brustzentrum Ostschweiz AG, St. Gallen, Switzerland; [8]Department of Radiation Oncology, Cantonal Hospital Winterthur, Winterthur, Switzerland; [9]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland; [10]Department of Biomedicine, University Hospital Basel, Basel, Switzerland; [11]Surgery Department, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria; [12]Department of Breast and Sarcoma Surgery, National Institute of Oncology Hungary, Budapest, Hungary; [13]Senology, University Hospital Basel, Basel, Switzerland; [14]Centre du Sein, CHUV, Lausanne, Switzerland; [15]Brust-Zentrum, Brust-Zentrum, Zurich, Switzerland; [16]Brustzentrum, University Hospital Heidelberg, Heidelberg, Germany; [17]Head Breast Surgery Department, Brustzentrum Ostschweiz AG, St. Gallen, Switzerland

Background: Complete lymph node removal through conventional axillary lymph node dissection (ALND) has been standard treatment for breast cancer patients for almost a century. However, ALND came under increasing scrutiny due to its association with significant patient morbidity. Several studies have since provided evidence to suggest omission of ALND, often in favor of axillary radiation, in selected clinically node-negative sentinel lymph node (SLN)-positive patients. Clinically node-positive patients, by contrast, continue to undergo ALND in many cases. There is a need for a clinical trial to evaluate the optimal treatment for clinically node-positive breast cancer patients in terms of surgery and radiotherapy. The TAXIS trial is designed to examine the value of tailored axillary surgery (TAS), a new technique for selectively removing positive lymph nodes.

Trial design: In this international, multi-center, phase-III, non-inferiority randomized controlled trial, including 32 study sites from five countries, we plan to randomize 1500 patients to either receive TAS followed by ALND and regional nodal irradiation excluding the dissected axilla, or receive TAS followed by regional nodal irradiation including the full axilla. All patients undergo adjuvant whole-breast irradiation after breast conserving surgery and chest wall irradiation after mastectomy. Inclusion of internal mammary nodes is recommended irrespective of treatment arm. The main objective of the trial is to test the hypothesis that treatment with TAS and axillary radiotherapy is non-inferior to ALND in terms of disease-free survival of clinically node-positive breast cancer patients. Secondary objective is to test if quality of life is significantly better with TAS. The trial was activated on 31 July 2018 and the first patient was randomized on 07 August 2018. As of 24 January 2020, 186 patients have been randomized. Accrual is planned until end of 2023, with a total study duration until the primary endpoint of 11 years.

Clinical trial identification: NCT03513614.

Legal entity responsible for the study: SAKK, GBG, ABCSG, IBCSG.

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IMMUNOTHERAPY

1270 Tumour mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo

T. Karn[1], C. Denkert[2], K.E. Weber[3], U. Holtrich[4], C. Hanusch[5], B.V. Sinn[6], B. Higgs[7], P. Jank[8], J. Huober[9], J-U. Blohmer[10], W.D. Schmitt[11], S. Wu[7], M. van Mackelenbergh[12], C. Schem[13], E. Stickeler[14], C. Jackisch[15], M. Untch[16], A. Schneeweiss[17], S. Loibl[18]

[1]University Hospital, Goethe University, Frankfurt am Main, Germany; [2]Institute of Pathology, Uniklinikum Giessen und Marburg, Marburg, Germany; [3]Statistics, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [4]University Hospital, Goethe University, Frankfurt, Germany; [5]Gynäkologie, Rotkreuzklinikum München, Munich, Germany; [6]Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [7]TM, MedImmune + LAP&P, Gaithersburg, MD, USA; [8]Pathology Department, Uniklinikum Giessen und Marburg (UKGM), Marburg, Germany; [9]Department of Gynecology, Breast Center, Universitaetsfrauenklinik Ulm, Ulm, Germany; [10]Gynäkologie, Charité - Universitätsmedizin Berlin, Berlin, Germany; [11]Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [12]Gynäkologie, University Hospital Kiel, Kiel, Germany; [13]Gynäkologie, Mammazentrum Hamburg, Hamburg, Germany; [14]Department of Gynecology and Obstetrics, Universitaetsklinikum Aachen (UKA), Aachen, Germany, Germany; [15]Frauenklinik, Klinikum Offenbach GmbH, Offenbach am Main, Germany; [16]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin Buch, Berlin, Germany; [17]Gynecological Oncology, National Center for Tumor Disease, Heidelberg, Germany; [18]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany

Background: The predictive value of tumor mutatio1nal burden (TMB), alone or in combination with an immune gene expression profile (GEP), for response to neoadjuvant therapy in early triple negative breast cancer (TNBC) is currently not known, neither for immune checkpoint blockade (ICB) nor conventional chemotherapy.

Methods: We obtained both whole exome sequencing and RNA-Seq data from pretreatment samples of 149 TNBC of the recent neoadjuvant ICB trial GeparNuevo. In a predefined analysis we assessed the predictive value of TMB and a previously developed immune GEP for pathological complete remission (pCR).

Results: Median TMB was 1.52 mut/Mb (range 0.02-7.65) and was significantly higher in patients with pCR (median 1.87 vs. 1.39; P=0.005). In multivariate analysis odds ratios for pCR per mut/Mb were 2.06 (95% CI 1.33-3.20, P=0.001) among all patients, 1.77 (95% CI 1.00-3.13, P=0.049) in the durvalumab treatment arm, and 2.82 (95% CI 1.21-6.54, P=0.016) in the placebo treatment arm, respectively. We also found that both continuous TMB and immune GEP (or tumor infiltrating lymphocytes) independently predicted pCR. When we stratified patients in groups based on the upper tertile of TMB and median GEP, we observed a pCR rate of 82% (95% CI 60%-95%) in the group with both high TMB and GEP, in contrast to only 28% (95% CI 16%-43%) in the group with both low TMB and GEP.

Conclusions: TMB and immune gene expression profile add independent value for pCR prediction. Our results recommend further analysis of TMB in combination with immune parameters to individually tailor therapies in breast cancer.

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Legal entity responsible for the study: The authors.

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1280 PDL1/CD274 gain/amplification as a predictive marker of checkpoint blockade inhibitor efficacy in metastatic breast cancer: Exploratory analysis of the SAFIR02-IMMUNO randomized phase II trial

T. Bachelot[1], T. Filleron[2], F. Dalenc[3], I. Bieche[4], I. Gaberis[5], E. Rouleau[5], A. Tran-Dien[5], J. Adam[6], A. Lusque[7], M. Jimenez[8], A. Jacquet[8], F. André[9]

[1]Centre Léon Bérard, Lyon, France; [2]Biostatistics, Centre Claudius-Regaud, Toulouse, France; [3]Centre Claudius-Regaud, Toulouse, France; [4]Institut Curie, Paris, France; [5]Gustave Roussy - Cancer Campus, Villejuif, France; [6]Pathology, Institut Gustave Roussy, Villejuif, France; [7]Biostatistics, Centre Claudius-Regaud, Toulouse, France; [8]R&D, Unicancer, Paris, France; [9]Breast Cancer Unit, Medical Oncology Department, Gustave Roussy - Cancer Campus, Villejuif, France

Background: PD(L)1 inhibitor have shown efficacy for limited sub population of patients (pts) with HER2 negative metastatic breast cancer (MBC). The main predictive marker of efficacy to date are the absence of ER and PR receptor, and pdl1 positivity by IHC. We investigated copy number alteration (CNA) of the PDL1 gene (also named CD274) located at 9p24.1 in the SAFIR02 Breast Immuno randomized phase II trial (NCT02299999).

Methods: SAFIR02 BREAST IMMUNO randomized 199 pts presenting a MBC without actionable genomic alterations, responding to 6 months standard chemotherapy, either on durvalumab (10 Mg/kg every two weeks) or on maintenance chemotherapy with a 2:1 ratio. Eighty-two (43%) pts had a triple negative (TN) MBC. Using metastatic tumor samples, PDL1 CNA were characterized from array CGH analysis (Affymetrix CytoscanHD or Oncoscan). A gain of copy number was defined as 3−4 copies and an amplification $\geq$ 5 copies. Treatment effect was estimated in each subgroup using a cox proportional hazard model.

Results: For PDL1 CNA were available for 153 pts (101 immuno, 52 chemotherapy). PDL1 copy loss, neutral, or copy gain/amplification were reported on 30 (20%), 93 (61%) and 30 (20%) of pts, respectively. Pts with TN MBC had a higher proportion of gain/amplification (23/65 pts, 35% for TN tumors; vs 7/82, 8.5% for non-TN). Improvement of OS with durvalumab was limited to the PDL1 CNA gain/amplification subgroup (HR = 0.17, 95% CI 0.05-0.55) with a median OS of 9 months (95%CI 4-18) in maintenance arm and not reached in durvalumab arm. Among pts with TN tumors, durvalumab was associated to a better OS in the gain/amplification subgroup (HR 0.18, 95%CI 0.05-0.71), compared to the neutral/loss subgroup (HR 1.1, 95%CI 0.47-2.6).

Conclusions: This exploratory subgroups analysis of the first randomized trial comparing a PDL1 inhibitor to chemotherapy in the maintenance setting shows that PDL1 CNA could be an important predictive marker for PD(L)1 inhibitors efficacy. If confirmed on larger series, it could have an important implication on the development of immunotherapy for MBC pts, in particular for subgroups with low immunogenicity such as the luminal subtype.

Clinical trial identification: NCT02299999; 2013-001652-36.

Legal entity responsible for the study: Unicancer.

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Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Lilly; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Eisai; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: MSD; Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: AstraZeneca. F. André: Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Lilly; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: AstraZeneca; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Daiichi Sankyo; Leadership role, Founder: Pegacsy. All other authors have declared no conflicts of interest.

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129P Phase II study of pembrolizumab and nab-paclitaxel in HER2-negative metastatic breast cancer: Hormone receptor-positive cohort

Y. Novik[1], N. Klar[1], S. Zamora[1], M. Kwa[1], J. Speyer[1], R. Oratz[1], F. Muggia[1], M. Meyers[1], T. Hochman[2], J. Goldberg[2], S. Adams[3]

[1]Oncology, NYU Cancer Institute NYU Medical School, New York, NY, USA; [2]Biostastics/Population Health, NYU Langone Medical Center, New York, NY USA; [3]Medicine, NYU Cancer Institute NYU Medical School, New York, NY, USA

Background: PD-1/PD-L1 checkpoint blockade in combination with chemotherapy has improved outcomes in triple-negative breast cancer, but its role in hormone receptor-positive (HR+) metastatic breast cancer (MBC) is less clear. We report the results of the HR+ cohort of a HER2-negative MBC trial.

Methods: Prospective phase 2 trial where 20 HR+/HER2- MBC patients (pts) received nab-paclitaxel (A) (100mg/m2 IV d1/8, q 3 wks) and pembrolizumab (P) (200mg IV d1, q 3 wks, starting with cycle 2). Eligibility: ER/PR $\geq$1%, HER2 negative, maximum of 2 lines of cytotoxic therapy for MBC, pts could have received prior endocrine and/or targeted therapy. Primary endpoint: best overall response rate (BORR) by RECIST v1.1; secondary endpoints: safety, PFS, clinical benefit rate (CBR), duration of response (DOR), and overall survival (OS). Biomarker analyses are ongoing.

Results: In this 20-patient cohort, the median age was 56 (34-75), median lines of cytotoxic chemotherapy was 1 (0-2), 70% (14/20) were ER>10%, 80% (16/20) received prior hormone therapy, and 60% (12/20) received prior CDK 4/6 inhibitors. BORR was partial response (PR) in 5/20, stable disease (SD) in 7/20, and progressive disease (PD) in 7/20. CBR was 35% (7/20). Median PFS was 5.6 mos (95%CI 2.07-8.18), median OS 15.7 mos (95%CI 3.88-27.70) and median DOR was 3.9 mos (95%CI 2.07-not yet reached). Out of 5 pts who achieved PR, 4 (80%) received prior CDK 4/6 inhibitors. The most common related adverse events (AE) were anemia (50%), diarrhea, nausea and ALT abnormalities (40% each). 14 pts experienced grade 3 AEs, the most common being neutropenia, 1 pt had grade 4 AEs (pneumonitis, blood/lymphatics, hyponatremia), and no grade 5 AEs.

Table 129P: Outcomes in HR+/HER2- MBC

HR+/HER2 cohort (n = 20)	
CR	0 (0%)
PR	5 (25%)
SD	7 (35%)
Not evaluable	1 (5%)
CBR (PR+SD>6mos)	7 (35%)
mDOR	3.9 mos
mPFS	5.6 mos
mOS	15.7 mos

Conclusions: P plus A was efficacious with PR in 5/20 and SD in 7/20 pts with a manageable toxicity profile. Importantly, responses were observed in patients previously treated with CDK 4/6 inhibitors. Further investigation of this regimen in HR+/HER2- MBC is warranted.

Clinical trial identification: NCT02752685.

Legal entity responsible for the study: NYU Langone Health.

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131P Abrogation of paclitaxel chemo-resistance via epigenetic immune checkpoints regulation in triple negative breast cancer

S.A. El Shihy[1], R.E. Abdeltawab[2], H.M. El Tayebi[1]

[1]Department of Pharmacology and Toxicology, GUC - German University in Cairo, Cairo, Egypt; [2]Surgical Oncology, Ain Shams University, Cairo, Egypt

Background: Chemotherapy is the standard monotherapy of Triple Negative Breast Cancer (TNBC) and a main cause for chemo-resistant cases. Anti-programmed death (PDL1) and Anti-Mesothelin (MSLN) therapies has thrust the immunotherapy into spotlight showing a potential cure for TNBC, yet they are understudied. Moreover, MSLN itself was proved to contribute in paclitaxel chemoresistance. MiR-34a along with our previously characterized LncRNA-XIST were proved to be potent tumor-suppressors in TNBC cell lines. This study aims to investigate the role of PD-L1 and MSLN epigenetic regulation in increasing chemo-sensitivity of paclitaxel in TNBC.

Methods: BC tumors, lymph nodes (LN) as well as normal breast tissues were resected from 20 BC patients (30% TNBC and 70% invasive ductal carcinoma-IDC). miR-34a expression manipulation was performed in MDA-MB231 cells followed by total RNA extraction using Trizol followed by reverse transcription (c-DNA) ending with Real Time qPCR (RNU6B, Beta-2-microglobulin as housekeeping genes). MTT Assay was conducted on MDA-MB 231 cell line followed by absorbance measurement.

Results: XIST and PD-L1 were downregulated and overexpressed, respectively, in BC tumors and malignant LN compared to controls (P=0.0102, P=0.0237 and P=0.0139, P=0.0065 respectively). MSLN was high in Luminal A&B and higher in TNBC tissues (P=0.0141, P=<0.0001, respectively). miR-34a overexpression in BC cell lines decreased MSLN and PDL-1 (P=0.0400, P= 0.0143, respectively) in contrast to anti-miR-34a. Silencing of XIST increased MSLN and PD-L1 (p= 0.0250, p=0.0008, respectively). Inducing XIST by siTSIX showed downregulation of MSLN and PD-L1 (p=0.0143, p=0.0258, respectively). Co-transfection of miR-34a and siXIST overexpressed MSLN (P= 0.0244) and showed no impact on PD-L1. However, co-transfection of miR-34a with siTSIX decreased MSLN and PD-L1 (P=0.0078, P=0.0157, respectively). Cells with the lowest MSLN and PDL1 (miR-34a+siTSIX) showed the lowest cell viability post-paclitaxel treatment (P=0.0004).

Conclusions: The tumor suppressive function of miR-34a was augmented by the induction of XIST expression leading to a potent suppression in MSLN and PD-L1 expression that revives paclitaxel chemo-sensitivity in TNBC.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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132P MALAT-1 ruling the miR-182/PIG-C/MSLN triad in triple negative breast cancer

A. Samir[1], F. Barsoum[1], R.E. Abdeltawab[2], H.M. El Tayebi[1]

[1]Department of Pharmacology and Toxicology, GUC - German University in Cairo, Cairo, Germany; [2]Surgical Oncology, Ain Shams University, Cairo, Egypt

Background: In the last decade, cancer immune evasion has brought immunotherapy to the light of oncology and became a principle approach in cancer therapy. microRNA-34a and Long non-coding RNA MALAT1 are examples of a newly emerged group of non-Coding RNAs that have grabbed attention towards understanding epigenetic manipulation in many cancers among which is triple negative breast cancer (TNBC) that is characterized by strong heterogeneity and aggressiveness. Our previous data revealed that Mesothelin (MSLN) and phosphatidylinositol glycan anchor biosynthesis class C (PIG-C) are overexpressed in breast cancer cell lines and biopsies. This study investigates the interplay between miRNAs and lncRNAs, and their impact on MSLN and PIG mRNA transcript expression in different BC subtypes specially TNBC.

Methods: BC as well lymph nodes biopsies were collected from 41 TNBC and Invasive Ductal Carcinoma (IDC) patients. Expression profiling of PIG-C, MALAT-1, MSLN and miR-182 was analyzed by Taqman Real Time qPCR and normalized by Beta-2-microglobulin and RNU6B. Manipulation of gene expressions as well as co-transfections were performed in MDA-MB-231 cells followed by quantifying MSLN and PIG-C genes by RT-qPCR.

Results: The relative expression of miR-182, MSLN, MALAT-1 and PIG-C were markedly increased in all BC subtypes than in controls (P= 0.0328, P=0.0021, P=0.0179 and P=0.0017). MSLN and PIG-C were higher in TNBC than IDC (P=0.0032 and P<0.0001). Overexpression of miR-182 in MDA-MB-231 cells resulted in significant increase in MSLN and PIG-C (p=0.0001 and p=0.0121) while inhibiting miR-182-5p did not show any significant impact (P=0.824 and P= 0.3122) compared to mock cells. Knocking down of PIG-C resulted in significant downregulation of MSLN (P=0.0181) whereas, knocking down of MALAT-1 resulted in dramatic decrease in MSLN and PIG-C expression levels (P=0.01 and P=0.0401) compared to mock cells. In addition to, significant downregulation of MSLN and PIG-C upon knocking down of MALAT-1 and miR-182 mimicked cell lines (P<0.0001 and P=0.0396).

Conclusions: This study sheds light on the differential expression and interplay between novel miRNA and lncRNAs in TNBC in an attempt to propose potential immunotherapeutic targets for the diagnosis and treatment of breast cancer.

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Disclosure: All authors have declared no conflicts of interest.

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133TiP A phase II trial of nivolumab + palbociclib + anastrozole in postmenopausal women with ER+/HER2− primary breast cancer: CheckMate 7A8

S.M. Tolaney[1], G. Jerusalem[2], R. Salgado[3], X. Liu[4], T. Chen[4], H. Zhang[4], M. Roberts[4], D. Zardavas[4], A. Prat[5]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA; [2]Medical Oncology, CHU Sart Tilman and Liège University, Liège, Belgium; [3]Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium; [4]Oncology Clinical Development, Bristol-Myers Squibb, Lawrence, KS, USA; [5]Medical Oncology, Hospital Clinic, Barcelona, Spain

Background: Cyclin-dependent kinase 4/6 (CDK 4/6) inhibition coupled with estrogen receptor (ER) signaling blockade is an efficient treatment approach for patients (pts) with metastatic hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) breast cancer (BC). Preclinical data suggest synergistic activity of CDK 4/6 inhibition and PD-1 blockade; in a syngeneic mouse tumor model, improved efficacy and complete tumor regression were observed with phased administration of abemaciclib + anti−programmed death ligand 1 (PD-L1) therapy.

Trial Design: CheckMate 7A8 is a randomized, noncomparative, multicenter, phase 2 study evaluating nivolumab + palbociclib + anastrozole in postmenopausal pts with ER+, HER2− primary BC. After determining safe doses for the nivolumab combination regimen in the safety run-in phase, pts will be randomized in a 4:4:3 ratio to 1 of 3 treatment arms (Table) stratified by PD-L1 expression (+ or −), node status (+ or −), and tumor size (> 3 cm or ≤ 3 cm). Following treatment, all pts will undergo surgery and safety follow-up.

Eligible pts are postmenopausal women with newly diagnosed, untreated, histologically confirmed ER+, HER2− BC with primary tumor ≥ 2 cm; suitable for neoadjuvant endocrine monotherapy and surgery; have an ECOG PS of 0 or 1; have tumor tissue available at baseline; and are willing to undergo on-treatment research biopsy and tissue collection at surgery.

Primary study endpoints are number of pts with occurrence of dose-limiting toxicity (safety run-in phase) and residual cancer burden 0—I rate by central assessment at time of definitive surgery (randomized phase). Secondary endpoints include safety and tolerability, pathologic complete response, objective response rate, and breast-conserving surgery rate.

Table 133TiP

Treatment arms in the safety run-in and randomized phases	
Safety run-in phase	NIVO + PAL 3 weeks on 1 week off + ANA × 5 cycles
Randomized phase	
Arm A	NIVO + PAL 3 weeks on 1 week off + ANA × 5 cycles
Arm B	PAL 3 weeks on 1 week off + ANA × 1 cycle then NIVO + PAL 3 weeks on 1 week off + ANA × 4 cycles
Arm C	PAL 3 weeks on 1 week off + ANA × 5 cycles

ANA, anastrazole 1 mg orally once daily; NIVO, nivolumab 480 mg intravenously every 4 wks; PAL, palbociclib 125 mg orally once daily.

Clinical trial identification: NCT04075604.

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Disclosure: S.M. 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G. Jerusalem: Honoraria (self), Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Honoraria (self), Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Honoraria (self), Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Honoraria (self), Travel/Accommodation/Expenses: Lilly; Honoraria (self), Travel/Accommodation/Expenses: Amgen; Honoraria (self), Travel/Accommodation/Expenses: BMS; Honoraria (self), Travel/Accommodation/Expenses: AstraZeneca; Honoraria (self): AbbVie; Honoraria (self): Daiichi-Sankyo; Travel/Accommodation/Expenses: MedImmune; Travel/Accommodation/Expenses: Merck KGaA. R. Salgado: Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Research grant/Funding (institution), Travel/Accommodation/Expenses: Merck; Travel/Accommodation/Expenses: AstraZeneca; Research grant/Funding (institution): Puma Biotechnology; Advisory/Consultancy: BMS; Research grant/Funding (institution): Breast Cancer Research Foundation. X. Liu: Shareholder/Stockholder/Stock options, Full/Part-time employment: BMS. T. Chen: Full/Part-time employment: BMS. H. Zhang: Full/Part-time employment: Bristol-Myers Squibb. M. Roberts: Shareholder/Stockholder/Stock options, Full/Part-time employment: BMS. D. Zardavas: Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb. A. Prat: Advisory/Consultancy, Contracted research and lectures fees: NanoString Technologies; Advisory/Consultancy, Advisory role: BMS; Advisory/Consultancy, Advisory role, Lecture fees, Contracted research, Clinical trials: Novartis; Advisory/Consultancy, Advisory role: MSD; Advisory/Consultancy, Research grant/Funding (institution), Advisory role, Lecture fees, Clinical trials: Pfizer; Advisory/Consultancy, Research grant/Funding (institution), Advisory role, Lectures fees, Contracted research, Clinical trials: Roche; Advisory/Consultancy, Advisory role, clinical trials: Lilly; Advisory/Consultancy, Advisory role: Oncolytics Biotech; Advisory/Consultancy, Advisory role, Lecture fees, Clinical trials: Amgen; Advisory/Consultancy, Lecture fees, Clinical trials: Daiichi Sankyo; Advisory/Consultancy, Advisory role: PUMA; Research grant/Funding (institution), Contracted research, Clinical trials: Boehringer Ingelheim.

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134TiP A phase III trial of nivolumab with neoadjuvant chemotherapy and adjuvant endocrine therapy in ER+/HER2− primary breast cancer: CheckMate 7FL

G. Curigliano[1], H. McArthur[2], N. Harbeck[3], L. Pusztai[4], S. Delaloge[5], K. Letrent[6], T. Chen[6], B. Li[6], K. Tatsuoka[6], D. Zardavas[6], S. Loi[7]

[1]Medical Oncology, Early Drug Development for Innovative Therapies, University of Milan, Istituto Europeo di Oncologia, Milan, Italy; [2]Breast Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Breast Center, University of Munich (LMU), Munich, Germany; [4]Medical Oncology, Yale School of Medicine, New Haven, CT, USA; [5]Breast Oncology, Institut Gustave Roussy, Villejuif, France; [6]Oncology Clinical Development, Bristol-Myers Squibb, Lawrence, KS, USA; [7]Cancer Therapeutics, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Patients (pts) diagnosed with primary estrogen receptor-positive (ER+), human epidermal growth factor 2-negative (HER2−) breast cancer (BC) of high grade and/or low ER expression are at increased risk of relapse, despite current standard of care (SoC). Promising data assessing programmed death-1 (PD-1) inhibition coupled with neoadjuvant chemotherapy for pts with high-risk ER+, HER2− BC noted improved pathologic complete response (pCR), which is identified as a valid surrogate endpoint for long-term clinical outcomes.

Trial design: CheckMate 7FL is a randomized, double-blind, placebo-controlled, multicenter, global phase 3 study evaluating nivolumab (NIVO) vs placebo (PBO) in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy (ET) in pts with high-risk, ER+, HER2− primary BC. Eligible pts are male or female, aged ≥18 years with newly diagnosed grade 2 with ER expression of 1—9%, or grade 3, T1c-2, cN1-2 (tumor size ≥2 cm) or T3-T4, cN0-cN2 ER+, HER2− BC. Pts eligible for neoadjuvant chemotherapy and surgery, with adequate organ function, ECOG PS of 0 or 1, and tissue available for biomarker assessments will be enrolled. Approximately 1200 pts will be randomized 1:1 to NIVO or PBO, stratified by programmed death ligand 1 (PD-L1) expression, tumor grade (2 or 3), axillary nodal status (+ or −), and anthracycline + cyclophosphamide schedule (Q3W or Q2W). In the neoadjuvant phase, pts will receive NIVO 360 mg Q3W or PBO + paclitaxel 80 mg/m^2 QW for four 3-week cycles, followed by NIVO 360 mg Q3W (or 240 mg Q2W) or matching PBO in combination with either doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 Q3W or Q2W for 4 cycles. Pts will undergo surgery after completion of the neoadjuvant phase. Following surgery, pts will enter the adjuvant phase and receive NIVO 480 mg Q4W or PBO for 7 cycles + investigator's choice of ET per local SoC. Primary endpoints are pCR (ypT0/is, ypN0) and event-free survival. Secondary endpoints include overall survival, disease-free survival, distant-metastasis-free survival, safety, pCR (ypT0 ypN0 and ypT0/is) rates, overall response rates, residual cancer burden, and quality of life. Reused with permission 2019 SABCS®

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135TiP GELATO-trial: Assessing the efficacy of carboplatin and atezolizumab in metastatic lobular breast cancer

L. Voorwerk[1], H.M. Horlings[2], M.V. Dongen[3], I. Kemper[3], I.A.M. Mandjes[4], J. Boers[5], C.P. Schröder[5], V. Tjan-Heijnen[6], A. Jager[7], T.N. Schumacher[8], C.U. Blank[9], K.E. De Visser[1], S. Linn[10], M. Kok[11]

[1]Division of Tumor Biology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands; [2]Department of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; [3]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; [4]Department of Biometrics, Netherlands Cancer Institute, Amsterdam, Netherlands; [5]Medical Oncology Department, University Hospital Groningen (UMCG), Groningen, Netherlands; [6]Medical Oncology, Maastricht University Medical Center (MUMC), Maastricht, Netherlands; [7]Department of Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands; [8]Division of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands; [9]Department of Medical Oncology; Division of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands; [10]Department of Medical Oncology; Division of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; [11]Department of Medical Oncology; Division of Tumor Biology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Invasive lobular breast cancer (ILC) is a special histological breast cancer subtype and is characterized by the loss of E-cadherin and a distinct metastatic pattern. For this difficult to treat breast cancer, no effective treatment options are available after patients become resistant to endocrine treatment. Despite its specific histology and disease behavior, only a few clinical trials focus specifically on ILCs. Recently, emerging translational data suggest that a subgroup of ILC has remarkably high expression of immune-related (IR) genes and harbor relatively high amounts of tumor-infiltrating lymphocytes. In addition, IR-ILC's seem to responsive to platinum agents in vitro and preliminary data suggests that the combination of platinum agents and immune checkpoint blockade (ICB) is effective in vivo, providing a rationale to combine ICB with platinum-based chemotherapy for the treatment of advanced ILC.

Trial design: In the single-arm, phase 2, multicenter GELATO-trial, patients with metastatic ILC are treated with 12 cycles of weekly carboplatin (AUC 1.5) and atezolizumab (anti-PD-L1; 1200 mg flat-dose) every three weeks starting from the third administration of carboplatin. Biopsies and blood are collected before the start of carboplatin, before the start of atezolizumab and after two cycles of atezolizumab. The trial has a Simon's two-stage design, in which 22 patients will be included in the first stage. Another 18 patients will be accrued when three or more responses are observed in the first stage. Main inclusion criteria are: metastatic ILC, negative or aberrant staining of E-cadherin, progression after an anti-estrogen and aromatase inhibitor (in ER-positive disease), maximum two lines of palliative chemotherapy and LDH below 500 U/L. The primary endpoint is progression-free survival (PFS) at 6 months. Secondary endpoints are PFS at 6 months in the IR-ILC's, PFS at 12 months, objective response rate (ORR), overall survival and safety. Translational objectives are to explore potential predictive markers for therapy response and to assess the immunomodulatory effects of carboplatin systemically and on the tumor microenvironment. Enrolment started in November 2017, with 18 patients enrolled so far.

Clinical trial identification: NCT03147040; 2017-001428-23.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

METASTATIC BREAST CANCER

LBA1 Interim results of a phase I/Ib study of LSZ102, an oral selective estrogen receptor degrader (SERD), in combination with ribociclib (RIB) or alpelisib (ALP) in patients with ER+ breast cancer (BC) who had progressed after endocrine therapy (ET)

K. Jhaveri[1], D. Juric[2], Y-S. Yap[3], S. Cresta[4], R. Layman[5], F. Duhoux[6], C. Terret[7], S. De Vita[8], N. Kundamal[9], W. He[8], A. Balbin[8], Q. Sheng[8], A. Crystal[8], G. Curigliano[10]

[1]Medicine Department, Memorial Sloan Kettering Evelyn H. Lauder Breast Center, New York, NY, USA; [2]Oncology/Hematology, Massachusetts General Hospital, Boston, MA, USA; [3]Medical Oncology, National Cancer Centre Singapore, Singapore; [4]Medical Oncology, Fondazione IRCCS — Istituto Nazionale dei Tumori, Milan, Italy; [5]Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Medical Oncology, Centre Léon Bérard, Lyon, France; [8]Clinical Research, Novartis Institutes for Biomedical Research, Cambridge, MA, USA; [9]Clinical Research, Novartis Institutes for Biomedical Research, East Hanover, NJ, USA; [10]Early Drug Development for Innovative Therapies Division, University of Milano, Istituto Europeo di Oncologia, Milan, Italy

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137O Tucatinib vs placebo added to trastuzumab and capecitabine in previously treated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB)

G. Curigliano[1], R. Murthy[2], S. Loi[3], A. Okines[4], E. Paplomata[5], E. Hamilton[6], S.A. Hurvitz[7], D. Cameron[8], V. Borges[9], P. Bedard[10], M. Oliveira[11], E.H. Jakobsen[12], T. Bachelot[13], S.S. Shachar[14], V. Mueller[15], L.A. Carey[16], S. Loibl[17], W. Feng[18], L.N. Walker[19], E. Winer[20]

[1]Early Drug Development for Innovative Therapies Division, University of Milan, Istituto Europeo di Oncologia, Milan, Italy; [2]Breast Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [3]Translational Breast Cancer Genomics Lab, Division of Research, Peter MacCallum Cancer Center, Melbourne, Australia; [4]Medicine Department, The Royal Marsden Hospital - NHS Foundation Trust, London, UK; [5]Hematology/Oncology, University of Wisconin, Madison, WI, USA; [6]Drug Development Unit, Sarah Cannon Research Institute-Cancer Centre, Nashville, TN, USA; [7]Hematology/Oncology Clinical Research Unit, University of California at Los Angeles, Los Angeles, CA, USA; [8]Oncology, Edinburgh Cancer Centre Western General Hospital, Edinburgh, UK; [9]Medical Oncology, University of Colorado Hospital, Aurora, CO, USA; [10]Clinical Cancer Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Department Medical Oncology, Vall d' Hebron University Hospital; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Department of Oncology, Vejle Hospital Sygehus Lillebaelt, Vejle Sygehus, Vejle, Denmark; [13]Medical Oncology, Centre Léon Bérard, Lyon, France; [14]Hematology and Bone Marrow Transplant Department, Rambam Health Care Campus, Haifa, Israel; [15]Gynaecology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [16]Medicine - Hematology/Oncology Division, UNC - The University of North Carolina at Chapel Hill - School of Medicine, Chapel Hill, NC, USA; [17]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [18]Biostatistics, Seattle Genetics, Bothell, WA, USA; [19]Clinical Development, Seattle Genetics, Inc., Seattle, WA, USA; [20]Breast Oncology Center, Dana Farber Cancer Institute, Boston, MA, USA

Background: Tucatinib (TUC) is an investigational oral TKI that is highly selective for HER2 with minimal EGFR inhibition. It has shown antitumor activity in preclinical models of HER2+ breast cancer (BC) and intracranial tumors.

Methods: HER2CLIMB (NCT02614794) is a randomized double-blind trial in pts with metastatic HER2+ BC (MBC) previously treated with trastuzumab (T), pertuzumab (P), and T-DM1, including pts with untreated, treated stable, or treated progressing brain metastases (BM). Pts were randomized 2:1 to TUC (300 mg BID) or placebo, in combination with T and capecitabine (C). Primary endpoint was progression free survival (PFS, defined as disease progression or death) per RECIST 1.1 (blinded independent review) in the first 480 pts. Multiplicity-adjusted secondary endpoints

were overall survival (OS,) PFS in pts with BM, and confirmed objective response rate (ORR). Clinical benefit rate (CBR), defined as CR + PR + SD>6 months, was evaluated in all pts. Ad hoc time to response (TTR) was assessed in pts with measurable disease.

Results: Baseline characteristics for the 612 pts were balanced across arms, including 48% of pts with BM. In the TUC arm, risk of progression or death was reduced by 46% (HR: 0.54; 95% CI: 0.42, 0.71; P<0.00001), risk of death was reduced by 34% (HR: 0.66; 95% CI: 0.50, 0.88; P=0.0048), and risk of progression or death in BM pts was reduced by 52% (HR: 0.48; 95% CI: 0.34, 0.69; P<0.00001). With TUC, PFS at 1 year was 20.8% higher and OS at 2 years was 18.3% higher. In pts with measurable disease at baseline, ORR was 41% in the TUC arm vs 23% in the control arm. Median TTR was 1.4 mo for both arms. CBR was 60% in the TUC arm vs 38% in the control arm. Most common AEs in the TUC arm were diarrhea, palmar-plantar erythrodysesthesia (PPE), nausea, fatigue, and vomiting. Grade ≥3 AEs higher in the TUC arm were diarrhea, PPE, and increased AST and ALT.

Conclusions: Adding TUC to T and C significantly prolonged PFS and OS in heavily pretreated pts with HER2+ MBC, including pts with BM. If approved, tucatinib in combination with trastuzumab and capecitabine has the potential to become a new standard of care in pts who previously received 3 HER2-targeted agents.

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E. 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Bedard: Research grant/Funding (institution): Seattle Genetics; Research grant/Funding (institution), Non-remunerated activity/ies, Uncompensated advisory boards: Bristol Meyers Squibb; Research grant/Funding (institution), Non-remunerated activity/ies, Uncompensated advisory boards: Sanofi; Research grant/Funding (institution), Non-remunerated activity/ies, Uncompensated advisory boards: Genentech/Roche; Research grant/Funding (institution): Novartis; Research grant/Funding (institution): GlaxoSmithKline; Research grant/Funding (institution): Nektar Therapeutics; Research grant/Funding (institution): Merck; Research grant/Funding (institution): Lilly; Research grant/Funding (institution): Servier; Research grant/Funding (institution): PTC Therapeutics; Non-remunerated activity/ies, Uncompensated advisory boards: Pfizer. M. 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Mueller: Honoraria (self), Advisory/Consultancy: Amgen; Honoraria (self): AstraZeneca; Honoraria (self): Celgene; Honoraria (self), Advisory/Consultancy: Daiichi-Sankyo; Honoraria (self), Advisory/Consultancy: Eisai; Honoraria (self): Pfizer; Honoraria (self), Advisory/Consultancy: MSD; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Novartis; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Roche; Honoraria (self): Teva; Advisory/Consultancy: Genomic Health; Advisory/Consultancy: Hexal; Advisory/Consultancy: Pierre Fabre; Advisory/Consultancy: ClinSol; Advisory/Consultancy: Lilly; Advisory/Consultancy: Tesaro; Advisory/Consultancy: Nektar; Research grant/Funding (institution): Seattle Genetics; Research grant/Funding (institution): Genentech. S. 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C-S. Huang: Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Amgen; Advisory/Consultancy, Research grant/Funding (institution): Eli Lilly; Advisory/Consultancy, Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Speaker Bureau/Expert testimony, Research grant/Funding (institution): Novartis; Research grant/Funding (institution): EirGenix; Research grant/Funding (institution): OBI Pharma; Research grant/Funding (institution), Travel/Accommodation/Expenses: AstraZeneca; Research grant/Funding (institution): MSD; Research grant/Funding (institution): Daiichi Sankyo. W. Feng: Full/Part-time employment: Seattle Genetics. L.N. Walker: Licensing/Royalties, Full/Part-time employment, Named inventor on patents: Seattle Genetics. E. 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1380 CNS metastases in HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan: DESTINY-Breast01 subgroup analyses

G. Jerusalem[1], Y.H. Park[2], T. Yamashita[3], S.A. Hurvitz[4], S. Chen[5], J. Cathcart[6], C. Lee[7], C. Perrin[8]

[1]Medical Oncology Department, Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium; [2]Samsung Medical Center, Seoul, Republic of Korea; [3]Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Yokohama, Japan; [4]Hematology/Oncology Clinical Research Unit, University of California at Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [5]Biostatistics, Daiichi Sankyo Inc., Basking Ridge, NJ, USA; [6]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [7]Global Oncology R&D, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [8]Medical Oncology, Centre Eugene - Marquis, Rennes, France

Background: Trastuzumab deruxtecan (T-DXd; DS-8201) is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable linker and a cytotoxic topoisomerase I inhibitor. In the pivotal DESTINY-Breast01 trial (NCT03248492), efficacy of T-DXd for HER2-positive metastatic breast cancer (mBC) was demonstrated with an objective response rate (ORR) of 60.9% and median PFS of 16.4 months. We report data on T-DXd for patients (pts) with CNS metastases at baseline and CNS status upon disease progression.

Methods: DESTINY-Breast01 was a single-group, open-label, phase 2 trial of T-DXd (5.4 mg/kg) in 184 pts with HER2-positive mBC previously treated with T-DM1. Pts with CNS metastases that were treated and asymptomatic were allowed on trial. Comparison of subgroup variables was descriptive.

Results: Of 184 pts enrolled at the 5.4 mg/kg dose, 24 had CNS metastases at baseline. Demographics were well matched although CNS pts were likely to have ECOG 0 status (62.5%) and hormone receptor negative disease (58.3%). Similar to the total population, the CNS subgroup was heavily pretreated (median 6 prior lines of therapy). Efficacy was seen in the CNS subgroup: ORR, 58.3% [95% CI: 36.6, 77.9]; mPFS, 18.1 months [95% CI: 6.7, 18.1]. CNS response was observed, case report of 55% regression of a metastatic brain lesion will be presented. At a median 11.1 mo follow-up, 26% of pts (48/184) had progressive disease prior to data cutoff date (01 Aug 2019); 33% (8/24) in the CNS subgroup. The most common sites of progression were in the liver, lung, or lymph nodes and were similar among all pts and the CNS subgroup. Progression involving the brain occurred in only 4 of 48 pts, including 2 of 8 pts with baseline CNS metastases. The 2 CNS progression events in the baseline CNS subgroup occurred at 78 and 85 days of treatment while those in pts without a history of CNS metastases occurred late, at 323 and 498 days.

Conclusions: T-DXd demonstrated efficacy in pts who had a history of CNS metastases at baseline that was similar to the overall population, including one who experienced an in-brain response on therapy. Progression in the brain was noted at time of progression in only 8% of pts with non-CNS disease at time of enrolment.

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139O Final results of the double-blind placebo (PBO)-controlled randomised phase II LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for inoperable locally advanced/metastatic triple-negative breast cancer (mTNBC)

R. Dent[1], M. Oliveira[2], S.J. Isakoff[3], S-A. Im[4], M. Espié[5], S. Blau[6], A.R. Tan[7], C. Saura[2], M. Wongchenko[8], N. Xu[9], D. Bradley[10], S-J. Reilly[10], A. Mani[11], S-B. Kim[12]

[1]Division of Medical Oncology, National Cancer Centre Singapore, Singapore; [2]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3]Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, USA; [4]Department of Internal Medicine, Seoul National University Hospital, and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Breast Disease Center, Hospital Saint Louis, Paris, France; [6]Oncology Division, Northwest Medical Specialties, Puyallup, WA, USA; [7]Department of Solid Tumor and Investigational Therapeutics, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [8]Oncology Biomarker Development, Genentech, Inc., South San Francisco, CA, USA; [9]Biostatistics, Genentech, Inc., South San Francisco, CA, USA; [10]Pharma Development, Roche Products Ltd, Welwyn Garden City, UK; [11]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA; [12]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: In LOTUS (NCT02162719), adding the oral AKT inhibitor IPAT to 1st-line PAC for mTNBC improved progression-free survival (PFS; primary endpoint) [Kim, Lancet Oncol 2017]. The stratified PFS hazard ratio in the intent-to-treat (ITT) population was 0.60 (95% CI 0.37–0.98; p=0.037; median PFS 6.2 vs 4.9 mo with IPAT vs PBO, respectively), with an enhanced effect in patients (pts) with PIK3CA/AKT1/PTEN-altered tumours. Overall survival (OS) results were immature at the primary and updated analyses (deaths in 21% and 55% of pts, respectively). Here we report final results.

Methods: Eligible pts had measurable mTNBC previously untreated with systemic therapy. Pts were stratified by prior (neo)adjuvant therapy, chemotherapy-free interval and tumour IHC PTEN status and randomised 1:1 to PAC 80 mg/m^2 (d1, 8 & 15) plus either IPAT 400 mg or PBO (d1–21) q28d until disease progression (PD) or unacceptable toxicity. OS (ITT, PTEN-low and PI3K/AKT pathway-actived [PIK3CA/AKT1/PTEN-altered] populations) was a prespecified secondary endpoint.

Results: By the final data cut-off (3 Sep 2019) all pts had discontinued treatment, predominantly because of PD. In the ITT population, median OS was numerically longer in the IPAT + PAC arm (Table). Similarly, median OS favoured IPAT + PAC vs PBO + PAC in the PTEN-low (n=48; 23.1 vs 15.8 mo) and PIK3CA/AKT1/PTEN-altered (n=42; 25.8 vs 22.1 mo) subgroups. There were few additional adverse events since previous reports and the safety profile of IPAT + PAC was unchanged.

Conclusions: Final OS results show a numerical trend favouring IPAT + PAC; median OS exceeds 2 years with IPAT + PAC. Consistent with the previously observed PFS benefit, these findings support further evaluation of first-line IPAT + PAC for mTNBC in the ongoing IPATunity130 (NCT03337724) randomised phase III trial.

Table 139O

Parameter	PBO + PAC (n=62)	IPAT + PAC (n=62)
Median duration of follow-up, mo (range)	16.0 (0.1–55.5)	19.0 (0.1–54.3)
Median treatment duration, mo (range) PBO/IPAT PAC	3.5 (0–27) 3.5 (0–27)	5.3 (0–43)[a] 5.1 (0–32)[a]
Adverse event leading to treatment discontinuation, n (%) PBO/IPAT PAC	1 (2) 6 (10)	4 (7)[a] 8 (13)[a]
OS events, n (%)	46 (74)	41 (66)
Median OS, mo (95% CI)	16.9 (14.6–24.6)	25.8 (18.6–28.6)
Stratified OS hazard ratio (95% CI)	0.80 (0.50–1.28)	
1-year OS rate, % (95% CI)	68 (56–80)	83 (73–93)
Subsequent systemic anti-cancer therapy, n (%)	56 (90)	48 (77)

[a] n=61 (safety population, all treated pts)

Clinical trial identification: NCT02162719.

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140O Veliparib plus carboplatin-paclitaxel in patients with HER2-negative advanced/metastatic gBRCA-associated breast cancer: Results in hormone receptor-positive and triple-negative breast cancer subgroups from the phase III BROCADE3 trial

J-P. Ayoub[1], M.L. Friedlander[2], V.C. Dieras[3], H. Wildiers[4], B. Arun[5], H.S. Han[6], S. Puhalla[7], Y. Shparyk[8], E.H. Jakobsen[9], M.G. Kundu[10], M. Wu[10], C. Ratajczak[11], D. Maag[11], B. Kaufman[12]

[1]Oncology Department, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [2]Prince of Wales Clinical School, University of New South Wales and Prince of Wales Hospital, Sydney, Australia; [3]Medical Oncology, Centre Eugène - Marquis, Rennes, France; [4]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [5]Breast Medical Oncology and Clinical Cancer Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Department of Breast Oncology, Moffitt Cancer Center, Tampa, FL, USA; [7]UPMC Cancer Centers, UPMC School of Medicine, Pittsburgh, PA, USA; [8]Department of Chemotherapy, Lviv State Regional Cancer Treatment and Diagnostic Center, Lviv, Ukraine; [9]Vejle Hospital Sygehus Lillebaelt, Vejle Sygehus, Vejle, Denmark; [10]Data and Statistical Sciences, AbbVie Inc., North Chicago, IL, USA; [11]Global Oncology Development, AbbVie Inc., North Chicago, IL, USA; [12]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel

Background: In BROCADE3 (NCT02163694), addition of the PARP1/2 inhibitor veliparib (Vel) to carboplatin-paclitaxel (C-P) significantly prolonged progression-free survival (PFS) in patients (pts) with HER2-negative locally advanced/metastatic gBRCA-associated breast cancer (BC; hazard ratio=0.71 [95% CI 0.57, 0.88], P=.002). Here we report efficacy and safety in hormone receptor-positive (HR+) and triple-negative BC (TNBC) subgroups separately.

Methods: Pts with ≤2 prior lines of cytotoxic therapy for metastatic BC were randomized 2:1 to Vel (120 mg PO BID) + C-P or placebo (Pbo) + C-P. Vel-Pbo was given on days (d) −2 to 5, C (AUC 6 mg/mL/min IV) on d 1, and P (80 mg/m^2 IV) on d 1, 8, and 15 (21-d cycles). Pts who discontinued C and P prior to progression (at investigator discretion) received blinded single-agent Vel or Pbo (300–400 mg BID) until progression. Primary endpoint was investigator-assessed PFS. Analysis of PFS in subgroups defined by hormone receptor status was preplanned. Analyses of PFS and overall survival (OS) were stratified by prior platinum status.

Results: Among the 509 pts in the intent-to-treat population, 266 (52%) were HR+ and 243 (48%) had TNBC. PFS and OS results in each subgroup are presented in the table below. Adverse events (not related to progression) led to study drug discontinuation in 8.0%/3.3% of HR+ pts and 10.5%/7.5% of TNBC pts in the Vel + C-P and Pbo + C-P arms, respectively.

Table 140O

	HR+ Subgroup N=266		TNBC Subgroup N=243	
	Veliparib + C-P n=174	Placebo + C-P n=92	Veliparib + C-P n=163	Placebo + C-P n=80
mPFS per INV, mo (95% CI)	13.0 (12.1, 16.6)	12.5 (10.2, 13.2)	16.6 (12.3, 22.7)	14.1 (11.0, 15.8)
PFS hazard ratio (95% CI) P value[a]	0.69 (0.52, 0.93) .013		0.72 (0.52, 1.00) .051	
PFS rate at 2 years, % (95% CI)	27.5 (20.6, 34.8)	15.3 (8.2, 24.5)	40.4 (32.3, 48.4)	25.0 (15.3, 35.9)
PFS rate at 3 years, % (95% CI)	17.5 (11.2, 25.0)	8.6 (3.3, 17.0)	35.3 (27.2, 43.6)	13.0 (5.3, 24.2)
mPFS per BICR, mo (95% CI)	18.7 (14.5, 22.9)	12.6 (11.4, 16.5)	21.0 (16.0, 29.3)	14.5 (12.5, 19.7)
PFS hazard ratio (95% CI)	0.68 (0.48, 0.97)		0.71 (0.49, 1.03)	
PFS rate at 2 years, % (95% CI)	39.5 (30.6, 48.2)	25.5 (13.9, 39.0)	47.4 (38.3, 56.0)	29.0 (17.7, 41.3)
PFS rate at 3 years, % (95% CI)	35.1 (26.0, 44.3)	18.6 (8.1, 32.4)	39.7 (30.2, 48.9)	20.9 (9.5, 35.3)
mOS (mo, 95% CI) [interim]	32.4 (26.5, 37.9)	27.1 (22.9, 35.2)	35.0 (24.9, NR)	30.0 (24.5, NR)
OS hazard ratio (95% CI)	0.96 (0.68, 1.36)		0.92 (0.62, 1.36)	

[a] On the basis of stratified log-rank test. P values are nominal. BICR, blinded independent central review; C-P, carboplatin plus paclitaxel; ER, estrogen receptor; HR+, hormone receptor positive (ER and/or PgR); INV, investigator; m, median; NR, not reached; OS, overall survival; PFS, progression-free survival; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

Conclusions: The addition of Vel to C-P improved PFS in gBRCA pts with HR+ BC and TNBC. In both subgroups, benefit of Vel was durable with an increase in proportion of pts progression free at 2 and 3 years compared with Pbo.

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141P Impact of pembrolizumab versus chemotherapy on health-related quality of life in patients with metastatic triple negative breast cancer

P. Schmid[1], A. Haiderali[2], J. Mejia[3], Z. Guo[4], X. Zhou[4], A. Martin-Nguyen[2], J. Cortés[5], E. Winer[6]

[1]Centre of Experimental Cancer Medicine, Barts Cancer Institute-Queen Mary University of London, London, UK; [2]Center for Observation and Real-World Evidence, MSD-Merck Sharp & Dohme, Kenilworth, NJ, USA; [3]Clinical Research, MSD-Merck Sharp & Dohme, Kenilworth, NJ, USA; [4]Biostatistics and Research Decision Science, MSD-Merck Sharp & Dohme, Kenilworth, NJ, USA; [5]IOB Institute of Oncology, Quironsalud Group, Madrid & Barcelona; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]Breast Oncology Center, Dana Farber Cancer Institute, Boston, MA, USA

Background: KEYNOTE-119 (NCT02555657), an open-label, randomized, phase 3 trial for metastatic triple-negative breast cancer (mTNBC), evaluated IV pembrolizumab (P) 200 mg Q3W for up to 2 years vs investigator's choice of chemotherapy (CT) as second-line or third-line treatment. In the primary analysis populations (all-comers, PD-L1 CPS≥1, PD-L1 CPS≥10), OS was not significantly different between P and CT. We present results of prespecified health-related quality of life (HRQoL) analyses in this study.

Methods: The EORTC QLQ-C30 and QLQ-BR23 were completed at baseline, various time points during treatment cycles up to 2 years or until end of treatment, and 30-day safety follow-up visit. Data were analyzed from patients receiving ≥1 dose of study treatment and completing ≥1 HRQoL assessment. Least-squares mean (LSM) change from baseline, 95% CIs, and nominal P values were calculated. Time to deterioration (TTD; ≥10-point worsening from baseline) was assessed by Kaplan-

Meier method and Cox regression model. No formal hypothesis testing was performed.

Results: The HRQoL population included all-comers (P, n = 306; CT, n = 288), subjects with PD-L1 positive CPS≥1 tumors (P, n = 188; CT, n = 183), and subjects with PD-L1 positive CPS≥10 tumors (P, n = 86; CT, n = 91). Compliance for QLQ-C30 and QLQ-BR23 at week 6 was ≥90% in both arms for all patient populations. The benefit of P vs CT was observed in nearly all pre-specified PRO endpoints, particularly in CPS≥10 population. In this CPS-enriched population, the difference in LSM between arms in pre-specified systemic therapy side effects scale (-9.14; 95%CI, -13.16, -5.11; p<0.0001) and the nausea and vomiting scale (-6.19; 95%CI, -11.29, -1.09; p=0.0177) favored the P arm. There were differences between arms in the CPS≥10 population that favored P for the pre-specified LSM change from baseline in global health status (GHS)/QoL (4.21 (95% CI: -1.38, 9.80). Importantly, TTD in the GHS/QoL scale was longer for P compared to CT (4.3 months vs 1.7 months; HR 0.70; 95%CI; 0.46, 1.05) in the CPS-enriched population.

Conclusions: In this CPS-enriched population of patients with mTNBC receiving second and third-line treatments, HRQoL was better for patients receiving P than those receiving CT.

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142P Quality-adjusted survival with ribociclib plus fulvestrant (R+F) versus placebo plus fulvestrant (P+F) in postmenopausal women (PMW) HR+/HER2- advanced breast cancer (ABC) based on the MONALEESA-3 trial

G. Jerusalem[1], T. Delea[2], M. Martin Jimenez[3], M. De Laurentiis[4], A. Nusch[5], J.T. Beck[6], A. Chan[7], S-A. Im[8], P. Neven[9], A. Lonshteyn[2], D. Chandiwana[10], B. Lanoue[10], P. Fasching[11]

[1]Medical Oncology, Centre Hospitalier Universitaire Liège and Liege University, Liège, Belgium; [2]Oncology, Policy Analysis Inc. (PAI), Brookline, MA, USA; [3]Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [4]Medical Oncology, IRCCS Istituto Nazionale Tumori "Fondazione G. Pascale", Naples, Italy; [5]Medical Oncology, Practice for Hematology and Internal Oncology, Velbert, Germany; [6]Medical Oncology, Highlands Oncology Group, Fayetteville, NC, USA; [7]Breast Cancer Research Centre-WA and School of Medicine, Curtin University, Perth, Australia; [8]Department of Internal Medicine, Seoul National University Hospital, and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [9]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [10]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [11]Comprehensive Cancer Center Erlangen—EMM, Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen—Nuremberg, Erlangen, Germany

Background: MONALEESA-3 demonstrated the efficacy and safety of R+F vs. P+F in PMW women with HR+/HER2- ABC. This exploratory study used data from MONALEESA-3 to estimate quality-adjusted survival outcomes for patients receiving R+F versus P+F in this trial.

Methods: For each treatment arm, Kaplan-Meier overall survival (OS) was partitioned into 3 states: toxicity (TOX) = time spent with grade 3-4 adverse events before disease progression; progression (PROG) = time between disease progression and death; and time without symptoms or toxicity (TWiST) = time not in TOX or PROG. Quality-adjusted time in each state for each arm was calculated by combining the estimated mean time in each state with treatment-group specific health-state utility values (HSUVs) estimated using EQ-5D-5L assessments from MONALEESA-3. Outcomes included quality-adjusted PFS (QAPFS), quality-adjusted OS (QAOS) and Q-TWiST. Q-TWiST was calculated with HSUVs for TOX and PROG defined relative to TWiST.

Results: Mean PFS and OS were significantly greater with R+F vs P+F (difference 0.56 and 0.19 years, respectively). Mean time in TOX and TWiST were greater with R+F, whereas mean time in PROG was greater with P+F. Results were similar for quality-adjusted time in the states. The difference in QAPFS for R+F vs P+F was 0.45 years (95%CI 0.27 to 0.63) greater (p<.0001). QAOS was numerically greater with R+F vs P+F although this difference was not statistically significant (0.16 years, 95%CI 0.07 to 0.45, p=0.0569). Q-TWiST was 0.23 years greater with R+F (95%CI 0.07 to 0.45, p=.0069). In a sensitivity analysis using a published estimate of disutility for PROG, the differences in QAOS was 0.23 years (95%CI 0.08 to 0.41, p=0.0022).

Conclusions: Adding ribociclib to fulvestrant in PMW with HR+/HER2- ABC improves QAPFS, results in clearly clinically important improvements in Q-TWiST and may result in improved QAOS.

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143P Quality of life (QoL) with palbociclib (PAL) plus endocrine therapy (ET) versus (vs) capecitabine (CAP) in luminal metastatic breast cancer (MBC) patients (pts) in the PEARL study

Z. Kahan[1], M. Gil-Gil[2], M. Ruiz-Borrego[3], E.M. Carrasco[4], E.M. Ciruelos[5], M. Muñoz[6], B. Bermejo De Las Heras[7], M. Margeli Vila[8], A. Anton[9], M. Casas[4], L. Calvo[10], J. de la Haba[11], M. Ramos[12], I. Álvarez-López[13], E. Gal-Yam[14], E. Gautier[15], M. Corsaro[16], G. Rodrigálvarez[4], C. Zielinski[17], M. Martin Jimenez[18]

[1]Department Oncotherapy, University of Szeged, Szeged, Hungary; [2]Department Medical Oncology, Institut Catala d' Oncologia, L'Hospitalet de Llobregat, Spain; [3]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain; [4]Scientific, GEICAM, San Sebastian De Los Reyes, Spain; [5]Department Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; [6]Department Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; [7]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain; [8]Medical Oncology, ICO - Institut Català d' Oncologia Badalona (Hospital Universitario Germans Trias i Pujol), Badalona, Spain; [9]Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain; [10]Medical Oncology, Complejo Hospitalario A Coruña, A Coruña, Spain; [11]Medical Oncology, University Hospital Reina Sofia, Cordoba, Spain; [12]Medical Oncology, Centro Oncológico de Galicia, A Coruña, Spain; [13]Medical Oncology, Hospital Universitario Donostia-Biodonostia, San Sebastian, Spain; [14]Medical Oncology, Institute of Oncology, Sheba Medical Center, Tel-Hashomer, Israel; [15]Medical Oncology, Pfizer Inc, San Francisco, CA, USA; [16]Oncology, Pfizer, Milan, Italy; [17]Medical Oncology, Vienna Cancer Center, Medical University Vienna and Vienna Hospital Association, Vienna, Austria; [18]Department Servicio de Oncologia Médica, Hospital General Universitario Gregorio Marañon, Madrid, Spain

Background: PAL+ET was not superior to CAP in progression free survival in postmenopausal pts with luminal MBC resistant to aromatase inhibitors, but was better tolerated. Patient-reported outcomes (PROs) were a secondary objective.

Methods: 601 pts were randomized to PAL (125 mg 3 weeks out of 4) + Exemestane/fulvestrant (standard doses) vs CAP (1250 mg/m^2, or 1000 mg/m^2 if >70 years, BID 2 weeks out of 3). Pts completed the European Organization for Research and Treatment of Cancer QoL C30 (EORTC QLQ-C30), the breast cancer specific module (EORTC QLQ-BR23) and the EuroQoL Health Utilities Index (EQ-5D-3L) questionnaires in the clinic prior to any test or discussion with healthcare personnel at baseline (BL), Day 1 every 2 (till cycle 7) or 3 cycles (thereafter) till end of treatment (EOT). High scores represent better level of functioning for functional and global QoL scales and more severe symptoms for symptom-oriented scales. Changes from BL and time to deterioration (TTD) were analyzed using linear mixed-effect and stratified Cox regression models, respectively.

Results: Questionnaire completion rate was >82% till cycle 13. Mean change of Global Health Status (GHS) scores from BL and cycle 3 was 2.9 for PAL+ET vs -2.07 for CAP (95% CI, 1.4-8.6; p=0.007). In certain timepoints between BL and EOT, significant differences were found for physical, role and social functioning and symptoms like nausea/vomiting, fatigue and diarrhea (favouring PAL+ET) and dyspnea, constipation and insomnia (favouring CAP). Significant differences in the Visual Analogue Scale of the EQ-5D-3L index score between BL and cycle 3 also favours PAL+ET. Median TTD in GHS was 8.6 months (m) for PAL+ET vs 6.2 m for CAP (HR 0.70, 95% CI, 0.56 to 0.89; p=0.003). Similar improvements for PAL+ET were also seen for other QLQ-C30 scales (physical, role, cognitive and social functioning, fatigue, nausea/vomiting, pain, loss of appetite and diahrrea) and for future perspective and systemic therapy side effects in the QLQ-BR23.

Conclusions: Pts with PAL+ET had better QoL compared to CAP in most items. TTD was significantly prolonged with PAL+ET vs CAP.

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144P Patient-reported outcomes (PROs) in advanced breast cancer (ABC) treated with ribociclib (RIB) + fulvestrant (FUL) as first-line (1L) and second-line (2L) therapy in MONALEESA-3 (ML-3)

P. Fasching[1], P. Neven[2], G. Jerusalem[3], J.T. Beck[4], A. Chan[5], M. De Laurentiis[6], G.V. Bianchi[7], M. Martin Jimenez[8], S. Chia[9], A. Gaur[10], M. Sondhi[11], K. Rodriguez-Lorenc[11], B. Lanoue[11], D. Chandiwana[11], A. Nusch[12]

[1]Comprehensive Cancer Center Erlangen—European Metropolitan Region of Nuremberg, and Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [2]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [3]Medical Oncology, Centre Hospitalier Universitaire Liège and Liege University, Liège, Belgium; [4]Medical Oncology, Highlands Oncology Group, Fayetteville, NC, USA; [5]Breast Cancer Research Centre-WA and School of Medicine, Curtin University, Perth, Australia; [6]Medical Oncology, IRCCS Istituto Nazionale Tumori "Fondazione G. Pascale", Naples, Italy; [7]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [9]Department of Medicine, British Columbia Cancer Agency, Vancouver, BC, Canada; [10]Oncology, Novartis Healthcare Pvt Ltd, Hyderabad, India; [11]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [12]Medical Oncology, Practice for Hematology and Internal Oncology, Velbert, Germany

Background: RIB + FUL improved progression-free survival (PFS) and overall survival (OS) vs placebo (PBO) + FUL in patients (pts) with hormone-receptor-positive/human epidermal growth factor receptor-2 negative (HR+/HER2−) ABC in ML-3 (NCT02422615). Here we report health-related quality of life (HRQOL) data in 1L and 2L (including early relapsers [ERs]) pts.

Methods: Pts were randomized 2:1 to RIB and PBO groups. HRQOL and pain were evaluated using EORTC QLQ-C30, EQ-5D-5L, and BPI-SF questionnaires. A linear effects model was used to determine least squares (LS) mean change from baseline (BL) in global health status (GHS). Times to definitive 10% deterioration (TTD) were compared between treatment arms using stratified log-rank tests.

Results: Questionnaire compliance rates were >90% at BL for each measure. Numbers of pts to complete questionnaire at cycles 3, 9, 15, and 22 in RIB vs PBO arms were 184 vs 98, 155 vs 80, 121 vs 67, and 102 vs 52, respectively, in 1L pts and 171 vs 67, 124 vs 49, 92 vs 26, and 65 vs 17 in 2L pts. Median TTD results generally favored RIB, including a trend toward GHS benefit especially evident in 1L pts (Table). HRQOL was generally improved from BL in both arms during treatment (data to be presented at congress); at end of treatment (EOT) in 1L pts, both arms showed GHS decrease from BL (LS mean change from BL: −5.2 points with RIB [n=104] vs −4.4 points with PBO [n=76]). In 2L + ER pts, GHS decreased from BL to EOT in both arms (LS mean change: −7.1 [n=139] vs −5.2 [n=67], respectively).

Table 144P

Median TTD, months	1L		2L + ER	
	RIB (n=237)	PBO (n=128)	RIB (n=237)	PBO (n=109)
GHS by ≥10%	41.5	33.5	30.4	19.4
Hazard ratio (95% CI)	0.76 (0.52-1.12)		0.84 (0.56-1.25)	
Physical functioning by ≥10%	39.6	35.9	38.7	19.4
Hazard ratio (95% CI)	0.79 (0.53-1.18)		0.74 (0.48-1.15)	
Emotional functioning by ≥10%	38.6	33.1	36.7	22.8
Hazard ratio (95% CI)	0.74 (0.50-1.09)		0.67 (0.44-1.03)	
Fatigue score by ≥10%	39.6	38.7	31.9	24.9
Hazard ratio (95% CI)	0.92 (0.60-1.41)		0.79 (0.52-1.18)	
Social functioning score by ≥10%	41.4	38.8	38.7	22.9
Hazard ratio (95% CI)	1.04 (0.66-1.63)		0.84 (0.52-1.33)	
Pain score by ≥10%	41.9	NE	NE	NE
Hazard ratio (95% CI)	1.22 (0.71-2.08)		0.84 (0.50-1.40)	

NE, not estimable.

Conclusions: Adding RIB to FUL as 1L or 2L therapy maintained QOL, with increased GHS benefit in 1L pts, although, 2L + ER pts showed consistent TTD benefit across PROs. Some TTD hazard ratios (eg, pain) had wide 95% CIs and must be interpreted cautiously. These results, along with PFS and OS benefits observed with RIB, support use of RIB + FUL as 1L or 2L therapy to treat HR+/HER2− ABC.

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146P Safety and metabolic effects of fasting-mimicking diet in breast cancer patients

C. Vernieri[1], A. Raimondi[1], F. Ligorio[1], E. Zattarin[1], F. Nichetti[1], S. Manglaviti[1], G.V. Bianchi[1], G. Capri[1], L. Rivoltini[2], F.G.M. De Braud[1]

[1]*Medical Oncology & Haemathology Department, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy;* [2]*Unit of Immunotherapy of Human Tumors, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy*

Background: Cycles of calorie-restricted, low-carbohydrate, low-protein diets, collectively referred to as fasting-mimicking diets (FMDs), have demonstrated synergistic antitumor activity in combination with cytotoxic chemotherapy (ChT) or endocrine therapies (ETs) in murine models of breast cancer (BC). These effects are mainly mediated through FMD-induced reduction of blood glucose, insulin and insulin-like growth factor 1 (IGF-1) levels. However, the safety and metabolic activity of the FMD in BC patients remain poorly investigated.

Methods: We concluded a first-in-human clinical trial to investigate the safety, feasibility and metabolic effects of triweekly cycles of a specific 5-day FMD regimen (day 1: 600 KCal; days 2-5: 300 KCal) in combination with standard antitumor therapies in 93 cancer patients (NCT03340935). FMD-related adverse events (AEs) were graded according to CTCAE v5.0. The concentration of relevant blood and urinary metabolites before and after the FMD in individual patients was compared through paired Wilcoxon test. Here we present results of a subgroup analysis in BC patients.

Results: Between February 2017 and February 2019 we enrolled 48 BC patients. Of them, 19 (39.6%) had limited-stage disease, whereas 29 (60.4%) had advanced BC. Most patients received the FMD in combination with ChT (72.9%) or ET (25%). The median number of completed FMD cycles was 5 (range: 1-8). Overall, the FMD was well tolerated, with an incidence of severe FMD-related AEs of 4.2% (G3 fatigue: 1 event; G3 hypoglycemia: 1 event). The FMD significantly reduced plasma glucose (median:-20.9%; range [-49.2%;+24%]), serum insulin (median:-52.8%; range [-91.3%;+200%]) and IGF-1 (median:-36.7%; range: [-72.3%;+24.5%]) concentration, while increasing urinary ketone bodies (median increase: 80 mg/dl; range [0;150]).

Conclusions: This is the first study to show that 5-day FMD is safe when combined with ChT or ETs in BC patients, and causes systemic metabolic changes that have been associated with promising antitumor effects in preclinical studies. Ongoing clinical trials are investigating if the FMD improves the anticancer activity of standard treatments in patients with different tumor types, including BC (NCT03700437; NCT03709147; NCT04248998).

Clinical trial identification: NCT03340935.

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147P Pharmacokinetics, safety, and efficacy of trastuzumab deruxtecan (T-DXd) with OATP1B/CYP3A inhibitors in patients with HER2-expressing advanced solid tumours

M. Takahashi[1], Y-J. Bang[2], M. Karayama[3], J. Watanabe[4], H. Minami[5], N. Yamamoto[6], I. Kinoshita[7], C.C. Lin[8], Y-H. Im[9], T. Fujiki[10], I. Achiwa[11], E. Kamiyama[12], Y. Okuda[13], C. Lee[14], S. Takahashi[15]

[1]*Department of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan;* [2]*Internal Medicine (Medical Oncology), Seoul National University Hospital, Seoul, Republic of Korea;* [3]*Clinical Oncology Department, Hamamatsu University School of Medicine, Hamamatsu, Japan;* [4]*Breast Oncology Department, Shizuoka Cancer Center, Shizuoka, Japan;* [5]*Kobe University Hospital, Kobe, Japan;* [6]*Thoracic, National Cancer Center Hospital, Tokyo, Japan;* [7]*Department of Medical Oncology, Hokkaido University, Sapporo, Japan;* [8]*Department of Oncology, National Taiwan University Hospital (NTUH), Taipei, Taiwan;* [9]*Department of Medicine, Division of Hematology/Medical Oncology, Samsung Medical Center (SMC) - Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;* [10]*Oncology Medical Science Department, Daiichi Sankyo Co, Ltd, Tokyo, Japan;* [11]*Clinical Development Department, Daiichi Sankyo Co, Ltd, Tokyo, Japan;* [12]*Clinical Pharmacology Department, Daiichi Sankyo Co, Ltd, Tokyo, Japan;* [13]*Biostatistics and Data Management Department, Daiichi Sankyo Co, Ltd, Tokyo, Japan;* [14]*Global Oncology R&D, Daiichi Sankyo, Inc, Basking Ridge, NJ, USA;* [15]*Medical Oncology, The Cancer Institute Hospital of JFCR, Tokyo, Japan*

Background: Trastuzumab deruxtecan (T-DXd; DS-8201) is an antibody drug conjugate composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and topoisomerase I inhibitor payload (DXd; exatecan derivative). DXd is a substrate for CYP3A enzymes and OATP1B drug transporter. T-DXd demonstrated antitumor activity and manageable safety in HER2-expressing/mutated solid tumors (NCT02564900). This study (NCT03383692) assessed the effect of concomitant ritonavir (OATP1B/CYP3A inhibitor) or itraconazole (CYP3A strong inhibitor) on the PK profile of T-DXd and DXd.

Methods: Eligible patients (pts) had HER2-expressing (IHC $\geq$1+ and/or ISH+) unresectable/metastatic solid tumors. T-DXd 5.4 mg/kg was administered IV in 3-week cycles (C). Ritonavir 200 mg bid (cohort 1) or itraconazole 200 mg qd/bid (cohort 2) were administered from day 17 of C 2 to end of C 3. Primary endpoints were C_{max} and AUC_{17d}. TEAEs and objective tumor response rate (ORR) were secondary endpoints.

Results: Forty pts were enrolled (17 in cohort 1; 23 in cohort 2). Breast cancer was the most common cancer (42.5%). In the PK analysis set (n = 26; majority of exclusions were due to inhibitor drug noncompliance), there was a small increase in AUC_{17d} for DXd and T-DXd with concomitant ritonavir or itraconazole (Table). In the safety analysis set (n = 40), 39 (97.5%) had a TEAE, 5 (12.5%) reported $\geq$1 serious TEAE, and 2 had ILD/pneumonitis (both grade 1 or 2 and had resolved). The most common TEAEs included nausea (80.0%), decreased appetite (55.0%), and constipation (37.5%). TEAE incidence did not increase in C 3 vs 2. Confirmed ORR was 15/36 (41.7%) in pts with measurable tumors at baseline (n = 36).

Table 147P: Pharmacokinetics of T-DXd and DXd without (cycle 2) and with (cycle 3) concomitant ritonavir (CYP3A/OATP1B inhibitor) or itraconazole (CYP3A strong inhibitor)

Ritonavir

	Parameters	LS means		Ratio	90% CI	
		C2	C3	C3/C2	Lower	Upper
	AUC_{17d}(d*ng/mL)[a]	30.2	36.6	1.215	1.078	1.370
DXd	C_{max} (ng/mL)[b]	8.49	8.38	0.987	0.854	1.140
T-DXd	AUC_{17d} (d*ug/mL)[a]	623	742	1.192	1.140	1.246
	C_{max} (ug/mL)[b]	131	138	1.049	0.976	1.128

Itraconazole

	Parameters	LS means		Ratio	90% CI	
		C2	C3	C3/C2	Lower	Upper
DXd	AUC_{17d} (d*ng/mL)[c]	28.8	33.9	1.178	1.108	1.252
	C_{max} (ng/mL)[c]	8.43	8.78	1.042	0.917	1.184
T-DXd	AUC_{17d}(d*ug/mL)[c]	617	685	1.110	1.073	1.147
	C_{max} (ug/mL)[c]	137	140	1.025	0.963	1.091

[a]N = 8; [b]N = 12; [c]N = 14.

Conclusions: There was a small increase in AUC_{17d} for T-DXd and DXd with concomitant ritonavir and itraconazole that was not considered to be clinically meaningful. Efficacy and safety of T-DXd were consistent with previous trials.

Clinical trial identification: NCT03383692.

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J. Watanabe: Honoraria (self), personal fees: Daiichi Sankyo. H. Minami: Research grant/Funding (institution), personal fees and grant, clinical trials: Novartis; Research grant/Funding (institution): Asahi-Kasei Pharma; Research grant/Funding (institution): Astellas; Non-remunerated activity/ies, Other-clinical trial: AstraZeneca; Research grant/Funding (institution), grant and personal fees, clinical trials: Bayer; Research grant/Funding (institution), grant and personal fees: Behringer; Research grant/Funding (institution), grant and personal fees: Bristol-Myers Squibb; Honoraria (self), Other-personal fees: Celgene; Research grant/Funding (institution), grant and personal fees, clinical trials: Chugai; Research grant/Funding (institution), clinical trial: Daiichi Sankyo; Research grant/Funding (institution), grant and personal fees: DaiNihonSumitomo; Research grant/Funding (institution), grant and personal fees: Tamagawa Eizai; Honoraria (self), Other-personal fees: Janssen; Honoraria (self), Other-personal fees: Kowa; Research grant/Funding (institution), grant and personal fees: Kyowa-Kirin; Research grant/Funding (institution), grant and personal fees: Lilly; Research grant/Funding (institution), grant and personal fees: Merck Serono; Research grant/Funding (institution), grant and personal fees, clinical trials: MSD; Research grant/Funding (institution): Nihon Shinyaku; Research grant/Funding (institution), grant and personal fees, clinical trials: Nippon Chemiphar. N. Yamamoto: Honoraria (institution), Research grant/Funding (institution): Chugai; Research grant/Funding (institution): Taiho; Advisory/Consultancy, Research grant/Funding (institution), consulting fees: Eisai; Honoraria (institution), Research grant/Funding (institution): Lilly; Research grant/Funding (institution): Quintiles; Research grant/Funding (institution): Astellas; Honoraria (institution), Research grant/Funding (institution): BMS; Research grant/Funding (institution): Novartis; Research grant/Funding (self): Daiichi Sankyo; Honoraria (institution), Research grant/Funding (institution): Pfizer; Advisory/Consultancy, Research grant/Funding (institution), consulting fees: Boehringer Ingelheim; Research grant/Funding (institution): Kyowa-Hakko Kirin; Research grant/Funding (institution): Bayer; Honoraria (self), Research grant/Funding (institution): Ono Pharmaceutical; Honoraria (institution): AstraZeneca; Advisory/Consultancy, consulting fees: Otsuka; Advisory/Consultancy, consulting fees: Takeda; Advisory/Consultancy, consulting fees: Cimic; Research grant/Funding (institution): Janssen Pharma; Research grant/Funding (institution): MSD. Y-H. Im: Advisory/Consultancy, advisory board role/grant: AstraZeneca; Leadership role, other-advisory board role: Novartis; Leadership role, other- advisory board role: Hanmi; Leadership role, advisory board role/grant: Pfizer; Leadership role, other- advisory board role: Eisai; Leadership role, other- advisory board role: Amgen; Leadership role, other- advisory board role: MediPacto; Leadership role, other- advisory board role: Roche; Leadership role, other- advisory board role: Lilly. T. Fujiki: Full/Part-time employment: Daiicho Sankyo. I. Achiwa: Full/Part-time employment: Daiichi Sankyo. E. Kamiyama: Shareholder/Stockholder/Stock options, Full/Part-time employment: Daiichi Sankyo. Y. Okuda: Full/Part-time employment: Daiichi Sankyo Co., Ltd. C. Lee: Shareholder/Stockholder/Stock options, Full/Part-time employment: Daiichi Sankyo, Inc. S. Takahashi: Research grant/Funding (institution), grants and personal fees: Daiichi Sankyo; Research grant/Funding (institution), grants and personal fees: Novartis; Research grant/Funding (institution), grants and personal fees: Chugai; Research grant/Funding (institution), grants and personal fees: Merck Sharp & Dohme (MSD); Research grant/Funding (institution), grants and personal fees: Eisai; Research grant/Funding (institution), grants and personal fees: Bayer; Research grant/Funding (institution), grants and personal fees: AstraZeneca; Research grant/Funding (institution): Quintiles; Research grant/Funding (institution), grants and personal fees: Taiho. All other authors have declared no conflicts of interest.

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148P Surgery (Sx) of the primary tumour in de novo metastatic breast cancer (BC) patients (pts) is associated with increased survival: A nationwide population-based study by the Belgian Cancer Registry (BCR) and the Belgian Society of Medical Oncology (BSMO)

M.D.R.A. Brandão[1], C. de Angelis[1], P. Vuylsteke[2], R.D. Gelber[3], N. Van Damme[4], E. Van Eycken[4], J. Verbeeck[4], L. van Walle[4], C. Colpaert[5], M. Lambertini[6], F. Poggio[6], D. Verhoeven[7], A. Barbeaux[8], F.P. Duhoux[9], K. Punie[10], H. Wildiers[10], C. Caballero[11], A.H. Awada[12], M. Piccart[12], E. de Azambuja[1]

[1]Academic Trials Promoting Team, Institut Jules Bordet, Brussels, Belgium; [2]CHU UCL Namur, Site Ste Elisabeth, Université Catholique de Louvain, Namur, Belgium; [3]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Research Department, Belgian Cancer Registry, Brussels, Belgium; [5]Pathology Department, UZ Leuven, Leuven, Belgium; [6]IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy; [7]Medical Oncology, AZ Klina, University of Antwerp, Antwerp, Belgium; [8]Medical Oncology, CHR Verviers East Belgium, Verviers, Belgium; [9]Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [10]Medical Oncology, UZ Leuven, Leuven, Belgium; [11]Breast International Group, Brussels, Belgium; [12]Department of Medicine, Institut Jules Bordet, Brussels, Belgium

Background: The role of Sx of the primary tumor remains highly debatable in de novo stage IV BC. We aimed to assess Overall Survival (OS) among de novo metastatic BC pts who underwent Sx of the primary tumor ≤9 months (m) after diagnosis vs pts who did not, adjusting for prognostic factors.

Methods: This is a retrospective population-based study on 2627 pts diagnosed with de novo metastatic BC from 2010-2014, with data obtained from the BCR and linked with administrative health care databases. A 9m landmark analysis excluding pts who died/were lost to follow-up <9m after diagnosis was performed. Baseline pts characteristics and treatment received were compared between Sx vs No Sx groups using Chi2 and t tests. OS was estimated using Kaplan-Meier method and compared using log-rank test and adjusted Cox proportional hazards models. Subgroup analysis for OS and a sensitivity analysis were performed.

Results: 1985 pts were included in the 9m landmark analysis (534 with Sx vs 1451 with No Sx). Pts receiving Sx were younger, had better performance status (PS) at diagnosis and higher rate of HER2+ subtype. Median OS was 41.9 m in the No Sx group vs 60.1 m in the Sx group (adjusted hazard ratio 0.56; 95% confidence interval 0.49-0.64). Survival differences were larger in pts with PS 0-1, ER+/HER2- or HER2+ BC (Table). OS was not better among pts with PS 2-4, while absolute differences were small among pts with triple negative BC. Sensitivity analysis showed similar results.

Table 148P

		No Sx	Sx	P	Adjusted HR* (95% CI)
		mOS (95% CI)	mOS (95% CI)		
All pts	-	41.9 (39.8-44.2)	60.1 (57.1-68.2)	<.001	0.56 (0.49-0.64)
Subtype	ER+/HER2-	42.6 (40.2-44.7)	62.4 (57.3-71.5)	<.001	0.58 (0.49-0.76)
	HER2+	51.4 (46.5-60.1)	72.4 (62.0-97.5)	.003	0.69 (0.50-0.95)
	Triple negative	18.5 (16.9-21.7)	21.6 (17.3-34.7)	.001	0.37 (0.23-0.60)
PS	0	47.5 (42.4-55.5)	73.7 (62.4-89.4)	<.001	0.58 (0.45-0.74)
	1	42.3 (39.6-44.5)	59.2 (54.2-68.2)	<.001	0.53 (0.44-0.64)
	2	34.0 (26.1-39.0)	33.2 (19.0-38.0)	.951	0.84 (0.46-1.52)
	3/4	28.6 (23.6-36.0)	48.0 (12.7-NR)	.137	0.76 (0.22-2.66)

* for age, PS, subtype, T status and histological grade. NR: not reached.
Data cutoff: 12-09-2019 (86.0 m of median follow-up)

Conclusions: Among de novo metastatic BC pts surviving ≥9 m after diagnosis, those receiving Sx have longer subsequent survival than those who did not undergo Sx within 9 m of diagnosis. Survival differences are more pronounced among pts with good PS and ER+/HER2- and HER2+ BC, but smaller among other subgroups. Sx of the primary tumor may thus be discussed as a potential therapeutic intervention to selected BC pts.

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149P Predicting prognosis of breast cancer patients with brain metastases in the BMBC registry: Comparison of three different prognostic scores

K. Riecke[1], V. Mueller[1], T. Neunhöffer[2], R. Weide[3], M. Schmidt[4], T-W. Park-Simon[5], C. Mundhenke[6], A. Polasik[7], T. Hesse[8], K. Lübbe[9], E. Laakmann[1], M. Thill[10], P. Fasching[11], C. Denkert[12], T. Fehm[13], V. Nekljudova[14], J. Rey[15], S. Loibl[16], I. Witzel[1]

[1]Gynaecology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Gynaecology, Frauenärzte am Dom, Mainz, Germany; [3]Haematology and Medical Oncology, Praxis für Hämatologie und Onkologie, Koblenz, Germany; [4]Gynaecology, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany; [5]Gynaecology, Medizinische Hochschule Hannover, Hannover, Germany; [6]Gynaecology, Klinikum Bayreuth GmbH, Bayreuth, Germany; [7]Gynaecology, Universitätsklinikum Ulm, Ulm, Germany; [8]Gynaecology, Agaplesion Diakoniklinikum Rotenburg, Rotenburg, Germany; [9]Gynecology, Henriettenstiftung, Hannover, Germany; [10]Gynaecology, Agaplesion Markus Krankenhaus, Frankfurt, Germany; [11]Medical Oncology, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMM, Department of Gynecology and Obstetrics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [12]Institute of Pathology, Uniklinikum Giessen und Marburg, Marburg, Germany; [13]Gynaecology, Universitätsklinikum Düsseldorf, Düsseldorf, Germany; [14]Head Statistician, GBG Forschungs GmbH, Neu-Isenburg, Germany; [15]Statistics, GBG Forschungs GmbH, Neu-Isenburg, Germany; [16]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany

Background: The incidence of brain metastases (BM) from breast cancer (BC) is increasing and treatment is still a major challenge. Several scores have been developed in order to estimate the prognosis of patients with BM by objective criteria.

Methods: The aim of this retrospective analysis from the Brain Metastases in Breast Cancer Network Germany Registry (BMBC) was to validate the diagnostic accuracy on the overall survival (OS) of three GPA scores in a large cohort of BC patients with BM (for 882 from overall 2589 patients the GPA-scores could be calculated). The original GPA includes age, Karnofsky performance status (KPS), number of BM and extracranial metastases (ECM), the breast GPA age, KPS and tumor subtype and the updated breast GPA adds subtype to the original GPA.

Results: Median age at the diagnosis of BM was 57 years. 22.6% of patients (n=197) had a triple-negative, 33.4% (n=295) luminal A, 25.1% (n=221) luminal B and 19.2% (n=169) HER2+ BC. 15.6% of patients (n=138) had no ECM and 45.7% had $\geq$4 BM. More than half of the patients had a good KPS at diagnosis of BM (KPS $\geq$80%: 58.1%). Age >60 years, evidence of ECM, higher number of BM, triple-negative subtype and low KPS were all associated with worse OS in univariate analysis ($p<0.0001$ each). The original GPA had a high time dependent sensitivity of 92.2% in predicting 12-months-survival between patients with good and worse prognosis (score values $>$ vs. $\leq$ 3), a low time dependent specificity of 21.8% and positive predictive value (PPV) of 62.6%. The breast-GPA scores showed lower sensitivities, but higher specificities (breast-GPA: 68.7%;updated breast-GPA: 48.1%) and higher PPV (breast-GPA: 75.6%;updated breast-GPA:69.9%). There were no significant differences between the area under the time dependent ROC curves of the scores after 12 months (breast-GPA (73%) vs. updated breast-GPA (74.2%): p=0.09; breast-GPA vs. original GPA (69.5%): p=0.18).

Conclusions: In this analysis, several clinical parameters and the GPA-scores were significantly associated with OS. But all GPA-scores show only a moderate diagnostic accuracy in predicting the OS. Even the updated breast-GPA with most of the statistically significant parameters included did not result ina better performance.

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150P Eligibility of real-world patients with metastatic breast cancer in clinical trials

A. Batra, S. Kong, R. Rigo, W. Cheung

Medical Oncology, Tom Baker Cancer Center, Calgary, AB, Canada

Background: The results of clinical trials in metastatic breast cancer (MBC) are often generalized to real-world patients. However, clinical trials have stringent inclusion and exclusion criteria, which can potentially lead to poor generalizability of results and slow accrual. This study was conducted to determine the proportion of real-world patients with MBC who would be eligible for clinical trials based on common eligibility criteria and to compare outcomes in eligible and ineligible patients.

Methods: Patients diagnosed with MBC in 2004-2015 from the Alberta cancer registry were included. Patients with one of the following criteria were deemed ineligible: age >75 years, comorbid conditions (uncontrolled diabetes, heart disease, liver disease, and kidney disease), anemia, and history of immunosuppression or a prior malignancy. The likelihood of receiving any therapy was analyzed using logistic regression and factors affecting overall survival (OS) were assessed by Cox model.

Results: A total of 1585 patients with MBC were identified with median age at diagnosis was 63 years (interquartile range: 53-75 years). Approximately 44% (693) patients were deemed trial-ineligible and the most common reasons for ineligibility were advanced age (24%), renal dysfunction (17%), and cardiac disease (8%), respectively. In the real-world, 87% of eligible patients received hormonal or chemotherapy as compared to 72% of ineligible patients [odds ratio 2.65; 95% confidence interval, 2.04-3.42; P< 0.0001]. The 5-year OS of trial-ineligible patients who received any therapy was significantly better than those who did not (Table).

Table 150P

Group	5-year OS	Hazard ratio	95% CI	P-value
Ineligible and no therapy (n=195)	2.1%	–	–	–
Ineligible and received therapy (n=498)	24.7%	0.75	0.59-0.96	0.02
Eligible (n=892)	34.8%	0.69	0.53-0.9	0.006

Conclusions: Despite being ineligible for clinical trials by the common eligibility criteria, most of the patients still derive benefit from treatment. Relaxation of an arbitrary upper limit of age as an inclusion criteria for clinical trials is likely to enhance the representation of real-world patients leading to faster accrual and increase in generalizability of results of such trials.

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151P The landscape of patients with metastatic breast cancer enrolled in phase I trials

Marra[1], C. Criscitiello[2], S. Morganti[1], P. Zagami[1], G. Viale[1], P. Tarantino[1], D. Trapani[1], E. Nicolò[1], M. Repetto[1], E. Ferraro[1], P. D'Amico[1], M. Locatelli[2], A. Esposito[2], G. Curigliano[1]

[1]Division of Early Drug Development for Innovative Therapies, IEO, European Institute of Oncology IRCCS, Department of Oncology and Haemato-Oncology, University of Milan, Milan, Italy; [2]Division of Early Drug Development for Innovative Therapies, IEO, European Institute of Oncology IRCCS, Milan, Italy

Background: Phase I trials (PH1s) testing new drugs allow accelerated access to novel therapies and may improve patients' outcomes. However, scant information is available in metastatic breast cancer (MBC). The aim of our study is to evaluate the clinical outcomes of MBC pts treated in PH1s.

Methods: We retrieved data from medical records on pts' characteristics, response and survival outcomes of all consecutive MBCs treated in PH1s at our institution evaluating targeted therapies (TT), immunotherapy (IO), and/or combinations. Efficacy was assessed by overall response rate (ORR), clinical benefit rate (CBR), progression-free

survival (PFS), and overall survival (OS). Multivariate analysis was carried out for the significant ($p<0.1$) variables by the univariate test, with p-value set to <0.05.

Results: From Dec2014 to Dec2018, 151 MBC pts were enrolled in PH1s, including 70 (46%) ER+/HER2-, 18 (12%) HER2+ and 63 (42%) triple-negative (TN); 92 pts (61%) had received less than two lines of therapy. Pts with ER+/HER2- tumors were more frequently included in TT trials rather than IO trials (97.1% vs 2.9%; $p<.001$). Overall, ORR and CBR were 18.9% and 51.4%, respectively. Pts with HER2+ and TN tumors as well as those treated with TT presented higher ORR (HER2+ vs ER+: 33.3% vs 10%, $p<.001$; TN vs ER+: 23.0% vs 10%, $p=.019$; TT vs IO: 23.1% vs 2.9%, $p=.005$). Conversely, pts with PS ECOG$\geq$1 and pts treated with IO had worse CBR (PS ECOG 0 vs $\geq$1: 55.1% vs 33.3%, $p=.017$; IO vs TT: 14.7% vs 60.7%, $p<.001$). At a median follow-up of 30.3 mo (24.9-35.6), 141 (94.6%) PFS events and 114 (75.5%) deaths had occurred. Pts aged $\geq$65 and pts treated with TT had longer median PFS ($\geq$65 vs $<$65: 6.4 vs 2.7 mo, HR 0.56, 95%CI 0.34-0.92, $p=.021$; TT vs IO: 3.9 vs 1.8 mo, HR 0.46, 95% CI 0.29-0.71, $p<.001$). TN tumors, more than 2 metastatic sites, and LDH level $>$ULN correlated with worse OS (TN vs ER+: 10.2 vs 20.0 mo, HR 3.11, 95%CI 1.26-7.65, p=013; metastatic sites >2 vs ≤ 2: 11.1 vs 20.3 mo, HR 2.14, 95%CI 1.18-3.89, $p=.012$; LDH $>$ULN vs $<$ULN: 25.5 vs 9.5 mo, HR 3.89, 95%CI 1.69-7.64; $p<.001$).

Conclusions: Our analysis showed that MBC pts enrolled in PH1s reported significant benefit with new experimental drugs. Considering the improved outcomes in TT trials which are largely biomarker-driven, biomarker selection should be fostered in IO trials too.

Legal entity responsible for the study: European Institute of Oncology IRCCS.

Funding: Has not received any funding.

Disclosure: G. Curigliano: Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche, Pfizer, Novartis, Seattle Genetics, Lilly, Ellipses Pharma, Foundation Medicine and Samsung. All other authors have declared no conflicts of interest.

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153P Clinical implications of body mass index (BMI) and weight in metastatic breast cancer (BC) patients treated with abemaciclib and endocrine therapy: A pooled individual patient level data analysis of MONARCH 2 and MONARCH 3 trials

M.A. Franzoi[1], L. Ameye[2], D. Eiger[1], M. Piccart[3], M.D.R.A. Brandão[1], N. Pondé[4], C. Desmedt[5], S. Di Cosimo[6], M. Paesmans[2], R. Caparica[1], N. Kotecki[3], M. Lambertini[7], C. De Angelis[1], A.H. Awada[3], E. de Azambuja[1]

[1]Clinical Trials Support Unit, Institut Jules Bordet, Brussels, Belgium; [2]Information Management Unit, Institut Jules Bordet, Brussels, Belgium; [3]Medical Oncology, Institut Jules Bordet, Brussels, Belgium; [4]Medical Oncology, AC Camargo Cancer Center, São Paulo, Brazil; [5]Oncology, KU Leuven, Leuven, Belgium; [6]Oncology, Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [7]IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

Background: Overweight and obesity have emerged as prognostic factors and predictors of toxicity in patients (pts) with hormone receptor-positive BC, especially in the early setting. There is limited data regarding the role of overweight/obesity in advanced BC. Besides cell cycle regulation, CDK 4/6 are involved in important metabolic processes such as adipogenesis. We analyzed the impact of BMI on progression free survival (PFS), response rate (RR) and toxicity in pts receiving endocrine therapy (ET) + abemaciclib (ABE).

Methods: Individual patient-level pooled analysis of MONARCH 2 and 3 trials. Pts were classified according to baseline BMI into underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese ($\geq$30 kg/m^2). PFS was estimated by Kaplan-Meier methods and comparisons were performed using log-rank test and Cox proportional hazards models. Results were considered significant if p-value <0.05.

Results: In total, 1138 pts were included (757 received ABE + ET and 381 placebo + ET). Overweight/obesity was present in 54% of pts and varied significantly according to ethnicity, geographic region, age, menopausal and performance status ($p<0.05$ for all). Obese/overweight pts had a higher prevalence of diabetes, use of metformin, insulin and statins ($p<0.001$ for all). Pts with normal BMI presented higher RR in the ABE + ET arm compared to overweight/obese (49.4% vs 41.6%, p=0.04; HR 0.73 95% CI 0.54-0.99). There was no statistical difference in PFS between BMI categories in both arms. Pts with normal weight experienced more diarrhea and neutropenia compared to overweight/obese pts when treated with ABE + ET. Pts under ABE + ET presented more weight loss at 6 months when compared to placebo + ET (odds ratio [OR] 3.23; 95% CI 2.09-5.01). Concomitant use of metformin, insulin or statin did not correlate with RR or PFS.

Conclusions: Overweight and obesity are prevalent among Pts with advanced BC. ET alone and ABE + ET were equally effective in normal and overweight/obese patients. Improved PFS was observed in the ABE + ET arm despite baseline BMI, showing that overweight/obese pts also benefited from this regimen.

Clinical trial identification: Subanalysis of NCT02107703 and NCT02246621.

Legal entity responsible for the study: Institut Jules Bordet.

Funding: Has not received any funding.

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154P Survival outcome of indigenous and non-indigenous women of Western Australia with breast cancer in relation to remoteness

A. Khan[1], H. Martin[1], L. Spalding[2], A. Redfern[2]

[1]Medical Oncology Department, Fiona Stanley Hospital, Murdoch, Australia; [2]Medical Oncology, University of Western Australia, Perth, Australia

Background: Between 2001 and 2010 Indigenous Western Australian women who developed breast cancer (BrCa) were four times more likely to die of the disease than age-matched non-Indigenous women. With remoteness also an established factor in BrCa mortality delineating the interplay between Indigenous status and remoteness could advise healthcare policy allowing tailored development of culturally specific services with appropriate geographical distribution to reduce the mortality risk.

Methods: Aim was to examine the impact of remoteness on survivals of Indigenous and non-Indigenous women with BrCa.Data were collected retrospectively from the Western Australian cancer Registry. A cohort of patients was selected comprising age- and remoteness matched Indigenous and non-Indigenous women in a 1:1 ratio, remoteness being defined by the ARIA system. In addition, distance from the nearest treatment centre was calculated in Kms. Overall survivals by Indigenous status and remoteness were calculated by Kaplan Meier analysis.

Results: The final cohort comprised 250 Indigenous and 261 non—Indigenous women. The 5 and 10-year overall survivals for Indigenous and non-Indigenous patients were 68 v 78%, p=0.013 and 55 v 68%, p=0.0025 respectively. Considering outcomes for those with metastatic disease at diagnosis, median survivals were also shorter for Indigenous patients, 39 v 56 months, p=0.026. Interestingly, no significant difference was observed in non-Indigenous patients when survivals were analyzed by remoteness or distance from treatment centres. In contrast Indigenous patients showed marked impact on survivals by geographical area of residence. Rural patients had substantially lower 10-year survivals than metropolitan dwelling people, 75 v 56%, p=0.03, However, sub-categorizing rural patients into those less than or more than 1000km from a treatment centre showed comparable survivals at 10 years, 57 v 55%, p=ns.

Conclusions: Indigenous women in WA diagnosed with breast cancer have inferior survival outcomes overall as well as when diagnosed with metastatic disease relative to non-Indigenous peers. Considering remoteness within cohorts, only Indigenous patients showed disadvantage for rural relative to urban patients.

Legal entity responsible for the study: Dr Andrew Redfern.

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Disclosure: All authors have declared no conflicts of interest.

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155P Prolonged clinical benefit with metronomic chemotherapy (VEX regimen) in metastatic breast cancer patients

E. Montagna[1], E. Pagan[2], G. Cancello[1], C. Sangalli[1], V. Bagnardi[2], E. Munzone[1], M. Iorfida[1], M. Mazza[1], S. Dellapasqua[1], N. Bianco[1], P. Veronesi[3], M.A. Colleoni[1]

[1]Division of Medical Senology, European Institute of Oncology IRCCS, Milan, Italy; [2]Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy; [3]Division of Senology, European Institute of Oncology IRCCS, Milan, Italy

Background: Metronomic chemotherapy is a dosing schedule strategy that includes frequent, even daily, administration of chemotherapeutics at doses significantly below the maximum tolerated dose, without any planned prolonged drug-free breaks. Metronomic chemotherapy is an attractive treatment option for metastatic breast cancer (MBC) patients who required prolonged disease control without cumulative toxicity. Data available on the efficacy and tolerability of prolonged usage of metronomic therapy are limited.

Methods: We analyzed the patients with MBC who obtained prolonged clinical benefit for a duration of 12 or more months (complete remission, partial remission or stabilization of disease) with vinorelbine 40 or 30 mg orally 3 times a week, cyclophosphamide 50 mg daily, and capecitabine 500 mg 3 times a day (VEX regimen). The patients were treated in the outpatient department at the European Institute Oncology, Milan.

Results: A total of 75 MBC patients were identified. The median age at the beginning of the VEX regimen was 54 years, 48% of patients had visceral involvement and 84% of patients had hormone-receptor positive and HER2 negative carcinoma. 39 patients received VEX as the first line treatment of MBC while 36 patients were pretreated, with 2 or more lines of treatment in 50% of cases. The objective response rate was 48% (95% CI, 36-60). The median duration of VEX after the first year was 13 months (range 0.3-81.3 months). The progression free survival at 3 years was 25.7% (95% CI, 16.4-36.1) and at 4 years was 19.0% (95% CI, 10.7-29.1; time 0 corresponds to 1 year after VEX start). 27 patients required a dose reduction, 1 case of febrile neutropenia was reported, no other G4 toxicity were registered. 7% of patients experienced G3 hand and foot syndrome.

Conclusions: Metronomic chemotherapy with VEX regimen can induce prolonged clinical benefit in MBC. Based on this long-term safety evaluation, there is no evidence of specific cumulative or delayed toxicities with metronomic chemotherapy.

Legal entity responsible for the study: The authors.

Funding: IEO Foundation.

Disclosure: E. Montagna, G. Cancello, E. Munzone: Advisory/Consultancy: Pierre Fabre. M.A. Colleoni: Advisory/Consultancy: Pierre Fabre, Pfizer, Obi Pharma, Puma Biotechnology Celldex AstraZeneca; Honoraria (self): Novartis. All other authors have declared no conflicts of interest.

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156P Matching-adjusted indirect comparison (MAIC) of palbociclib versus ribociclib and abemaciclib in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (HR+/HER2 ABC)

H.S. Rugo[1], A. Haltner[2], L. Zhan[3], A. Tran[2], E. Bananis[4], D. Mitra[3], C. Cameron[2]

[1]Department of Medicine (Hematology/Oncology), University of California San Francisco Helen Diller Family Comprehensive Center, San Francisco, CA, USA; [2]Value & Evidence Division, EVERSANA, Nova Scotia, NS, Canada; [3]Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [4]Global Medical Affairs, Pfizer Oncology, Pfizer Inc, New York, NY, USA

Background: Palbociclib, ribociclib, and abemaciclib, cyclin-dependent kinase (CDK) 4/6 inhibitors approved for the treatment of HR+/HER2- ABC, have been evaluated in separate randomized clinical trials, although no head-to-head trials have been conducted. Traditional indirect treatment comparisons (ITC) based on summary data from these trials are limited by patient population differences. MAIC adjusts for cross-trial differences by leveraging individual patient data (IPD).

Methods: IPD were available for palbociclib from PALOMA-3. Only published summary data were available for abemaciclib (MONARCH 2) and ribociclib (MONALEESA-3). An anchored MAIC was conducted wherein patients in PALOMA-3 were matched to the inclusion criteria of each comparator study and then reweighted to adjust for remaining imbalances in treatment-effect modifiers, such as prior lines of therapy for ABC and prior endocrine therapy. Treatment-effect modifiers were selected considering both extent of treatment modification and imbalances between trials and were validated by engaging clinical experts. Overall survival (OS) was the outcome for each MAIC.

Results: Hazard ratios (HR) and 95% confidence intervals (CI) were computed comparing palbociclib + fulvestrant (P+F) to abemaciclib + fulvestrant (A+F) and ribociclib + fulvestrant (R+F) through traditional ITC and MAIC. Traditional ITC yielded numerically but not statistically significant unfavorable OS for P+F compared to A+F and R+F. After adjusting for cross-trial differences, P+F had numerically but not statistically significant favorable OS compared to A+F and R+F.

Table 156P

P+F vs.	Traditional ITC	MAIC leveraging IPD	
	HR (95% CI)	HR (95% CI)	No. of adjusted treatment-effect modifiers
A+F	1.05 (0.76, 1.44)	0.87 (0.54, 1.40)	12
R+F	1.09 (0.78, 1.53)	0.92 (0.49, 1.71)	7

Conclusions: P+F was associated with comparable OS compared with A+F and R+F after adjusting for cross-trial differences. Numerical differences between the MAIC and traditional ITC underscore the importance of leveraging IPD to adjust for cross-trial differences.

Clinical trial identification: PALOMA-3: NCT01942135 MONARCH 2: NCT02107703 MONALESSA-3: NCT02422615.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: H.S. Rugo: Research grant/Funding (institution): Eisai; Research grant/Funding (institution): Roche/Genentech; Research grant/Funding (institution): Eli Lilly; Research grant/Funding (institution): Macrogenics; Research grant/Funding (institution): Merck; Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Research grant/Funding (institution): OBI Pharma; Research grant/Funding (institution): Odonate; Research grant/Funding (institution): Immunomedics; Research grant/Funding (institution): Daichi; Research grant/Funding (institution), Travel/Accommodation/Expenses: Pfizer; Travel/Accommodation/Expenses: Mylan. A. Haltner: Full/Part-time employment, EVERSANA were paid consultants to Pfizer in connection with the development of this abstract: EVERSANA. L. Zhan: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer Inc. A. Tran: Full/Part-time employment, EVERSANA were paid consultants to Pfizer in connection with the development of this abstract: EVERSANA. E. Bananis: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer Inc. D. Mitra: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer Inc. C. Cameron: Shareholder/Stockholder/Stock options, Full/Part-time employment, EVERSANA were paid consultants to Pfizer in connection with the development of this abstract: EVERSANA.

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157P Germline BRCA1/2 (gBRCA1/2) testing patterns among oncologists (ONC) treating HER2- advanced breast cancer (ABC): Results from a multi-country real-world study

R. Mahtani[1], A. Niyazov[2], K. Lewis[3], R. Wild[4], A. Rider[3], B. Arondekar[5], M.P. Lux[6]

[1]Medical Oncology Department, Sylvester Cancer Center, University of Miami, Deerfield Beach, FL, USA; [2]US Oncology, Pfizer, New York, NY, USA; [3]Oncology, Adelphi Real World, Cheshire, UK; [4]Statistics, Adelphi Real World, Cheshire, UK; [5]HEOR & Market Access, Patient & Health Impact, Pfizer Inc, Collegeville, PA, USA; [6]Kooperatives Brustzentrum Paderborn, Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten; Frauen- und Kinderklinik St. Louise, Paderborn, Germany

Background: Recently, poly ADP-ribose polymerases inhibitors (PARPi) in HER2- ABC have become available and international guidelines have broadened the eligibility criteria for gBRCA1/2 testing. We assessed gBRCA1/2 testing patterns among ONC treating HER2- ABC in the US, Israel and France, Germany, Italy and Spain (EU4).

Methods: ONC were recruited to complete an online survey as well as extract data from medical charts for the next 8-10 presenting patients (pts) with HER2- ABC in 2019/2020. gBRCA1/2 testing rates were assessed from medical charts and linked to the ONC survey. Differences in ONC gBRCA1/2 testing patterns by demographics and region (EU4, Israel, US) were compared using t-tests.

Results: 2,156 records were provided by 260 ONC [n=214 (82.3%) US, n=24 (9.2%) EU4, n=22 (8.5%) Israel]. Across all regions, significant differences in gBRCA1/2 testing rates by ONC were observed (Table). ONC practicing at an academic medical center vs. community practice were more likely to perform gBRCA1/2 testing [38.0% (SD=37.6) vs 25.3% (SD=31.2) (p = 0.005)]. ONC currently or previously involved in clinical trials were numerically more likely to perform gBRCA1/2 testing compared to ONC who have never been involved in clinical trials 33.6% (SD=35.9) vs 30.3% (SD=39.9) (p=0.567).

Table 157P: ONC gBRCA1/2 Testing patterns

	EU4 (N=214)	US (N=24)	Israel (N=22)	P value EU4 vs. US	P value EU4 vs. Israel	P value US vs. Israel
% (SD) of pts tested	26.0 (31.2)	39.8 (38.3)	93.4 (14.8)	0.046	<0.0001	<0.0001

Conclusions: In this analysis, regional differences in gBRCA1/2 testing rates were observed. Significantly lower gBRCA1/2 testing rates were observed among ONC in community practice settings vs academic settings. Given the availability of PARPi,

these data highlight the need to increase ONC awareness about gBRCA1/2 testing especially among ONC in community practice and/or with no prior clinical trial experience.

Legal entity responsible for the study: Pfizer.

Funding: Pfizer.

Disclosure: R. Mahtani: Research grant/Funding (self), Research grant/Funding (institution): Genentech; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Eli Lilly; Advisory/Consultancy: Novartis; Advisory/Consultancy: Celgene; Advisory/Consultancy: Eisai; Advisory/Consultancy: AstraZeneca; Advisory/Consultancy: Puma; Advisory/Consultancy: Amgen. A. Niyazov: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer. K. Lewis: Full/Part-time employment: Adelphi Real World. R. Wild: Full/Part-time employment: Adelphi Real World. A. Rider: Full/Part-time employment: Adelphi Real World. B. Arondekar: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer. M.P. Lux: Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: AstraZeneca; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Lilly; Advisory/Consultancy, Advisory boards: MSD; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Novartis; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Travel/Accommodation/Expenses, Advisory boards, Honoraria for lectures medical education activities, Travel support: Pfizer; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Eisai; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Genomic Health; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Roche; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: Medac; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: onkowissen.de; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: ClinSol.

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158P Patient (pt) demographics, treatment patterns (tx) and hematologic (heme) toxicities among pts with HER2− advanced breast cancer (ABC) and BRCA1/2 mutation(s) (BRCA1/2mut): A multi-country real-world (RW) study

R. Mahtani[1], A. Niyazov[2], K. Lewis[3], M. Last[3], A. Rider[3], B. Arondekar[4], M.P. Lux[5]

[1]Sylvester Cancer Center, University of Miami, Deerfield Beach, FL, USA; [2]Pfizer Inc., New York, NY, USA; [3]Adelphi Real World, Cheshire, UK; [4]Pfizer Inc., Collegeville, PA, USA; [5]Kooperatives Brustzentrum Paderborn, Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten, Frauen- und Kinderklinik St. Louise, Paderborn, Germany

Background: PARP inhibitors (PARPi) have demonstrated improved progression-free survival compared to chemotherapy (CTX) in clinical trials. Limited information is available on the use of the agents in the RW. We assessed RW tx patterns and heme toxicities in HER2− ABC with BRCA1/2mut in the US and France, Germany, Italy and Spain.

Methods: Oncologists (ONC) extracted data from medical charts for the next 8-10 presenting pts with HER2− ABC in 2019/2020. ONC who performed BRCA1/2 testing were asked to provide additional germline BRCA1/2mut (gBRCA1/2mut) pts. Pts with known HR status and BRCA1/2mut were categorized into two mutually exclusive groups, gBRCA1/2mut (somatic BRCA1/2mut [sBRCA1/2mut] or unknown) or sBRCA1/2mut (gBRCA wild type or unknown). Pt characteristics, tx patterns and heme toxicities were summarized descriptively.

Results: 431 pts were included; 97.4% female, 90.7% Caucasian, 4.9% Ashkenazi Jewish. Median age was 56.0 yrs. 67.3% were HR+/HER2−, 32.7% TNBC. Common txs (>10% in HR+/HER2− or TNBC) varied by HR and BRCA1/2 status in the advanced setting (Table). Heme toxicities varied by regimen; platinum (Pl)-based CTX: anemia (25.9%), neutropenia (17.2%), low platelet count (6.9%); non-Pl based CTX: anemia (19.6%), neutropenia (22.3%), low platelet count (8.0%); PARPi: anemia (15.1%), neutropenia (13.7%), low platelet count (9.6%); endocrine-based therapy (EBT) including endocrine +/- non-PARP targeted txs (mTOR, CDK 4/6 inhibitors, PIK3CA inhibitors): anemia; (13.5%), neutropenia (20.6%), low platelet count (1.2%).

Table 158P

	HR+/HER2−		TNBC	
	gBRCA1/2mut (n=214)	sBRCA1/2mut (n=76)	gBRCA1/2mut (n=114)	sBRCA1/2mut (n=27)
Pl-based CTX	5.1%	5.3%	29.8%	33.3%
Non-Pl-based CTX	21.0%	18.4%	37.7%	37.0%
PARPi	10.7%	15.8%	27.2%	25.9%
EBT	59.3%	52.6%	2.6%	0.0%

Conclusions: In this analysis of BRCA1/2mut HER2− ABC, CTX was frequently utilized. More heme toxicities were observed among CTX users. Heme toxicities should be considered when selecting tx regimens for HER2− ABC pts with BRCA1/2mut.

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Disclosure: R. Mahtani: Research grant/Funding (self): Genentech; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Eli Lilly; Advisory/Consultancy: Novartis; Advisory/Consultancy: Celgene; Advisory/Consultancy: Eisai; Advisory/Consultancy: AstraZeneca; Advisory/Consultancy: Puma; Advisory/Consultancy: Amgen. A. Niyazov: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer. K. Lewis: Full/Part-time employment: Adelphi Real World. M. Last: Full/Part-time employment: Adelphi Real World. A. Rider: Full/Part-time employment: Adelphi Real World. B. Arondekar: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer. M.P. Lux: Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: AstraZeneca; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Lilly; Advisory/Consultancy, Advisory boards: MSD; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Novartis; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Travel/Accommodation/Expenses, Advisory boards, Honoraria for lectures medical education activities, travel support: Pfizer; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Eisai; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Genomic Health; Honoraria (self), Honoraria (institution), Advisory/Consultancy, Advisory boards, Honoraria for lectures medical education activities: Roche; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: Medac; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: onkowissen.de; Honoraria (self), Honoraria (institution), Honoraria for lectures medical education activities: ClinSol.

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159P The clinical landscape of central nervous system (CNS) involvement in metastatic triple-negative breast cancer (TNBC) patients (pts)

D. Eiger[1], E. de Azambuja[1], M. Moreau[2], J. Bondele[3], C. Sotiriou[4], M.A. Franzoi[1], M.D.R.A. Brandão[1], M. Rediti[5], X. Wang[5], A.H. Awada[6], N. Kotecki[7]

[1]Clinical Trials Support Unit, Institute Jules Bordet, Brussels, Belgium; [2]Information Management Unit, Institute Jules Bordet, Brussels, Belgium; [3]Medical School, Université Libre de Bruxelles, Bruxelles, Belgium; [4]Breast Cancer Translational Research Laboratory J-C. Heuson, Institute Jules Bordet, Brussels, Belgium; [5]Breast Cancer Translational Research Laboratory, Institute Jules Bordet, Brussels, Belgium; [6]Department of Medicine, Institute Jules Bordet, Brussels, Belgium; [7]Medical Oncology Clinic, Institute Jules Bordet, Brussels, Belgium

Background: CNS involvement in metastatic TNBC occurs in 25-46% of pts, negatively impacting their prognosis. It is important to understand the clinical landscape of brain metastases, in order to delineate screening strategies for it.

Methods: Retrospective analysis of TBNC pts treated at a Belgian institute between 02/2000 and 12/2014. Brain metastases free survival (BMFS) was defined as the date from the diagnosis of metastatic TNBC to the date of 1st CNS event (parenchymal and/or leptomeningeal metastases), and BMFS2 from the diagnosis of a 1st CNS event to the diagnosis of a 2nd CNS event. χ^2 test was used to compare clinical characteristics according to the occurrence of a 1st CNS event, and regression analysis with Cox proportional hazards model was done to determine risk factors for the 1st CNS event. Kaplan-Meier method was used to plot survival curves. P-value < 0.05 was considered statically significant. All analyses were performed with SAS v9.4.

Results: Median follow-up was 5.7 years (IQR 2.1-10.9) for 487 TNBC pts, of whom 111 developed metastatic disease. Fifty-five (11.3%) of all pts experienced a 1st CNS

Table 159P: Risk factors for a 1st CNS event

UV Analysis

Characteristic		N of Pts	N of Events (%)	HR	95% CI	p-value
Age (years)	≤ 50	183	29 (16)	1.7	1.0-2.9	0.05
	> 50	304	26 (9)	-	-	-
cT	1/2	370	29 (8)	-	-	-
	3/4	90	21 (23)	3.4	2.0-6.0	<0.01
cN	0	344	26 (8)	-	-	-
	1	127	23 (18)	3.0	1.7-5.2	<0.01
	2/3	10	3 (30)	10.6	3.2-35.6	
De Novo metastatic	No	458	45 (10)	-	-	-
	Yes	22	8 (36)	33.5	13.7-81.7	<0.01
Axillary Surgery	No	19	5 (26)	8.8	3.4-22.6	<0.01
	Yes	467	50 (11)	-	-	-
(Neo)Adjuvant ChT	No	25	8 (32)	16.1	7.2-35.7	<0.01
	Yes	462	47 (10)	-	-	-
Adjuvant RdT	No	86	12 (14)	-	-	-
	Yes	390	41 (11)	2.2	1.2-4.3	0.02
MV Analysis						
cT	1/2	370	29 (8)	-	-	-
	3/4	90	21 (23)	2.5	1.3-4.7	0.01
cN	0	344	26 (8)	-	-	-
	1	127	23 (18)	2.2	1.1-4.1	0.01
	2/3	10	3 (30)	5.8	1.5-22.7	
De novo metastatic	No	458	45 (10)	-	-	-
	Yes	22	8 (36)	33.2	10.7-103.5	<0.01

event, with more pts being of young age (≤50 years), higher primary tumor stage (≥cT3), higher nodal stage (≥N1), no (neo)adjuvant chemotherapy use, and de-novo metastatic, as compared to pts without a CNS event. Regression analysis showed cT3-4, cN1-3, and de novo metastatic disease as risk factors for CNS events (Table). Among those who developed metastases, median BMFS was 15.2 months (95% CI 9.5-33.5), with a numerically lower survival for those with a 1st CNS event vs those without (12.3 vs 15.9 months). Thirty-five pts experienced a 2nd CNS event, with median BMFS2 of 4.1 months (95% CI 2.3-6.6).

Conclusions: Pts with locally advanced or de novo metastatic TNBC are at a higher risk of developing CNS metastases, thus prospectively testing a periodic imaging assessment strategy of the CNS warrants consideration in this setting.

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162P Overcoming resistance to endocrine therapy in hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer: A meta-analysis of randomized clinical trials

W. Zhu[1], B. Xu[2]

[1]*Department of Comprehensive Oncology, Chinese Academy of Medical Sciences - National Cancer Center, Cancer Hospital, Beijing, China;* [2]*Department of Medical Oncology, Chinese Academy of Medical Sciences - National Cancer Center, Cancer Hospital, Beijing, China*

Background: New targeted therapies have been developed to overcome resistance to endocrine therapy (ET) and improve the outcome of HR+/HER2- advanced breast cancer (ABC). We conducted a meta-analysis and systemic review on randomized controlled trials (RCT) evaluating various targeted therapies in combination with ET in HR+/HER2- ABC.

Methods: PubMed and Embase databases were searched for eligible trials. Phase II and III RCTs with intervention arm (therapy of interest + standard ET) and control arm (standard ET + placebo) which enrolled adult women with advanced or metastatic HR+/HER2- breast cancer resistant to previous ET in either adjuvant or advanced setting were included. Hazard ratios (HRs) for progression-free survival (PFS), odds ratios (ORs) for objective response rate (ORR), clinical benefit rate (CBR) and toxicity were meta-analysed.

Results: Twenty-six studies with data on 10,347 patients were included and pooled. Addition of cyclin-dependent kinase 4/6 inhibitors to ET significantly improved median PFS (pooled HR 0.547, p=0.000, I^2=0.0%) and tumor response rates (ORR, pooled OR 1.478, p=0.000, I^2=43.9%; CBR, pooled OR 1.201, p=0.000, I^2=69.2%) with manageable toxicities (pooled OR 3.280, p=0.000, I^2=85.7%). Mammalian target of rapamycin inhibitors plus exemestane, however were not clinically beneficial (pooled HR 0.606, p=0.054, I^2=93.6%) in this pooled population including both ET-naïve and ET-resistant patients. Moderate improvement in PFS (pooled HR 0.744, p=0.000, I^2=0.0%) yet pronounced toxicities (pooled OR 2.154, p=0.000, I^2=37.1%) were noted in the combination of phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors with fulvestrant. Adding tyrosine kinase inhibitors (pooled HR 0.787, p=0.026, I^2=0.1%) or anti-angiogenesis agents (pooled HR 0.794, p=0.007, I^2=0.0%) to ET resulted in statistically significant reduction in risk of progression but also higher risk of toxicity. Histone deacetylase inhibitors have demonstrated promising efficacy in ET-resistant patients.

Conclusions: Future studies are warranted to optimize the population and the dosing sequence of these available options.

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163P Population-adjusted comparison of SOLAR-1 and BOLERO-2: PFS with second-line alpelisib + fulvestrant vs everolimus + exemestane in postmenopausal pts with PIK3CA-mut hormone-receptor positive (HR+) human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer (ABC)

E.M. Ciruelos[1], T. Delea[2], A. Moynahan[2], I. Mayer[3], J. Park[4], D. Chandiwana[4], A. Ridolfi[5], I. Lorenzo[6], H.S. Rugo[7]

[1]*Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain;* [2]*Medical Oncology, Policy Analysis Inc. (PAI), Brookline, NY, USA;* [3]*Hematology/Oncology, Vanderbilt Ingram Cancer Center, Nashville, TN, USA;* [4]*Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA;* [5]*Novartis Pharmaceuticals Corporation, Novartis Pharmaceuticals Corporation, Rueil-Malmaison, France;* [6]*Medical Oncology, Novartis Farmaceutica, S.A., Barcelona, Spain;* [7]*Breast Department, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA*

Background: The SOLAR-1 trial (NCT02437318) demonstrated the efficacy and safety of alpelisib (A) + fulvestrant (F) vs placebo + fulvestrant as first- or second-line (2L) treatment (trt) in postmenopausal women with PIK3CA-mutated (mut), HR+, HER2− ABC. Everolimus + exemestane (E+E) is often used as 2L trt of HR+, HER2− ABC based on the BOLERO-2 trial (NCT00863655). This study was a population-adjusted indirect trt comparison of PFS for A+F vs E+E as 2L trt in patients (pts) with PIK3CA-mut, HR+, HER2− ABC using pt-level data from SOLAR-1 and BOLERO-2.

Methods: Pts who progressed on an endocrine therapy in the metastatic setting in BOLERO-2 with a PIK3CA mutation based on tissue samples were selected to match corresponding pts in SOLAR-1. Selected BOLERO-2 pts were weighted to match on baseline characteristics of pts in SOLAR-1 using average trt effect in the treated inverse probability of trt weighting. Weights were calculated using propensity scores estimated by logistic regression with covariates for age, race, performance status, tumor histology/cytology and grade, number and location of metastatic sites, time since diagnosis/most recent recurrence/metastasis, and receipt of prior chemotherapy in advanced setting. Hazard ratios (HRs) for PFS for A+F vs E+E were estimated by Cox regression with variances based on robust sandwich estimates.

Results: A total of 36 2L pts with a PIK3CA mutation receiving E+E from BOLERO-2 were matched to 79 pts from the corresponding SOLAR-1 2L population. Before weighting, the PFS was statistically significantly higher for A+F vs E+E (HR 0.549, 95% CI, 0.338-0.893, P=0.0157). The results were consistent after weighting, with an HR for PFS of 0.513 (95% CI, 0.263-0.999, P=0.0497).

Conclusions: Analysis of comparable populations from the SOLAR-1 and BOLERO-2 trials suggest A+F may yield clinically and statistically significant improvement in PFS compared with E+E as 2L trt for postmenopausal women with PIK3CA-mut, HR+, HER2− ABC; however, low pt numbers may limit conclusions.

Clinical trial identification: NCT02437318; NCT00863655.

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164P A prospective approach for the evaluation of a one-step RT-qPCR based test for the quantification of HER2 protein in formalin-fixed and paraffin-embedded breast cancer tissues

B. Al Banyahyati

Biology, MAScIR - Moroccan Foundation for Advanced Science, Innovation ans Research, Rabat, Morocco

Background: Detection of the human epidermal growth factor receptor 2 gene (HER2, also known as erbB2) expression is important to decide a treatment strategy for breast cancer patients. 20 to 30% of breast cancer patients overexpress HER2. The reference methods for determining HER2 protein expression are Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Although both methods are reliable, they are complex, time-consuming and expensive.

Methods: In the present study, we performed a prospective approach to evaluate a "one step" reverse transcription qPCR method in the determination of HER2 status. We compared IHC and FISH to a "one step" RT-qPCR in 246 formalin-fixed and paraffin-embedded FFPE tissue samples from breast cancer patients.

Results: Our results show that the "one step" RT-qPCR method was highly concordant with IHC/FISH methods for detecting HER2 expression. The concordance between RT-qPCR and IHC results was 95.53%, whereas that of RT-qPCR and FISH attained 100%. We also determined a diagnostic cut-off to the one-step RT-qPCR test using ROC method. Our results demonstrate high clinical performance in the detection and evaluation of HER2 gene expression in breast cancer, confirmed by Sensitivity and Specificity values of 89.4% and 100% respectively for a threshold value of 11,954 (AUC = 0,955).

Conclusions: In conclusion, this prospective study shows that the one-step RT-qPCR method gave correlated results with those of classical IHC / FISH methods. The RT-qPCR could be the first choice for determining HER2 expression in clinical samples of breast cancer patients and may be able to give decisive information for estimating the effects of trastuzumab therapy toward breast cancer patients.

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165P Immune characterization of the de novo oligometastatic breast cancer

S. Chretien[1], L. Buisseret[2], X. Wang[2], G. Rouas[2], N. Kotecki[3], S. Garaud[4], A. Mailliez[5], D. Larsimont[6], F. Rothé[2], C. Sotiriou[2]

[1]Medical Oncology, Centre Oscar Lambret, Lille, France; [2]Breast Cancer Translational Research Laboratory J-C. Heuson, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium; [3]Medical Oncology Clinic, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium; [4]Molecular Immunology Unit, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium; [5]Medical Oncology, Centre Oscar Lambret, Lille, France; [6]Pathology Department, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium

Background: De novo oligometastatic breast cancer (OMBC) is a rare presentation of advanced stage breast cancer (BC) with $\leq$ 5 metastatic lesions at diagnosis. Its clinical management is not well defined because of varying definitions, lack of specific biomarkers and lack of dedicated prospective clinical studies. Here, we investigated tumor immune microenvironment, classical clinic-pathological parameters including treatment and correlated them with survival in a cohort of de novo OMBC patients to better characterize this disease entity.

Methods: Clinico-pathological characteristics of 115 de novo OMBC and 117 de novopolymetastatic (PM) patients treated in two cancer centers between 2000 and 2016 were retrospectively collected. Tumor-Infiltrating Lymphocytes (TILs) were quantified (n=54) and immune subsets were characterized using multiplex multispectral immunohistochemistry (n=31). Survival analyses were performed using Cox regression models.

Results: De novo OMBC was associated with more Luminal B and less Luminal A subtypes (as defined by IHC), lower LDH and CA 15-3 levels compared to PM patients. Most OMBC patients were first treated with systemic therapy (66.1%), mainly by chemotherapy (71%) followed by surgery. Patients treated with upfront surgery (33.9%) received pseudo-adjuvant systemic therapy (92.3%). OMBC had better survival than PM with median progression-free and overall survival of 23.9 and 50.4 months respectively. Surgery of the primary tumor before 1stprogression, the use of poly-chemotherapy and a lower histological grade were associated with a better outcome in de novo OMBC. These breast tumors showed low immune infiltration (median TIL levels 5% (0 — 60%)) with 50% of the cases defined as "cold" tumors. Median CD4 T cell, CD68 macrophage and CD8 T cell infiltration in primary tumors were 8%, 5% and 4% respectively. Interestingly, CD8 T cell level was associated with a better survival.

Conclusions: De novo OMBC is a specific subset of metastatic BC with distinct clinico-pathological characteristics and favorable outcome. An "aggressive" multimodal therapeutic strategy should be considered in this disease entity. We report limited TIL infiltration but revealed the importance of specific tumor immune-infiltrates that should be further investigated.

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166P Awareness and availability of routine germline BRCA1/2 (gBRCA1/2) mutation testing in patients (pts) with advanced breast cancer (ABC) in Germany

M.P. Lux[1], T. Decker[2], E.D. Runkel[3], A. Niyazov[4], R.G.W. Quek[5], E. Glastetter[3], N.W. Marschner[6], N. Harbeck[7]

[1]Kooperatives Brustzentrum Paderborn, Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten, Frauen- und Kinderklinik St. Louise, Paderborn, Germany; [2]Onkologie, Onkologie Ravensburg, Ravensburg, Germany; [3]Oncology, Pfizer Pharma GmbH, Berlin, Germany; [4]US Oncology, Pfizer Inc., New York, NY, USA; [5]Health Economics and Outcomes Research Department, Pfizer Inc., San Francisco, CA, USA; [6]Medical Oncology Department, IOMEDICO AG, Freiburg, Germany; [7]Breast Center, Brustzentrum, Frauenklinik der Universität München (LMU), Munich, Germany

Background: gBRCA1/2 testing in HER2- ABC is critical to assess eligibility for PARP inhibitors (PARPi). However, testing is heterogeneous across healthcare sectors in Germany. We investigated clinical practice, awareness and availability of routine gBRCA1/2 testing in the German outpatient oncology setting.

Methods: A 23-item online survey was completed by 50 office-based medical oncologists (66.0%) and gynecological oncologists (34.0%) (ONC) from Oct 2019-Feb 2020. Responses were evaluated collectively/in predefined subgroups by demography.

Results: Known family history (FH) of gBRCA1/2-related cancer(s) and hormone receptor status influenced gBRCA1/2 testing rate (Table). Most ONC routinely test ABC pts with triple-negative breast cancer (TNBC) independent of FH [rate (%) with FH 98.0, without (w/o) FH 92.0]; only reason for not testing TNBC pts (n=3) was reimbursement difficulties. Testing rates for HR+/HER2- ABC pts were generally lower and depended on FH [rate (%) with FH 82.0%, w/o FH 30.0%]. Reasons for not testing HR+/HER2- ABC pts (n; with FH 7, w/o FH 33) were: available therapy alternatives [rate (%) with FH 100.0, w/o FH 54.5], reimbursement difficulties [rate (%) with FH 28.6, w/o FH 24.2] or other [rate (%) with FH 0, w/o FH 24.2]. Other influencing factors included guideline recommendations and age at BC onset. Test turnaround time [median (range); 4.0 (1.0-21.0) weeks] and availability of genetic counseling influenced when ONC routinely initiate gBRCA1/2 testing (46.0% and 36.0%, respectively). Most ONC reported access to gBRCA1/2 testing as satisfactory (30.0%) or good (36.0%), and rated awareness of testing among ONC as satisfactory (40.0%).

Table 166P: gBRCA1/2 testing rates in ABC patients

ABC subtype	gBRCA1/2 testing rates	
	With known family history of gBRCA1/2 related cancer(s), % (n/N)	Without known family history of gBRCA1/2 related cancer(s), % (n/N)
TNBC	98.0 (49/50[a])	92.0 (46/50)
HR+/HER2-	82.0 (41/50[b])	30.0 (15/50[b])
HR+/HER2+	76.0 (38/50[b])	10.0 (5/50[b])
HR-/HER2+	82.0 (41/50[b])	16.0 (8/50[b])

n= number of physicians who answered yes; N= number of physicians asked; [a]1 physician responded "no answer"; [b]2 physicians responded "no answer"

Conclusions: gBRCA1/2 testing is established in Germany's outpatient oncology setting; however, opportunities exist to improve testing of HR+ ABC pts w/o FH given the advent of gBRCA1/2-targeted PARPi.

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167P TRIP13 is upregulated in liver metastasis of breast cancer and is a potential poor prognostic indicator of metastatic relapse

Z. Du, Y. Wang, Q. Lv

Breast Surgery, West China Medical Center of Sichuan University, Chengdu, China

Background: Liver metastasis is very common in breast cancer (BC) patients and associated with very poor prognosis. Hence, new molecular targets for therapeutic intervention are needed for BC patients with liver metastasis. In this study, we aimed to investigate the molecular pathways regulating BC liver metastasis which is essential for developing more effective therapies.

Methods: Raw gene expression data including GSE14018、GSE7390、GSE60502, and GSE33116 were obtained from the Gene Expression Omnibus. Animal liver metastasis models were constructed by injecting the first, second, and third generations of liver metastasis tumor cells to the splenic subcapsular of the nude mice. Weighted gene co-expression network analysis (WGCNA) and tissue microarray (TMA) were performed to dynamically analyze the gene module and hub genes associated with the BC liver metastasis.

Results: WGCNA identified that the brown (Pearson = 0.86, p =4e-102), blue(-Pearson = 0.48, p = 4e-21), and yellow (Pearson = 0.65, p = 2e-43) modules showed a higher expression trend in the development of BC liver metastasis, while green (Pearson = -0.26, p = 6e-07) and red (Pearson = -0.23, p = 2e-05) modules displayed a completely different trend. WGCNA further revealed 6 hub genes in the brown module which were most closely associated with the BC liver metastasis, namely, RACGAP1, UBE2C, ZWINT, TRIP13, KIF2C, MCM2. Survival analysis predicted a poor survival among BC patients if these hub genes were upregulated. TMA showed that the expression of TRIP13 was dynamic higher and higher from the first generation of BC liver metastasis tissue to the third generation of BC liver metastasis tissue. Real-time PCR and western blot also confirmed that TRIP13 was most closely related to liver metastasis in BC. CCK-8, wound healing and transwell assays revealed that TRIP13 knockdown could inhibit the proliferation, migration and invasion of MDA-MB-231 human BC cells.

Conclusions: TRIP13 which is most closely related to the proliferation, migration and invasion of BC cells, may promote the occurrence of liver metastasis in BC patients.

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168P Development of a combined clinical model to predict progression-free survival (PFS) in advanced breast cancer (ABC) treated with CDK4/6 inhibitors (CDK4/6i)

O. Martínez-Sáez[1], A. Menichetti[2], L. Pare Brunet[3], G. Griguolo[2], A. Rodriguez Hernandez[1], T. Pascual[1], M.V. Dieci[2], P.F. Conte[2], C.A. Giorgi[2], F. Brasó-Maristany[4], N. Chic[1], D. Martínez[4], A. Rodríguez[1], F. Schettini[1], B. Conte[1], M. Vidal[1], B. Adamo[1], M. Muñoz[1], A. Prat[1], V. Guarneri[2]

[1]Department Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain; [2]Oncologia Medica 2, IOV - Istituto Oncologico Veneto IRCCS, Padua, Italy; [3]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [4]Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain

Background: CDK4/6i improve survival in patients (pts) with hormone receptor (HR+)/HER2 negative (HER2-) ABC. However, prognostic and predictive markers are still needed to design future clinical trials and to better choose the optimal treatment for each patient.

Methods: Clinical data were available from pts treated with CDK4/6i from March/14 to June/19 in Hospital Clinic of Barcelona (HCB). To derive a prognostic model, we evaluated: age, ECOG, type of CDK4/6i, type of endocrine therapy (ET), line of treatment, visceral disease, more than 3 sites of metastasis, "de novo" metastasis, menopause status and hormone resistance. Using data from the HCB (train set), we performed a PFS cox model in 2/3 pts using Elastic Net (Monte Carlo CV). C-index of the model was estimated in 1/3 pts. The final model was finally tested blinded in pts prospectively treated from June/17 to April/19 with palbociclib and ET at Istituto Oncologico Veneto (Padua) in Italy (independent testing set).

Results: The final model combined 7 clinical variables with different weights, 4 being associated with worse PFS (ECOG, line of treatment, hormone resistance and type ET) and 3 being associated with better PFS (menopause status, type of CDK4/6i and "de novo" metastasis). In the training set (n=167), the prognostic score as a continuous variable was associated with PFS (hazard ratio [HR]=8.09, 95% CI 4.03-16.23, p<0.0001) and the C-index was 0.72. The median PFS in the good prognosis group (defined by the median) was 20.1 months compared to 8.4 months in poor prognosis patients (HR=0.33 p<0.0001). In the testing and independent dataset (n=128), the score as a continuous variable was significantly associated with a worse PFS (HR=6.46, 95% CI 1.99-21.00, p=0.002). The median PFS in the good prognosis group (defined by the median) was 19.6 months compared to 9.9 months in poor prognosis patients (HR=0.50, 95% CI 0.30-0.81, p=0.005).

Conclusions: A simple combined clinical model predicts PFS in HR+/HER2- advanced disease treated with CDK4/6i and ET. This prognostic model may help clinicians and patients in clinical decision making, as well as investigators in research planning.

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169P Trastuzumab use among patients with HER2-positive metastatic breast cancer in an electronic health records database

N. Lindegger[1], C. Ike[2], N.R. Schwartz[2], A. Surinach[3], Y. Liu[3], K. Debusk[2]

[1]Medical Affairs, Seattle Genetics - SeaGen International GmbH, Zug, Switzerland; [2]Health Economics & Outcomes Research, Seattle Genetics, Bothell, WA, USA; [3]Real World Evidence (RWE) Solutions, Genesis Research, Hoboken, NJ, USA

Background: Trastuzumab (TRA) is a commonly used anti-HER2 directed agent among breast cancer (BC) patients in the adjuvant and metastatic settings, however, real-world evidence of retreatment with TRA in the metastatic setting is lacking. We describe TRA use among HER2-positive (HER2+) metastatic breast cancer (MBC) patients in an electronic health records database.

Methods: Adult HER2+ MBC patients who received TRA were identified in the Flatiron database from 2011 through August 31, 2019. Patient demographics, TRA use and time to next TRA-containing regimen were described.

Results: The Flatiron MBC database identified 3,187 HER2+ BC patients who had evidence of TRA treatment (297 in the neo-adjuvant/adjuvant BC setting and 2,890 in the metastatic setting). In the metastatic setting, patients had a median age of 60 years, 74.5% were hormone receptor-positive; 47% were initially diagnosed stage I—III, 45% stage IV, and 8% had a missing/unknown stage at initial diagnosis. Median follow-up was 26.2 (range 12.4 to 44.9) months. Most (73.4%) MBC patients received TRA in the first line (1L) for a median duration of 5.2 months; duration of TRA decreased with increasing line of therapy. Almost half (48.1%, n=1,390) of patients had re-exposure to TRA in the metastatic setting: 89.2% of these had TRA in consecutive lines and 30.1% in non-consecutive lines. Mean time to re-exposure was 9.5 months. Among patients who received TRA in the metastatic BC setting, a total of 419 (30.1%) patients were re-exposed to TRA in a non-consecutive line; 52.7% of whom received T-DM1 prior to re-exposure to TRA.

Conclusions: Almost half of HER2+ MBC patients were treated with TRA in multiple lines of therapy, with most of those with re-exposure receiving TRA in consecutive lines. Our data demonstrate that physicians are continuing to treat with TRA after patients have progressed on TRA therapy.

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170P 18F-FDG PET/CT features of the metastases from intrinsic NSIBC molecular types and its prognostic value

M. Xu, J. Chen

Nuclear Medicine Department, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: To analyze the ^{18}F-FDG PET/CT imaging features of the metastases from nonspecific invasive breast cancer (NSIBC) according to intrinsic molecular subtypes, and its prognostic value in metastatic NSIBC.

Methods: Female breast cancer patients has ^{18}F-FDG PET/CT at our hospital 12/2013-10/2018 were collected retrospectively, including image features, clinicopathological, and disease status after PET/CT. All patients were divided as five groups: Luminal A (LA), Luminal B (LB), HER2 positive luminal (LHER), HER2 enriched (HER) and Basal like (TN). Nonparametric tests were used to analyze the difference of maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), heterogeneity index (HI) and coefficient of variation (COV) among metastases. And, ROC curve was used to evaluate the diagnostic performance of SUVmax for bone and lymph node metastases. Cox regression was used to test for relationship among PET/CT parameters, clinicopathological and progression-free survival (PFS).

Results: 54 metastatic NSIBC with 747 metastases were enrolled. There was significant in SUVmax and HI of the metastases among five groups (P=0.00). The metastases in lung had the highest HI (P=0.00). LA had the smallest SUVmax and HI (P=0.00); LHER had the highest SUVmax (P=0.00). Among different molecular subtypes, SUVmax for bone were: LA < HER < LB < LHER. ROC curve analysis showed that among LHER and TN, the SUVmax cutoff values of 4.55 and 2.65 identified bone and lymph node metastases with high sensitivity (92.90% and 95.30%) and specificity (100.00% and 86.20%). More than 12 months follow-up after PET/CT, 34 metastatic NSIBC cases had progressive disease (PD), 17 cases had non PD. The whole body MTV (HR=1.01, P=0.00), molecular subtypes (LA (HR=0.309, P=0.028) and LHER (HR=0.312, P=0.031))and presence of recurrent (HR=2.15, P=0.035) were identified as independent prognostic factors of PFS.

Conclusions: The metastases of NSIBC from different molecular subtypes presented with diverse ^{18}F-FDG PET/CT imaging features. Based on individualized analysis of molecular subtypes and metastatic sites, can yield a better diagnostic performance. Moreover, wMTV is one of independent prognostic factors in metastatic NSIBC.

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171P An outcomes summary of the clinical advances curriculum on CDK4 & 6 inhibition in breast cancer

N. Dorkhom[1], D. Middleton[2], P. Guedj[3], P. Chen[4], K. Lucero[4], G. Curigliano[5]

[1]Medical Education, Medscape, Naarden, Netherlands; [2]Medical Education, Medscape, Chicago, IL, USA; [3]Medical Education, Medscape, Paris, France; [4]Medical Education, Medscape, New York, NY, USA; [5]Division of Early Drug Development for Innovative Therapy, University of Milan, Milan, Italy

Background: The treatment of patients with HR+/HER2-ve breast cancer has changed rapidly in the last 3 years. The introduction of CDK4 & 6 inhibitors as combinations in the metastatic setting has significantly improved outcomes for patients, increasing PFS, OS and response rates in both first and second-line. The objective of this study was to assess the impact of this educational curriculum on oncologists' knowledge, competence and confidence as a result of educational activities on CDK4 & 6 inhibitors.

Methods: A series of 9 online continuing medical education (CME) activities were launched in 2017-2019 covering a range of educational gaps regarding the role of CDK4 & 6 inhibitors in the management of advanced HR+/HER2- breast cancer. To assess educational impact, participants were asked pre-education and post-education questions; the scores for each participant were compared to determine change in the outcomes. These questions were designed to assess if certain learning objectives were met, which in turn were designed to cover the educational gaps identified. Statistical significance was assessed using McNemar's test ($P < .05$ level).

Results: A total of 22,559 learners participated in these activities, of whom 9,641 were oncologists. The learning objectives were grouped under 5 themes: mechanism of action of CDK4 & 6 inhibitors, implications of clinical trial data, patient eligibility for CDK4 & 6 combination therapy, selecting the optimal therapy and adverse events of CDK4 & 6 inhibitors. The analysis set consisted of responses from oncologists (n's ranged from 141-243). While all 19 learning objectives showed improved outcomes, 17 out of the 19 showed statistical significance. The relative percentage improvement in pre/post correct answers in knowledge and competence learning objectives ranged from 14% to 163% while improvement of pre/post confidence ranged from 24% to 95%.

Conclusions: This online CME curriculum resulted in a significant improvement of oncologists' knowledge, competence, and confidence regarding the different aspects of education on CDK4 & 6 inhibitors. As new data emerge it would be important to provide new educational activities to improve clinical implementation of new insights in the use of CDK4 & 6 inhibitors in clinical practice.

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172P REACHAUT: Real-world study of first-line (1L) ribociclib (RIB) + endocrine therapy (ET) in HR+, HER2- metastatic breast cancer (MBC)

C.F. Singer[1], D. Egle[2], R. Greil[3], L. Öhler[4], E. Petru[5], C. Suppan[6], M. Marhold[7], G. Pfeiler[1], C. Brunner[2], C. Tinchon[8], S. Halper[9], A. Galid[10], U. Pluschnig[11], F. Haslbauer[12], M. Hubalek[13], A. Redl[14], J. Flatschacher[15], M. Hennebelle[15], B. Mraz[15], R. Bartsch[7]

[1]Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [2]Department of Gynecology and Gynecological Oncology, Medical University of Innsbruck, Innsbruck, Austria; [3]III Medical Department with Hematology and Medical Oncology, Paracelsus Medical University Salzburg, Salzburg, Center for Clinical Cancer and Immunology Trials, Salzburg Cancer Research Institute, Cancer Cluster Salzburg, Salzburg, Austria; [4]Department of Internal Medicine/Oncology, St Joseph Hospital, Vienna, Austria; [5]Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria; [6]Department of Oncology, Medical Universitiy of Graz, Graz, Austria; [7]Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria; [8]Department of Hematooncology, Leoben State Hospital, Leoben, Austria; [9]Department of Surgery, Breast Health Center, State Hospital Wiener Neustadt, Wiener Neustadt, Austria; [10]Department of Gynecology, Breast Center Hanusch KH, Vienna, Austria; [11]Department of Hematology and Internal Oncology, Klinikum Klagenfurt, Klagenfurt, Austria; [12]Department of Internal Medicine, Saizkammergut Klinikum Vocklabruck, Voclabruck, Austria; [13]Department of Gynecology and Obstetrics, Brustzentrum Schwaz, Schwaz, Austria; [14]Biostatistics, Datamedrix GmbH, Vienna, Austria; [15]Department of Oncology, Novartis Pharma GmbH, Vienna, Austria

Background: Real-world data on efficacy and safety of RIB + ET (approved 1L treatment [tx] for HR+, HER2− MBC) are limited. Preliminary safety results of REACH AUT, a real-world, prospective, non-interventional RIB + ET trial in postmenopausal patients (pts) with HR+, HER2− MBC were consistent with those observed in the MONALEESA-2 study.[1] Efficacy and safety results from the 2nd interim analysis are presented.

Methods: Post protocol amendment (Feb-2019) premenopausal pts were also included and RIB + aromatase inhibitor (AI) or FUL combination was defined. Pts with HR+, HER2− MBC, QTc <450msec, and no prior ET for advanced disease were enrolled at 13 sites. 1L chemotherapy was allowed.

Results: At data cutoff (18-Oct-2019), 100 (65.8%) out of 152 enrolled pts (11 pre- and 141 postmenopausal), were ongoing tx. Median age of pts was 65 years (<65, n=75; ≥65, n=77); ECOG performance status 0: n=105; 1: n=26; 2: n=3; 3: n=1. 63 pts (41.4%) had visceral (lung, liver) metastases (mets) and 47 (30.9%) had bone only mets.

Most common (>20% pts) prior adjuvant tx were AI (25.7%). 26 pts (17.1%) received RIB + FUL and 125 (82.2%) received RIB + AI. At restaging (for available pt data), the objective response rate was 19.1%. Median progression-free survival (PFS) and overall survival were not reached (NR) at a median follow-up of 7.2 months. Median PFS in pts visceral mets 13.9 (95% CI: 5.19-13.87) months while it was NR in pts with bone only mets. 135 pts (88.8%) had ≥1 adverse event (AE, Grade 1: n=115 [75.7%]; Grade 2: n=96 [63.2%]; Grade 3: n=67 [44.1%]; Grade 4: n=7 [4.6%]). Most common AE (>20% pts) was neutropenia (47.4%). 11.2% pts had hepatobilliary AEs (all grades; Grade 2: n=8 [5.3%]; Grade 3: n=9 [5.9%]). 8 pts (5.3%) had Grade 2 and 1 pt (0.7%) had Grade 3 QTcF prolongation. 141 pts (92.8%) had dose interruptions and 44 pts (28.9%) had ≥ 1 dose reduction (1 dose reduction to 400 mg: n=35 [23.0%]; 2 dose reductions to 200 mg: n=7 [4.6%]). 17 pts (11.2%) discontinued the study due to AEs.

Conclusions: RIB + ET showed favorable efficacy and tolerable safety in routine clinical practice. Results of this real-world study are consistent with those seen in MONALEESA trials. [1]JClin Oncol 2019 37:15_suppl, e12527-e12527.

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173P Clinical characteristics of long-term responders to anti-HER2 therapy in metastatic breast cancer: A review of the charactHER clinical data

D. Skrobo[1], N. Walsh[2], C. Quinn[3], J. Walshe[4], L.M. Smyth[5], G. Gullo[4], J.P. Crown[4]

[1]Department of Oncology, St Vincents University Hospital, Dublin, Ireland; [2]School of Biotechnology, National Institute for Cellular Biotechnology, Dublin, Ireland; [3]Pathology, St Vincents University Hospital, Dublin, Ireland; [4]Medical Oncology, St Vincents University Hospital, Dublin, Ireland; [5]St Vincents University Hospital, Dublin, Ireland

Background: Her2 positive breast cancer accounts for approximately 15-20% of all breast cancer cases. Anti-Her2 therapy has been shown to reduce rates of relapse, in metastatic breast cancer it has been shown to be an effective long-term treatment option which can lead to a prolonged survival, significant period of disease control and in some cases a complete cure. Aims and Objectives: To determine if there are any clinical characteristics which can help predict which patients may turn out to be long term responders to anti-HER2 therapy. We sought to identify and characterize long term responders to better understand potential refined predictive clinical markers of durable response.

Methods: Retrospective review of a prospectively maintained institutional database of patients with Her2 positive breast cancer diagnosed on or before December 2014. Exceptional responders, defined as patients who maintain clinical stability for >3 years on anti-her2 monotherapy and those with primary resistance defined as patients who progressed within 2 years of treatment. Comparison was made of the clinical and disease characteristics in these two groups.

Results: Of 1000 patients with HER2 positive breast cancer, 300 patients with metastatic disease were identified. Long-term responders (LTR's) N=37 (57%) and rapid non-responders (RNR's) N=28 (43%). The median age was 55 and 68 years respectively at first anti-Her2 treatment for metastatic disease with 57% vs 32% diagnosed with de-novo metastatic disease. The median follow up for the LTR's is 101.32 months and the median overall survival for the RNR group reached 6.11 months. 57% of LTR's did not have visceral involvement vs 86%, and 89% of LTR's had 1-2 disease sites only. Complete response was achieved in 43% the LTR group vs 0% in RNR's.

Conclusions: The main characteristics that seem to be associated with achieving Long Term Response to 1st line anti-HER2 therapy in metastatic breast cancer are a younger age (~ 55 years of age), de-novo metastatic disease. Having a right sided primary. Less than 3 disease sites with NO visceral involvement. Achieving complete response to initial 1st line chemo+anti-HER2 treatment.

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174P Occurrence of brain metastasis and treatment patterns among patients with HER2-positive metastatic breast cancer

G.A. Vidal[1], K. Debusk[2], S. Gautam[3], A. Vlahiotis[3], M. Fisher[3], S. Pulgar[2]

[1]Breast Cancer Research, West Cancer Center and Research Institute, Germantown, PA, USA; [2]Health Economics & Outcomes Research, Seattle Genetics, Bothell, WA, USA; [3]Outcomes Science & Services, Concerto HealthAI, Memphis, TN, USA

Background: The risk of brain metastasis (BM) is high (up to 50%) among patients diagnosed with HER2-positive (HER2+) metastatic breast cancer (MBC) compared with HER2-negative MBC. There are limited real-world data on the timing of BM development and subsequent treatment among such patients. The objective of this observational study was to assess BM occurrence and treatment among women with HER2+ MBC.

Methods: Women ≥18 years old and diagnosed with HER2+ MBC between 6/1/2012 and 5/31/2018 were included in the study. Data were abstracted from electronic medical records from a network of community oncology practices maintained in the Vector Oncology Data Warehouse and included clinical and demographic characteristics, timing of BM diagnosis and treatment patterns.

Results: Of 372 study eligible patients, 165 (44.4%) had a record of BM. The majority of patients with BM were white (n=99; 60.0%) with a median age of 54 (range 29-83) years at MBC diagnosis. There were 82 patients (49.7%) with de novo MBC and 89 (53.9%) had hormone-receptor positive tumours. There were 37 patients (22.4%) with a record of BM at the time of initial MBC diagnosis (baseline), 63 (38.2%) developed BM during the first-line treatment, 23 (13.9%) during the second-line and 42 (25.5%) during the third-line or beyond. The median time to develop BM from initial MBC diagnosis was 12.5, 18.3 and 22.8 months, respectively. Post-BM systemic treatments varied. Among those with baseline BM (n=37), the most common regimens were trastuzumab plus pertuzumab along with taxane (n=13; 35.1%), trastuzumab monotherapy (n=3; 8.1%) and tamoxifen monotherapy (n=3; 8.1%). In patients who developed BM during follow-up (n=128), the most common regimens included pertuzumab plus trastuzumab (n=27; 21.1%), ado-trastuzumab emtansine monotherapy (n=13; 10.2%), and trastuzumab monotherapy (n=11; 8.6%).

Conclusions: BM were common among patients with HER2+ MBC, and occurred at various points during the course of treatment. Post-BM systemic therapy varied widely, which may indicate a lack of standard of care for patients with HER2+ MBC after BM diagnosis and an unmet need in this patient population. Further analysis on treatment efficacy is required to understand whether treatment needs are met.

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175P Real-world patient and practice characteristics associated with use of CDK4/6 inhibitors among patients receiving first therapy for HR+/HER2- advanced or metastatic breast cancer in Italy and Germany

S. de Placido[1], S. Brucker[2], E. Law, Pharmd[3], M. Ajmera[4], D. Mitra[5], K.L. Davis[4], N. Harbeck[6], M. De Laurentiis[7]

[1]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [2]Department of Obstetrics and Gynecology, Tübingen University Hospital, Tübingen, Germany; [3]Global Health Economics & Outcomes Research (Oncology), Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [4]Health Economics, RTI Health Solutions, Research Triangle Park, NC, USA; [5]Patient & Health Impact (PHI), Pfizer Inc, New York, NY, USA; [6]Department of Obstetrics and Gynecology, Brustzentrum der Universität München (LMU), Munich, Germany; [7]Department Breast and Thoracic Oncology, National Cancer Institute "Fondazione Pascale", Naples, Italy

Background: Since approval in 2016, clinical practice guidelines in Europe recommend the use of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy for the treatment of advanced or metastatic breast cancer (a/mBC). Few studies have examined factors associated with use of CDK4/6i therapy. This study aimed to characterize patient and practice characteristics associated with first-line selection of CDK4/6i therapy among patients with a/mBC.

Methods: Patients with a/mBC enrolled in a prospective non-interventional study between January 2017 and April 2019 at participating sites in Italy and Germany were categorized as receiving a CDK4/6i or not. Patient and practice characteristics at the time of 1st-line treatment decision were collected. Multivariable logistic regression models were conducted to evaluate the relationship between patient and practice characteristics and CDK4/6i use and non-use.

Results: A total of 193 patients (52% Germany) across 67 sites were included. Of these, 38% and 67% patients received CDK4/6i in Italy and Germany, respectively. In the core model assessing patient-level characteristics only, treatment year (2018 vs. 2017; odds ratio [OR] 4.3; 95%CI 2.1 to 8.7) and de-novo disease at diagnosis (OR 0.47; 95%CI 0.2 to 1.8) were associated with ased CDK4/6i use, respectively. In the model with additional practice-level variables, CDK4/6i use was independently associated with country (Germany vs. Italy; OR 6.8; 95%CI 1.6 to 29.3) and type of practice, with lower odds of CDK4/6i use in designated cancer centers (OR 0.2; 95%CI 0.1 to 0.8) and private hospitals (OR 0.6; 95%CI 0.1 to 4.0) compared to public institutions.

Conclusions: This study identified patient- and system-level factors associated with CDK4/6i use since regulatory approval in Europe. Patients who presented with recurrent a/mBC, initiated treatment ≥1 year after CDK4/6i approval, receiving care at a public institution, or located in Germany were more likely to receive a CDK4/6i. Future research is needed to better understand the nature of these associations to ensure appropriate utilization of these therapies.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: S. de Placido: Advisory/Consultancy: Pfizer, Novartis, Roche, Celgene, AstraZeneca; Speaker Bureau/Expert testimony: Pfizer, Novartis, Roche, Celgene, AstraZeneca. S. Brucker: Honoraria (institution): Novartis, Pfizer, Roche, MSD, Olympus. E. Law, Pharmd: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer Inc. M. Ajmera: Advisory/Consultancy, RTI were paid consultants to Pfizer in connection with the development of this abstract: RTI Solutions. D. Mitra: Shareholder/Stockholder/Stock options, Full/Part-time employment: Pfizer Inc. K.L. Davis: Advisory/Consultancy, RTI Health Solutions were paid consultants to Pfizer in connection with developing this abstract: RTI Health Solutions. N. Harbeck: Honoraria (institution): Lilly, Novartis, Pfizer; Advisory/Consultancy: Celgene, Lilly, Novartis, Pfizer, Roche. M. De Laurentiis: Honoraria (institution): Pfizer, Novartis, Roche, Celgene, AstraZeneca, Eisai, Eli Lilly.

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176P Real-world tumour response of palbociclib plus letrozole vs letrozole for metastatic breast cancer in US clinical practices

A. Brufsky[1], X. Liu[2], B. Li[3], L. McRoy[4], R.M. Layman[5]

[1]Division of Hematology/Oncology, Comprehensive Breast Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]US Medical Affairs, Pfizer Oncology, Pfizer Inc, New York, NY, USA; [3]Statistics, Pfizer Inc, New York, NY, USA; [4]Pfizer Oncology, Pfizer Inc, New York, NY, USA; [5]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Palbociclib is the first clinically available oral CDK4/6 inhibitor for HR+/HER2- advanced/metastatic breast cancer (MBC). Real-world studies of palbociclib have demonstrated clinical effectiveness in MBC. This study compared real-world best tumor response (rwBTR) of palbociclib plus letrozole (PB+LE) vs letrozole alone (LE) for MBC in routine clinical practices.

Methods: We conducted a retrospective analysis of MBC patients from the Flatiron Health longitudinal database, which contains electronic health records from >280 cancer clinics representing more than 2.2 million actively treated cancer patients in the US. Between February 2015 and September, 2018; 1383 HR+/HER2− MBC women started PB+LE (n=754) or LE (n=629) as first-line therapy. Patients were followed from start of PB+LE or LE to end of study or death. rwBTR was defined as best tumor response over the course of treatment based on the treating clinician's assessments of radiologic evidence for change in burden of disease.

Results: Of 1383 eligible patients, 662 on PB+LE therapy and 306 on LE had ≥1 tumor response assessment during first line of therapy. Patients on PB+LE had significantly better overall tumor response (complete response + partial response) rate than patients on LE (59.8% vs. 39.2%, X^2= 35.7, p < .0001). After adjusting for demographic and clinical characteristics, patients were 2 times more likely to respond to PB+LE therapy than LE alone (OR = 2.07, 95%CI=1.54-2.79). The table presents key patient characteristics and rwBTR rates.

Table 176P: Patient characteristics and real-world best tumour response

Variable	PB+LE (N=662)	LE (N=306)
Median age (years)	65.0	72.0
White (%)	69.8	70.6
Practice type (Community, %)	94.6	95.1
Number of metastatic sites (median)	1.5	1.0
Bone only disease (%)	37.2	39.5
Visceral disease (%)	42.9	31.4
Overall tumor response (%)	59.8	39.2
Complete response (%)	9.7	8.8
Partial response (%)	50.2	30.4
Stable disease (%)	23.4	23.9
Progressive disease (%)	14.2	30.1
Indeterminate (%)	2.6	6.9
Median follow-up (months)	20.6	22.3

PB+LE= Palbociclib plus letrozole; LE= Letrozole alone

Conclusions: This comparative analysis suggests that HR+/HER2- MBC patients are more likely to respond to PB+LE therapy than LE alone. Acknowledging the limitations of real-world data and absence of scheduled tumor assessments in routine practice, this finding supports the use of palbociclib in combination with endocrine therapy as standard of care for HR+/HER2- MBC.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

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177P Real world treatment patterns and clinical outcomes associated with palbociclib combination therapy in Germany: Results from the IRIS study

G. Taylor-Stokes[1], L. Zhan[2], K.L. Mycock[1], G. Milligan[1], A. Ghale[1], D. Mitra[2]

[1]Adelphi Real World, Adelphi Group, Bollington, UK; [2]Patient and Health Impact, Pfizer Inc, New York, NY, USA

Background: Palbociclib was the first CDK 4/6 inhibitor approved in Germany for HR+/HER2- advanced/metastatic breast cancer (aBC/mBC) in combination with an aromatase inhibitor (P+AI) or fulvestrant (P+F). Here we report treatment patterns and clinical outcome data from Germany, as part of the multi-country Ibrance® Real World Insights (IRIS) study.

Methods: A retrospective chart review of women with HR+/HER2- aBC/mBC was conducted in Germany between July — October 2019. Patient characteristics, treatment patterns and outcomes data were abstracted for those receiving palbociclib combination therapies (approved November 2016). Progression free rates (PFR) and survival rates (SR) up to 24 months were estimated via Kaplan-Meier analysis.

Results: A total of 35 physicians completed 251 electronic case record forms (eCRFs). Overall, 152 patients received P+AI and 99 patients received P+F. Mean (SD) age at palbociclib initiation was 54.9 (9.0) years for P+AI and 56.3 (7.9) years for P+F. 50-60% of patients had ECOG performance status at initiation of 0 (57.2% P+AI; 46.5% P+F) or 1 (22.4% P+AI; 28.3% P+F). 5.2% P+AI and 4.0% P+F patients had an ECOG score ≥2; 15.1% P+AI and 21.2% P+F had an ECOG "unknown/not assessed". Of those with metastases (P+AI n=123, P+F n=77), 51.2% P+AI and 58.4% P+F had visceral disease; 26.0% P+AI and 24.7% P+F had bone only metastases. Most patients (73.7% P+AI and 83.8% P+F) were ongoing treatment at the time of data collection. Median follow-up (FU) time since palbociclib initiation was 8.2 months P+AI and 5.3 months P+F. Almost all patients initiated at 125 mg/day (98.7% P+AI and 96.0% P+F). Of these, dose reductions occurred in 14.0% P+AI patients and 11.6% P+F patients. PFR and SR for P+AI at 18 months was 84.9% and 92.2% respectively. PFR and SR for P+F at 12 months was 72.3% and 85.8% respectively.

Conclusions: Rates of dose reduction were low in this group of patients in this real-world study. Palbociclib combination therapy demonstrates effectiveness in terms of progression free and survival rates however follow-up is limited at this time.

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178P Risks of distant metastasis of different breast cancer subtypes after surgery: A cohort study in indigenous Indonesian population

H.L. Sakti[1], W.S. Avanti[2], L. Choridah[2], E.K.D. Dwianingsih[3], W.A. Harahap[4], T. Aryandono[1], S.L. Anwar[1]

[1]Surgery, Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [2]Radiology, Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [3]Anatomical Pathology, Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [4]Surgery, Dr M Jamil Hospital/Faculty of Medicine Universitas Andalas, Padang, Indonesia

Background: More than one third of breast cancer patients including those that are diagnosed in early stages will develop distant metastasis. Patterns of distant metastasis and the associated risks according to the clinicopathological determinants and molecular subtypes are not completely revealed particularly in population of patients with delayed diagnosis in limited resource setting.

Methods: Breast cancer patients (n=1304) admitted to our institute (2014-2017) were evaluated to identify the metastatic patterns and the associated risks. Metastatic breast cancers at diagnosis were found in 249 patients (19%) and 1055 patients were then grouped into non-metastatic and metastatic group after a median follow up of 3.8 years.

Results: Infiltration of tumor to the skin and chest wall prevailed as the most powerful predictor for distant metastasis (OR 1.839, 95% CI: 1.308-2.585, $p < 0.001$) particularly in Luminal A-like subtype (OR 2.572, 95% CI: 1.547-4.278, $p < 0.001$). Nodal involvement was also significantly associated with risk of distant metastasis (OR 1.839, 95% CI: 1.308-2.585, $p < 0.001$) and the risk was higher in Luminal A-like subtype (OR 2.572, 95% CI: 1.547-4.278, $p < 0.001$). Luminal B-like was associated with higher risk of pulmonal metastasis (OR 2.162, 95% CI: 1.031-4.539, $p = 0.042$). Luminal A-like had significant higher risk of bone metastasis (OR 1.626, 95% CI: 1.121-2.358, $p = 0.01$. Classification into Luminal and Non-Luminal subtypes revealed significant higher risks of bone metastasis in Luminal subtypes (OR 1.769, 95% CI: 1.192-2.625, $p = 0.005$) and pulmonal metastasis in non-Luminal subtypes (OR 1.445, 95% CI: 1.003-2.083, $p = 0.048$). Patients with Her-2 expression had significant higher risk for brain and lung metastasis (OR, CI, respectively). In addition to guide the treatment plan, comprehensive analysis of clinicopathological variables including the molecular subtypes could assist in the determination of distant metastasis risks of breast cancer patients.

Conclusions: Our study concedes new perspectives in the prediction of breast cancer distant metastasis to plan intensive surveillance or escalation treatment particularly in a setting where patients are predominantly diagnosed in late stages.

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179TiP EMERALD: A randomized, open-label, phase III trial to evaluate the efficacy and safety of elacestrant (RAD1901), a novel oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine therapy for ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy

A. Bardia[1], J. Lu[2], V. Kaklamani[3], J. Jung[4], A.T. Anderson-Villaluz[5], M.G. Conlan[5], F-C. Bidard[6], J. Cortés[7], P.G. Aftimos[8]

[1]Medical Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [3]Hematology/Oncology, UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX, USA; [4]Biostatistics, Radius Health, Inc., Waltham, MA, USA; [5]Clinical Development, Radius Health, Inc., Waltham, MA, USA; [6]Medical Oncology, Institut Curie, Paris, France; [7]Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [8]Clinical Trials Conduct Unit, Institute Jules Bordet, Brussels, Belgium

Background: Estrogen receptor-positive (ER+) breast cancer (BC) comprises ~70% of all BC and ER+ advanced BC (ABC) remains a clinical challenge. The addition of CDK4/6 inhibitor (i) to endocrine therapy (ET) has improved PFS; however, novel treatments are needed after progression. Putative mechanisms of endocrine resistance, such as ESR1 mutations (mESR1), also indicate the need for additional therapies. Elacestrant, an oral SERD, demonstrated anti-tumor activity in preclinical models of ER+ BC, including models resistant to CDK4/6i and models with mESR1. Data from a phase 1 trial (NCT02338349) of elacestrant given at 400 mg QD in heavily pretreated pts with ABC, demonstrated an overall response rate (ORR) of 19% and a PFS of 4.5 mo; ORR in pts with mESR1 was 33%. Responses were observed following CDK4/6i and prior fulvestrant (Kaklamani, SABCS, 2019).

Trial design: This is a multicenter, international, randomized, open-label, active-controlled phase 3 trial for post-menopausal women or men with ABC. Pts must have received 1-2 prior lines of ET, ≤1 line of chemotherapy for ABC, and have documented progression on a CDK4/6i. Pts with measurable disease (RECIST v1.1) or bone-only disease are eligible. Pts are randomized 1:1 to elacestrant (400 mg PO QD) or investigator's choice of fulvestrant or an aromatase inhibitor. Stratification factors include ESR1 mutation status, prior fulvestrant treatment and presence of visceral disease. Co-primary endpoints are PFS by blinded independent review committee in pts with mESR1 and in all pts. Secondary endpoints include: OS; PFS by investigator review; ORR, duration of response, and clinical benefit rate; safety; pharmacokinetics; and quality of life. Approximately 466 pts will be enrolled to detect 340 PFS events in all pts (power ≥90%, HR = 0.667) and 160 PFS events in the mESR1 subset (power ≥80%, HR = 0.610), overall α level at 2-sided 5% using the Hochberg procedure. The EMERALD study is open for enrollment in 15 countries in North America, Europe, and Pacific Asia.

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Legal entity responsible for the study: Radius Health, Inc.

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180TiP Palbociclib, trastuzumab and endocrine therapy (ET) versus treatment of physician's choice (TPC) in metastatic HER2-positive and hormone receptor-positive (HER2+/HR+) breast cancer (BC) with PAM50 luminal intrinsic subtype (SOLTI-1303 PATRICIA II): A randomized phase II trial

E.M. Ciruelos[1], P. Villagrasa[2], M. Oliveira[3], S. Pernas Simon[4], J. Cortés[5], S. Vazquez[6], N. Martínez[7], A. Perelló[8], B. Bermejo De Las Heras[9], E. Martínez[10], I. Garau Llinas[11], M. Mele Olive[12], A. Montaño[13], E. Vega[14], B. Cantos[15], M.J. Echarri[16], T. Pascual[17], P. Celiz[18], X. González-Farré[19], A. Prat[17]

[1]Department Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; [2]Breast Cancer Research Group, SOLTI, Barcelona, Spain; [3]Department Medical Oncology, Vall d' Hebron University Hospital; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Medical Oncology Breast Unit, ICO - Institut Català d'Oncologia l'Hospitalet (Hospital Duran i Reynals), Hospitalet de Llobregat, Spain; [5]Department Medical Oncology, IOB Institute of Oncology, Quiron Group, Barcelona, Spain; [6]Medical Oncology Breast Unit, ICO - Institut Català d'Oncologia l'Hospitalet (Hospital Duran i Reynals), L'Hospitalet de Llobregat, Spain; [7]Department Medical Oncology, Ramon y Cajal Hospital, Madrid, Spain; [8]Department Medical Oncology, Hospital Universitari Son Espases, Palma de Mallorca, Spain; [9]Department Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain; [10]Department Medical Oncology, Consorcio Hospitalario Provincial de Castellón, Castelló De La Plana, Spain; [11]Department Medical Oncology, Hospital Son Llatzer, Palma de Mallorca, Spain; [12]Department Medical Oncology, Hospital Universitari Sant Joan de Reus, Reus, Spain; [13]Department Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain; [14]Department Medical Oncology, Centro Integral Oncológico Clara Campal, Madrid, Spain; [15]Dev. Medical Oncology, Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Spain; [16]Department Medical Oncology, Hospital Severo Ochoa, Leganes, Spain; [17]Medical Oncology Department, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [18]Department Scientific, SOLTI Breast Cancer Research Group, Barcelona, Spain; [19]Department Medical Oncology, Hospital General de Catalunya, San Cugat Del Valles, Spain

Background: Efficacy interim results from PATRICIA phase II trial in HER2+/HR+ advanced BC showed that PAM50 luminal disease was associated with larger and clinically meaningful progression-free survival (PFS) following palbociclib, trastuzumab and endocrine therapy compared to PAM50 non-luminal disease (Ciruelos E. et al, SABCS 2018). Based on these preliminary results, PATRICIA II was designed to select patients based on PAM50 and to include a randomization to a control arm.

Trial design: PATRICIA II is a randomized open-label, adaptive design, phase II study. Patients must have centrally confirmed HR+/HER2+ and PAM50 Luminal A or B intrinsic subtype tumors and have received at least 1 (and no more than 4) prior lines of anti-HER2 regimens for locally advanced or metastatic BC. Patients are randomized 1:1 to trastuzumab plus palbociclib 125 mg/day orally 3 weeks on/1 week off and endocrine therapy (cohort C1) or treatment of physician's choice (TPC): T-DM1 or chemotherapy (gemcitabine, vinorelbine, capecitabine, eribulin, paclitaxel or docetaxel) plus trastuzumab (cohort C2). ET options are either an aromatase inhibitor, fulvestrant or tamoxifen +/- ovarian suppression. Stratification factors include the number of previous regimens for advanced BC (1-2 vs 3-4) and the presence of visceral disease (yes vs no). Primary objective is to compare the PFS between two arms. The study has an 80% power with two-sided alpha=0.05 to detect a HR of 0.62 in favor of the palbociclib arm. An interim analysis (IA) adjusted for multiplicity from O'Brien-Fleming method and an estimation of the conditional power (CP) will be performed at 70% of the events. Secondary objectives include response rate, overall survival, safety, and Quality of Life. Tumor tissue and blood samples will be collected for biomarker analyses. A total of 516 patients will be screened and 232 patients will be recruited. As of January 16th, 2020, 7 patients were randomized in the trial. The study is sponsored by SOLTI and financially supported by Pfizer.

Clinical trial identification: NCT02448420.

Legal entity responsible for the study: SOLTI Breast Cancer Research Group.

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181TiP Xentuzumab (Xe) in combination with everolimus (Ev) and exemestane (Ex) in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC) and non-visceral involvement (XENERA™-1)

P. Schmid[1], H.S. Rugo[2], J. Cortés[3], P. Blum[4], K. Crossley[5], D. Massey[6], H.A. Burris, III[7]

[1]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [2]Department of Medicine (Hematology/Oncology), University of California at San Francisco, San Francisco, CA, USA; [3]IOB Institute of Oncology, Quironsalud Group, Madrid & Barcelona, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Therapeutic Area Oncology, Boehringer Ingelheim International GmbH, Biberach, Germany; [5]Clinical Research, Boehringer Ingelheim Ltd, Bracknell, UK; [6]Statistics, Boehringer Ingelheim International GmbH, Biberach, Germany; [7]Clinical Operations, Sarah Cannon Research Institute, Nashville, TN, USA

Background: Ev, an mTOR inhibitor, plus Ex is a standard therapy for post-menopausal women with HR+/HER2- mBC. The activity of Ev in cancer cells is restricted by compensatory mechanisms, including reactivation of insulin-like growth factor (IGF)/mTOR signalling. Combining Ev with the IGF-1/-2 ligand-neutralising antibody Xe limits this feedback, thereby intensifying inhibition of tumour growth. These effects are more pronounced in patients with non-visceral metastases.

Trial design: This phase II, double-blind, placebo-controlled, randomised study will assess the efficacy and safety of Xe in combination with Ev and Ex, in up to 80 women with HR+/HER2- locally advanced/mBC and non-visceral disease. Eligibility criteria include being pre-menopausal and on ovarian suppression therapy, or post-menopausal; and having progressed on or within 12 months of completing adjuvant endocrine therapy, or on or within 1 month after endocrine therapy for advanced/mBC. Patients must have an Eastern Cooperative Oncology Group performance status $\leq$1, adequate organ function, and presence of only non-visceral disease (absence of brain, liver, lung, peritoneal or pleural metastases). Exclusion criteria include: $>$1 prior line of chemotherapy for mBC; $>$1 prior line with a CDK4/6 inhibitor; and prior therapy targeting IGF, AKT or mTOR. Patients are randomised (1:1) to Xe (1000 mg/week, iv) or placebo (weekly, iv), in combination with Ev (10 mg/day) and Ex (25 mg/day). Treatment will continue until disease progression, unacceptable toxicity or other reasons. The primary endpoint is progression-free survival. Secondary endpoints include overall survival, disease control, duration of disease control, objective response, and time to progression of pain/intensification of pain palliation. Safety, pharmacokinetics and exploratory biomarkers will also be evaluated. The first patient was enrolled in January 2019. Participating sites are in Australia, Belgium, Canada, France, Germany, Greece, Ireland, Italy, Portugal, Spain, the United Kingdom and the United States.

Clinical trial identification: 2017-003131-11/NCT03659136.

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182TiP Effectiveness of niraparib plus aromatase inhibitors (AI) for germinal BRCA1/2-mutated (gBRCAm) or homologous recombination deficient (HRD), hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer (ABC). The LUZERN Strategy

S. Blanch[1], J.M. Pérez-García[2], J. Balmaña[3], A. Prat[4], J.E. Alés-Martínez[5], J. de la Haba[6], E. Alba[7], P. Palacios-Ozores[8], M. Ramos[9], L. Lema[10], J.Á. García Sáenz[11], M. Sampayo-Cordero[12], A. Malfettone[12], J. Cortés[13], A. Llombart Cussac[14]

[1]Medical Oncology, Instituto Valenciano de Oncología, Valencia, Spain; [2]Medical Oncology, IOB, Institute of Oncology, QuironSalud Group, Madrid and Barcelona; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; [3]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [5]Medical Oncology, Hospital Nuestra Señora de Sonsoles, Ávila, Spain; [6]Medical Oncology, University Hospital Reina Sofia, Cordoba, Spain; [7]Medical Oncology, Hospital Virgen de la Victoria, Málaga, Spain; [8]Medical Oncology, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain; [9]Medical Oncology, Centro Oncológico de Galicia, A Coruña, Spain; [10]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [11]Medical Oncology, Hospital Clínico San Carlos, Madrid, Spain; [12]Scientific Department, Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; [13]Medical Oncology, IOB, Institute of Oncology, QuironSalud Group, Madrid and Barcelona; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Medical Oncology, Hospital Universitario Arnau de Vilanova, Universidad Catolica, Valencia, Spain; Medica Scientia Innovation Research (MedSIR), Ridgewood, New Jersey and Barcelona, Spain

Background: Niraparib is a potent and orally active poly(ADP-ribose)polymerase (PARP)1/2 inhibitor that has demonstrated clinical activity in patients (pts) with advanced gBRCAm ovarian and breast cancers. About 5% of HR+/HER2- breast cancer pts result gBRCAm and 10-20% are HRD. This study will evaluate the efficacy and safety of niraparib plus AI in gBRCAm or HRD, HR+/HER2- pretreated ABC pts.

Trial design: This is a multicenter, open-label, single-arm, two-cohort, phase II trial. The cohort A and the exploratory cohort B will include gBRCAm and HRD, HR+/HER2- ABC pts, respectively. Pts will receive niraparib (200 or 300 mg depending on baseline body weight and platelet counts, PO, QD, during 28-day cycle) plus the same AI administered during the last endocrine therapy (ET) until progressive disease (PD) or unacceptable toxicity. Main selection criteria are: (1) Men or pre- and post-menopausal women with HR+/HER2- ABC; (2) $\leq$1 prior regimen of chemotherapy for ABC; (3) At least 1 and up to 2 prior lines of ET (AIs or fulvestrant) for ABC (except for pts with PD in the [neo]adjuvant setting); (4) Confirmed PD during the last AI-containing regimen with secondary endocrine resistance criteria; (5) Evaluable or measurable disease. Primary endpoint is clinical benefit rate (CBR) defined as pts who achieve overall response or stable disease $\geq$24 weeks as per RECIST 1.1. Secondary endpoints include progression-free survival, overall response rate, time to response, duration of response, overall survival, and maximum tumor reduction. The trial uses a Simon's two-stage minimax design. If $\geq$1 out of the first 6 pts of the cohort A achieve clinical benefit (CB), 8 additional pts will be recruited during stage II. At least 3 out of 12 evaluable pts with CB will be adequate to justify this strategy in further studies. Considering a drop-out rate of 10%, 14 pts will be needed to attain 80% power at nominal level of one-sided alpha of 0.025. The exploratory cohort B will be initiated if the criterion of the cohort A for continuing to the stage II is met.

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Legal entity responsible for the study: MedSIR.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SUPPORTIVE CARE AND SURVIVORSHIP

183O Use of physical activity (PA) and supportive care (SC) among patients (pts) with early breast cancer (BC) reporting cancer-related fatigue (CRF)

A. Di Meglio[1], C. Charles[2], E. Martin[1], J. Havas[1], A.S. Gbenou[1], A-L. Martin[3], S. Everhard[3], E. Laas[4], O. Tredan[5], L. Vanlemmens[6], C. Jouannaud[7], C. Levy[8], O. Rigal[9], M. Fournier[10], P. Soulie[11], A. Dumas[12], G. Menvielle[13], F. André[1], S. Dauchy[2], I. Vaz-Luis[1]

[1]INSERM UMR 981, Gustave Roussy, Villejuif, France; [2]DISSPO, Gustave Roussy, Villejuif, France; [3]R&D, Unicancer, Paris, France; [4]Medical Oncology, Institut Curie, Paris, France; [5]Medical Oncology, Centre Léon Berard, Lyon, France; [6]Medical Oncology, Centre Oscar Lambret, Lille, France; [7]Medical Oncology, Institut Jean Godinot, Reims, France; [8]Medical Oncology, Centre François Baclesse, Caen, France; [9]Medical Oncology, Centre Henri Becquerel, Rouen, France; [10]Medical Oncology, Institut Bergonié, Bordeaux, France; [11]Medical Oncology, Institut de Cancérologie de L'ouest -Paul Papin, Angers, France; [12]Universite de Paris, ECEVE UMR 1123, INSERM, Paris, France; [13]Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France

Background: CRF is highly prevalent in early BC. PA and psychosocial interventions were proven to be effective in several meta-analyses and are recommended management strategies for CRF. Some randomized trials support the use of acupuncture, while there are no data showing benefits of homeopathy for CRF. We aimed to assess use of PA and SC among pts with early BC.

Methods: Pts with stage I-III BC were prospectively included from the CANTO cohort (NCT01993498). Baseline CRF was evaluated shortly after treatment using EORTC-C30 for global CRF and EORTC-FA12 for its physical, emotional and cognitive domains. A score of 40 or higher defined CRF as severe (Abrahams HJ, Ann Oncol 2016). Data on adherence to PA recommendations (10 MET-hours/week or more) and SC consultations with a psychologist, acupuncturist or homeopath were collected in CANTO and therefore served as outcomes. Multivariable logistic regression examined associations between baseline CRF status (severe v not) and use of PA or SC consultations over the 12 months after baseline CRF assessment. Covariates included socio-demographics and psychological distress.

Results: Among 9691 pts included in CANTO, 6282 had available data on PA and 7598 on SC consultations. At baseline, 36% pts reported severe global CRF, and 36%, 23% and 14% pts reported severe physical, emotional and cognitive CRF, respectively. Overall, 64% pts were adherent to PA recommendations and only 10% pts saw a psychologist, whereas 8% saw an acupuncturist and 7% a homeopath. Pts reporting severe global CRF (v not severe) were less likely to adhere to PA recommendations (60% v 67%; adjusted odds ratio [aOR] 0.82, 95% CI 0.72-0.94), but more likely to see a psychologist (14% v 7%; aOR 1.31, 1.07-1.59), acupuncturist (10% v 6%; aOR 1.51, 1.22-1.86) or homeopath (10% v 6%; aOR 1.55, 1.25-1.92). There were differences in use of PA and SC consultations by CRF domain: pts reporting severe physical CRF showed lower adherence to PA (59% v 67%; aOR 0.73, 0.63-0.85), whereas pts with severe emotional CRF were more prone to psychology consultations (17% v 8%; aOR 1.41, 1.10-1.82).

Conclusions: This large study calls for the need to optimize and personalize the uptake of recommendations to manage CRF among pts with early BC.

Clinical trial identification: NCT01993498.

Legal entity responsible for the study: Unicancer.

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184O The risk of late breast cancer recurrence in Denmark during 17 years of follow-up

R.N. Pedersen[1], B. Öztürk[1], L. Mellemkjær[2], S. Friis[2], B. Ejlertsen[3], T. Lash[4], M. Nørgaard[1], D. Cronin-Fenton[1]

[1]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [2]Danish Cancer Society Research Center, Copenhagen, Denmark; [3]Clinical Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [4]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

Background: Breast cancer (BC) may recur many years after primary diagnosis. We investigated the incidence of late breast cancer recurrence (BCR) (>= 10 years after primary surgery) and identified potential associations between clinico-pathological factors at baseline and late BCR.

Methods: Using the Danish Breast Cancer Group's (DBCG) database we identified all women with incident stage I-III operable BC diagnosed during 1987-2002, who were alive and without a recurrence or new primary cancer 10 years after diagnosis. We derived an algorithm to identify late BCR using Danish population-based registries. Follow-up began 10 years after primary surgery date and continued until late BCR, death, emigration, second cancer or 31/12/2013. Crude incidence rates (IRs) per 1,000 person-years (PY) and cumulative incidence proportions (CIPs) for late BCR were calculated by patient- and tumor characteristics at baseline. Cox regression models were used to calculate hazard ratios (HRs), accounting for competing risks. The HRs were adjusted for tumor- and patient characteristics.

Results: 18,117 women of 31,528 (57%) reached year 10 without BC recurrence, a contralateral breast cancer or other primary cancer, and were followed for a total of 106,602 PY with a median follow-up of 4.9 years (IQR; 2.4-8.7). Of these 10-year survivors, 1,763 developed late BCR corresponding to an IR of 16.5 (95% CI, 15.8-17.3) per 1,000 PY and a CIP of 15% maximum 27 years after primary diagnosis. The CIP was higher among patients with estrogen receptor $(ER)^+$ tumors, stage III disease and high nodal status. We found an adjusted HR of 3.0 (95% CI, 2.47-3.55) for patients with 4 or more positive lymph nodes versus patients with no lymph node involvement, an adjusted HR of 1.85 (95% CI, 1.59-2.15) for patients with stage III disease versus stage I disease and an adjusted HR of 0.57 (95% CI, 0.45-0.72) for patients with an ER^- tumor versus patients with an ER^+ tumor.

Conclusions: Our findings suggest that women with breast cancer can remain disease-free for at least ten years, but recurrences continue to occur from 10 to 27 years after primary diagnosis. Baseline tumor characteristics such as lymph node status, stage, and ER receptor status seems to be associated with late breast cancer recurrence.

Legal entity responsible for the study: Aarhus University.

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186P Using a new controlled thermotherapy (Hilotherapy®) during chemotherapy prevents chemotherapy induced polyneuropathy (CIPN)

T. Schaper, B. Gross, L. Franzmann, M. Darsow

Luisenkrankenhaus, Luisenkrankenhaus GmbH &Co KG, Düsseldorf, Germany

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of many commonly used chemotherapeutic agents, especially taxane-based regimen (Paclitaxel, nab-Paclitaxel, Docetaxel). CIPN reduces patients health-related quality of life for years and often results in dose delay, dose reduction or treatment discontinuation. The prophylactic use of controlled thermotherapy (Hilotherapy®) prevents CIPN.

Methods: 168 breast cancer patients used a new method of physical thermotherapy, a device equiped with hand and foot cuffs to allow a constant cooling. Cooling medium is demineralized water. Continous cooling of hands and feet was performed 30 minutes before to 60 minutes after completing drug infusion with a temperature of 10-12°C. CIPN symptoms were evaluated after each cytotoxic cycle using common terminology criteria for adverse events (CTCAE). Sustainability of the impact was assessed by long-term datas (every 3 months). 130 patients used the prophylactic Hilotherapy® for each cytotoxic treatment (Group 1: primary Prophylactic Hilotherapy® - pPHT). 38 patients used reactive secondary Hilotherapy (Group 2: rSHT). Hands and feet were cooled after onset of symptoms of CIPN (grade 1-3).

Results: Group pPHT: Out of 130 patients who used pPHT, 121 patients (93%) developed none or mild symptoms of CIPN (grade 0-1). 8 patients (6,1%) reported grade 2, 1 patient grade 3 (0,8%) toxicity. The symptoms of CIPN were reversible. 4 months after chemotherapy, 98% of the patients had no CIPN > grade 1. 2 patients (2%) suffered intermittent toxicity grade 2. Follow Up datas confirmed the results. Group rSHT: Without using pPHT 50% of the patients developed grade 3 and 2 CIPN. Using rSHT progression was stopped and reduction of toxicities was reached: at last chemotherapy treatment grade 2 & 3 toxicities were reduced from 50% to 25%.

Conclusions: Prophylactic Hilotherapy prevented symptoms > grade 1 in 93% of patients. 4 months after chemotherapy treatment, 98% of the patients were without limiting symptoms > grade 1. No dose modifications or treatment interruptions had been necessary. Without pPHT, 50 % of the patients developed CIPN grade 2-3. rSHT stopped progression of CIPN and reduced first symptoms of CIPN.

Legal entity responsible for the study: Trudi Schaper.

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187P Patient-reported outcomes near end-of-life in patients with breast cancer

A. Batra[1], C. Cuthbert[2], R. Rigo[1], A. Harper[3], D. Boyne[4], L. Yang[3], W. Cheung[1]

[1]Medical Oncology, Tom Baker Cancer Center, Calgary, AB, Canada; [2]Nursing, University of Calgary, Calgary, AB, Canada; [3]Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, AB, Canada; [4]Community Health Sciences, Alberta Health Services, Calgary, AB, Canada

Background: There are limited data on symptom burden in patients dying with breast cancer. This study aimed to assess the burden of symptoms near end-of-life in a real-world cohort of patients with breast cancer using patient-reported outcomes (PROs).

Methods: Patients with breast cancer who completed the revised version of Edmonton Symptom Assessment System (ESASr) questionnaire within 6 months of death in a large Canadian province from 2016 to 2019 were eligible for the study. The symptoms within physical and psychological categories were categorized as mild (0-3), moderate (4-6), and severe (7-10). We further compared the severity of symptoms with time-to-death (TTD), categorized as 0-90 days and 91-180 days from completing the ESASr questionnaire.

Results: We identified 188 patients with breast cancer for the current analysis, with median age of 63 (interquartile range: 32-89) years. The physical, and psychological symptoms were severe in 18%, and 14%, respectively. While severe tiredness and drowsiness were the most common physical symptoms, severe anxiety was reported more frequently than depression. There was no association of age of the patients with severity of symptoms. Although psychological symptoms were not related with TTD, total and physical symptoms scores were more likely to be severe in patients within 90 days of death (21% vs 8%, P=0.007; 26% vs 8%, P=0.003, respectively), as compared to those who were 91-180 days from death. This was contributed predominantly by tiredness (P=0.02) and shortness of breath (P=0.001). The proportion of patients who rated overall wellbeing as severe was twice (41% vs 20%, P=0.01) as common during the final 90 days of life, when compared with those who were 91-180 days from death.

Table 187P

Symptom	TTD: 0-90 days (n=136)	TTD: 91-180 days (n=52)	P-value
Physical	35 (26%)	4 (8%)	0.003
Pain	39 (29%)	13 (25%)	0.19
Tiredness	73 (54%)	16 (31%)	0.02
Drowsiness	52 (39%)	12 (23%)	0.08
Nausea	23 (17%)	4 (8%)	0.2
Lack of appetite	48 (35%)	10 (19%)	0.08
Shortness of breath	38 (28%)	3 (6%)	0.001
Psychological	21 (15%)	9 (17%)	0.84
Depression	20 (15%)	9 (17%)	0.88
Anxiety	26 (19%)	8 (16%)	0.84
Others wellbeing	51 (41%)	10 (20%)	0.01
Total score	28 (21%)	4 (8%)	0.007

Conclusions: There is significant deterioration of unique symptoms when patients with breast cancer approach end-of-life, as reported in PROs, using ESASr. Symptom targeted palliative measures are likely to alleviate burden of symptoms near end-of-life and thereby improving the 'quality of death'.

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188P Impact of HIV infection (HIV+) on baseline characteristics and survival of breast cancer (BC) patients (pts): A systematic review and meta-analysis

M.D.R.A. Brandão[1], M. Bruzzone[2], M.A. Franzoi[1], C. de Angelis[1], D. Eiger[1], R. Caparica[1], N. Dauby[3], M. Ceppi[2], M. Piccart[4], C. Carrilho[5], N. Lunet[6], L. Buisseret[4], E. de Azambuja[1], M. Lambertini[2]

[1]Academic Trials Promoting Team, Institut Jules Bordet, Brussels, Belgium; [2]IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy; [3]Infectious Diseases Department, Centre Hospitalier Universitaire Saint-Pierre, Bruxelles, Belgium; [4]Medical Oncology, Institut Jules Bordet, Brussels, Belgium; [5]Pathology Department, Faculty of Medicine University Eduardo Mondlane, Maputo, Mozambique; [6]EPI Unit, Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal

Background: The number of HIV+ women diagnosed with BC is increasing. Yet, data are conflicting regarding their stage at diagnosis, distribution of BC subtypes and prognosis. We aimed to assess differences in baseline characteristics and overall survival (OS) between HIV+ vs HIV-uninfected (HIV-) BC pts.

Methods: Systematic review using MEDLINE, Scielo and conference abstracts (hand search of studies presented in major meetings) up to 1 Jan 2020 with no language restrictions was performed. Cross-sectional or cohort studies comparing baseline characteristics (mean age, stage or BC subtypes) or OS of HIV+ vs HIV- BC pts were included. Main endpoints were age, late stage at diagnosis, proportion of subtypes and OS. Subgroup analyses were performed according to world region. Other endpoints were detailed stage and estrogen receptor (ER) status. Summary estimates (pooled mean age ratios [MR], odds ratios [OR] and hazard ratios [HR]) were calculated using random effects models.

Results: 20 publications (5 from North America, 15 from Sub-Saharan Africa [SSA]) were included, with 3,174 HIV+ and 2,394,598 HIV- pts. Mean age was 18% lower among HIV+ pts vs HIV- pts (MR 0.82, 95% CI 0.76-0.89) and HIV+ pts had a 53% increased risk of presenting with late stage BC (OR 1.53, 95% CI 1.37-1.71). HIV+ pts had smaller odds of having ER+/HER2- BC, but there were no differences regarding other subtypes (Table). HIV+ pts had a 90% increased risk of dying compared to HIV- pts (adjusted HR 1.90, 95% CI 1.21-2.99), with similar results in North America and SSA.

Table 188P

		HIV+ pts	HIV- pts	Pooled estimate (95% CI)	P
Age	All	144	316	MR 0.82 (0.76-0.89)	<.001
Late stage (III/IV)	All	3014	2331751	OR 1.53 (1.37-1.71)	<.001
	SSA	1374	6107	OR 1.38 (1.22-1.57)	<.001
	North America	1640	2325643	OR 1.76 (1.58-1.95)	<.001
ER+/HER2-	All	498	1925	OR 0.81 (0.66-0.99)	.043
HER2+	All	519	1969	OR 1.10 (0.80-1.52)	.553
TNBC	All	610	3147	OR 1.14 (0.90-1.43)	.269
Luminal A	All	326	1957	OR 0.65 (0.42-1.02)	.059
Luminal B	All	326	1957	OR 1.03 (0.79-1.35)	.800
HER2-enriched	All	326	1957	OR 1.08 (0.49-2.38)	.842
OS (adjusted)	All	1741	1561217	HR 1.90 (1.21-2.99)	.005
	SSA	291	890	HR 1.58 (1.25-1.98)	<.001
	North America	1426	1560131	HR 2.45 (1.11-5.41)	.026
OS (unadjusted)	All	291	890	HR 1.43 (1.06-1.92)	.019

Conclusions: HIV+ pts are diagnosed with BC at a younger age and at a later stage. Even after adjusting for prognostic factors, HIV+ pts have a worse OS as compared to HIV- pts, both in SSA and North America. Further studies are needed to decipher the reasons behind these disparities that can be related to HIV infection, distinct BC biology and anti-cancer immune response and/or to a lower access to timely diagnosis and effective treatment.

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Advisory/Consultancy, Research grant/Funding (institution), Travel/Accommodation/Expenses: Novartis; Advisory/Consultancy: SeaGen; Research grant/Funding (institution): AstraZeneca; Research grant/Funding (institution): Servier. M. Lambertini: Advisory/Consultancy: Roche Diagnostics; Speaker Bureau/Expert testimony: Roche; Speaker Bureau/Expert testimony: Takeda; Speaker Bureau/Expert testimony: Theramex. All other authors have declared no conflicts of interest.

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189P Recommendation for "a start to move" program: A 8-week program of incremental physical activity in sedentary breast cancer survivors

K. Mazzocco[1], M. Masiero[1], M. Mazza[2], D. Radice[3], P. Maisonneuve[3], G. Pravettoni[1]

[1]Applied Research Division for Cognitive and Psychological Science, IEO - Istituto Europeo di Oncologia, Milan, Italy; [2]Senologia Medica, Istituto Europeo di Oncologia, Milan, Italy; [3]Division of Epidemiology and Biostatistics, IEO - Istituto Europeo di Oncologia, Milan, Italy

Background: Routine physical activity is proven to reduce side effects of oncological treatments, prevent cancer recurrence, improve immunological status and psychological adjustment in breast cancer survivors (BCS). Nevertheless, adherence to physical activity in BCS remains pointedly low.

Methods: The present RCT aims to measure whether a short (8 weeks) and easy to implement incremental physical activity program is sufficient to achieve significant physical and psychological positive results. Eighty-five sedentary BCS were enrolled at the European Institute of Oncology and randomized in two groups: control group (CG, 41 BCS aged M=51.4 SD=7.6) and intervention group (IG, 44 BCS aged M=48.4 SD=8.9). BCS in IG received a program of physical activity incrementing from 120 minutes walking (9,5-12,5 km) in week 1 to 155 minutes of running-walking alternation (18,3 km) in week 8. In order to be recruited, treatment (surgery, chemotherapy, radiotherapy, trastuzumab) had to be completed since at least 6 months and up to 3 years. The daily assessment was performed using a wearable pedometer device. Questionnaires to assess psychological wellbeing and quality of Life (QoL) were administered at baseline (T0) and after 8 weeks (T1). Qualitative data were collected to investigate barriers and facilitators of physical activity adherence.

Results: Physical symptoms and physical challenges, especially associated with side effects of treatments were the most commonly mentioned barriers. The strongest facilitators are: feedbacks by the oncologist, positive experience with exercise on physical and psychological dimensions, and increased self-esteem and self-efficacy. BCS in IG reported a significant improvement at T1 in health-related QoL (difference between groups M=-5.25 $p<0.01$), in general QoL (M=-5.25 $p<0.01$), in functional outcomes (M=-5.06 $p<0.04$) and in physical wellbeing (M=-2.42 $p<0.02$).

Conclusions: Comparing with previous studies, these results suggest that a short, easy to implement program might be the perfect boost to increase self-efficacy and motivation to adopt a long-term healthy life style. A short and easy program should be considered by Breast Units as Start To Move Recommendation for BCS.

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190P Phyllodes tumour of the breast: 10 years of experience in a Mexican oncology reference center

M.I. Contreras Salcido, J.L. González Vela, J.G. Lara Campos, E. Llerena Hernandez, D. Hernández Barajas, O. Vidal Gutiérrez, A. Adriana González Gutiérrez, R.J. Martínez Granados, M.A. Ponce Camacho, M. Molina Ayala

Medical Oncology, Hospital Universitario Dr José Eleuterio Gonzalez, Monterrey, Mexico

Background: Phyllodes tumor (PT) of the breast is a rare fibroepithelial neoplasm representing 1% of all breast tumors. The objective of this report is to describe the characteristics of patients in the Hispanic population with PT and describe the clinical and pathological variables of our population.

Methods: We performed a retrospective analysis of patients with PT treated at an Oncology referral center in North-East Mexico from the years 2013 to 2019.

Results: We registered 51 cases; 28 were excluded due to a lack of follow up. We included 23 cases in the final analysis. The mean age of diagnosis was 51 years, the diagnosis was made by self-detection in all cases, with a median time of evolution of 17.5 months and a median tumor size 12.8 cm, approximately 26% had a history of mammary resection with benign pathology. 39.1% were treated with radical mastectomy, simple mastectomy in 39.1% and 21.7% breast conservative surgery. PT were classified as benign 17.3%, borderline 13% and malignant 69.5%. Patients with malignant PT showed a heterologous component in 21.7%, 60% with mixed histology, (chondrosarcoma, liposarcoma, undifferentiated sarcoma, neural cystosarcoma, chondroid and bone), 20% fibromyxosarcoma and 20% osteosarcoma. 13% of the entire population had metastatic lung disease at the beginning of diagnosis; We observed 8 recurrences, 2 in borderline and 6 in malignant subtype. The recurrence-free interval in borderline subtype was 51 months and the main site of the recurrence were local; The recurrence-free interval was 5 months in malignant subtype, and the types of recurrence in order of frequency were in multiple sites 4 cases (lung, nervous central system, bone and liver), 1 case local and 1 case lung metastases. The treatments were chemotherapy (66.6%), radiotherapy (16.6%) and concurrent radiotherapy and chemotherapy (16.6%). The overall survival in the subgroup that developed distance disease was 6.9 months.

Conclusions: To our knowledge, this is one of the first studies, analyzing the clinical-pathological characteristics of phyllodes tumors in the North-East of Mexico. We found more cases with malignant subtype, bigger tumors and more heterologous component than other Hispanic reports.

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192P Strategies and results of oncofertility counselling in young breast cancer patients

J. Kufel-Grabowska[1], M. Litwiniuk[2], S. Marszałek[3], M. Górecki[4], M. Malinowska[4], J. Doś[3], A. Marszalek[5], W. Suchorska[6], M. Lesiak[7], E. Straburzynska-Migaj[7], A. Nowak[7], A. Bartczak-Rutkowska[7], M. Dudek[7], P. Nowaczyk[8], P. Jedrzejczak[9]

[1]Chemotherapy Department, Wielkopolskie Centrum Onkologii, Poznan, Poland; [2]Chemotherapy Department, Wielkopolskie Centrum Onkologii-Greater Poland Cancer Centre i Uniwersytet Medyczny w Poznaniu, Poznan, Poland; [3]Department of Physiotherapy, Wielkopolskie Centrum Onkologii i Uniwersytet Medyczny w Poznaniu, Poznan, Poland; [4]Department of Physiotherapy, Wielkopolskie Centrum Onkologii, Poznan, Poland; [5]Department of Pathology, Wielkopolskie Centrum Onkologii-Greater Poland Cancer Centre, Poznan, Poland; [6]Department of Electroradiology, Wielkopolskie Centrum Onkologii-Greater Poland Cancer Centre, Poznan, Poland; [7]1st Department of Cardiology, University of Medical Sciences in Poznan, Poznan, Poland; [8]Department of Surgical Oncology, Wielkopolskie Centrum Onkologii, Poznan, Poland; [9]Division of Infertility and Reproductive Endocrinology, University of Medical Sciences in Poznan, Poznan, Poland

Background: Breast cancer (BC) is the most common female neoplasm in Poland and worldwide, yet up to 7% of all cases are diagnosed <40 years of age. Increased BC morbidity rate in this age group as well as hopes for late maternity need special attention. Chemotherapy constitutes an important element of complex therapy, but it may lead to fertility impairment. Therefore, it is vital that every woman of reproductive age should be informed about the consequences of oncological treatment and about (onco)fertility preservation techniques prior to therapy, which decrease the fear and improve psychological aspects of QoL.

Methods: The data concerning the number of children and further procreation needs in women (N=70), aged 18-40, diagnosed and treated for early breast cancer at Greater Poland Cancer Center in 2018-2019, were taken from patients' history by an oncologist before (neo-)adjuvant systemic therapy. According to the patients' wish, consultation with a specialist in reproductive medicine was provided. Additionally, each patient had genetic studies done.

Results: Out of 70 females, aged 18-40 (mean age 29), 14 (20%) were childless at the time of diagnosis. After being informed about the therapy, prognosis, side effects and oncofertility, 12 patients (17%) decided to have a consultation with a specialist in reproductive medicine; 5 of them (7%) already had children. In 2 women (3%), hormonal stimulation in combination with tamoxifen was used; then, oocytes were collected and cryopreserved. In 20 (29%), gonadotropin analogues were added to (neo-)adjuvant chemotherapy. In 17 patients (24%) pathogenic mutations in BRCA1/2 genes were found.

Conclusions: Oncofertility counselling in young BC patients should be one of the basic elements of complex patient care. High frequency of pathogenic mutations in BRCA1/2 genes in young females should be taken into consideration according to possible childbearing wishes after termination of therapy and before prophylactic oophorectomy.

Legal entity responsible for the study: The authors.

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194P Follow up after breast cancer in real life

J. Zaluska-Kusz, M. Litwiniuk

Chemotherapy Department, Wielkopolskie Centrum Onkologii-Greater Poland Cancer Centre, Poznan, Poland

Background: Breast cancer (BC) is the most common malignancy among women. The increased incidence of BC and better results of its treatment lead to an increased number of BC survivors. International guidelines specify clearly the follow-up procedure. Unfortunately, often under pressure from the patients, physicians do not always follow recommendations. The aim of our survey was to analyse the follow-up procedures performed in Outpatient Cancer Clinic in Poznan, Poland, and to find out patients' expectations.

Methods: We examined the follow-up visits of 484 women who underwent breast surgery in 2013 and had follow-ups for 5 years after the completion of the treatment. The patients were asked to fill in a questionnaire, stating their follow-up expectations.

Results: Out of the total number of 484 patients, 256 continued follow-up visits on a regular basis. Many of them had laboratory and imaging tests which are not recommended done: 193 patients (75%) had the CA 15.3 level checked, 226 women (88.2%) had ultrasonography of abdomen done, and 218 (85.1%) had a chest X-ray carried out at least once. In a significant number of cases these tests have been done regularly, once a year, despite of any symptoms. The recommended mammography once a year was prescribed to only 132 (51.6%) women. Recurrences: 9 patients had distant metastases, of whom 6 had the tests done because of symptoms they presented, 3 patients had metastases diagnosed by imaging (2 women) or a laboratory test (1 patient). 8 women developed second BC which in 7 cases was diagnosed in the yearly mammography. In the group of locoregional recurrence (6 patients) — 4 were diagnosed by annual mammography and 2 had a palpable tumour. The questionnaires showed that 82% of the patients were informed about follow-up visits rules, 78% knew the recommendations concerning the healthy life style and diet. 78% would prefer to have more tests done than are recommended. 93% preferred to have follow-up visits in their Cancer Centre than at the family doctor's.

Conclusions: 1. Both physicians and patients need to be further educated about the follow-up procedures. 2. Annual mammography is the essential part of BC follow-up. 3. It is necessary to perform trials to determine needs for separate follow-up procedures depending on the different subtypes of BC.

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196P Menopausal symptoms in premenopausal patients with luminal early breast cancer developing chemotherapy-induced amenorrhea

A. Zribi, I. Ben Abdallah, S. Ben Nasr, J. Ayari, S. Fendri, M. Balti, A. Haddaoui

Medical Oncology Department, Hopital Militaire de Tunis, Tunis, Tunisia

Background: Chemotherapy-induced amenorrhea (CIA) has been identified as a prognostic factor for better outcome in luminal breast cancer (BC) patients. Though, it may be associated to menopausal symptoms affecting patients' quality of life. The aim of this study was to assess patients' complaints related to CIA.

Methods: We analyzed data of premenopausal patients who received adjuvant chemotherapy then Tamoxifen for stage I-III luminal BC and developed amenorrhea. Perimenopausal patients were not included. CIA was defined as absence of menses for at least 6 months, occuring during chemotherapy or within 3 months after chemotherapy. We searched menopausal symptoms such as: hot flashes, dyspareunia, bone loss, fertility problems and cognitive disorders.

Results: We identified 83 patients with luminal early breast cancer treated with adjuvant chemotherapy followed by tamoxifen. Sixty percent of them experienced CIA (n=50). Thirty-three of these patients had menstruation resumption. We note that all patients received anthracycline based regimen, followed by taxane in 77% of patients. Menopausal symptoms were present in 83% of patients who did not experience menstruations resumption (MR) versus 47% in patients who had MR. Main symptoms were: hot flashes (38%), dyspareunia (33%), reduced libido (22%), and osteopenia in 20% of cases. Osteoporosis was noted in 5 patients. There was no fertility problems due to CIA in our study. Memory lapses occurred in 8% of patients. Although CIA significantly improved outcome in luminal BC patients after a median follow up time of 67 months [18-335] (hazard ratio for Disease-Free Survival was 0.1, 95%CI 0.01-0.30; p<0,001 and hazard ratio for Overall Survival was 0.32, 95%CI 0.07-0.805; p=0.032), the presence or the absence of menopausal symptoms didn't significantly impact survival in these patients (p=0.5).

Conclusions: Although CIA is now correlated to better outcome in luminal early BC patients, it can alter quality of life attributable to menopausal symptoms. The occurrence of these symptoms didn't impact prognosis in our study while developing CIA did. Therefore, these symptoms should be screened and treated regularly to improve patients' satisfaction.

Legal entity responsible for the study: Department of Medical Oncology of the Military Hospital of Tunis: Dr. Ichrak Ben Abdallah and Dr Aref Zribi.

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Disclosure: All authors have declared no conflicts of interest.

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197P Epirubicin-induced cardiotoxicity: Use of myocardial strain for early detection of left ventricular dysfunction before LVEF declines

I. Ben Abdallah[1], S. Ben Nasr[1], C. Chourabi[2], S. Fendri[1], M. Balti[1], A. Zribi[1], W. Fehri[2], A. Haddaoui[1]

[1]Medical Oncology Department, Hopital Militaire de Tunis, Tunis, Tunisia; [2]Cardiology Department, Hopital Militaire de Tunis, Tunis, Tunisia

Background: Although epirubicin has improved outcome in breast cancer (BC) patients, it is associated to myocardial dysfunction that affects patients' quality of life. The use of 2D-myocardial strain echocardiography for Global Longitudinal Strain (GLS) measurment allows to detect early myocardial dysfunction. The aim of this study was to evaluate early changes in GLS and their association with onset of later cardiotoxicity.

Methods: We conducted a prospective study from Jan 2016 to Nov 2019 on 77 patients with no cardiovascular risk factors, who presented with BC and received epirubicin. Twenty-five patients received further Trastuzumab. We measured LVEF and GLS before chemotherapy, at 3 and 12 months from the last epirubicin dose. Chemotherapy-Related-Cardiac-Dysfunction (CTRCD) was defined as a decrease of 10% in LVEF to a value under 53% according to ASE and EACI 2014 expert consensus.

Results: Mean age at diagnosis was 45 years. At baseline, mean LVEF was 69% ±4 and mean GLS was -21% ± 1.8. Three months after epirubicin regimen, mean LVEF was 64%±6 and mean GLS was -19% ±2. Two patients already presented acute heart failure within one month after the end of epirubicin and one patient presented transient dyspnea while on Trastuzumab (Tzb). At one year, 9 patients presented CTRCD. They had mean LVEF of 51% while their mean LVEF at 3 months was 64%±2. Their mean GLS at 3 months was -15%±1 (versus -19%±2 in patients who did not develop CTRCD) and their GLS variation from baseline was 24%±5 (versus 7%±4 in normal patients). Only GLS values and variations at 3 months were predictive of CTRCD at 12 months (p<0,001) with threshold values: -17%(Se= 100% and Sp=88%) for GLS and 19%(Se= 100% and Sp=88%) for GLS variation. The maximum additional effect of Tzb was noted at 3 months as there were five patients with CTRCD in the Tzb group versus two patients in the non Tzb group (p=0.06).

Conclusions: This was the 1st tunisian study assessing the value of measuring GLS to early detect and prevent cardiotoxicity. Decrease in GLS at 3 months after epirubicin was significantly associated with onset of CTRCD at 12 months. Further studies should be conducted to identify the best cardioprotective molecules to be initiated in these patients before LVEF decrease.

Legal entity responsible for the study: Department of Medical Oncology of the Military Hospital of Tunis and the Department of Cardiology of the Military Hospital of Tunis.

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198P Comparative study between the clinical effect of palonosetron and granisetron as antiemetic therapy for patients receiving highly emetogenic chemotherapy regimens

M.A. Mahrous

Oncology and Nuclear Medicine, Egypt Air Hospital, Cairo, Egypt

Background: Chemotherapy induced nausea and vomiting (CINV) is considered as the main fear for both oncologists and patients. It affects quality of life dramatically especially the food intake and nutritional status. This can be clearly observed in highly emetogenic chemotherapy (HEC) such as AC protocol in breast cancer patients or cisplatin based regimens in other types of cancer.

Methods: We carried out an open-label randomized trial including 115 patients receiving at least 4 courses of highly emetogenic chemotherapy regimens. All patients received dexamethasone in combination with the 5-HT3 receptor antagonist. Clinical and biochemical characteristics of patients were recorded and blood samples were drawn to monitor serum substance P in correlation with chemotherapy induced nausea and vomiting (CINV). Besides, (MASCC) antiemetic tool in acute phase (0hr-24hr) and delayed phase (24hr-120hr) was used to evaluate patient`s outcomes in both phases.

Results: One hundred and fifteen patients received study medication. In pa lonosetrone group 5% of population showed acute nausea and vomiting, whereas 35%

showed acute vomiting and 65% showed acute nausea in granisetrone group ($p<0.0001$). For delayed CINV only 15% showed delayed vomiting and 17% showed delayed nausea in palono group, while 85% patients showed delayed emesis and 83% patients showed delayed nausea in granisetrone group ($p<0.0001$). Adverse events were mostly mild to moderate, with quite low rates among the two groups.

Conclusions: Palonosetron in combination with dexamethasone is more effective granisetron and dexamethasone combination against both acute and delayed emesis induced by highly emetogenic cisplatin-based chemotherapy and highly emetogenic combination of cyclophosphamide and anthracyclines (AC).

Legal entity responsible for the study: Clinical Pharmacy Department - Faculty of Pharmacy Tanta University / Medical Oncology Department - Faculty of Medicine Tanta University / Oncology Pharmacy and Medical Oncology Department - Tanta Cancer Center - Egypt.

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199TiP A single-arm, open label, single center study to evaluate the safety and clinical outcome of using FR-Mask in breast cancer patients with radiation-irritated skin

C-N. Chu[1], S-C. Wu[2], D-T. Bau[3]

[1]Department of Radiation Oncology, China Medical University Hospital, Taichung, Taiwan; [2]Department of Anesthesiology, China Medical University Hospital, Taichung, Taiwan; [3]Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan

Background: Breast radiotherapy after breast-conserving surgery reduces the risk of recurrence and death and is widely used as standard treatment for breast cancer. Radiation-irritated skin is a treatment-induced symptom caused by radiation dose-limiting toxicity. It damages skin structure and causes a variety of symptoms, including cuticle thinning, sweat gland damage, sebaceous gland damage and basal membrane damage. Radiation-irritated skin can greatly impact quality of life (QOL). Previous studies have shown that deer antler velvet extract possess inflammatory function and promotes repair of damaged follicles, sweat glands and sebaceous glands. And bio-cellulose membrane is a highly efficient media to introduce velvet extract to damaged skin tissue. FR-Mask is a breast mask combines bio-cellulose membrane, velvet extract and other active ingredients, such as COENZYME Q10 and allantoin. In this study, FR-Mask will be used in breast cancer patients to test the safety and efficacy to alleviate their radiation-irritated skin symptoms.

Trial design: Patients who complete the post-operative radiotherapy and meet the inclusion and exclusion criteria will be enrolled into the study after the study team obtains their informed consent. Each subject will receive 12 packages of FR-Mask (1 mask in each individual package) and be instructed to put the patch on the irritated-skin area caused by radiation for 20 minutes every 3 days. Subjects will need to come back to clinics for evaluation every 4 weeks for 3 months. Up to 10 subjects will be enrolled in this study. Subjects will also be asked to come back to clinics after completion of the treatment period for 3 months. The total study duration for each subject will take 4.5 months. This study will be conducted in China Medical University Hospital.

Clinical trial identification: NCT04190381.

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Table 199TiP: Study schedule

Visit	Treatment					Follow up period
	Screening	Visit 1 (baseline)	Visit 2	Visit 3	Visit 4 (EOT¥)	1 month
Study day*	Day -14	Day 1 (±2 Days)	Day 29 (±2 Days)	Day 57 (±2 Days)	Day 85 (±2 Days)	Day 113 (±2 Days)
Informed consent	X					
Medical history (past 2 years)		X				
Physical exam		X	X	X	X	X
Demographic data		X				
Concomitant medication		X	X	X	X	X
Vital sign		X	X	X	X	X
Inclusion/Exclusion criteria	X	X				
FR-Mask accountability		X	X	X	X	
FR-Mask and patient diary dispense		X	X	X		
Patient diary review			X	X	X	
Study questionnaires		X	X	X	X	X
Skin observation		X	X	X	X	X
AE/SAE monitoring			X	X	X	X

*In cases of public holidays, the investigator can rearrange the visit day to the nearest working day. ¥ EOT= end of treatment