MUNICH 2018 ESMO congress

EARLY BREAST CANCER, HER2-POSITIVE

CLINICAL CASE DISCUSSION

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DISCLOSURES

Honoraria: Amgen, Astellas, AstraZeneca, Bayer, BMS, Celgene, Clinigen, Egis, Eli Lilly, Janssen, Novartis, Pfizer, Pierre Fabre, prIME, Roche and Teva

Travel support: Amgen, AstraZeneca, Egis, Novartis, Pfizer and Roche

Clinical research: Amgen, Astellas, AstraZeneca, Bayer, BMS, Boehringer, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Roche and Samsung

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Case summary

- 32 years old, premenopausal, healthy female
- Left breast cancer cT2N1M0
- HER2 positive, ER/PR negative
- No relevant family history

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; cTNM, clinical tumour, node, metastasis

HER2 and *BRCA1/2* mutations

Table 1 HER2 and ER status in primary BRCA screens

	BRCA1	*BRCA2*	Negative	Total	Proportion *BRCA1/2* (%)
ER− HER2+	3	1	40	44	9.0
ER+ HER2+	1	4	107	112	4.5
Total HER2+	4/156 (2.6 %)	5/156 (3.2 %)	147	156	5.8
ER− HER2−*	115	34	266	415	35.9
ER+ HER2−	25	48	419	492	14.8
Total HER2−	140	82	685	907	24.5
Total All	144	87	832	1063	22.1

Table 2 HER2 status in *BRCA1/2* mutation carriers

	BRCA1	Percentage	*BRCA2*	Percentage	χ^2 *p* value
ER− HER2+	3	1.6	1	0.6	0.62
ER+ HER2+	1	0.5	11	6.2	0.002
ER− HER2−	129	66.1	49	27.7	<0.0001
ER+ HER2−	62	31.8	116	65.5	<0.0001
Total	195		177		
Any ER HER2+	4	2.1	12	6.8	0.04

1063 *BRCA1/2* tested patients

Evans, BCRT 2016

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ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2

BASSER CENTER FOR BRCA
Penn Medicine

The Penn II Risk Model

Part A. Select the side of the family being evaluated: ◉ **Maternal** ○ **Paternal**

Part B. Please provide the following information:

1.	Presence of Ashkenazi (Eastern European) Jewish ancestry in the family?	◉ no ○ yes
2.	Number of women in the family diagnosed with both breast and ovarian cancer?	(0-100)
3.	Number of women in the family diagnosed with ovarian, fallopian tube, or primary peritoneal cancer (in the absence of breast cancer)?	(0-100)
4.	Number of breast cancer cases in the family diagnosed in women under the age of 50?	(0-100)
5.	What is the age of the youngest breast cancer diagnosis in the family?	(18-130)
6.	Presence of mother-daughter breast cancer diagnoses in the family?	◉ no ○ yes
7.	How many women with bilateral breast cancer in the family? (**Note**: Count women with cancer in both breasts, not two primaries in one breast.)	(0-100)
8.	Number of men diagnosed with breast cancer in the family?	(0-100)
9.	Presence of pancreatic cancer in the family?	◉ no ○ yes
10.	Number of men diagnosed with prostate cancer in the family?	(0-100)

Part C. Closest relative with breast or ovarian Cancer: ▾

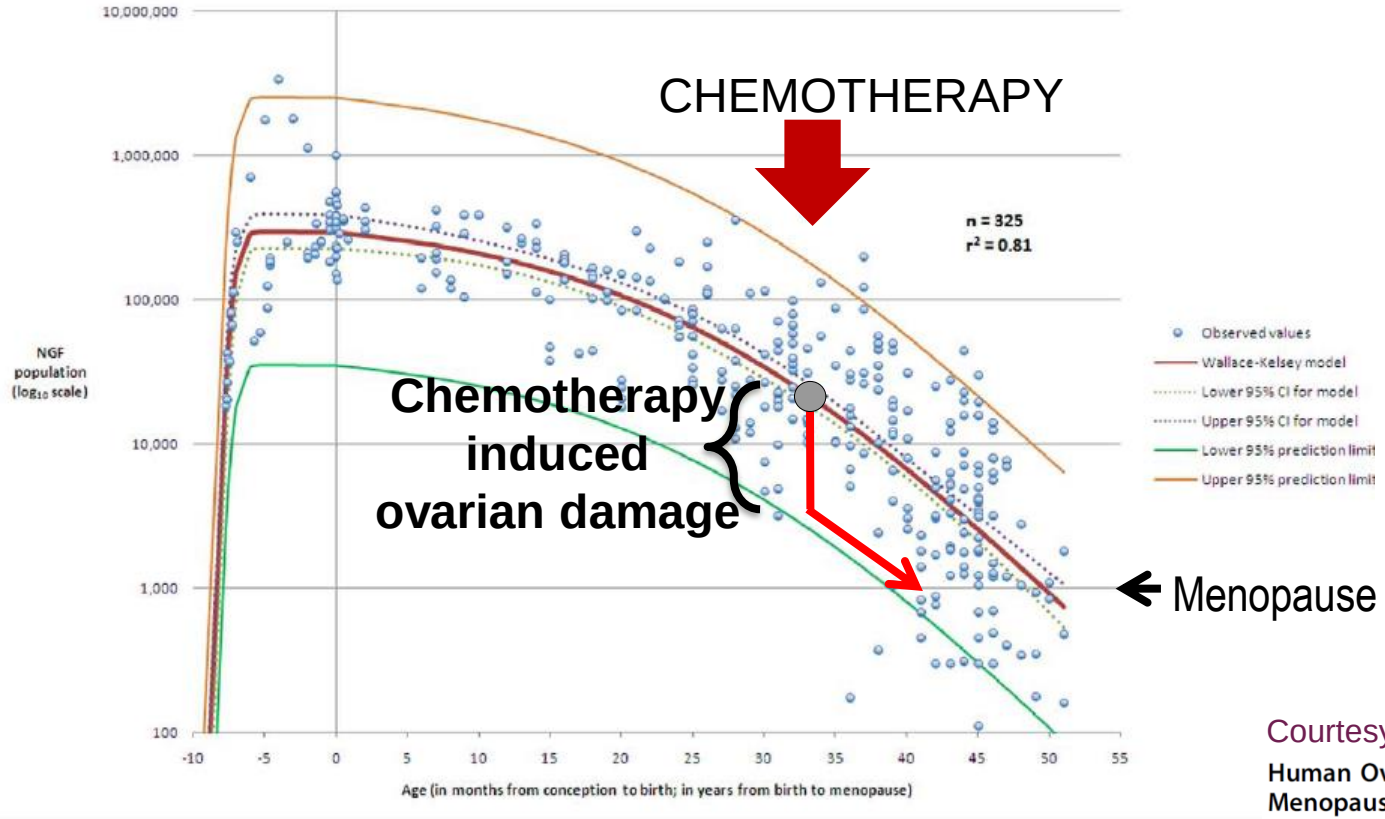
Genetic counselling and testing for germline *BRCA1* and *BRCA2* mutations should be offered to breast cancer patients from high-risk groups, i.e. those with:

- strong family history of breast and/or ovarian cancer,
- diagnosis of breast cancer before the age of 50,
- diagnosis of TNBC before the age of 60,
- personal history of ovarian cancer or second breast cancer or male sex

LoE, GoR [II, A]

GoR, grade of recommendation; LoE, level of evidence; TNBC, triple-negative breast cancer

Fertility preservation



Courtesy of F. Peccatori

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace[1]*, Thomas W. Kelsey[2]

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CI, confidence interval; NGF, non-growing follicles

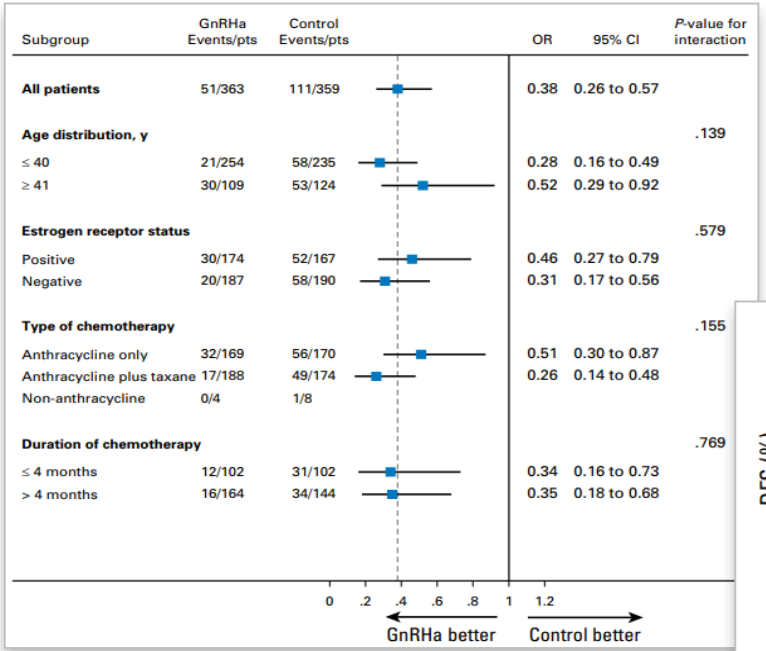
Fertility preservation

Effective method for emergency fertility preservation: random-start controlled ovarian stimulation

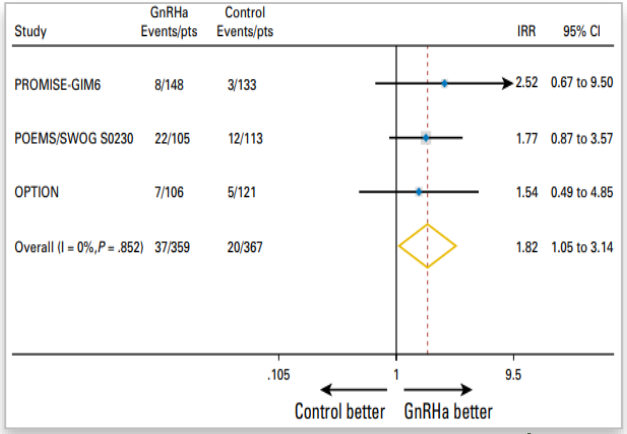
Hakan Cakmak, M.D., Audra Katz, R.N., Marcelle I. Cedars, M.D., and Mitchell P. Rosen, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

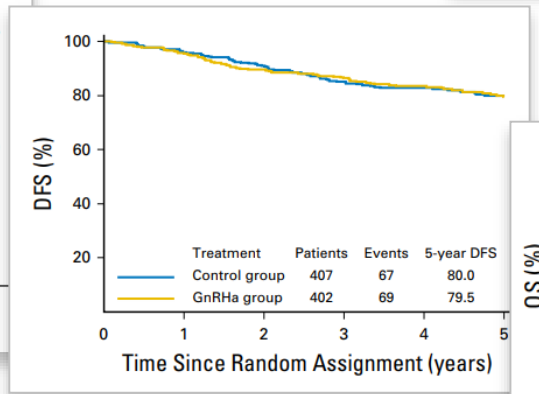
Fertility preservation

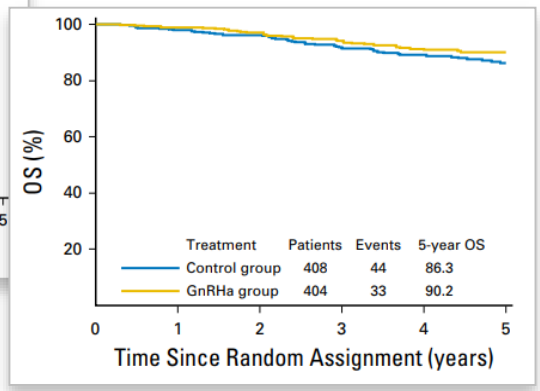


Premature ovarian insufficiency



Post-treatment pregnancies





873 patients from 5 RCT

Lambertini, JCO 2018

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CI, confidence interval; DFS, disease-free survival; GnRHa, gonadotropin-releasing hormone agonist; OR, odds ratio; OS, overall survival; RCT, randomised clinical trials

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v8–v30, 2015
doi:10.1093/annonc/mdv298

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

In younger premenopausal patients, possible fertility issues should be discussed and guidance about fertility-preservation techniques should be provided, before the initiation of treatment

Senkus, Ann Oncol 2015

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi160–vi170, 2013
doi:10.1093/annonc/mdt199
Published online 27 June 2013

Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Fertility preservation methods in cancer patients:

(i) Young women desiring future fertility should be counselled on available fertility preserving options before starting anti-cancer treatment. Counselling should be implemented soon after diagnosis to allow prompt referral to fertility specialists.

(ii) The use of GnRH analogues concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility.

(iii) Embryo or oocyte cryopreservation is the main method to preserve female fertility.

(iv) Ovarian stimulation should be carried out before commencing chemotherapy.

(v) The use of gonadotropins and letrozole or tamoxifen for ovarian stimulation is suggested for cancer patients. Consideration of such an approach in patients with ER-positive breast cancer should be made during a discussion with the patient and requires intensive interdisciplinary discussion including oncologists, radiotherapists and reproductive medicine specialists.

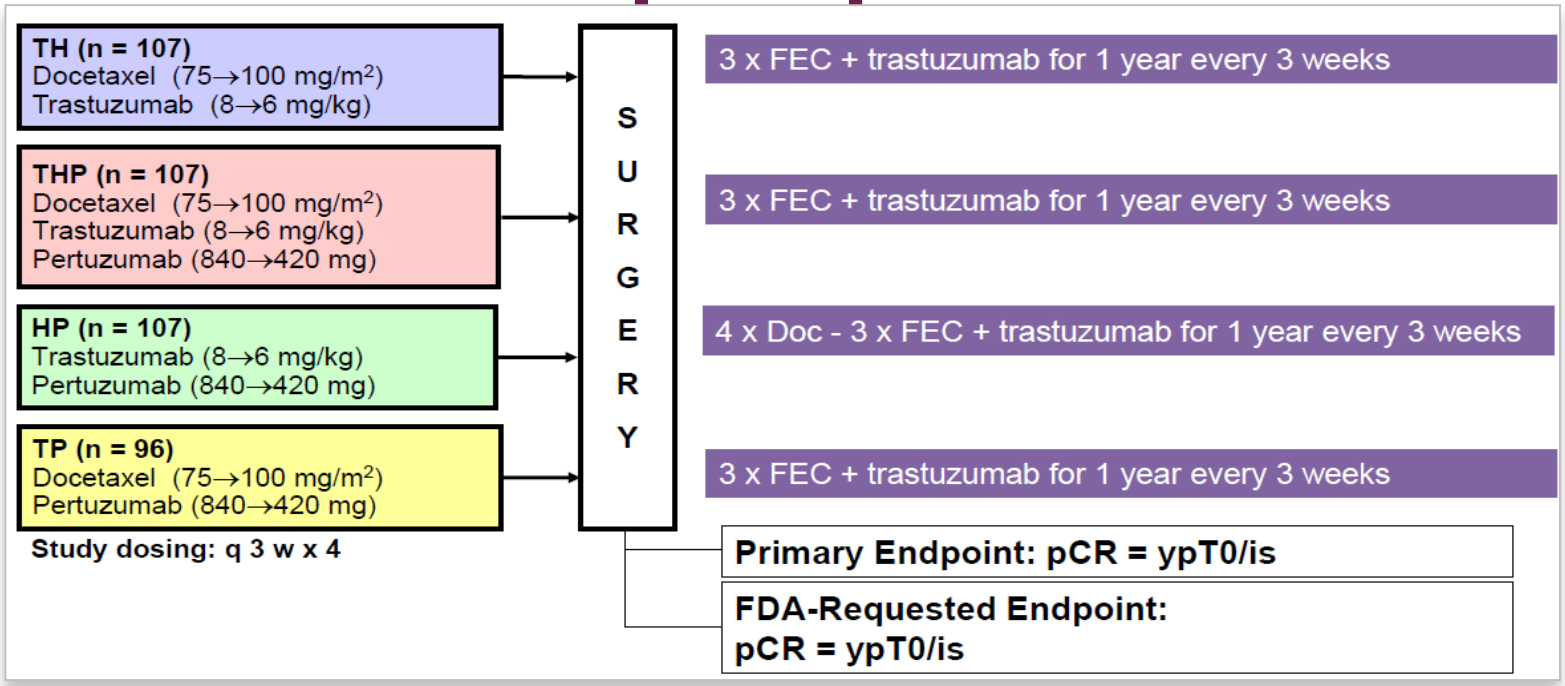
(vi) Chemotherapy and radiotherapy-induced sterility can be prevented also by freezing ovarian tissue before treatment.

Peccatori, Ann Oncol 2013

ER, oestrogen receptor;GnRHa, gonadotropin-releasing hormone

Neoadjuvant systemic therapy: Trastuzumab plus pertuzumab

NeoSphere



Gianni, Lancet Oncol 2012

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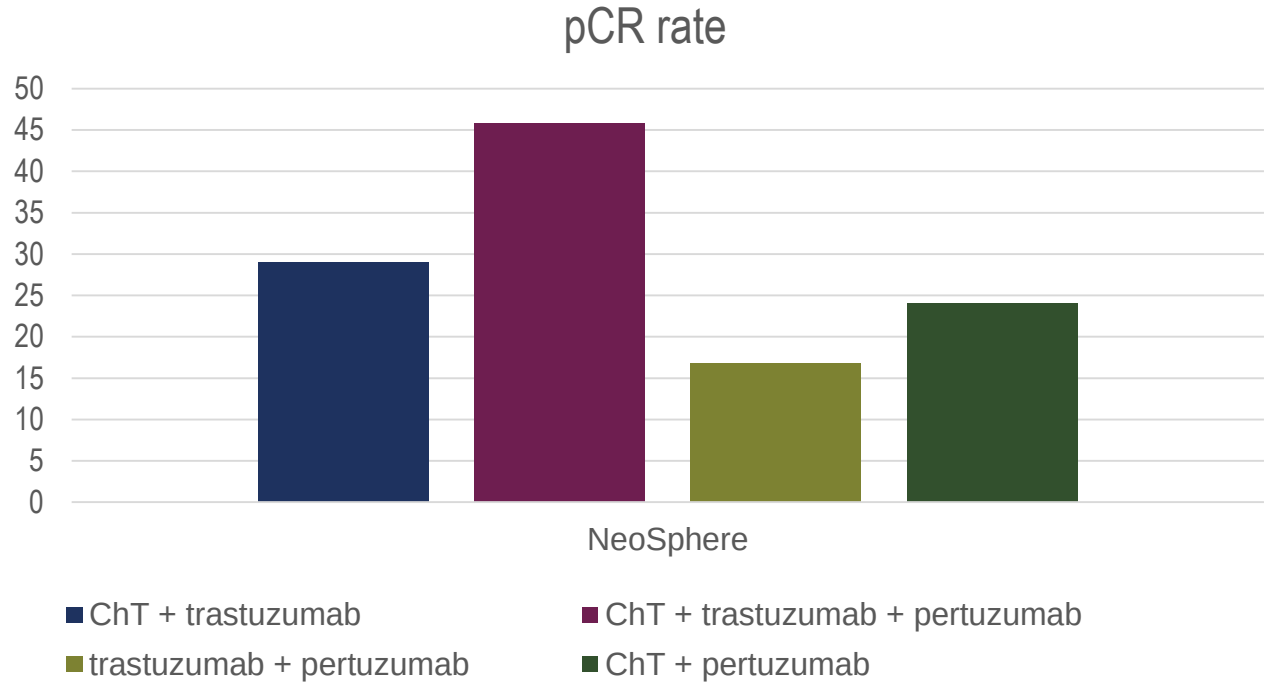
FDA, US food and drug investigartion; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; pCR, pathological complete response; HP, trastuzumab/pertuzumab; TH, docetaxel/trastuzumab; THP, docetaxel/trastuzumab/pertuzumab; TP, docetaxel/pertuzumab

Neoadjuvant systemic therapy: Trastuzumab plus pertuzumab



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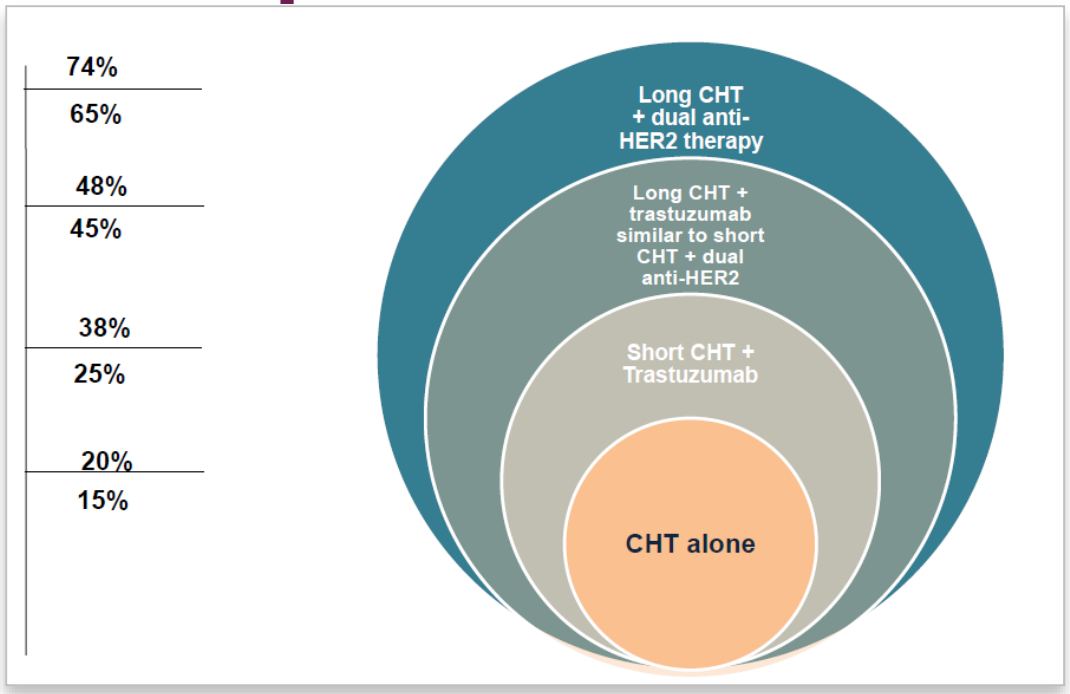
ChT, chemotherapy; pCR, pathological complete response

Gianni, Lancet Oncol 2012

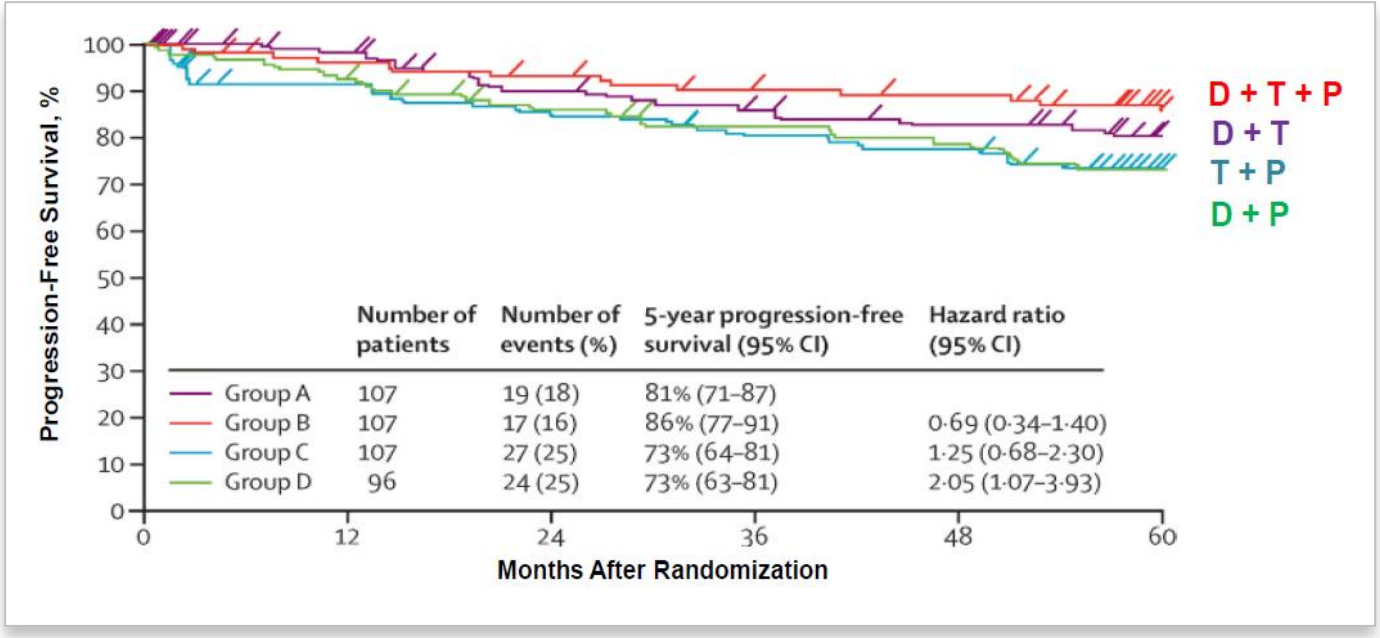
Neoadjuvant systemic therapy
pCR in HER2-positive + breast cancer



Loibl, Curr Opin Obstet Gynecol 2015

ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response

Neoadjuvant systemic therapy trastuzumab + pertuzumab



CI, confidence interval; D, docetaxel; P, pertuzumab; T, trastuzumab

Gianni, Lancet Oncol 2016

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v8–v30, 2015
doi:10.1093/annonc/mdv298

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

In the neoadjuvant setting, dual anti-HER2 blockade associated with chemotherapy (trastuzumab/lapatinib, trastuzumab/pertuzumab) has led to improvements in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent

For the trastuzumab/pertuzumab combination, after reviewing potential risks and benefits (including the financial impact), in selected higher-risk cases it can be considered an acceptable option as primary systemic therapy

LoE, GoR [II, B]

Senkus, Ann Oncol 2015

GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; pCR, pathological complete response;

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Situation cN1/cN0 (40% turn over rate)

ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

FNR with dual tracer or >2SLN detected acceptable

FNR	Sentina cN1/ycN0	Alliance cN1/ycN0	SN FNAC cN1/ycN0	Spain cN1/ycN0
In all	14.2%	12.6%	8.4%	8.3%
Dual tracer	8,6%	9,1%	5,2%	
>2 SLN removed	7,3%	10,8%	4,9%	

→ SNB is a good option for cN1/cN0 patients

Gnant, ESMO 2017

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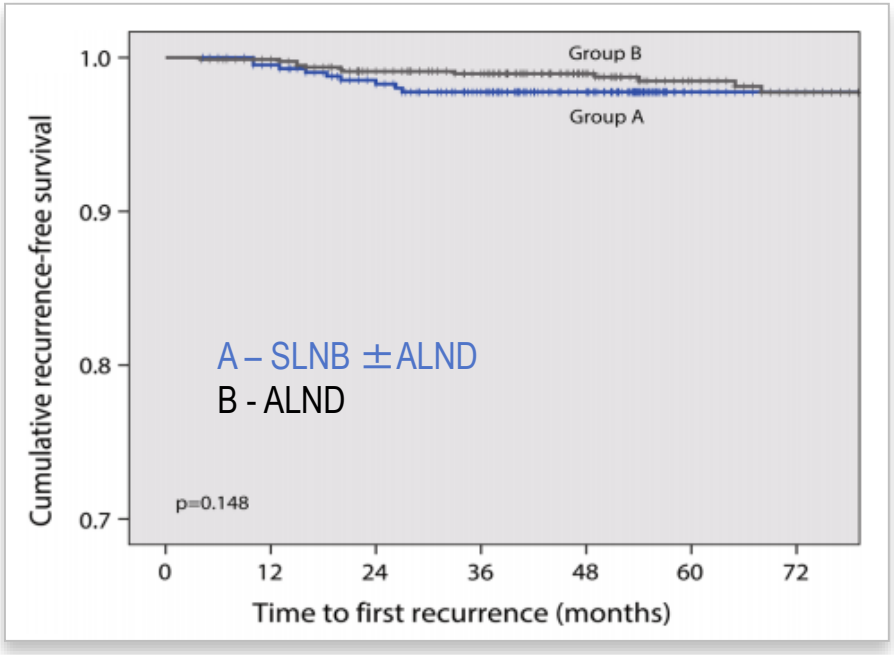
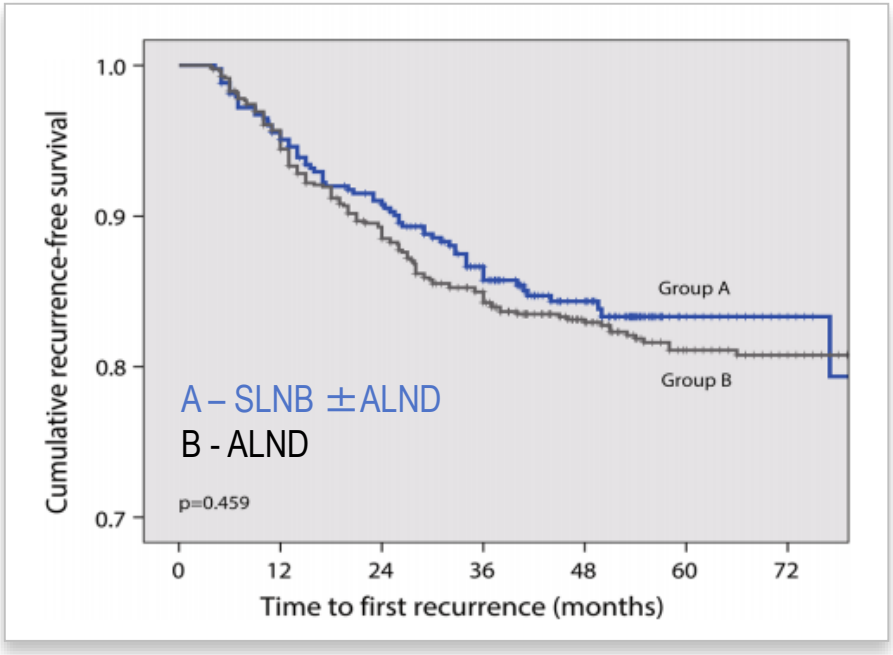
FNAC, fine-needle aspiration cytology; FNR, false-negative rate; SLN, sentinel lymph node; SNB, sentinel node biopsy

Avoiding ALND in cN+/ycN0 patients



Axillary recurrence



Distant metastases

1247 cN+/ycN0 patients

Kang, BCRT 2017

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ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy

In patients with cytologically positive proven axillary nodes who convert to negative … false-negative rates of SLN post systemic therapy range from 8% to 14.2%. False-negative rates can be improved by marking the biopsied positive nodes to verify their removal, as well as using dual tracer and removing ≥ 3 SLNs

- In patients with baseline axillary involvement converting to negative, SLNB may be carried out in selected cases, and, if negative, further axillary surgery may be avoided

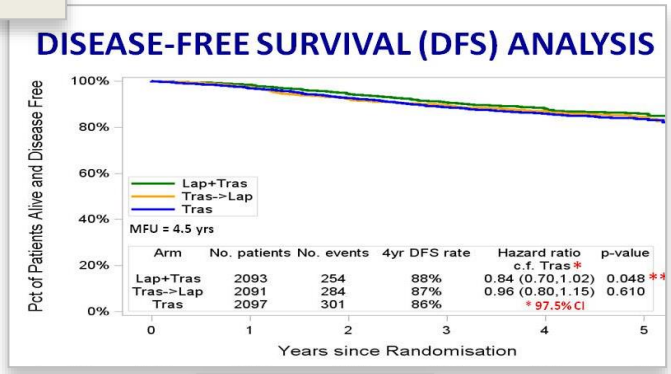
- Identification of any tumour deposits in post-PST SLNB prompts ALND

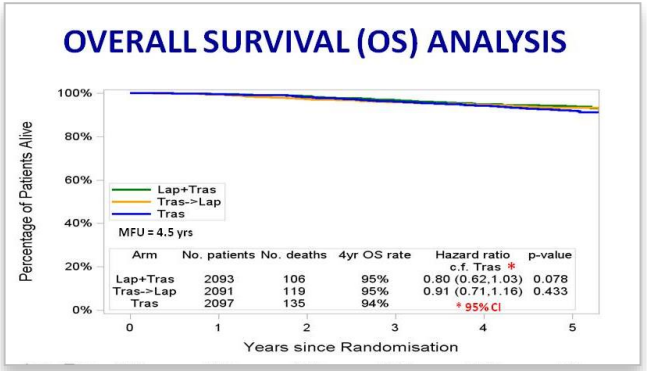
LoE, GoR [II, B]

ALND, axillary lymph node dissection; GoR, grade of recommendation; LoE, level of evidence; PST, primary systemic therapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

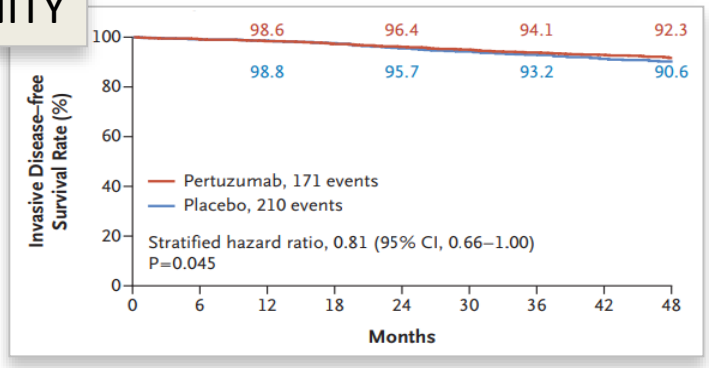
Escalation of systemic adjuvant therapy

ALTTO





APHINITY

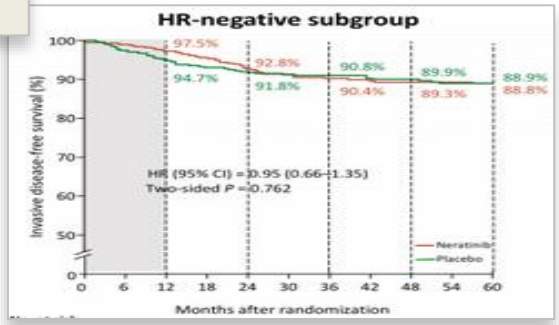


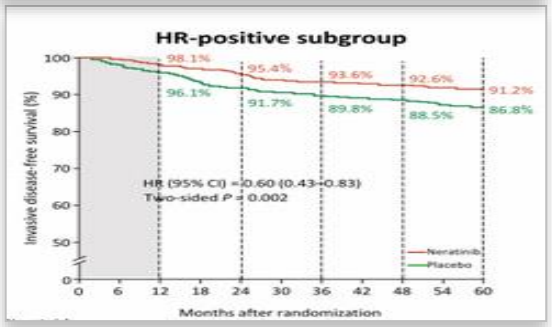
Piccart-Gebhart, JCO 2015;
von Minckwitz, NEJM 2017

CI, confidence interval; Lap, lapatinib; Tras, trastuzumab

Escalation of systemic adjuvant therapy

ExteNET





N %	Neratinib (n=14080)		Placebo (n=1408)	
	All grades	G3-4	All grades	G3-4
Diarrhea	1343 (95.4)	562 (39,9)	499 (35,4)	23 (1,6)
	Dose reduction: 26%			
	Tx termination: 17%			

What does G 3 diarrhea mean ?

- ≥ 7 stools daily
- incontinence;
- hospitalization indicated
- limiting self care ADL

iDFS at 5 years

Martin, Lancet Oncol 2017

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ADL, activities of daily living; CI, confidence interval; HR, hormone receptor; iDFS, invasive disease-free survival

In the adjuvant setting, however, addition of pertuzumab resulted in a very small (about 0.9%) improvement in invasive DFS, which albeit statistically significant has a small clinical impact that must be balanced against its very high cost. Therefore, it should not be used routinely, although it may be an option in very high-risk patients.

LoE, GoR [I, C]

ESMO-MCBS: C

Extended anti-HER2 therapy with neratinib should not be used routinely but may be considered in highly selected high-risk patients, due to its important toxicity

LoE, GoR [I, C]

ESMO-MCBS: B

DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; MCBS, Magnitude of Clinical Benefit Scale; GoR, grade of recommendation; LoE, level of evidence

https://thinkpinkpola

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