MADRID 2017 ESMO congress

ESMO Clinical Practice Guidelines

Metastatic breast cancer: sequence of therapies

Clinical Case Discussion

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LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Brustzentrum im Klinikum der Universität München

DISCLOSURES

Honoraria for consulting: Lilly, Novartis, Pfizer

Honoraria for lectures: Novartis, Pfizer

Clinical features – Case presentation by Carmen Criscitiello, EIO, Milan, Italy

PS ECOG 0

58-year-old woman

Bone, liver and lymph node metastases: Biopsy verified luminal BC (HR+ HER2-)

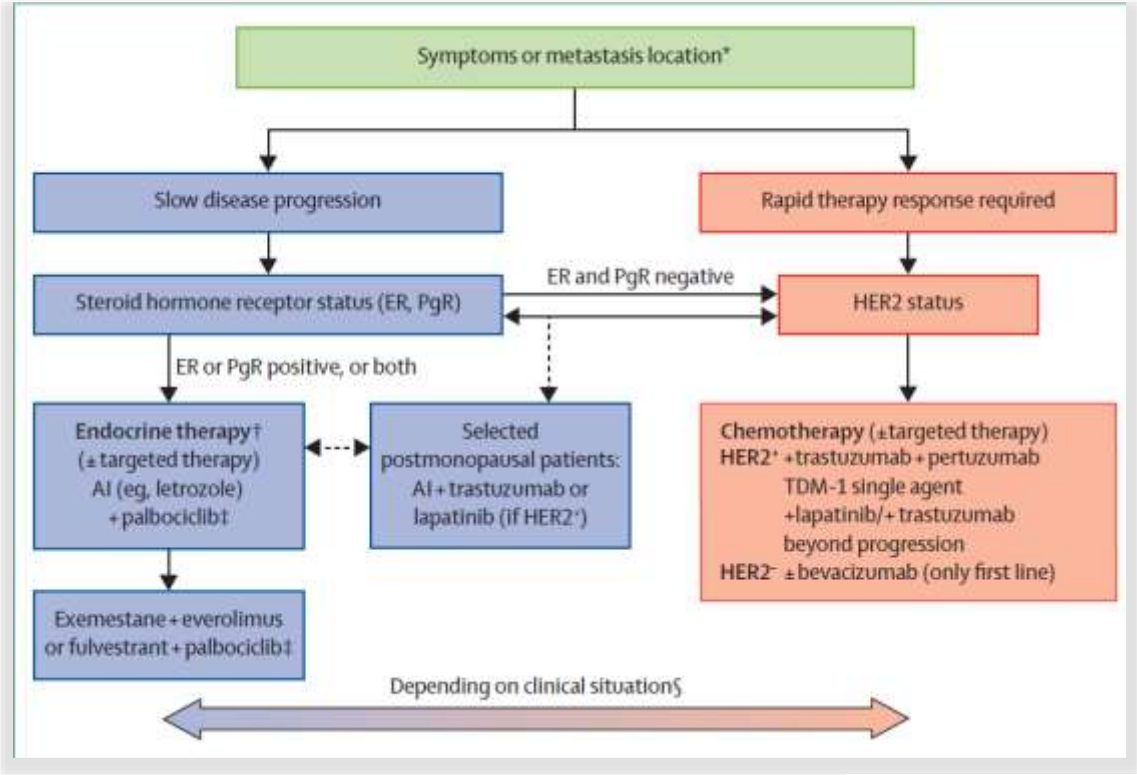
Asymptomatic

??? Therapy concept for 1st and 2nd line MBC therapy ???

No comorbidity

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; PS, performance status

Therapy concepts in metastatic breast cancer



Harbeck and Gnant, Lancet 2017

AI, aromatase inhibitor; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; TDM-1, Trastuzumab emtansine

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Annals of Oncology 28: 16–33, 2017
doi:10.1093/annonc/mdw544
Published online 5 December 2016

SPECIAL ARTICLE

3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)

F. Cardoso[1*], A. Costa[2], E. Senkus[3], M. Aapro[4], F. André[5], C. H. Barrios[6], J. Bergh[7], G. Bhattacharyya[8], L. Biganzoli[9], M. J. Cardoso[10], L. Carey[11], D. Corneliussen-James[12], G. Curigliano[13], V. Dieras[14], N. El Saghir[15], A. Eniu[16], L. Fallowfield[17], D. Fenech[18], P. Francis[19], K. Gelmon[20], A. Gennari[21], N. Harbeck[22], C. Hudis[23], B. Kaufman[24], I. Krop[25], M. Mayer[26], H. Meijer[27], S. Mertz[28], S. Ohno[29], O. Pagani[30], E. Papadopoulos[31], F. Peccatori[32], F. Penault-Llorca[33], M. J. Piccart[34], J. Y. Pierga[35], H. Rugo[36], L. Shockney[37], G. Sledge[38], S. Swain[39], C. Thomssen[40], A. Tutt[41], D. Vorobiof[42], B. Xu[43], L. Norton[44] & E. Winer[45]

The Breast 31 (2017) 244–254

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3)

F. Cardoso [a, *], A. Costa [b, c], E. Senkus [d], M. Aapro [e], F. André [f], C.H. Barrios [g], J. Bergh [h], G. Bhattacharyya [i], L. Biganzoli [j], M.J. Cardoso [k], L. Carey [l], D. Corneliussen-James [m], G. Curigliano [n], V. Dieras [o], N. El Saghir [p], A. Eniu [q], L. Fallowfield [r], D. Fenech [s], P. Francis [t], K. Gelmon [u], A. Gennari [v], N. Harbeck [w], C. Hudis [x], B. Kaufman [y], I. Krop [z], M. Mayer [aa], H. Meijer [ab], S. Mertz [ac], S. Ohno [ad], O. Pagani [ae], E. Papadopoulos [af], F. Peccatori [b, c], F. Penault-Llorca [ag], M.J. Piccart [ah], J.Y. Pierga [ai], H. Rugo [aj], L. Shockney [ak], G. Sledge [al], S. Swain [am], C. Thomssen [an], A. Tutt [ao], D. Vorobiof [ap], B. Xu [aq], L. Norton [ar], E. Winer [z]

ER POSITIVE / HER2 NEGATIVE MBC

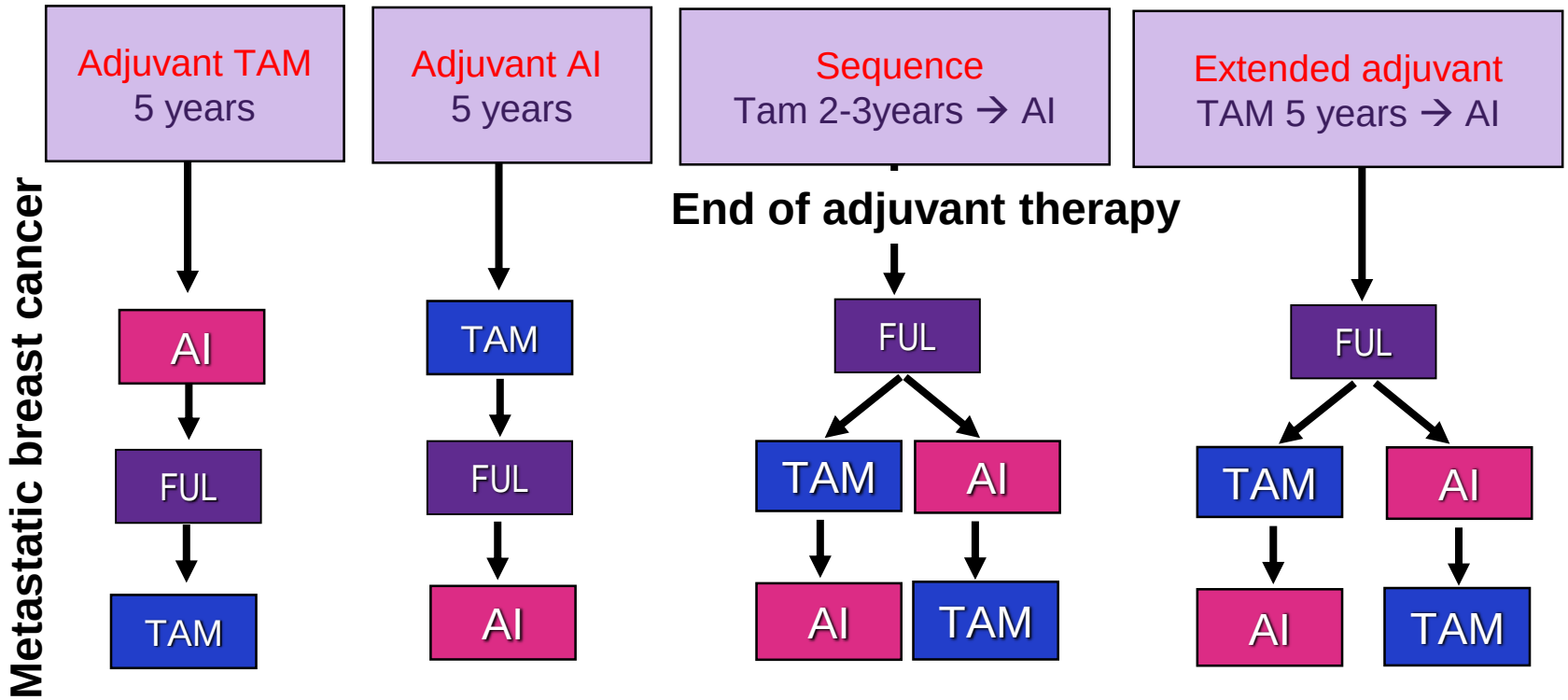
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.

LoE, GoR: [I, A]

Total # of votes:			**(41)**
1.	**YES:**	**92.6%**	**(38)**
2.	**NO:**	**0.0%**	**(00)**
3.	**ABSTAIN:**	**7.3%**	**(03)**

ER, oestrogen receptor; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC , metastatic breast cancer

Endocrine therapy* in MBC (before availability of novel targeted therapies)



* premenopausal: + GnRH

AI, aromatase inhibitor; FUL, fulvestrant; GnRH, gonadotrophin-releasing hormone; MBC, metastatic breast cancer; TAM, tamoxifen

ER POSITIVE / HER2 NEGATIVE MBC

Modified statement

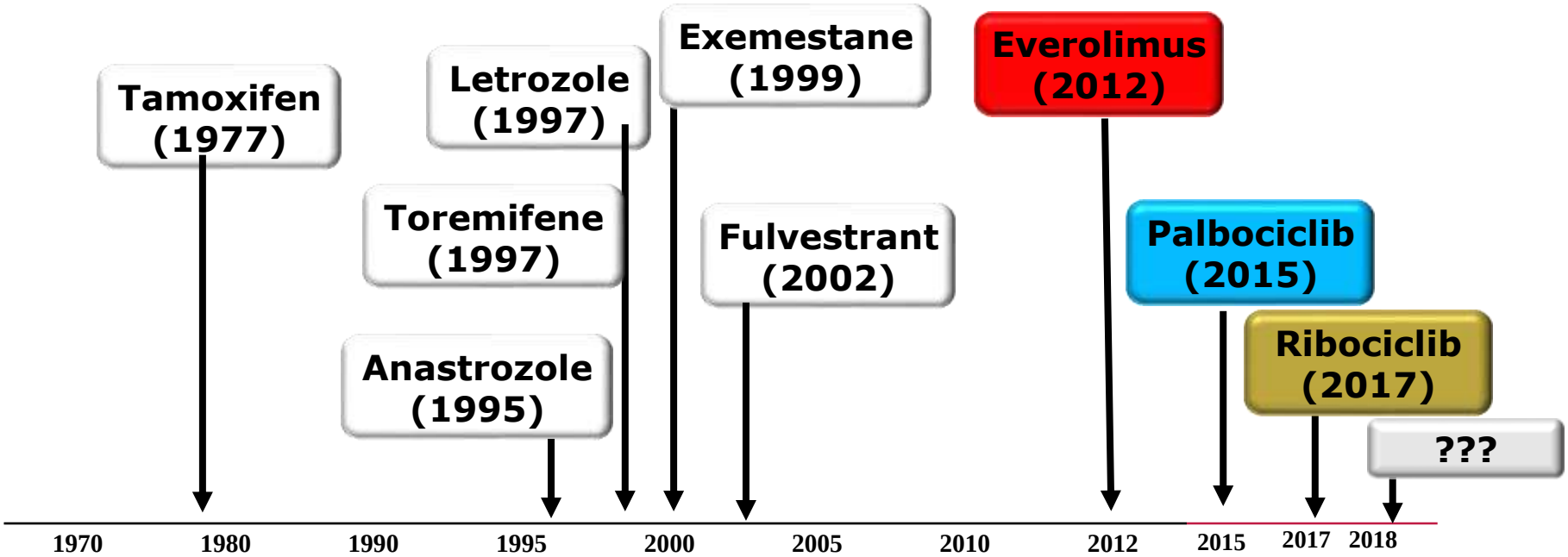
The preferred 1st line ET for postmenopausal patients depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant.

LoE, GoR: [I, A]

Total # of votes:		**(44)**	
1.	**YES:**	**84.0%**	**(37)**
2.	**NO:**	**9.0%**	**(04)**
3.	**ABSTAIN:**	**6.8%**	**(03)**

ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC , metastatic breast cancer

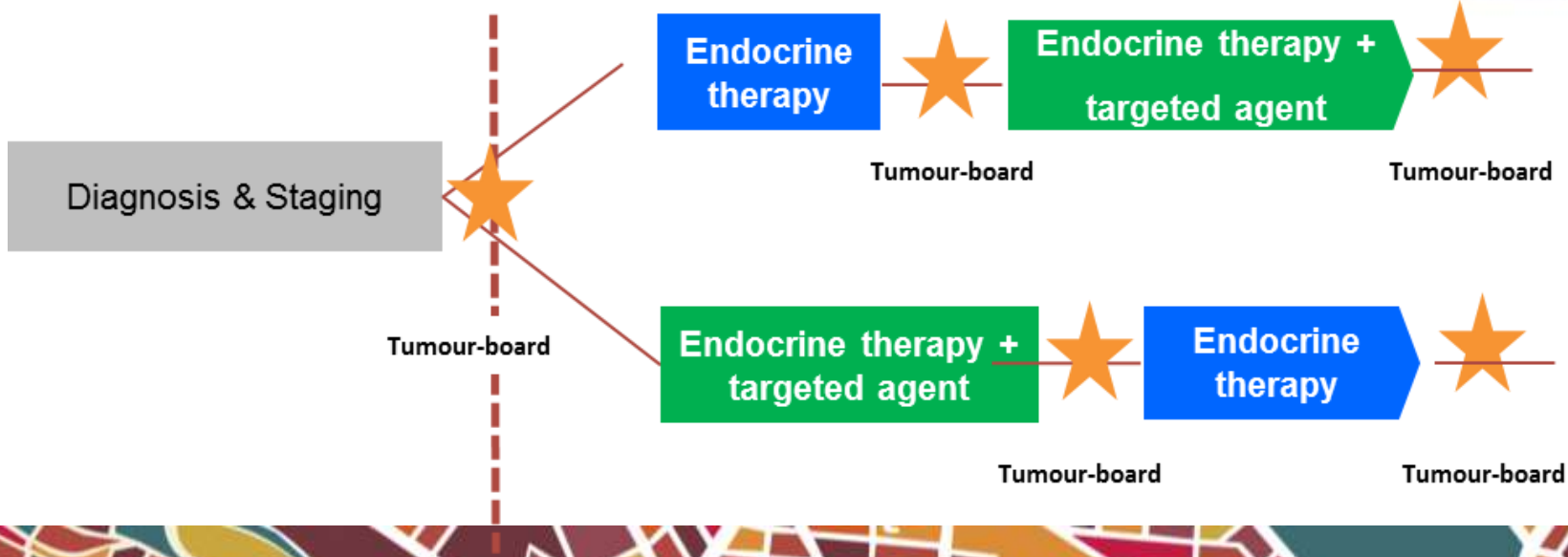
New agents for HR+ MBC are becoming available



Modified after Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

FDA, Food and Drug Administration; HR, hormone receptor; MBC, metastatic breast cancer

Luminal MBC: how to sequence endocrine ± targeted agents



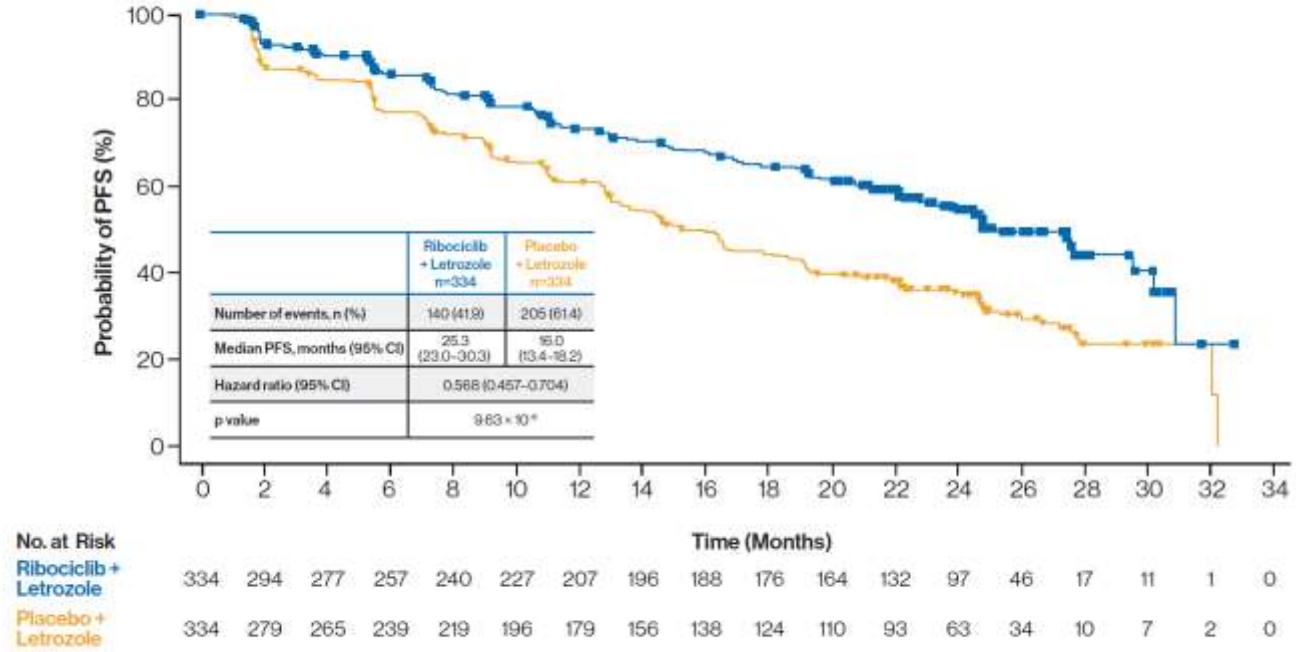
First line efficacy of endocrine ± targeted agents

Phase III trial	PALOMA 2 (n=666)	MONALEESA 2 (n=668)	MONARCH 3
Targeted agent	Palbociclib	Ribociclib	Abemaciclib
Endocrine agent	Letrozole	Letrozole	Anastrozole / Letrozole
PFS	24.8 vs. 14.5 months	25.3 vs. 16.0 months	significant improvement
HR (PFS)	0.58	0.57	ESMO Presidential Symposium II Sunday Sep 10, 2017 4:30 pm presented by Dr. Di Leo
Most frequent G3/4 side effects	neutropenia, leukopenia, anemia, fatigue	Neuropenia, vomiting, back pain, fatigue	

Finn et al, NEJM 2016; Hortobagyi et al, ASCO 2017; Lilly press release 24.04.2017; Di Leo et al, ESMO 2017

First line CDK 4/6 inhibitor therapy: consistent PFS benefit over AI alone

Figure 2. Kaplan–Meier Plot of Locally Assessed Progression-free Survival



Data cut-off: January 2, 2017.

CDK, cyclin-dependent kinase; CI, confidence interval; PFS, progression-free survival

Hortobagyi et al. ASCO 2017

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FIRST LINE THERAPY WITH A CDK 4/6 INHIBITOR

ESMO

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SPECIAL ARTICLE

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The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for postmenopausal patients (except patients relapsing <12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available. OS results are still awaited. 1 A

Voters: 37
Yes: 92% (34)
Abstain: 3% (1)

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; PFS, progression-free survival

PALOMA 1 Trial: OS (Part 1 and Part 2)

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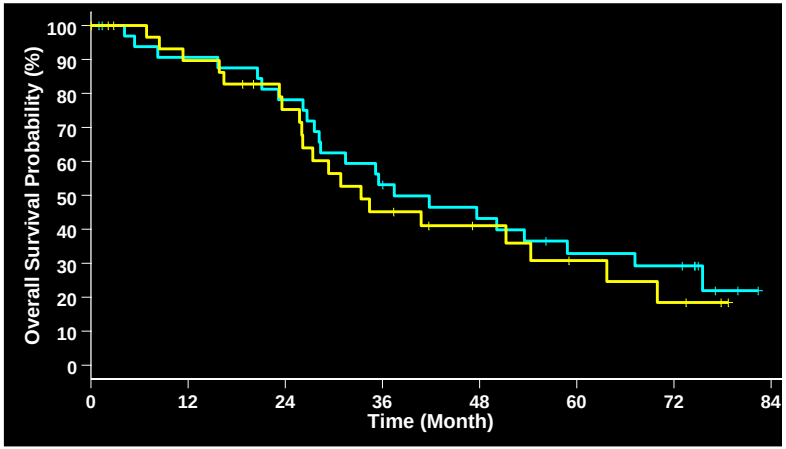
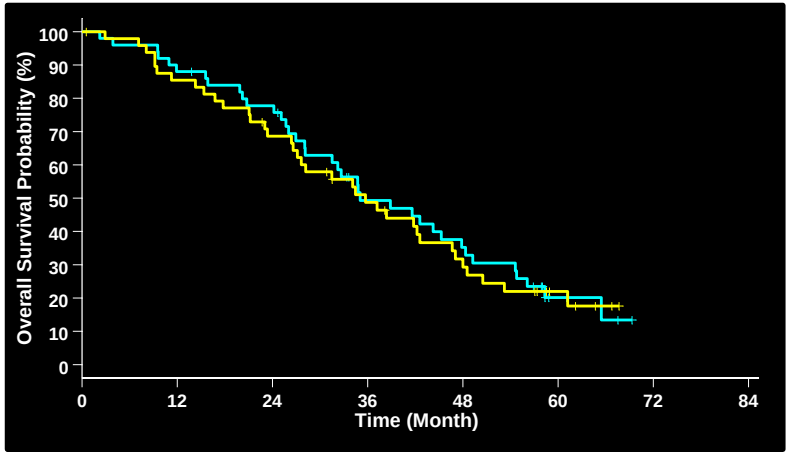
Part 1	PAL+LET (N=34)	LET (N=32)
Patients with events, n (%)	23 (68)	20 (63)
Median OS, months (95% CI)	37.5 (27.6, 58.8)	33.3 (26.0, 54.3)
Hazard ratio (95% CI)	0.837 (0.458, 1.527)	
P value	0.280	

Part 2	PAL+LET (N=50)	LET (N=49)
Patients with events, n (%)	37 (74)	36 (73)
Median OS, months (95% CI)	35.1 (28.1, 47.8)	35.7 (26.6, 46.7)
Hazard ratio (95% CI)	0.935 (0.590, 1.480)	
P value	0.388	





CI confidence interval; LET, letrozole; OS, overall survival; PAL, palbociclib

Finn et al, ASCO 2017

Luminal MBC: how to decide between endocrine mono-therapy and combination therapy

- Drug availability
- Treatment costs

- Importance of PFS prolongation
- Quality of life
- Side effects
- Convenience
- …

MBC, metastatic breast cancer; PFS, progression-free survival

Fewer patients for each new line of MBC therapy

- After failure of first line therapy, a proportion of patients cannot undergo second line therapy due to rapid disease progression
- In general, response to further lines of therapy is worse
- About one third of patients stop their treatment with each new line of therapy. These results are concordant with large retrospective cohort studies.

Study	2nd Line	3rd Line	4th Line	5th Line
Dufresne A et al. Breast Cancer Res Treat 2008	100%	56%	25%	11%
Tacca O et al. Cancer Invest 2009	100%	68%	43%	23%
Bernardo G, et al. Cancer Res 2010	100%	82%	36%	11%
Planchat E, et al. Breast 2011	100%	76%	56%	37%
Current study: Jackisch C et al. BMC Cancer 2014	**100%**	**70%**	**46%**	**27%**

MBC, metastatic breast cancer

Jackisch et al. P4-13-28, SABCS 2016

Second line (and beyond) efficacy of endocrine ± targeted agents

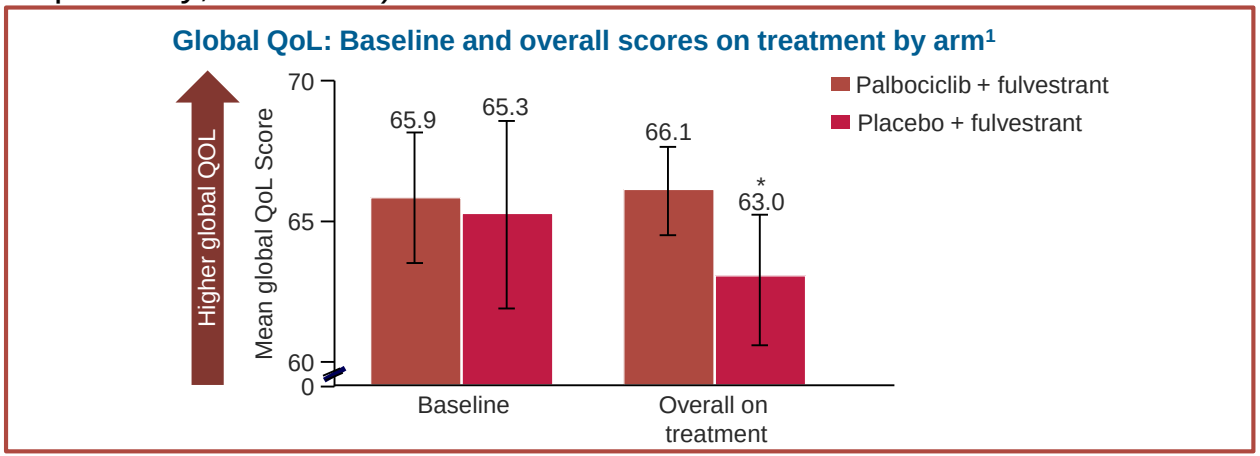
Phase III trial	PALOMA 3 (n=521)	MONARCH 2 (n=669)	BOLERO 2 (n=724)
Targeted agent	Palbociclib	Abemaciclib	Everolimus
Endocrine agent	Fulvestrant	Fulvestrant	Exemestane
PFS	11.2 vs. 4.6 months	16.4 vs. 9.3 months	10.6 vs. 4.1 months
HR (PFS)	0.580	0.553	0.43
Most frequent G3/4 side effects	neutropenia, leukopenia, anaemia	Diarrhoea, neutropenia, leukopenia, anaemia, nausea, fatigue	Stomatitis, anaemia, dyspnea, hyperglycemia, fatigue, pneumonitis

Turner et al. SABCS 2016; Christofanilli et al. 2016; Sledge et al. 2017; Baselga et al. 2012

HR, hazard ratio; PFS, progression-free survival

PALOMA-3 pro analysis: global QoL – results at interim analysis

A statistically significant difference was seen in overall change from baseline score for global QoL with palbociclib + fulvestrant compared with placebo + fulvestrant (66.1 [95% CI: 64.5–67.7] vs. 63.0 [95% CI: 60.6–65.3], respectively; P=0.0313)[1,2]



*P=0.0313 vs. palbociclib + fulvestrant for overall on-treatment score
Data cutoff December 5 2014 used for interim analysis; median follow-up 5.6 months

CI, confidence interval; QoL, quality of life

1. Harbeck N, et al. EBCC 2015: P004
2. Harbeck N, et al. Ann Oncol 2016

ER POSITIVE / HER2 NEGATIVE MBC

New statement

The addition of CDK 4/6 inhibitor palbociclib to fulvestrant, beyond 1st line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal patients, an LHRH-agonist must also be used. LoE, GoR: [I, B]

At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue.

Total # of votes:		**(42)**	
1.	**YES:**	**85.7%**	**(36)**
2.	**NO:**	**4.7%**	**(02)**
3.	**ABSTAIN:**	**9.5%**	**(04)**

CDK, cyclin-dependent kinase; ER, oestrogen receptor; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LHRH, luteinizing hormone-releasing hormone; LoE, level of evidence; MBC , metastatic breast cancer; OS, overall survival; PFS, progression-free survival; QoL, quality of life

ER POSITIVE / HER-2 NEGATIVE MBC

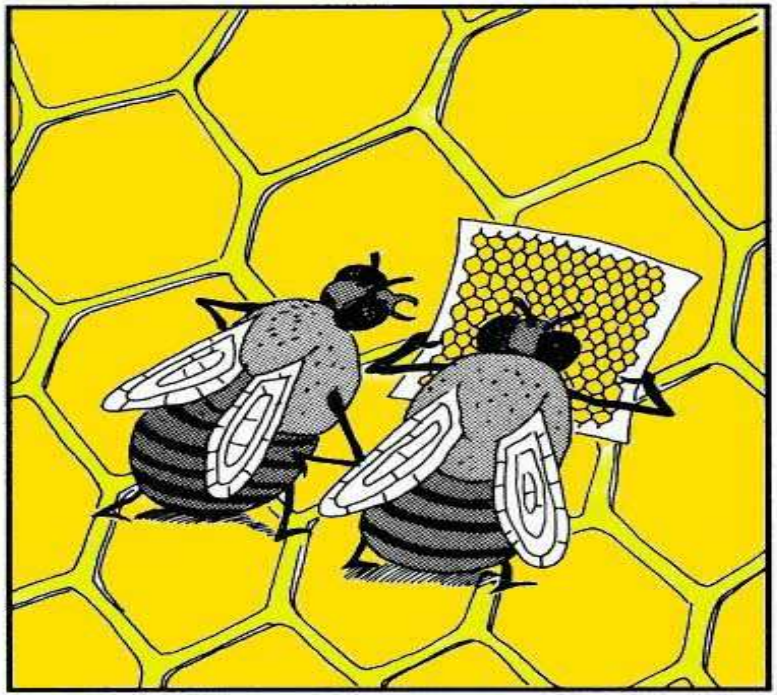
Modified statement

The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it significantly prolongs PFS, albeit without OS benefit.
The decision to treat must take into account the individual relevant toxicities associated with this combination and should be made on a case by case basis. LoE, GoR: [I, B]
Tamoxifen can also be combined with everolimus. LoE, GoR: [II, B]

Notes in manuscript: a) At present, no predictive biomarker exists to identify those patients who will benefit from this approach. b) some studies have shown an excess in mortality with this combination in patients > 70 years-old.

Total # of votes:			**(40)**
1.	**YES:**	**85%**	**(34)**
2.	**NO:**	**2.5%**	**(01)**
3.	**ABSTAIN:**	**12.5%**	**(05)**

AI, aromatase inhibitor; ER, oestrogen receptor; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC , metastatic breast cancer; OS, overall survival; PFS, progression-free survival



So, Where are we exactly?

Optimal therapy in luminal MBC

- Verification of diagnosis and tumour biology by biopsy is recommended
- **Endocrine-based therapy** is the first choice – independent of site of metastasis - unless there is a life-threatening situation (*visceral crisis*) that warrants chemotherapy
- Combination of endocrine agents with targeted agents (CDK 4/6 inhibitors, everolimus) are able to substantially prolong PFS in first and later lines of therapy
- Optimal sequence is yet to be determined as an OS survival advantage has not (yet) been demonstrated for any particular endocrine-based therapy approach
- Therapy for premenopausal patients should be the same as those for postmenopausal patients provided that ovarian suppression is added to endocrine therapy

CDK, cyclin-dependent kinase; MBC , metastatic breast cancer; OS, overall survival; PFS, progression-free survival

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clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012
doi:10.1093/annonc/mds232

Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1,2], N. Harbeck[3], L. Fallowfield[4], S. Kyriakides[5] & E. Senkus[6], on behalf of the ESMO Guidelines Working Group*

[1]European School of Oncology, Milan, Italy; [2]Breast Cancer Unit, Champalimaud Cancer Center, Lisbon, Portugal; [3]Breast Center, Department of Obstetrics and Gynecology, and Comprehensive Cancer Center (CCC LMU), University of Munich, Germany; [4]Brighton and Sussex Medical School, University of Sussex, UK; [5]Europa Donna Cyprus, Cyprus; [6]Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

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ESMO

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