# *Endocrine-based Therapy for ER+/HER2 neg ABC*

**F. Cardoso, MD**

**Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal**

**ESMO Board of Directors & Director of Membership**

**Chair, ABC Global Alliance and ABC Guidelines**

**ESO Breast Cancer Program Coordinator**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

European School of Oncology

Learning to care

ABC GlobAlliance

An ESO initiative

# DISCLOSURES SLIDE

**Financial disclosures**:
*Personal financial interest in form of consultancy role for*: Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, Teva.

*Institutional financial support for clinical trials from*: Amgen, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi, Eisai, Fresenius GmbH, Genentech, GlaxoSmithKline, Ipsen, Incyte, Nektar Therapeutics, Nerviano, Novartis, Macrogenics, Medigene, MedImmune, Merck, Millenium, Pfizer, Pierre-Fabre, Roche, Sanofi-Aventis, Sonus, Tesaro, Tigris, Wilex, Wyeth.

**Non-Financial disclosures**:
Chair ABC Global Alliance and ABC Consensus Conference and Guidelines.
Member/Committee Member of ESMO, ESO, EORTC-BCG, IBCSG, SOLTI, ASCO, AACR, EACR, SIS, ASPIC

# ESO-ESMO ABC4 GUIDELINES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

*Annals of Oncology* 0: 1–24, 2018
doi:10.1093/annonc/mdy192

SPECIAL ARTICLE

## 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†

F. Cardoso[1*], E. Senkus[2], A. Costa[3], E. Papadopoulos[4], M. Aapro[5], F. André[6], N. Harbeck[7], B. Aguilar Lopez[8], C. H. Barrios[9], J. Bergh[10], L. Biganzoli[11], C. B. Boers-Doets[12], M. J. Cardoso[13], L. A. Carey[14], J. Cortés[15], G. Curigliano[16], V. Diéras[17], N. S. El Saghir[18], A. Eniu[19], L. Fallowfield[20], P. A. Francis[21], K. Gelmon[22], S. R. D. Johnston[23], B. Kaufman[24], S. Koppikar[25], I. E. Krop[26], M. Mayer[27], G. Nakigudde[28], B. V. Offersen[29], S. Ohno[30], O. Pagani[31], S. Paluch-Shimon[32], F. Penault-Llorca[33], A. Prat[34], H. S. Rugo[35], G. W. Sledge[36], D. Spence[37], C. Thomssen[38], D. A. Vorobiof[39], B. Xu[40], L. Norton[41] & E. P. Winer[42]

**1300 participants from 88 countries**

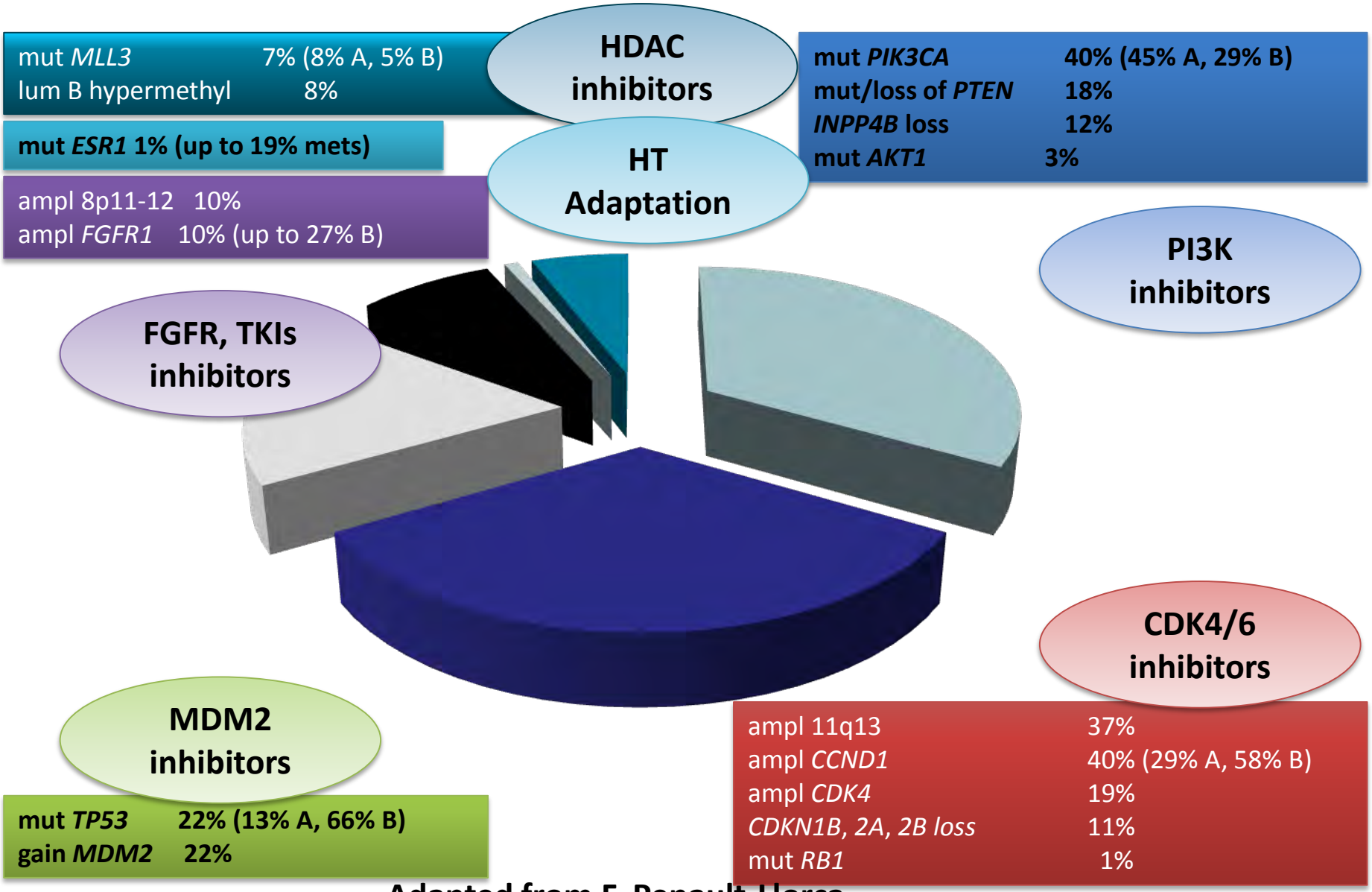
European School of Oncology
learning to care

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

www.abc-lisbon.org

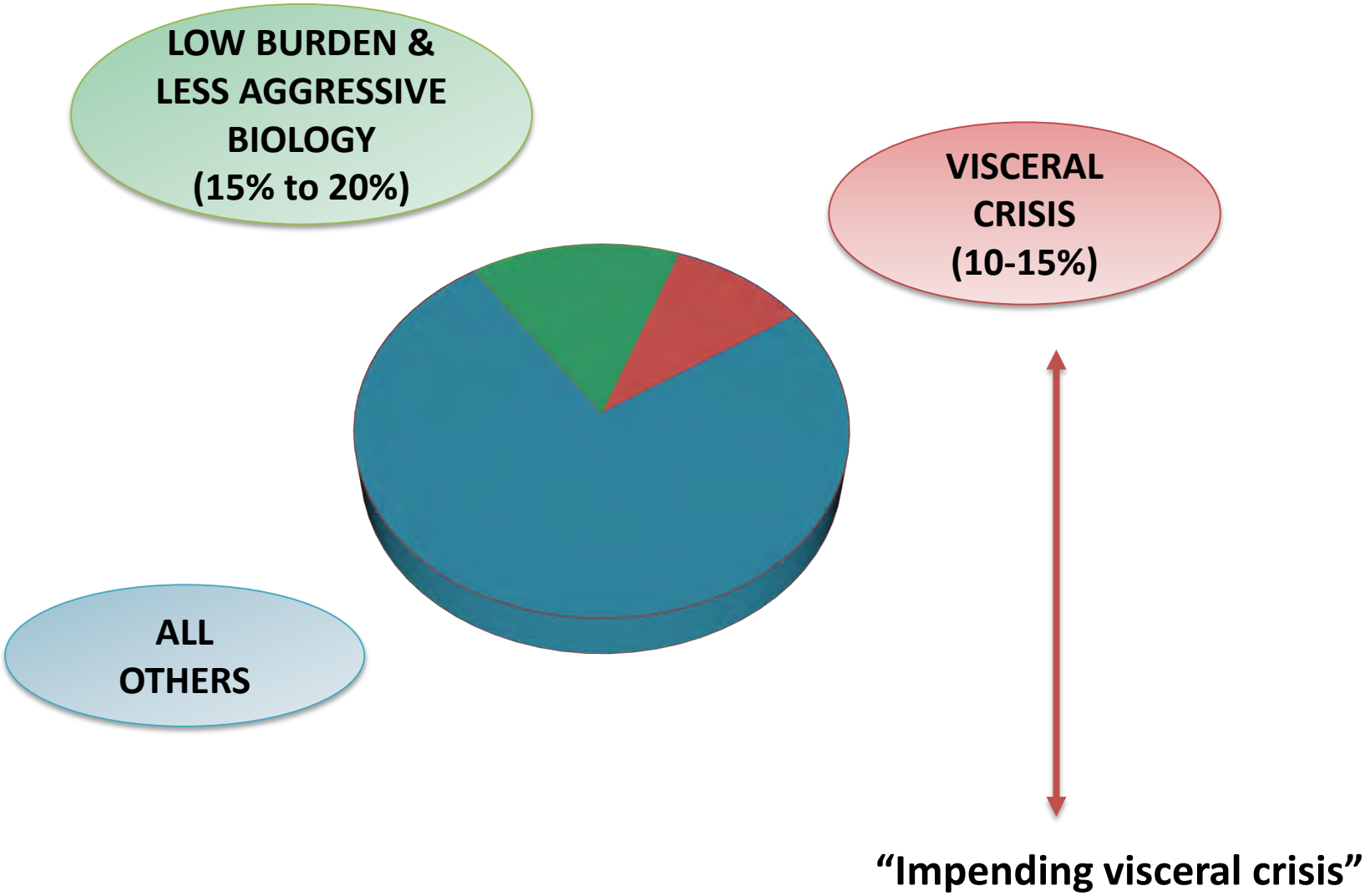
https://oncologypro.esmo.org/Guidelines/

# BIOLOGICAL HETEROGENEITY OF LUMINAL TUMOURS




Adapted from F. Penault-Llorca

# CLINICAL HETEROGENEITY OF LUMINAL TUMOURS
## Implications for therapeutic decisions



# HETEROGENEITY OF LUMINAL TUMOURS

## Implications for therapeutic decisions

- **PATIENT HETEROGENEITY:**
  - **age/menopausal status, preferences, genetics and pharmaco-genomics (and other determinants for toxicity)**
- **DISEASE HETEROGENEITY**
  - **visceral/non-visceral metastases/visceral crisis**
- **TUMOR BIOLOGICAL HETEROGENEITY**
  - **ESR1 mutations, PI3K mutations, AKT/mTOR, HER pathway activation, other resistance mechanisms**

# HETEROGENEITY OF LUMINAL TUMOURS
## Implications for therapeutic decisions

- PATIENT HETEROGENEITY:
  - age/menopausal status, preferences, genetics and pharmaco-genomics (and other determinants for toxicity)
- DISEASE HETEROGENEITY
  - visceral/non-visceral metastases/visceral crisis
- TUMOR BIOLOGICAL HETEROGENEITY
  - **ESR1 mutations, PI3K mutations, AKT/mTOR, HER pathway activation, other resistance mechanisms**

# BIOLOGICAL HETEROGENEITY OF LUMINAL TUMOURS

- The principal characteristic of the luminal group is the **luminal expression signature**, composed of ***ESR1*, *GATA3*, *FOXA1*, *XBP1*, and *cMYB***
  - the most frequent mutations in the **luminal A** subtype are ***PIK3CA* (45%)**, *MAP3K1* (13%), *GATA3* (13%), *TP53* (12%), and *CDH1* (9%)
  - the most frequent mutations in **luminal B** tumors are ***TP53* (29%), *PIK3CA* (29%)**, *GATA3* (13%), and *TTN* (12%)
- In addition to *TP53* mutations, several other events may intervene in other steps of the same pathway, including *ATM* loss and *MDM2* amplification
- **ESR1** mutations (up to 19%) after **AI treatment => resistance**

**Courtesy F. Penault-Llorca**

# Predictive markers for endocrine therapy: Lessons from the early BC setting

- ER (Tam and AIs)
- PgR (Tam and AIs)
- HER-2
- PROLIFERATION (Ki67)
- Bcl-2 (Tam)
- AIB-1 (Tam)
- ER-beta (Tam)
- MTA1s (Tam)
- Cyclin E (Tam)
- Intratumoral Aromatase (AIs)
- Genomic signatures
- *ESR1 mutations*

- HR are the only predictive factors with Level 1 evidence for ET
- NO BIOMARKER CAN HELP DECIDE BETWEEN TAM and AI
- Also no biomarker to decide for or against the use of Fulvestrant

# ESR1 mutations seem to be associated with resistance to AIs

| Biomarker | Clinical studies | Findings (mutant/amplified/loss vs wildtype) |
|---|---|---|
| ESR1 | PALOMA-3 | PALOMA-3: no difference between mut vs wt |
| | SoFEA | SoFEA: treatment less effective in mut vs wt |
| | BOLERO-2 | BOLERO-2: improved OS and PFS in wt vs mut* |
| | Schiavon et al | Schiavon et al: ESR1 mutations predict resistance to subsequent AI therapy** |

*no statistical analysis carried out; **small sample size (n=45); mut = mutant; wt = wildtype

[PALOMA-3] Turner N, presented at ASCO 2016 (abstract 512); [SoFEA] Fribbens et al. J Clin Oncol 2016; 34:2961–2968; [BOLERO-2] Chandarlapaty, presented at SABCS 2015 (abstract S2-07); Schiavon et al. Sci Transl Med 2015;7

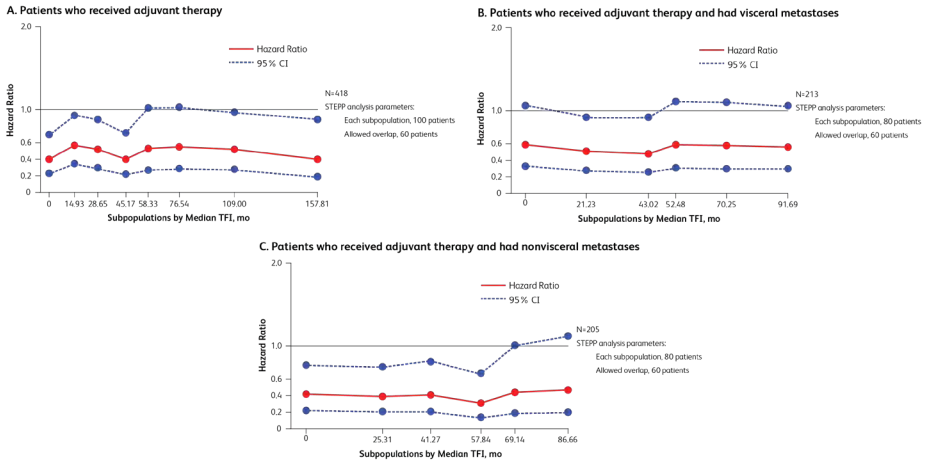
# Many biomarkers have shown little or no association with response to therapy

| Biomarker | Clinical studies | Findings (mutant/amplified/loss vs wildtype) |
|---|---|---|
| PIK3CA | BOLERO-2, PALOMA-3, FERGI | PIK3CA: no significant difference in treatment effect |
| CCND1 | BOLERO-2, PALOMA-1 | CCND1 (BOLERO-2): no significant difference in treatment effect |
| p16 | PALOMA-1 | CCND1/p16 (PALOMA-1): changes in copy number did not improve patient selection beyond ER/HER2 status |
| FGFR | BOLERO-2 | FGFR: no significant difference in treatment effect |

[BOLERO-2] Hortobagyai et al. J Clin Oncol 2016;34:419–429; [PALOMA-3] Cristofanilli et al. Lancet Oncol 2016;17:425–-39; [FERGI] Krop et al. Lancet Oncol 2016;17:811–821 [PALOMA-1] Finn et al. Lancet Oncol 2015; 16:25–35

# Treatment Effect of Palbociclib Plus Endocrine Therapy by Prognostic and Intrinsic Subtype: A Joint Analysis of PALOMA-2 and PALOMA-3

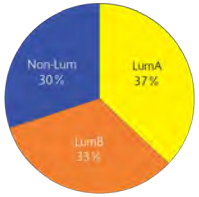
## PALOMA-2 STEPP Analysis

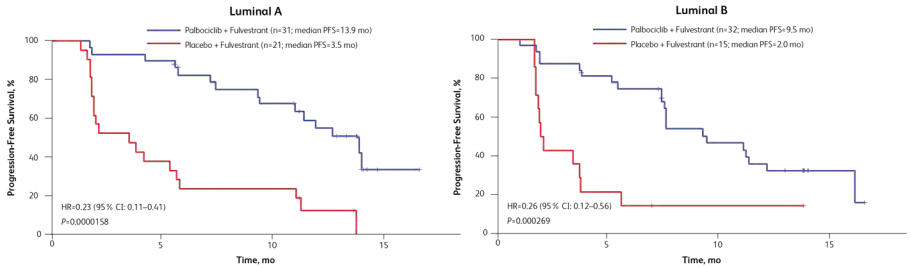



CI=confidence interval; STEPP=Subpopulation Treatment Effect Pattern Plot; TFI=treatment-free interval.

**Degree of benefit** observed was **consistent** across **different lengths of TFI** (PALOMA-2) **or DFI** (PALOMA-3) based on the STEPP analyses, **regardless** of whether patients had **visceral or nonvisceral metastases.**

## PALOMA-3 PFS by Luminal Subtype*



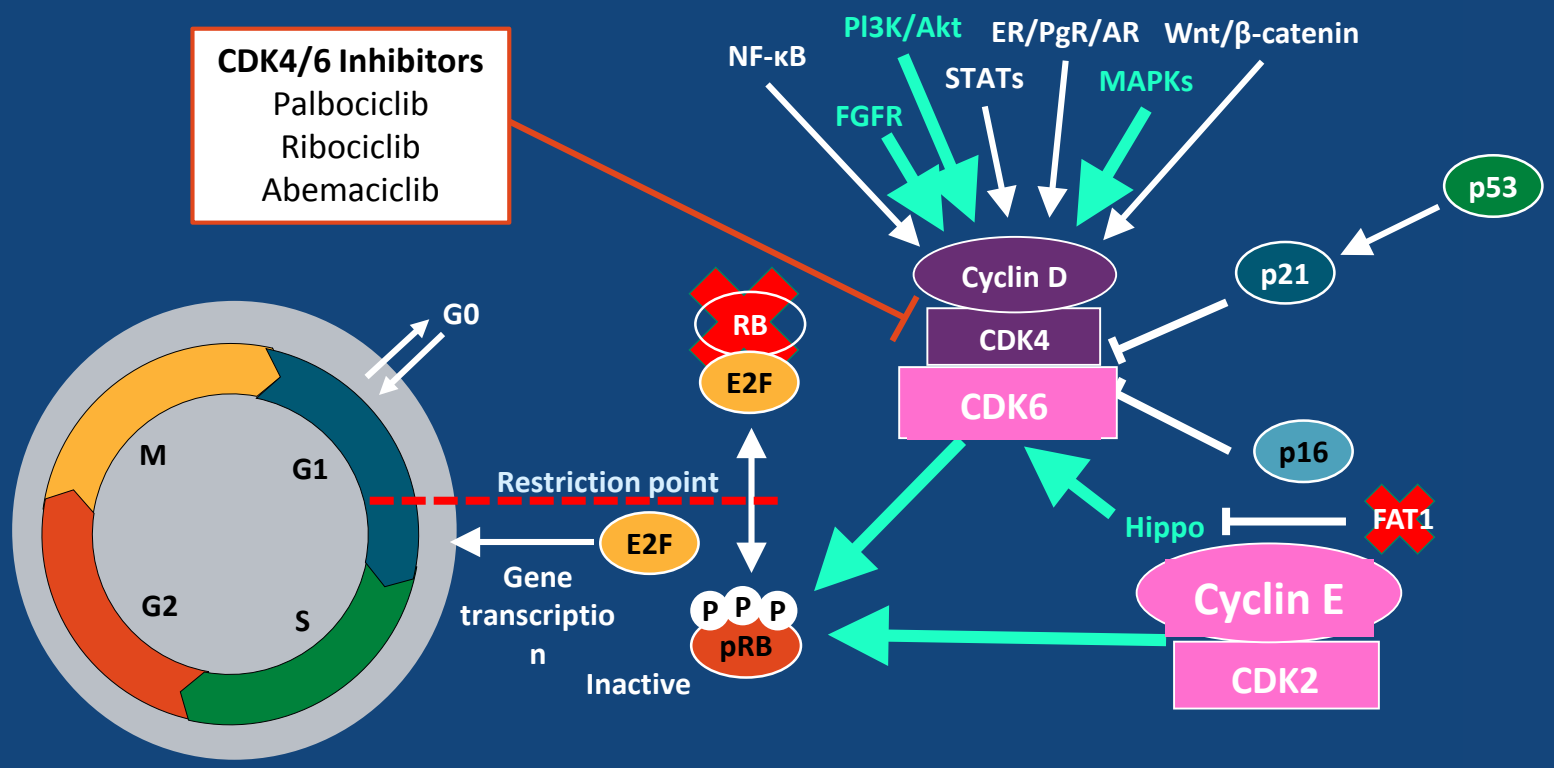




**Luminal A or luminal B tumor subtypes both benefited from palbociclib plus ET**

**N. Turner, ASCO 2018**

*Among patients who provided metastatic disease tumor tissues (n=142).
HR=hazard ratio; LumA=luminal A; LumB=luminal B; Non-Lum=non-luminal; PFS=progression-free survival.

# Mechanisms of Resistance to CDK4/6 Inhibitors





Slides are the property of the author, permission required for reuse.

Adapted from
Slide credit: clinicaloptions.com

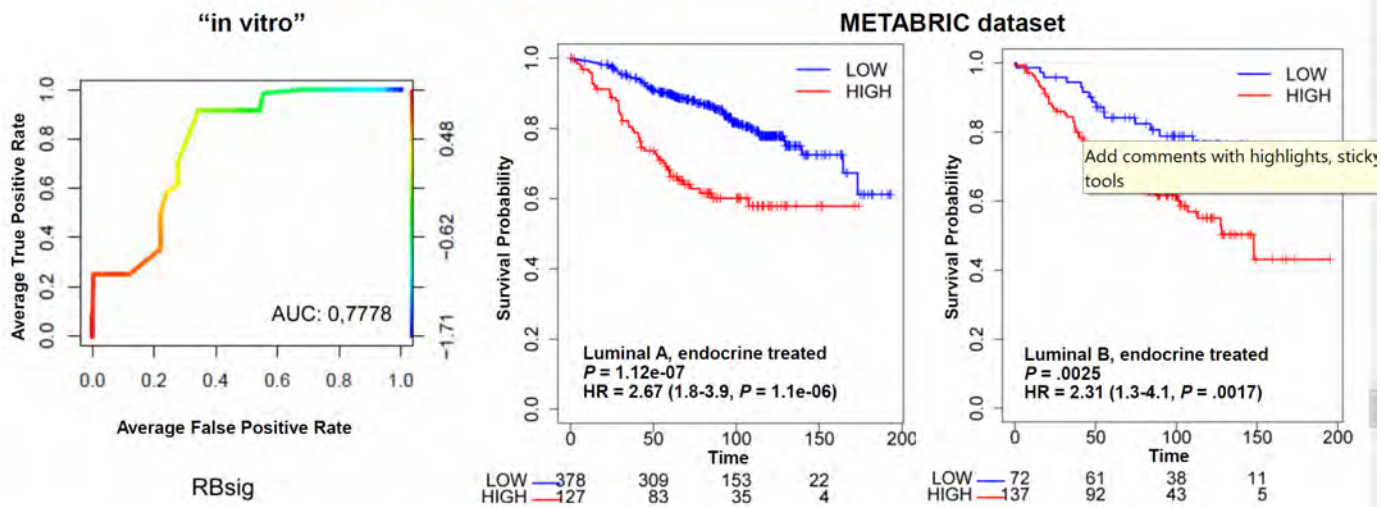
# Potential Mechanisms of Acquired Resistance to CDK4/6 Inhibitors

- RB loss*
- Cyclin E1 over-expression*
- Lineage plasticity** (via epigenetics)

→ sensitivity to CDK4/6 inhibitors may potentially be retained

* Herrera-Abreu MT, et al. *Cancer Res.* 2016;76(8):2301-2313. ** Liu T, et al. *Nat Commun.* 2017;8:13923. Mu P, et al. *Science.* 2017;355(6320):84-88.

# The RBsig Predicts Resistance to Palbociclib *In Vitro* and Clinical Outcome




Malorni L, et al. *Oncotarget.* 2016;7(42):68012-68022.

# P. Bedard Discussion at ASCO 2019

- Understanding of CDK4/6 inhibitor resistance has rapidly advanced
- Multiple genomic biomarkers identify patients at risk of early progression
  - **No clinically validated markers for treatment selection**
- ***RB1* mutation** is the most identifiable mechanism of acquired resistance (~10%)
  - Implications for trials testing CDK4/6 inhibitor beyond progression
  - Induces cell cycle vulnerabilities that can be targeted
  - Monitoring of clonal dynamics will be important
- **Endocrine resistance alterations** can also be identified
  - ***PIK3CA* mutation, *FGFR1*$^{amp}$, *ESR1* mutation** – improved upfront therapy?
- For most patients, acquired CDK4/6 inhibitor resistance mechanisms are unexplained
  - Selection pressures in earlier lines of therapy may be different


Slides are the property of the author, permission required for reuse.

# ER POSITIVE / HER-2 NEGATIVE MBC

**At present, no validated predictive biomarker other than hormone receptor status exist to identify patients who will/will not benefit from the addition of a targeted agent (i.e. CDK4/6 inhibitor, mTOR inhibitor) to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.**

**(LoE/GoR: I/E) (95%)**

# HETEROGENEITY OF LUMINAL TUMOURS

## Implications for therapeutic decisions

- **PATIENT HETEROGENEITY:**
  - **age/menopausal status, preferences, genetics and pharmaco-genomics (and other determinants for toxicity)**
- **DISEASE HETEROGENEITY**
  - **visceral/non-visceral metastases/visceral crisis**
- **TUMOR BIOLOGICAL HETEROGENEITY**
  - **ESR1 mutations, PI3K mutations, AKT/mTOR, HER pathway activation, other resistance mechanisms**

**VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.**

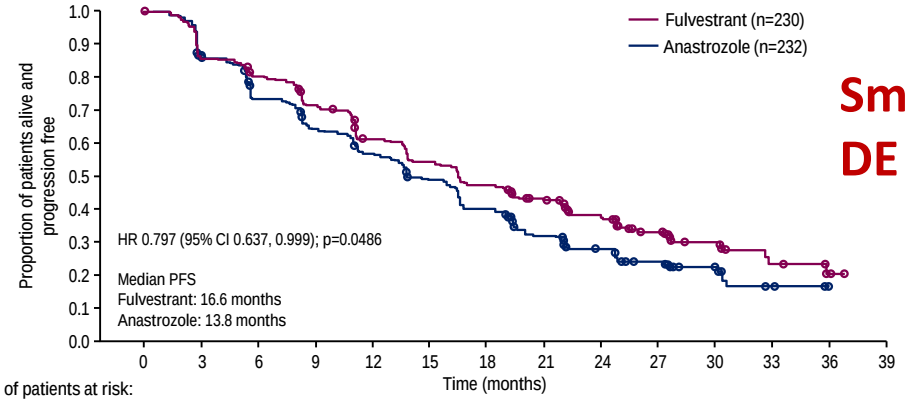
**Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.**

**(LoE: Expert opinion) (95%)**

**UPDATED DEFINITION AT ABC 5**
**Including "impending visceral crisis"**

**ESTIMATION OF % OF PATIENTS: 10 to 15%**

## FALCON: PRIMARY ENDPOINT, PFS




Number of patients at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fulvestrant | 230 | 187 | 171 | 150 | 124 | 110 | 96 | 81 | 63 | 44 | 24 | 11 | 2 | 0 |
| Anastrozole | 232 | 194 | 162 | 139 | 120 | 102 | 84 | 60 | 45 | 31 | 22 | 10 | 0 | 0 |

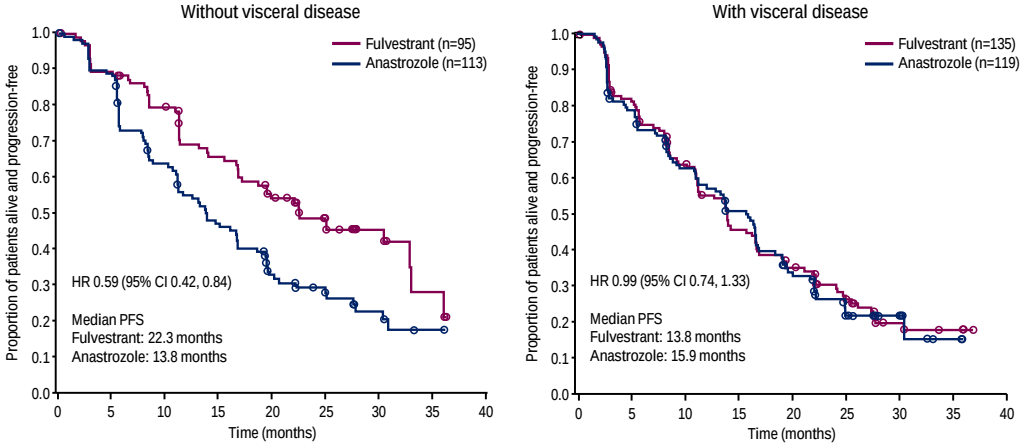
A circle represents a censored observation

**Small PFS benefit for Fulvestrant**
**DE NOVO BC (what if AI pre-treated?)**

**WHY?**
**No known biological rationale**
**Subgroup analysis?!**

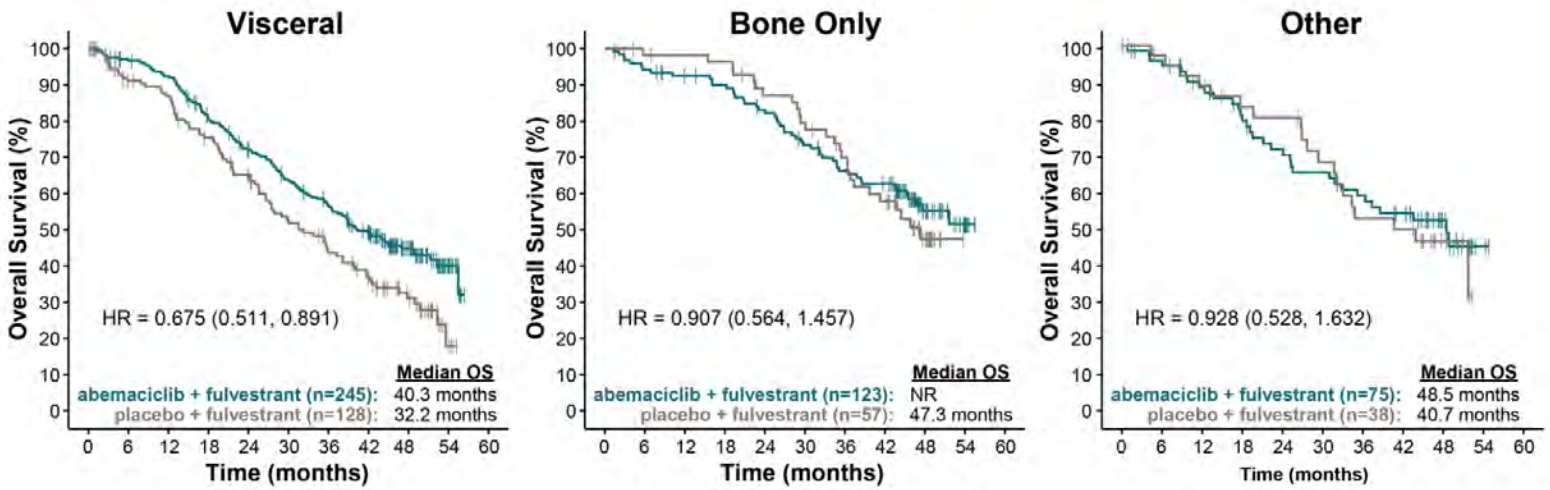
**But…**
**more data at ESMO 2019…**

## FALCON: PFS IN PATIENTS WITH OR WITHOUT VISCERAL DISEASE




Post hoc interaction test p<0.01
A circle represents a censored observation

# Overall Survival by Metastatic Site[a]
## MONARCH 2




[a]Interaction P-value: 0.424

© 2019 Eli Lilly and Company

**Reversed curves!**

**Why does Fulvestrant seem to be specifically efficacious for bone metastases? (Research question)**

Sledge et al, ESMO 2019

# ER POSITIVE / HER-2 NEGATIVE ABC

**Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.**
**(LoE/GoR: Expert Opinion/A) (95%)**

**Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women, and men.**
**(LoE/GoR: Expert Opinion/A) (92%)**

# MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

- Pre/perimenopausal women with HR+, HER2– ABC
- No prior endocrine therapy for advanced disease
- ≤1 line of chemotherapy for advanced disease
- N=672

Randomization (1:1)

*Stratified by:*
- *Presence/absence of liver/lung metastases*
- *Prior chemotherapy for advanced disease*
- *Endocrine therapy partner (tamoxifen vs NSAI)*

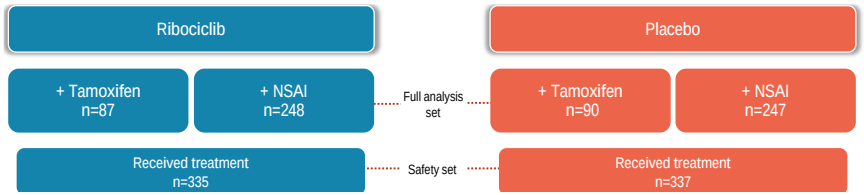
**Ribociclib** (600 mg/day; 3-weeks-on/1-week-off) + tamoxifen/NSAI + goserelin* n=335

**Placebo** + tamoxifen/NSAI + goserelin* n=337

**Primary endpoint**
- PFS (locally assessed per RECIST v1.1)‡

**Secondary endpoints**
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety
- Patient-reported outcomes

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients




± 40% de novo

± 57% visceral mets

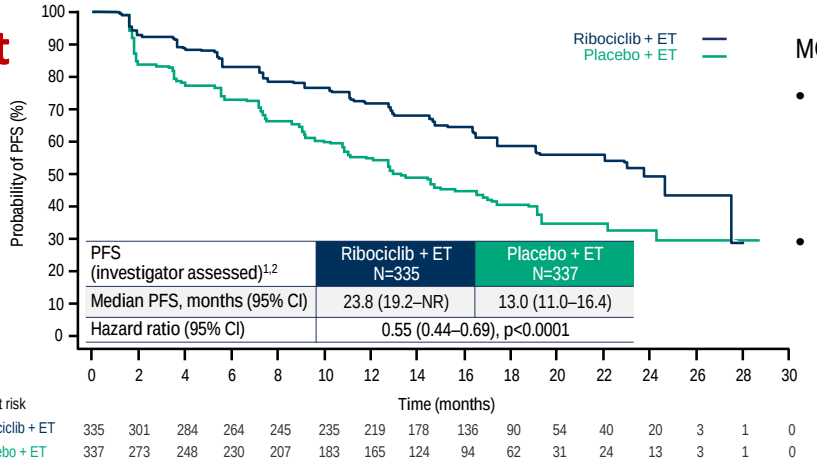
NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.

1. Klijn JG, *et al. J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al. J Clin Oncol* 2001;19:2596–2606.

This presentation is the intellectual property of Debu Tripathy.
Contact DTripathy@mdanderson.org for permission to reprint and/or distribute.

## MONALEESA-7: RESULTS

**± 10 ms PFS benefit**




| PFS (investigator assessed)[1,2] | Ribociclib + ET N=335 | Placebo + ET N=337 |
|---|---|---|
| Median PFS, months (95% CI) | 23.8 (19.2–NR) | 13.0 (11.0–16.4) |
| Hazard ratio (95% CI) | 0.55 (0.44–0.69), p<0.0001 | |

MONALEESA-7:

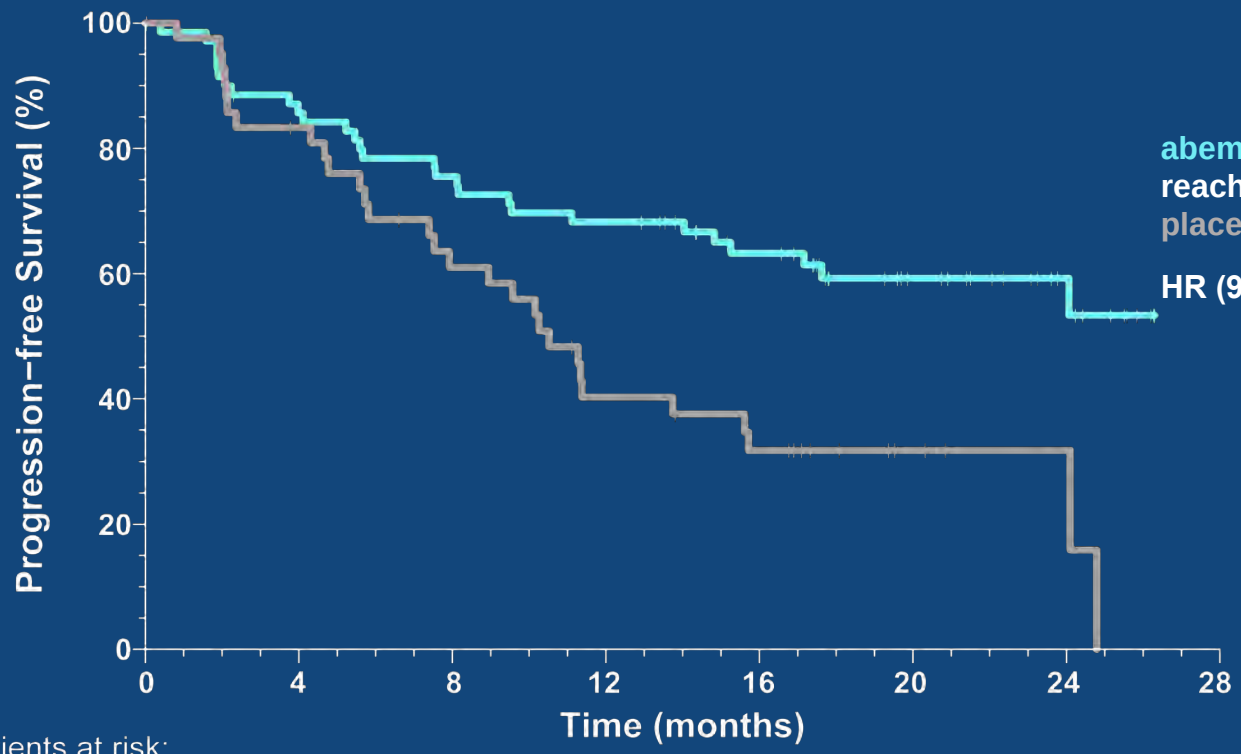
- Ribociclib + ET reduced the risk of progression by 45% vs the placebo arm (p<0.0001)[1,2]
- Manageable safety profile consistent with prior studies of ribociclib[1,2]

D. Tripatthy, SABCS 2017
N. Harbeck, ESMO 2018

CI, confidence interval; NR, not reached.

1. Tripathy D et al. SABCS 2017;abst GS2-05 (oral); 2. Tripathy D et al. *Lancet Oncol* 2018;19:904–915.

# MONARCH 2: PFS in Pre/Peri-menopausal Population




**Median PFS**

**abemaciclib + fulvestrant: not reached**

**placebo + fulvestrant: 10.5 months**

**HR (95% CI): .446 (.264, .754) p=.002**

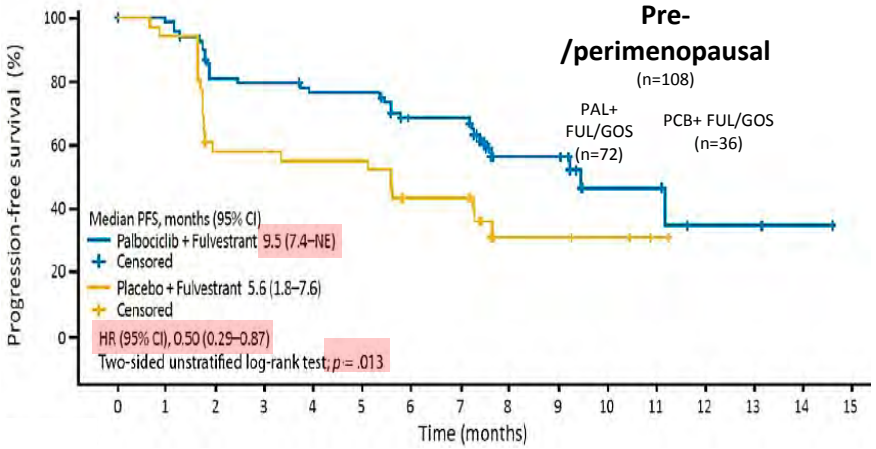
Patients at risk:

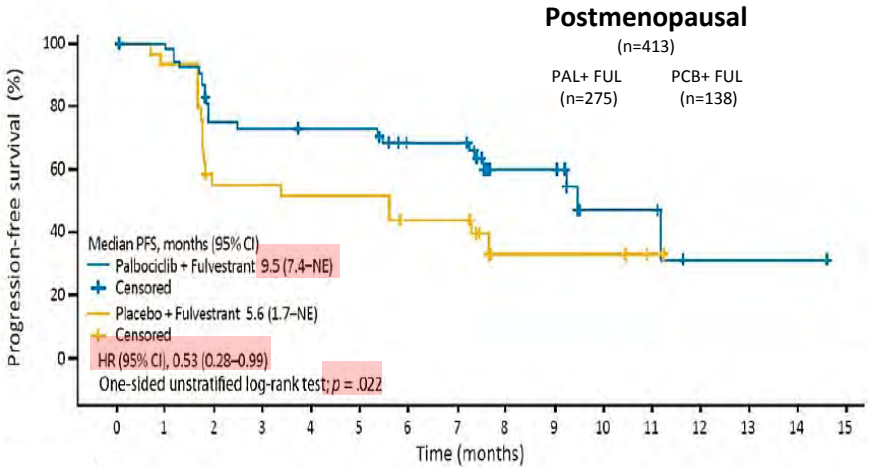
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| abemaciclib | 72 | 59 | 52 | 47 | 36 | 20 | 10 | 0 |
| placebo | 42 | 34 | 24 | 15 | 11 | 4 | 2 | 0 |

**PFS benefit confirmed by blinded independent central review HR: .432; 95% CI: .236, .793 p< .005**


Slides are the property of the author, permission required for reuse.

# PALBOCICLIB + FULVESTRANT SIGNIFICANTLY IMPROVED PFS IN PRE-/PERIMENOPAUSAL WOMEN WITH HR+/HER2- MBC, CONSISTENT WITH THE BENEFIT OBSERVED IN POSTMENOPAUSAL WOMEN, AND WITH THAT SEEN IN THE OVERALL POPULATION




Loibl et al, The Oncologist 2017;22:1–11, "Palbociclib Combined with Fulvestrant in PremenopausalWomen with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results"

# ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF ABC

**Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is not always effective and therefore is the least preferred option). (LoE/GoR: I/A) (85%)**
**If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. (LoE/GoR: II/B) (85%)**

**Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, specially if an AI is administered. (LoE/GoR: Expert Opinion/B)**

**As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient's wish for potentially preserving fertility, compliance with frequent injections over along period of time, and cost.**

## Are there ready-to-use (bio)markers to individualize therapeutic decisions?

- None ready for clinical practice yet!
- So, how do we choose?

## HOW TO TREAT ER+/HER-2 neg (LUMINAL) ABC:

**MAIN QUESTIONS:**

1. Do we need Chemotherapy (CT)?
2. If Endocrine Therapy (ET) which agent?
3. Is a targeted agent also necessary or is ET alone sufficient?
4. If CT: combination vs. sequential monotherapy?
5. If CT: which agent(s)?

## 1st QUESTION

## Is CT needed?

ABC4

# ER POSITIVE / HER-2 NEGATIVE MBC

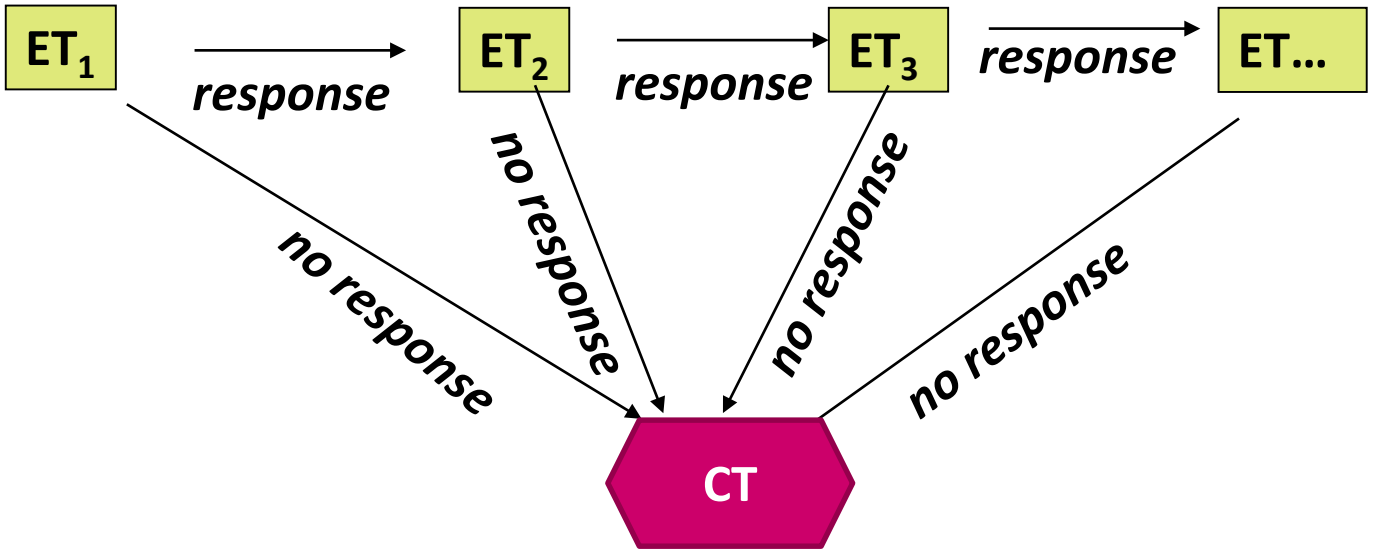
**Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.**

**(LoE/GoR: I/A) (93%)**

**ALL guidelines are in agreement for this recommendation**

# ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

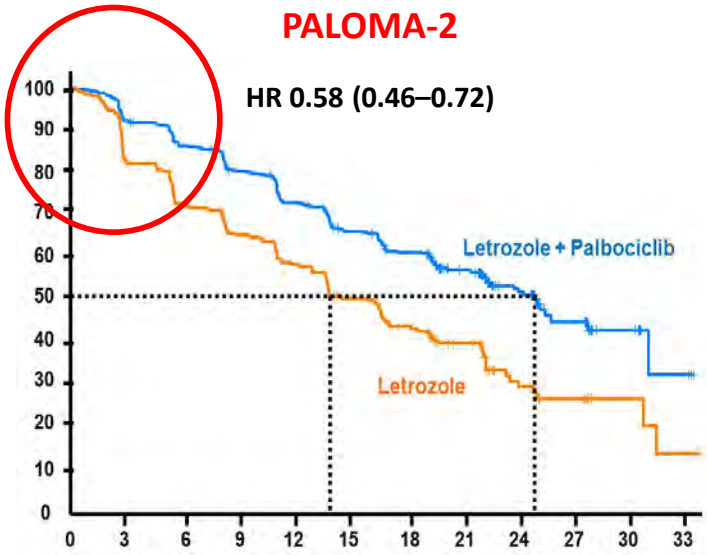
## ENDOCRINE TREATMENT STRATEGY

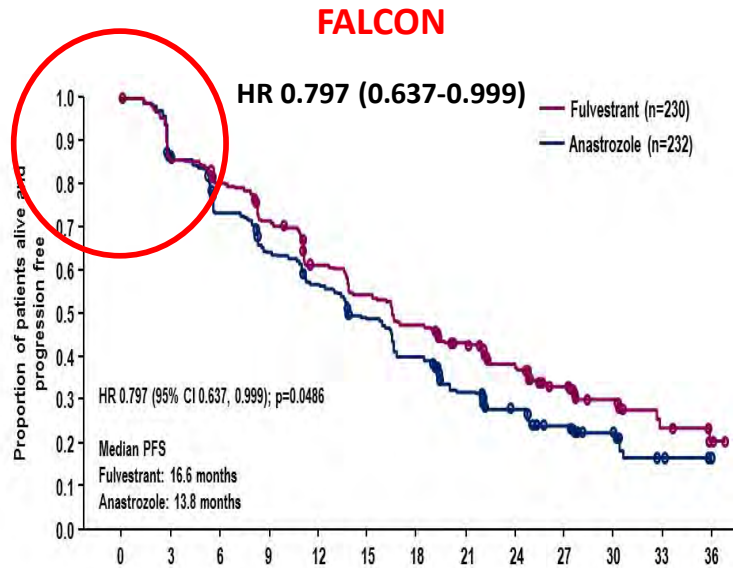



**MAIN RESEARCH QUESTION: OPTIMAL SEQUENCE**

Image adapted from Senkus & Cardoso F, et al. *Ann Oncol*. 2013, ESMO GUIDELINES

# MAIN CHALLENGE:
# Identify small percentage of "fast progressors"




COPENHAGEN 2016 ESMO congress

Finn et al. ESMO 2016, LBA-15; Ellis et al. ESMO 2016, LBA-14

**Courtesy Peter Schmid, ESMO 2016, Discussant**

## 2nd and 3rd QUESTIONS

**Can ET alone be given or should combination with a targeted agent be considered?**

**Which agents to use?**

# ER POSITIVE / HER-2 NEGATIVE MBC

**The preferred 1st line ET *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) (84%)**

*** for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

# ER POSITIVE / HER-2 NEGATIVE ABC

**The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.**

**OS results are still awaited. QoL was comparable to that with ET alone.**

**(LoE/GoR : I/A) (90%)**

**ESMO-MCBS: 3**

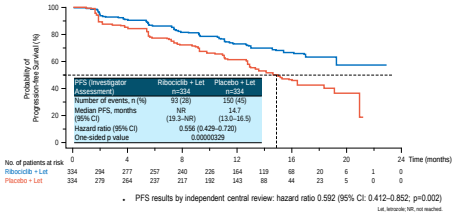
*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

**ATTENTION: WILL BE UPDATED AT ABC5 IN VIEW OF OS RESULTS OF MONALEESA 7 AND OTHER CDKi TRIALS (ESMO 2019)**

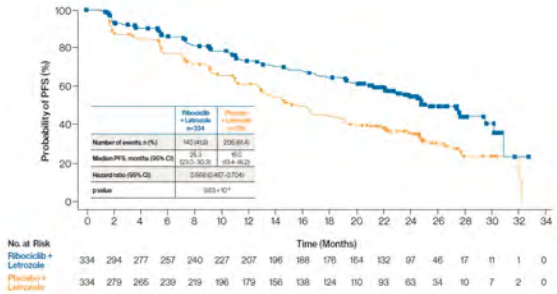
# 1st Line CDK 4/6 INHIBITORS: EFFICACY

# Consistent ± 10 MONTHS BENEFIT IN PFS

MONALEESA 2: PRIMARY ENDPOINT WAS MET EARLY

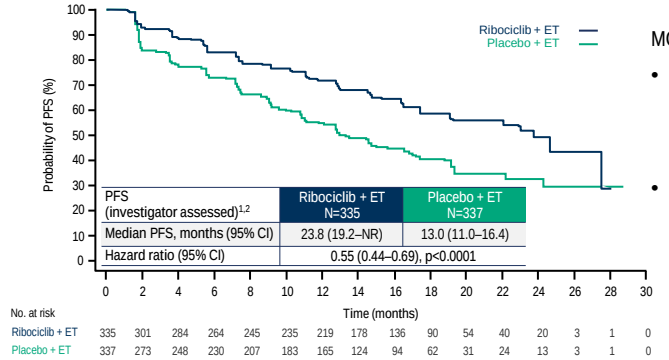



## Monaleesa 2 - Updated results ASCO 2017




Hortobagyi et al, ESMO 2016, updated ASCO 2017
NEJM 2017

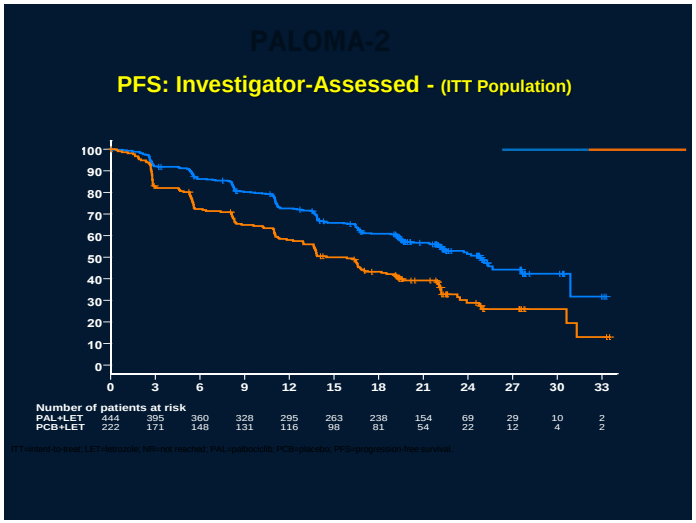
## MONALEESA-7: RESULTS



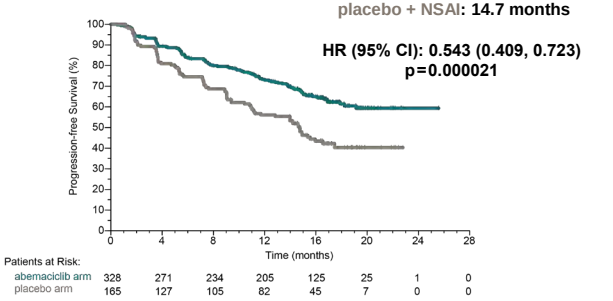

MONALEESA-7:

- Ribociclib + ET reduced the risk of progression by 45% vs the placebo arm (p<0.0001)[1,2]
- Manageable safety profile consistent with prior studies of ribociclib[1,2]

CI, confidence interval; NR, not reached.
1. Tripathy D et al. SABCS 2017;abst GS2-05 (oral); 2. Tripathy D et al. *Lancet Oncol* 2018;19:904–915.




## MONARCH 3: Primary Endpoint: PFS (ITT)




PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p=0.000102

Di Leo et al, ESMO 2017

# 1st Line CDK 4/6 INHIBITORS: EFFICACY

## OS BENEFIT

# MONALEESA-7 Study Design

**First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients**

Pre/perimenopausal women[a] with HR+/HER2− ABC

No prior ET for ABC[b]
≤ 1 prior CT for ABC

N = 672

→ Randomized 1:1 →

**Ribociclib**
600 mg/day;
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 335

**Placebo**
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 337

**Primary endpoint**
- PFS (local)

**Key secondary endpoint**
- OS

**Select secondary endpoints**
- HRQOL
- ORR
- TTDD of ECOG PS
- Safety

**Stratification Factors**
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

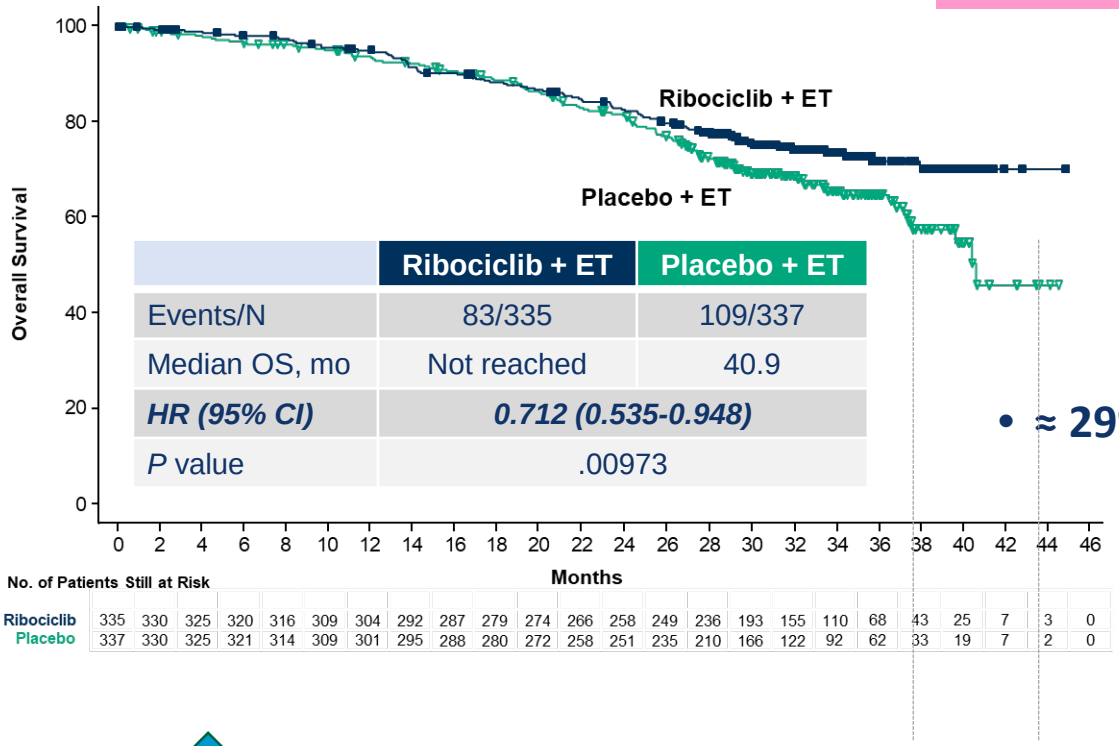
**S. Hurvitz, ASCO 2019**

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.
[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.


Slides are the property of the author, permission required for reuse.

# Overall Survival

**RIBOCICLIB 1st line Pre-menopausal:**
**MCBS: ?**




| | Ribociclib + ET | Placebo + ET |
|---|---|---|
| Events/N | 83/335 | 109/337 |
| Median OS, mo | Not reached | 40.9 |
| ***HR (95% CI)*** | ***0.712 (0.535-0.948)*** | |
| *P* value | .00973 | |

- **≈ 29% relative reduction in risk of death**

**Interesting shape of the curve!**

**Hypothesis: acquired resistance to ET?**

**Landmark Analysis (3.5 years)**

| Kaplan-Meier Estimate | Ribociclib + ET | Placebo + ET |
|---|---|---|
| 36 months | 71.9% | 64.9% |
| ***42 months*** | ***70.2%*** | ***46.0%*** |

# Evaluation form 2a: for therapies that are not likely to be curative with primary endpoint OS

IF median OS with the standard treatment >24 months

| | Mark with X if relevant |
|---|---|
| **Grade 4** | |
| HR ≤0.70 AND Gain ≥9 months | |
| Increase in 5 year survival alone ≥10% | |
| **Grade 3** | |
| HR ≤0.70 AND Gain ≥6 - <9 months | |
| **Grade 2** | |
| HR ≤0.70 AND Gain ≥4 - <6 months | |
| HR >0.70-0.75 AND Gain ≥4 months | |
| **Grade 1** | |
| HR >0.75 OR Gain <4 months | |

**RIBOCICLIB IN ML7**

**HR: 0.712**

**Absolute gain: Not yet possible to calculate**

**5-year survival no yet reached**

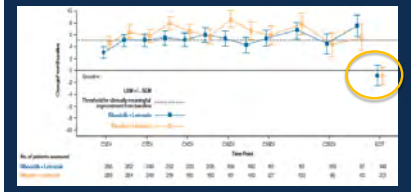
**NEED FOR A LONGER FU (≥ 60 ms)**

**RIBOCICLIB 1st line Pre-menopausal:**
**Efficacy score: 3 (PFS)**
**Improved QoL**
**MCBS: still a 4 but ….**

# 1st Line CDK 4/6 INHIBITORS: IMPACT ON QoL

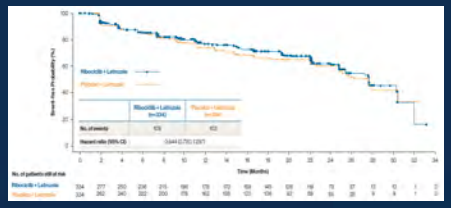
## Only 1 study showed improved QoL (ML7). Why?

### HR QoL Monaleesa 2 (no significant differences)



Time to definitive deterioration of the global health status/QoL scale score of the EORTC QLQ-C30 questionnaire by at least 10%

Change From Baseline in Global Health Patient-reported Outcomes, by Treatment Arm –EORTC QLQ-C30 Questionnaire



PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

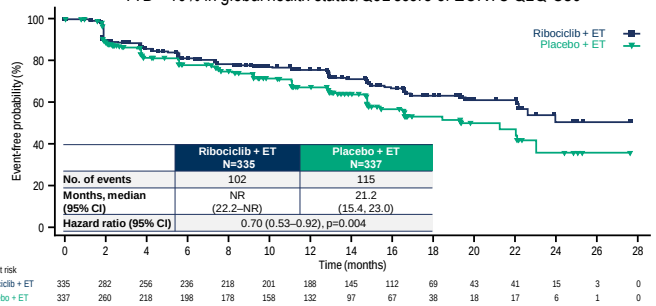
Slides are the property of the author. Permission required for reuse.

Verma et al. ASCO 2017

**TTD ≥10% IN GLOBAL HRQ**oL WAS DELAYED WITH RIBOCICLIB VS PLACEBO

MONALEESA-7

TTD ≥10% in global health status/QoL score of EORTC QLQ-C30[a,b]




| | Ribociclib + ET N=335 | Placebo + ET N=337 |
|---|---|---|
| No. of events | 102 | 115 |
| Months, median (95% CI) | NR (22.2–NR) | 21.2 (15.4, 23.0) |
| Hazard ratio (95% CI) | 0.70 (0.53–0.92), p=0.004 | |

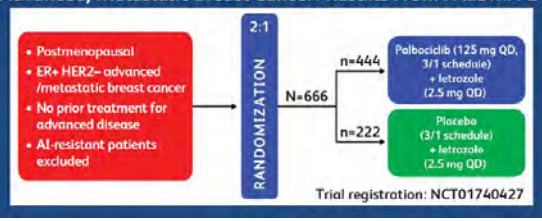
N. Harbeck et al, ESMO 2018

MUNICH 2018 ESMO congress

[a]Patients censored at progression; [b]Similar results obtained with TTD ≥5%, ≥10%, and ≥15%.

Abstract ID 2627: Rugo et al

**Impact of Palbociclib Plus Letrozole on Health-Related Quality of Life Compared With Letrozole Alone in Treatment-Naive Postmenopausal Patients With ER+ HER2– Advanced/Metastatic Breast Cancer: Results From PALOMA-2**




**Abemaciclib: no QoL yet reported**

**Initial QoL Presentation: no difference in QoL!**

# 1st Line CDK 4/6 INHIBITORS: ESMO-MCBS Score

**Evaluation form 2b:** non-curative intent, primary endpoint **PFS**

Efficacy

| 3 | 2 | 1 |
|---|---|---|
| X | | |

**Toxicity and QoL adjustment when only a PFS improvement**

**PALBOCICLIB 1st line:**
Efficacy score: 3 (PFS)
No improved QoL
**MCBS = 3**

**ABEMACICLIB 1st line:**
Efficacy score: 3 (PFS)
No QoL reported
**MCBS = 3**

**RIBOCICLIB 1st line Post-menopausal:**
Efficacy score: 3 (PFS)
No improved QoL
**MCBS: 3**

**RIBOCICLIB 1st line Pre-menopausal:**

Efficacy score: 3 (PFS & OS)
Improved QoL
**MCBS: 4**

# ER POSITIVE / HER-2 NEGATIVE ABC

**The addition of a CDK4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6 to 7 months) as well as improvement of QoL, and is one of the preferred treatment options, if a CDK4/6 inhibitor was not previously used.**

**OS results are awaited.**

**(LoE/GoR : I/A) (90%)**

**ESMO-MCBS: 4**

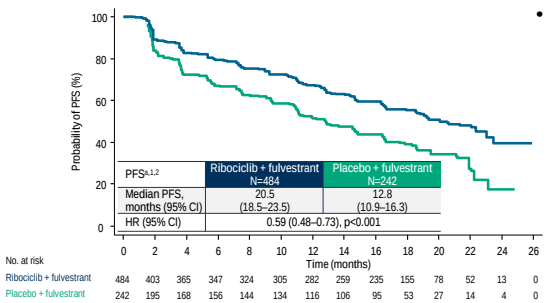
*** For pre and peri with OFS/OFA, and post-menopausal women and men**

**ATTENTION: WILL BE UPDATED AT ABC5 IN VIEW OF OS RESULTS OF PALOMA 3 AND OTHER CDKi TRIALS (ESMO 2019)**

# 2nd Line CDK 4/6 INHIBITORS: EFFICACY

# Consistent 6.5 TO 7.5 MONTHS BENEFIT IN PFS

MONALEESA-3: FINAL PFS

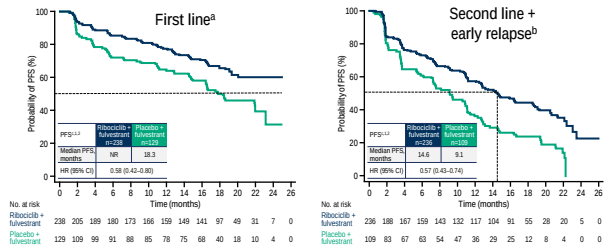



- Ribociclib + fulvestrant reduced the risk of progression by 41% vs placebo + fulvestrant (p<0.001)[1,2]

P. Fasching, ESMO 2018

CI, confidence interval; HR, hazard ratio.
[a]Investigator assessed.
1. Slamon DJ et al. ASCO 2018;abst 1000 (oral); 2. Slamon DJ et al. *J Clin Oncol* 2018;36:2465–2472.

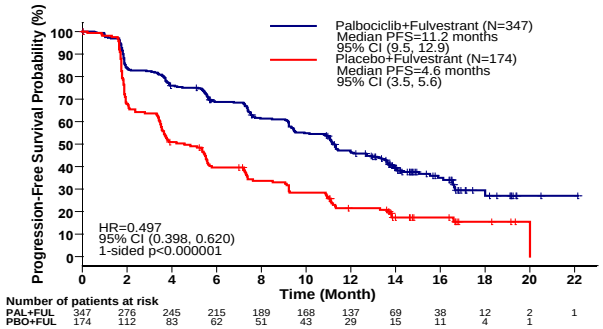
**PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS**

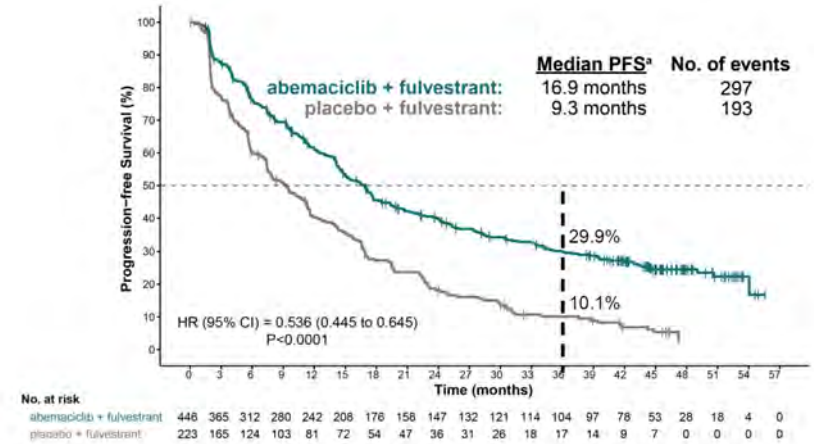



P. Fasching, ESMO 2018

[a]No prior endocrine therapy for ABC.
[b]Up to one line of prior endocrine therapy for ABC or relapse on/within 12 months of (neo)adjuvant endocrine therapy; [a]Investigator assessed.
1. Slamon DJ et al. ASCO 2018;abst 1000 (oral); 2. Slamon DJ et al. *J Clin Oncol* 2018;36:2465–2472.

# MONARCH 2 UPDATED PFS (ESMO 2019)



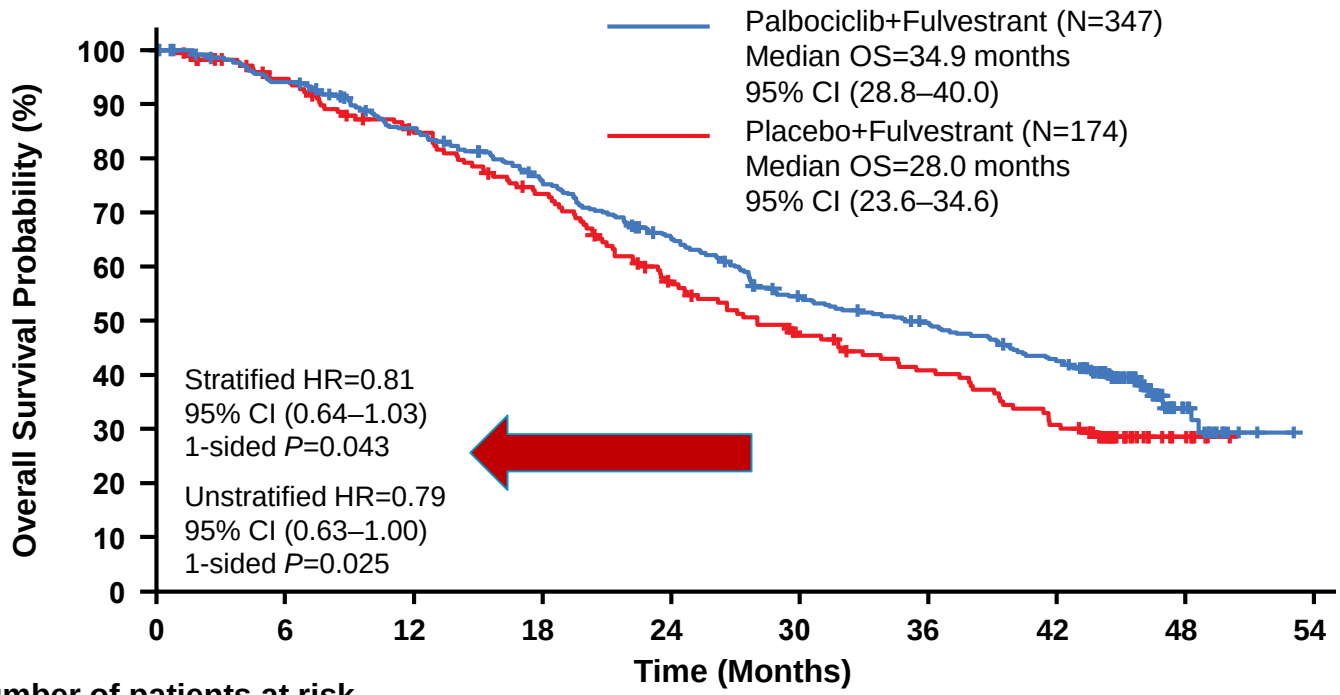

© 2019 Eli Lilly and Company

[a]PFS results at primary analysis: Median: 16.4 vs 9.3 months (HR: 0.553; 95% CI: 0.449, 0.681; P<0.001), 222 events abemaciclib arm vs 157 events placebo arm

# 2nd Line CDK 4/6 INHIBITORS: EFFICACY

## OS BENEFIT

### OS IN PALOMA-3 (ITT)




**Number of patients at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **PAL+FUL** | 347 | 321 | 286 | 247 | 209 | 165 | 148 | 126 | 17 |
| **PBO+FUL** | 174 | 155 | 135 | 115 | 86 | 68 | 57 | 43 | 7 |

**Absolute improvement in median OS was 6.9 months**

**BUT**

**NOT STATISTICALLY SIGNIFICANT**

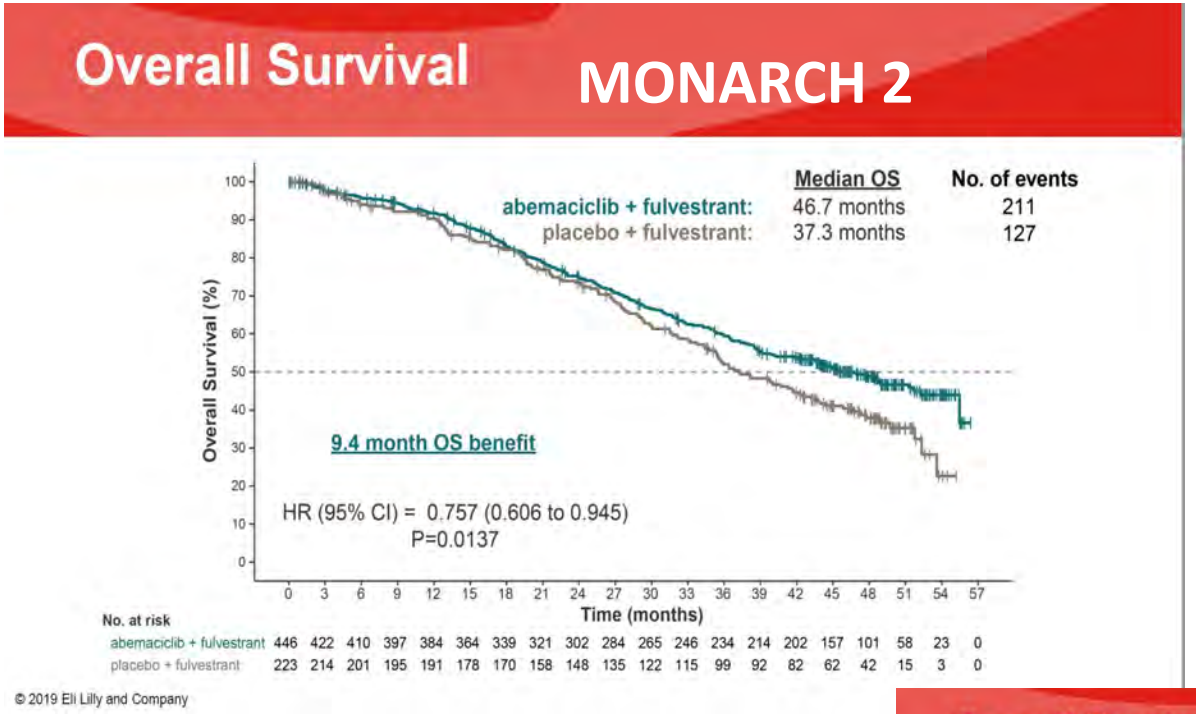
MUNICH 2018 ESMO congress

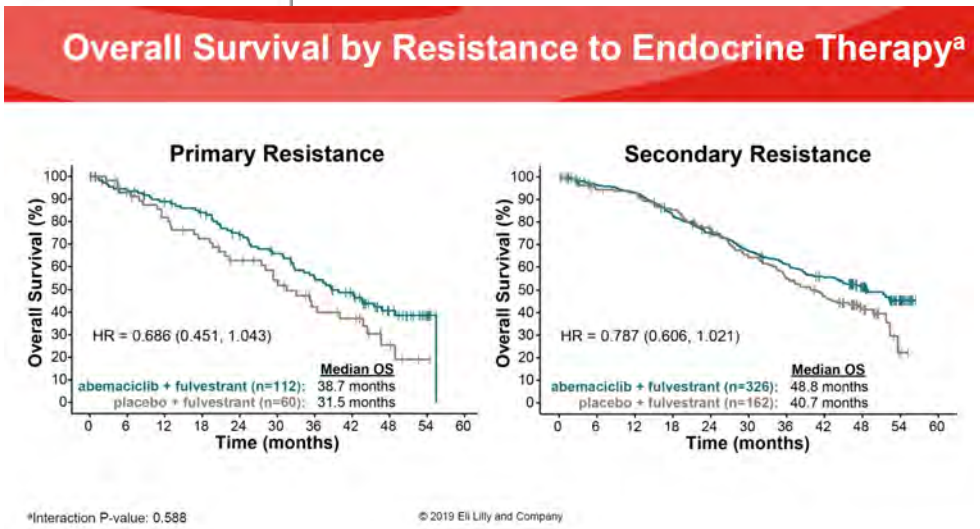
**Cristofanilli et al, ESMO 2018**

# 2nd Line CDK 4/6 INHIBITORS: EFFICACY

## OS BENEFIT

Sledge et al, ESMO 2019



# Evaluation form 2a: for therapies that are not likely to be curative with primary endpoint OS

IF median OS with the standard treatment >24 months

| | Mark with X if relevant |
|---|---|
| **Grade 4** | |
| HR ≤0.70 AND Gain ≥9 months | |
| Increase in 5 year survival alone ≥10% | |
| **Grade 3** | |
| HR ≤0.70 AND Gain ≥6 - <9 months | |
| **Grade 2** | |
| HR ≤0.70 AND Gain ≥4 - <6 months | |
| HR >0.70-0.75 AND Gain ≥4 months | |
| **Grade 1** | |
| HR >0.75 OR Gain <4 months | |

**ABEMACICLIB IN MON 2**

**HR: 0.757**

**Absolute gain: 9.4 ms**

**5-year survival no yet reached**

**NEED FOR A LONGER FU (≥ 60 ms)**

**ABEMACICLIB 2nd line:**

**Efficacy score: 3 (PFS & OS)**

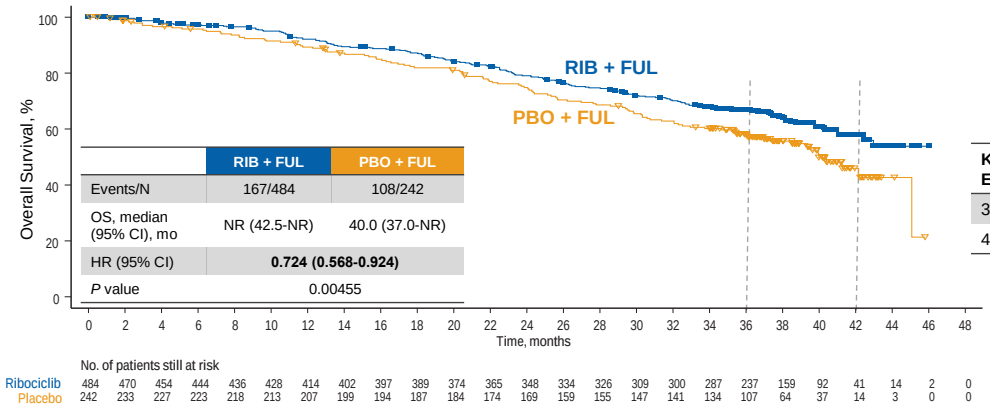
**Waiting for QoL**

**MCBS = 3**

# MONALEESA-3 Trial
# OS results with median FU of 39.4 months

## Overall Survival

*The reduction in relative risk of death with RIB was 28%*




| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 167/484 | 108/242 |
| OS, median (95% CI), mo | NR (42.5-NR) | 40.0 (37.0-NR) |
| HR (95% CI) | **0.724 (0.568-0.924)** | |
| *P* value | 0.00455 | |

**Landmark Analysis**

| KM Estimate | RIB + FUL | PBO + FUL |
|---|---|---|
| 36 months | 67.0% | 58.2% |
| 42 months | 57.8% | 45.9% |

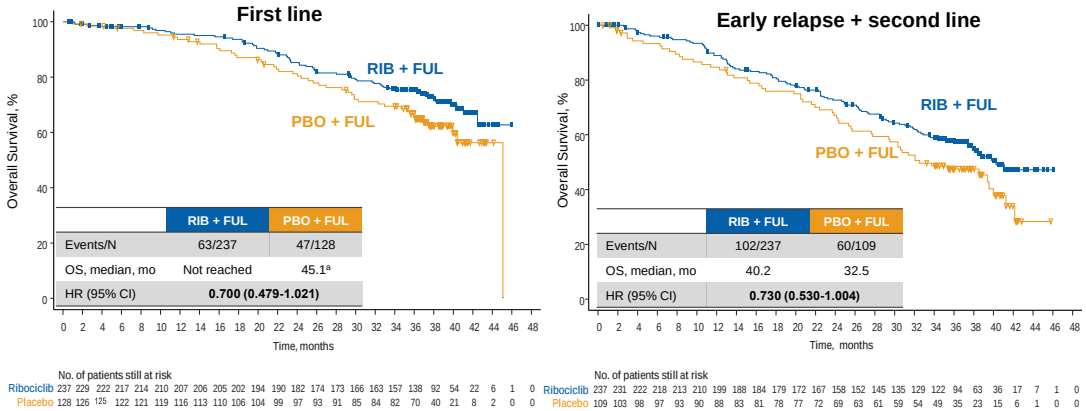
- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy ($P < 0.01129$)

BARCELONA 2019 ESMO congress

FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PBO

## Overall Survival by Line of Therapy

*OS by line of therapy was consistent with overall population*




| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 63/237 | 47/128 |
| OS, median, mo | Not reached | 45.1[a] |
| HR (95% CI) | **0.700 (0.479-1.021)** | |

| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 102/237 | 60/109 |
| OS, median, mo | 40.2 | 32.5 |
| HR (95% CI) | **0.730 (0.530-1.004)** | |

BARCELONA 2019 ESMO congress

FUL, fulvestrant; HR, hazard ratio; OS, overall survival; PBO, placebo; RIB, ribociclib.

[a] This median value may not be estimated reliably due to the last patient on follow-up, who had an event at 45.1 months.

# Evaluation form 2a: for therapies that are not likely to be curative with primary endpoint OS

IF median OS with the standard treatment >24 months

| Grade 4 | Mark with X if relevant |
|---|---|
| HR ≤0.70 AND Gain ≥9 months | |
| Increase in 5 year survival alone ≥10% | |

| Grade 3 | |
|---|---|
| HR ≤0.70 AND Gain ≥6 - <9 months | |

| Grade 2 | |
|---|---|
| HR ≤0.70 AND Gain ≥4 - <6 months | |
| HR >0.70-0.75 AND Gain ≥4 months | |

| Grade 1 | |
|---|---|
| HR >0.75 OR Gain <4 months | |

**RIBOCICLIB IN ML 3**

**HR: 0.724**

**Absolute gain: Not yet possible to calculate**

**5-year survival no yet reached**

**NEED FOR A LONGER FU (≥ 60 ms)**

**RIBOCICLIB + Fulvestrant (1st and 2nd line):**

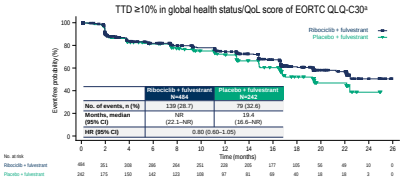
**Efficacy score: 3 (PFS)**

**No improvement in QoL**

**MCBS = 3**

# 2nd Line CDK 4/6 INHIBITORS: IMPACT ON QoL

**GLOBAL HRQoL**

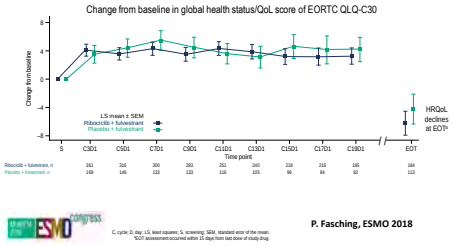



| | Ribociclib + fulvestrant N=484 | Placebo + fulvestrant N=242 |
|---|---|---|
| No. of events, n (%) | 139 (28.7) | 79 (32.6) |
| Months, median (95% CI) | NR (22.1–NR) | 19.4 (16.6–NR) |
| HR (95% CI) | 0.80 (0.60–1.05) | |

NR, not reached.
+Patients censored at progression.

P. Fasching, ESMO 2018

**GLOBAL HRQoL IMPROVED/MAINTAINED VS BASELINE WHILE ON TREATMENT IN BOTH ARMS**



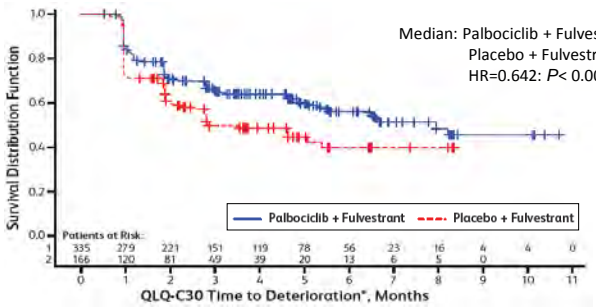

C, cycle; D, day; LS, least squares; S, screening; SEM, standard error of the mean.
[b]EOT assessment occurred within 15 days from last dose of study drug.

P. Fasching, ESMO 2018

**QoL similar in both arms**

## PALOMA 3: Impact on Global QOL, Functioning and Symptoms

**Time to Deterioration¥ in Pain Scores (QLQ-C30)**




Median: Palbociclib + Fulvestrant (8 mo) vs Placebo + Fulvestrant (2.8 mo); HR=0.642: $P < 0.001$

*Deterioration defined as a ≥10-point increase from baseline.

+Censored.

**Conclusions**

Compared to placebo + fulvestrant, addition of palbociclib to fulvestrant in endocrine resistant HR+/HER2– MBC patients was associated with:

- **Significantly higher on treatment overall Global QOL scores**
- **Significantly greater improvement from baseline in emotional functioning and pain scores**
- **Significant delay in deterioration of pain**

ECCO 2015: Harbeck et al

## Abemaciclib: no QoL yet reported

# 2nd Line CDK 4/6 INHIBITORS: ESMO-MCBS Score

**Evaluation form 2b:** non-curative intent, primary endpoint **PFS**

Efficacy

| 3 | 2 | 1 |
|---|---|---|
| X | | |

**Toxicity and QoL adjustment when only a PFS improvement**

**PALBOCICLIB 2nd line:**
Efficacy score: 3 (OS)
Improved QoL
**MCBS: 4**

**RIBOCICLIB + Fulvestrant (1st and 2nd line):**
Efficacy score: 3 (PFS)
No improvement in QoL
**MCBS = 3**

**ABEMACICLIB 2nd line:**
Efficacy score: 3 (PFS & OS)
Waiting for QoL
**MCBS = 3**

# OTHER OPTIONS OF ET + TARGETED THERAPY?
# When to use them?
# What is the best option after a CDK4/6i?

# ER POSITIVE / HER-2 NEGATIVE ABC

**The addition of everolimus to an AI is a valid option for some patients previously exposed to endocrine therapy, since it significantly prolongs PFS, albeit without evidence of OS benefit.**
**The decision to treat must take into account the toxicities associated with this combination, lack of statistical significant OS benefit, cost and availability.**
**(LoE/GoR : I/B) (88%)**

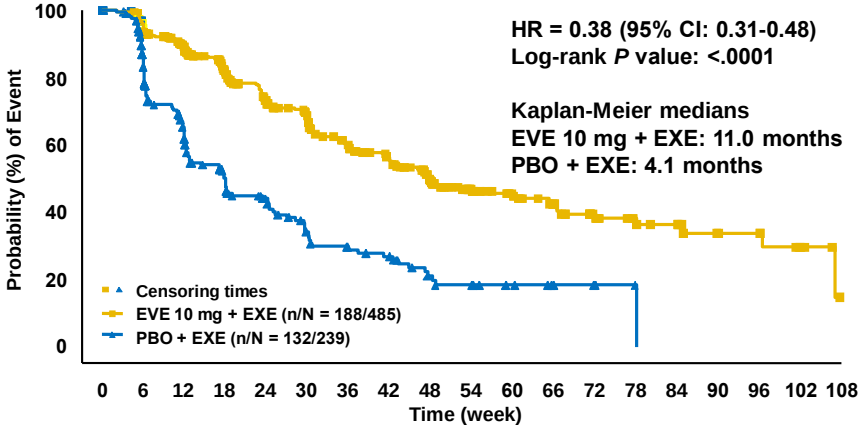
**Tamoxifen or fulvestrant can also be combined with everolimus.**
**(LoE/GoR : II/B) (80%)**

**LEO TRIAL**
**(HT + Everolimus in PRE-MENOPAUSAL)**
**ESMO 2019**

*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

## BOLERO-2 (18-ms FU): PFS Central

BOLERO-2




Number of patients still at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EVE 10 mg + EXE | 485 | 427 | 359 | 292 | 239 | 211 | 166 | 140 | 108 | 77 | 62 | 48 | 32 | 21 | 18 | 11 | 10 | 5 | 0 |
| PBO + EXE | 239 | 179 | 114 | 76 | 56 | 39 | 31 | 27 | 16 | 13 | 9 | 6 | 4 | 1 | 0 | 0 | 0 | 0 | 0 |

2

Piccart M, et al. ASCO 2012. Abstract 559.

# BOLERO-2

# Everolimus + AI

## 4.6 to 6.9 ms benefit PFS

## 4 months "absolute benefit" in OS BUT NOT STATISTICAL SIGNIFICANT

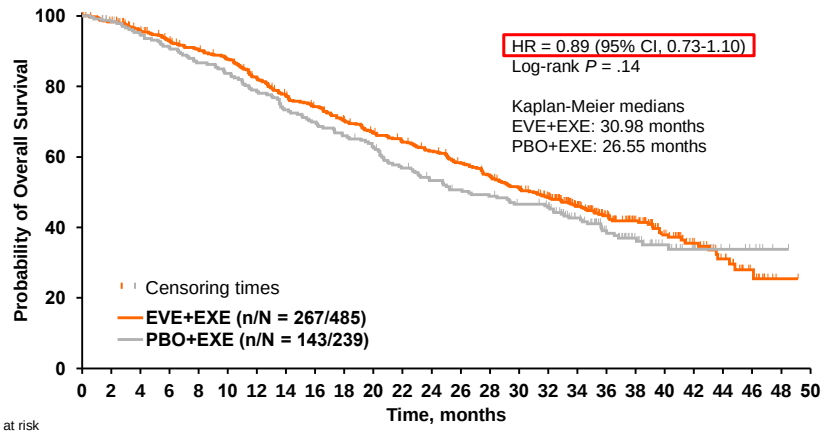
**Everolimus 2nd line:**

**Efficacy score: 3 (OS)**

**Decreased QoL/Toxicity: loose 1**

**MCBS = 2**

## BOLERO-2 (39-mo): Final OS Analysis




No. at risk

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EVE+EXE | 485 | 471 | 448 | 429 | 414 | 399 | 373 | 347 | 330 | 311 | 292 | 279 | 266 | 248 | 232 | 216 | 196 | 154 | 118 | 91 | 58 | 39 | 23 | 11 | 1 | 0 |
| PBO+EXE | 239 | 232 | 220 | 211 | 201 | 194 | 182 | 170 | 162 | 153 | 145 | 130 | 120 | 113 | 109 | 102 | 98 | 77 | 56 | 41 | 28 | 18 | 8 | 5 | 1 | 0 |

- At 39 months median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013): 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

Piccart M, et al, EBCC 2014,LBA

# Management of MUCOSITIS/STOMATITIS

**Steroid mouthwash should be used for prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5mg/5ml dexamethasone, 10 ml to swish x 2 minutes then spit out qid). (LoE/GoR: I/B)**

**Early intervention is recommended.**
**For > Grade 2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended.**
**Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis.**
**Consider adding steroid dental paste to treat developing ulcerations.**
**(LoE/GoR: Expert opinion/B).**

**Probably today**
**MCBS = 3**

# BOLERO-4: Open-label, Phase II, single-arm study

**Key eligibility criteria**

- Postmenopausal women with ER+, HER2– ABC not amenable to curative treatment by surgery or radiotherapy
- No prior metastatic BC treatment
- No prior treatment with, or known hypersensitivity to, mTOR inhibitors
- Prior neoadjuvant or adjuvant NSAI therapy must have been completed >1 year prior to enrollment
- ECOG performance status 0–2

**1L setting (n=202)**
EVE 10 mg/day
+ LET 2.5 mg/day

Patients progressing in the 1L setting had the option to receive 2L treatment at the investigator's discretion

**2L setting (n=50)**
EVE 10 mg/day
+ EXE 25 mg/day

**Primary endpoint**

- 1L PFS

**Secondary endpoints**

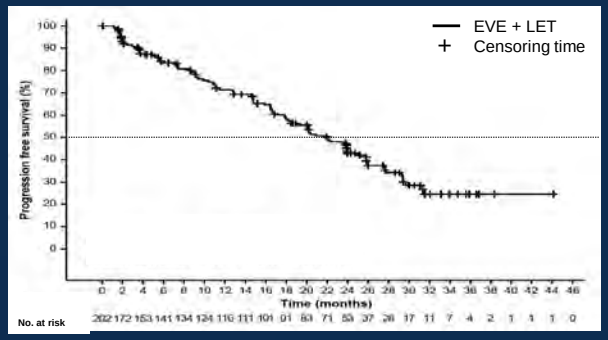
- 2L PFS
- 1L OS
- 1L/2L ORR, CBR, and safety

1L, first-line; 2L, second-line; ER+, CBR, clinical benefit rate; ECOG, Eastern Cooperative Oncology Group; estrogen receptor positive; HER2–, human epidermal growth factor receptor 2-negative LET, letrozole; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
CRAD001Y24135 Study Protocol v04 (August 10, 2015).


Slides are the property of the author. Permission required for reuse.

# BOLERO-4: PFS in the 1L setting

- At data cut-off, median progression-free survival was 22.0 months (95% CI 18.1–25.1) at a median duration of follow-up of 29.5 months



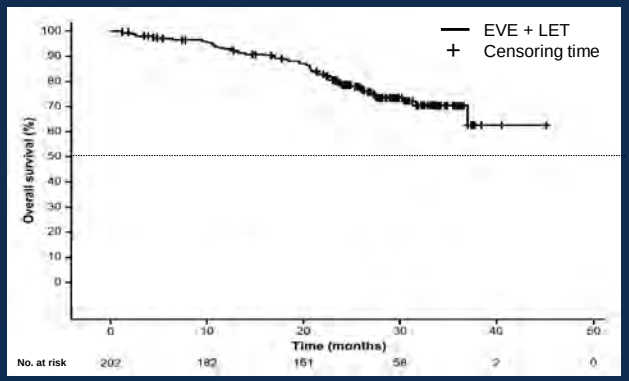

CI, confidence interval; KM, Kaplan-Meier.

| EVE + LET (n=202) | |
|---|---|
| No. of PFS events, n (%) | 108 (54) |
| Progression, n (%) | 103 (51) |
| Death, n (%) | 5 (2) |
| No. censored, n (%) | 94 (47) |
| Median PFS, months (95% CI) | **22.0 (18.1–25.1)** |

PROBLEM:
Single-arm study!



# BOLERO-4: OS in the 1L setting




| EVE + LET (n=202) | |
|---|---|
| No. of OS events, n (%) | 50 (25) |
| Median OS, months (95% CI) | **NE (37.0–NE)** |
| KM-estimated OS rate, % (95% CI) | |
| 12-month | 92.8 (88.1–95.7) |
| 18-month | 88.5 (83.1–92.3) |
| 24-month | 78.7 (72.1–83.9) |
| 30-month | 73.4 (66.0–79.4) |

OS following 1L treatment with EVE + LET is defined as the time from the start of treatment to date of death due to any cause
LPFV, last patient first visit; NE, not evaluable.

PROBLEM:
Single-arm study!

Abstract : 311PD

# Leuprorelin combined with Letrozole with/without Everolimus in Ovarian suppressed premenopausal women with hormone receptor positive, HER2-negative metastatic breast cancer (LEO Study)

Jae Ho Jeong[1*], Jeong Eun Kim[1*], Jin-Hee Ahn[1], Kyung Hae Jung[1], Su-Jin Koh[2], Jaekyung Cheon[2], Joo Hyuk Sohn[3], Gun Min Kim[3], Keun Seok Lee[4], In Hae Park[4], Sung Hoon Sim[4], and **Sung-Bae Kim**[1] *on behalf of the **LEO** investigators*

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Division of Hematology and Oncology, Ulsan University Hospital, Ulsan, Korea
[3]Department of Oncology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Center for Breast Cancer, National Cancer Center, Goyang, Korea

**N = 137**

- Premenopausal women
- ER+, HER2- recurrent or metastatic BC
- Recurrent or progression after tamoxifen and ovarian ablation (or GnRH-A)

→ **R** *2:1 ratio*

→ **Everolimus 10 mg/day + Letrozole 2.5 mg/day + Leuprorelin 3.75 mg q 28 days (N = 92)**

→ **Letrozole 2.5 mg/day + Leuprorelin 3.75 mg q 28 days (N = 45)**

- **Stratification factors**

1. **Presence of visceral metastases**
2. **Sensitivity to prior endocrine therapy**
   at least 24 months of endocrine therapy before recurrence in the adjuvant setting
   a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease

# Baseline Characteristics *(1)*

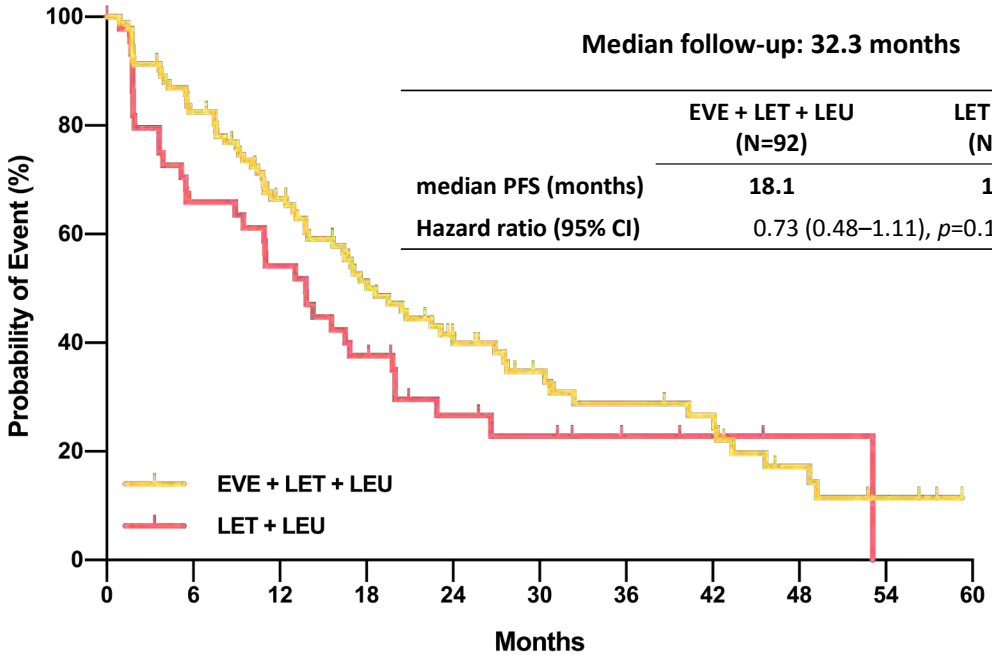
| Characteristic | EVE + LET + LEU (N=92) | LET + LEU (N=45) |
|---|---|---|
| **Age (years), median (range)** | 44 (24–54) | 45 (25–56) |
| **ECOG performance status (%)** | | |
| 0 | 53.3 | 48.9 |
| 1 | 45.7 | 51.1 |
| 2 | 1.1 | 0 |
| **Visceral disease (%)** | 60.9 | 60.0 |
| **Bone only disease (%)** | 5.4 | 13.3 |
| **Previous sensitivity to endocrine therapy (%)** | 73.9 | 75.6 |
| **Previous endocrine therapy (%)** | | |
| Tamoxifen | 58.7 | 57.8 |
| Tamoxifen → GnRH-A | 19.6 | 20.2 |
| Tamoxifen + GnRH-A | 21.7 | 22.2 |

# Baseline Characteristics *(2)*

| Characteristic | EVE + LET + LEU (N=92) | LET + LEU (N=45) |
|---|---|---|
| **Measurable disease (%)** | 90.2 | 86.7 |
| **Metastatic site (%)** | | |
| Lung | 31.5 | 40.0 |
| Liver | 27.2 | 26.7 |
| Bone | 64.1 | 60.0 |
| **Purpose of most recent treatment (%)** | | |
| Adjuvant therapy | 48.9 | 58.1 |
| Palliative therapy | 51.1 | 41.9 |
| **Line of treatment (%)** | | |
| 1st line | 48.9 | 57.8 |
| 2nd line | 33.7 | 29.9 |
| ≥3rd line | 17.4 | 13.3 |

# Progression-free survival, ITT population

# LEO STUDY



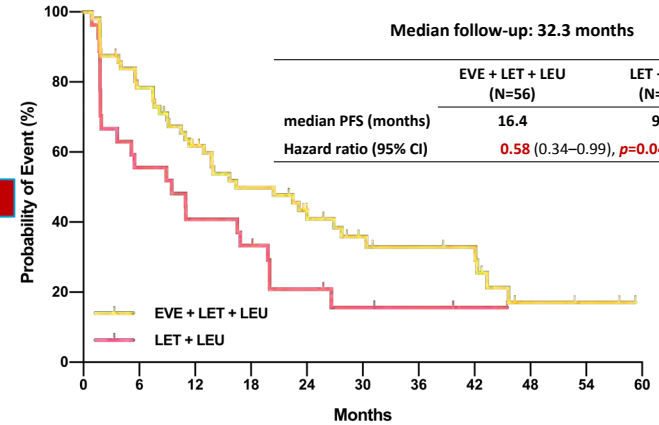

Median follow-up: 32.3 months

| | EVE + LET + LEU (N=92) | LET + LEU (N=45) |
|---|---|---|
| median PFS (months) | 18.1 | 13.8 |
| Hazard ratio (95% CI) | 0.73 (0.48–1.11), *p*=0.137 | |

**4.3 ms non-significant benefit PFS (very small study!)**

## Progression-free survival, visceral metastasis

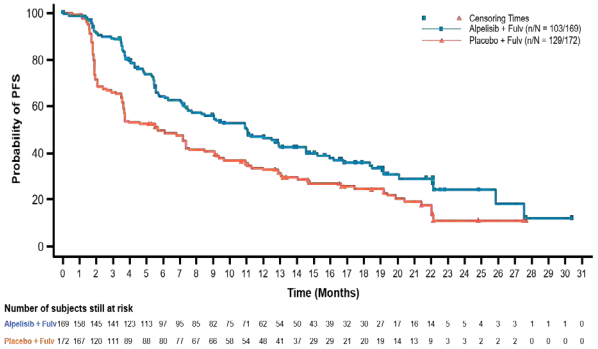
**Young woman with ER+/HER2neg ABC, with visceral mets DON'T ALWAYS NEED CT**




Median follow-up: 32.3 months

| | EVE + LET + LEU (N=56) | LET + LEU (N=27) |
|---|---|---|
| median PFS (months) | 16.4 | 9.5 |
| Hazard ratio (95% CI) | 0.58 (0.34–0.99), *p*=0.048 | |

## SOLAR-1 (NCT02437318, Alpelisib) Primary endpoint: Locally assessed PFS in the PIK3CA-mutant cohort




| Data cut-off: Jun 12, 2018 | Alpelisib + fulvestrant (N=169) | Placebo + fulvestrant (N=172) |
|---|---|---|
| Number of PFS events, n (%) | 103 (60.9) | 129 (75.0) |
| Progression | 99 (58.6) | 120 (69.8) |
| Death | 4 (2.4) | 9 (5.2) |
| Censored | 66 (39.1) | 43 (25.0) |
| Median PFS (95% CI) | 11.0 (7.5–14.5) | 5.7 (3.7–7.4) |
| HR (95% CI) | 0.65 (0.50–0.85) | |
| p-value | 0.00065 | |

- The primary endpoint crossed the pre-specified Haybittle-Peto boundary (one-**sided p≤0.0199)**

**F. André et al, ESMO 2018**

This presentation is the intellectual property of Fabrice Andre.
Contact Fabrice.andre@gustaveroussy.fr for permission to reprint and/or distribute.

# PI3K inhibitors
# ALPELISIB

***Only ~ 7% pretreated with CDK 4/6i***



## SOLAR 1
## Adverse events in the total population*

| AEs ≥20% in either arm, % | Alpelisib + fulvestrant N=284 | | | Placebo + fulvestrant N=287 | | |
|---|---|---|---|---|---|---|
| | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| Any adverse event | 282 (99.3) | 183 (64.4) | 33 (11.6) | 264 (92.0) | 87 (30.3) | 15 (5.2) |
| Hyperglycemia | 181 (63.7) | 93 (32.7) | 11 (3.9) | 28 (9.8) | 1 (0.3) | 1 (0.3) |
| Diarrhea | 164 (57.7) | 19 (6.7) | 0 | 45 (15.7) | 1 (0.3) | 0 |
| Nausea | 127 (44.7) | 7 (2.5) | 0 | 64 (22.3) | 1 (0.3) | 0 |
| Decreased appetite | 101 (35.6) | 2 (0.7) | 0 | 30 (10.5) | 1 (0.3) | 0 |
| Rash | 101 (35.6) | 28 (9.9) | 0 | 17 (5.9) | 1 (0.3) | 0 |
| Vomiting | 77 (27.1) | 2 (0.7) | 0 | 28 (9.8) | 1 (0.3) | 0 |
| Decreased weight | 76 (26.8) | 11 (3.9) | 0 | 6 (2.1) | 0 | 0 |
| Stomatitis | 70 (24.6) | 7 (2.5) | 0 | 18 (6.3) | 0 | 0 |
| Fatigue | 69 (24.3) | 10 (3.5) | 0 | 49 (17.1) | 3 (1.0) | 0 |
| Asthenia | 58 (20.4) | 5 (1.8) | 0 | 37 (12.9) | 0 | 0 |

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) discontinued alpelisib due to rash; no patients discontinued placebo due to either hyperglycemia or rash

*Safety profiles were similar in the *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

This presentation is the intellectual property of Fabrice Andre.
Contact Fabrice.andre@gustaveroussy.fr for permission to reprint and/or distribute.

**F. André et al, ESMO 2018**



## SOLAR 1
## Treatment exposure and dose adjustments

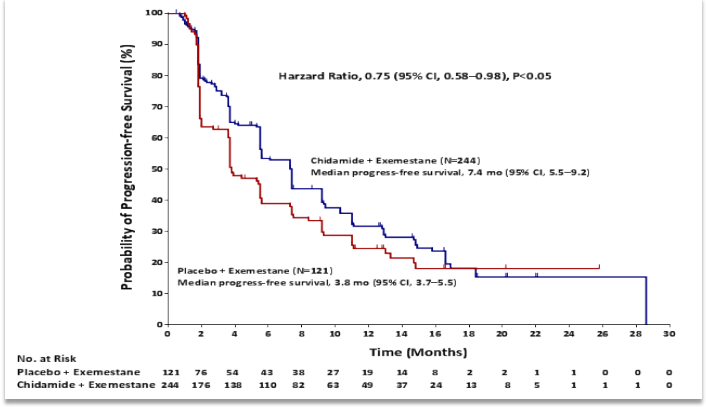
| Treatment exposure | *PIK3CA*-mutant* | | *PIK3CA*-non-mutant* | |
|---|---|---|---|---|
| | Alpelisib + fulvestrant (N=169) | Placebo + fulvestrant (N=171)† | Alpelisib + fulvestrant (N=115) | Placebo + fulvestrant (N=116) |
| Exposure to alpelisib/placebo | | | | |
| Median duration of exposure to alpelisib/placebo, months (range) [n exposed] | 5.5 (0.0–29.0) [168] | 4.6 (0.0–30.1) [170] | 5.6 (0.3–30.8) [115] | 6.2 (0.5–29.5) [116] |
| Median relative alpelisib/placebo dose intensity, % | 82.7 | 100 | 84.5 | 100 |
| Alpelisib/placebo dose adjustments, n (%) | | | | |
| Patients with dose interruptions | 125 (74.0) | 55 (32.2) | 80 (69.6) | 31 (26.7) |
| Dose interruptions due to AEs | 116 (68.6) | 27 (15.8) | 73 (63.5) | 13 (11.2) |
| Patients with dose reductions | 108 (63.9) | 15 (8.8) | 60 (52.2) | 6 (5.2) |
| Dose reductions due to AEs | 105 (62.1) | 8 (4.7) | 59 (51.3) | 5 (4.3) |

*The data cut-off for both groups was June 12, 2018.
†1 patient in the placebo arm of the *PIK3CA*-mutant cohort did not receive fulvestrant or placebo.

This presentation is the intellectual property of Fabrice Andre.
Contact Fabrice.andre@gustaveroussy.fr for permission to reprint and/or distribute.

**F. André et al, ESMO 2018**

## ACE (Chidamide) Trial: PFS in ITT Population




Z. Jiang et al, ESMO 2018

# HDAC inhibitors
# Chidamide?
# Entinostat?

***Not pretreated with CDK 4/6i***

## ACE Study (Chidamide, HDAC inhibitor)

### Non-hematologic Adverse Events

| AEs > 20% in either arm, n (%) | Chidamide + Exemestane (N=244) | | | Placebo + Exemestane (N=121) | | |
|---|---|---|---|---|---|---|
| | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| Hypokalemia | 62 (25.4) | 14 (5.7) | 1 (0.4) | 3 (2.5) | 1 (0.8) | 0 |
| Nausea | 61 (25.0) | 1 (0.4) | 0 | 7 (5.8) | 0 | 0 |
| Hyperglycemia | 60 (24.6) | 5 (2.1) | 0 | 17 (14.1) | 0 | 0 |
| Hypocalcemia | 58 (23.8) | 2 (0.8) | 0 | 3 (2.5) | 0 | 0 |
| Hypertriglyceridemia | 57 (23.3) | 10 (4.1) | 2 (0.8) | 15 (12.4) | 0 | 0 |
| Diarrhea | 53 (21.7) | 4 (1.6) | 0 | 9 (7.4) | 0 | 0 |
| Aspartate aminotransferase increased | 50 (20.5) | 0 | 0 | 24 (19.8) | 4 (3.3) | 0 |
| Alanine aminotransferase increased | 49 (20.1) | 0 | 0 | 20 (16.5) | 2 (1.7) | 0 |

### Hematologic Adverse Events

| AEs > 10% in either arm, n (%) | Chidamide + Exemestane (N=244) | | | Placebo + Exemestane (N=121) | | |
|---|---|---|---|---|---|---|
| | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| Neutropenia# | 199 (81.6) | 102 (41.8) | 22 (9.0) | 31 (25.6) | 1 (0.8) | 2 (1.7) |
| Leukopenia | 194 (79.5) | 45 (18.4) | 1 (0.4) | 31 (25.6) | 1 (0.8) | 2 (1.7) |
| Thrombocytopenia | 183 (75.0) | 61 (25.0) | 6 (2.5) | 16 (13.2) | 1 (0.8) | 2 (1.7) |
| Anemia | 78 (32.0) | 9 (3.7) | 0 | 22 (18.2) | 2 (1.7) | 0 |

#No febrile neutropenia was reported

Z. Jiang et al, ESMO 2018

## Phase III E2112: Exemestane ± Entinostat in Advanced Breast Cancer

- Entinostat: oral, histone deacetylase inhibitor

Pre/peri/postmenopausal women and men with HR+/HER2-, inoperable, locally advanced or metastatic BC, with progression on/after NSAI therapy (N ≈ 600)

→ **Entinostat** PO Days 1, 8, 15, 22 + **Exemestane** PO QD Days 1-28 (n ≈ 300)

→ **Placebo** PO Days 1, 8, 15, 22 + **Exemestane** PO QD Days 1-28 (n ≈ 300)

→ *Until disease progression or unacceptable toxicity*

*Pre/perimenopausal female and all male pts receive goserelin acetate SC Day 1.

- Primary endpoints: OS, PFS
- Secondary endpoints: ORR (CR or PR), TTD, toxicity
- Other outcomes: adherence, QoL, protein lysine acetylation

ClinicalTrials.gov. NCT02115282.

Slide credit: clinicaloptions.com

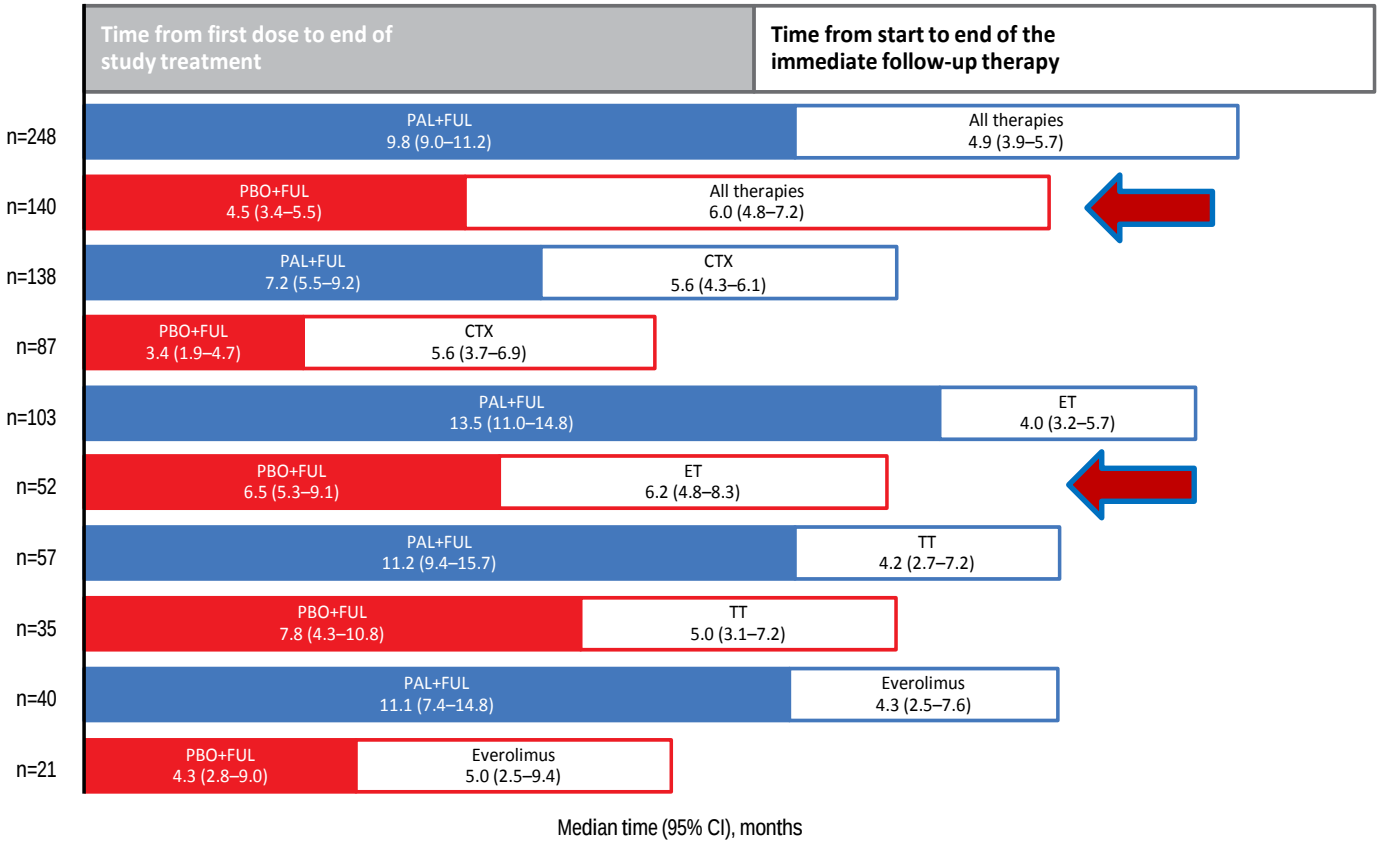
# OTHER OPTIONS OF ET + TARGETED THERAPY?
# When to use them?
# What is the best option after a CDK4/6i?

# Unconfirmed hypothesis:

## PALOMA 3:
## DURATION **OF IMMEDIATE SUBSEQUENT THERAPY**
## POST-**PROGRESSION**

**If**

- 
- 

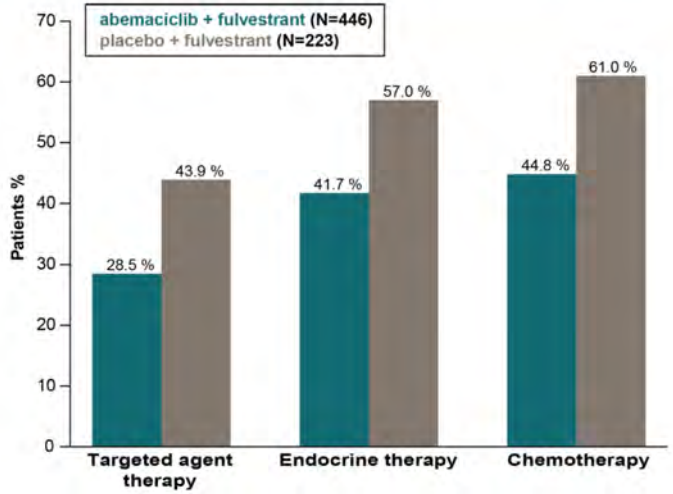



MUNICH 2018 ESMO congress

CTX=chemotherapy; TT=targeted treatment.

**Cristofanilli et al, ESMO 2018**

# Post discontinuation therapy



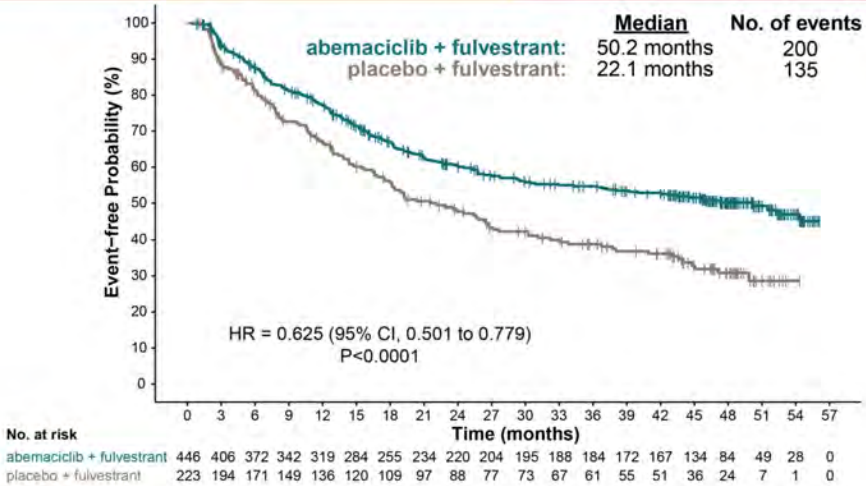

| Subsequent CDK4 & 6 Inhibitor therapy | |
|---|---|
| abemaciclib + fulvestrant | 5.8% |
| placebo + fulvestrant | 17.0% |

© 2019 Eli Lilly and Company

At the time of data cutoff, a total of 584 patients in the ITT population had discontinued from study treatment (82.7% (n=369) in abemaciclib arm, 96.4% (n=215) in the placebo arm)

## MONARCH 2 TRIAL

# Exploratory Analysis: Time to Chemotherapy[a]




© 2019 Eli Lilly and Company

[a]Time to chemotherapy was analyzed from randomization to initiation of first post discontinuation chemotherapy (censoring patients who died prior to initiation of chemotherapy)

**Sledge et al, ESMO 2019**

# Subsequent Therapy After Discontinuation

| First Subsequent Therapy After Discontinuation by Type, n (%)[a] | RIB + FUL n = 484 n discontinued = 362 | PBO + FUL n = 242 n discontinued = 209 |
|---|---|---|
| Any medication | 295 (81.5) | 177 (84.7) |
| Chemotherapy alone | 84 (23.2) | 42 (20.1) |
| Chemotherapy + hormone therapy/other[b] | 46 (12.7) | 33 (15.8) |
| Hormone therapy alone | 94 (26.0) | 38 (18.2) |
| Hormone therapy + other[c] | 66 (18.2) | 61 (29.2) |
| Targeted therapy alone | 5 (1.4) | 3 (1.4) |

**MONALEESA 3 TRIAL**

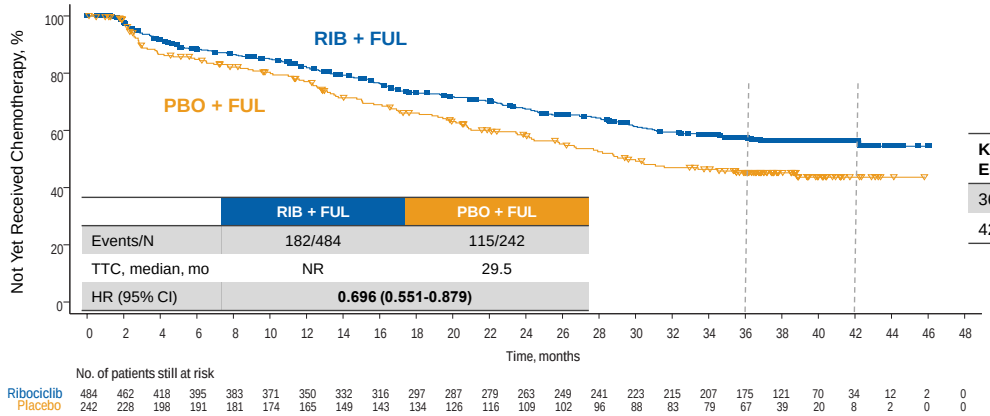
- CDK4/6 inhibitors as any line of subsequent therapy after discontinuation were received by 11% of patients in the RIB arm and 25% of patients in the PBO arm

CDK4/6i, cyclin-dependent kinase inhibitor; FUL, fulvestrant; PBO, placebo; RIB, ribociclib.
[a] For all rows, patients counted only once in each medication type, and categories are mutually exclusive except for CDK4/6 inhibitors; percentages are based on the number of patients who discontinued. [b] Includes patients who received chemotherapy + any nonchemotherapy. [c] Includes patients who received hormonal therapy + other without chemotherapy.



# Time to First Chemotherapy

*Time to first chemotherapy was longer with RIB + FUL*




| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 182/484 | 115/242 |
| TTC, median, mo | NR | 29.5 |
| HR (95% CI) | **0.696 (0.551-0.879)** | |

**Landmark analysis**

| KM Estimate | RIB + FUL | PBO + FUL |
|---|---|---|
| 36 months | 57.4% | 45.2% |
| 42 months | 56.4% | 43.7% |

FUL, fulvestrant; HR, hazard ratio; NR, not reached; PBO, placebo; RIB, ribociclib; TTC, time to first chemotherapy.

# ER POSITIVE / HER-2 NEGATIVE MBC

**The optimal sequence of endocrine-based therapy is uncertain.**
**It depends on *which agents were previously used (in the (neo)adjuvant or advanced settings), the burden of the disease, patients' preference, costs and availability.***

**Available options include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and estradiol, as well as repetition of previously used agents, may be used.**
**(LoE/GoR : I/A) (95%)**

**It is currently unknown how the different combinations of endocrine + targeted agents compare with each other, and with single agent CT. Trials are ongoing.**

*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

# BOLERO 6: Randomized, Open-Label, Phase II Study

- BOLERO-6 randomized 309 patients to receive EVE + EXE (n = 104), EVE alone (n = 103), or CAP (n = 102)

**Eligibility Criteria**

- Postmenopausal women with ER+ HER2– metastatic or recurrent BC, or locally advanced BC not amenable to curative surgery or radiotherapy
- Recurrence or progression on ANA or LET
- Measurable disease per RECIST v1.1 or bone lesions (lytic or mixed), and ECOG PS 0–2
- **N = 309**

→ **Randomization (1:1:1)***

→ **EVE 10 mg PO QD + EXE 25 mg PO QD (n = 104)**

→ **EVE 10 mg PO QD (n = 103)**

→ **CAP 1250 mg/m² PO BID (2 weeks on, 1 week off) (n = 102)**

**Primary Objective**

- Estimate HR of investigator-assessed PFS for EVE + EXE vs EVE alone†

**Key Secondary Objective**

- Estimate HR of PFS for EVE + EXE vs CAP†

**Other Secondary Endpoints**

- OS,† ORR, CBR, and safety

- BOLERO-6 was not powered to perform statistical comparisons between arms

*Stratified by presence or absence of visceral disease (lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion, or malignant ascites; †Stratified multivariate Cox regression models were adjusted on treatment and the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions (yes vs no); prior chemotherapy (yes vs no); ECOG PS (0 vs 1–2); organs involved (2 vs 1, and ≥3 vs 1); race (Caucasian vs non-Caucasian); age (<65 vs ≥65 years).

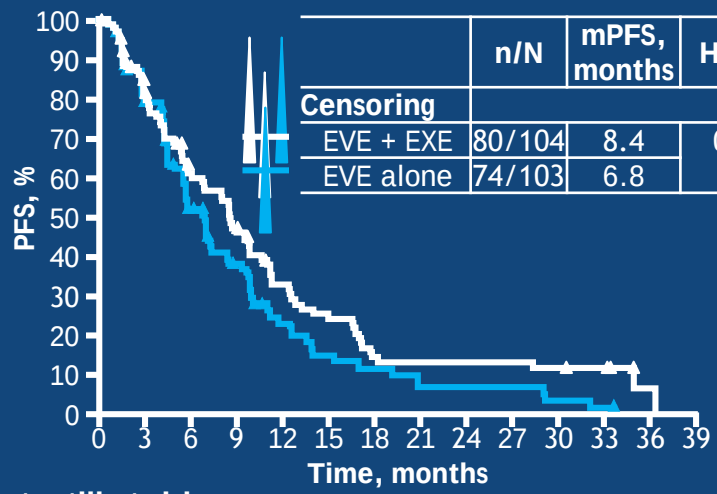
ANA, anastrozole; BID, twice daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PO, oral administration; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors.


Slides are the property of the author, permission required for reuse.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

# BOLERO 6: Primary Objective
# Estimated HR of PFS for EVE + EXE vs EVE alone

***EVE + EXE offers a PFS benefit vs EVE alone***




| | n/N | mPFS, months | HR* (90% CI) |
|---|---|---|---|
| **Censoring** | | | |
| EVE + EXE | 80/104 | 8.4 | 0.74 (0.57–0.97) |
| EVE alone | 74/103 | 6.8 | |

**Patients still at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EVE + EXE** | 104 | 73 | 52 | 39 | 26 | 19 | 11 | 10 | 10 | 10 | 9 | 5 | 1 | 0 |
| **EVE alone** | 103 | 66 | 40 | 26 | 14 | 9 | 7 | 4 | 4 | 4 | 2 | 1 | 0 | 0 |

- Estimated HR of PFS for EVE + EXE vs EVE alone was 0.74 (90% CI 0.57–0.97)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - EVE alone arm, 18%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a consistent HR (0.73; 90% CI 0.56-0.97)** for EVE + EXE vs EVE alone

*EVE + EXE vs EVE alone (obtained from a stratified Cox model).
mPFS, median progression-free survival.

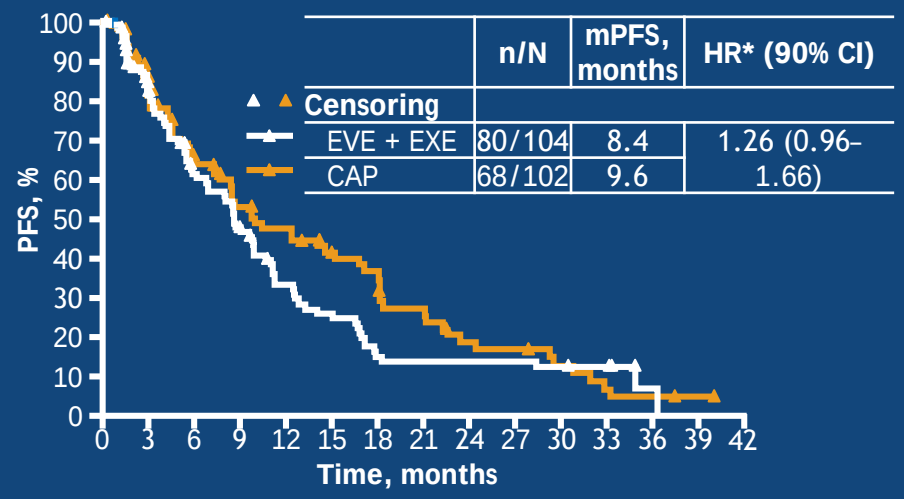
http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262



Slides are the property of the author, permission required for reuse.

# BOLERO 6: Key Secondary Objective
# Estimated HR of PFS for EVE + EXE vs CAP

***CAP may have been favored by baseline imbalances and potential informative censoring***




| | n/N | mPFS, months | HR* (90% CI) |
|---|---|---|---|
| EVE + EXE | 80/104 | 8.4 | 1.26 (0.96–1.66) |
| CAP | 68/102 | 9.6 | |

**Patients still at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EVE + EXE** | 104 | 73 | 52 | 39 | 26 | 19 | 11 | 10 | 10 | 10 | 9 | 5 | 1 | 0 | 0 |
| **CAP** | 102 | 68 | 48 | 38 | 33 | 26 | 19 | 14 | 10 | 9 | 6 | 3 | 2 | 1 | 0 |

- Estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96–1.66)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - CAP arm, 20%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a HR of 1.15 (90% CI 0.86–1.52)** for EVE + EXE vs CAP

*EVE + EXE vs CAP (obtained from a stratified Cox model).



Slides are the property of the author, permission required for reuse.



http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

# Adverse Events

| AE,* % | EVE + EXE (n = 104) | | EVE alone (n = 103) | | CAP (n = 102) | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3-4 | All grades | Grade 3-4 | All grades | Grade 3-4 |
| **Total** | **100** | **70** | **98** | **59** | **100** | **74** |
| Stomatitis† | 49 | 9 | 46 | 5 | 25 | 7 |
| Fatigue | 38 | 8 | 31 | 3 | 35 | 8 |
| **Diarrhea** | **35** | 5 | **33** | 3 | **54** | 8 |
| Anemia | 32 | 13 | 25 | 10 | 22 | 7 |
| Elevated GGT | 15 | 9 | 16 | 12 | 2 | 2 |
| Elevated AST | 15 | 7 | 14 | 8 | 9 | 1 |
| Hypertension | 14 | 6 | 8 | 2 | 5 | 3 |
| Hyperglycemia | 13 | 4 | 17 | 8 | 8 | 1 |
| Pneumonia | 11 | 7 | 9 | 3 | 3 | 2 |
| Neutropenia | 4 | 0 | 4 | 2 | 15 | 6 |
| **PPE syndrome** | **3** | 1 | **3** | 0 | **61** | 27 |

- Most frequent all-grade AEs:
  - Stomatitis in EVE-containing arms
  - **PPE syndrome and diarrhea in CAP arm**
- Grade 3-4 AEs more frequent in EVE + EXE arm vs EVE alone arm, and comparable between EVE + EXE and CAP arms

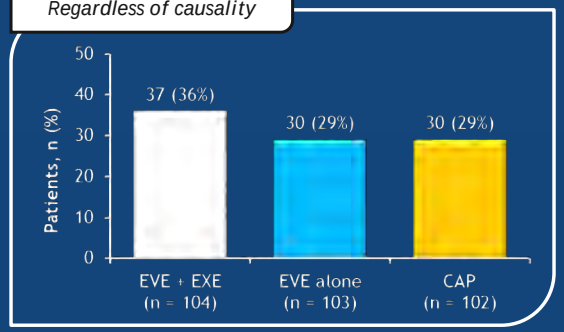
*≥5% grade 3-4 events in any arm; †BOLERO-6 was not designed to use the SWISH[1] protocol for stomatitis prevention.
AE, adverse event; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.

1. Rugo HS et al. *Lancet Oncol* 2017;18:654-662.

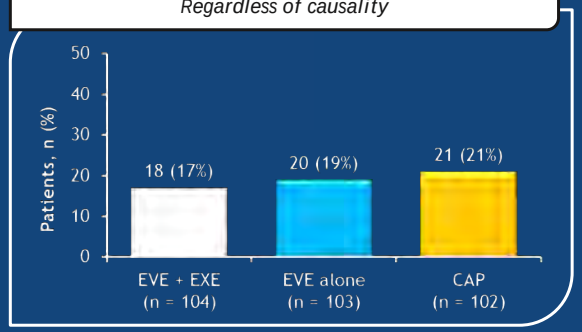


# Other Safety

All-grade serious AEs
*Regardless of causality*




All-grade AEs leading to discontinuation
*Regardless of causality*




- Serious AEs more frequent with EVE + EXE vs EVE alone or CAP
- Incidence of AEs leading to discontinuation comparable in each arm

대한항암요법연구회 KOREAN CANCER STUDY GROUP

# A randomized phase II study of palbociclib plus exemestane with GnRH agonist versus capecitabine in premenopausal women with hormone receptor-positive metastatic breast cancer (KCSG-BR 15-10, NCT02592746)


Yeon Hee Park[a], Tae-Yong Kim[b], Gun Min Kim[c], Kyung Hae Jung[d], Seok Yun Kang[e], In Hae Park[f], Jee Hyun Kim[g], Kyoung Eun Lee[h], Hee Kyung Ahn[i], Moon Hee Lee[j], Hee-Jun Kim[k], Han Jo Kim[l], Jong In Lee[m], Su-Jin Koh[n], Ji-Yeon Kim[a], Kyung-Hun Lee[b], Joo Hyuk Sohn[c], Sung-Bae Kim[d], Young-Hyuck Im[a], and Seock-Ah Im[b]

*Korean Cancer Study Group (KCSG)*

[a]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, [b]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University, College of Medicine, [c]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, [d]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, [e]Department of Hematology-Oncology, Ajou University School of Medicine, [f]Center for Breast Cancer, National Cancer Center, [g]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, [h]Department of Hematology and Oncology, Ewha Womans University Hospital, [i]Division of Medical Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, [j]Department of Internal Medicine, Inha University School of Medicine, [k]Department of Internal Medicine, Chung-Ang University College of Medicine, [l]Division of Hematology and Oncology, Department of Internal Medicine, Soonchunhyang University Hospital, [m]Division of Hematology-Oncology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, [n]Department of Hematology and Oncology, Ulsan University Hospital, Ulsan University College of Medicine




대한항암요법연구회 KOREAN CANCER STUDY GROUP

# Young-PEARL (KCSG BR 15-10) Study Design

- **Prospective, multi-center, open-label, randomized phase II study**

- Premenopausal women
- HR+/HER2- MBC
- Tamoxifen pretreated
- Prior 1 line of cytotoxic chemotherapy for MBC was allowed

→ 1:1 Randomization (N=184)

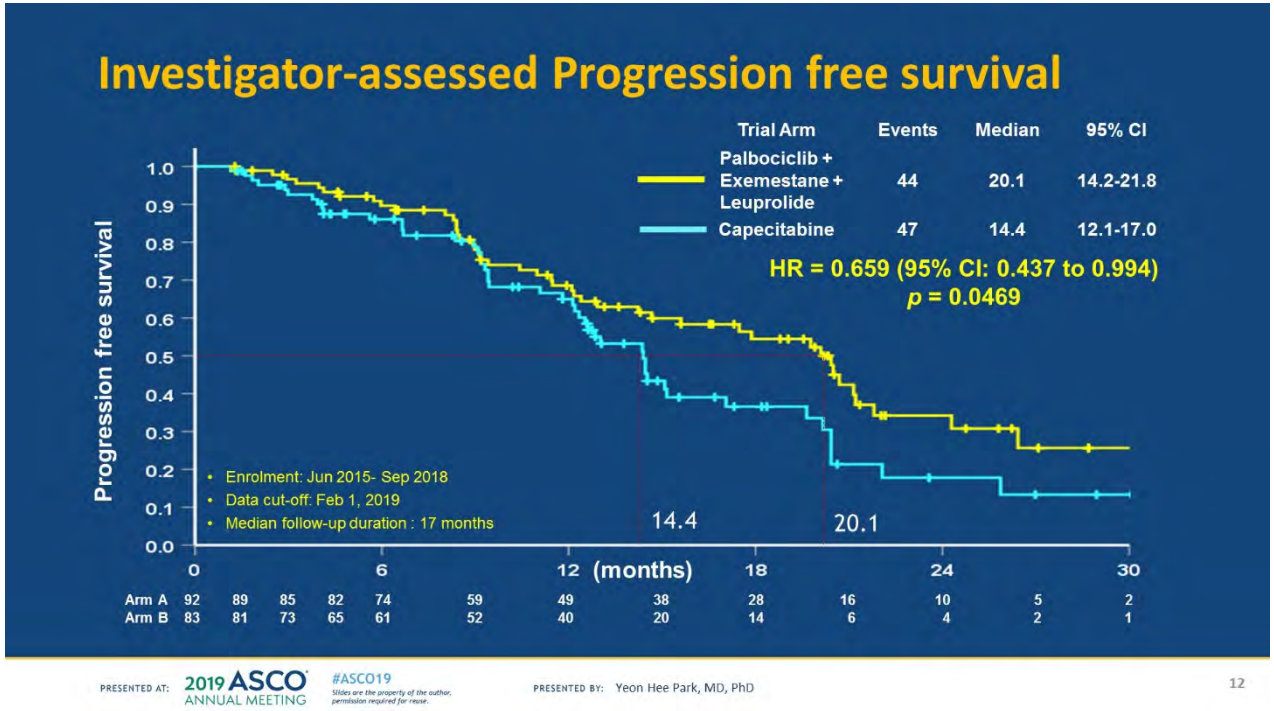
→ D1-21 Palbociclib 125mg QD for 3wks
D1-28 Exemestane 25mg QD for 4wks
D1 Leuprolide 3.75mg SC q4weeks

→ D1-14 Capecitabine 1250mg/m$^2$ bid for 2weeks q3weeks

Stratification factors
- Prior cytotoxic chemotherapy for MBC
- Presence of visceral metastases

- **Primary endpoint: Investigator-assessed progression-free survival**
- Secondary endpoints: Disease control rate (DCR), Overall survival (OS), Toxicity, QoL, Biomarkers

HR, hormone receptor; HER2, human epidermal receptor-2; MBC, metastatic breast cancer QoL, quality of life; GnRH, gonadotropin releasing hormone



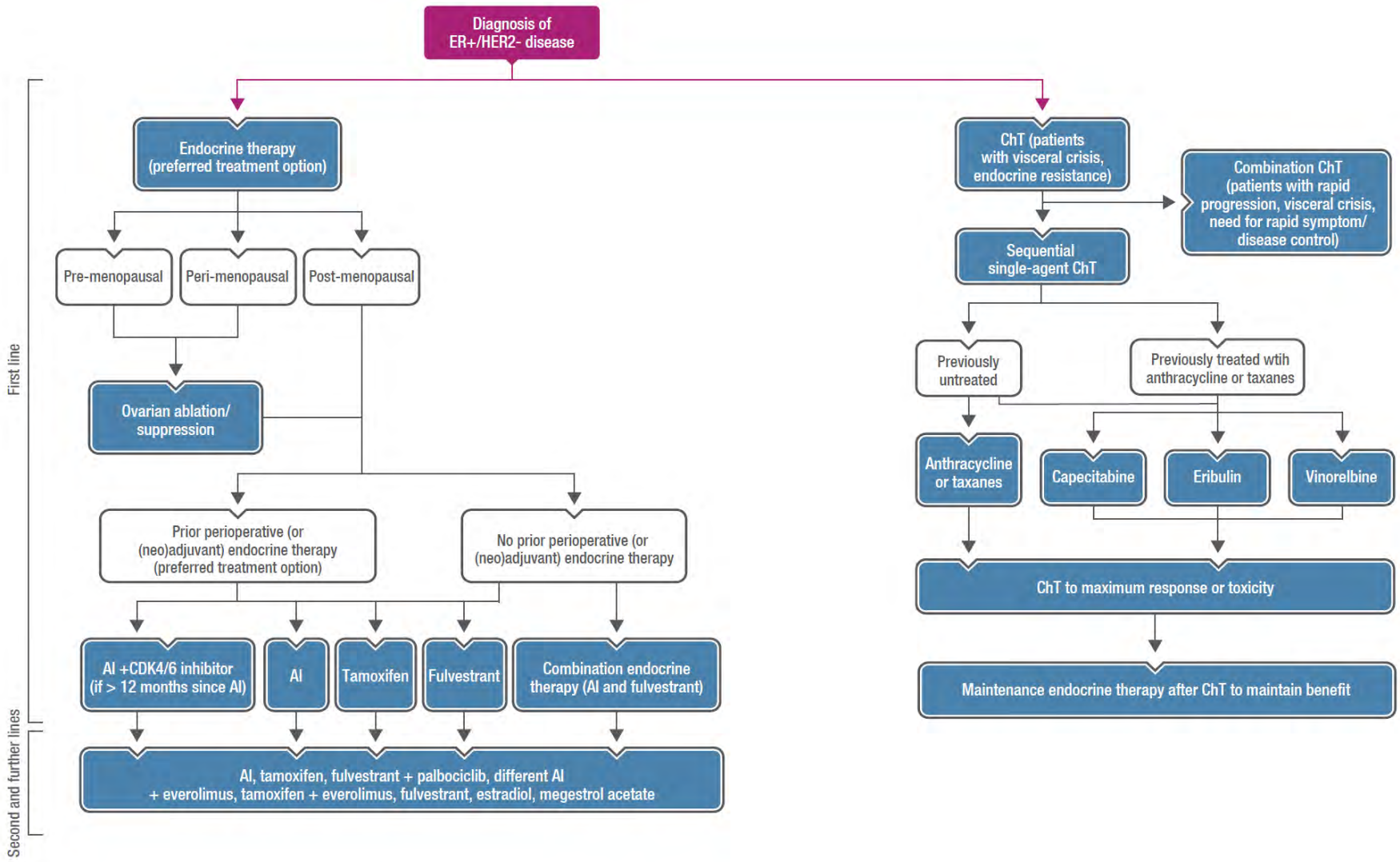

**Small phase 2 trial**
**But**
**Important question**
**Relevant results for clinical practice (why keep prescribing CT??!!)**

## Nonhematologic Toxicities

| Adverse events | Palbociclib + Exemestane + Leuprolide N=92 (%) | | | Capecitabine N=86 (%) | | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Arthralgia | 20 (21.7%) | 0 | 0 | 5 (5.8%) | 0 | 0 |
| Headache | 19 (20.7%) | 0 | 0 | 8 (9.3%) | 0 | 0 |
| Fatigue | 25 (27.2%) | 0 | 0 | 17 (19.8%) | 0 | 0 |
| Mucositis | 28 (30.4%) | 1 (1.1%) | 0 | 19 (22.1%) | 3 (3.5%) | 0 |
| Nausea | 11 (12.0%) | 0 | 0 | 30 (34.9%) | 1 (1.2%) | 0 |
| Diarrhea | 11 (12.0%) | 1 (1.1%) | 0 | 33 (38.4%) | 0 | 0 |
| Hand-Foot syndrome | 1 (1.1%) | 0 | - | 66 (76.7%) | 12 (14.0%) | - |

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Yeon Hee Park, MD, PhD 17

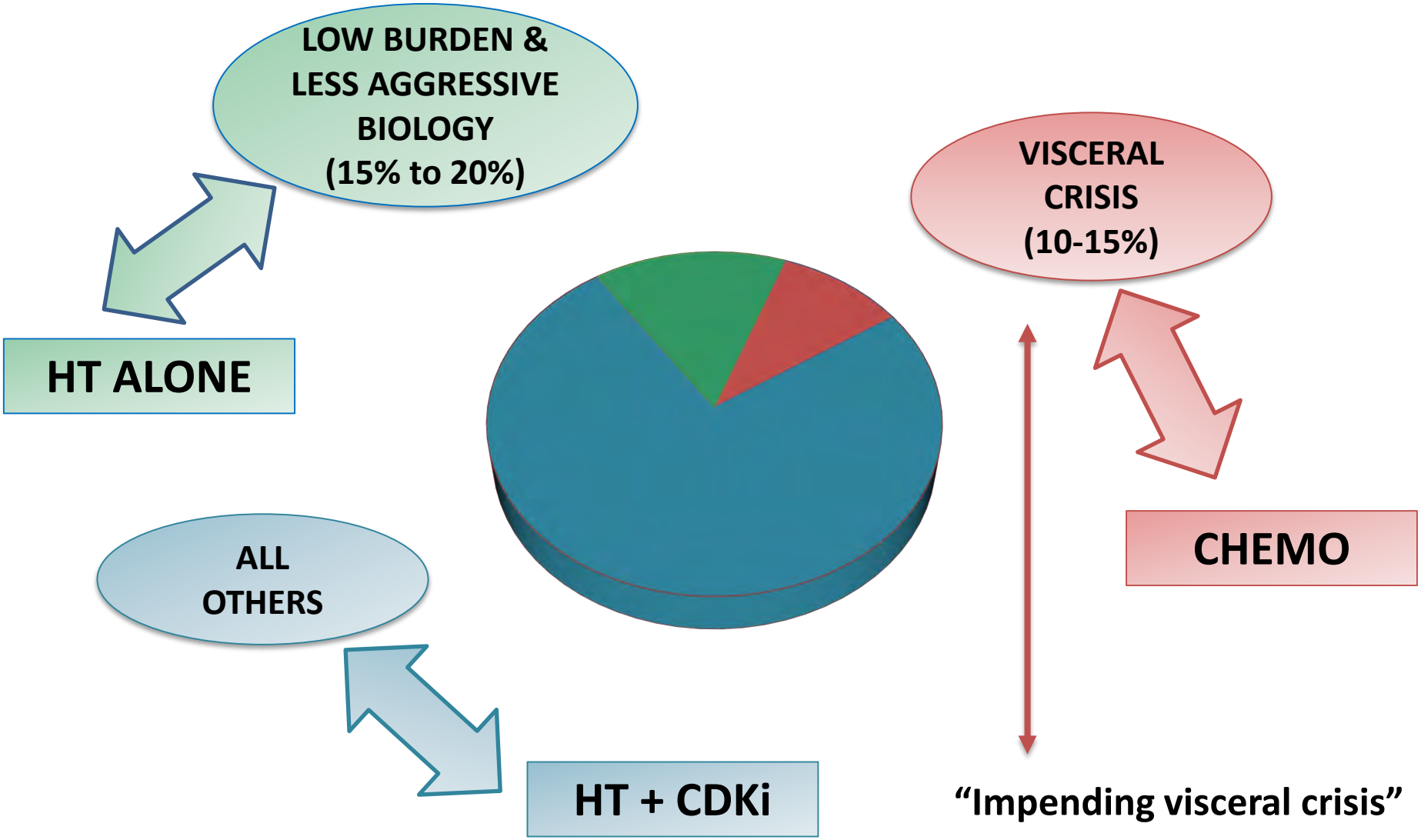
# MANAGEMENT OF LUMINAL ABC




ABC, advanced breast cancer; AI, aromatase inhibitor; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2

F Cardoso et al, Annals of Oncology 2018

# CLINICAL HETEROGENEITY OF LUMINAL TUMOURS
## Implications for therapeutic decisions



# OPEN QUESTIONS

1) **BIOMARKERS** to identify patient who can still be treated with ET alone

2) Head-to-head comparison and sequences of **ET + mTORi and ET + CDK4/6i**

3) How and when to integrate **the classes of agents?**

4) **Triple combinations** and **comparison with oral CT:** ongoing trials

5) **Mechanisms of resistance** to new drugs

6) **RETHINK CLINICAL RESEARCH**: *primary endpoints, inclusion/exclusion criteria, control arm, etc (more flexibility needed!)*

# Fifth ESO-ESMO International Consensus Conference

**14-16 November 2019 | Lisbon, Portugal**

Coordinating Chair: F. Cardoso, PT

Chairs: E.P. Winer, US - L. Norton, US - A. Costa, IT/CH

Co-Chairs: G. Curigliano, IT - S.A. Mertz, US

Scientific Committee Members: K. Gelmon, CA

F. Penault-Llorca, FR - E. Senkus, PL - C. Thomssen, DE

The ABC5 guidelines will be developed by ESO and ESMO

The ABC5 conference and guidelines are endorsed by

The ABC5 conference is held

under the auspices of

with official representatives of

and is endorsed by

RECEIVE UPDATES AT WWW.ABC-LISBON.ORG | #ABCLISBON