

Update mBC

endokrine Therapie

Breast Cancer Mortality Trends in the United States According to Estrogen Receptor Status and Age at Diagnosis

Ismail Jatoi, Bingshu E. Chen, William F. Anderson, and Philip S. Rosenberg

ABSTRACT

Purpose

Since 1990, overall breast cancer mortality rates in the United States decreased 24%. This decline has been attributed to mammography screening and adjuvant systemic therapy. However, the efficacy of these modalities may depend on estrogen receptor (ER) expression and age. We therefore examined breast cancer mortality trends in the United States according to ER status and age.

Methods

Using the Surveillance, Epidemiology, and End Results (SEER) program (1990-2003), we calculated trends in incidence-based mortality (IBM), annual hazard rates for breast cancer deaths after diagnosis, and relative hazard rates for women with ER-positive and ER-negative tumors. Relative hazard rates were assessed with Cox proportional hazards models, adjusted for stage and grade, and stratified by age at diagnosis.

Results

During the study period, IBM and annual hazard rates for breast cancer deaths decreased among women with ER-positive and ER-negative tumors, although declines were greater for those with ER-positive tumors. Among women younger than 70 years, relative hazard rates declined 38% for those with ER-positive tumors versus 19% for those with ER-negative tumors. Among women 70 years or older, relative hazard rates declined 14% for those with ER-positive tumors versus no significant decline for those with ER-negative tumors.

Conclusion

In the United States, breast cancer mortality rates have declined among women with ER-positive and ER-negative tumors, with greater declines among younger women and those with ER-positive tumors. Although mortality in all groups remains unacceptably high, additional emphasis should be placed on improving outcomes of breast cancer patients older than 70 years and those of all ages with ER-negative tumors.

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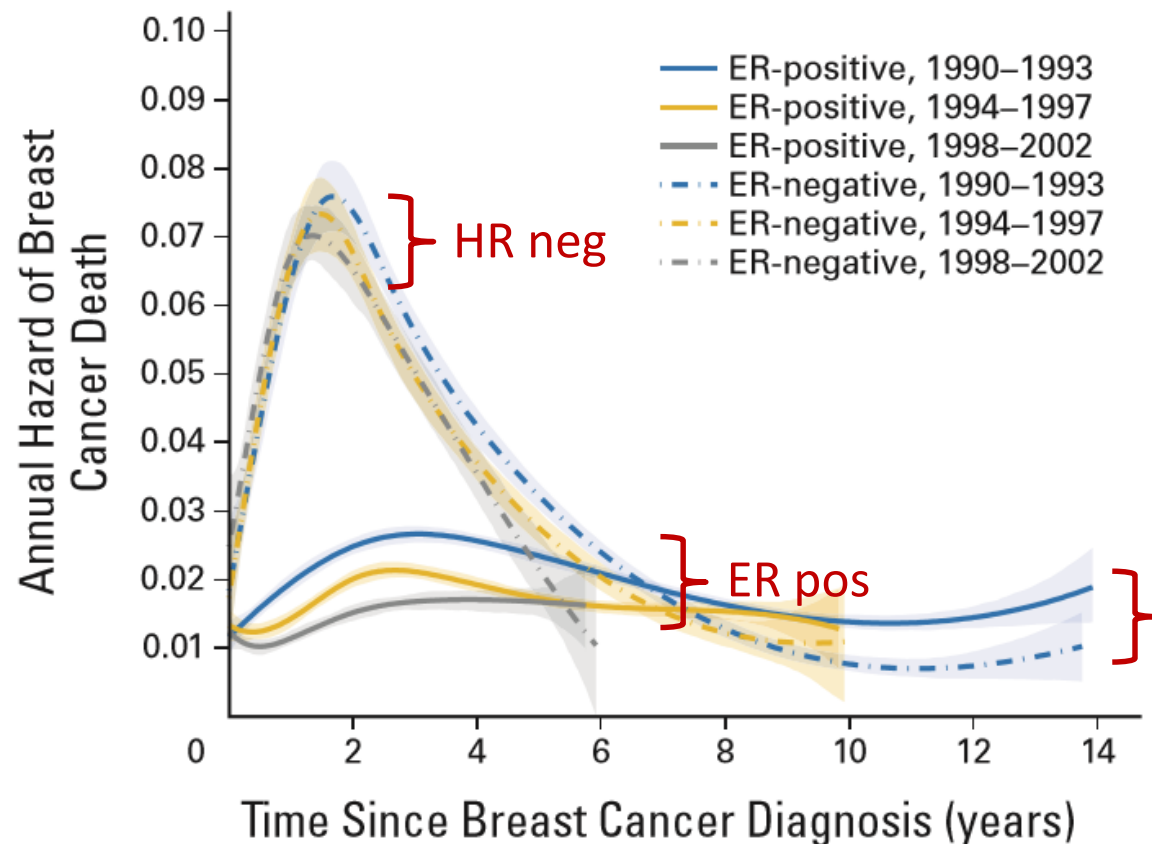
INTRODUCTION

Breast cancer mortality in the United States peaked in 1989 with an age-adjusted (2000 United States standard) mortality rate of 33 per 100,000 woman-years.¹ Thereafter, mortality rates declined 24% to 25 per 100,000 woman-years in 2003. Mathematical models and clinical trial results suggest that mammography screening and adjuvant systemic therapy are largely responsible for the overall decline in mortality.²⁻⁵

However, population-based mortality rates in subgroups of breast cancer patients have not been systematically described. Mammography screening preferentially detects indolent tumors, a disproportionate number of which are estrogen receptor (ER)-positive.⁶ In addition, ER status is a clinically

important predictive factor, forecasting response to systemic hormone therapy as well as to chemotherapy.^{7,7} Age at diagnosis is another potentially important predictive factor.^{8,9} Therefore, we hypothesized that national trends in breast cancer mortality may vary according to ER expression and age at diagnosis, as well as other variables such as stage and grade at diagnosis.

To examine breast cancer mortality trends in the United States according to these factors, we used the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program. SEER is a consortium of regional cancer registries with meticulous and consistent data collection and standards. SEER rates are considered to be nationally representative. Using SEER, we evaluated national trends in overall mortality, trends in incidence-based mortality



Crosstalk between Estrogen Receptor and Growth Factor Receptor Pathways as a Cause for Endocrine Therapy Resistance in Breast Cancer

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ABSTRACT

Data suggest that breast cancer growth is regulated by coordinated actions of the estrogen receptor (ER) and various growth factor receptor signaling pathways. In tumors with active growth factor receptor signaling (e.g., HER2 amplification), tamoxifen may lose its estrogen antagonist activity and may acquire more agonist-like activity, resulting in tumor growth stimulation. Because treatments designed to deprive the ER of its ligand estrogen will reduce signaling from both nuclear and membrane ER, aromatase inhibitors might be expected to be superior to tamoxifen in tumors with high growth factor receptor content, such as those overexpressing HER2. Recent clinical studies suggest that this is the case in humans, as trials of aromatase inhibitors show superior results compared with tamoxifen, especially in tumors overexpressing HER2. Although estrogen deprivation therapy is often effective in ER-positive breast cancer, *de novo* and acquired resistance are still problematic. Experimental models suggest that in one form of resistance to estrogen deprivation therapy, the tumor becomes supersensitive to low residual estrogen concentrations perhaps because of activation of mitogen-activated protein kinase. Such tumors respond to additional treatment with fulvestrant or even tamoxifen. On the other hand, in tumors overexpressing HER2, acquired resistance to estrogen deprivation therapy involves the loss of ER and ER-regulated genes and further up-regulation of growth factor signaling rendering the tumor hormonal therapy resistant. This process can be delayed or reversed by simultaneous treatment with growth factor pathway inhibitors. This strategy is now being tested in clinical trials.

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EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY IN BREAST CANCER

There is growing evidence that crosstalk between estrogen receptor (ER) and growth factor receptor signaling pathways, especially the epidermal growth factor receptor (EGFR) family, is one of the mechanisms for resistance to endocrine therapy in breast cancer (1-3). cErbB2 (HER2) is a member of this EGFR family of transmembrane tyrosine kinases. The family also includes HER3 and HER4 (ref. 4; Fig. 1). The role of HER4 is poorly understood. HER3 lacks a tyrosine kinase domain, and HER2 does not have a ligand to bind and activate it. These two proteins, therefore, mostly heterodimerize with another member of the family to generate the kinase cascade and downstream signals. This explains why tumors developing in transgenic mice engineered to overexpress HER2 in the ductal epithelium always overexpress HER3 as well (5). Growth factors such as epidermal growth factor (EGF), transforming growth factor α , and amphiregulin bind to the external domain of EGFR, which then induces either homo- or heterodimerization with another receptor in the family to activate the tyrosine kinase of the receptor (4). Heregulin and other ligands, on the other hand, bind to the external domain of HER3. This also initiates heterodimerization and then activation of Akt, Erk1/2 mitogen-activated protein kinase (MAPK) or other intermediates. Because HER2 does not have a ligand, it may be relatively inactive unless the cell also expresses EGFR or HER3, which can be activated by their respective ligands. HER2 is the preferred dimer partner for EGFR and HER3 because of its open conformation (6).

Activation of the EGFR/HER2 signaling pathway initiates a kinase signaling cascade that has a variety of effects on the tumor cells, including inhibition of apoptosis, stimulation of cell proliferation, enhanced invasion and cell motility, and induction of angiogenesis stimuli (Fig. 1). Cell survival and cell proliferation are mediated predominantly through the phosphatidylinositol 3'-kinase (PI3K)/Akt and the Erk1/2 MAPK pathways. These kinases are also important for ER activity in some tumors because they phosphorylate and thereby activate either ER itself or ER coregulators such as AIB1 and nuclear receptor corepressor (NCoR; refs. 2, 7-9). This phosphorylation augments the transcriptional activation potential of ER and enhances its effects on cell proliferation and survival. Working together in tumors expressing both ER and abundant HER2, these two pathways provide a strong stimulus for tumor growth and may contribute to hormonal therapy resistance.

ER IN BREAST CANCER

ER functions in the nucleus as a transcriptional regulator of specific genes (Fig. 2). The protein has a ligand-binding domain, several transcription activation domains, and a DNA-binding domain that interacts with specific regions in the promoter of

Endokrine Resistenz

overexpressing HER2. Although estrogen deprivation therapy is often effective in ER-positive breast cancer, *de novo* and acquired resistance are still problematic. Experimental models suggest that in one form of resistance to estrogen deprivation therapy, the tumor becomes supersensitive to low residual estrogen concentrations perhaps because of activation of mitogen-activated protein kinase. Such tumors respond to additional treatment with



ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)*



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* **Important note:** These Guidelines were developed by ESO and ESMO and are published in 2014.08.009 and Annals of Oncology (Ann Oncol 2014; 25: <http://dx.doi.org/10.1093/annonc/>

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Original article

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



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Guideline statement

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.

PRIMARY ENDOCRINE RESISTANCE is defined as: relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE

RESISTANCE is defined as: relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD \geq 6 months after initiating ET for MBC, while on ET.

LoE

Expert
opinion

Expert
opinion

Consensus

95.0% (38) Yes
5.0% (2)
Abstain
(40 voters)

66.6% (22) Yes
21.2% (7)
Abstain
(33 voters)

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sa and Karolinska University Hospital, Stockholm, Sweden

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Guideline statement	LoE	Consensus
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.	1 A	Voters: 41 Yes: 93% (38) Abstain: 7% (3)
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.	1 A	Voters: 44 Yes: 84% (37) Abstain: 7% (3)
The combination of a nonsteroidal AI and fulvestrant as first-line therapy for postmenopausal patients resulted in significant improvement in both PFS and OS compared to AI alone in one phase III trial and no benefit in a second trial with a similar design. Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen). Based on these data, combination ET may be offered to some patients with MBC without prior exposure to adjuvant ET.	2 B	Voters: 43 Yes: 33% (14) No: 53% (23) Abstain: 14% (6)

The addition of everolimus to an AI is a valid non-steroidal AI, since it significantly prolonged OS compared to AI alone on a subgroup basis.

Tamoxifen can also be combined with everolimus. The addition of the CDK4/6 inhibitor palbociclib to endocrine therapy in postmenopausal patients (except patients relapsing <12 months after PFS (10 months), with an acceptable toxicity profile) is a valid option. OS results are still awaited.

ESMO MCBS: 3*

The addition of CDK4/6 inhibitor palbociclib to endocrine therapy in postmenopausal patients, provided significant improvement in OS compared to endocrine therapy alone. OS results are awaited.

For pre/peri-menopausal pts, an LHRH-agonist is the preferred option. At present, no predictive biomarker other than the type of agents and research efforts are ongoing.

ESMO MCBS: 4*

The optimal sequence of endocrine agents after (neo)adjuvant and 1st line ABC settings. A combination of AI + everolimus, tamoxifen + everolimus, or AI + fulvestrant + everolimus. It is currently unknown how the different combinations compare with single agent CT. Several trials are ongoing. For pre-menopausal women, for whom ET was not used, endocrine therapy is the preferred choice.

Ovarian ablation by laparoscopic bilateral oophorectomy avoids potential initial tumor flare with LHRH-agonist. Patients should be informed on the options of ovarian suppression/ablation. For pre-menopausal women, the additional use of endocrine therapy prior adjuvant endocrine therapy but AI alone is not recommended. Fulvestrant is also a valuable option, but for

• Endokrine Therapie 1st line

• Postmenopause

- AI/Tam/Fulvestrant 84%
- AI+ Fulvestrant 33%
- AI (Tam) + Everolimus 84%
- AI + CDK4/6 92%

• Prämenopause

- OS + endokrine Therapie 91%
- Fulvestrant 95%

5.18.	<p>Konsensbasierte Empfehlung</p> <p>Fulvestrant bei postmenopausalen Patientinnen</p>
EK	<p>Eine <u>Behandlung mit Fulvestrant sollte insbesondere nach Vorbehandlung mit einem Aromatasehemmer erfolgen</u>, kann aber auch als erste Therapielinie eingesetzt werden, insbesondere bei noch nicht endokrin vorbehandelten Patientinnen.</p>
5.19.	<p>Konsensbasierte Empfehlung</p> <p>Kombinationstherapien bei postmenopausalen Patientinnen</p>
EK	<p>Eine bestimmte Therapiesequenz kann nicht empfohlen werden. Eine <u>Kombinationsbehandlung von Letrozol oder Fulvestrant mit einem CDK4/6-Inhibitor stellt eine Therapiealternative zur Monotherapie dar.</u></p> <p><u>Nach antihormoneller Vortherapie mit einem nicht-steroidalen Aromatasehemmer kann eine Folgetherapie mit Exemestan und dem mTOR-Inhibitor Everolimus durchgeführt werden.</u></p> <p>Kombinationstherapien konnten in Studien eine Verlängerung des Progressionsfreien Überlebens, bislang aber nicht des Gesamtüberlebens zeigen.</p>

Tam

AI

Fulvestrant

PI3ki



Wohin geht die Reise???

CDK4/6i

Tam

AI

Fulvestrant

PI3Ki



Wohin geht die Reise???

CDK4/6i

Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFACT

Stephen Chia, William Gradishar, Louis Mauriac, Jose Bines, Frederic Amant, Miriam Federico, Luis Fein, Gilles Romieu, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Kurt Possinger, Pamela Rennie, Francisco Sapunar, Elizabeth Lowe, and Martine Piccart

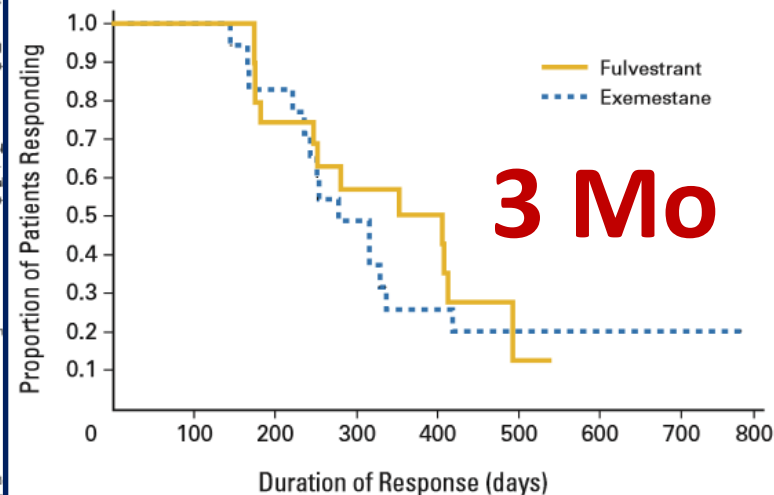
ABSTRACT

Purpose

The third-generation nonsteroidal aromatase inhibitors (AIs) are increasingly used as adjuvant and first-line advanced therapy for postmenopausal, hormone receptor–positive (HR+) breast cancer. Because many patients subsequently experience progression or relapse, it is important to identify agents with efficacy after AI failure.

Materials and Methods

Evaluation of Everlast versus Exemestane Clinical Trial (EFACT) is a randomized, double-blind



Days	0	50	100	150	200	250	300	350	400	450	500	550	600	650	700
Fulvestrant at risk	20	20	20	20	15	13	10	9	8	3	1	0	0	0	0
Exemestane at risk	18	18	18	17	15	12	9	5	5	4	3	3	3	3	2

therapeutic options in breast cancer.

postmenopausal advanced breast cancer (ABC),

Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment

By A. Howell, J.F.R. Robertson, J. Quaresma Albano, A. Aschermannova, L. Mauriac, U.R. Kleeberg, I. Vergote, B. Erikstein, A. Webster, and C. Morris

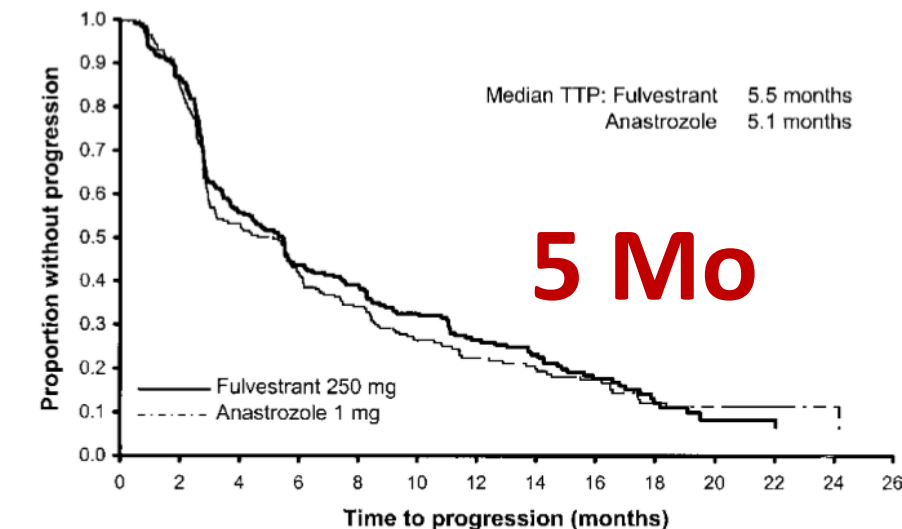
Purpose: To compare the efficacy and tolerability of fulvestrant (formerly ICI 182,780) and anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.

Patients and Methods: Patients (n = 451) with advanced breast cancer were randomized to receive fulvestrant 250 mg as a once-monthly (one × 5 mL) intramuscular injection or an oral dose of anastrozole 1 mg in this open, parallel-group, multicenter trial. The primary end point was time to progression (TTP). Secondary end points included objective response (OR) rates, defined as complete response (CR) or partial response (PR), duration of response (DOR), and tolerability.

Results: Patients were followed for a median period of 14.4 months. In terms of TTP, fulvestrant was as effective as anastrozole (hazard ratio, 0.98; confidence interval [CI], 0.80 to 1.21; P = .84). Median TTP was 5.5 months for fulvestrant and 5.1 months for anastrozole.

OR rates showed a numerical advantage for fulvestrant (20.7%) over anastrozole (15.7%) (odds ratio, 1.38; CI, 0.84 to 2.29; P = .20). Clinical benefit rates (CR + PR + stable disease ≥ 24 weeks) were 44.6% for fulvestrant and 45.0% for anastrozole. Median DOR was 14.3 months for fulvestrant and 14.0 months for anastrozole. Both treatments were well tolerated, with 3.2% and 1.3% of fulvestrant- and anastrozole-treated patients, respectively, withdrawn from treatment because of an adverse event.

Conclusion: Fulvestrant was as effective as anastrozole. These data confirm that fulvestrant is an additional, effective, and well-tolerated treatment for advanced breast cancer in postmenopausal women whose disease progressed on prior endocrine therapy. *J Clin Oncol* 20:3396-3403. © 2002 by American Society of Clinical Oncology.



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activity in tamoxifen-resistant breast cancer and also sug-

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ORIGINAL ARTICLE

Combination Anastrozole and Fulvestrant in Metastatic Breast Cancer

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ABSTRACT

BACKGROUND

The aromatase inhibitor anastrozole inhibits estrogen synthesis. Fulvestrant binds and accelerates degradation of estrogen receptors. We hypothesized that these two agents in combination might be more effective than anastrozole alone in patients with hormone-receptor (HR)-positive metastatic breast cancer.

METHODS

Postmenopausal women with previously untreated metastatic disease were randomly assigned, in a 1:1 ratio, to receive either 1 mg of anastrozole orally every day (group 1), with crossover to fulvestrant alone strongly encouraged if the disease progressed, or anastrozole and fulvestrant in combination (group 2). Patients were stratified according to prior or no prior receipt of adjuvant tamoxifen therapy. Fulvestrant was administered intramuscularly at a dose of 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter. The primary end point was progression-free survival, with overall survival designated as a prespecified secondary outcome.

RESULTS

The median progression-free survival was 13.5 months in group 1 and 15.0 months in group 2 (hazard ratio for progression or death with combination therapy, 0.80; 95% confidence interval [CI], 0.68 to 0.94; $P=0.007$ by the log-rank test). The combination therapy was generally more effective than anastrozole alone in all subgroups, with no significant interactions. Overall survival was also longer with combination therapy (median, 41.3 months in group 1 and 47.7 months in group 2; hazard ratio for death, 0.81; 95% CI, 0.65 to 1.00; $P=0.05$ by the log-rank test), despite the fact that 41% of the patients in group 1 crossed over to fulvestrant after progression. Three deaths that were possibly associated with treatment occurred in group 2. The rates of grade 3 to 5 toxic effects did not differ significantly between the two groups.

CONCLUSIONS

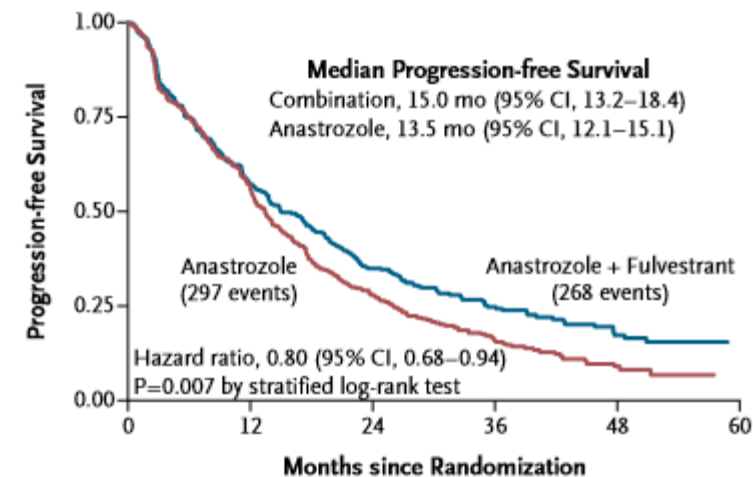
The combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of HR-positive metastatic breast cancer, despite the use of a dose of fulvestrant that was below the current standard. (Funded by the National Cancer Institute and AstraZeneca; SWOG ClinicalTrials.gov number, NCT00075764.)

From the University of California Irvine Medical Center, Chao Family Comprehensive Cancer Center, Orange (R.S.M.); SWOG Statistical Center (W.E.B., D.L.L.) and Puget Sound Cancer Consortium/Seattle Cancer Care Alliance (J.R.G.) — both in Seattle; Loyola University Chicago Stritch School of Medicine, Maywood, IL (K.S.A.); London Health Sciences Center/ National Cancer Institute of Canada Clinical Trials Group, London, ON, Canada (T.A.V.); Wichita Community Clinical Oncology Program (CCOP), Wichita, KS (S.R.D.); Northwest CCOP/Northwest Permanente, Portland, OR (N.R.T.); University of Michigan, Ann Arbor (D.F.H.); University of Arizona/Arizona Cancer Center, Tucson (R.B.L.); and University of Texas M.D. Anderson Cancer Center, Houston (G.N.H.). Address reprint requests to Dr. Mehta at the University of California Irvine Medical Center, Chao Family Comprehensive Cancer Center, 101 The City Dr., Bldg. 23, Orange, CA 92668, or at rsmehta@uci.edu.

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No. at Risk						
Anastrozole + fulvestrant	349	199	114	53	21	8
Anastrozole	345	193	92	39	11	3

1.5 Mo

CONCLUSIONS

The combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of HR-positive metastatic breast cancer, despite the use of a dose of fulvestrant that was below the current standard. (Funded by the National Cancer Institute and AstraZeneca; SWOG ClinicalTrials.gov number, NCT00075764.)

FALCON

Secondary endpoints

Primary endpoint: PFS^a

1:1

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and / or PgR+
- HER2-
- Endocrine therapy-naïve

Fulvestrant 500 mg
(500 mg IM on Days 0, 14 and 28, then every 28 days)
+ placebo to anastrozole

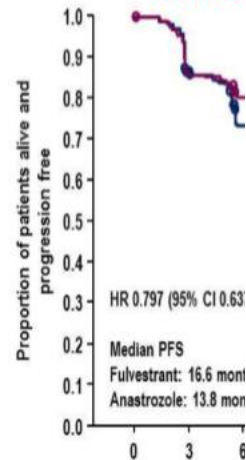
Anastrozole 1 mg
(daily PO)
+ placebo to fulvestrant

- OS^b
- ORR
- CBR
- DoR, EDoR
- DoCB, EDoCB
- HRQoL (FACT-B total and TOI)
- Safety

^aAssessed via RECIST 1.1, surgery / radiotherapy for disease worsening, or death; ^bInterim analysis at the time of PFS analysis
EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; FACT-B, Functional Assessment of Cancer Therapy – Breast;
TOI, Trial Outcome Index

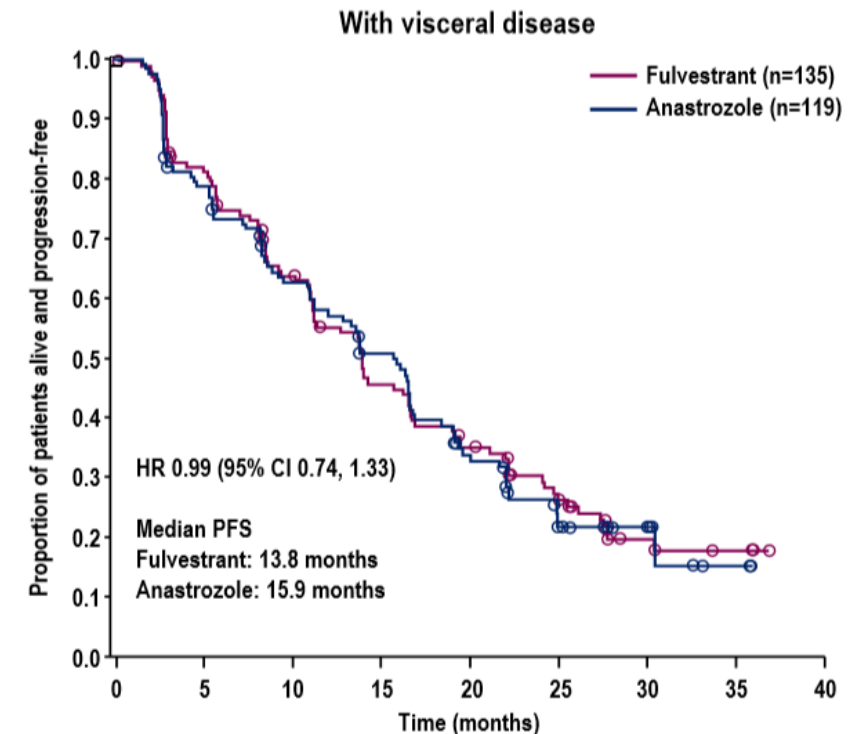
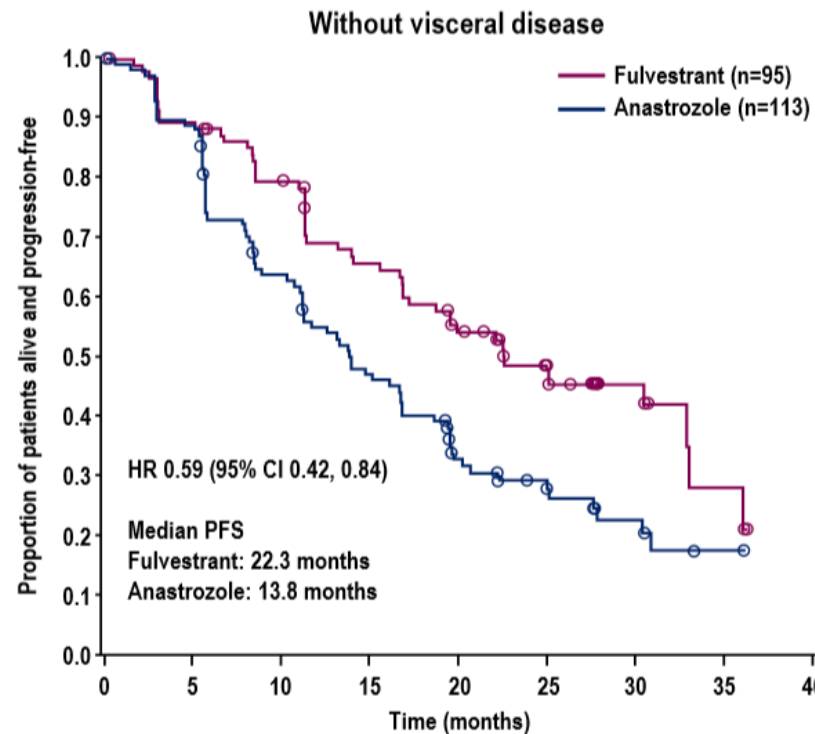
FALCON Study: Efficacy

FALCON: PFS In Patients With/Without Visceral Disease



Number of patients at risk:

	0	3	6
Fulvestrant	230	187	17
Anastrozole	232	194	16



Tam

AI

Fulvestrant

PI3ki



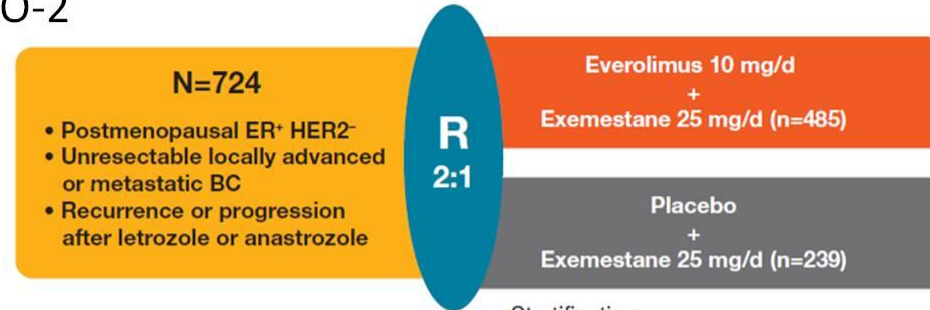
Wohin geht die Reise???

CDK4/6i

5.18.	<p>Konsensbasierte Empfehlung</p> <p>Fulvestrant bei postmenopausalen Patientinnen</p>
EK	<p>Eine <u>Behandlung mit Fulvestrant sollte insbesondere nach Vorbehandlung mit einem Aromatasehemmer erfolgen</u>, kann aber auch als erste Therapielinie eingesetzt werden, insbesondere bei noch nicht endokrin vorbehandelten Patientinnen.</p>
5.19.	<p>Konsensbasierte Empfehlung</p> <p>Kombinationstherapien bei postmenopausalen Patientinnen</p>
EK	<p>Eine bestimmte Therapiesequenz kann nicht empfohlen werden. Eine <u>Kombinationsbehandlung von Letrozol oder Fulvestrant mit einem CDK4/6-Inhibitor stellt eine Therapiealternative zur Monotherapie dar.</u></p> <p><u>Nach antihormoneller Vortherapie mit einem nicht-steroidalen Aromatasehemmer kann eine Folgetherapie mit Exemestan und dem mTOR-Inhibitor Everolimus durchgeführt werden.</u></p> <p>Kombinationstherapien konnten in Studien eine Verlängerung des Progressionsfreien Überlebens, bislang aber nicht des Gesamtüberlebens zeigen.</p>

mTOR Inhibition for AI Resistant HR+ HER2- MBC

BOLERO-2

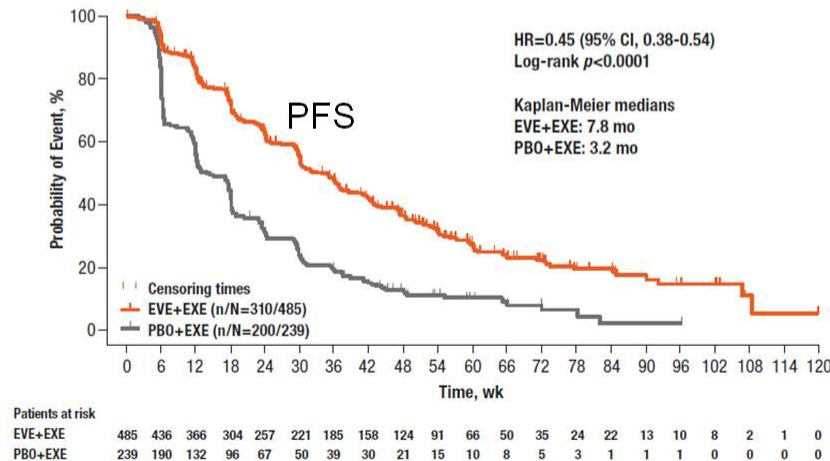


Endpoints

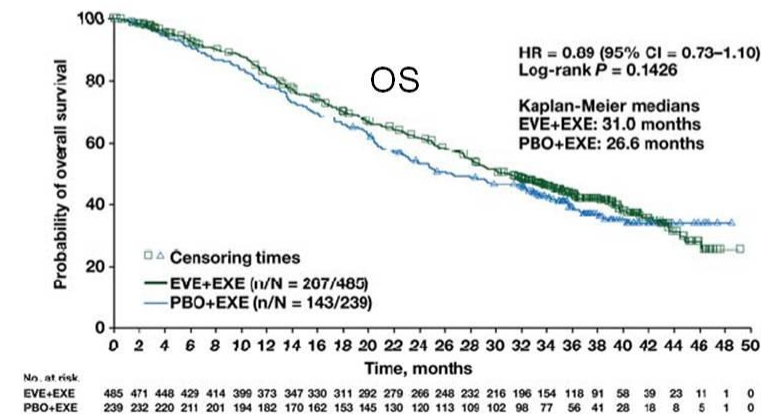
- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, CBR, QOL, safety,

- Stratification:
 1. Sensitivity to prior hormonal therapy
 2. Presence of visceral disease
- No crossover

Endpoints



Yardley DA, et al. *Adv Ther.* 2013;30:870-884



Piccart, et al, *Ann Oncol.* 2014



JUNE 2-6, 2017
McCormick Place | Chicago, Illinois
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BOLERO-4



DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

June 1-5, 2018
McCormick Place | Chicago, IL
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BOLERO-6

Everolimus + Exemestane vs Everolimus Alone or Capecitabine for Estrogen Receptor-Positive, HER2– Advanced Breast Cancer

BOLERO-6, a Randomized, Open-label, Phase II Study

Guy Jerusalem,¹ Elena Kovalenko,² Denise A. Yardley,³ Richard de Boer,⁴ Sara Hurvitz,⁵ Bent Ejlersen,⁶ Sibel Blau,⁷ Mustafa Özgüroğlu,⁸ László Landherr,⁹ Marianne Ewertz,¹⁰ Tetiana Taran,¹¹ Jenna Fan,¹¹ Florence Noel-Baron,¹² Anne-Laure Louveau,¹³ Howard Burris³

¹CHU Sart Tilman Liège and Liège University, Liège, Belgium; ²Russian Cancer Research Center, Moscow, Russia; ³Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; ⁴Royal Melbourne Hospital, Victoria, Australia; ⁵UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; ⁶Copenhagen University Hospital, Copenhagen, Denmark; ⁷Rainier Hematology-Oncology/Northwest Medical Specialties, Tacoma, WA; ⁸Cerrahpaşa School of Medicine, Istanbul University, Istanbul, Turkey; ⁹Uzsoki Teaching Hospital, Budapest, Hungary; ¹⁰Odense University Hospital, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; ¹¹Novartis Pharmaceuticals Corporation, East Hanover, NJ; ¹²Novartis Pharma AG, Basel, Switzerland ¹³Novartis Pharma S.A.S., Paris, France

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PRESENTED BY: Guy Jerusalem

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

1

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

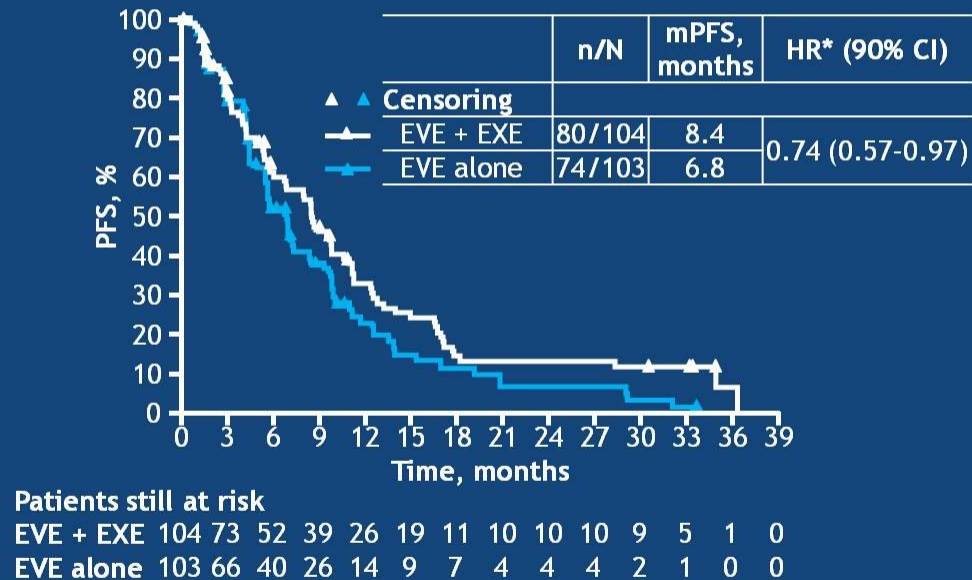
- BOLERO-6 was not powered to perform statistical comparisons between arms

*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.

Primary Objective

Estimated HR of PFS for EVE + EXE vs EVE alone

EVE + EXE offers a PFS benefit vs EVE alone



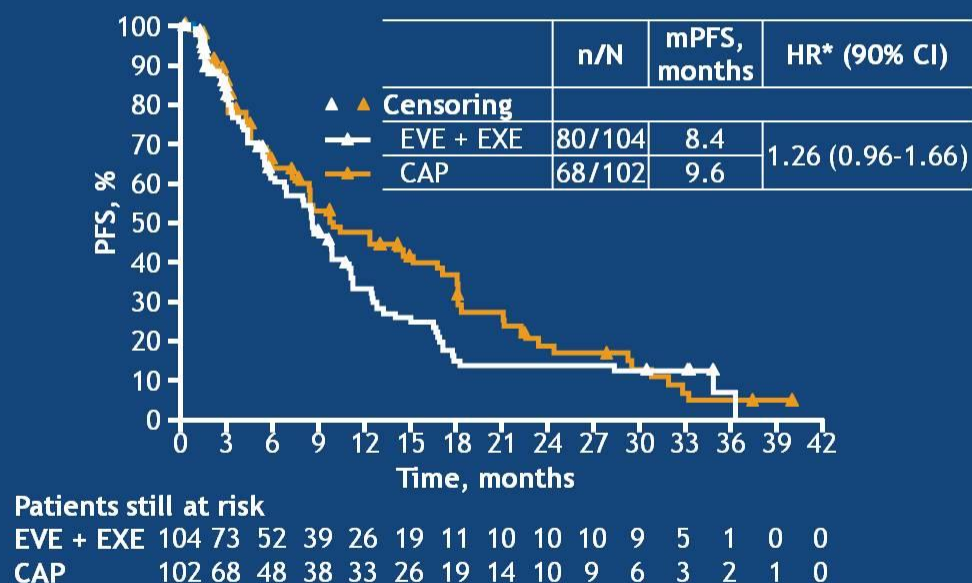
- Estimated HR of PFS for EVE + EXE vs EVE alone was 0.74 (90% CI 0.57-0.97)
- Censored for initiating new antineoplastic therapies:
 - EVE + EXE arm, 9%
 - EVE alone arm, 18%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave a **consistent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

Key Secondary Objective

Estimated HR of PFS for EVE + EXE vs CAP

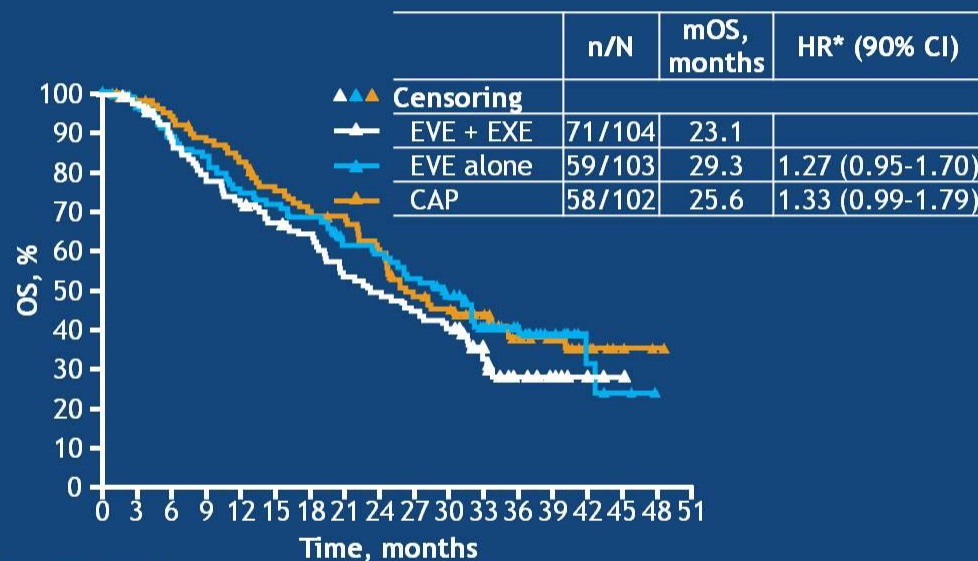
CAP may have been favored by baseline imbalances and potential informative censoring



- 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).

Overall Survival EVE + EXE vs EVE alone or CAP



Patients still at risk

EVE + EXE	104	101	92	81	74	67	63	53	48	43	39	22	13	8	3	1	0	0
EVE alone	103	96	86	81	72	69	66	57	55	49	43	27	21	11	4	2	0	0
CAP	102	94	88	83	78	70	64	61	54	43	38	31	21	16	7	3	1	0

- New antineoplastic therapies initiated at EOT:

- EVE + EXE arm, 78%
- EVE alone arm, 81%
- CAP arm, 79%

- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave a HR of 1.27 (90% CI 0.94-1.70) for EVE + EXE vs EVE alone and a HR of 1.19 (90% CI 0.88-1.62) for EVE + EXE vs CAP

*EVE + EXE vs EVE alone or CAP (obtained from a stratified Cox model).
EOT, end of treatment; mOS, overall survival.

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 SWISH¹ protocol for stomatitis prevention.
 AE, adverse event; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.
 1. Ruqo HS et al. *Lancet Oncol* 2017;18:654-662.

Zusammenfassung

- Median PFS Eve + EXE vs Eve 8.4 mo vs 6.8 mo
- Resultate konsistent mit BOLERO 2 (7.8 mo)
- Resultate bestätigen Benefit Eve + Exe vs Eve
- Risikoprofil unverändert im Vergleich mit BOLERO 2

Publication in *JAMA Oncology*

Research

JAMA Oncology | **Original Investigation**

Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer (BOLERO-6) A Phase 2 Randomized Clinical Trial

Guy Jerusalem, MD, PhD; Richard H. de Boer, MBBS, FRACP; Sara Hurvitz, MD; Denise A. Yardley, MD; Elena Kovalenko, MD; Bent Ejlersen, MD; Sibel Blau, MD; Mustafa Özgüroğlu, MD; László Landherr, PhD; Marianne Ewertz, MD; Tetiana Taran, MD; Jenna Fan, MD, PhD; Florence Noel-Baron, PhD; Anne-Laure Louveau, MS; Howard Burris, MD

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Memorial Sloan Kettering
Cancer Center

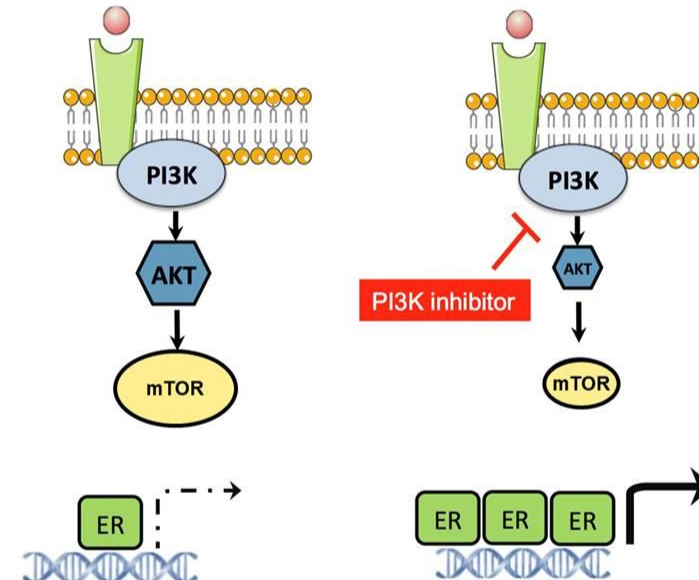
Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, *PIK3CA*-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER.

José Baselga,¹ Susan Dent,² Javier Cortés,³ Young-Hyuck Im,⁴ Véronique Diéras,⁵ Nadia Harbeck,⁶
Ian E. Krop,⁷ Sunil Verma,⁸ Timothy R. Wilson,⁹ Huan Jin,⁹ Lijia Wang,⁹ Frauke Schimmoller,⁹
Jerry Y. Hsu,⁹ Jing He,⁹ Michelino De Laurentiis,¹⁰ Pamela Drullinsky,¹ William Jacot¹¹

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada;
³Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, and Ramón y Cajal University Hospital, Madrid, Spain; ⁴Samsung
Medical Center, Seoul, Republic of Korea; ⁵Institut Curie, Paris, and Centre Eugène Marquis, Rennes, France; ⁶Brustzentrum der
Universität München (LMU), Munich, Germany; ⁷Dana-Farber Cancer Institute, Boston, MA, USA; ⁸Tom Baker Cancer Centre,
Department of Oncology, University of Calgary, AB, Canada; ⁹Genentech Inc., South San Francisco, CA, USA; ¹⁰Istituto Nazionale
Tumori Fondazione G. Pascale, Naples, Italy; ¹¹Institut du Cancer de Montpellier, Montpellier, France.

PI3K signaling is frequently dysregulated¹ and PI3K inhibition augments ER function and dependence in hormone receptor-positive breast cancer^{2,3}

- PI3K signaling is involved in tumor growth, proliferation, and survival, and is frequently activated in solid tumours¹
- The PI3K pathway may be activated by gain-of-function mutations and/or amplification of the *PIK3CA* gene^{1,4-7}
 - *PIK3CA* encodes the α -isoform of the catalytic subunit of PI3K (PI3K α)
- Mutations in *PIK3CA* are detected in ~40% of ER-positive, HER2-negative breast cancer⁸
- There is significant crosstalk between the ER and PI3K signaling pathways; inhibition of PI3K results in an adaptive upregulation of ER signaling^{2,3}



AKT, protein kinase B; ER, estrogen receptor;
 HER2, human epidermal growth factor receptor 2;
 mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase;
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.

1. Fruman DA, et al. *Cell* 2017; **170**:605–635; 2. Bosch A, et al. *Sci Transl Med* 2015; **7**:283ra51;
3. Toska E, et al. *Science* 2017; **355**:1324–1330. 4. Samuels Y, et al. *Science* 2004; **304**:554;
5. Zhang Y, et al. *Cancer Cell* 2017; **31**:820–832; 6. Zehir A, et al. *Nat Med* 2017; **23**:703–713;
7. Janku F, et al. *Nat Rev Clin Oncol* 2018; Epub ahead of print;
8. Arthur LM, et al. *Breast Cancer Res Treat* 2014; **147**:211–219;

Rationale for SANDPIPER: Taselisib is a mutant-selective next-generation PI3K inhibitor

Greater selectivity *in vitro* against mutant PI3Kα isoforms and cells than wildtype PI3Kα¹⁻⁴

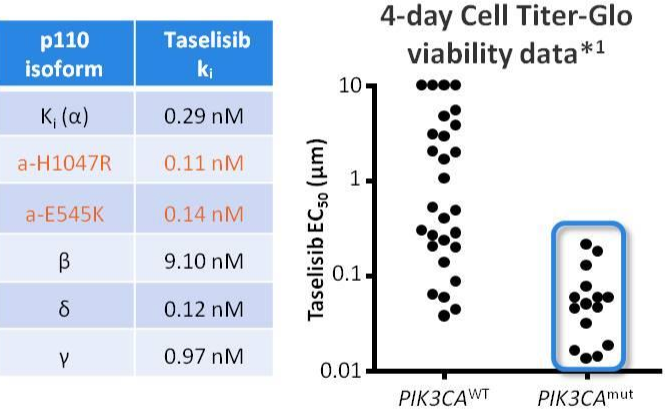
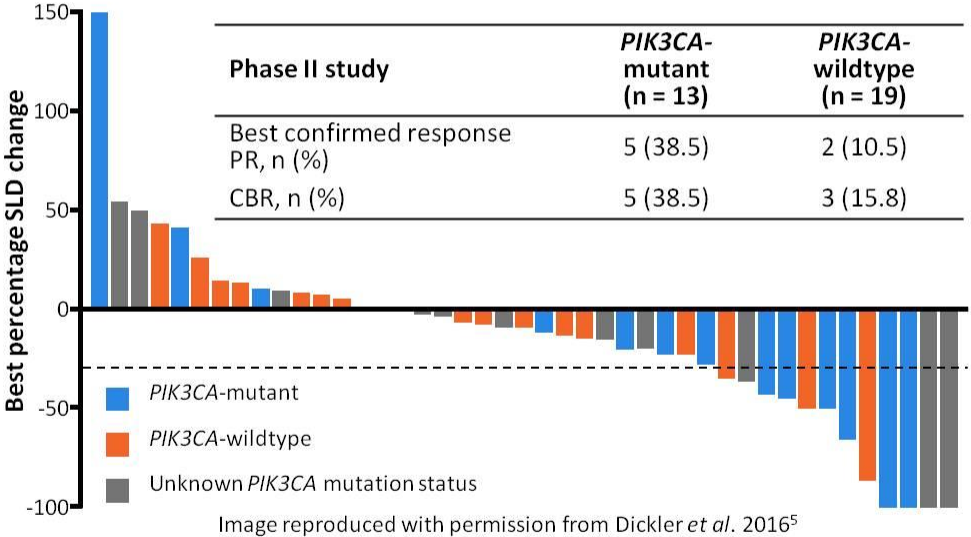


Table and image adapted with permission from Olivero *et al.* 2014.¹

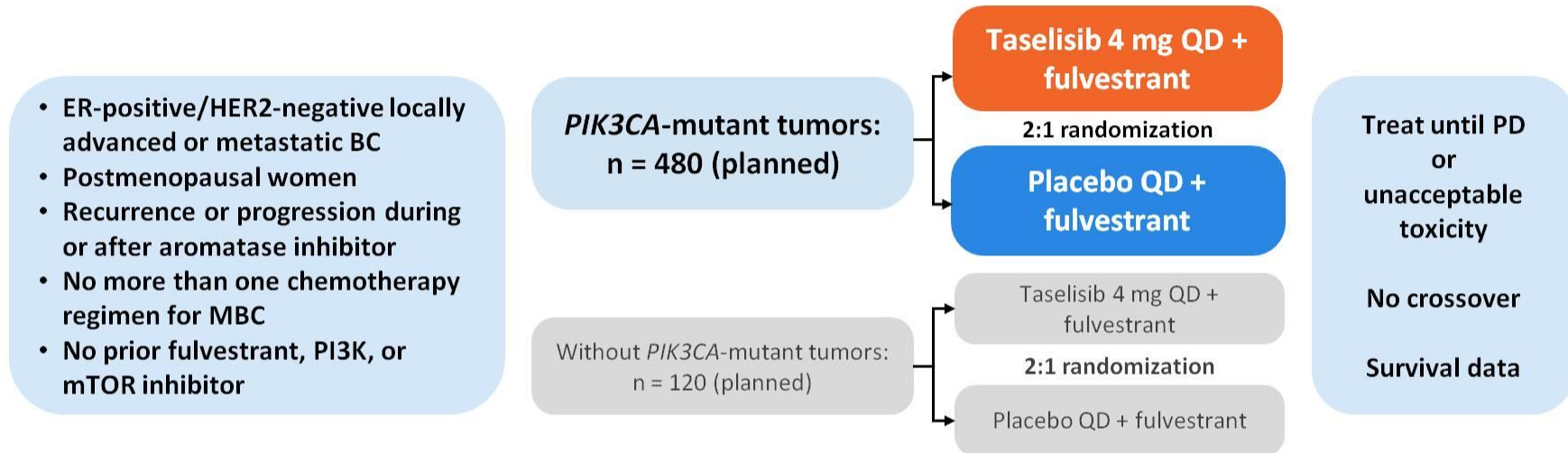
* Each dot represents a different cancer cell line in a viability assay. EC_{50} is the effective concentration required to induce a 50% effect. CBR, clinical benefit rate; mut, mutant; PR, partial response; SLD, sum of the longest diameter; WT, wildtype.

High response rates in patients with *PIK3CA*-mutated tumors treated with taselisib plus fulvestrant (v *PIK3CA*-wildtype tumors)⁵



1. Olivero AG, *et al. Cancer Res* 2013; **73**: Abstract DDT02-01 (and associated oral presentation);
 2. Ndubaku CO, *et al. J Med Chem* 2013; **56**:4597-4610;
 3. Wallin J, *et al. Cancer Res* 2014; **73**: Abstract P2-17-01 (and associated poster presentation);
 4. Juric D, *et al. Cancer Discov* 2017; **7**:704-715;
 5. Dickler M, *et al. J Clin Oncol* 2016; **34** (suppl): Abstract 520 (and associated poster presentation).

SANDPIPER study design



Primary Endpoint:

- INV-PFS in patients with *PIK3CA*-mutant tumors (central Roche cobas® test*)

Secondary Endpoints:

- ORR, OS, CBR, DoR, BICR-PFS in patients with *PIK3CA*-mutant tumors
- Safety

Exploratory Endpoint:

- Efficacy in patients without *PIK3CA*-mutant tumors

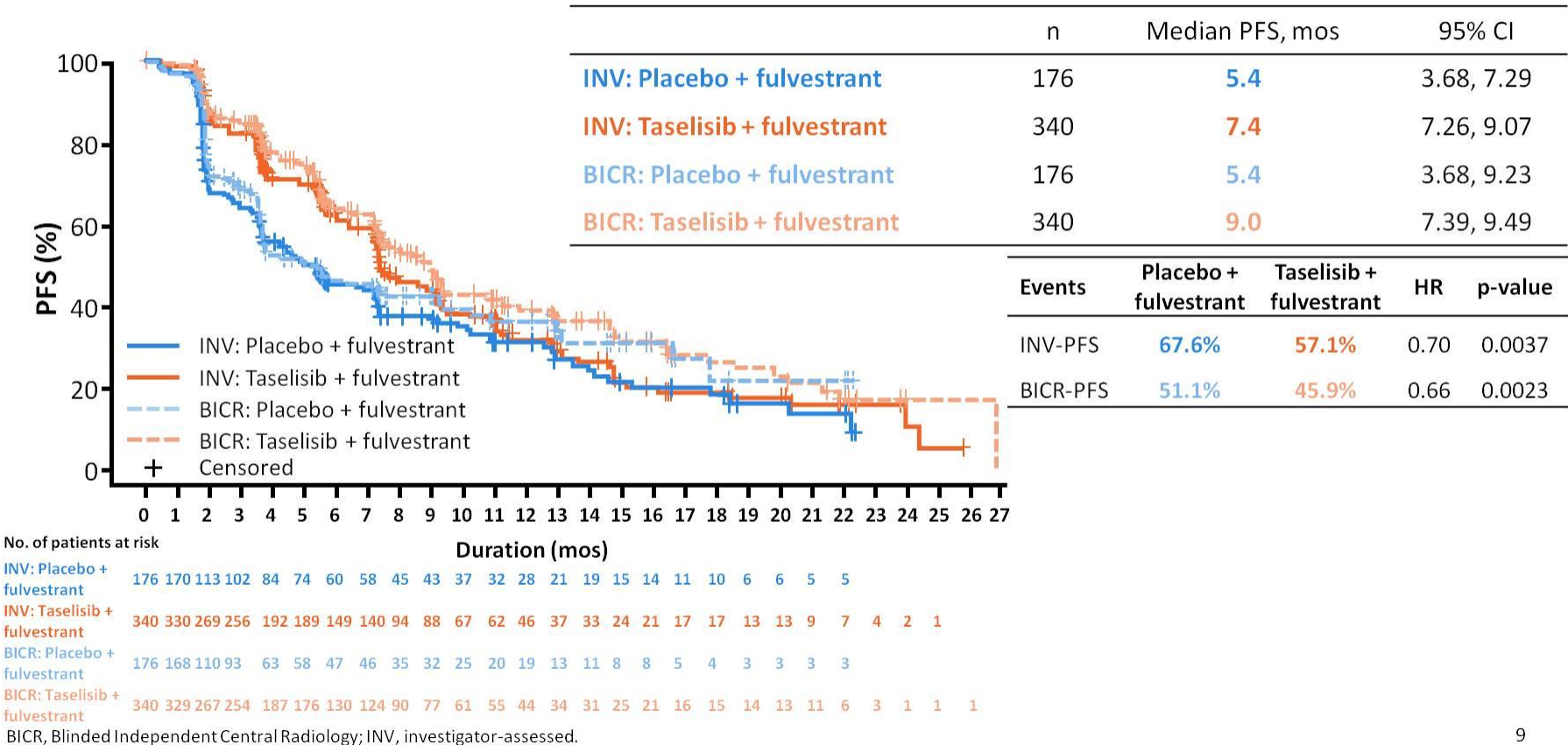
Stratification:

1. Visceral disease
2. Endocrine sensitivity
3. Geographic region

Endocrine sensitivity: 1) If no endocrine treatment in advanced or MBC, ≥24 months of adjuvant endocrine treatment prior to recurrence; 2) Documented clinical benefit (CR, PR, or SD ≥24 weeks) to most recent endocrine treatment in advanced or MBC.

* Roche cobas® test detects the following *PIK3CA* mutations: R88Q, N345K, C420R, E542K, E545A/G/K/D, Q546K/R/E/L, M1043I, H1047L/R/Y, and G1049R. BICR, Blinded Independent Central Radiology; CR, complete response; DoR, duration of response; INV, investigator-assessed; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease; QD, daily.

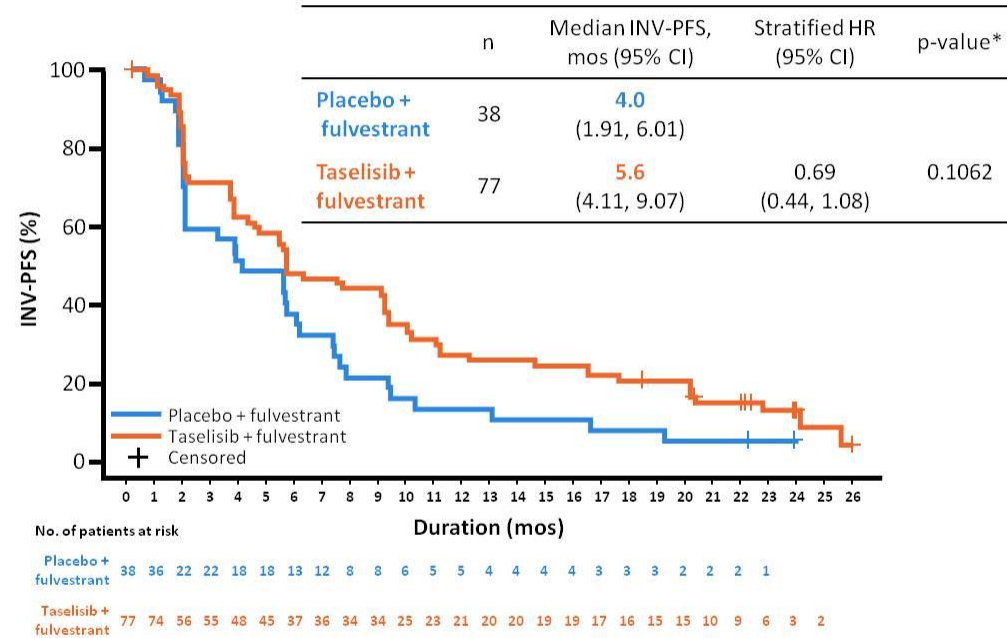
Blinded Independent Central Radiology confirmed INV-PFS



Exploratory endpoint

Efficacy in patients without PIK3CA-mutant tumors

Patients with baseline measurable disease	Placebo + fulvestrant (n = 35)	Taselisib + fulvestrant (n = 61)
Responders	14.3%	19.7%
p-value difference in response rate	p = 0.37	



* Stratified log-rank.

14

Summary of AEs (*safety-evaluable patients; regardless of causality*)

Most frequent AEs, any grade (≥10% in the taselisib arm)

MedDRA-preferred term (unless specified)	Placebo + fulvestrant (n = 213)	Taselisib + fulvestrant (n = 416)
Diarrhea*	19.7%	60.1%
Hyperglycemia*	9.4%	40.4%
Nausea	24.4%	34.1%
Decreased appetite	10.3%	26.4%
Fatigue	17.8%	24.3%
Headache	11.7%	20.2%
Stomatitis*	8.5%	33.2%
Vomiting	11.3%	18.8%
Asthenia	18.3%	18.5%
Rash*	11.3%	25.2%
Cough	13.1%	13.0%
Back pain	11.3%	13.0%
Abdominal pain	8.9%	12.3%
Dry mouth	7.5%	12.3%
Arthralgia	12.7%	11.5%
Alopecia	2.8%	11.3%
Pruritus	7.5%	11.1%
Pyrexia	3.3%	10.6%
Dyspnea	8.0%	10.3%

Grade ≥3 AEs (>1% in the taselisib arm)

MedDRA-preferred term (unless specified)	Placebo + fulvestrant (n = 213)	Taselisib + fulvestrant (n = 416)
Diarrhea*	0.9%	11.5%
Hyperglycemia*	0.5%	10.8%
Rash*	—	3.8%
Stomatitis*	—	3.6%
ALT/AST increase	0.5%	3.3%
Colitis*	—	3.1%
Hypertension	3.3%	2.4%
Dehydration	0.5%	1.9%
Lipase increased	0.9%	1.7%
Neutropenia	0.9%	1.7%
Vomiting	0.9%	1.7%
Pneumonitis*	0.5%	1.7%
Pneumonia	—	1.7%
Sepsis	0.5%	1.2%
Diarrhea infectious	—	1.2%
Hypokalemia	—	1.2%

* Frequencies of selected AEs are based on “group” terms of relevant events associated with taselisib, not preferred terms.
 Selected AEs were grade 3, except for grade 5 pneumonitis in the placebo arm and two grade 4 hyperglycemia events in taselisib arm.
 ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Zusammenfassung

- PIK3Ca Mut
 - Median PFS Taselisib + Fulv vs PI + Fulv 7.4 mo vs 5.4 mo ; HR 0.70; $p=0.0037$
- PIK3Ca Nicht- Mut
 - Keine schlüssige Resultate
 - Median PFS Taselisib + Fulv vs PI + Fulv 5.6 mo vs 4.0 mo ; HR 0.69; $p=0.1062$
- AE: GI & Hyperglycemia
- Tolerabilität? Klinische Anwendung?

The PI3K-AKT-mTOR Pathway: Are We Making Headway?

Cynthia X. Ma, M.D., Ph.D.

Associate Professor of Medicine

Clinical Director of the Breast Cancer Program

Section of Medical Oncology, Division of Oncology, Department of Medicine

Washington University School of Medicine, St. Louis, MO

PRESENTED AT: **2018 ASCO**
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PRESENTED BY: Cynthia X Ma, MD, PhD

<http://clicktoeditURL.com>

1

mTOR Inhibition for AI Resistant HR+ HER2- MBC

BOLERO-2

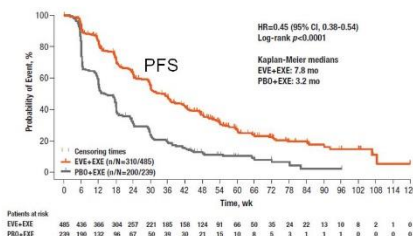


Endpoints

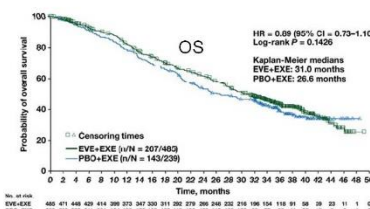
- Primary: PFS (local assessment)
- Secondary: OS, ORR, CBR, QOL, safety,

- Stratification:
 - Sensitivity to prior hormonal therapy
 - Presence of visceral disease
- No crossover

Endpoints



Yardley DA, et al. *Adv Ther*. 2013;30:870-884

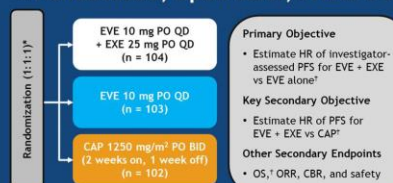


Piccari, et al, *Ann Oncol*. 2014

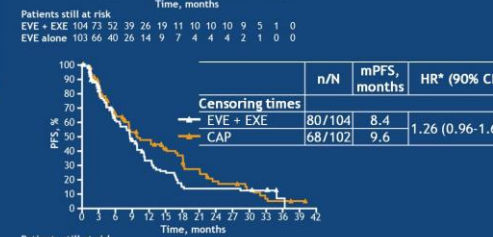
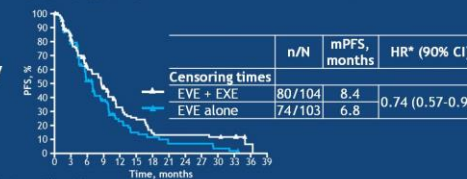
mTOR Inhibition for AI Resistant HR+ HER2- MBC

BOLERO-6:

A Randomized, Open-label, Phase II Study



	n/N	mOS, months	HR* (90% CI)
Censoring times			
EVE + EXE	71/104	23.1	
EVE alone	59/103	29.3	1.27 (0.95-1.70)
CAP	58/102	25.6	1.33 (0.99-1.79)



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6

PI3K Inhibition for AI Resistant HR+ HER2- MBC

BELLE-2 (Pan-PI3K Inhibitor Buparlisib)

	BELLE 2 (AI resistant)				BELLE 3 (AI and mTORi resistant)			
	FUL + Placebo	FUL + Buparlisib	HR (95% CI)	P value	FUL + Placebo	FUL + Buparlisib	HR (95% CI)	P value
Overall population	5.0 m. (N=571)	6.9 m. (N=576)	0.78 (0.67, 0.89)	0.00021	1.8 m. (N=143)	3.9 m. (N=289)	0.67 (0.53, 0.84)	0.00030
Tumor PI3K-activated*	4.0 m. (N=184)	6.8 m. (N=188)	0.76 (0.60, 0.97)	0.014	1.4 m. (N=34)	4.7 m. (N=75)	0.39 (0.23, 0.65)	<0.001
Tumor PI3K WT					2.7 m. (N=69)	2.8 m. (N=135)	0.83 (0.60, 1.14)	0.117
ctDNA PIK3CA Mut.	3.2 m. (N=113)	7.0 m. (N=87)	0.58 (0.41, 0.82)	0.001	1.6 m. (N=35)	4.2 m. (N=75)	0.46 (0.29, 0.73)	<0.001
ctDNA PIK3CA WT	6.8 m. (N=188)	6.8 m. (N=199)	1.02 (0.79, 1.3)	0.557	2.7 m. (N=69)	3.9 m. (N=135)	0.73 (0.53, 1)	0.026

AEs in BELLE3: G3-4 AE: ALT elevation (22% vs 3%); AST elevation (18% vs 3%); hyperglycemia (12% vs 0%)

Dose Interruption: 36% vs 9%; Dose Reduction: 31% vs 8%; Discontinuation: 21% vs 5%

Depressive (All grade): 21% vs 8%; Anxiety (All grade): 18% vs 10%; Suicidal attempt: 3 vs 0.

Baselga, et al *Lancet Oncol* 2017; 18: 904-16

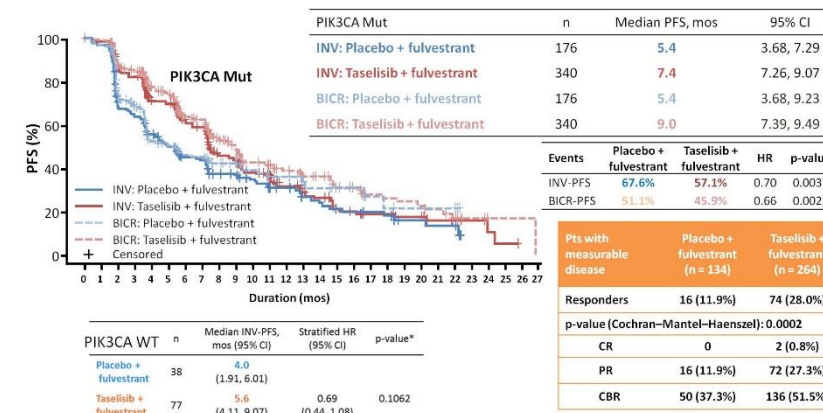
Di Leo, et al *Lancet Oncol* 2018; 19: 87-100

PRESENTED AT: 2018 ASCO ANNUAL MEETING

PRESENTED BY: Cynthia X Ma, MD, PhD

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SANDPIPER Efficacy Data



Baselga J. et al, ASCO 2018

Presented By Cynthia Ma at 2018 ASCO Annual Meeting

Zusammenfassung

- PI3K/AKT/mTOR
 - Standardtherapie für mBC ER +
 - Toxizität
 - PI3CA Mutation- prädiktive Biomarker für die alpha Isoform PI3CA Inhibitoren
 - Klinische Anwendung?

Tam

AI

Fulvestrant

PI3Ki



Wohin geht die Reise???

CDK4/6i

2018 ASCO[®] ANNUAL MEETING

DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

June 1-5, 2018

McCormick Place | Chicago, IL
#ASCO18

MONALEESA 3

MONALEESA-3: Phase III placebo-controlled study of ribociclib + fulvestrant

- Postmenopausal women and men with HR+/HER2-ABC
- No or ≤ 1 line of prior endocrine therapy for advanced disease
- N=726

Randomization (2:1)

Stratified by:

- Presence/absence of liver/lung metastases
- Prior endocrine therapy

Ribociclib
(600 mg/day orally;
3-weeks-on/1-week-off)
+
fulvestrant
(500 mg)*
n=484

Placebo
+
fulvestrant
(500 mg)*
n=242

Primary endpoint

- PFS (locally assessed per RECIST v1.1)

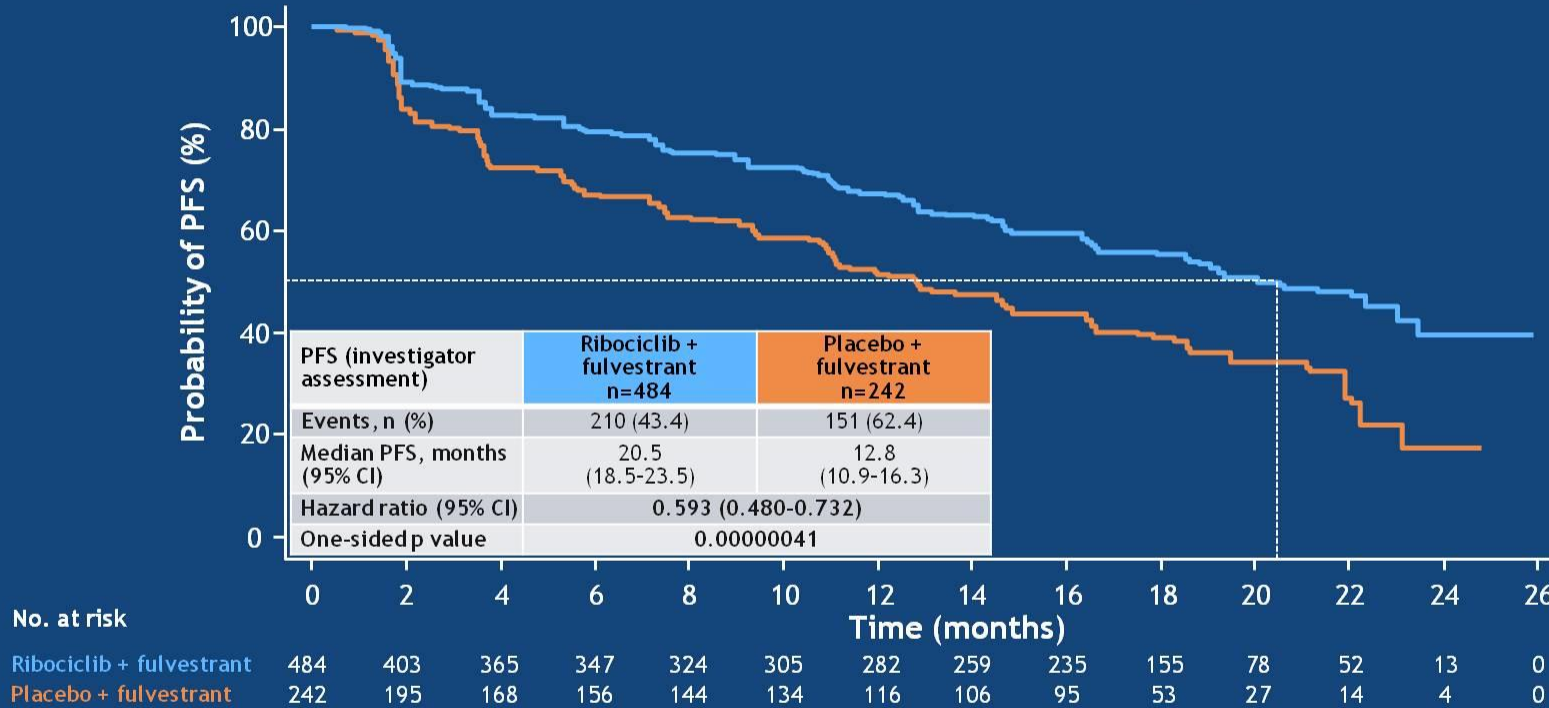
Secondary endpoints

- Overall survival
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~364 PFS events
 - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided $\alpha=2.5\%$, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm), and a sample size of 660 patients

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria In Solid Tumors.
*Fulvestrant administered intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every 28-day cycle thereafter.

Primary endpoint: PFS (investigator-assessed)



- The hazard ratio of 0.593 corresponds to a 41% reduction in risk of progression in the ribociclib vs placebo arm

CI, confidence interval.

Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3

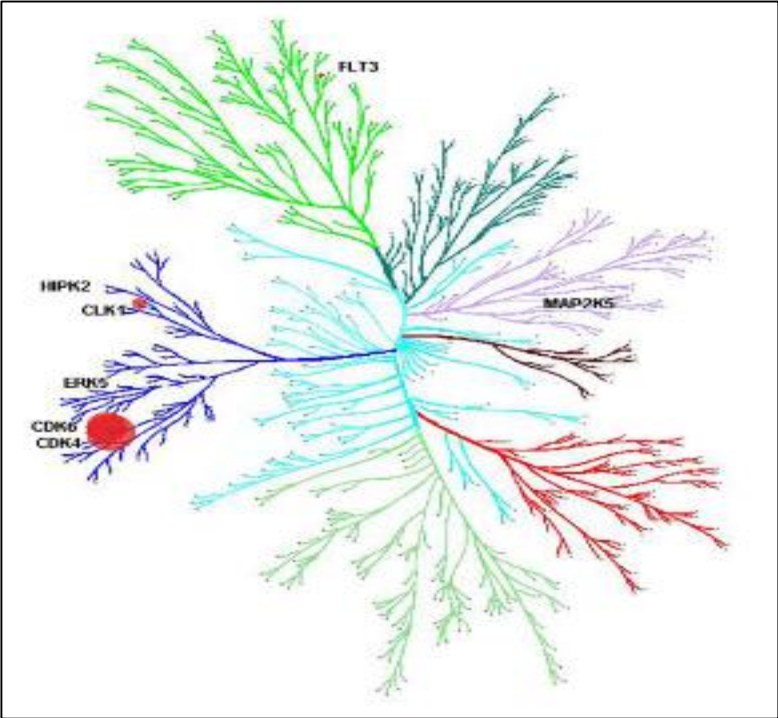
Dennis J. Slamon, Patrick Neven, Stephen Chia, Peter A. Fasching, Michelino De Laurentiis, Seock-Ah Im, Katarina Petrakova, Giulia Val Bianchi, Francisco J. Esteva, Miguel Martín, Arnd Nusch, Gabe S. Sonke, Luis De la Cruz-Merino, J. Thaddeus Beck, Xavier Pivot, Gena Vidam, Yingbo Wang, Karen Rodriguez Lorenc, Michelle Miller, Tetiana Taran, and Guy Jerusalem

<http://ascopubs.org/doi/abs/10.1200/JCO.2018.78.9909>

DOI: 10.1200/JCO.2018.78.9909

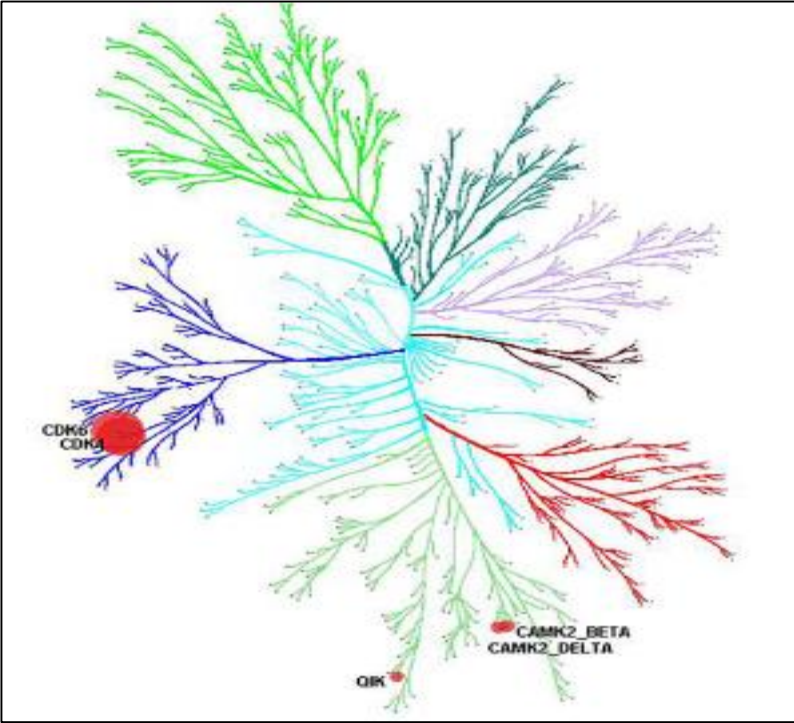
CDK4/6 inhibitors

Palbociclib



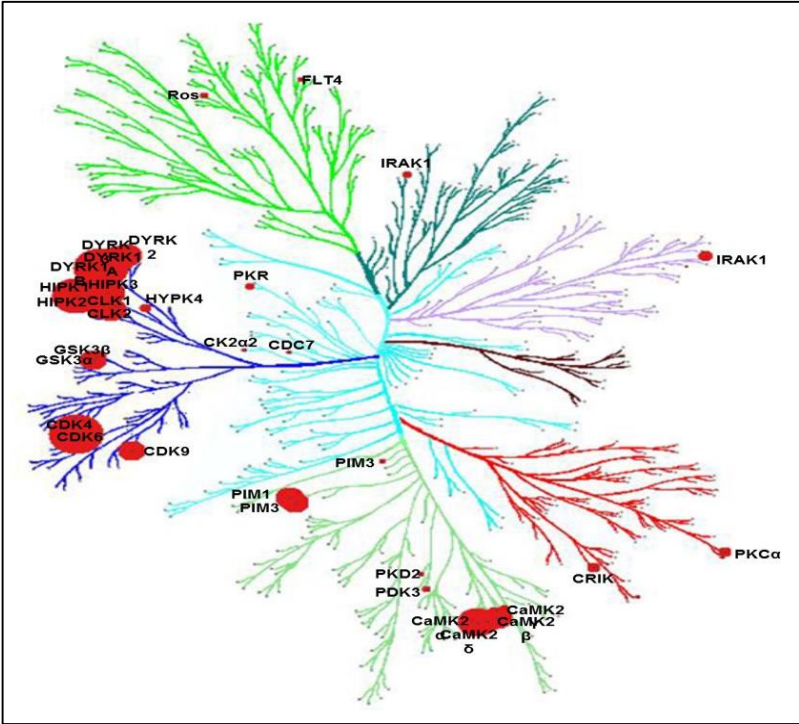
PALOMA

Ribociclib



MONALEESA

Abemaciclib



MONARCH



ER+ Metastatic Breast Cancer: Beyond CDK Inhibitors

**Matthew P. Goetz
Professor of Oncology and Pharmacology
Mayo Clinic
Rochester, MN**

CP1229323-1



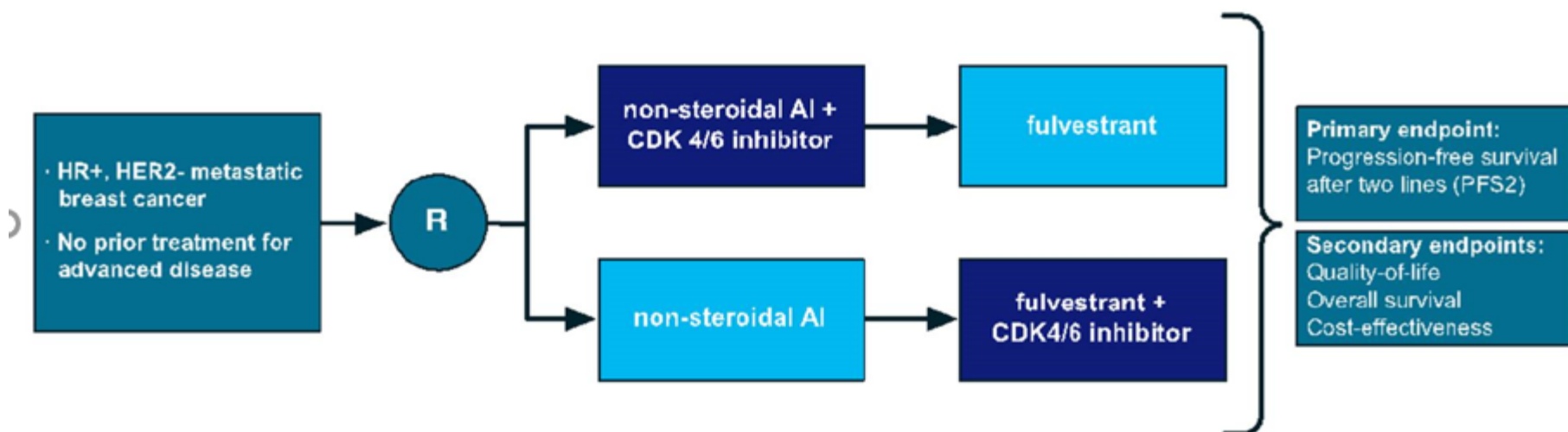
FDA Registration

- Palbo-, Ribo-, Abemaciclib (in Kombination mit AI)
 - Firstline Therapie mBC ERpos, Her-2 neu neg
 - Palbo- & Abemaciclib (in Kombination mit Fulvestrant)
 - Secondline Therapie mBC ERpos, Her-2 neu neg
 - Abemaciclib (Monotherapie)
 - Endokrinrefraktore mBC ERpos,
-
- Ähnlicher Antitumoraktivität (PFS)
 - Direkter Vergleich fehlt
 - Lebermetastasen Abemaciclib + AI vs AI RR 54% vs 20%
 - Abemaciclib & Ribociclib >> CNS Penetration vs Palbociclib



Welche Subgruppe?

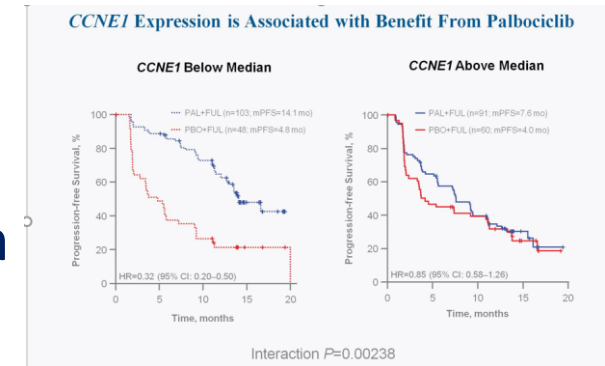
- ALLE
 - Weniger Vorteil:
 - Neu diagnostizierter (longer TFI)
 - Bone only Meta
- UP Front vs Sequenz – SONIA TRIAL





Biomarker?

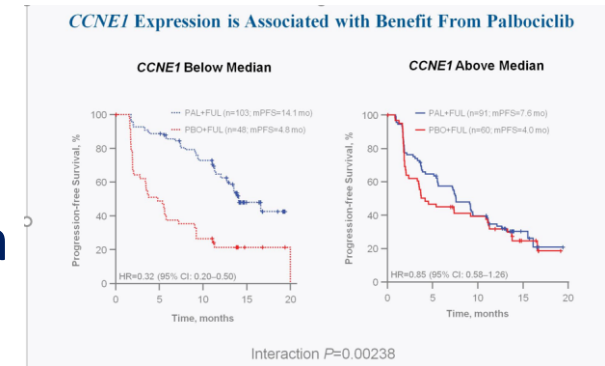
- Ciclin D1+ vs Ciclin D1-
- p16+ vs p16-
- Rb+ vs Rb-
- CCNE1 (Ciclin E) below median vs CCNE1 above median
- FGFR1 Amplifikation vs keine





Biomarker?

- Ciclin D1+ vs Ciclin D1-
- p16+ vs p16-
- Rb+ vs Rb-
- CCNE1 (Ciclin E) below median vs CCNE1 above median
- FGFR1 Amplifikation vs keine



Nach CDK4/6?



How could we manage our patients at progression?

Switch endocrine therapy,
maintain CDKi



ESR-1

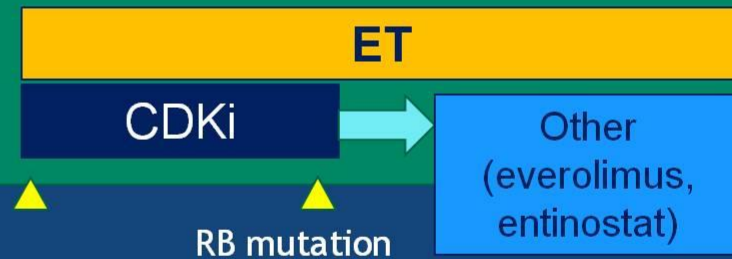


How could we manage our patients at progression?

Switch endocrine therapy,
maintain CDKi



Switch CDK to something else,
maintain endocrine therapy





How could we manage our patients at progression?

Switch endocrine therapy,
maintain CDKi



Switch to something else,
maintain endocrine therapy



Maintain ET and CDKi,
Target a collateral pathway





Phase II trials combining cdk/mTOR inhibition

Trial	Additional Agent/Strategy
TRINITI-1 NCT02732119	mTor inhibitor (Everolimus)
PASTOR NCT02599714	mTORC 1/2 inhibitor (Vistusertib)



Progression on CDK4/6 inhibitor and AI after ≥4 months as last therapy

- Ribociclib 300 mg/day
- Everolimus 2.5 mg/day
- Exemestane 25 mg/day

Endpoint	Response (n=43)
Clinical Benefit	39.5%
Partial Response	7%

Moulder, AACR, 2018, Abstract CT-108-28



Palbociclib After CDK and Endocrine Therapy Trial (PACE)

Phase II, Randomized, Pilot Study

- Progression on AI + CDK4/6 inhibitor
- ≤ 1 prior line of chemo

1:2:1
Randomization

Fulvestrant
(crossover to Palbociclib
at progression)

Fulvestrant + Palbociclib

Fulvestrant + Palbociclib
+ Avelumab

NCT03147287

Mundi PS et al. SABCS 2016. Abst. OT2-01-19.

PRESENTED AT: **2018 ASCO**
ANNUAL MEETING

#ASCO18
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PRESENTED BY: Angie DeMichele, MD, MSCE

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Der Weg verzweigt sich

Tam

AI

Fulvestrant

PI3ki

AI



CDK4/6i

AI

PI3Ki

Wohin geht die Reise???

Danke

