Poster Discussion
Breast cancer, locally advanced and metastatic

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Paclitaxel-based vs docetaxel-based regimens in metastatic breast cancer (MBC): a systematic review and meta-analysis of Randomized controlled trials

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(326PD)

Paclitaxel-based vs docetaxel-based regimens in MBC

- ✓ Seven eligible trials involving 1694 patients with MBC were selected.
- ✓ Paclitaxel-based regimen was comparable to docetaxel-based regimen in terms of OS (HR: 0.87, 95%CI: 0.60-1.27, p=0.476), PFS (HR:0.76,95%CI:0.58-1.00, p=0.052), TTP (HR: 1.13, 95%CI: 0.81-1.58, p=0.459), and ORR (RR:1.01, 95%CI: 0.88-1.15, p=0.915), but less grade 3 or 4 adverse events were observed in paclitaxel-based regimen.
- ✓ Paclitaxel-based regimen is associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens.

Qi W. et al. ESMO 2012, abstract 326PD

Paclitaxel-based vs docetaxel-based regimens in MBC

Use of paclitaxel in weekly regimen give overall survival advantages compared with the standard every three weeks regimen.

The use of weekly paclitaxel regimens is therefore recommended for the treatment of locally advanced/metastatic breast cancer.

Mauri D et al. Cancer Treat Rev. 2010; 36(1):69-74

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)

- Alessandra Gennari, Matteo Puntoni, Oriana Nanni, Pier Franco Conte, Dino Amadori, Vito Lorusso, Andrea DeCensi, Mariapia Sormani, Valentina Guarneri, Mauro D'Amico, Alberto Gozza, Paolo Bruzzi

(327PD)

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)

- ✓ Obesity is a known risk factor for the development of breast cancer and an adverse prognostic factor in those women who have already been diagnosed with breast cancer.
- ✓ The effect of obesity on the prognosis of MBC women has not been assessed.
- ✓ The relationship between BMI (kg/m2), progression free (PFS) and overall survival (OS) was assessed on 698 MBC patients enrolled into 3 clinical trials of first line chemotherapy.

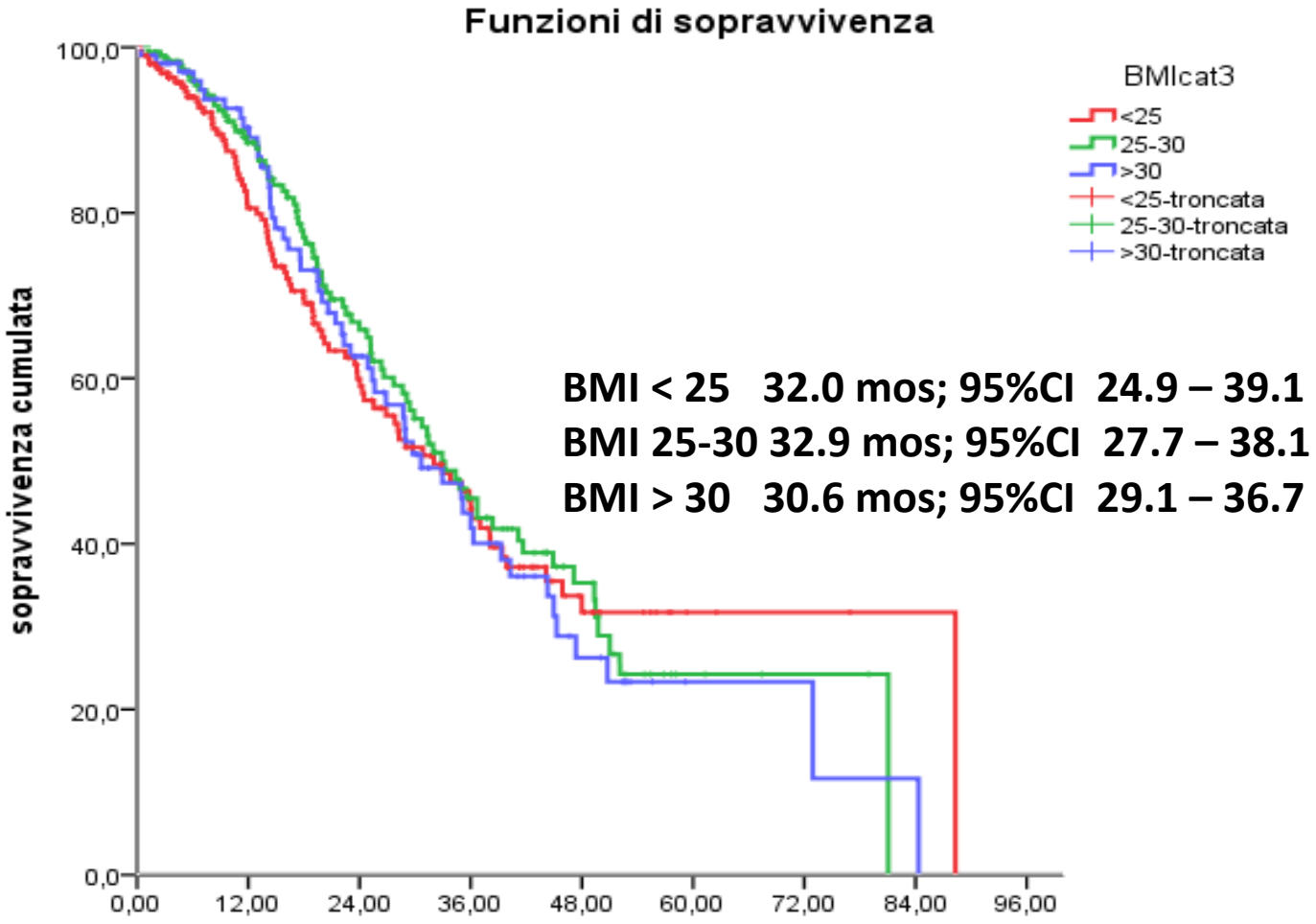
Gennari A. et al. ESMO 2012, abstract 327PD

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)

- ✓ Information on BMI at the time of study entry, was available on 489 women.
- ✓ Median follow up was 18 months (range 0.4 to 88.3).
- ✓ 40.3% of the patients were normal, 38.2% were overweight and 21.5% were obese.
- ✓ BMI at baseline was not significantly associated with the outcome of MBC patients treated with first line chemotherapy

Gennari A. et al. ESMO 2012, abstract 327PD

Overall Survival



BMI < 25 32.0 mos; 95%CI 24.9 – 39.1
BMI 25-30 32.9 mos; 95%CI 27.7 – 38.1
BMI > 30 30.6 mos; 95%CI 29.1 – 36.7

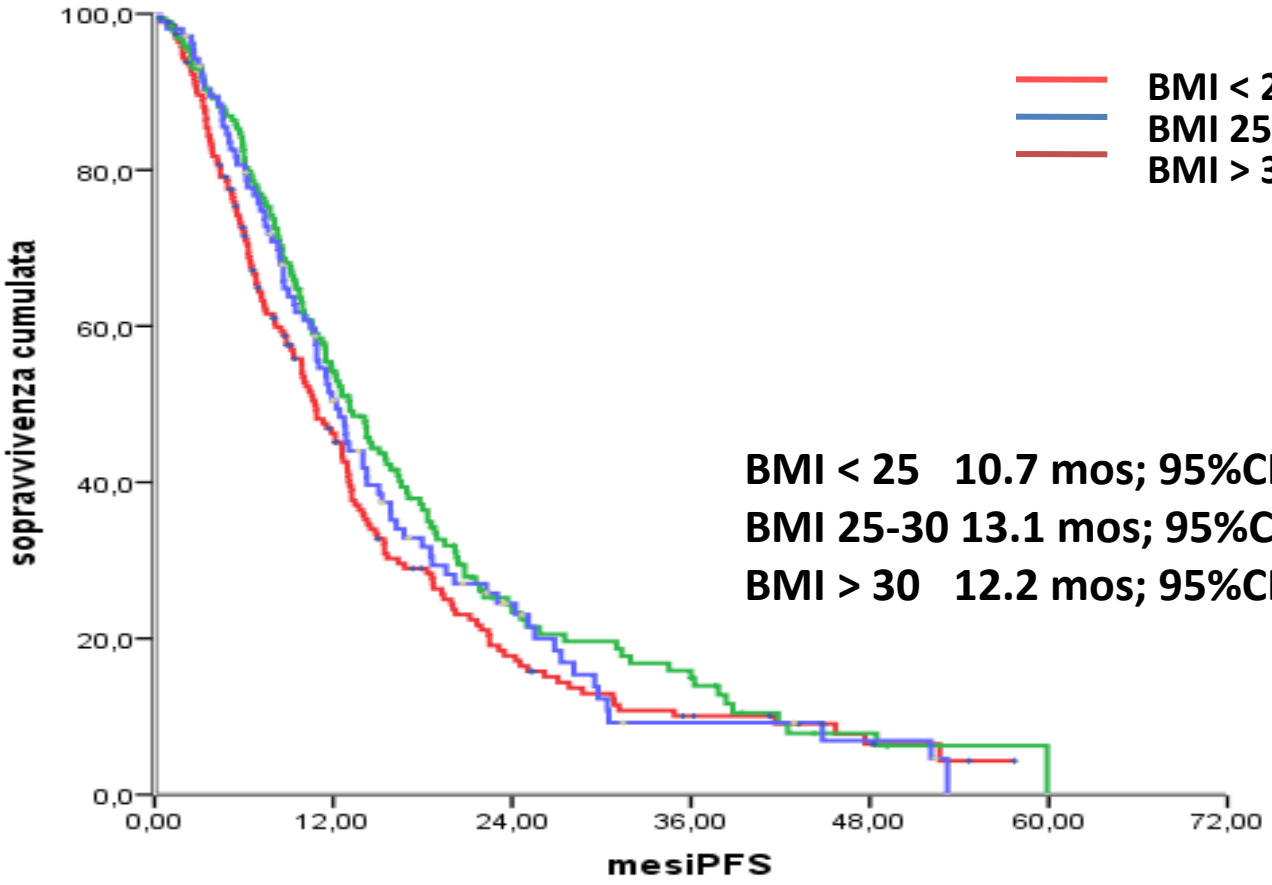
Gennari A. et al. ESMO 2012, abstract 327PD

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)

- In this study BMI at baseline was not significantly associated with the outcome of MBC patients treated with first line chemotherapy; however, a non significant trend for an improved PFS was observed in overweight women as compared to normal weight and obese patients.

Gennari A. et al. ESMO 2012, abstract 327PD

Progression Free Survival



BMI < 25 10.7 mos; 95%CI 8.9 – 12.6
BMI 25-30 13.1 mos; 95%CI 11.0 – 15.2
BMI > 30 12.2 mos; 95%CI 10.4 – 14.0

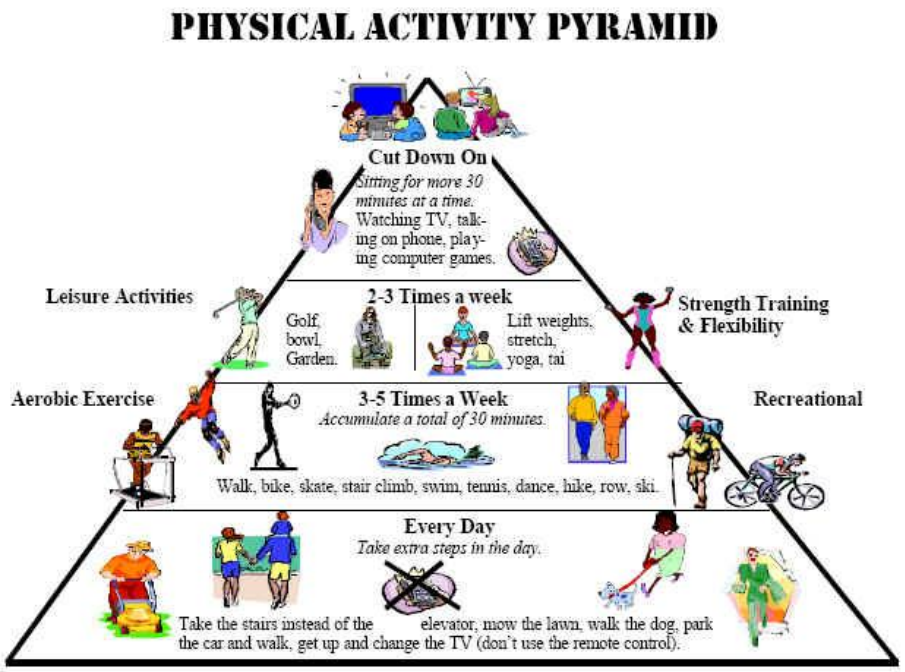
Gennari A. et al. ESMO 2012, abstract 327PD

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)

- Primary analyses were multi-level regression models with the outcomes of 90-day mortality, intensive care unit (ICU) admission, need for mechanical ventilation and vasopressor utilization.
- The cohort comprised of 18,746 subjects. Three percent were underweight, 30% were normal, 35% were overweight, 26% were obese, and 4% were morbidly obese.
- Obesity was associated with decreased mortality (0.86, 95% 0.74-0.99).

King P et al. Eur Respir J. 2012 Aug 30.

Body mass index (BMI) and prognosis in women with metastatic breast cancer (MBC)



Progression-free survival as a surrogate for overall survival in metastatic breast cancer

Beauchemin C, Cooper D, Lapierre ME, Yelle L, Lachaine J.

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Methods

- A systematic literature review was performed using the **PICO** method:
  - **P**opulation consisted of women with mBC
  - **I**nterventions and **C**omparators were standard treatments for mBC or best supportive care
  - **O**utcomes of interest were median PFS or TTP and median OS
- A correlation analysis between median PFS and OS was performed and subgroup analyses were conducted to explore possible reasons for heterogeneity.
- The relationship between the treatment effect on PFS and OS was assessed.

Results and Conclusion

- ✓ In total, 5041 studies were identified and 144 fulfilled the eligibility criteria.
- ✓ There was a significant relationship between median PFS and median OS across included trials ($r=0.428$; $p<0.01$).
- ✓ Results of the regression analysis predict that a difference in median PFS of 5, 10, 15, and 20 months would translate into a difference in median OS of 8.7, 17.4, 26.2, and 35.0 months respectively.

Progression-free survival as a surrogate for overall survival in metastatic breast cancer

- Data were collected on 3,953 patients in 11 randomized trials
- No end point could be demonstrated as a good surrogate for OS in these trials.
- Tumor response may be an acceptable surrogate for PFS.

Burzykowski T et al. JCO, 2008, 26, 12 1987-1992

Progression-free survival as a surrogate for overall survival in metastatic breast cancer

- The question of whether PFS is a surrogate for OS in advanced breast cancer is increasingly pressing in view of the numerous trials showing improved PFS but no gain in OS
- PFS currently represents a sensitive parameter to assess the efficacy of a new drug or combination in advanced breast cancer
- When coupled with a favorable toxicity profile, the demonstration of an improved PFS appears to constitute enough evidence for the superiority of a treatment both in the setting of clinical trials and for translating this information into treatment decisions for clinical practice

Burzykowski T et al. JCO, 2008, 26, 12 1987-1992

Efficacy and Safety of Everolimus in Postmenopausal Women With Advanced Breast Cancer (BOLERO-2): Effect of Visceral Metastases

Mario Campone, Shinzaburo Noguchi, Kathleen I. Pritchard, Hope S. Rugo, Gabriel N. Hortobagyi, José Baselga, Ashok Panneerselvam, Tetiana Taran, Tarek Sahmoud, Martine Piccart

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BOLERO-2: Trial design

N = 724

- **Postmenopausal ER$^+$**
- **Unresectable locally advanced or metastatic BC**
- **Recurrence or progression after letrozole or anastrozole**

R
2:1

EVE 10 mg daily
+
EXE 25 mg daily (n = 485)

Placebo
+
EXE 25 mg daily (n = 239)

Stratification

1. Sensitivity to prior hormonal therapy
2. **Presence of visceral disease**

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

Abbreviations: BC, breast cancer; ER$^+$, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2

Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%).

At a median follow-up of 18 months, BOLERO-2 demonstrated that everolimus (EVE) plus exemestane (EXE), prolonged progression-free survival (PFS) compared with EXE alone in this setting

PFS: 7.8 vs 3.2 mo, respectively; hazard ratio = 0.45 [95% confidence interval (CI) = 0.38, 0.54]; log-rank P < .0001)

Campone M, et al. ESMO 2012; abstract 324PD.

Patient Demographics and Baseline Disease Characteristics

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	Everolimus + Exemestane		Placebo + Exemestane	
	Visceral (n = 271)	Non-visceral (n = 214)	Visceral (n = 135)	Non-visceral (n = 104)
Mean age, y (SD)	62.7 (10.3)	62.2 (10.3)	61.3 (9.9)	61.1 (9.6)
≥ 65, %	42	38	35	32
ECOG PS, %				
0	61	60	62	56
1	35	37	33	38
2	2	1	2	4
Unknown	2	2	2	3
Time between initial diagnosis and first recurrence/metastasis, %				
< 3 mo	19	22	21	15
3 to < 6 mo	2	1	2	2
≥ 6 mo	72	71	70	77
Unknown	7	7	7	6
Histology/cytology, %				
Invasive ductal carcinoma	80	73	80	71
Invasive lobular carcinomas	9	19	13	22
Other	9	7	7	7
Not applicable	2	1	1	0
Number of metastatic sites involved, %				
1	19	49	11	47
2	33	27	36	34
3	26	15	29	13
4	14	6	18	6
5	6	2	4	1
> 5	2	1	2	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
Note: Percentages are rounded to the nearest whole number.

Campone M, et al. ESMO 2012; abstract 324PD.

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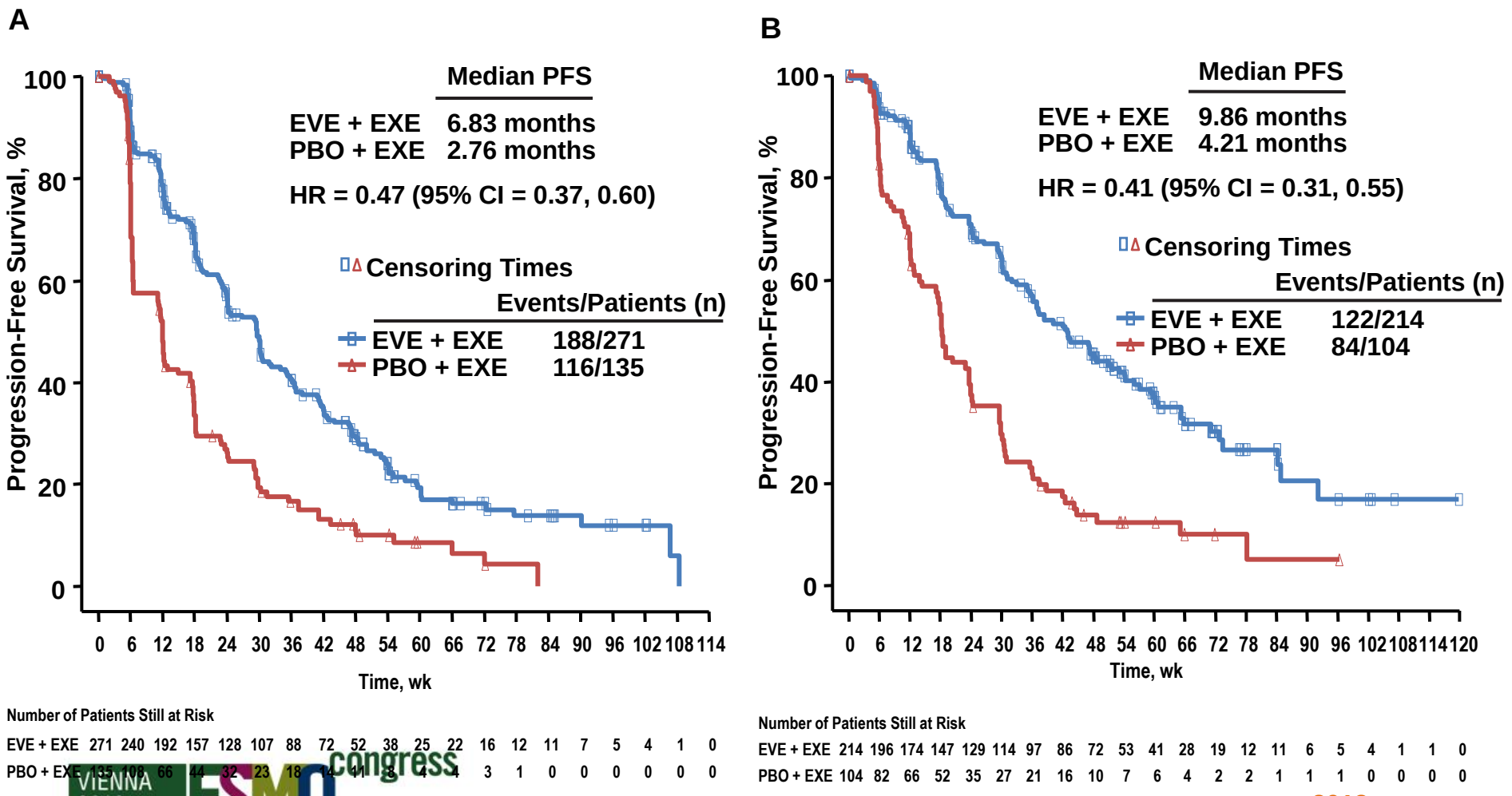
Kaplan-Meier Curves for PFS in Patients (A) With and (B) Without Visceral Involvement



Abbreviations: CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Campone M, et al. ESMO 2012; abstract 324PD.

Everolimus in postmenopausal women with breast cancer

- Patients with visceral involvement had shorter PFS compared with patients with bone-only disease regardless of treatment.

- Adding EVE to EXE markedly extended PFS by ≥ 4 mo among patients with advanced HR+ HER2– BC regardless of the presence of visceral metastases.

Campone M, et al. ESMO 2012; abstract 324PD.

Will this change practice in advanced breast cancer?

- In July 2012, the U.S. Food and Drug Administration approved the mTOR inhibitor everolimus for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole

Everolimus in postmenopausal women with breast cancer

- Inclusion Criteria
- Postmenopausal women with ER+ locally advanced or metastatic breast cancer whose disease is **refractory** to non steroidal aromatase inhibitors (NSAI) and has a documented recurrence or progression on last therapy for breast cancer.

✓ Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole or anastrozole, or

✓ Progression while on, or within one month of end of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer

Will this change practice in advanced breast cancer?

- The magnitude of the clinical benefit seen for the addition of everolimus is very substantial, and this trial, together with the related phase II TAMRAD study, correctly identified the best group of patients to target with the combination: namely those with acquired endocrine resistance following prior hormonal responsiveness

Bachelot T, et al. J Clin Oncol. 2012 Aug 1;30(22):2718-24

Everolimus in postmenopausal women with breast cancer

- ER-positive tumour cells that, during long-term NSAI therapy, develop survival pathways driven by PI3K signalling, and as such have become primed to respond to a combination of an mTOR inhibitor with exemestane.

- The absence of the activated pathway in many untreated hormone-sensitive ER-positive breast cancers probably means that the addition of an mTOR inhibitor as first line is unlikely to produce greater anticancer effects over an aromatase inhibitor alone.

Everolimus in postmenopausal women with breast cancer

- There will probably be a few untreated ER-positive tumours that may already have an activated pathway that could cause 'de novo' endocrine resistance, and these cases could respond very well to the combination.

- In the neo-adjuvant study of letrozole plus everolimus, some patients had ER-positive tumours with activated PIK3CA mutations, and in these tumours the combination of letrozole plus everolimus had a significantly greater anti-proliferative effect than letrozole alone

Campone M, et al. ESMO 2012; abstract 324PD.

Everolimus in postmenopausal women with breast cancer

- Two mTOR activation biomarkers were assessed in 35 patients in the primary tumor in the TAMRAD study.
- pS6K and 4EBP1 are downstream effectors of the mTOR pathway: pS6K is upregulated and 4EBP1 is downregulated by mTOR.
- Patients with high pS6K expression and low 4EBP1 expression showed the greatest benefit for TTP as a function of biomarker expression.

Villarreal-Garza C, et al. Ann Oncol. 2012 Oct;23(10):2526-35

Everolimus in postmenopausal women with breast cancer

- A phase III trial, 1,112 patients with hormone therapy–naïve, metastatic breast cancer were randomly assigned to letrozole or letrozole combined with the mTOR inhibitor temsirolimus.

- The study was closed for futility by the data monitoring committee when it became clear that the experimental arm was highly unlikely to demonstrate improvement in PFS, the primary end point, and subsequent analysis showed no difference in response.

Chow LWC, et al. Breast Cancer Res Treat 100(suppl 1):S286, abstr 6091

Everolimus in postmenopausal women with breast cancer

- SAE were reported among 23% of patients in the combination-therapy group and 12% in the exemestane-alone group.
- A higher percentage of patients discontinued everolimus in the combination-therapy group than discontinued placebo in the control group because of adverse events (19% vs. 4%) and withdrawal of consent (5% vs. 2%).
- G3 or G4 adverse events were stomatitis (8% in the combination-therapy group vs. 1% in the exemestane-alone group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%)

Baselga J, et al. N Engl J Med. 2012;366(6):520-529.

Everolimus in postmenopausal women with breast cancer

- The benefit seen in the pivotal trial BOLERO-2 is clinically meaningful and we need to consider the addition of everolimus to AIs for women with HR-positive MBC.
- It is essential that clinicians are educated about key recommendations for toxicity management and specific guideline dose modifications.
- Additional research efforts are needed to identify predictive surrogate biomarkers of response.