Evaluation of Everolimus (EVE) in HER2+ Advanced Breast Cancer (BC) with Activated PI3K/mTOR Pathway: Exploratory Biomarker Observations from the BOLERO-3 Trial

Guy Jerusalem,[1] Fabrice André,[2] David Chen,[3] Douglas Robinson,[3] Mustafa Ozguroglu,[4] Istvan Lang,[5] Michelle White,[6] Masakazu Toi,[7] Tetiana Taran,[3] Luca Gianni[8]

[1]CHU Sart Tilman Liège and University of Liège, Liège, Belgium; [2]Institut Gustav Roussy, Villejuif, France; [3]Novartis Pharmaceuticals, East Hanover, New Jersey, USA; [4]Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey; [5]Országos Onkológiai Intézet, Budapest, Hungary; [6]Monash Medical Center Moorabbin, Victoria, Australia; [7]Kyoto University, Kyoto, Japan; [8]Ospedale San Raffaele, Milan, Italy

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- Ownership: D. Chen, D. Robinson, and T. Taran are Novartis stockholders
- Advisory board: G. Jerusalem, A. Fabrice, M. Ozguroglu, and M. White for Novartis; L. Gianni for Novartis, Roche, Genentech, GSK, Pfizer, BI, Celgene, Tahio
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BOLERO-3: Study Design

N = 572*

- Locally advanced or metastatic HER2$^+$ breast cancer
- Prior taxane required
- Trastuzumab (TRAS) resistance
  - Adjuvant: progression on or within 12 months of TRAS
  - Metastatic: progression within 4 weeks of TRAS
- Measurable disease only

Randomize 1:1

Everolimus (5 mg PO daily) + vinorelbine (25 mg/m^2 weekly) + TRAS (2 mg/kg week†) (n = 284)

Placebo (PO daily) + vinorelbine (25 mg/m^2 weekly) + TRAS (2 mg/kg weekly*) (n = 285)

Therapy until progressive disease or intolerable toxicity

- Stratification by prior lapatinib use

Endpoints

Primary: Progression-free survival

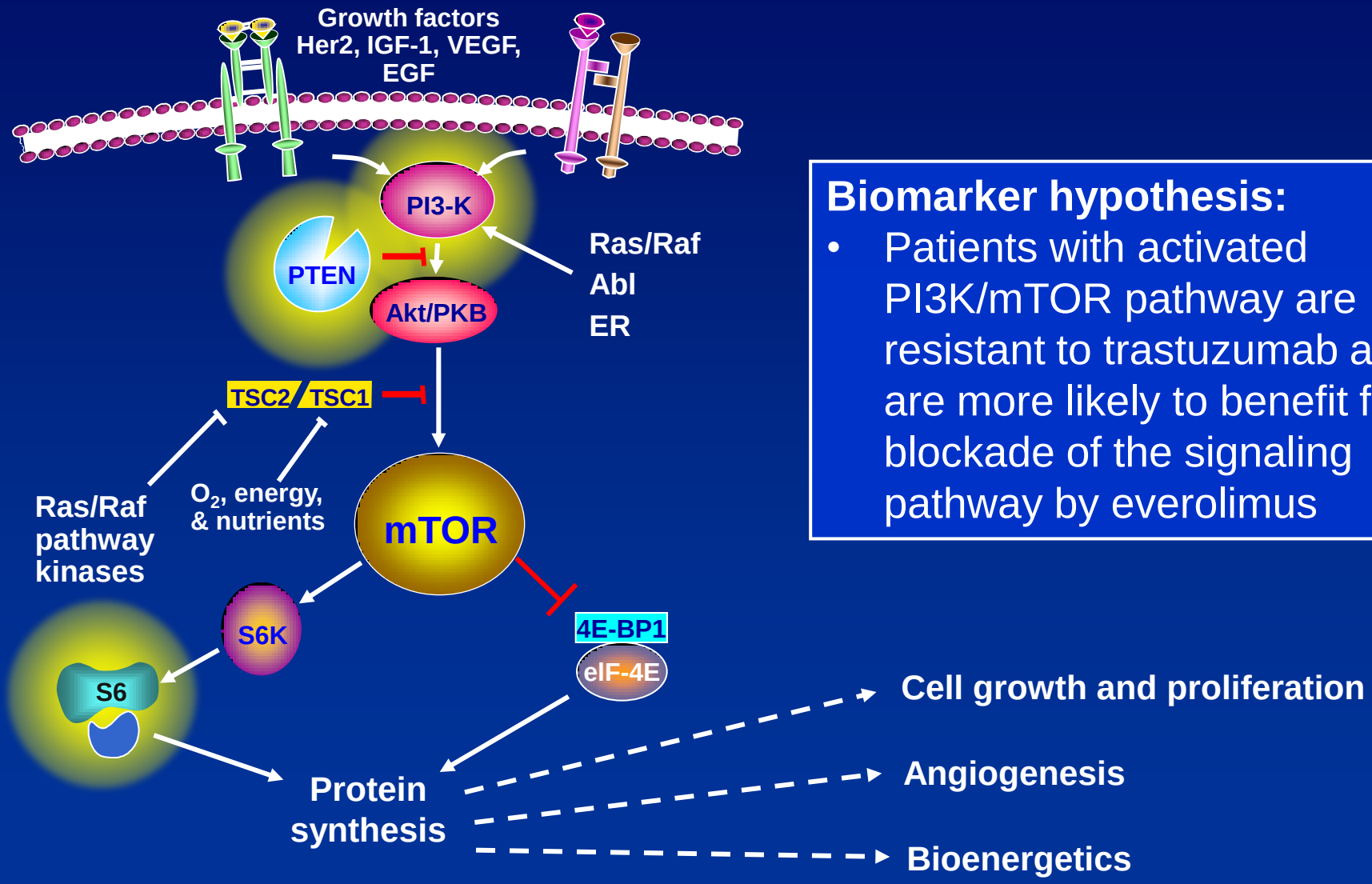
Secondary: Overall survival, overall response rate, time to deterioration of ECOG performance status, safety, duration of response, clinical benefit rate, and quality of life

*Actual enrollment was 569.

†Following a 4-mg/kg loading dose on day 1, cycle 1 (1 cycle = every 21 days).

http://www.clinicaltrials.gov/ct2/show/NCT01007942?term=BOLERO3&rank=1.

HER2/PI3K/mTOR Signaling Pathway



Biomarker hypothesis:

- Patients with activated PI3K/mTOR pathway are resistant to trastuzumab and are more likely to benefit from blockade of the signaling pathway by everolimus

Biomarker Specimens and Analyses

- Archival tumor samples were available for biomarker analysis from 283/569 patients (50% of ITT)
  - 80% from primary tumor
- Statistics: Median PFS and 95% CI, Cox models HR and 95% CI, KM curves; Cox models adjusted for covariate imbalance, where required

Biomarker	Assay	Evaluable Sample Size (n)	% ITT
PTEN	Immunohistochemistry	237	42
PIK3Ca	Sanger sequencing, exons 9 and 20	182	32
pS6	Immunohistochemistry	188	33

CI, confidence interval; ITT, intention-to-treat; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival.

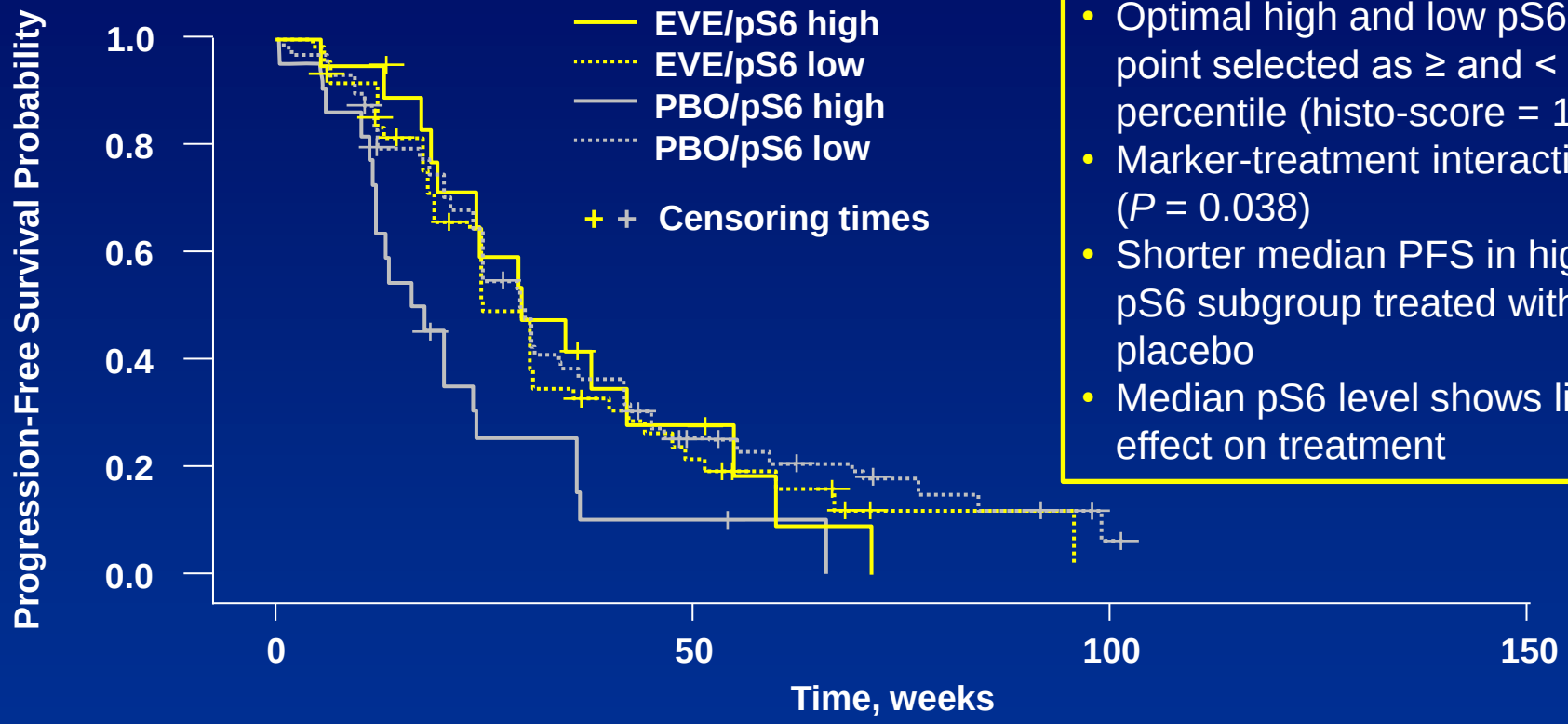
Efficacy Is Comparable Between ITT and Biomarker-Evaluable Populations

Treatment	n	Number of Events	Median PFS, weeks (95% CI)	HR (95% CI)
ITT EVE	284	196	30.4 (29.3, 35.6)	0.78 (0.65, 0.96)
ITT PBO	285	219	25.1 (23.9, 30.0)	
BM EVE	130	95	29.7 (24.2, 35.3)	0.88 (0.67, 1.17)
BM PBO	132	104	24.7 (23.1, 30.1)	

- Biomarker-evaluable population: Individuals with at least 1 of 3 biomarkers with evaluable result (N = 262, 46% ITT)
- Demographic and clinical characteristics were similar between the ITT and biomarker-evaluable populations

BM, biomarker-evaluable population; PBO, placebo.

Patients with High pS6 May Derive More Benefit from Addition of Everolimus



- Optimal high and low pS6 cut-point selected as ≥ and < 75th percentile (histo-score = 160)
- Marker-treatment interaction (P = 0.038)
- Shorter median PFS in high pS6 subgroup treated with placebo
- Median pS6 level shows little effect on treatment

Subgroup	n	Events	Median PFS, weeks (95% CI)	HR (95% CI)
EVE pS6 high	23	15	29.4 (18.1, 55.1)	0.48 (0.24, 0.96)
PBO pS6 high	22	20	17.1 (11.7, 24.0)	
EVE pS6 low	66	47	24.9 (23.6, 31.0)	1.14 (0.77, 1.68)
PBO pS6 low	77	57	30.0 (24.0, 36.1)	

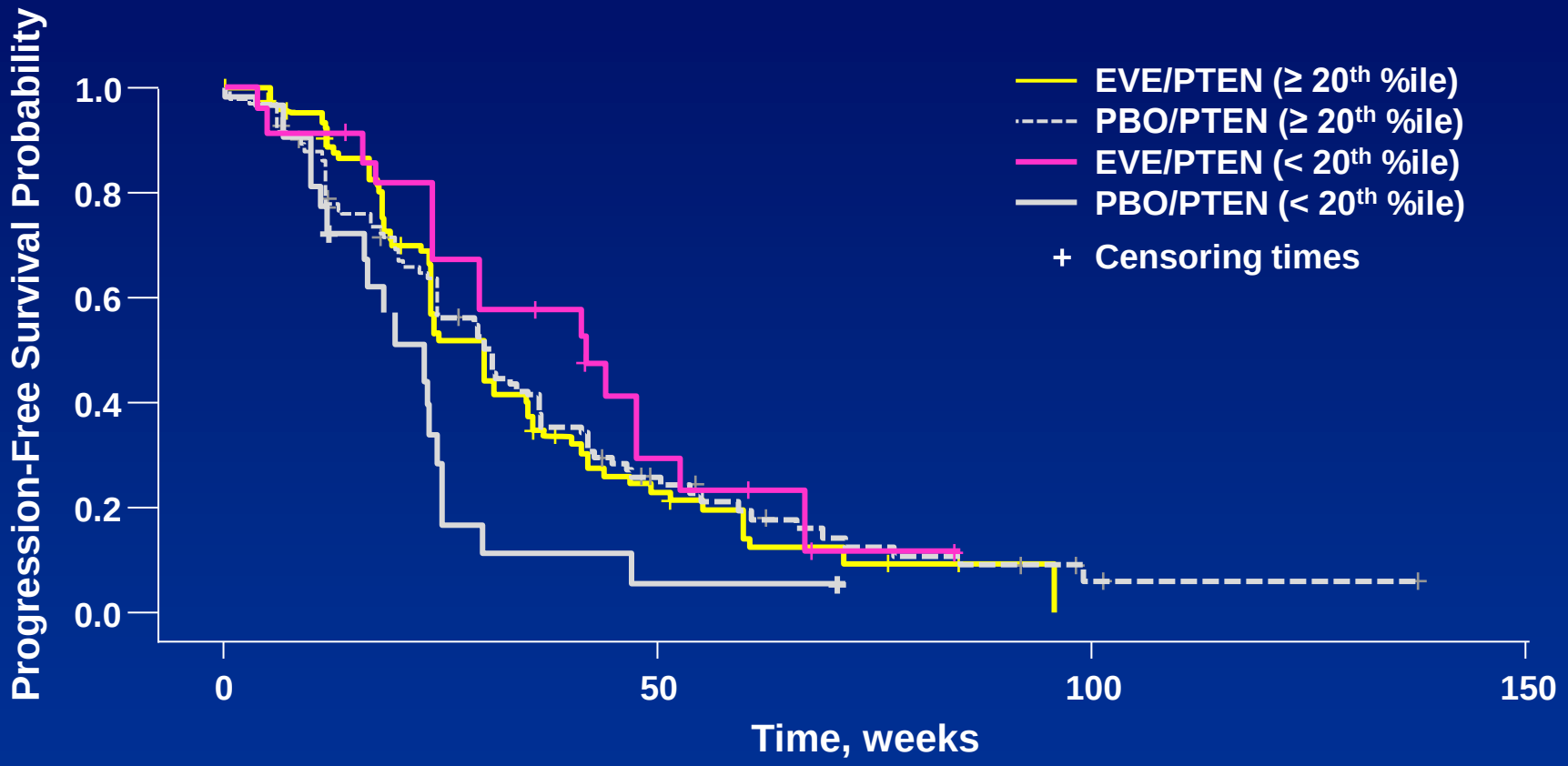
Effect of PTEN Levels on Treatment Benefit from Addition of Everolimus

Subgroup	Therapy	n (# of Events)	Median PFS, wks (95% CI)	HR (95% CI)	*P* Value*
Subgroups defined by low or normal PTEN level					
H-score ≥ 50	EVE	100 (72)	30.1 (24.3, 35.6)	0.97 (0.71, 1.33)	0.11
	PBO	108 (85)	30.0 (24.0, 35.4)		
H-score < 50	EVE	15 (11)	41.4 (17.3, 66.9)	0.52 (0.21, 1.26)	
	PBO	14 (11)	23.7 (10.6, 25.1)		
Subgroups defined by optimal cut-point of PTEN level (20th %ile)					
H-score ≥ 20th %ile	EVE	89 (67)	30.1 (24.0, 35.3)	1.05 (0.75, 1.45)	0.01
	PBO	100 (78)	30.1 (24.0, 36.0)		
H-score < 20th %ile	EVE	26 (16)	41.9 (24.0, 53.1)	0.41 (0.20, 0.82)	
	PBO	22 (18)	23.1 (12.1, 24.7)		

- Median PFS gain is 18-19 weeks for the low PTEN subgroup

*Treatment-biomarker interaction.
PTEN optimal cut-point selected as ≥ and < 20th percentile. Histo-score = 100.

Patients with Low PTEN May Derive More Benefit from Everolimus



- Marker-treatment interaction ($P = 0.01$)

PIK3CA Mutations Did Not Significantly Affect Everolimus Treatment Benefit

Group	Biomarker	n	Events	Median PFS (95% CI)	HR (95% CI)
Everolimus	PIK3Ca mutant	15	9	5.52 (*)	0.65* (0.29, 1.45)
Placebo		21	19	6.74 (4.83, 7.59)	
Everolimus	PIK3Ca wildtype	69	51	6.83 (5.52, 8.18)	0.98 (0.67, 1.44)
Placebo		77	56	5.72 (5.22, 7.79)	

- No significant marker-treatment interaction (*P* = 0.32)

*Not evaluable due to small sample size/event number.

Conclusions

- Observations are consistent with hypothesis that mTOR inhibitor attenuates PI3K pathway activation–related trastuzumab resistance
- Addition of everolimus may be most beneficial to patients with HER2+ advanced breast cancer with low PTEN or high pS6 levels
  - No clear benefit observed in patients with normal PTEN or low pS6 levels
- The exploratory analysis is based on ~ 40% of ITT and limited number of PI3K/mTOR pathway biomarkers
  - Observations need to be validated in independent cohorts

Future Analyses

- PIK3Ca mutations and PTEN levels are being analyzed in additional samples; PTEN level by different scoring methods will be used as part of the sensitivity test of the signal
- Analysis of the impact of ER/PR status on the benefit from everolimus therapy observed in the discussed marker-defined subpopulations when data from additional samples are available
- Genetic analysis of a broad oncogene and tumor suppressor gene panel by next-generation sequencing on the archival tumor samples is ongoing

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