GRUPPO C

3 - QUESITO CLINICO: Nelle pazienti con carcinoma mammario HR positivo/HER2 negativo non candidate a chemioterapia, pretrattate con antiaromatasico non steroideo e con ricaduta durante oppure inferiore a 12 mesi dal termine dell'ormonoterapia adiuvante, è opportuno considerare la combinazione fulvestrant+palbociclib rispetto alla combinazione exemestane+everolimus?

La declinazione del Quesito Clinico

P	Nei **P**azienti con…	Pazienti con ca. mammario HR+/HER2- non candidate a CT pretrattate con NSAI ricadute durante o entro 12 mesi dal termine dell'OT adiuvante
I	l'**I**ntervento…	Fulvestrant + Palbociclib
C	in **C**onfronto con…	Exemestane + Everolimus
O	**O**utcome di beneficio/danno…	

La declinazione del Quesito Clinico

P	Nei **P**azienti con…	Pazienti con ca. mammario HR+/HER2- non candidate a CT pretrattate con NSAI ricadute durante o entro 12 mesi dal termine dell'OT adiuvante
I	l'**I**ntervento…	Fulvestrant + Palbociclib
C	in **C**onfronto con…	Exemestane + Everolimus
O	**O**utcome di beneficio/danno…	Di Beneficio: 1. OS 2. PFS 3. QoL Di Danno: 1. Tasso di interruzione del trattamento per AE 2. Mucosite 3. Neutropenia 4. Rash cutaneo

Le evidenze

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campon
Martine Piccart, M.D., Ph.D., Howard A. Burris III, M
Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M
Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D.,
Yoshinori Ito, M.D., Denise Yardley, M.D., Ir
Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph
Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D.,
and Gabriel N. Hortobagyi, M.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2015 VOL. 373 NO. 3

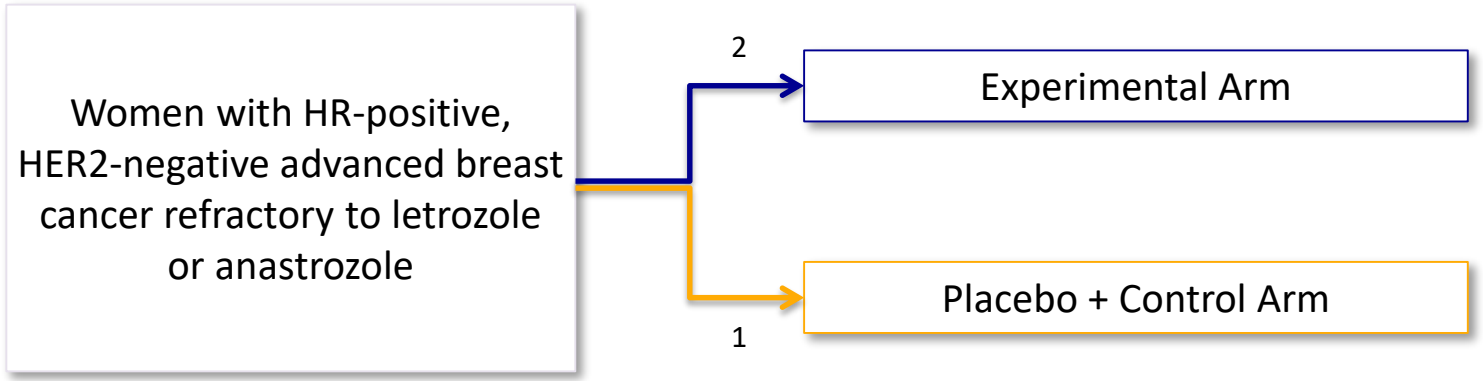
Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D.,
Sunil Verma, M.D., Hiroji Iwata, M.D., Nadia Harbeck, M.D., Sibylle Loibl, M.D., Cynthia Huang Bartlett, M.D.,
phia Randolph, M.D., Ph.D., Maria Koehler, M.D., Ph.D.,
simo Cristofanilli, M.D.

Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial

Massimo Cristofanilli, Nicholas C Turner*, Igor Bondarenko, Jungsil Ro, Seock-Ah Im, Norikazu Masuda, Marco Colleoni, Angela DeMichele, Sherene Loi, Sunil Verma, Hiroji Iwata, Nadia Harbeck, Ke Zhang, Kathy Puyana Theall, Yuqiu Jiang, Cynthia Huang Bartlett, Maria Koehler, Dennis Slamon*

Studies design



- Refractory to therapy:
  - Recurrence during or within 12 mos of end of adjuvant treatment
  - Progression during or within 1 mo after end of treatment for advanced disease
- Stratification:
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease
- No crossover allowed
- Primary endpoint: PFS
  - Secondary endpoints: OS, ORR, CBR, safety, QoL, bone markers

BOLERO2 *vs* PALOMA3: pts characteristics

	BOLERO 2 [a]	PALOMA 3 [b]
	Exe + Eve (n= 485)	Fulv + Palbo (n= 347)
N. of previous line of therapies % *:		
0	NS	24
1	16	38
2	30	26
≥ 3	54	12
Median lines	3	NS
Prior chemotherapy for ABC %	26	31
Purpose of most recent treatment %:		
Adjuvant therapy	21	21 [c]
Treatment for ABC	79	79 [c]
Tumor assessment	6 w	8 w

*: Bolero2: number of previous lines used in the adjuvant or metastatic setting
Paloma3: number of previous lines for ABC
NS: not specified
- In Bolero2: 100/485 (20.6%) pts received treatment as first line therapy

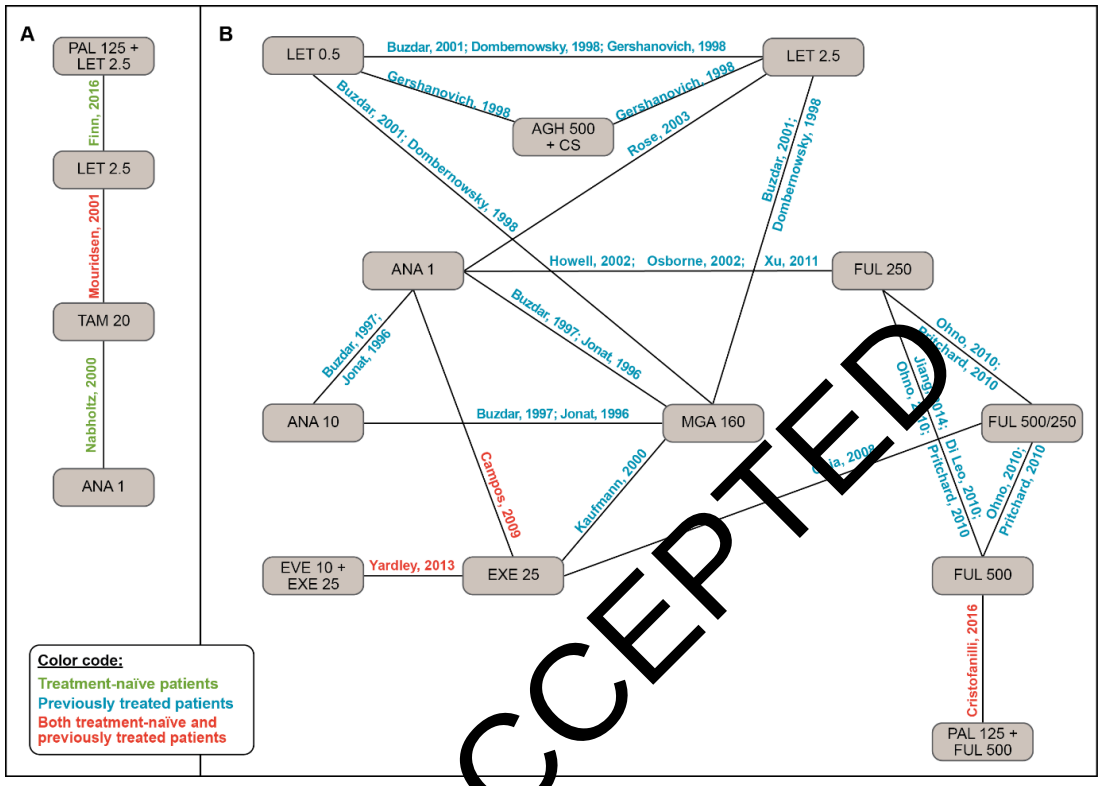
a) Baselga, NEJM 2012; b) Turner, NEJM 2015; c) Cristofanilli, 2016

Le evidenze

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

Comparison of palbociclib in combination with letrozole or fulvestrant with endocrine therapies for advanced/metastatic breast cancer: network meta-analysis



Le evidenze

Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†

M. Piccart[1*], G. N. Hortobagyi[2], M. Campone[3], K. I. Pritchard[4], F. Lebrun[1], Y. Ito[5], S. Noguchi[6], A. Perez[7], H. S. Rugo[8], I. Deleu[9], H. A. Burris III[10], L. Provencher[11], P. Neven[12], M. Gnant[13], M. Shtivelband[14], C. Wu[15], J. Fan[15], W. Feng[15], T. Taran[15] & J. Baselga[16]

Annals of Oncology 27: 1719–1725, 2016
doi:10.1093/annonc/mdw249
Published online 29 June 2016

Health-Related Quality of Life of Patients With Advanced Breast Cancer Treated With Everolimus Plus Exemestane versus Placebo Plus Exemestane in the Phase 3, Randomized, Controlled, BOLERO-2 Trial

Howard A. Burris, III, MD[1]; Fabienne Lebrun, MD[2]; Hope S. Rugo, MD[3]; J. Thaddeus Beck, MD[4]; Martine Piccart, MD, PhD[2]; Patrick Neven, MD, PhD[5]; Jose Baselga, MD, PhD[6]; Katarina Petrakova, PhD[7]; Gabriel N. Hortobagyi, MD[8]; Anna Komorowski, MD[9]; Edmond Chouinard, MD[10]; Robyn Young, MD[11]; Michael Gnant, MD[12]; Kathleen I. Pritchard, MD[13]; Lee Bennett, MS[14]; Jean-Francois Ricci, PhD[15]; Hounayda Bauly, PhD[16]; Tetiana Taran, MD[17]; Tarek Sahmoud, MD, PhD[17]; and Shinzaburo Noguchi, MD[18]

Safety of everolimus plus exemestane in patients with hormone-receptor–positive, HER2–negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET)

G. Jerusalem[1*], G. Mariani[2], E. M. Ciruelos[3], M. Martin[4], V. C. G. Tjan-Heijnen[5], P. Neven[6], J. G. Gavila[7], A. Michelotti[8], F. Montemurro[9], D. Generali[10], E. Simoncini[11], I. Lang[12], J. Mardiak[13], B. Naume[14,15], M. Camozzi[16], K. Lorizzo[16], S. Bianchetti[16] & P. Conte[17,18]

Annals of Oncology 27: 1047–1054, 2016
doi:10.1093/annonc/mdw139
Published online 30 March 2016

Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial

N. Harbeck[1*], S. Iyer[2], N. Turner[3], M. Cristofanilli[4], J. Ro[5], F. André[6], S. Loi[7], S. Verma[8], H. Iwata[9], H. Bhattacharyya[2], K. Puyana Theall[10], C. H. Bartlett[2] & S. Loibl[11]

[1]Department of Obstetrics and Gynecology, Brustzentrum der Universität München, München (LMU), Germany; [2]Pfizer Inc, New York, USA; [3]Department of Molecular Oncology, Royal Marsden Hospital and Institute of Cancer Research, London, UK; [4]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, USA; [5]Department of Medicine, National Cancer Center, Goyang-si, Korea; [6]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [7]Department of Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia; [8]Department of Medicine, Sunnybrook Odette Cancer Centre, Toronto, Canada; [9]Department of Transfusion, Aichi Cancer Center Hospital, Nagoya, Japan; [10]Pfizer Inc, Cambridge, USA; [11]Department of Oncology, German Breast Group Forschungs GmbH, Neu-Isenburg, Germany

Palbociclib-Fulvestrant compared to Everolimus Exemestane for HER2 negative, HR positive, metastatic breast cancer, early progressing after aromatase inhibitor

Bibliography:

Certainty assessment							Summary of findings		
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Impact
							With Everolimus Exemestane	With Palbociclib-Fulvestrant	
Overall Survival (Cristofanilli, 2016) (assessed with: Kaplan-Meier estimate)									
347 (1 RCT)						-	no data		
Overall Survival (Piccart, 2014) (assessed with: Kaplan-Meier estimate)									
485 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	median OS 31.0 months (95%CI 28.0 to 34.6)		
Progression-Free Survival (Chirila, 2017) (assessed with: Kaplan-Meier estimate)									
832 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	HR 1.04 (CrI 0.58 to 1.76)		
Progression-Free Survival (Cristofanilli, 2016) (assessed with: Kaplan-Meier estimate)									
347 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	median PFS 9.5 months (95% CI 9.2 to 11.0)		
Progression-Free Survival (Baselga, 2012 - central review) (assessed with: Kaplan-Meier estimate)									
485 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	median PFS 10.6 (95% CI 9.5 to NR)		
Time to deterioration of QoL (Harbeck, 2016) (assessed with: EORTC QLQ-C30 GHS)									
347 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	median TTD 8 months (95%CI 5.6 to NE)		
Time to deterioration of QoL (Burris, 2013) (assessed with: EORTC QLQ-C30 GHS)									
335 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	median TTD 8.3 months (95%CI 7.9 to 9.7)		

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Indirect comparison from a network meta-analysis
b. Credible interval limits consistent with opposite recommendations
c. Right side 95%CL not estimable)

Palbociclib-Fulvestrant compared to Everolimus Exemestane for HER2 negative, HR positive, metastatic breast cancer, early progressing after aromatase inhibitor

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							With Everolimus Exemestane	With Palbociclib-Fulvestrant	
Discontinuation due to adverse events (Chirila, 2017) (assessed with: cumulative incidence)									
832 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	OR 0.14 (CrI 0.05-0.39)		
Discontinuation due to adverse events (Cristofanilli 2016) (assessed with: Cumulative incidence)									
345 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	14/345; cumulative incidence 0.04 (95%CI 0.02 to 0.07)		
Discontinuation due to adverse events (Baselga, 2012) (assessed with: cumulative incidence)									
482 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	92/482; cumulative incidence 0.19 (95%CI 0.16 to 0.23)		
Mucositis (G3-5) (Cristofanilli, 2016) (assessed with: cumulative incidence)									
345 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	2/345; cumulative incidence 0.006 (95%CI 0.001 to 0.021)		
Mucositis (G3-5) (Baselga, 2012) (assessed with: cumulative incidence)									
482 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	39/482; cumulative incidence 0.08 (95%CI 0.06 to 0.11)		

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Indirect comparison from a network meta-analysis

Palbociclib-Fulvestrant compared to Everolimus Exemestane for HER2 negative, HR positive, metastatic breast cancer, early progressing after aromatase inhibitor

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							With Everolimus Exemestane	**With Palbociclib-Fulvestrant**	
Neutropenia (G3-5) (Cristofanilli, 2016) (assessed with: cumulative incidence)									
345 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	223/345; cumulative incidence 0.65 (95%CI 0.59 to 0.69)		
Neutropenia (all grades) (Cristofanilli, 2016) (assessed with: cumulative incidence)									
345 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	279/345; cumulative incidence 0.81 (95%CI 0.76 to 0.85)		
Neutropenia (all grades) (Jerusalem, 2016) (assessed with: cumulative incidence)									
2131 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	77/2131; cumulative incidence 0.036 (95%CI 0.03 to 0.04)		
Rash (all grades) (Cristofanilli, 2016) (assessed with: cumulative incidence)									
345 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	52/345; cumulative incidence 0.15 (95%CI 0.12 to 0.19)		
Rash (all grades) (assessed with: cumulative incidence)									
482 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	178/482; cumulative incidence 0.37 (95%CI 0.33 to 0.41)		

CI: Confidence interval; **HR:** Hazard Ratio

Palbociclib-Fulvestrant compared to Everolimus Exemestane for HER2 negative, HR positive, metastatic breast cancer, early progressing after aromatase inhibitor

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Rash (all grades) (Baselga, 2012) (assessed with: cumulative incidence)									
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