Antiangiogenic Therapy

In Breast Cancer

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UOC Oncologia Medica Senologica

Istituto Nazionale Tumori "Fondazione Pascale"

Napoli, Italia

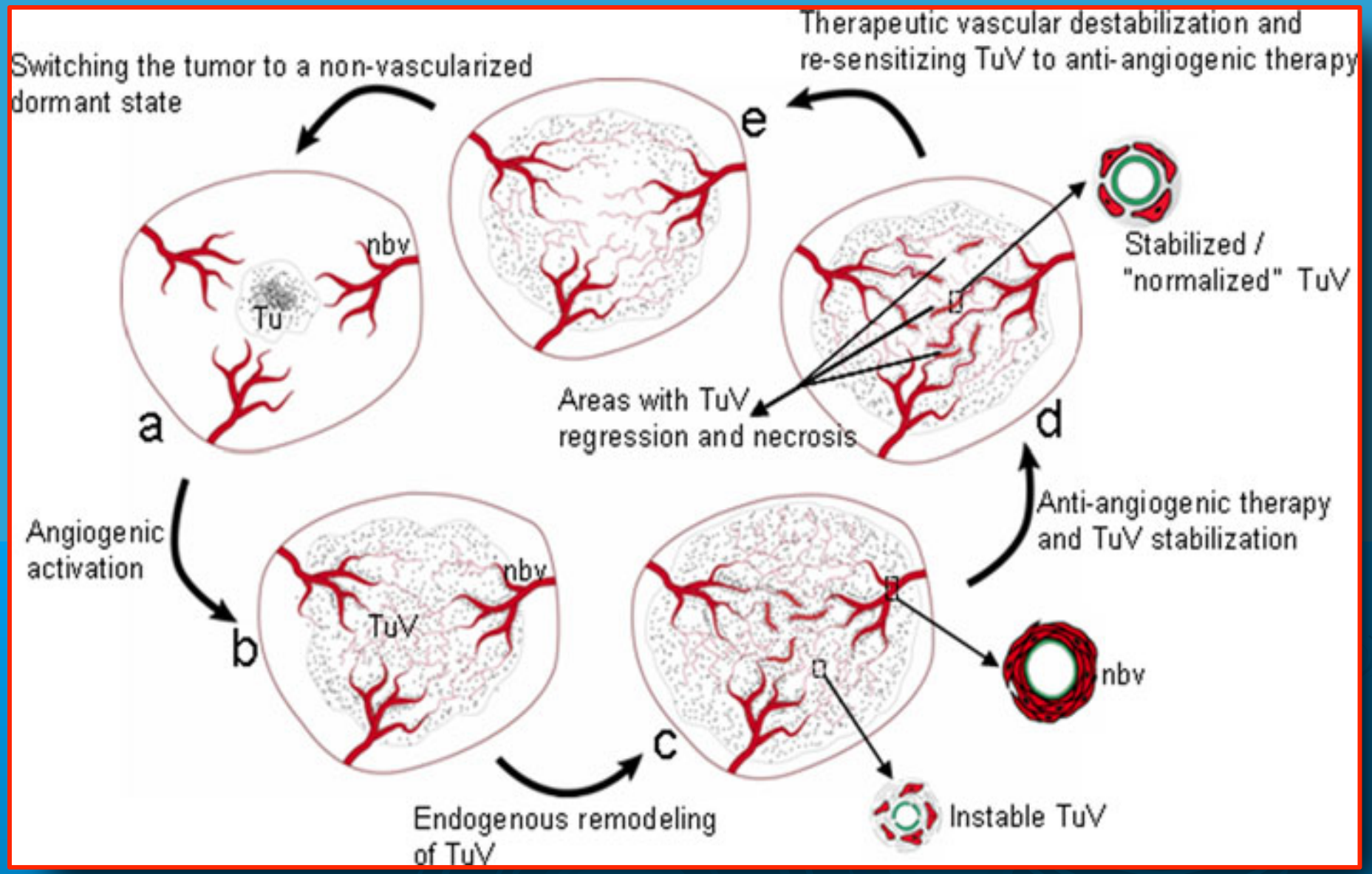
1971

Judah Folkman

Bevacizumab in MBC

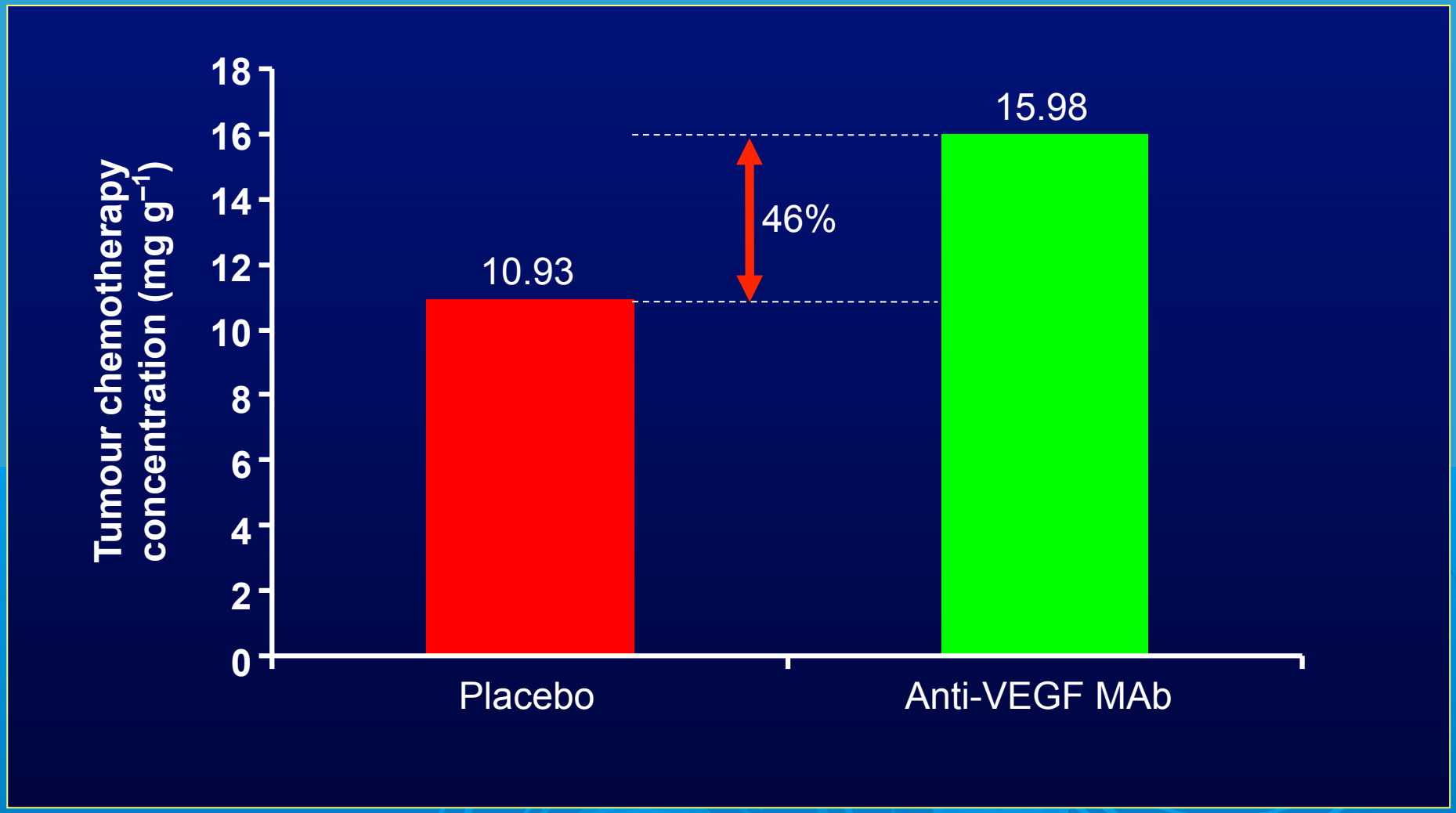
- Biologic Rationale
- Efficacy & Safety
- Additional Data inBC
- Provocative Thoughts

Hypothetical Circle of Antiangiogenic Therapy



Weißhardt et al. Histochem Cell Biol 2012

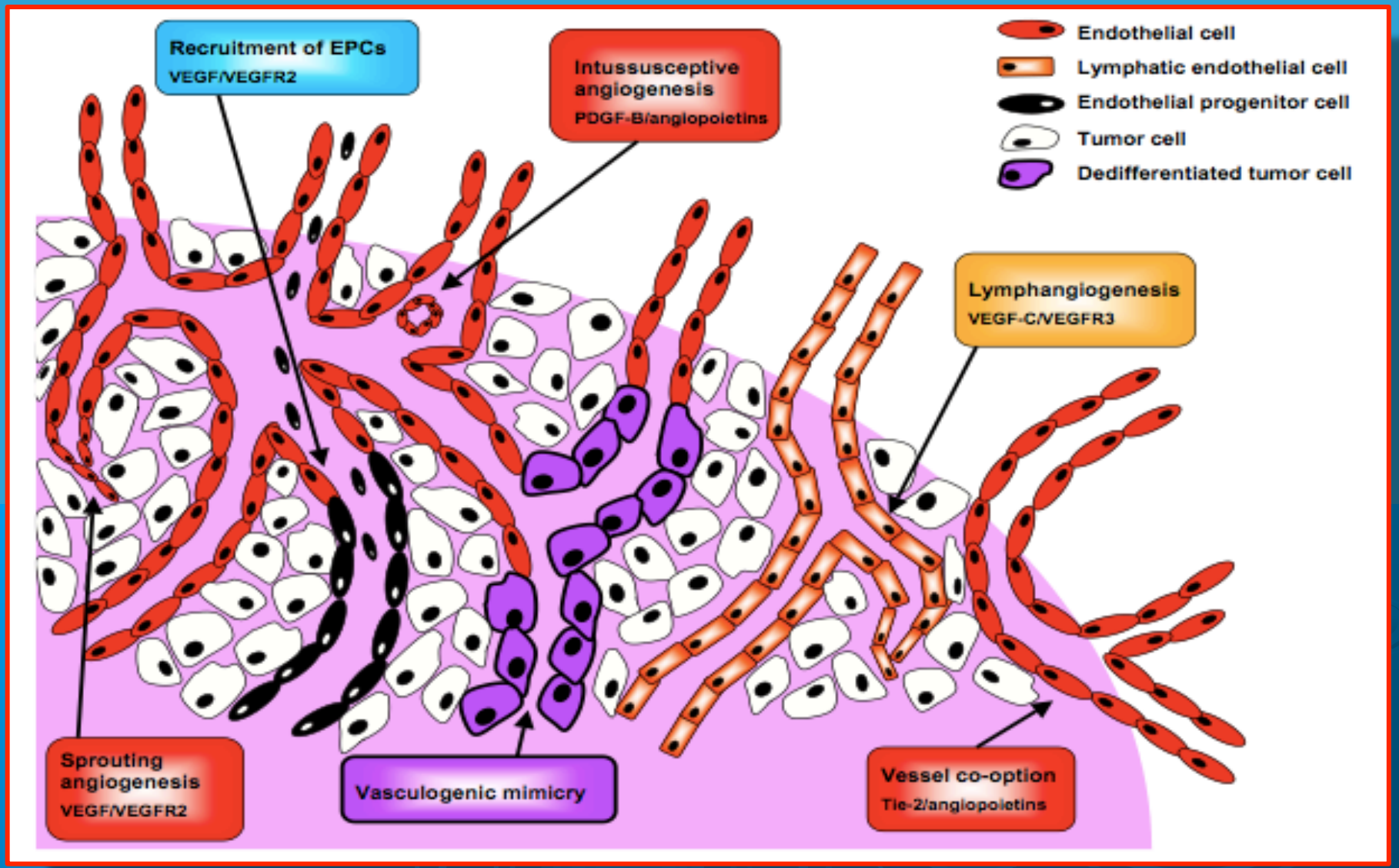
Normalisation: improves delivery of chemotherapy to tumours



Wildiers, et al. Br J Cancer 2003

VEGF System

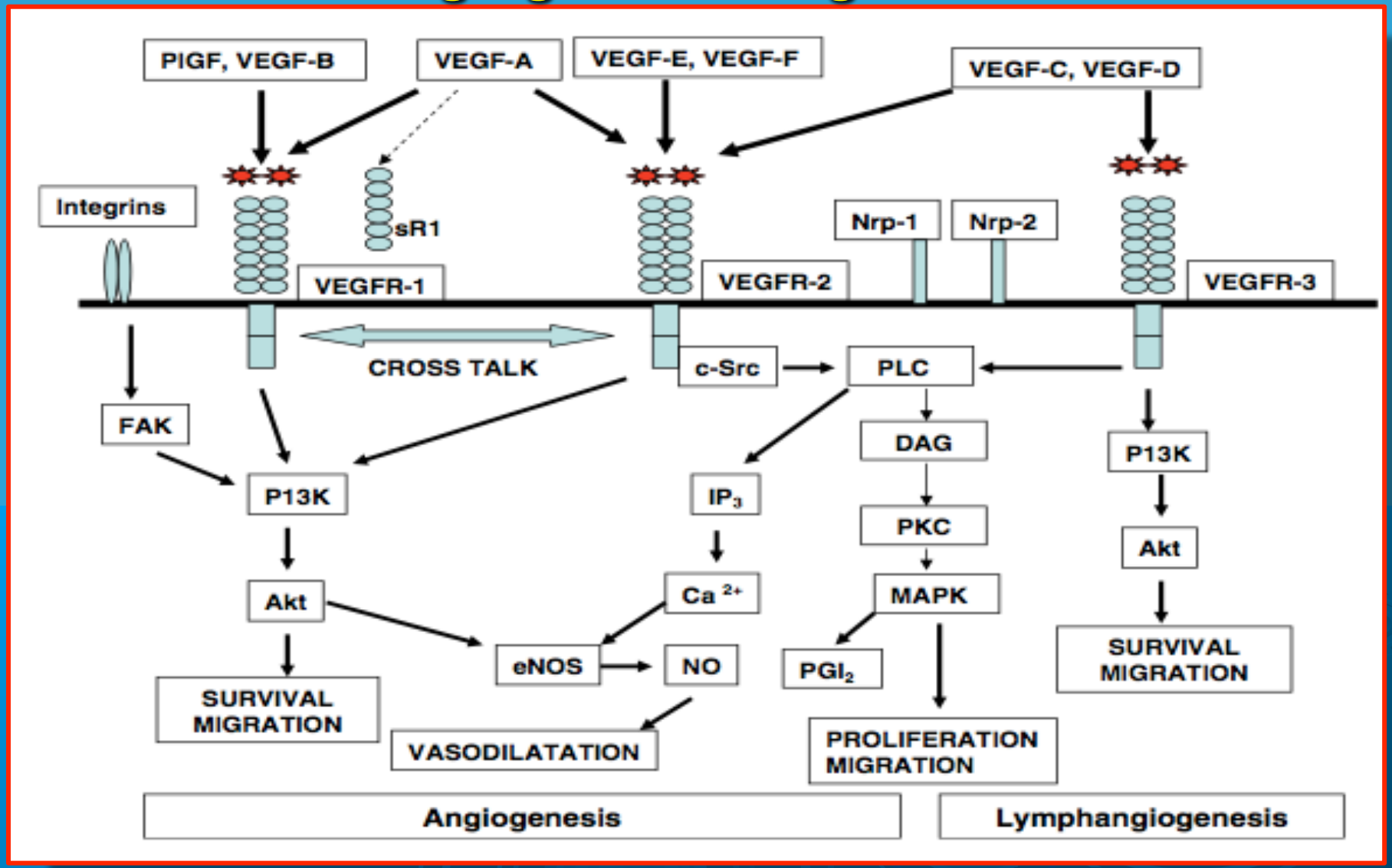
Angiogenesis Regulation



Roy H et al, FEBS Letters 2006

VEGF System

Angiogenesis Regulation

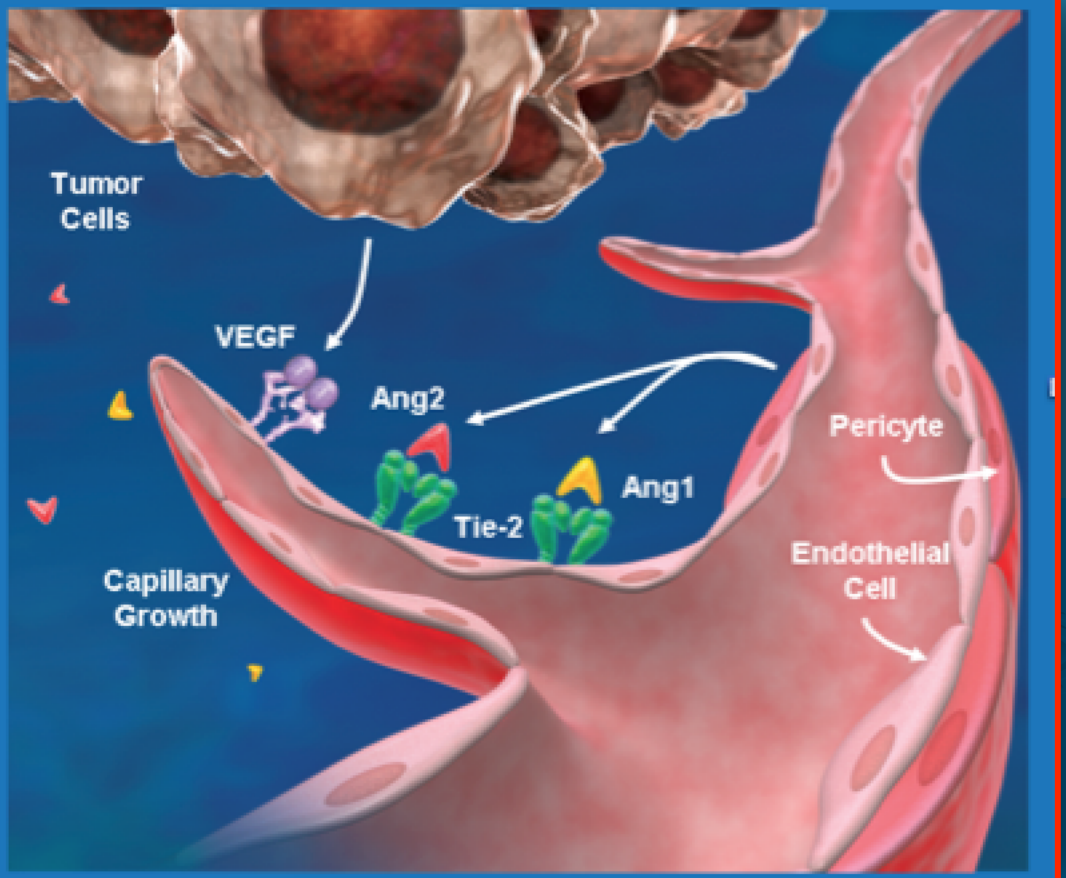


Roy H et al, FEBS Letters 2006

Angio poietinSystem

Angiogenesis Regulation

- Angiogenesis is a complex process that requires proliferation, migration, and survival of endothelial cells[1]
- These functions may be regulated by a number of different factors (eg, VEGF and angiopoietins)[1]
- Angiopoietins interact with the Tie-2 receptor, which mediates the vascular remodeling process[1,2]



Bevacizumab in MBC

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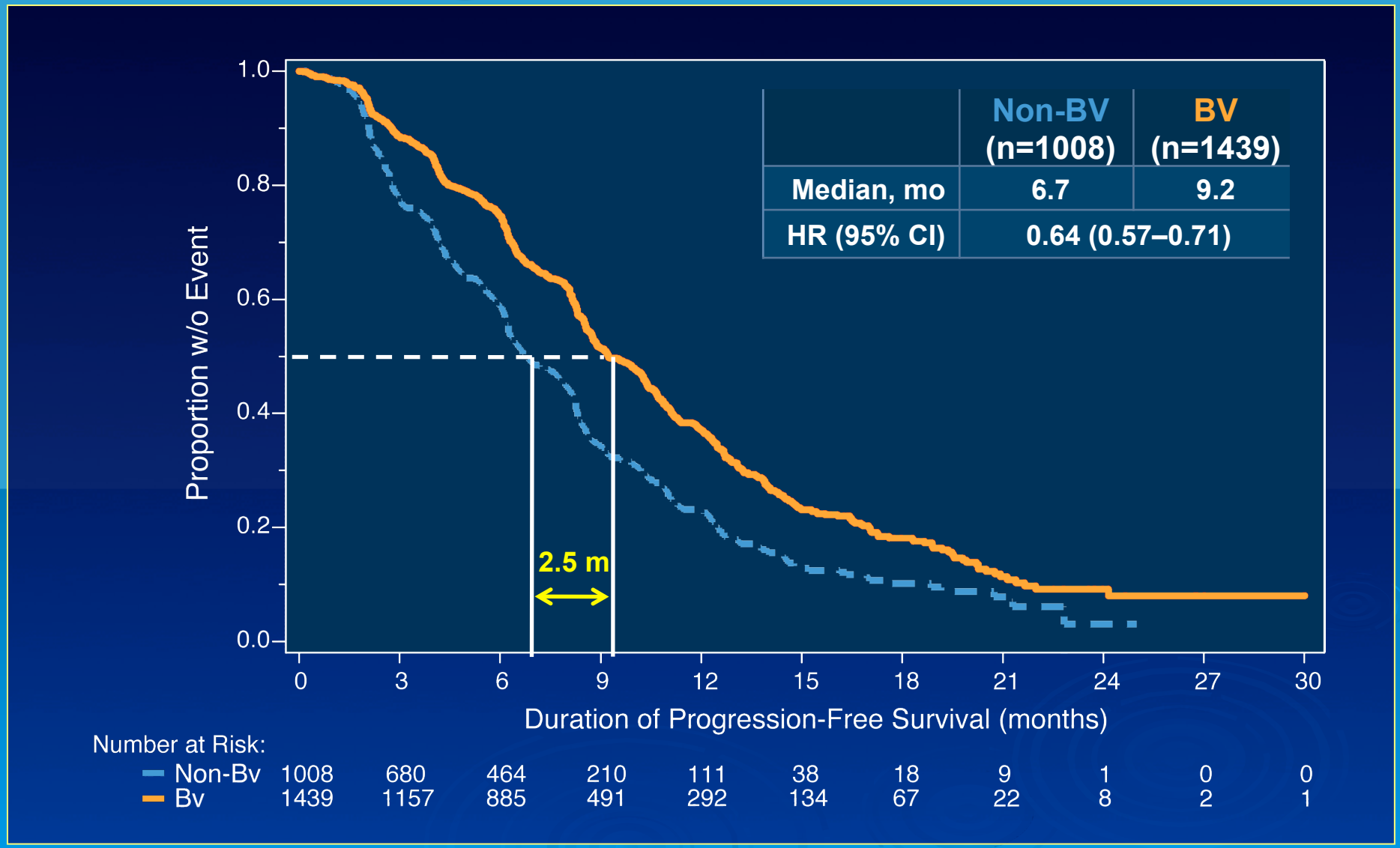
Metanalysis of 1st line RCT

Progression-Free Survival



O'Shaugnessy et al, ASCO 2010

Metanalysis of 1st line RCT

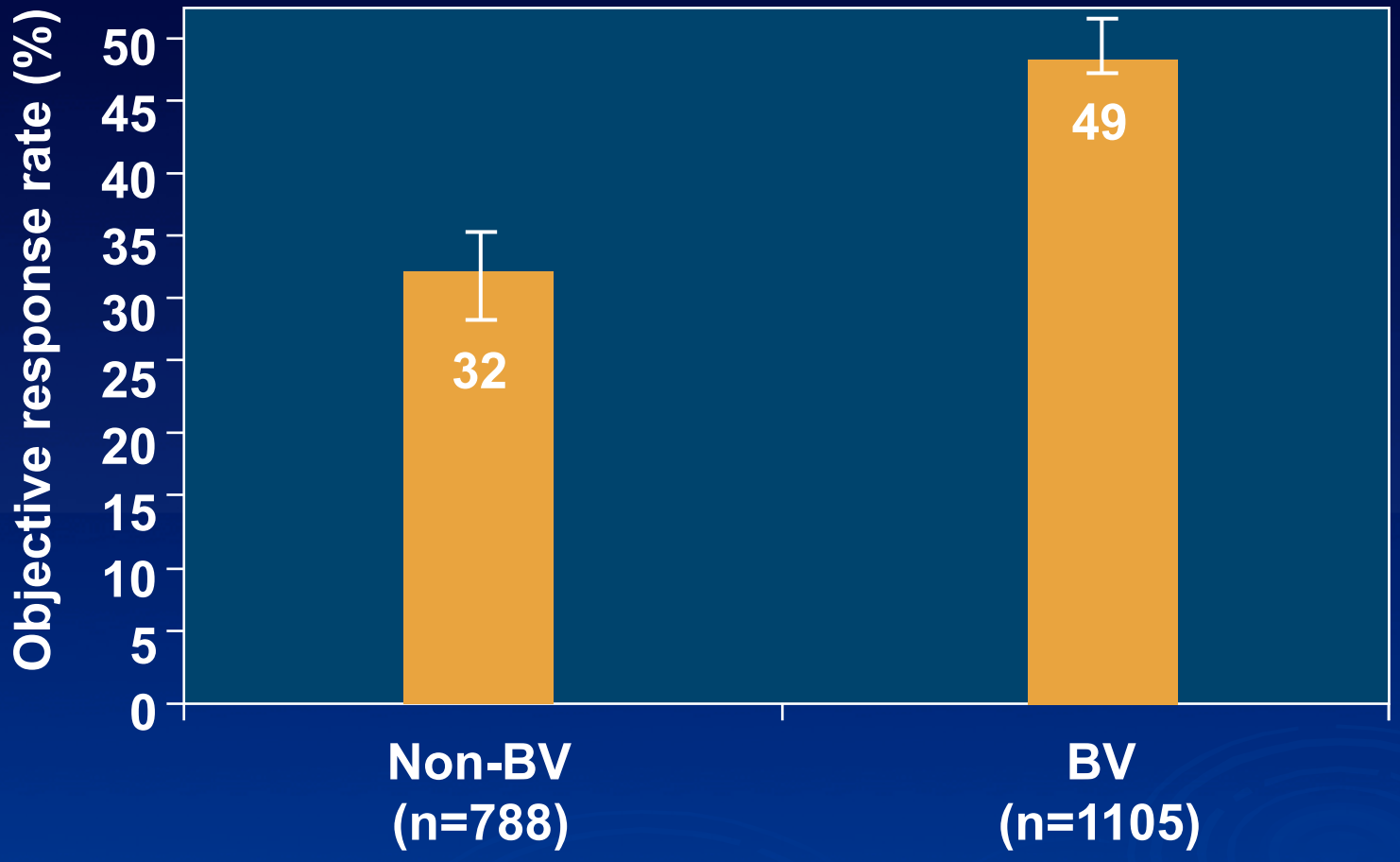
PFS by Subgroups

Baseline risk factor	n	Hazard ratio	(95% CI)
All patients	2447	0.64	(0.58–0.71)
Age (years)			
<65	1917	0.62	(0.56–0.70)
≥65	530	0.70	(0.56–0.88)
Triple negative (ER- and PgR- and HER2-)			
Yes	621	0.63	(0.52–0.76)
No	1762	0.64	(0.57–0.73)
Visceral disease			
Yes	1707	0.66	(0.59–0.75)
No	740	0.60	(0.49–0.74)
Number of metastatic sites			
<3	1463	0.62	(0.54–0.71)
≥3	980	0.64	(0.55–0.75)
Disease-free interval			
≤24 months	924	0.65	(0.55–0.77)
>24 months	1519	0.63	(0.56–0.72)
Prior adjuvant/ neo-adjuvant chemotherapy			
Yes	1525	0.60	(0.53–0.68)
No	922	0.71	(0.60–0.84)

O'Shaugnessy et al, ASCO 2010

Metanalysis of 1st line RCT

Objective Response Rate

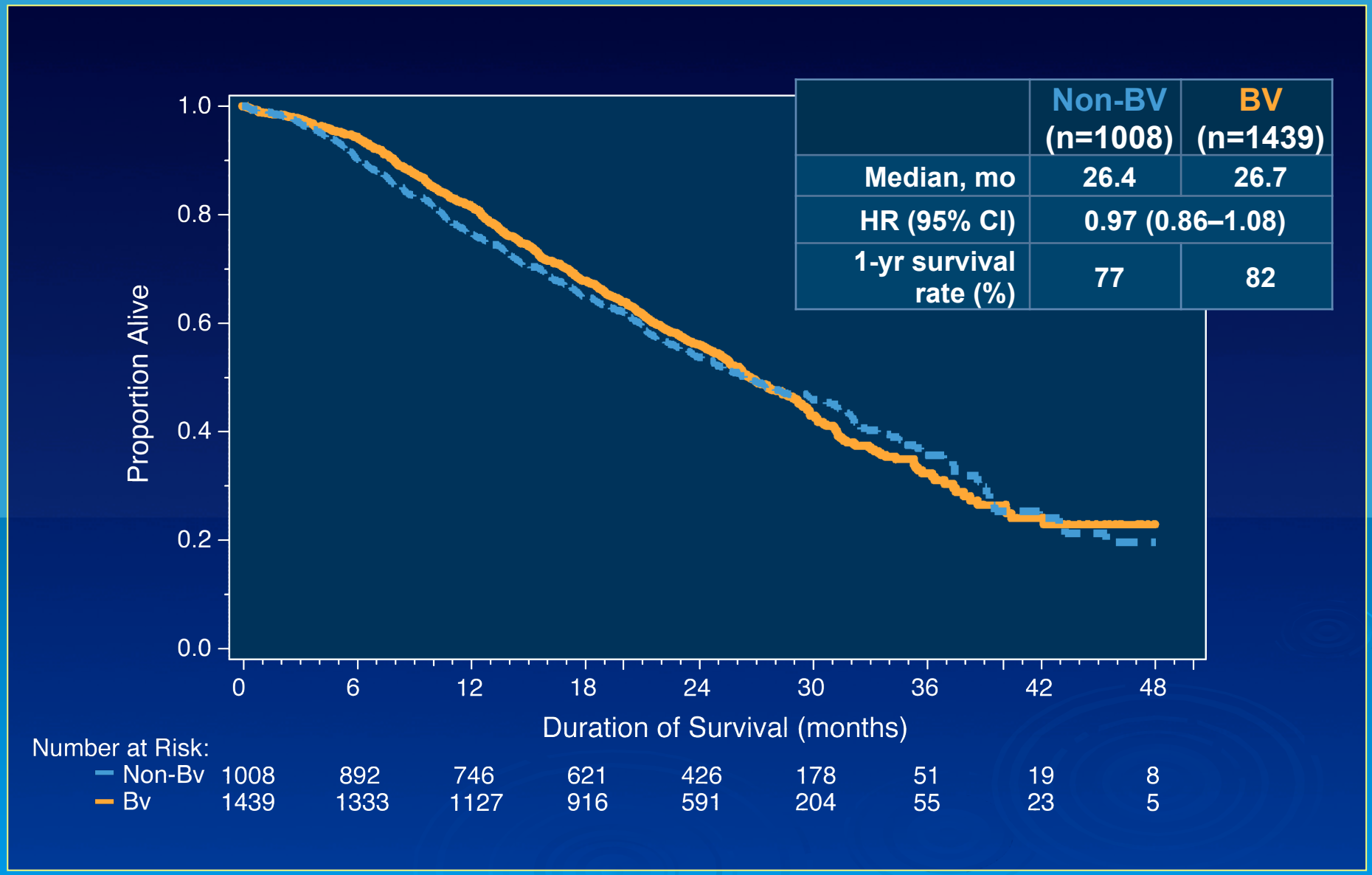


*Includes only patients with measurable disease at baseline.

O'Shaugnessy et al, ASCO 2010

E2100, AVADO & RIBBON1 Metanalysis

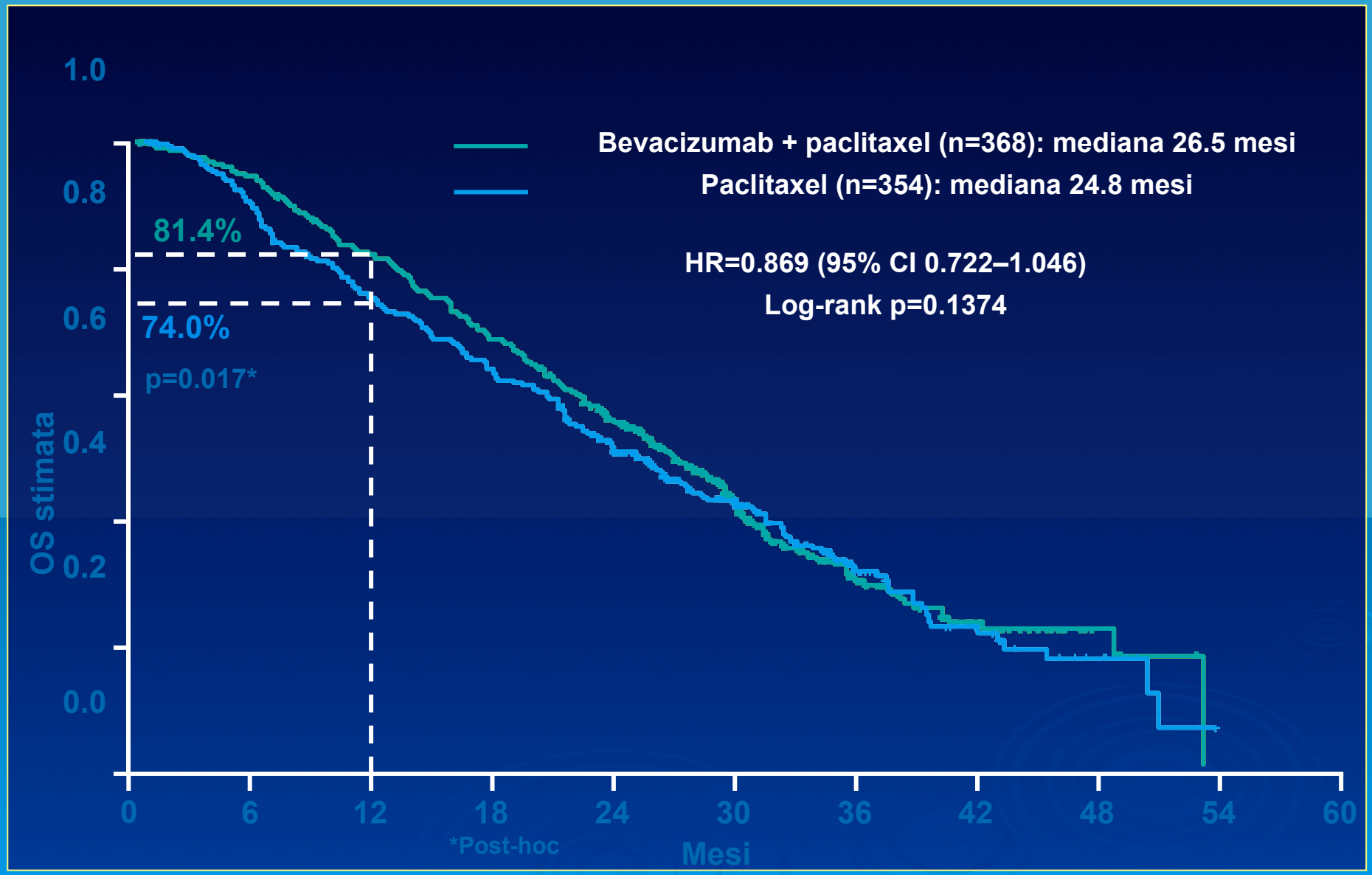
Overall Survival



	Non-BV (n=1008)	BV (n=1439)
Median, mo	26.4	26.7
HR (95% CI)	0.97 (0.86–1.08)	
1-yr survival rate (%)	77	82

O'Shaugnessy et al, ASCO 2010

E2100: sopravvivenza globale



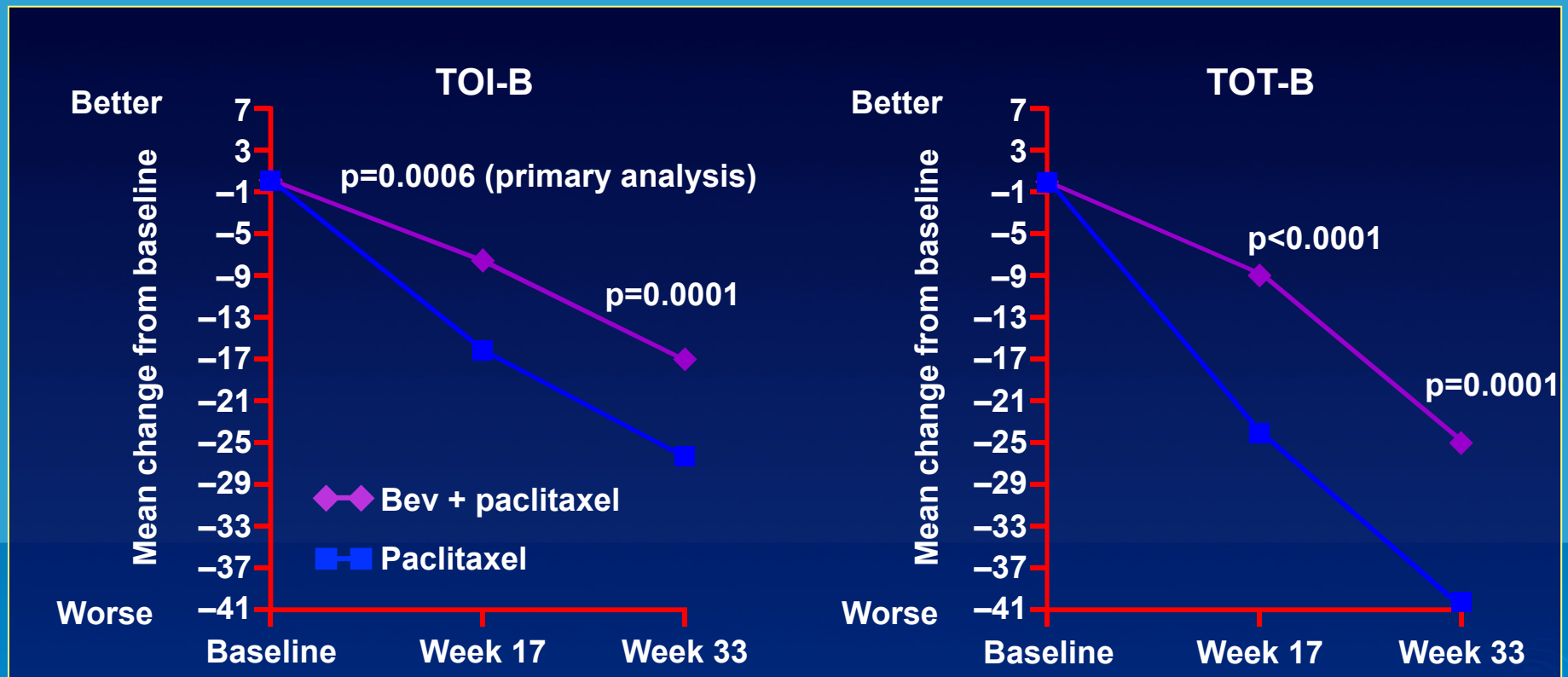
E2100, AVADO & RIBBON1 Metanalysis

Grade ≥3 Selected Adverse Events (Aes)

%	Non-BV (n=982)	BV (n=1679)
Neutropenia	7.1	10.0
Sensory neuropathy	8.5	9.5
Hypertension	1.2	9.0
Febrile neutropenia	3.5	6.5
Venous thromboembolic event	3.8	2.8
Proteinuria	0	2.3
Arterial thromboembolic event	0.3	1.6
Bleeding	0.4	1.5
Left ventricular systolic function	0.2	1.5
Wound dehiscence	0.3	0.8
Fistula	0.3	0.5
GI perforation	0.3	0.5
RPLS	0	<0.1

O'Shaugnessy et al, ASCO 2010

E2100: quality of life



- TOI-B: incorporates physical, functional and BC-specific quality of life
- TOT-B: emotional and social/family well-being in addition to the above
- Lesser effects were observed using different imputation rules, but bevacizumab-treated patients scored higher in all analyses

Roche data on file submitted to regulatory authority in 2006

Bevacizumab in MBC

- Biologic Rationale
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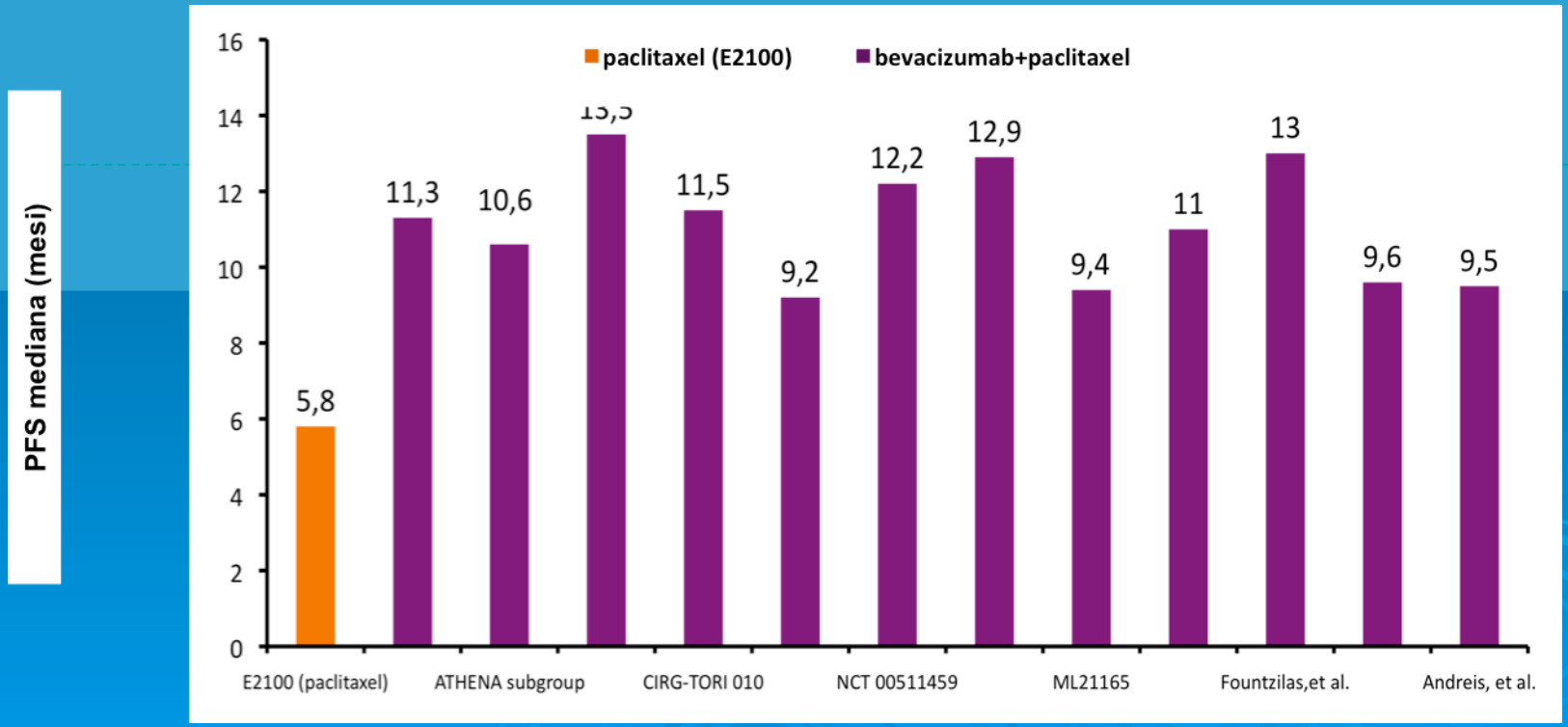
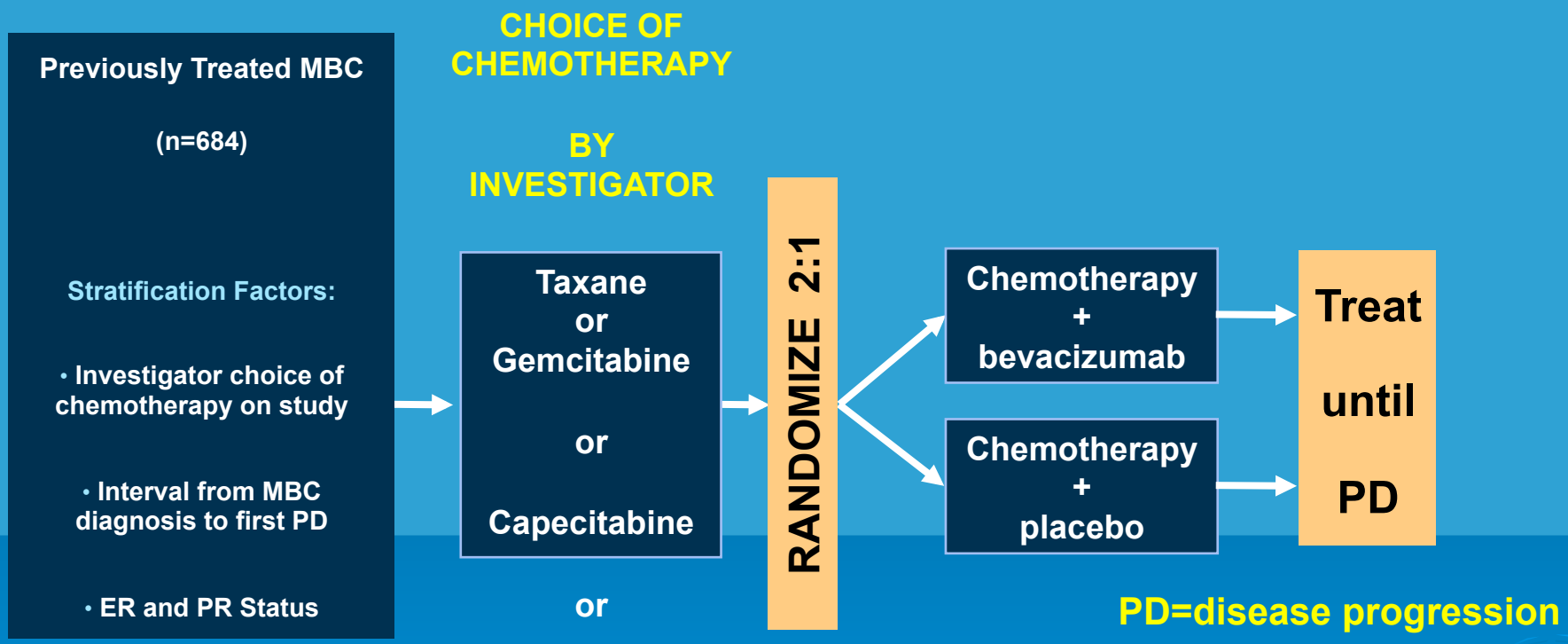
L'efficacia e la sicurezza di bevacizumab più paclitaxel osservata nello studio E2100 è stata confermata su oltre 2000 pazienti in 11 studi: [28, 41-51]

- 8 studi prospettici, randomizzati o a singolo braccio
- 3 studi retrospettivi, fotografia della pratica clinica quotidiana



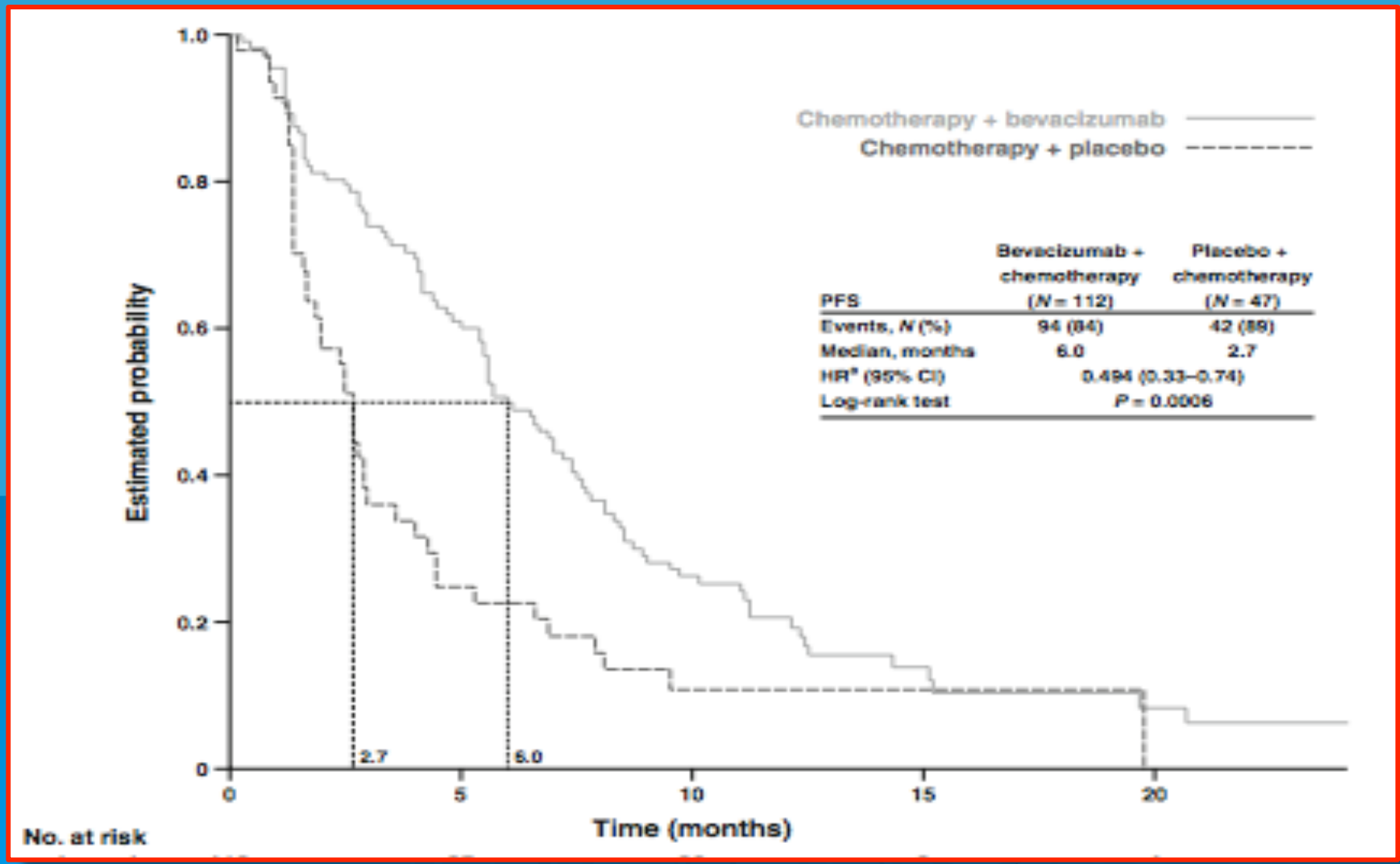
RIBBON 2 Study Design



- Taxane (paclitaxel 90 mg/m²/wk for 3 of 4 wk; paclitaxel 175 mg/m², nab-paclitaxel 260 mg/m², or docetaxel 75–100 mg/m² q3w)
- Gemcitabine (1250 mg/m² on Days 1 and 8 q3w)
- Capecitabine (2000 mg/m² Days 1–14 q3w)
- Vinorelbine (30 mg/m²/wk)

RIBBON 2

TNBC Subgroup Analysis

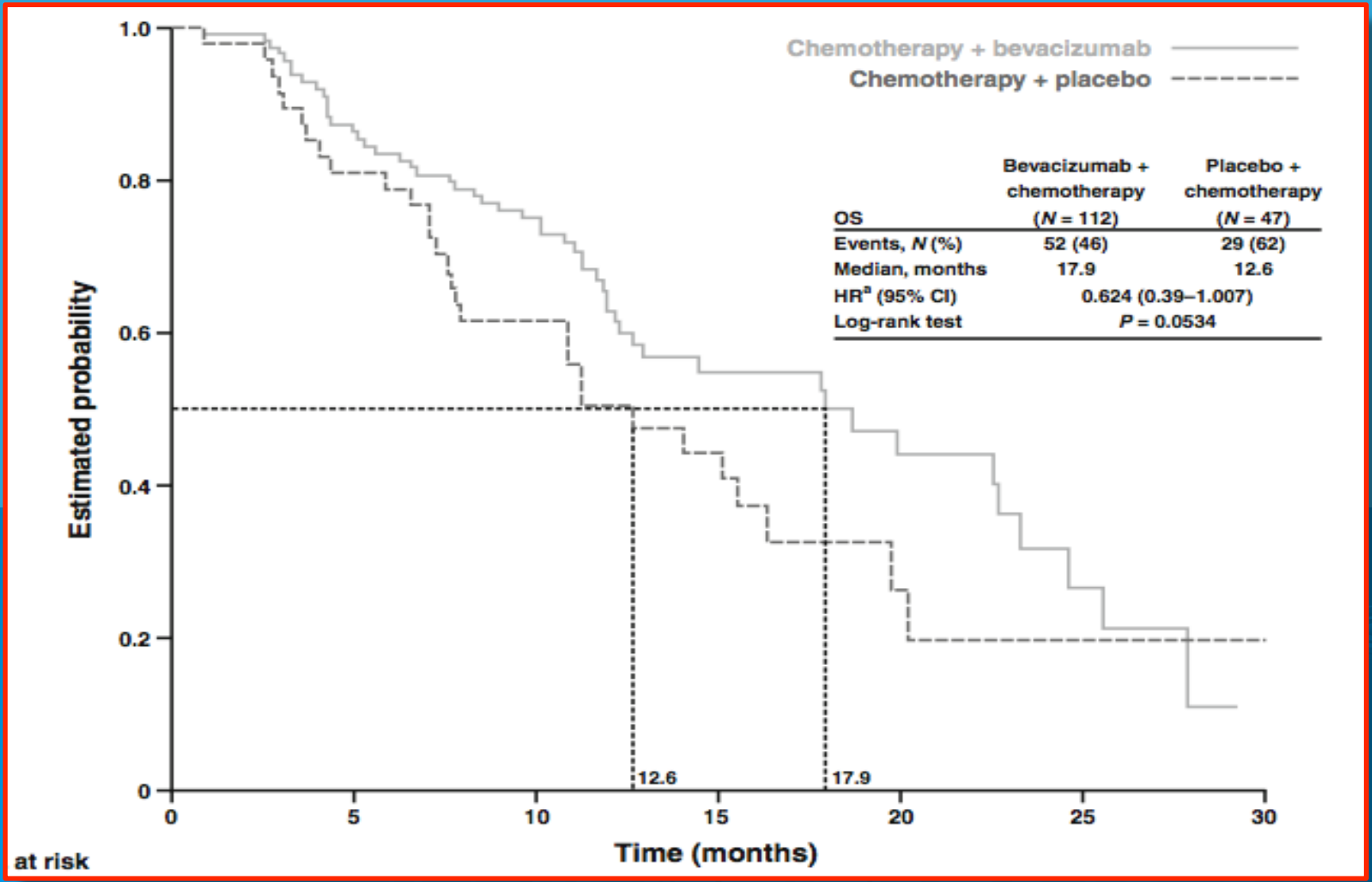


PFS	Bevacizumab + chemotherapy (*N* = 112)	Placebo + chemotherapy (*N* = 47)
Events, *N* (%)	94 (84)	42 (89)
Median, months	6.0	2.7
HR[a] (95% CI)	0.494 (0.33–0.74)	
Log-rank test	*P* = 0.0006	

Brufsky et al, Breast Cancer Res Treat 2012

RIBBON 2

TNBC Subgroup Analysis



OS	Bevacizumab + chemotherapy (*N* = 112)	Placebo + chemotherapy (*N* = 47)
Events, *N* (%)	52 (46)	29 (62)
Median, months	17.9	12.6
HR[a] (95% CI)	0.624 (0.39–1.007)	
Log-rank test	*P* = 0.0534	

Brufsky et al, Breast Cancer Res Treat 2012

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Beva+Chemo in 1st line MBC

Summary of Efficacy Data

- ORR: ≈ 50%-65%
- PFS ↑: ≈ 2.0-5.5 months (average 2.5 m)

VOLUME 26 · NUMBER 12 · APRIL 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Taxanes Alone or in Combination With Anthracyclines As First-Line Therapy of Patients With Metastatic Breast Cancer

Martine J. Piccart-Gebhart, Tomasz Burzykowski, Marc Buyse, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

- ORR: ≈ 57%
- PFS ⇧: ≈ 0.8 months
- No OS ⇧

Volume 20 – Number 12 – June 2002

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Superior Survival With Capecitabine Plus Docetaxel Combination Therapy in Anthracycline-Pretreated Patients With Advanced Breast Cancer: Phase III Trial Results

By Joyce O'Shaughnessy, David Miles, Svetislava Vukelja, Vladimir Moiseyenko, Jean-Pierre Ayoub, Guadalupe Cervantes, Pierre Fumoleau, Stephen Jones, Wing-Yiu Lui, Louis Mauriac, Chris Twelves, Guy Van Hazel, Shailendra Verma, and Robert Leonard

- ORR: ≈ 42%
- PFS ⇧: ≈ 1.9 months
- Yes OS ⇧(*)

(*) only ≈ 33% 1° line pts;
only 17% pts in docetaxel arm crossed-over to capecitabine post-progression.

VOLUME 26 · NUMBER 24 · AUGUST 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gemcitabine Plus Paclitaxel Versus Paclitaxel Monotherapy in Patients With Metastatic Breast Cancer and Prior Anthracycline Treatment

Kathy S. Albain, Shona M. Nag, German Calderillo-Ruiz, Johann P. Jordaan, Antonio C. Llombart, Anna Pluzanska, Janusz Rolski, Allen S. Melemed, Jose M. Reyes-Vidal, Jagdev S. Sekhon, Lorinda Simms, and Joyce O'Shaughnessy

- ORR: ≈ 40.8%
- PFS ⇧: ≈ 2.1 months
- Yes OS ⇧ (p=0.049) (*)

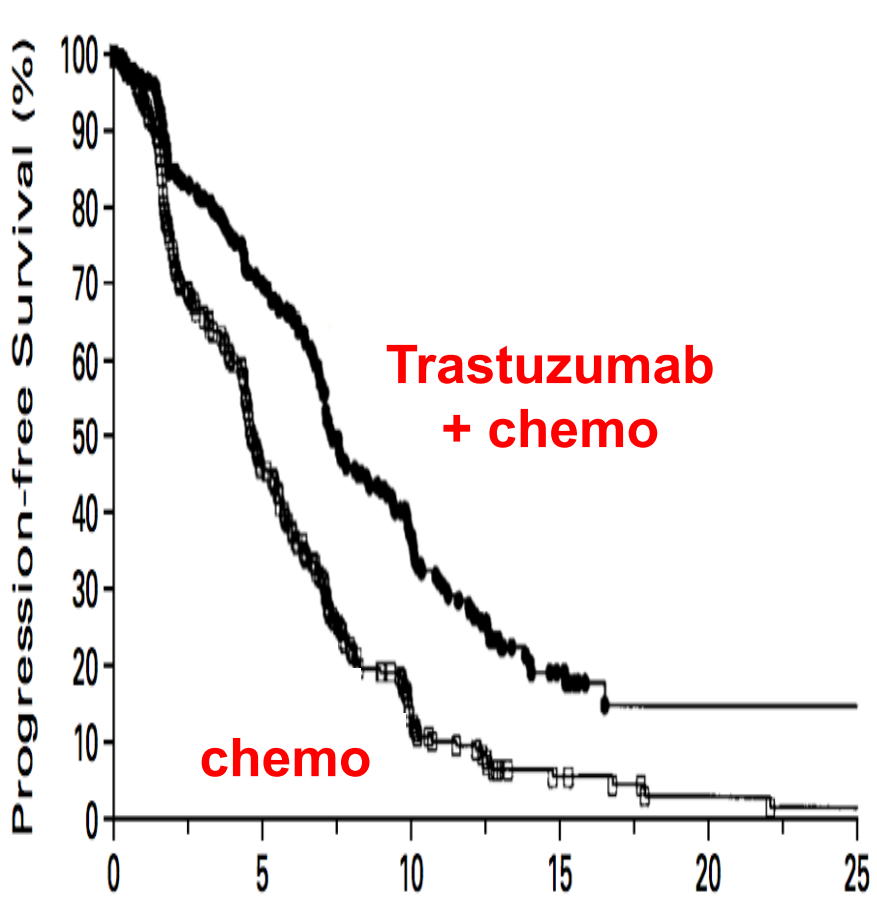
(*) paclitaxel was given at 175 mg/m^2 q21;
only 15.6% pts in paclitaxel arm crossed-over to gemcitabine post-progression.

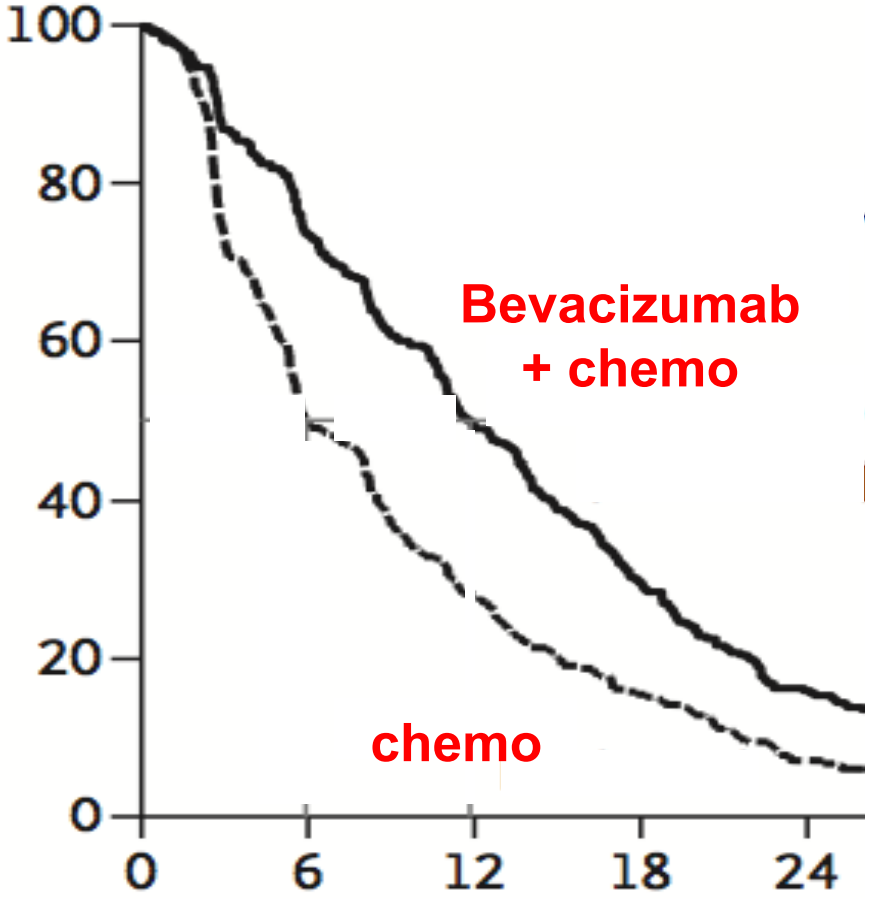
Monochemo: Equally Tolerated but Less Effective

Polichemo: Equally Effective but More Toxic

Who is Who?

"Miraculous" drugs in Breast Cancer

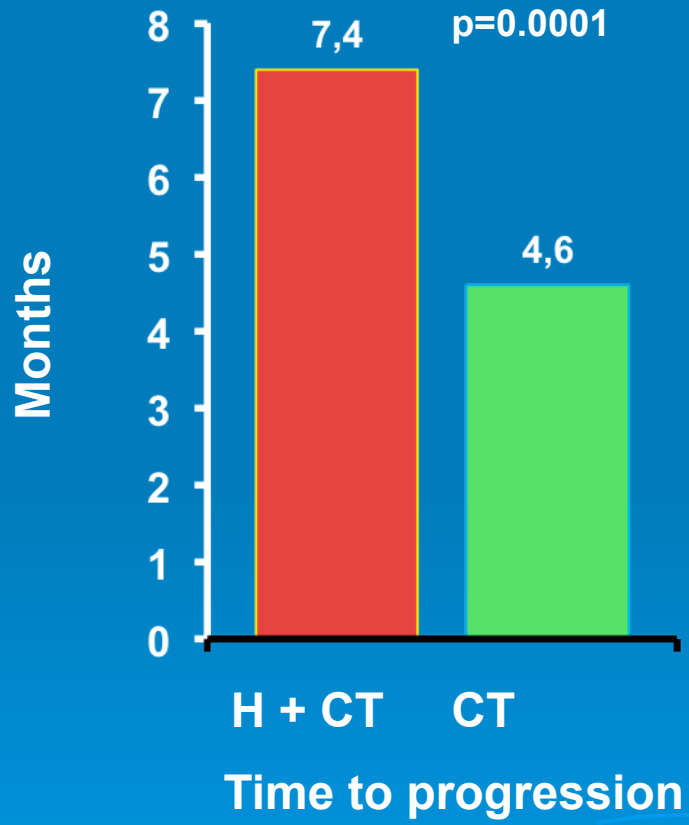


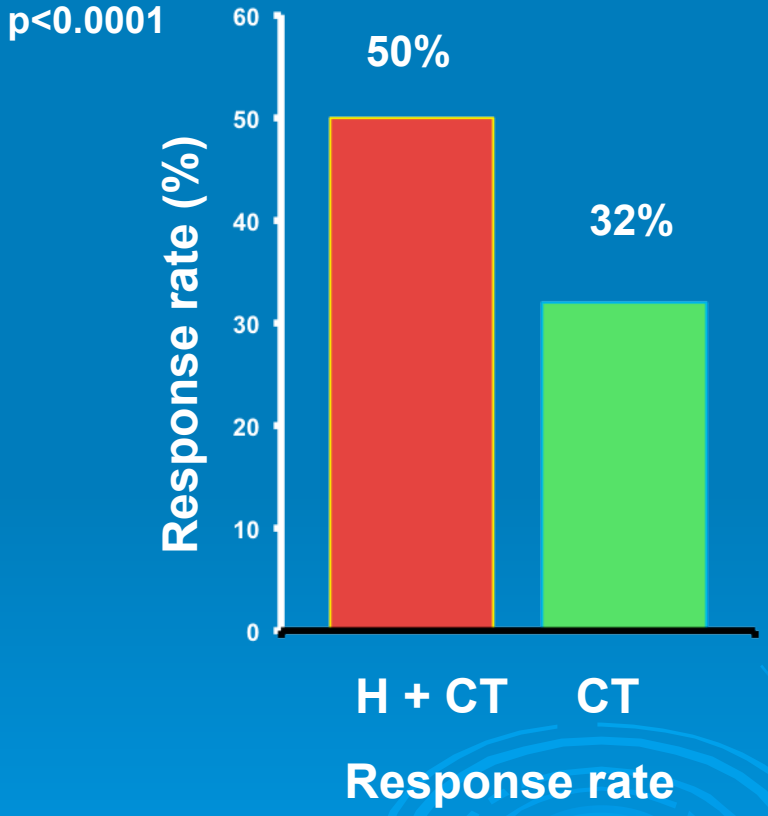


Slamon et al NEJM 2001

Miller et al NEJM 2007

Pivotal Herceptin® combination therapy trial (H0648g) Summary of results (cont'd)

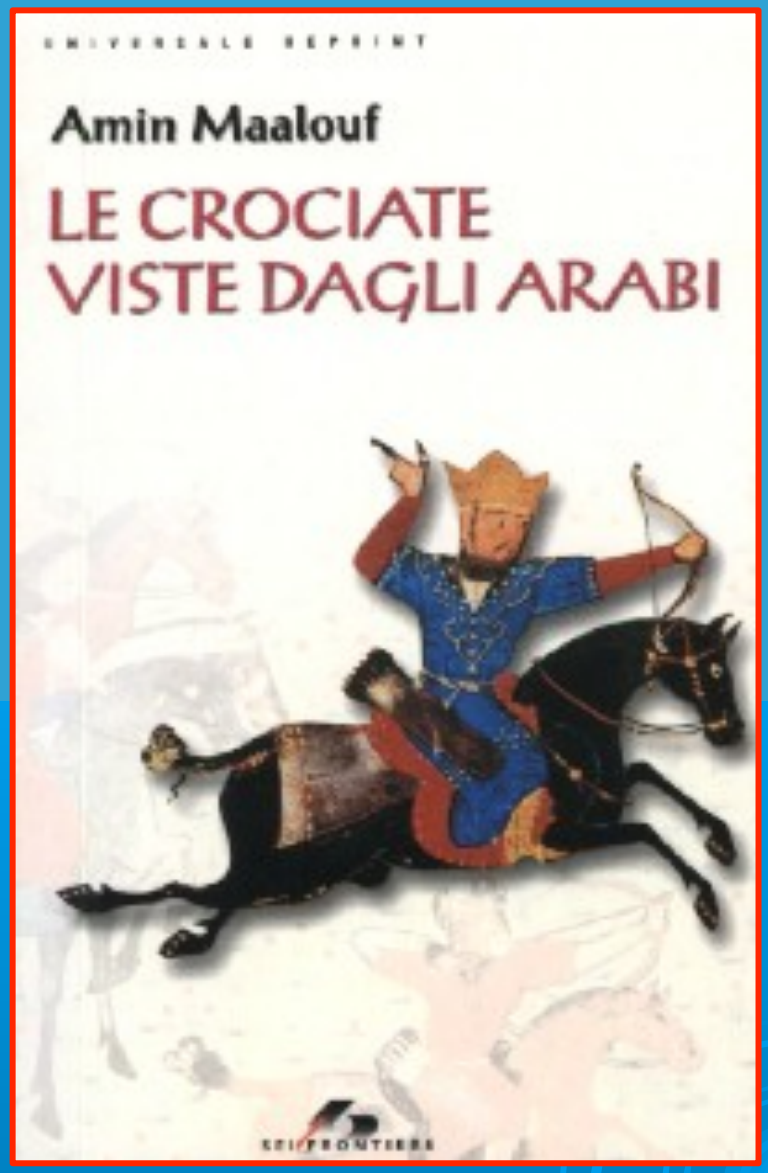




H = Herceptin®
CT = chemotherapy

Norton L et al. Proc ASCO 1999;18:Abstract 483

Summing-Up



- Substantial improvement of ORR and PFS as compared to chemotherapy alone
- No improvement of OS so far: further follow-up needed
- Well tolerated in MBC pts and AE are fairly manageable
- QoL preserved or improved
- In an Unselected Population Beva yields similar benefits to what Trastuzumab produce in a very targeted population
- TNBC pts seems particularly suited to Beva Treatment
- Cost are in line with other generally accepted anti-cancer treatments

AIFA
Agenzia Italiana del Farmaco

Condizioni in regime di rimborso SSN:

- risk share al 50% dopo 1.5 mesi (6 settimane) di trattamento, equivalente al rimborso del valore di 1,5 cicli o 1 ciclo, rispettivamente per somministrazioni pari a 10 mg/kg ogni 2 settimane o 15 mg/kg ogni 3 settimane, con meccanismo automatico di pay-back sulla base della prima scheda di follow-up;

-- al fine di allineare il costo/anno per terapia e per paziente, ciascun centro applica su base annua un meccanismo di ripiano ponendo a carico dell'azienda per ciascun paziente i cicli dal 15° (per somministrazione con posologia pari a 10 mg/kg ogni 2 settimane) o dal 11° ciclo (per somministrazione con posologia pari a 15 mg/kg ogni 3 settimane), sulla base delle schede del registro dei farmaci oncologici.

Comparative Efficacy/Costs

approximate costs for a 70kg/170cm pts

	PFS ↑	OS ↑	Cost/year
Bevacizumab + Chemo	2.5	-	≈ 50.000 EUR
Trastuzumab + AI	2.3	-	≈ 52.000 EUR
Lapatinib + AI	5.2	-	≈ 60.000 EUR
Trastuzumab + chemo BP	2.4	-	≈ 52.000 EUR
Trabectedina	1.5	-	≈ 98.000 EUR

De Laurentiis M, personal calculations,
based on AIFA reimbursemnt criteria and no discounts