資料 2-2

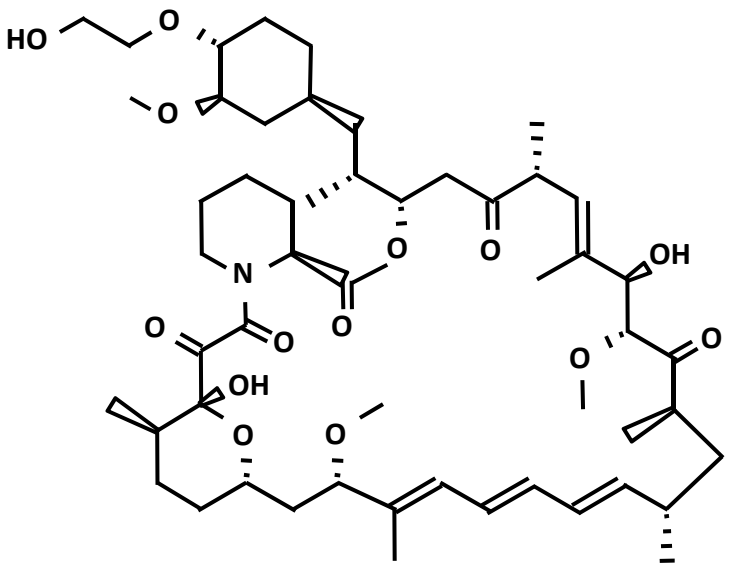
非臨床試験
臨床の立場から

京都大学医学部附属病院
戸井雅和

Preclinical studies

- **Therapeutic Window: Efficacy/Toxicity**
- **Disease Specificity**
- **Subtype Specificity**
- **Combination: Concurrent/Sequential**
- **Therapeutic situation: Response/ Survival**
- **Therapeutic Resistance**

RAD001: Oral mTOR Inhibitor



Everolimus

- **Active rapamycin derivative**
- Orally bioavailable; $T_{1/2}$ ≈30 hours; CYP3A4 metabolism
- Sustained inhibition of mTOR through daily administration
- Inhibits cell growth and angiogenesis
- **Broad antitumor activity**
  - Potential synergy with chemotherapy, radiation, and other targeted agents
  - Demonstrated single-agent efficacy and safety in a phase 3 trial in renal cell carcinoma
  - Other diseases: NET, Metastatic breast cancer…

2011.6

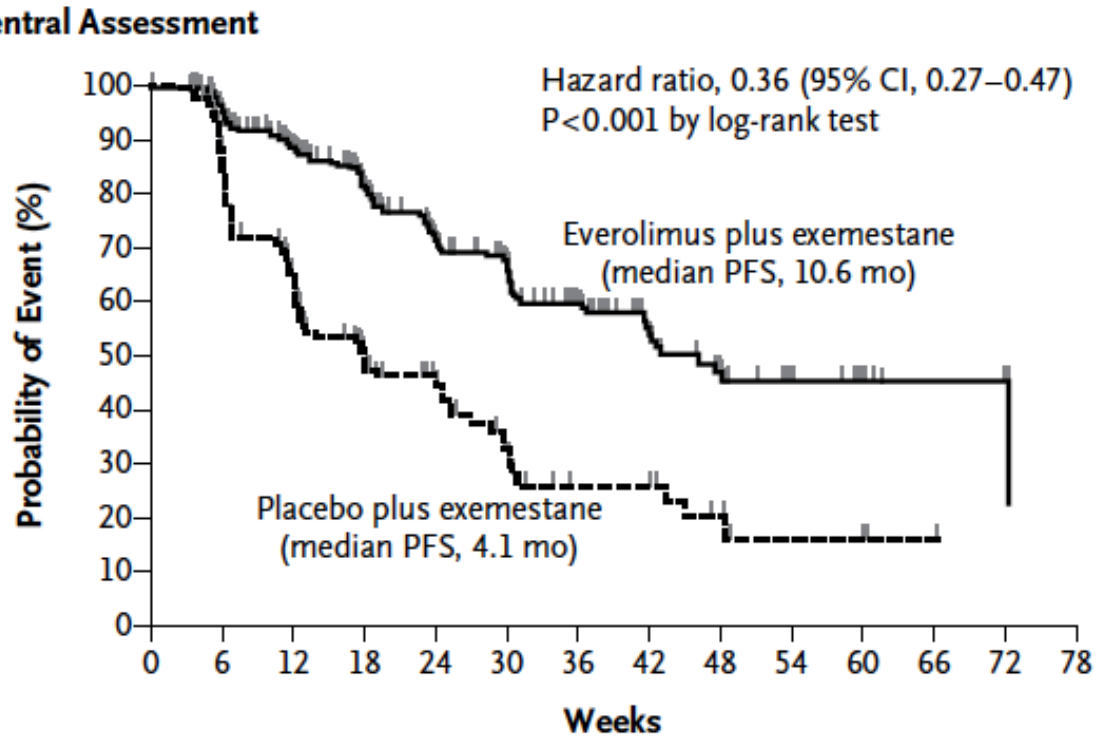
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

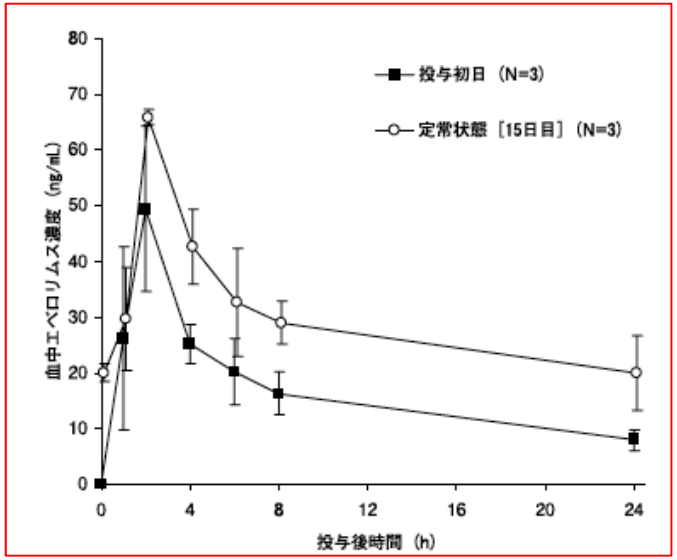
José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

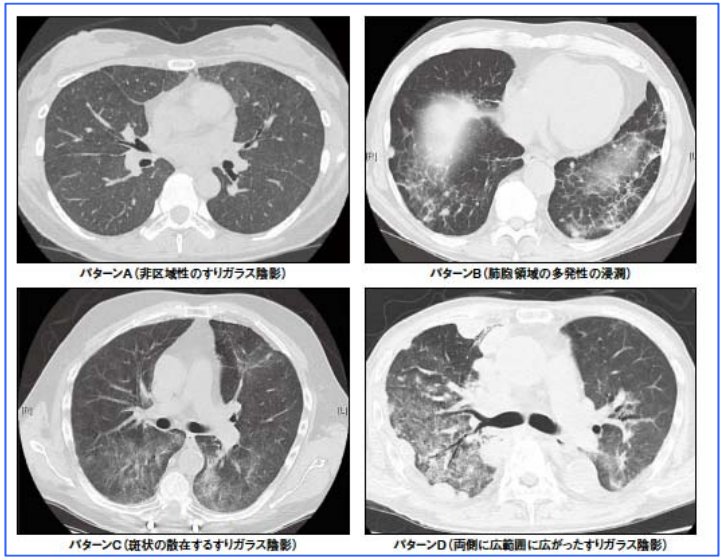
N Engl J Med 2012;366:520-9.



Tumor subtype:
Hormone receptor +
HER2 –

The most common grade 3 or 4 adverse events were **stomatitis** (8% vs. 1%), (any grade: 12% vs. 5%) **anemia** (6% vs. <1%), **dyspnea** (4% vs. 1%), **hyperglycemia** (4% vs. <1%), **fatigue** (4% vs. 1%), and **pneumonitis** (3% vs. 0%).





BOLERO-2試験の国内症例（n=71）

発現日（日）	1-28	29-56	57-84	85-112	113-140	141-168	169-196	197-224	225-252	253-280	281-
発現率（例）	87.3%（62例）	4.2%（3例）	0%	0%	0%	1.4%（1例）	0%	0%	0%	0%	0%

■口内炎

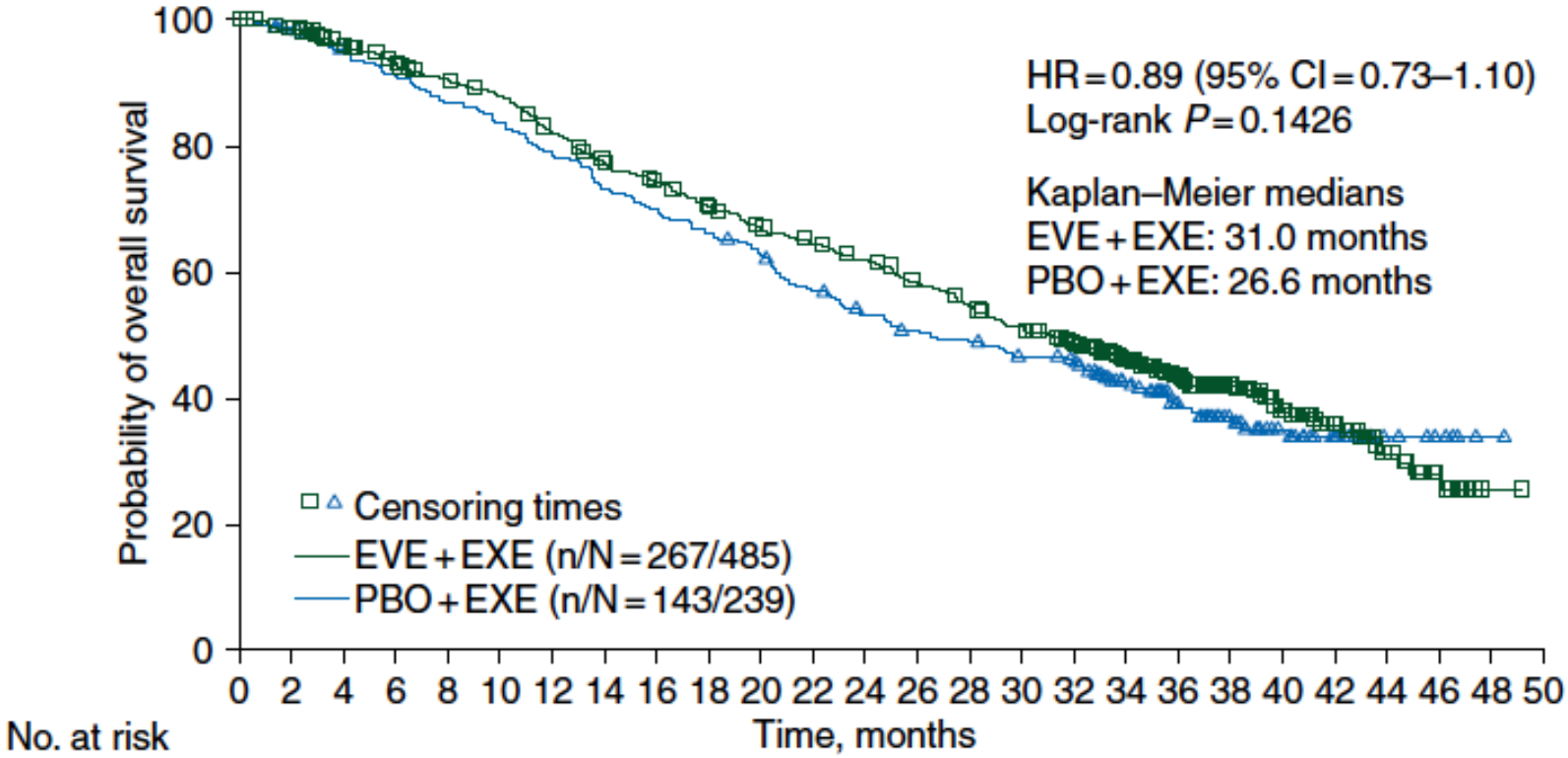
➡投与再開後の用法・用量の調節等の詳細はp.40を参照してください。

	グレード1	グレード2	グレード3	グレード4
口内炎	投与継続	グレード1以下に回復するまで休薬 ・投与再開の場合は、1日1回10mgで開始 ・2回目以降の場合、1日1回5mgに減量して投与再開	グレード1以下に回復するまで休薬 ・投与再開の場合は、1日1回5mgで投与開始	投与中止

Annals of Oncology 25: 2357–2362, 201
doi:10.1093/annonc/mdu45
Published online 17 September 201

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]



BOLERO-3: Anti-HER2 trastuzumab resistant

N = 572*

- Locally advanced or metastatic HER2⁺ breast cancer
- Prior taxane required
- **Trastuzumab 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/m² weekly) + TRAS (2 mg/kg week‡) (n = 284)

Placebo (PO daily) + Vinorelbine (25 mg/m² weekly) + TRAS (2 mg/kg weekly*) (n = 285)

- Stratification by prior lapatinib use (yes/no)

Therapy until PD or intolerable toxicity

Endpoints:
Primary: PFS
Secondary: OS, ORR, time to deterioration of ECOG PS, safety, DoR, CBR, and QoL

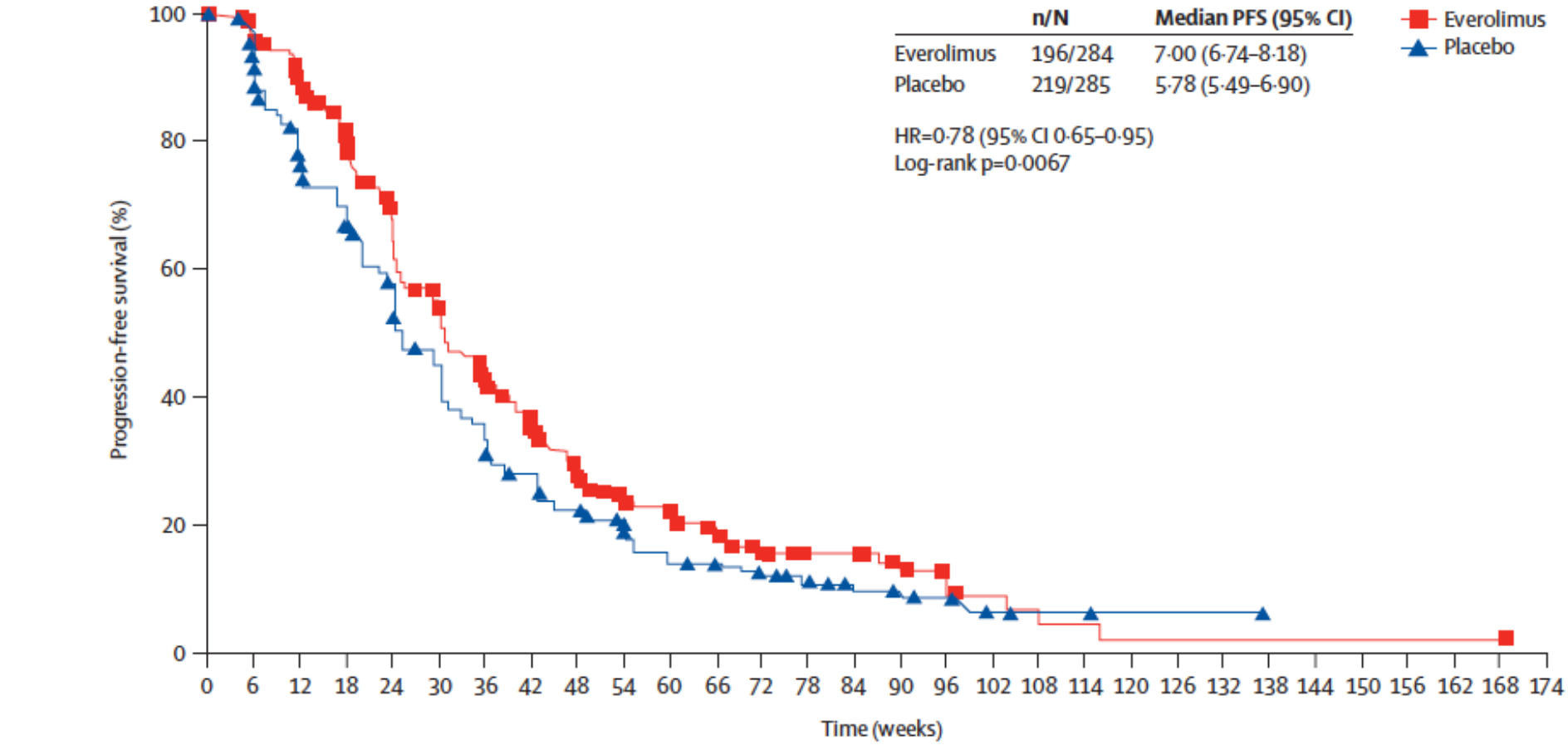
Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial

Lancet Oncol 2014; 15: 580–91
Published Online
April 15, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70138-X

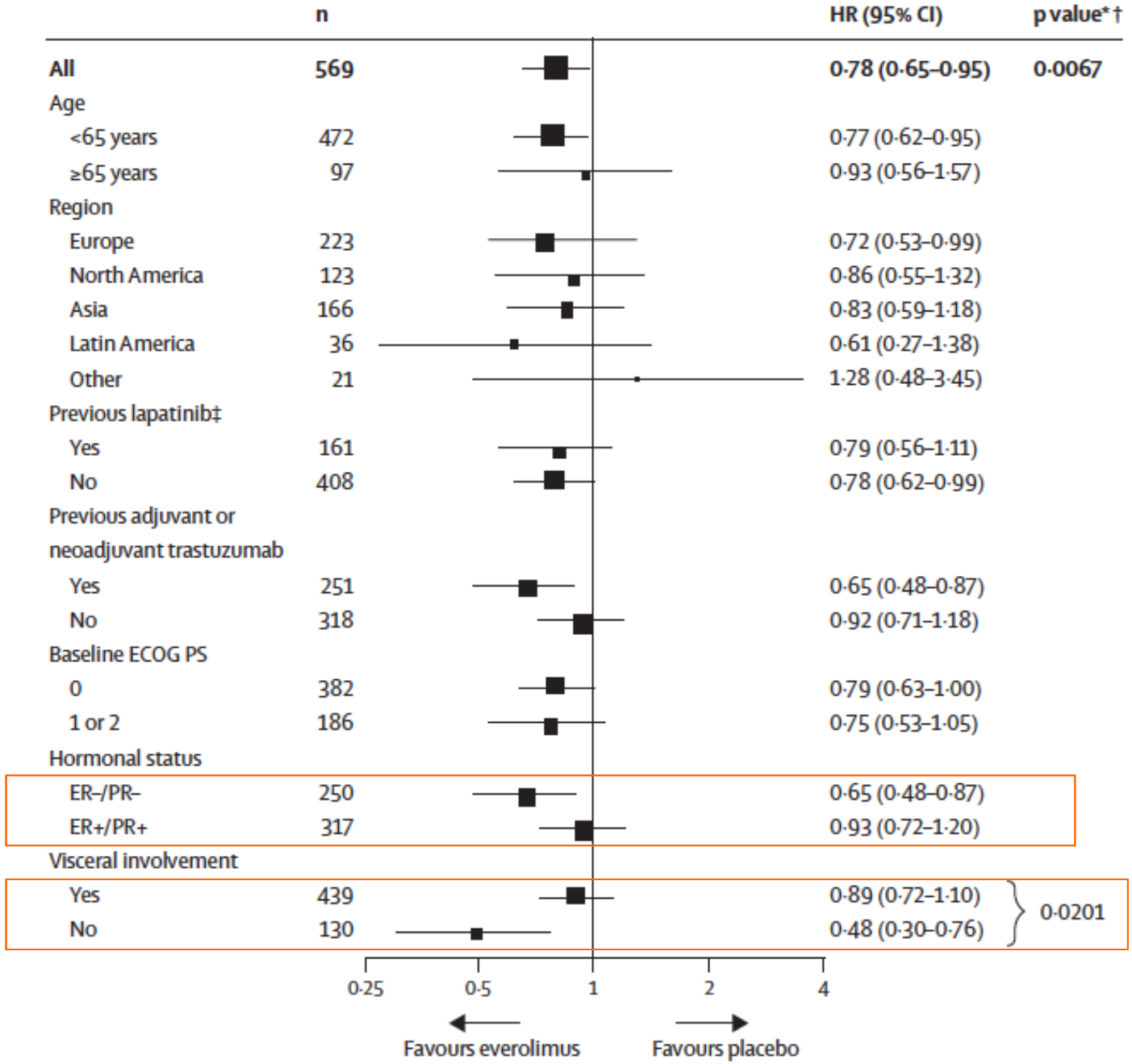
Fabrice André, Ruth O'Regan, Mustafa Ozguroglu, Masakazu Toi, Binghe Xu, Guy Jerusalem, Norikazu Masuda, Sharon Wilks, Francis Arena, Claudine Isaacs, Yoon-Sim Yap, Zsuzsanna Papai, Istvan Lang, Anne Armstrong, Guillermo Lerzo, Michelle White, Kunwei Shen, Jennifer Litton, David Chen, Yufen Zhang, Shyanne Ali, Tetiana Taran, Luca Gianni

BOLERO-3: Primary Endpoint

Progression-Free Survival by Local Assessment

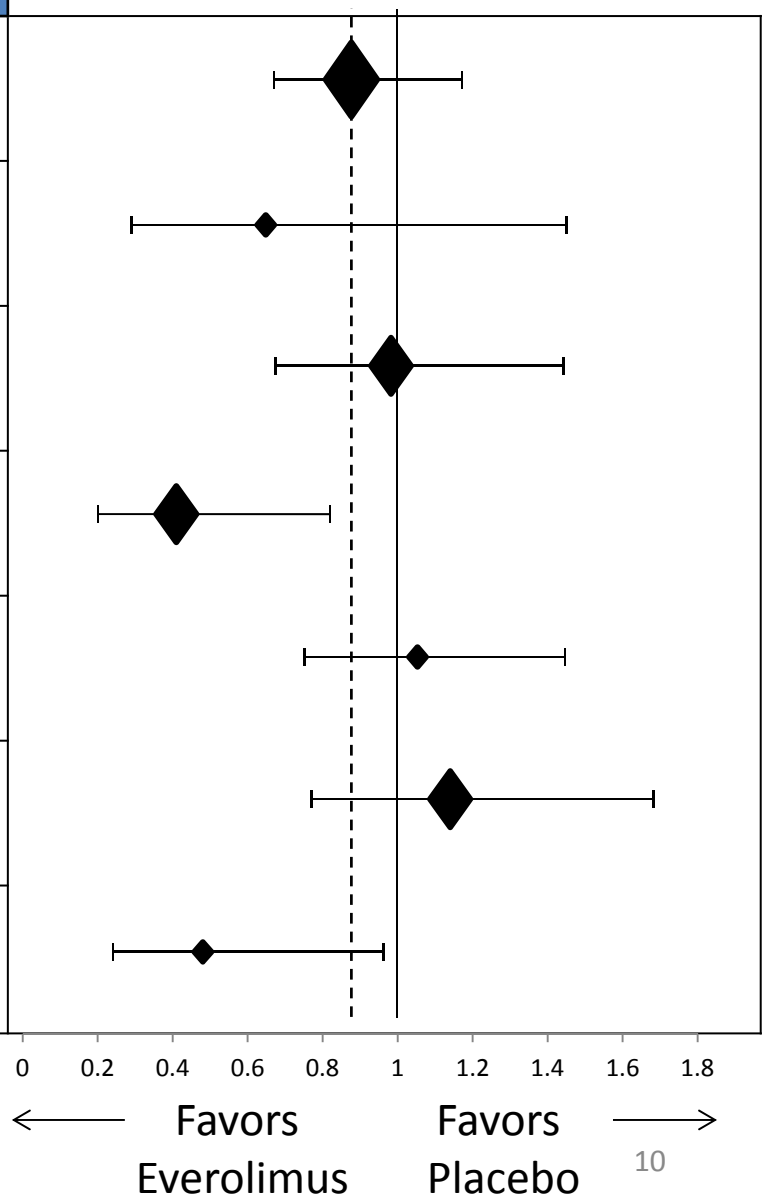


Subgroup analysis



Biomarker study

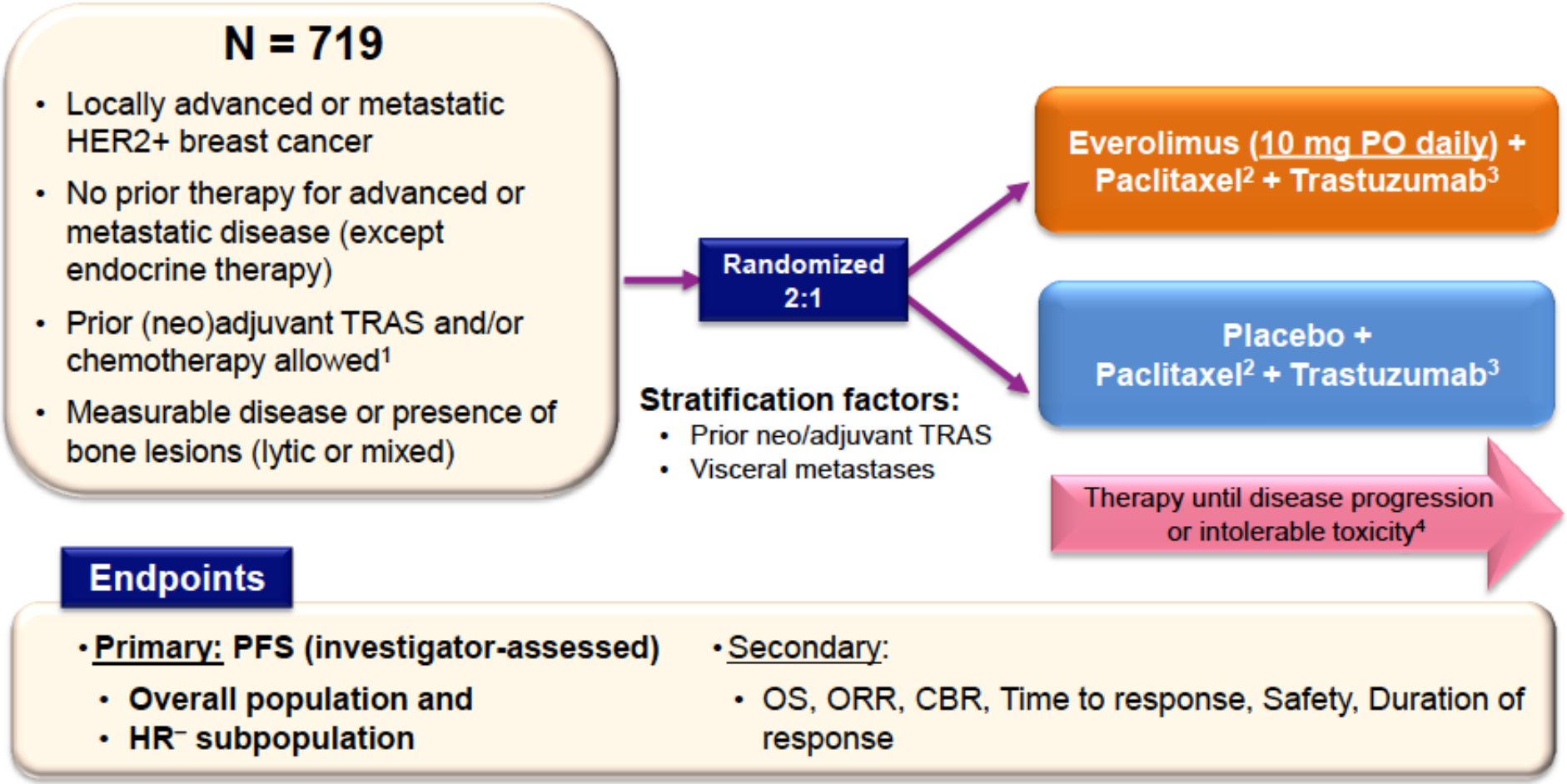
Treatment	Biomarker	n	Events	Median PFS (95% CI)	HR (95% CI)
Everolimus	Biomarker population	130	95	7.0 (5.6, 8.1)	0.88 (0.67,1.17)
Placebo		132	104	5.7 (5.3, 6.9)	
Everolimus	**PIK3Ca mutant**	**15**	**9**	**5.5 (*)**	**0.65* (0.29, 1.45)**
Placebo		**21**	**19**	**6.7 (4.8, 7.6)**	
Everolimus	PIK3Ca wildtype	69	51	6.8 (5.5, 8.2)	0.98 (0.67, 1.44)
Placebo		77	56	5.7 (5.2, 7.8)	
Everolimus	**PTEN <20th %ile**	**26**	**16**	**9.6 (5.5, 12.2)**	**0.40 (0.20, 0.82)**
Placebo		**22**	**18**	**5.3 (2.8, 5.7)**	
Everolimus	PTEN ≥20th %ile	89	67	6.9 (5.5, 8.1)	1.05 (0.75, 1.45)
Placebo		100	78	6.9 (5.5, 8.3)	
Everolimus	pS6≤75th %ile	66	47	5.7 (5.4, 8.3)	1.14 (0.77, 1.68)
Placebo		77	57	6.9 (5.5, 8.3)	
Everolimus	**pS6>75th %ile**	**23**	**15**	**6.8 (4.2, 12.7)**	**0.48 (0.24, 0.96)**
Placebo		**22**	**20**	**3.9 (2.7, 5.5)**	



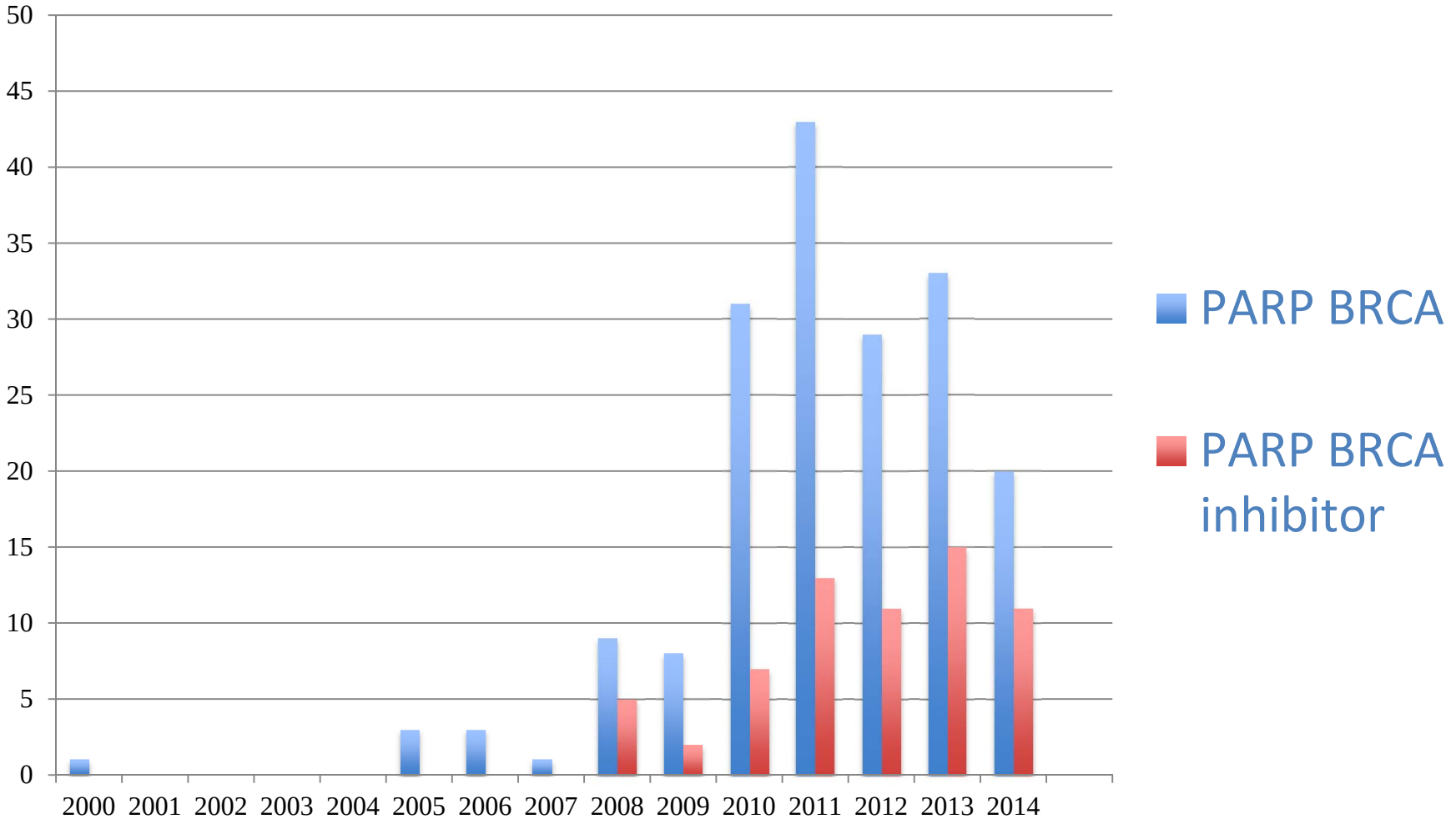
*Not evaluable due to small sample size.

PIK3CAmt in exons 9 and 20, pS6 and PTEN levels by IHC

BOLERO-1/TRIO 019: Study Design

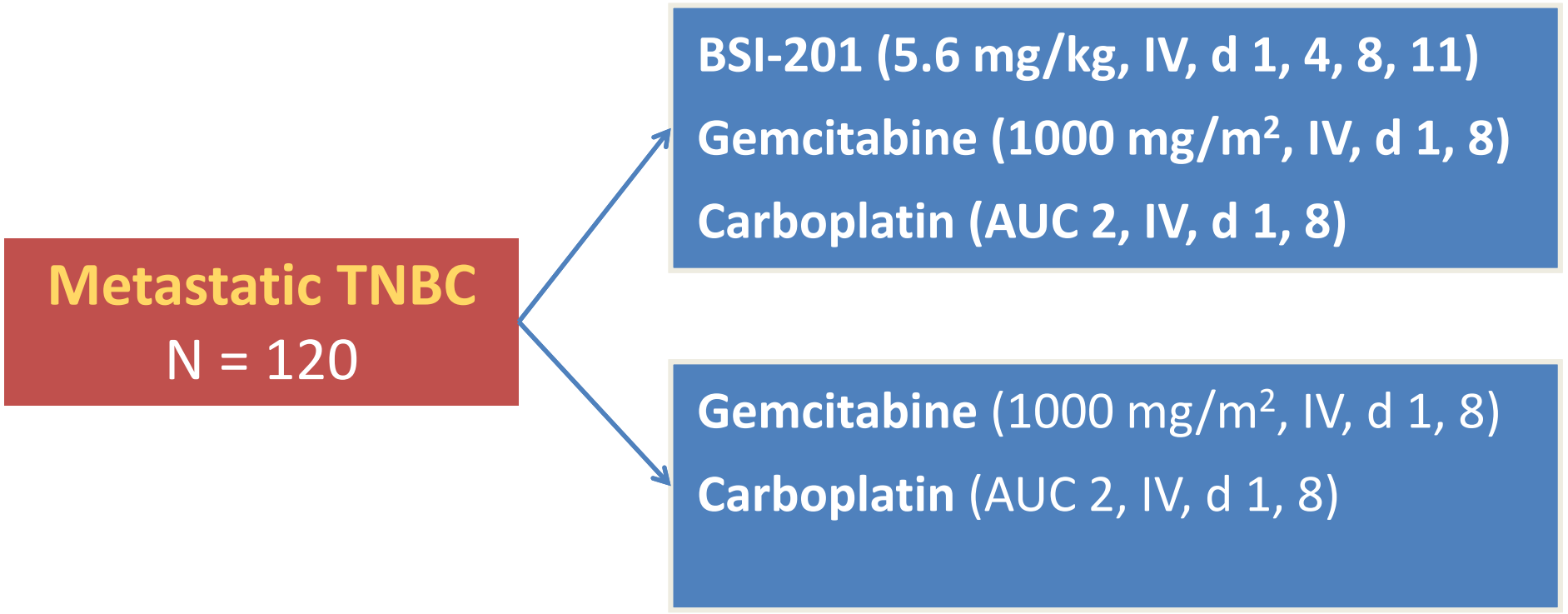


Publications of BRCA and PARP



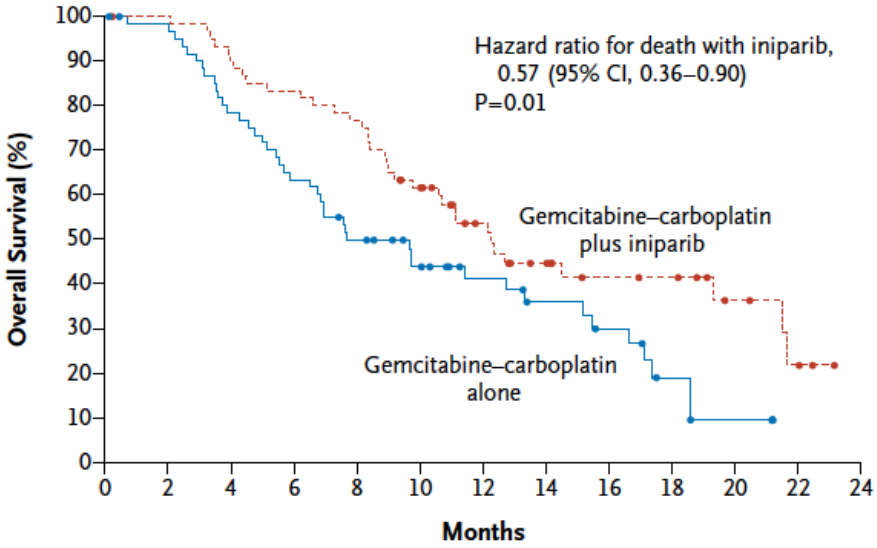
2014.05

BSI 201 Iniparib for HR-/ HER2- subtype (rP2)



* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

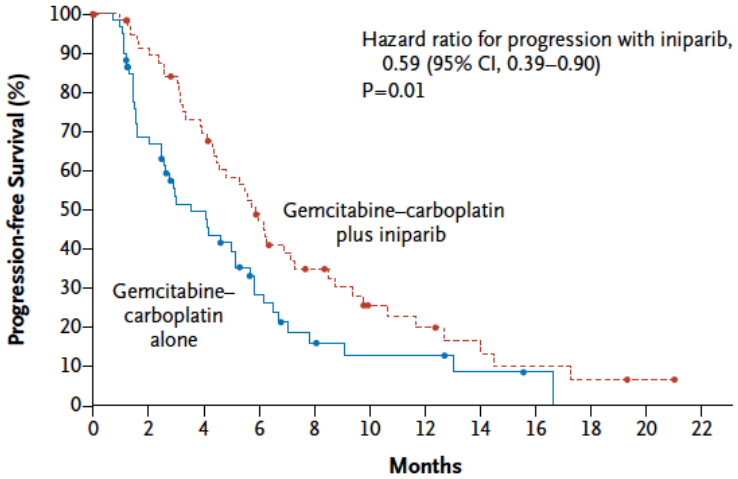
Overall Survival



No. at Risk

Gemcitabine–carboplatin plus iniparib	61	60	54	50	46	35	24	17	12	11	6	3	0
Gemcitabine–carboplatin alone	62	59	47	38	29	22	16	12	9	4	1	0	0

Progression-free Survival



No. at Risk

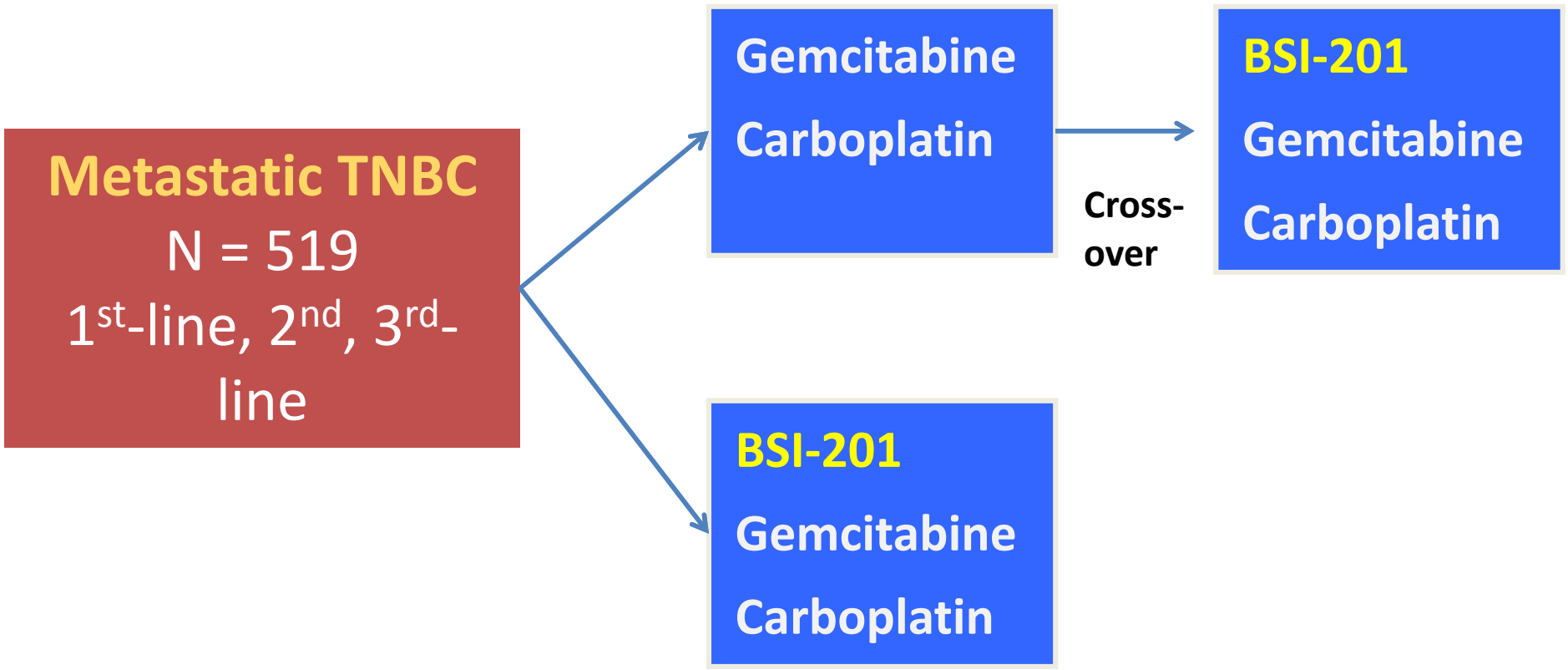
Gemcitabine–carboplatin plus iniparib	61	51	38	25	16	9	7	5	3	2	1	0
Gemcitabine–carboplatin alone	62	38	25	12	6	4	4	2	1	0	0	0

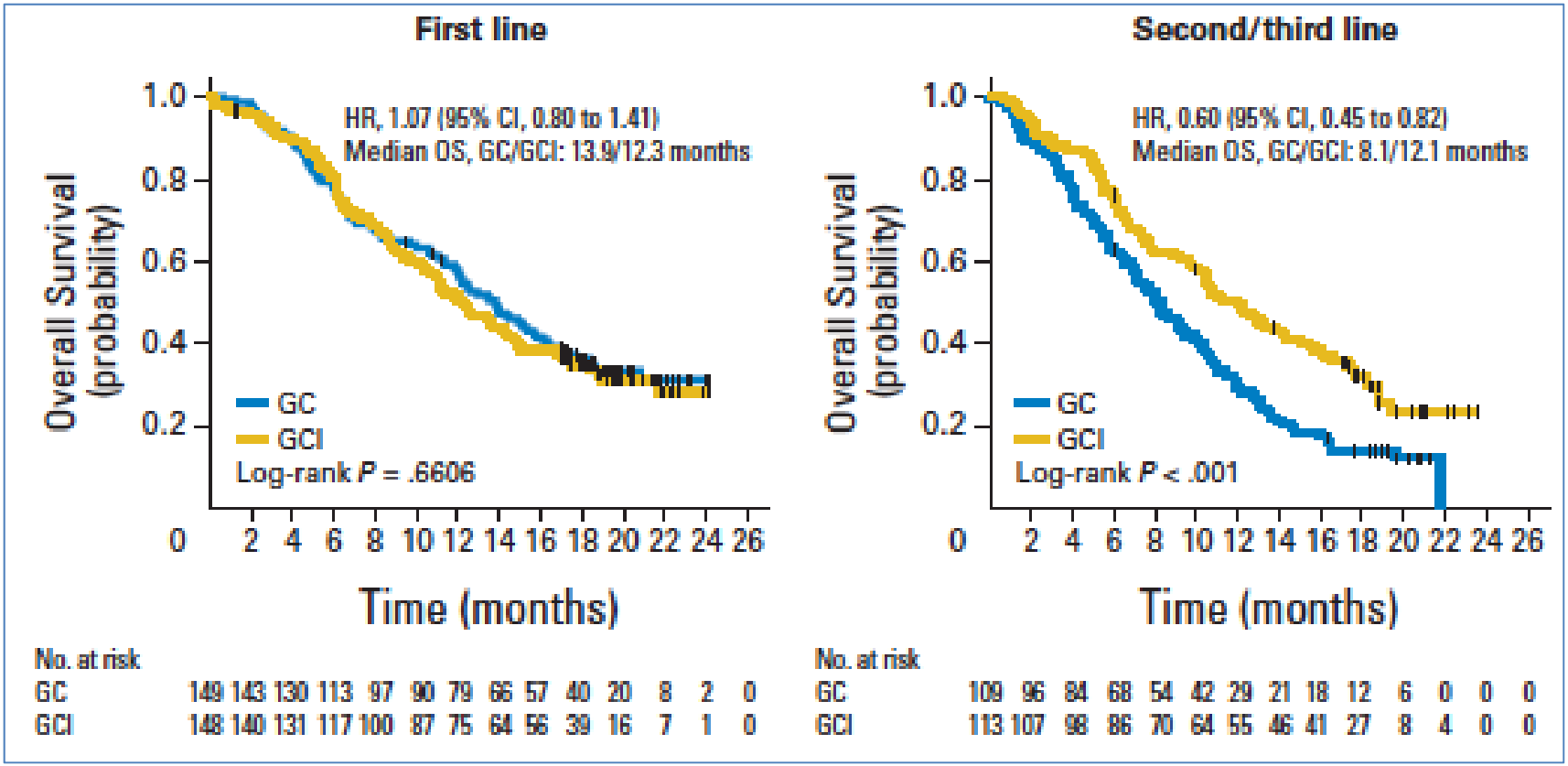
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 20, 2011 VOL. 364 NO. 3

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.

BSI 201 Iniparib for HR-/ HER2- subtype (P3)





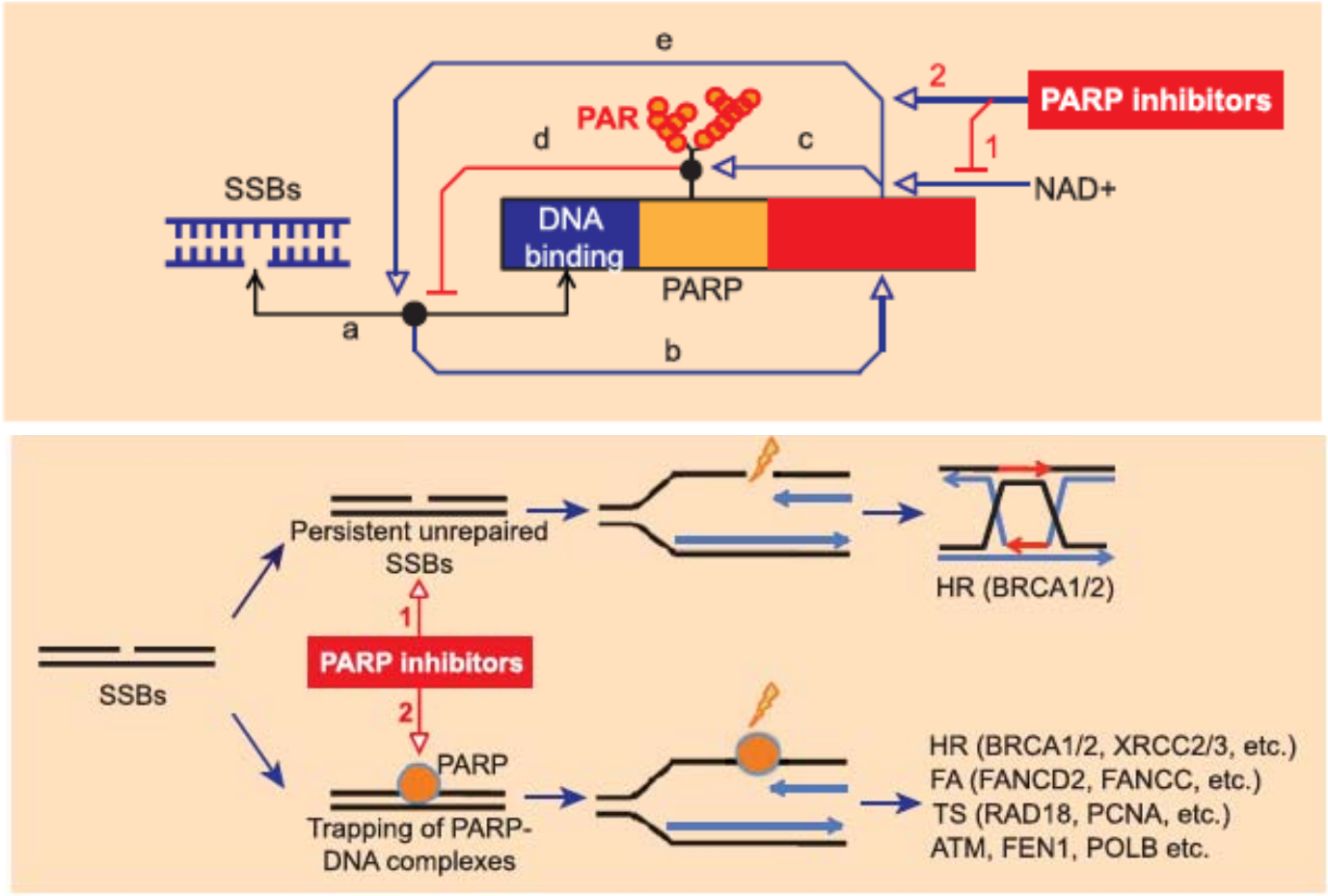
VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, Lee Schwartzberg, Michael A. Danso, Kathy D. Miller, Hope S. Rugo, Marcus Neubauer, Nicholas Robert, Beth Hellerstedt, Mansoor Saleh, Paul Richards, Jennifer M. Specht, Denise A. Yardley, Robert W. Carlson, Richard S. Finn, Eric Charpentier, Ignacio Garcia-Ribas, and Eric P. Winer

PARP inhibitors



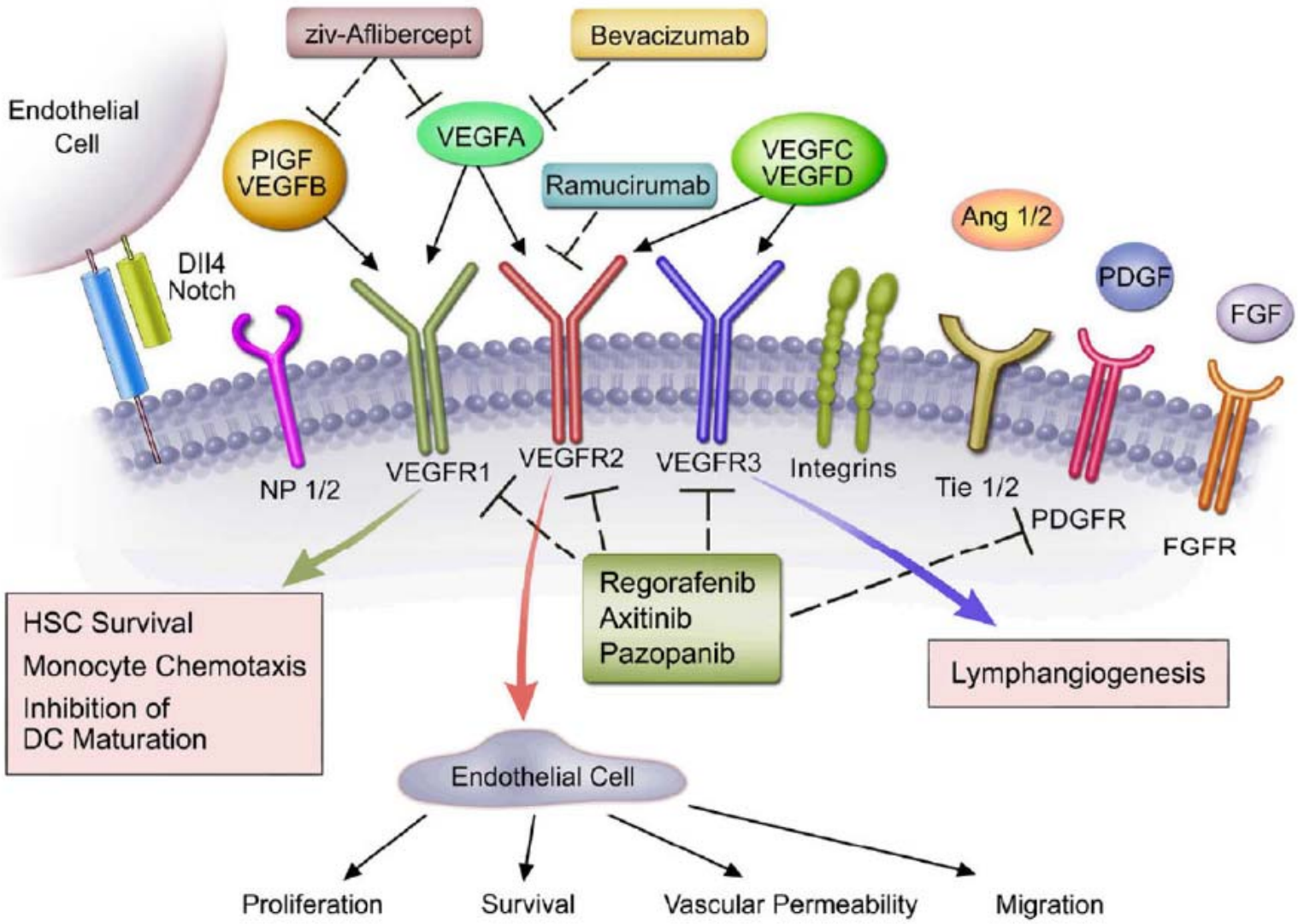
Murai J et al. Cancer Res 2012;72:5588-5599.

Primary breast cancer

BRCA mutation
High risk HER2-

Chemotherapy +

Angiogenesis inhibitors



JM Clarke and HI Hurwitz. Expert Opin Biol Ther. 2013 13(8): 1187–1196.

Review Article

Pharmacology and Pharmacodynamics of Bevacizumab as Monotherapy or in Combination with Cytotoxic Therapy in Preclinical Studies

Hans-Peter Gerber and Napoleone Ferrara

Cancer Res 2005; 65: (3). February 1, 2005

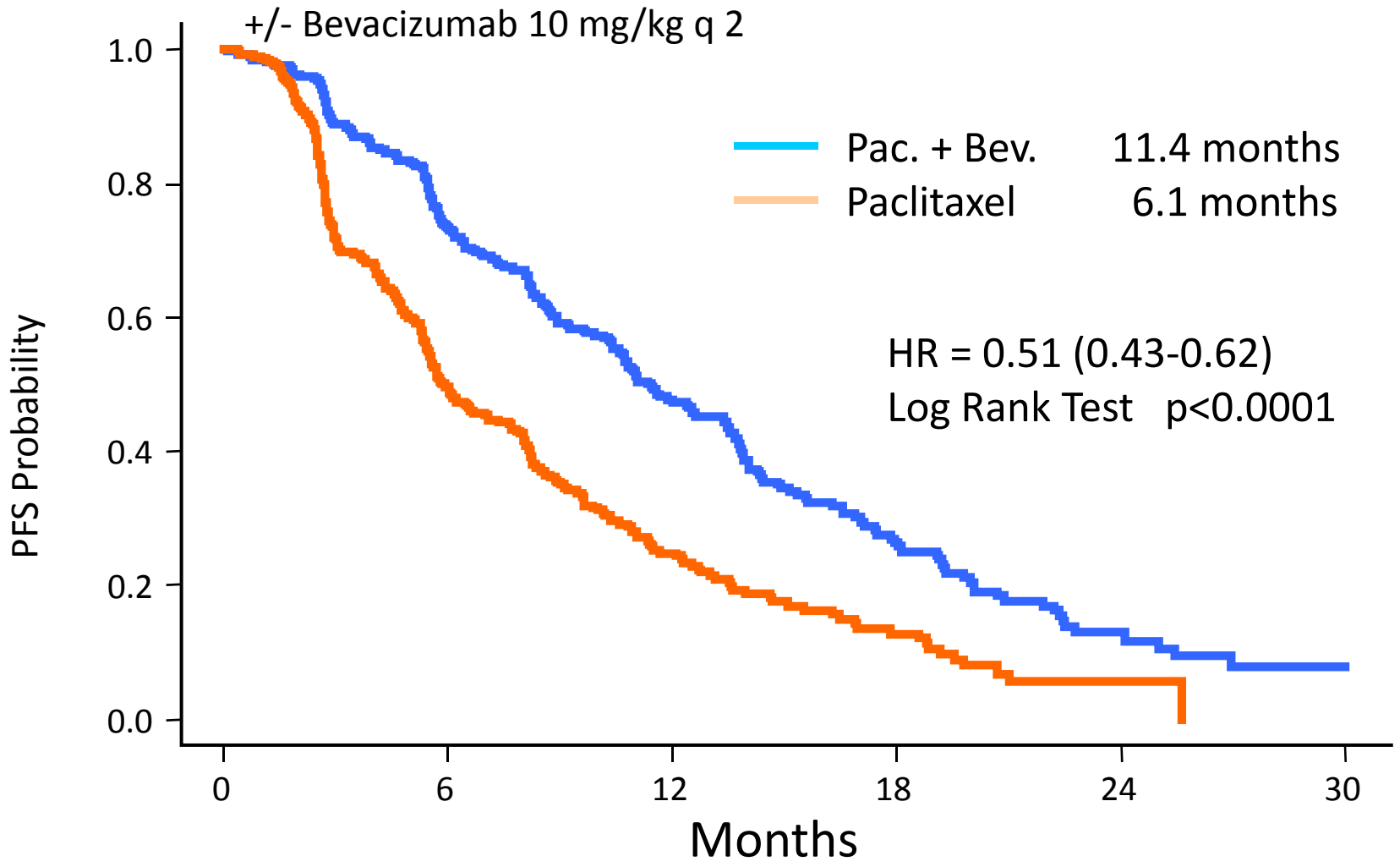
Preclinical studies

- Pharmacologic and Pharmacodynamic Characteristics
- Inhibition of Primary Tumor Growth
- Inhibition of Metastases
- Tumor Growth Inhibition with Combination Therapy
- Combination with Radiotherapy, Chemotherapy, and Other Targeted Agents
- Correlation between Pharmacologic Effects of Tumor Growth Inhibition and Vascular Changes
- Safety Profile of Bevacizumab in Animals

Table 2. Pharmacology of bevacizumab and A4.6.1 examined in various human tumor xenograft models

Tumor type	Cell line (graft location)	Antibody	Dosing regimens	Species	End points	Noteworthy observations
Rhabdomyosarcoma	A673 (s.c.)	A4.6.1	10-100 μg i.p. twice weekly	Mouse/beige nude	Tumor weight, sites, vascularity	96% tumor inhibition; decrease in vessel density (36)
Rhabdomyosarcoma	A673 (s.c.)	A4.6.1	0.05-5 mg/kg i.p. twice weekly	Mouse/beige nude	Tumor area and weight, serum concentration of A4.6.1	Dose-dependent inhibition of tumor growth >80% at >10 μg/mL (76)
Rhabdomyosarcoma	A673 (intradermal)	A4.6.1	10-200 μg i.p. twice weekly	Mouse/beige nude	Tumor growth, vascularization, mitotic index tumor cells	Complete inhibition of tumor growth and neovascularization (77)
Glioblastoma	G55 (s.c.)	A4.6.1	10-100 μg i.p. twice weekly	Mouse/beige nude	Tumor weight, sites, vascular density	80% tumor inhibition; decrease in vessel density (36)
Glioblastoma	G55 (intracranial)	A4.6.1	600 μg i.p. q2d	Rat/athymic nude	Survival, tumor sites, and vascularity	99% increase in survival; decrease in tumor vascularity and growth rates (40)
Glioblastoma	U87 (intracranial, intradermal)	A4.6.1	98.4 μg i.p. q3d	Mouse/SCID	Tumor growth, vascularization, vascular permeability, vessel diameter	Vessel disappearance; reduction in vessel permeability and diameter (64)
Glioblastoma	U87 (s.c.)	A4.6.1	100 μg i.p. q2d, six doses combination and radiation therapy	Mouse/athymic NCr/Sed nu/nu	Tumor growth, vascular density, oxygenation (pO_2), apoptosis of tumor cells, IFP	Decrease in tumor growth and IFP (73% in U87); increase in apoptosis; increase in pO_2 in some tumors (51)
Glioblastoma	U87 (intracerebrally)	A4.6.1	1 mg i.p. q3d, three doses	Rat/athymic nude	MRI: tumor vascular permeability and tumor growth	Inhibition of microvascular permeability and tumor growth (67)
Leiomyosarcoma	SK-LMS-1 (s.c.)	A4.6.1	10-100 μg i.p. twice weekly	Mouse/beige nude xid	Tumor weight, sites, vascular density	70% tumor inhibition; decrease in vessel density (36)
Ovarian carcinoma	SKOV-3 (s.c.)	A4.6.1	100 μg i.p. twice weekly	Mouse/BALB/c nu/nu	Tumor weight and ascites formation in the peritoneal cavity	Inhibition of s.c. tumor growth; complete inhibition of ascites formation (38)
Ovarian carcinoma	SKOV-3 (i.p.)	A4.6.1	1 mg i.p. q3d, five doses	Rat/athymic mice	Microvascular permeability and ascites formation	Reduction in tumor microvascular permeability and ascites production (68)
Ovarian carcinoma	OVCAR3 (i.p.)	A4.6.1	5 mg/kg i.p. twice weekly combination with (paclitaxel)	Mouse/athymic	Tumor burden and ascites formation, tumor cell apoptosis	Significant reduction in tumor burden in the combination treatment (83.3%). Complete absence of ascites fluid in the combined or A4.6.1 only group (58)
Prostate carcinoma	DU145 (intradermal)	A4.6.1	100 μg i.p. twice weekly	Mouse/beige nude xid	Tumor growth and vascularization	Complete inhibition of tumor growth and neovascularization (78)
Prostate carcinoma	DU145 (s.c.)	A4.6.1	10 + 100 μg i.p. twice weekly	Mouse/CB-17 SCID/SCID	Primary tumor growth and lung metastases	Suppression of primary tumor growth (82%) and lung metastases (37)
Prostate carcinoma	CWR22R (s.c.)	Bevacizumab	5 mg/kg i.p. twice weekly combination with chemotherapy (paclitaxel)	Mouse/athymic nude BALB/c	Tumor growth and microvessel density	Inhibition of established tumor growth by 85% ($P < 0.01$). Combination treatment resulted in greater inhibition of tumor growth than either agent alone (57)
Colon adenocarcinoma	LS174T (intracranial, intradermal)	A4.6.1	98.4 μg i.p. q3d	Mouse/SCID	Tumor growth, vascularization, vascular permeability, and vessel diameter	Vessel appearance; reduction in vessel permeability and diameter (64)
Colon adenocarcinoma	HM7 LS LiM6 splenic portal injections	A4.6.1	10-200 μg i.p. twice weekly	Mouse/athymic	Tumor growth and liver metastases	90% Reduction in tumor size of primary tumor; reduction in liver metastases (43)
Colon adenocarcinoma	LS174T (s.c.)	A4.6.1	100 μg i.p. q2d, six doses combination with radiation therapy	Mouse/athymic NCr/Sed nu/nu	Tumor growth, vascular density, oxygenation (pO_2), apoptosis of tumor cells, IFP	>70% decrease in tumor growth and IFP increase in tumor cell apoptosis; increase in pO_2 in some tumors (51)
Wilms' tumor	SK-NEP-1 (intrarenal)	A4.6.1	100 μg i.p. twice weekly	Mouse/nude	Tumor weight and lung metastases	Significant >95% reduction in tumor weight and >40% in lung metastases (44)
Wilms' tumor	SK-NEP-1 (intrarenal)	A4.6.1	100 μg i.p. twice weekly	Mouse NCr athymic	Tumor weight and growth and vascular architecture	Significant repression of tumor growth (79)
Wilms' tumor	SK-NEP-1 (intrarenal)	A4.6.1	100 μg i.p. twice weekly, 10 doses combination with chemotherapy (topotecan)	Mouse/athymic	Tumor vasculature, endothelial cell apoptosis, and tumor weight	Significant reduction in tumor growth, vascularity, and lung metastases. Increased endothelial cell apoptosis (55)
Hepatoblastoma	HuH-6 (intrarenal)	A4.6.1	100 μg i.p. twice weekly	Mouse/NCr athymic	Tumor growth and vascularity	Significant inhibition of tumor growth ($P < 0.0003$) decreased vascularity and dilated vessels (80)
Neuroblastoma	NGP-GFP (intrarenal)	A4.6.1	100 μg i.p. twice weekly	Mouse/NCr athymic	Tumor weight and growth and vascular architecture	Neuroblastoma less effectively suppressed than Wilms' tumors. Novel vascular structures induced by anti-VEGF in neuroblastoma (79)
Neuroblastoma	NGP-GFP (intrarenal)	A4.6.1	100 μg i.p. twice weekly combination with chemotherapy (topotecan)	Mouse/NCr athymic	Tumor weights and vascularity	Tumor weights significantly reduced in topotecan and combination treatment ($P < 0.0007$) (81)
Breast carcinoma	MDA-MB-435 (s.c.)	A4.6.1	30 mg/kg i.p. q3d, three doses	Rat/nude	Vascular permeability and tumor growth	58% Reductions in tumor growth; reduction in microvascular permeability (82)
Breast carcinoma	MDA-MB-435 (s.c.)	A4.6.1	Bolus 30 mg/kg i.v., one dose	Rat/athymic	24-hour tumor fractional blood volume permeability surface area product	No significant change in vascularity 24 hours after treatment, but significant suppression of vascular permeability (65)
Breast carcinoma	MCF-7, ZR-75, SK-BR-3 (intradermal)	A4.6.1	200 μg i.p. q3d combination with chemotherapy (doxorubicin)	Mouse nu/nu	Vascularization and tumor growth	Tumor growth and inhibition of angiogenesis (54)
Breast carcinoma	MCF-7 (s.c.)	Bevacizumab	0.25 mg/kg i.p. days 7 + 10 combination with chemotherapy (docetaxel) and 2-methoxyestradiol	Mouse/nude		
Melanoma	P-MEL (intracranial, intradermal)	A4.6.1	98.4 μg i.p. q3d	Mouse/SCID		
Pancreatic cancer	AsPC-1, HPAF-2 (s.c.)	A4.6.1	100 μg i.p. twice weekly combination with matrix metalloproteinase inhibitor (BB-94)	Mouse/nude mice		
Pancreatic cancer	PANC-1 (s.c.)	A4.6.1	300 μg i.p. every 3 days	Immunodeficient mice		

E2100 PFS: 1st-line Metastatic Breast Cancer with Bevacizumab Added to Paclitaxel



Miller K, NEJM 2007

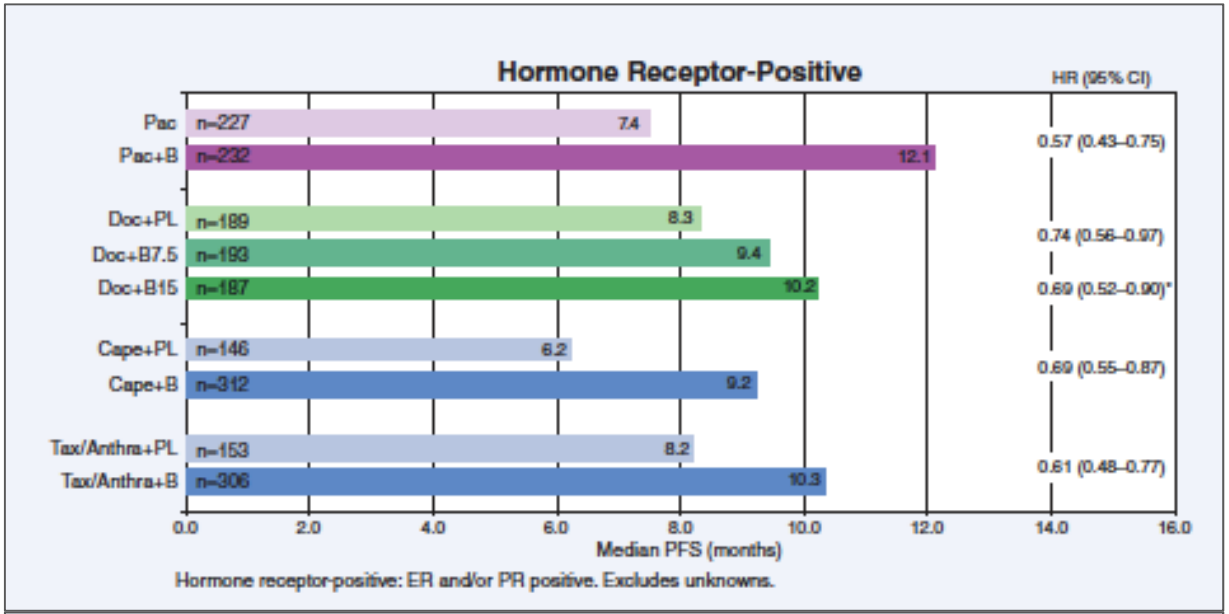
No difference was seen on OS.

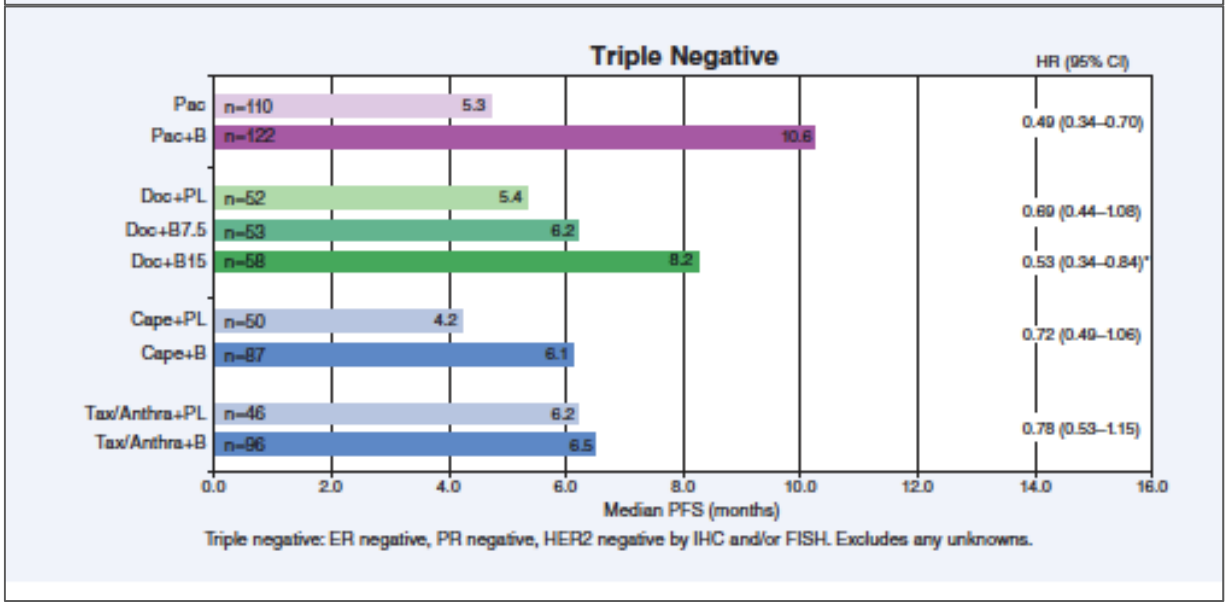
Bevacitumab + chemotherapy
1st line therapy for metastatic/advanced breast cancer
Phase III

Trial	E2100[1] (n=722)	AVADO[2] (n=736)	RIBBON-1[3] +Cape (n=615)	RIBBON-1[3]+A/T (n=622)
Placebo controlled	No	Yes	Yes	Yes
Chemo	weekly Paclitaxel	Docetaxel	Capecitabine	Anthra or Taxane
BV dosage	10mg/kg q2w	7.5 or 15mg/kg q3w	15mg/kg q3w	15mg/kg q3w
Endpoint	PFS	PFS	PFS	PFS
IRF	Retrospective	Yes	Yes	Yes

[1] Miller K et al. N Engl J Med. 2007; 357: 2666-76.
[2] Miles D et al. ASCO2008 abstr#1011.
[3] N. J. Robert et al. ASCO2009 abstr#1005.

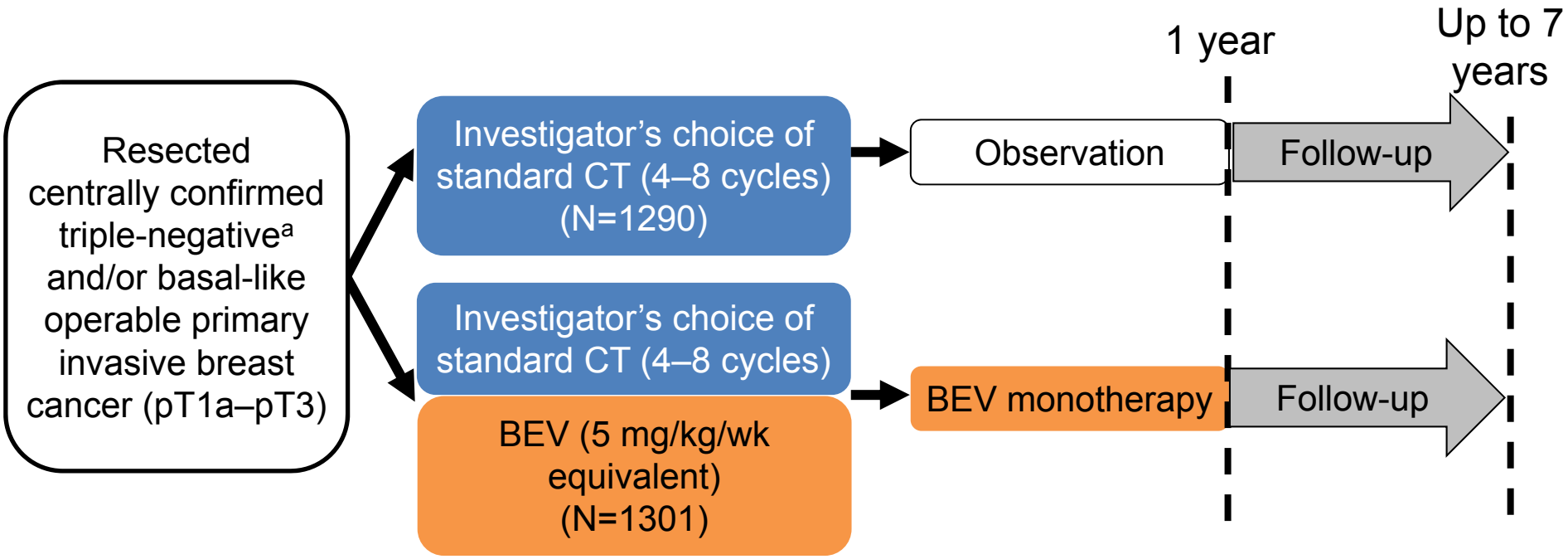
Subgroup: Bevacizumab + chemotherapy





O'Shaughnessy J et al. SABCS 2009 #207

BEATRICE: ER-/ HER2- subtype PBC



Stratification factors:

- Axillary nodal status
- Selected adjuvant CT
- Hormone receptor status
- Surgery

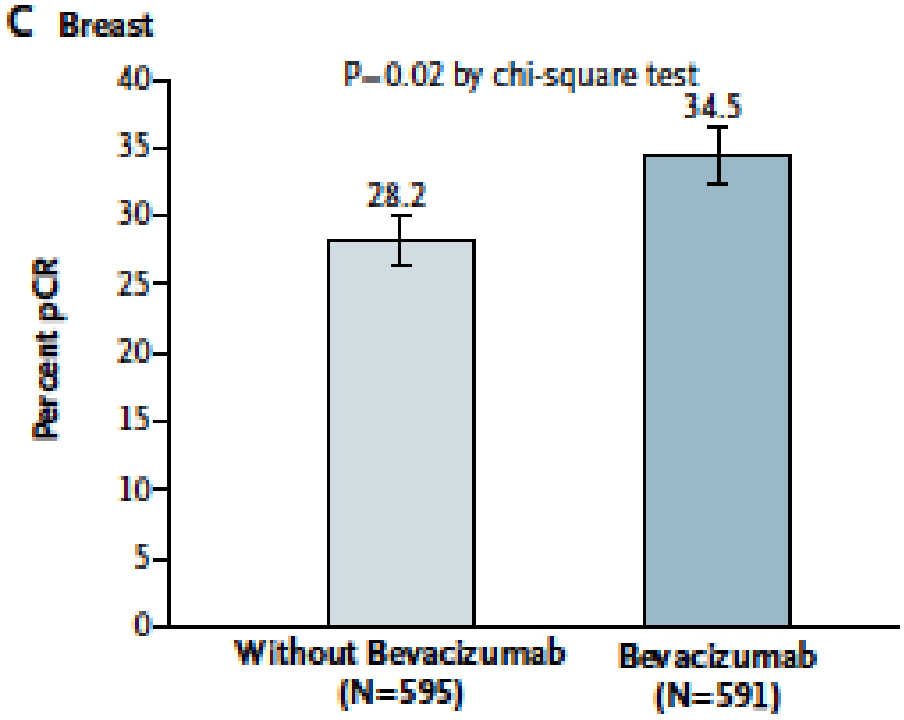
CT options:

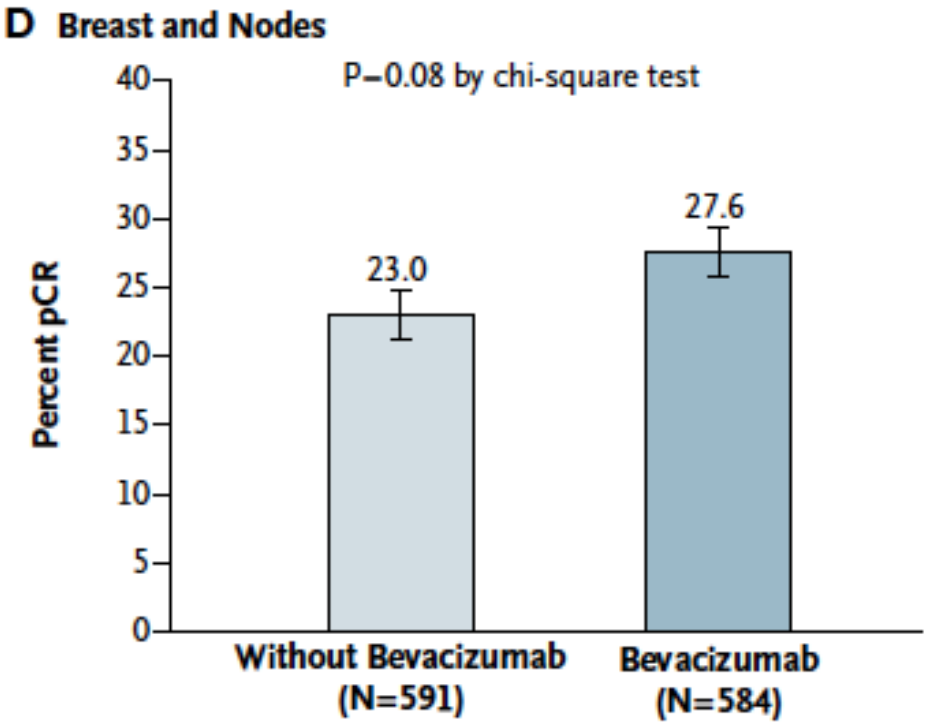
- Taxane based (≥4 cycles)
- Anthracycline based (≥4 cycles)
- Anthracycline + taxane (3–4 cycles each)

Cameron D, et al. Lancet Oncol 2013;14:933–42.

Preoperative NSABP B40

1206 pts, HER2 (-)
A-T 8 cycles +/- BEV



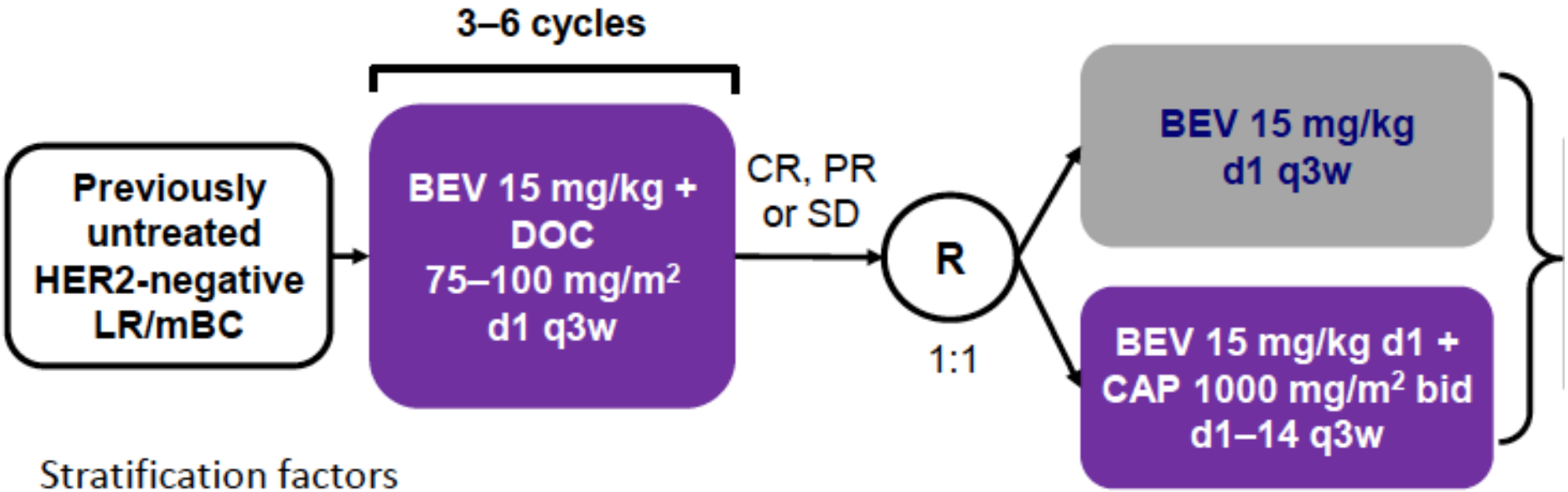


High-grade and N0 tended to be associated

Bear HD et al. NEJM 2012

BEV vs BEV+CAPE (IMELDA)

Metastatic BC: 284 pts, HER2-



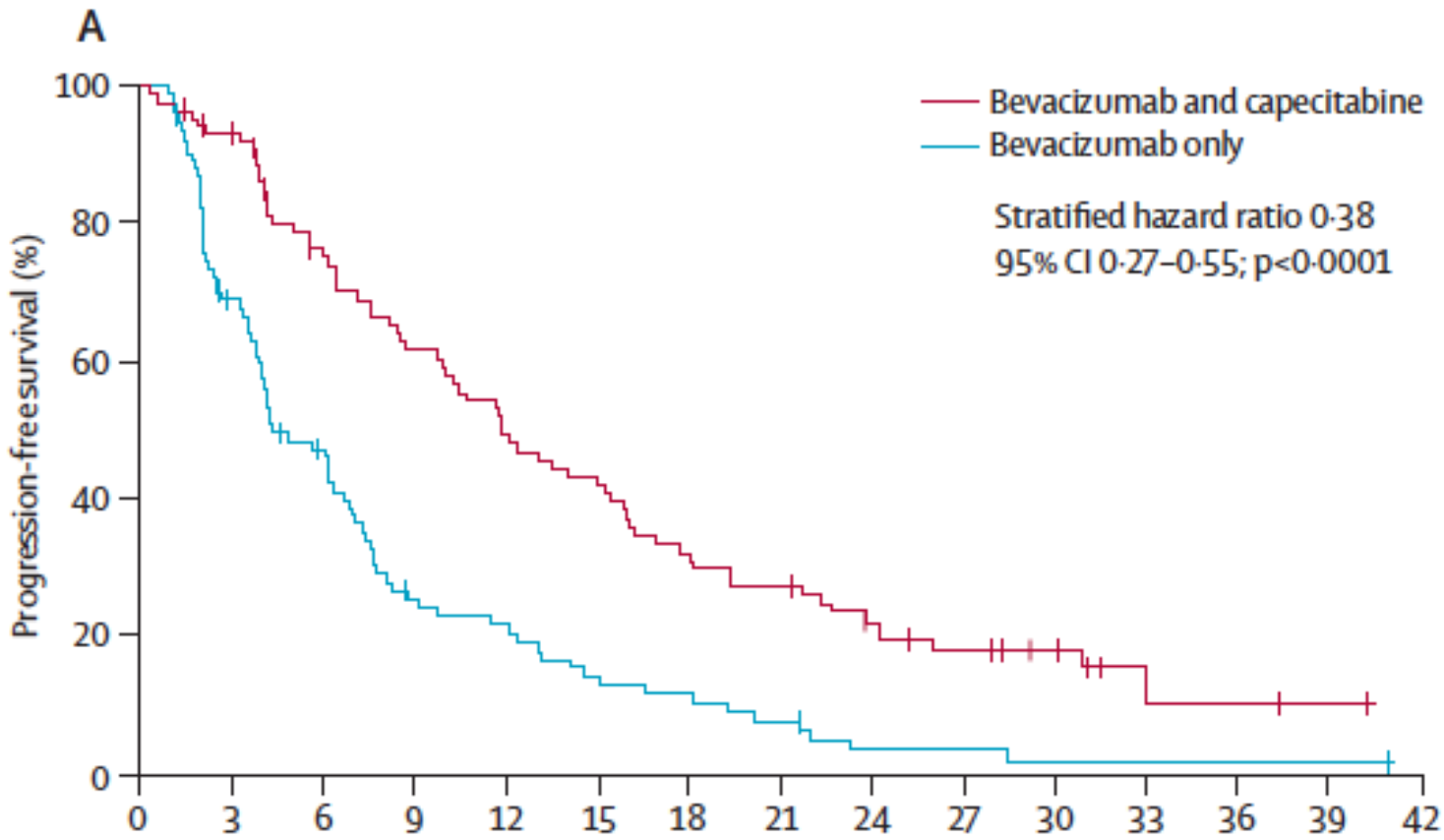
Stratification factors

- ER status (positive vs negative)
- Visceral metastasis (present vs absent)
- Stable disease/response/non-measurable disease
- LDH concentration (≤1.5 vs >1.5 × ULN)

Joseph Gligorov et al. Lancet Oncol 2014; 15: 1351–60

BEV vs BEV+CAPE (IMELDA)

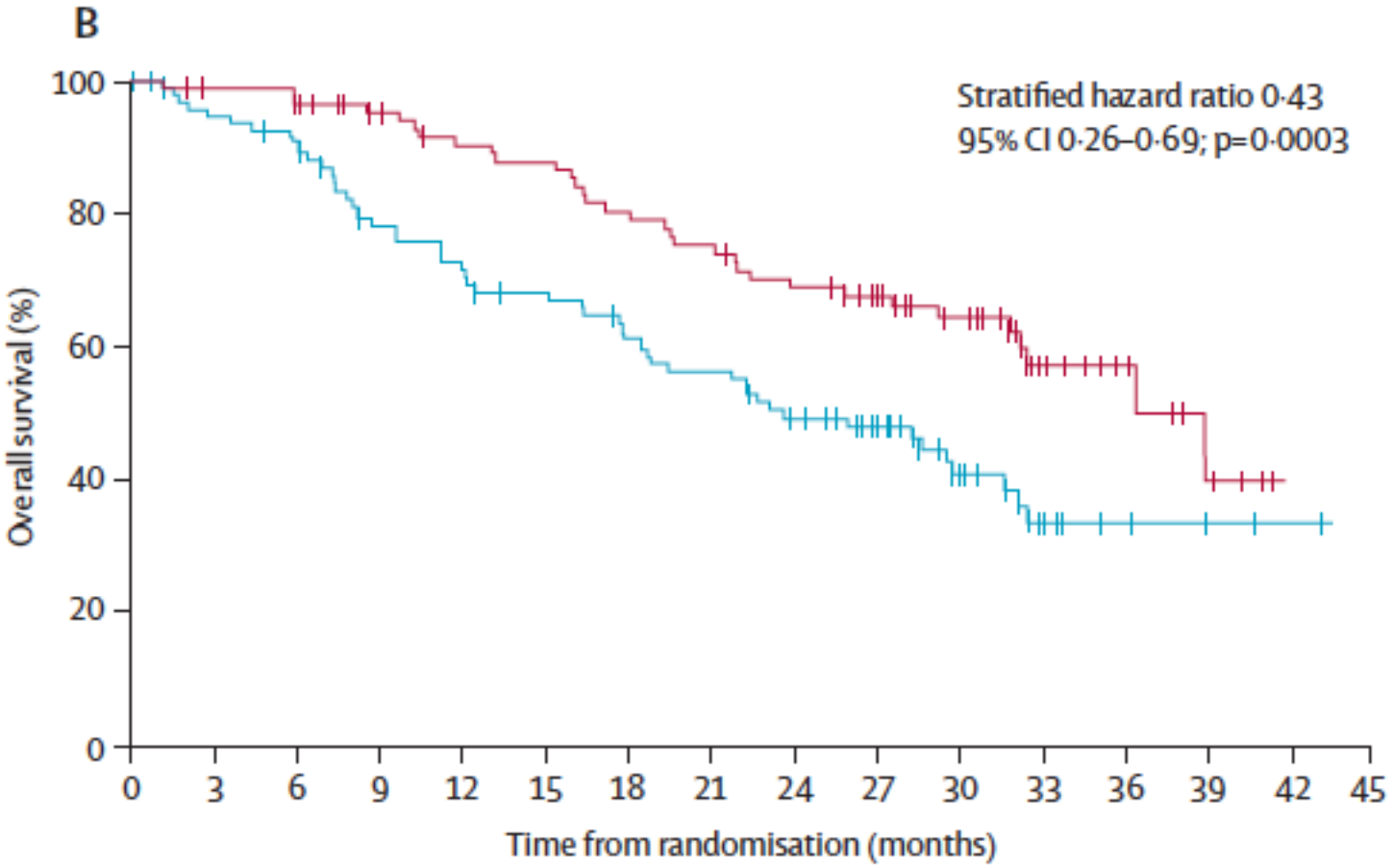
PFS: 284 pts, HER2-



Joseph Gligorov et al. Lancet Oncol 2014; 15: 1351–60

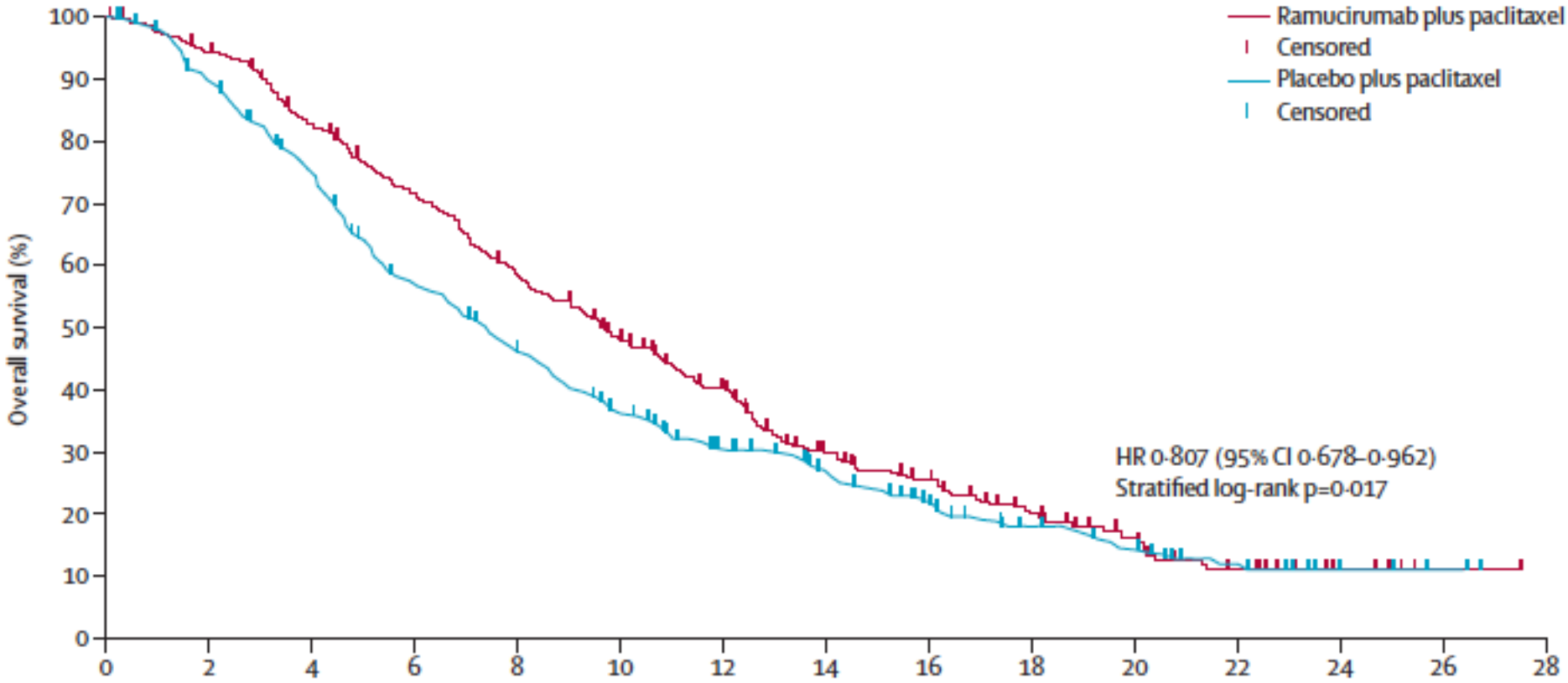
BEV vs BEV+CAPE (IMELDA)

OS: 284 pts, HER2-



Joseph Gligorov et al. Lancet Oncol 2014; 15: 1351–60

OS impact of Anti-VEGFR2 in GC



Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

*Hansjochen Wilke, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka, Naotoshi Sugimoto, Oleg Lipatov, Tae-You Kim, David Cunningham, Philippe Rougier, Yoshito Komatsu, Jaffer Ajani, Michael Emig, Roberto Carlesi, David Ferry†, Kumari Chandrawansa, Jonathan D Schwartz, Atsushi Ohtsu, for the RAINBOW Study Group**

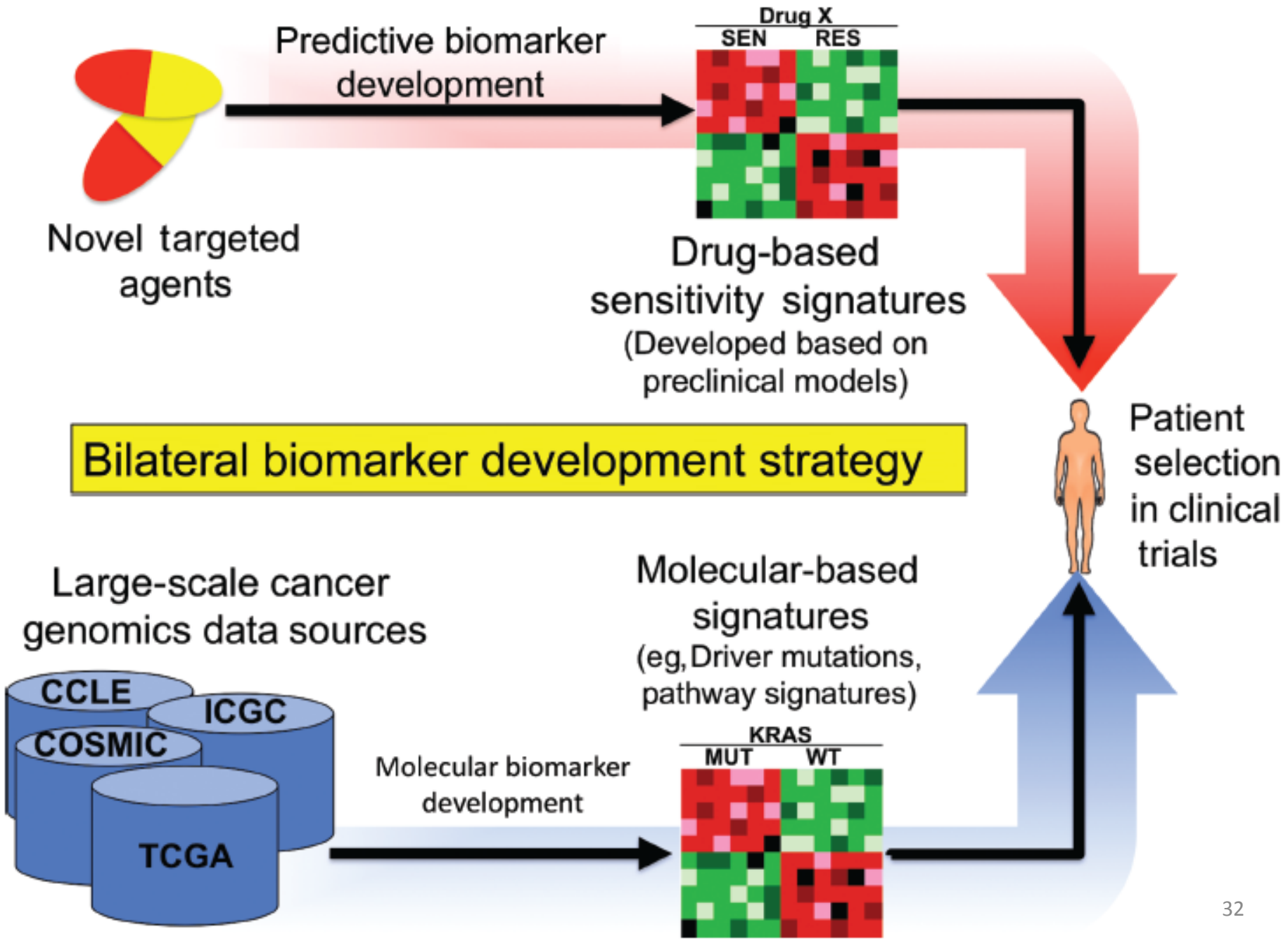
Lancet Oncol 2014; 15: 1224–35
Published Online
September 18, 2014

Summary

Background VEGFR-2 has a role in gastric cancer pathogenesis and progression. We assessed whether ramucirumab, a monoclonal antibody VEGFR-2 antagonist, in combination with paclitaxel would increase overall survival in patients previously treated for advanced gastric cancer compared with placebo plus paclitaxel.

Clinical studies

- Subtype-specific
- Combination with other drugs
- Combination: Concurrent/ Sequential
- Metastatic disease: PFS/ OS
- Primary disease: Preoperative/ Postoperative Adjuvant
- PGX markers
- Pathological markers/ Biomarkers
- Molecular signatures..
- QOL
- COST



Christopher H et al JNCI 2013 105:1441-56

Perspectives

- Subtype-specific/ **Genome-based**
- Combination with other drugs
- Combination: Concurrent/ Sequential
- Metastatic disease: PFS/ **OS**
- **Evolution/ Heterogeneity (Intra-tumor/ Inter-tumor)**
- Primary disease: Preoperative/ Postoperative Adjuvant
- **Clonal Selection by treatment**
- PGX markers
- **Response-guided/ Imaging**
- Pathological markers/ Biomarkers
- Molecular signatures..
- QOL
- COST