

Incontro del GIC
Neoplasie della Mammella

LE TERAPIE ANTIANGIOGENICHE

P Pronzato

Torino, 23.11.2011



(Anti-) Angiogenesis

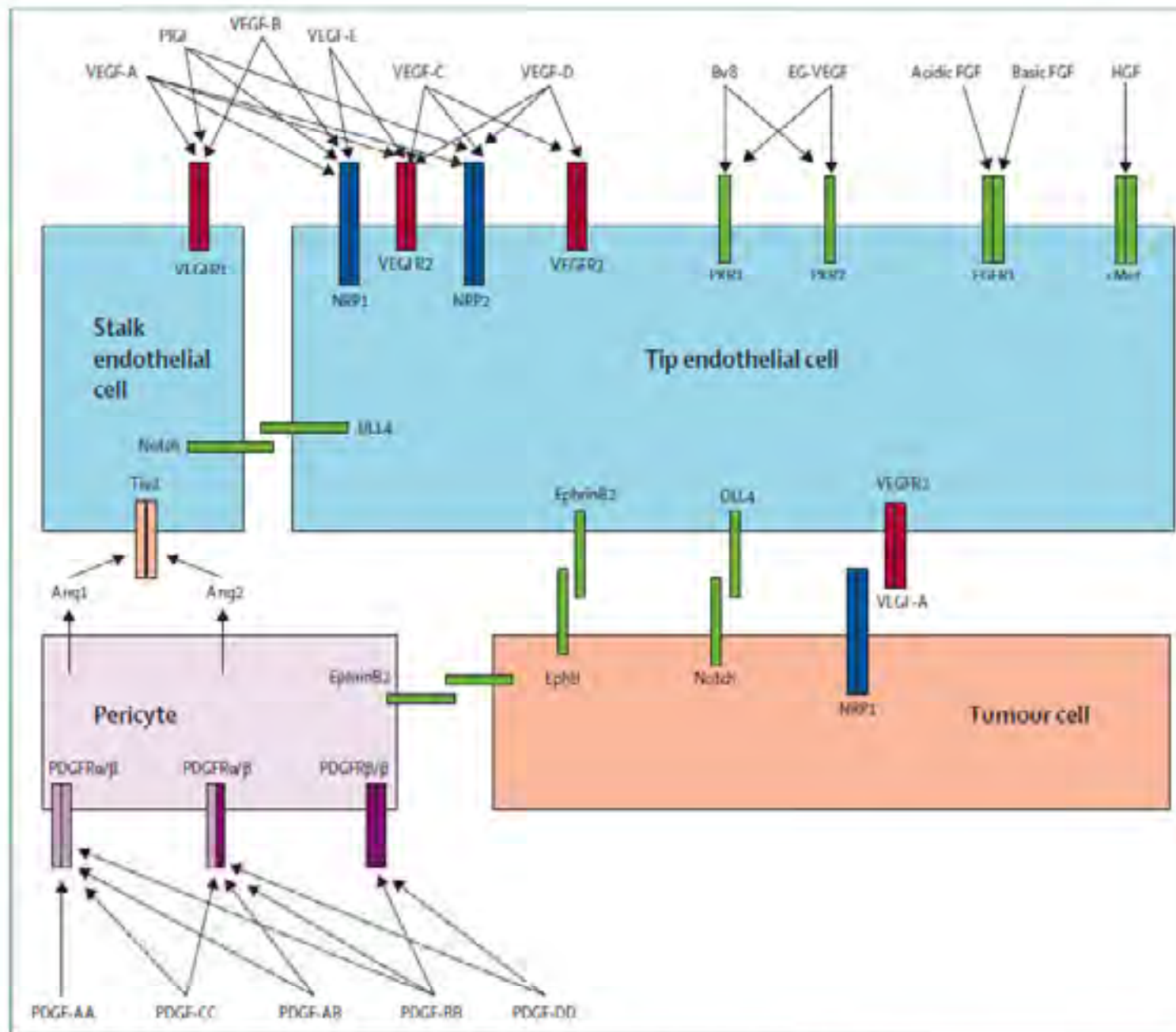
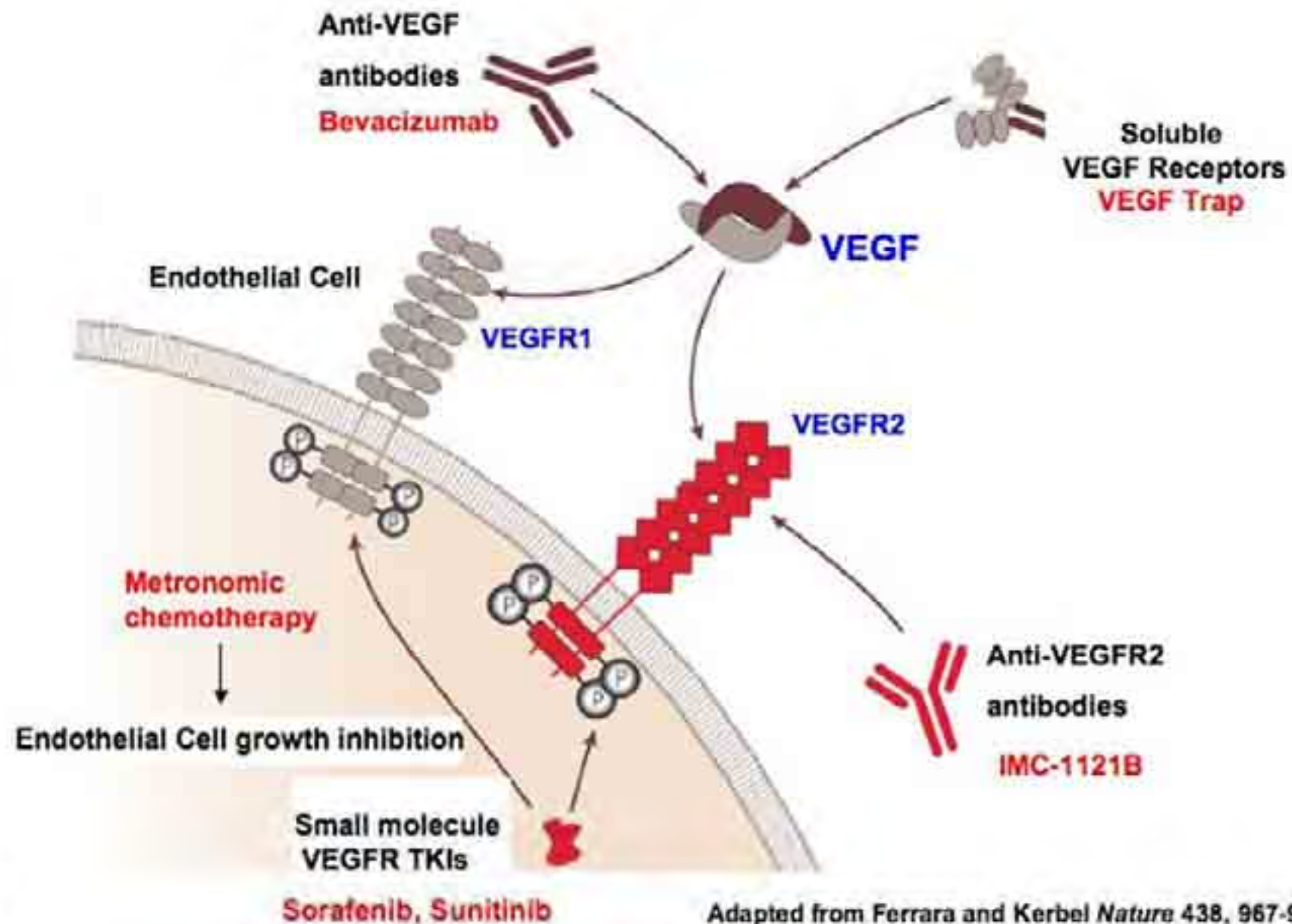


Figure 1: Schematic of proangiogenic ligands and receptors to illustrate complexity and redundancy in angiogenesis

VEGF Signal Inhibition Strategies



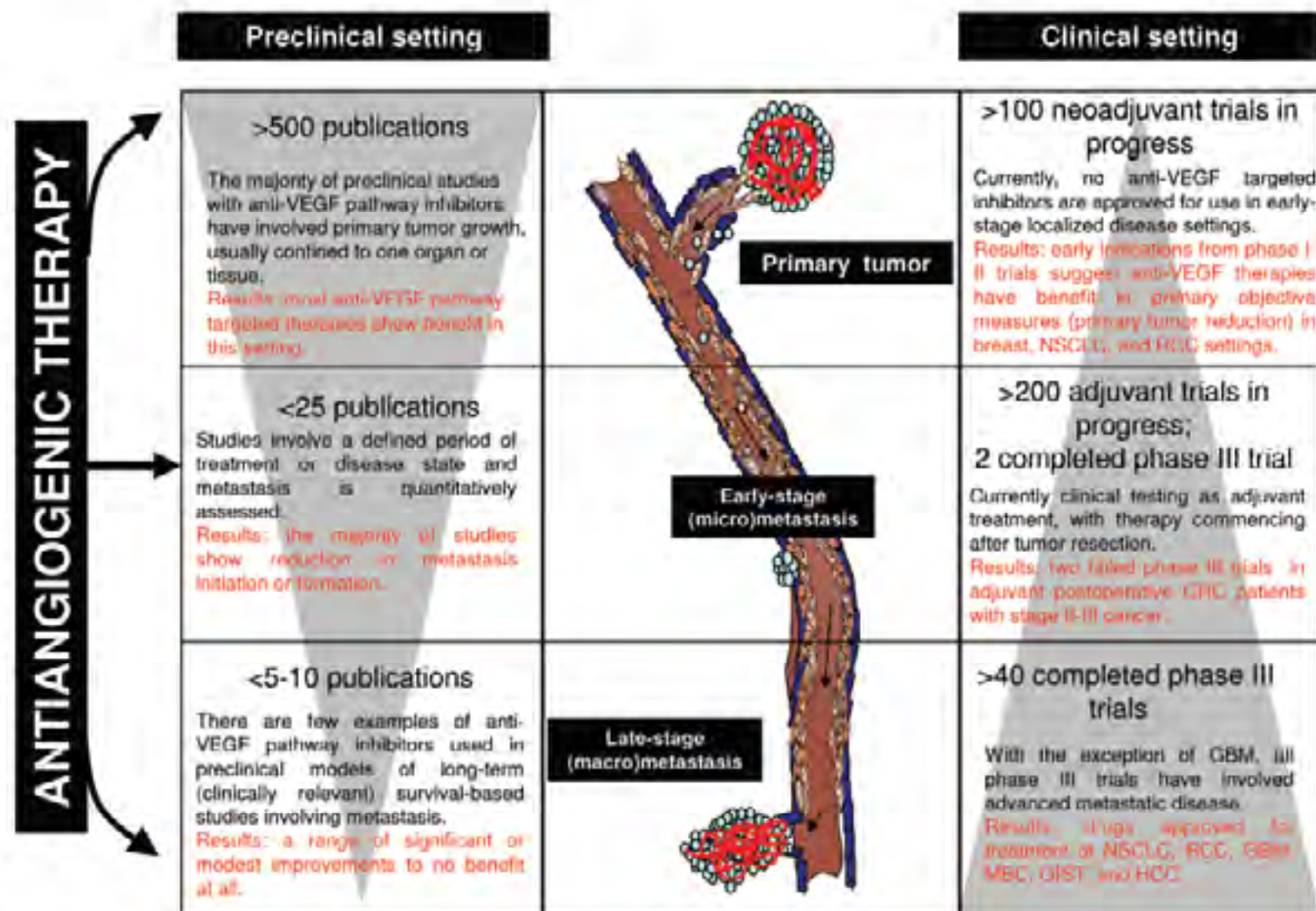


Fig. 1. Variable efficacy of VEGF pathway-targeted therapies: Exposing the gap between preclinical and clinical testing. The number of studies that have been completed in the clinic in each setting are inversely correlated with the number of preclinical publications that model each setting.¹³

Abbreviations: VEGF, vascular endothelial growth factor; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CRC, colorectal cancer; GBM, glioblastoma multiforme; MBC, metastatic breast cancer; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma.

RCTs of ChemoRx +/- VEGFR TKI

Trial	Line of Rx	Regimen	N	RR %	PFS mo.
SUN 1064 Bergh, 2010	1 st	Docetaxel +/- Sunitinib	593	+	-
SUN 1099 Crown, 2010	2 nd	Cape +/- Sunitinib	442	-	-
Gradishar, 2009	1 st	Paclitaxel + Sorafenib/Placebo	237	+	-
SOLTI-0701 Baselga, 2009	1 st - 2 nd	Cape + Sorafenib/Placebo	229	-	+
Hudis, ASCO Ab 1009; 2011	After Bev	Gem or Cape + Sorafenib/Placebo	160	-	+
Rugo, 2011	1 st	Docetaxel +/- Axitinib	56 112	+	-
Boer, SABCS 2007	2 nd	Docetaxel +/- Vandetinib	64	-	-

HER2- Metastatic Breast Cancer

(CT Needed)

DecisionMakingProblems

The Challenges of Metastatic Breast Cancer

- Metastatic breast cancer is still virtually incurable (with few exceptions) and remains an important medical problem
- Treatment is mainly palliative and should always balance the benefits of treatment and the quality of life of patients
- There are currently no international consensus guidelines for the treatment of heavily pretreated patients with metastatic disease

Chemotherapy for Recurrent or Metastatic Breast Cancer

Single Agents

- Anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin)
- Antimetabolites (capecitabine, gemcitabine)
- Antitubulins
 - *Vinca alkaloids* (vinorelbine, vinflunine)
 - *Taxanes* (docetaxel, paclitaxel, albumin-bound paclitaxel)
 - *Epothilones* (ixabepilone) (not available in EU)
 - *Halichondrins* (eribulin)
- Other single agents (cyclophosphamide, mitoxantrone, cisplatin, etoposide, vinblastine, fluorouracil)

Combinations

- Cyclophosphamide/doxorubicin/fluorouracil (FAC)
- Fluorouracil/epirubicin/cyclophosphamide (FEC)
- Doxorubicin/cyclophosphamide (AC)
- Epirubicin/cyclophosphamide (EC)
- Doxorubicin/paclitaxel
- Cyclophosphamide/methotrexate/fluorouracil (CMF)
- Docetaxel/capecitabine
- Gemcitabine/paclitaxel
- Paclitaxel/bevacizumab
- Cisplatin + 5-FU
- Metronomic CT??

Systemic Approach for HER2-Negative, Metastatic Breast Cancer (cont)

- Variety of options: no guidelines or single “gold standard”
- Sequential single agents?
 - Preferred for most patients
 - Supported by clinical trial data
 - Limits toxicity
- Combination therapy?
 - May be preferable for rapidly progressive symptomatic disease
 - Reduction in symptoms outweighs potential toxicity
 - May not be candidate for subsequent therapy if continued progression

Tailoring Therapy in Metastatic Breast Cancer: Factors to Consider

Patient Factors

- ✓ Biological age
- ✓ Comorbidities
- ✓ Performance status
- ✓ Menopausal status
- ✓ Socioeconomic and psychological factors (eg, distance between home and hospital, costs)
- ✓ Patient's preferences
- ✓ Pharmacogenetics

Disease Factors

Clinical

- ✓ Disease-free interval

✓ Previous therapies and response

- ✓ Tumor burden
- ✓ Need for rapid disease/symptom control

Biological

- ✓ ER status
- ✓ PgR status

✓ HER-2 status

- ✓ Proliferation
- ✓ Novel biomarkers

MBC: maindrivers in 2010s

- **Clinico
PathologicalFactors**
 - HER2 /HR
 - Previous Treatment
 - BurdenofDisease

MBC: main drivers in 2010s

- **Goals**

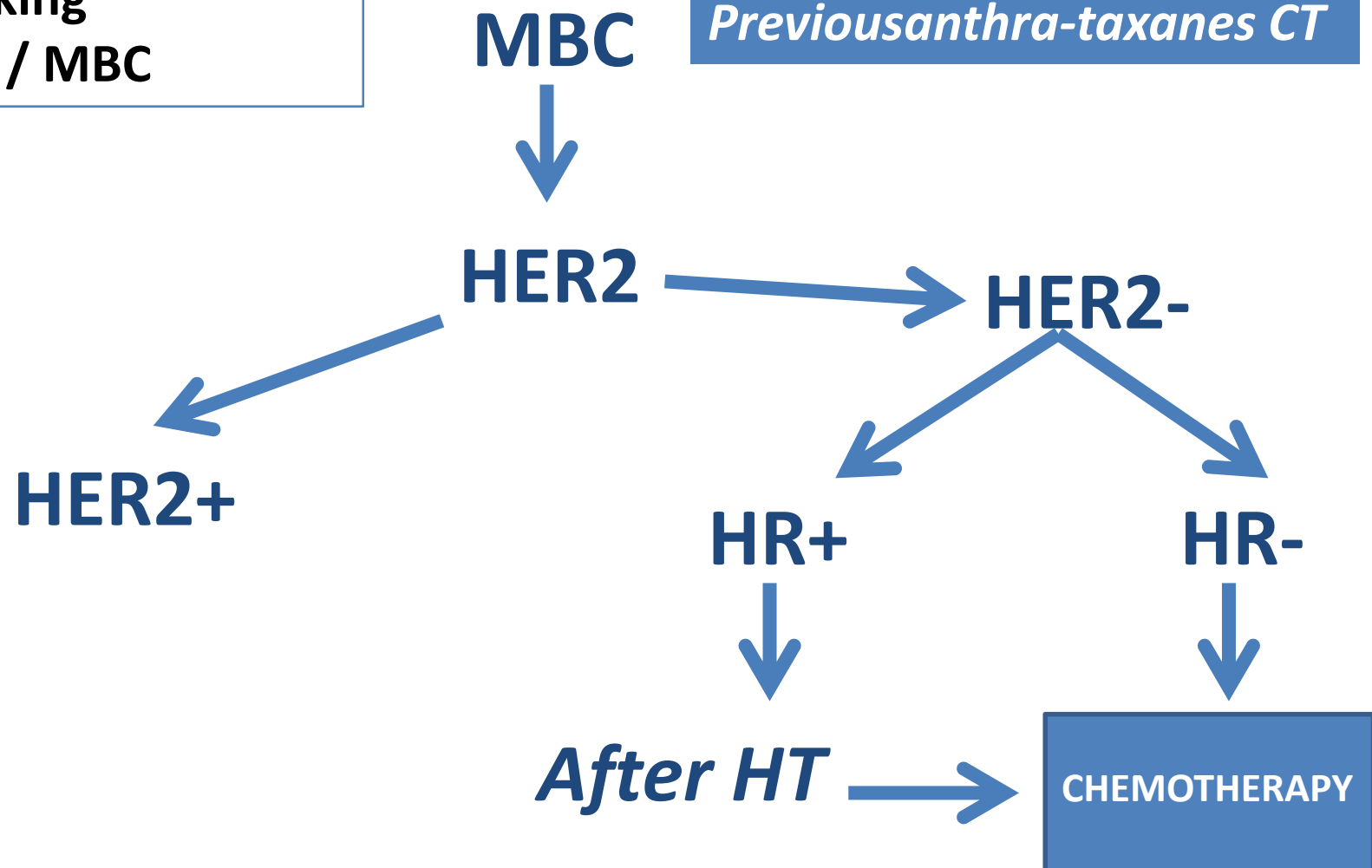
- Prolongation of Survival
- Quality of Life
- Symptom Relief
- Response
- Delay of Progression

- **Clinico**

Pathological Factors

- HER2 /HR
- Previous Treatment
- Burden of Disease

EvidenceBasedDecisi
onMaking
HER2- / MBC



EvidenceBasedDecisi
onMaking
HER2- / MBC

MBC

Previous anthra-taxanes CT

HER2

HER2-

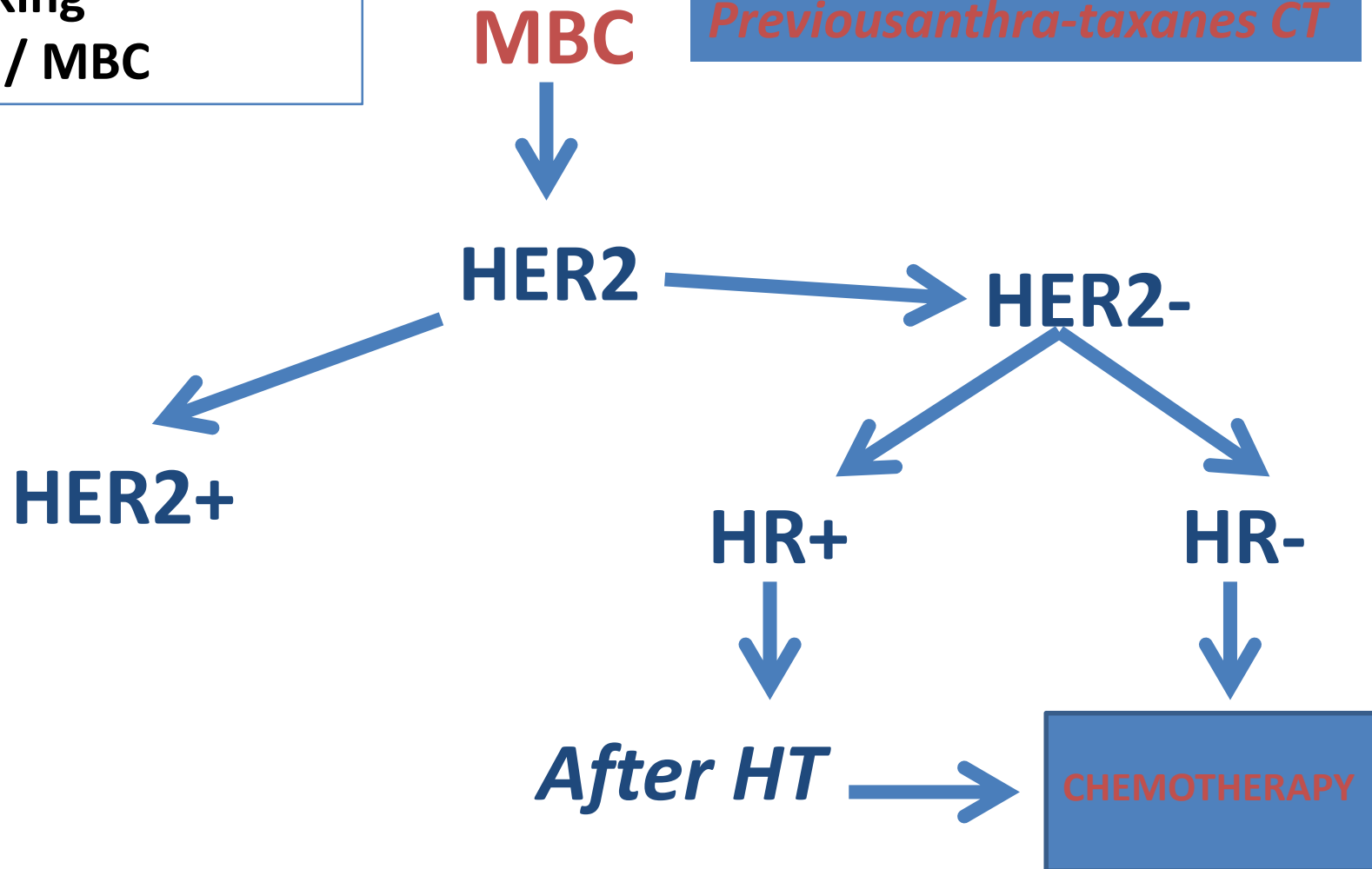
HER2+

HR+

HR-

After HT

CHEMOTHERAPY



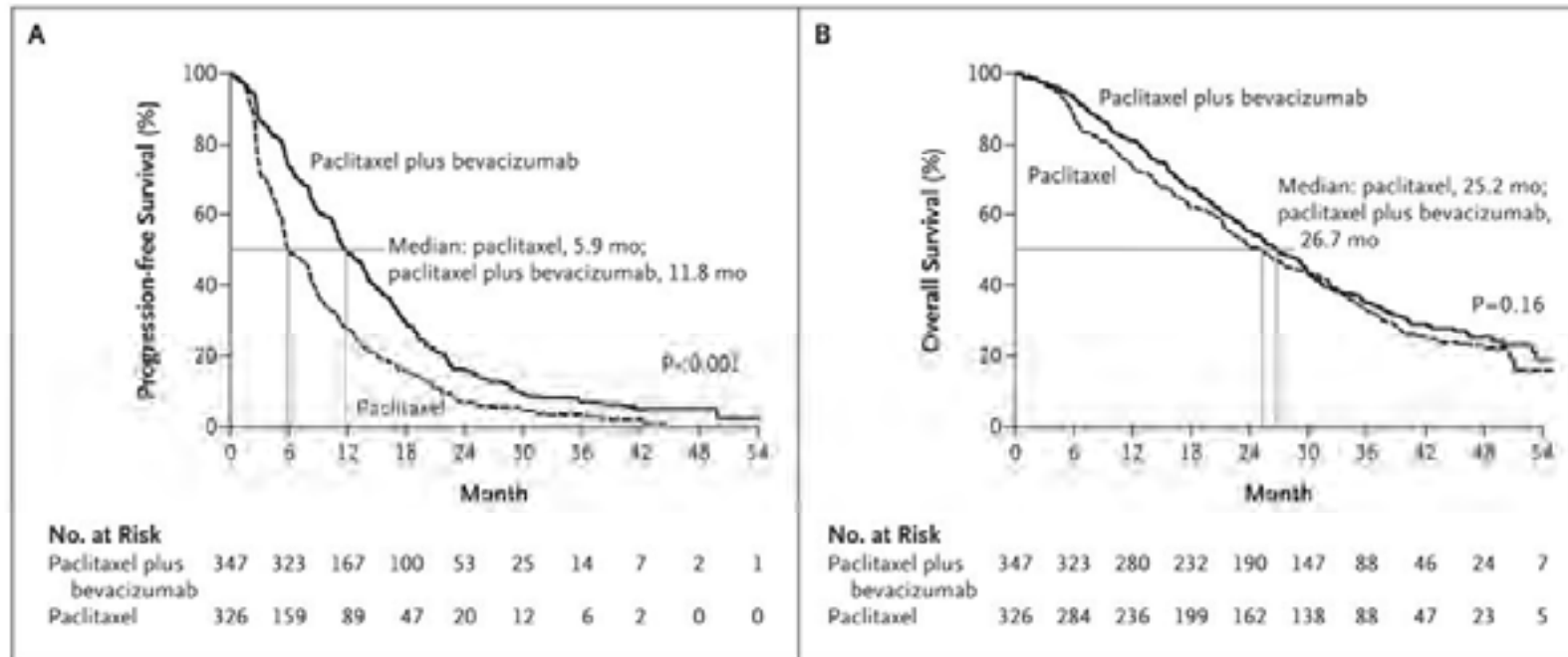
Randomized Controlled Trials (RCTs) of Bevacizumab (Bev) in MBC

Trial	Line of Rx	Regimen	N	RR %	PFS mo.	PFS HR	OS mo.
AVF2119 Miller, 2005	after A and T	Cape +/- Bev	462	19.8% 9.1%	4.86 4.17	0.98	15.1 14.5
E2100 Miller, 2007	1 st line	Weekly Paclitaxel +/- Bev	722	49% 21%	11.8 5.9	0.60 P<0.001	26.7 25.2
AVADO Miles, 2010	1 st line	Docetaxel + Bev 7.5 Docetaxel + Placebo Docetaxel + Bev 15	736	55% 46% 64%	9.0 8.1 10.1	0.86 0.77 P=.006	30.8 31.9 30.2
RIBBON-1 Robert, 2011	1 st line	Cape + Bev/Placebo T or A + Bev/Placebo	615 622	35% 24% 51% 38%	8.6 5.7 9.2 8.0	0.69 P<.001 0.64 P<.001	29 21.2 25.2 23.8
RIBBON-2 Brufsky, 2009	2 nd line	Taxane/Gem/Cape/ Vino + Bev/Placebo	684	40% 30%	7.2 5.1	0.78 P=0.0072	18.0 16.4
Brufsky, ASCO Ab 1010; 2011	2 nd line	Triple-negative subgroup	159 (23%)	41% 18%	6.0 2.7	0.494 P=0.0006	17.9 12.6 P=0.05

MN Dickler, ASCO

RCTs and Meta-Analysis

Survival Analyses

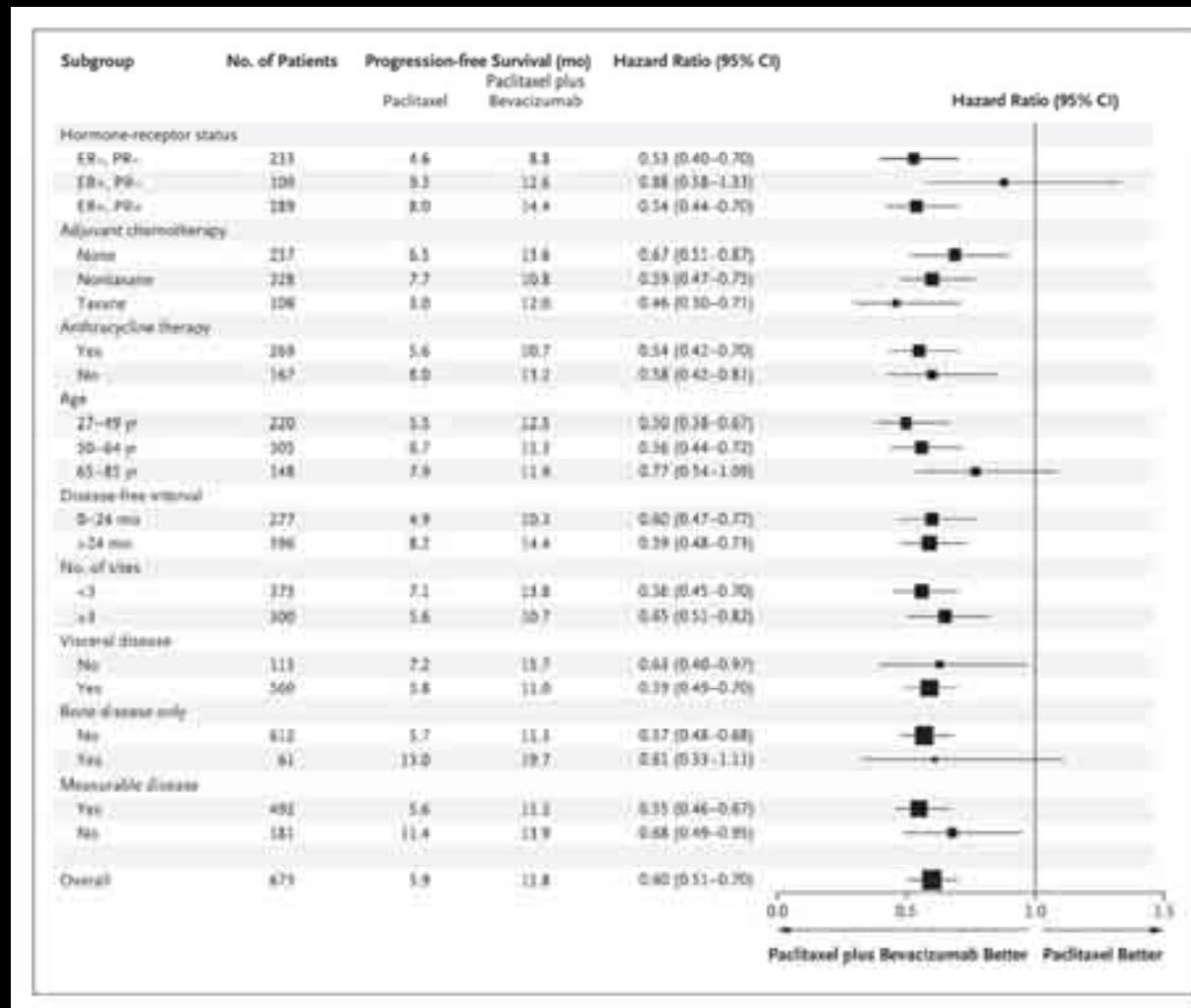


Miller K et al. N Engl J Med 2007;357:2666-2676



The NEW ENGLAND
JOURNAL of MEDICINE

Hazard Ratios for Disease Progression

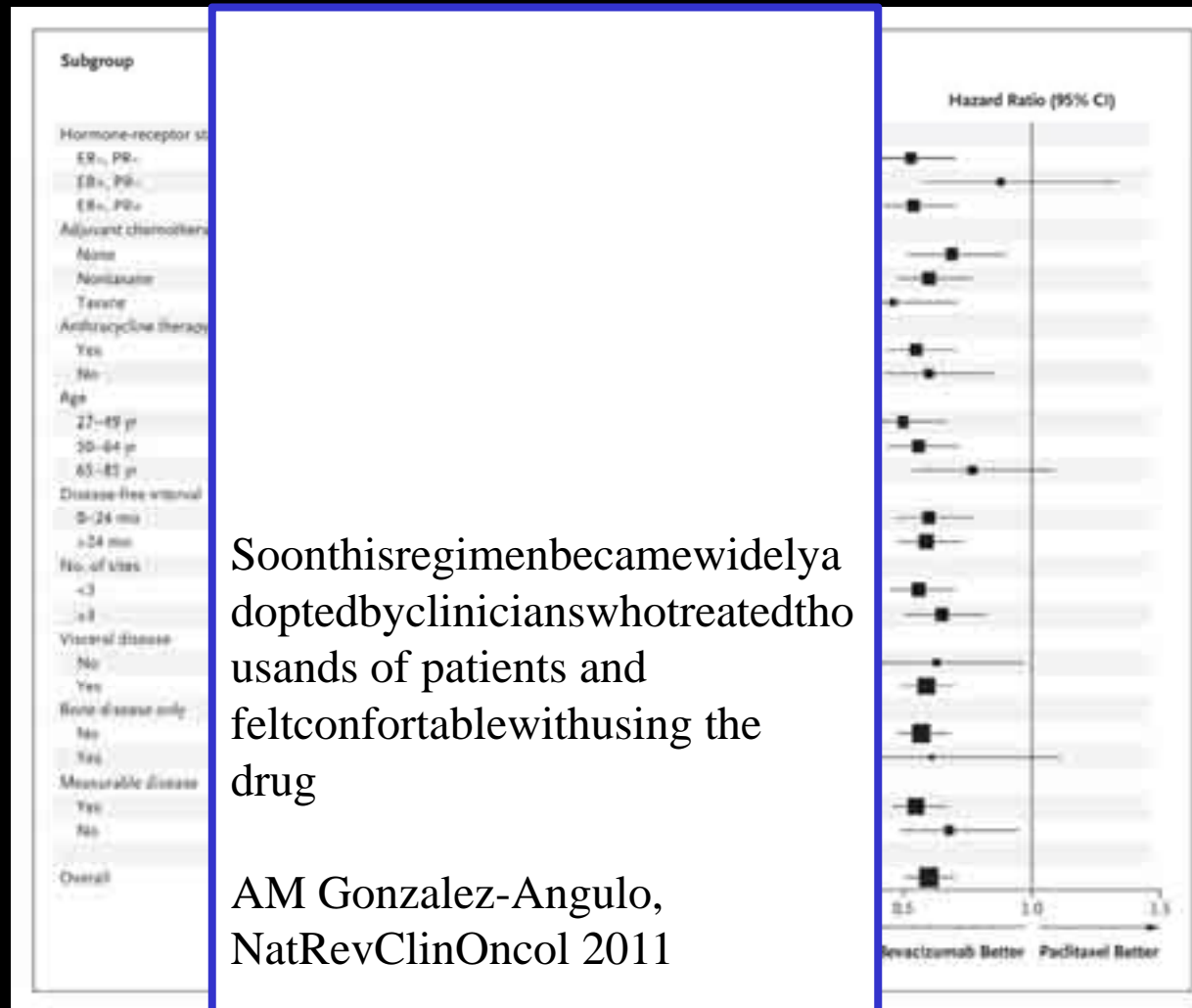


Miller K et al. N Engl J Med 2007;357:2666-2676



The NEW ENGLAND
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Hazard Ratios for Disease Progression

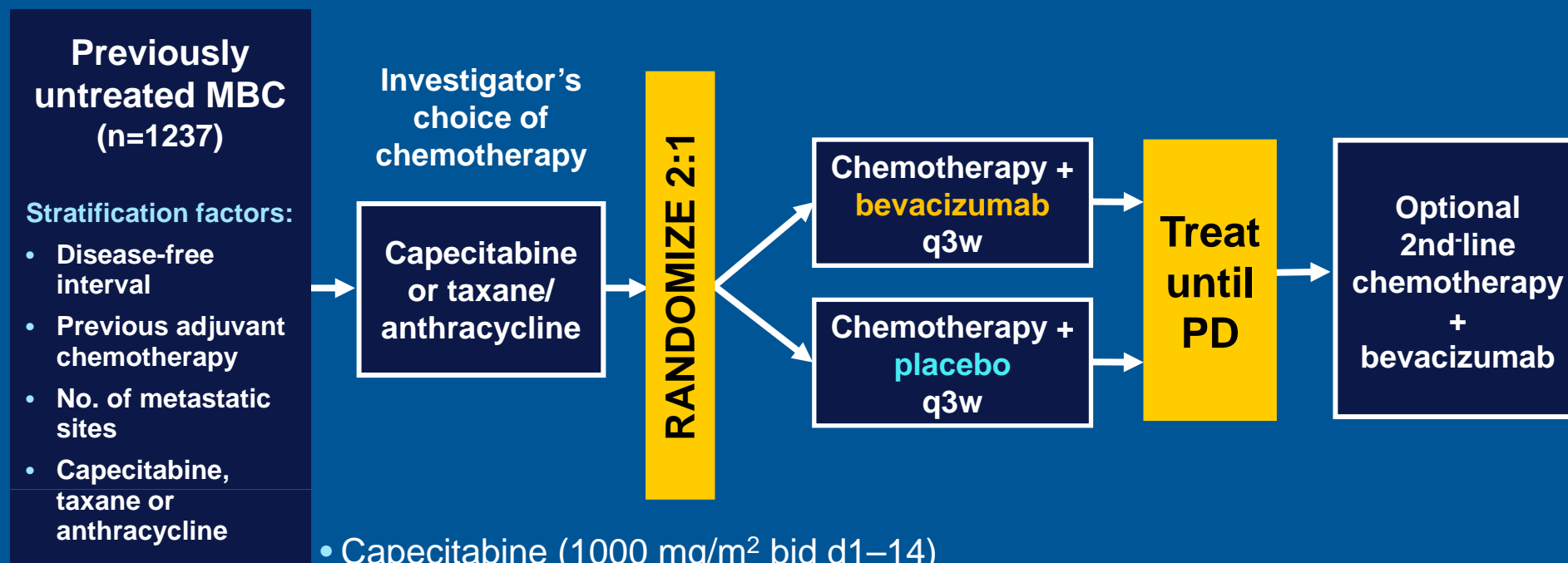


Miller K et al. N Engl J Med 2007;357:2060-2070



The NEW ENGLAND
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Trial Design

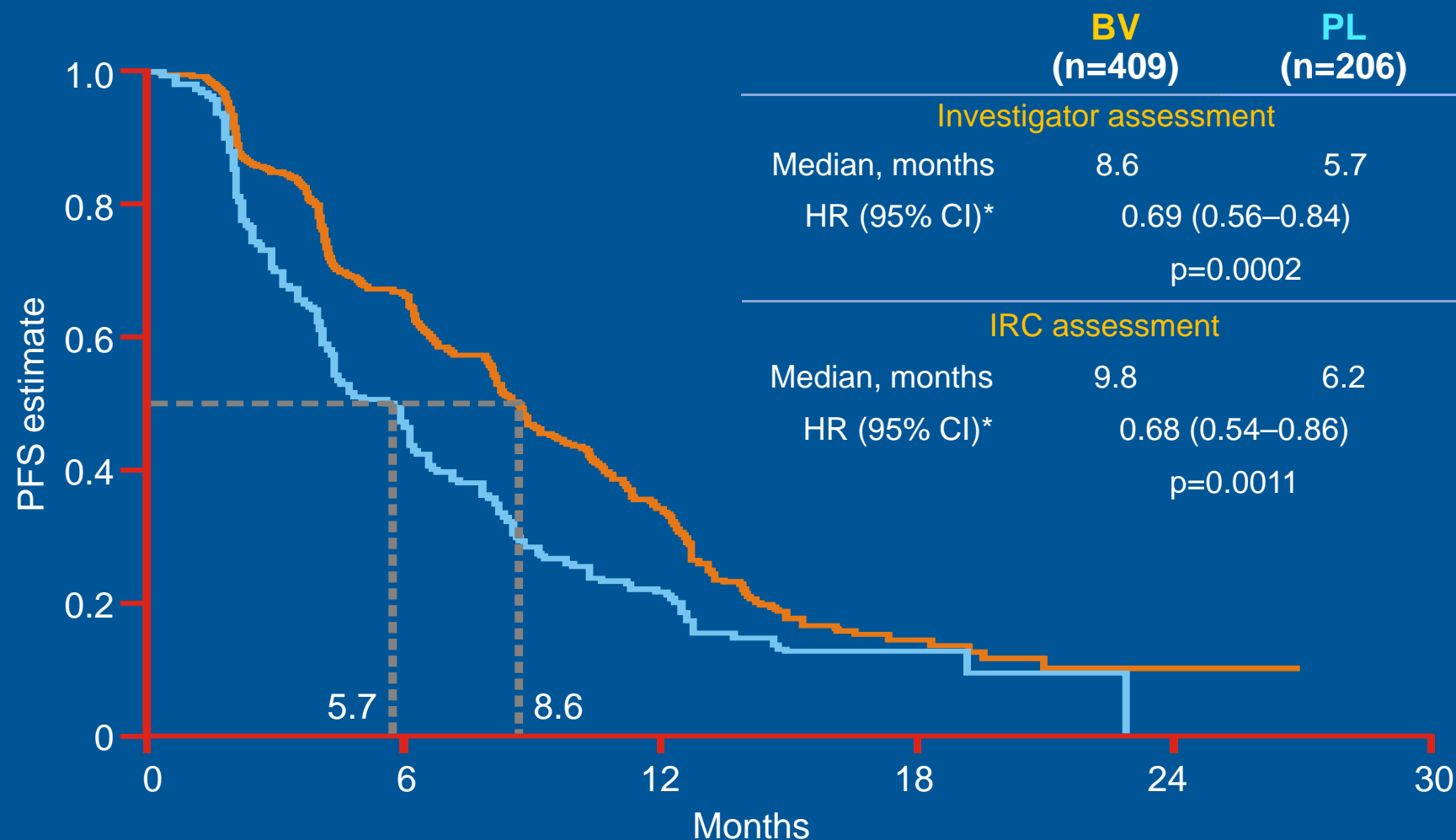


- Capecitabine (1000 mg/m² bid d1–14)
- Taxane (docetaxel 75–100 mg/m² or nab-paclitaxel 260 mg/m²)
- Anthracycline-based chemotherapy
 - AC (doxorubicin 50–60 mg/m², cyclophosphamide 500–600 mg/m²)
 - EC (epirubicin 90–100 mg/m², cyclophosphamide 500–600 mg/m²)
 - FAC (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²)
 - FEC (5-FU 500 mg/m², epirubicin 90–100 mg/m², cyclophosphamide 500 mg/m²)
- Bevacizumab or placebo (15 mg/kg)

NJ Robert, JCO 2011

Robert et al. ASCO 2009

PFS: Capecitabine Cohort

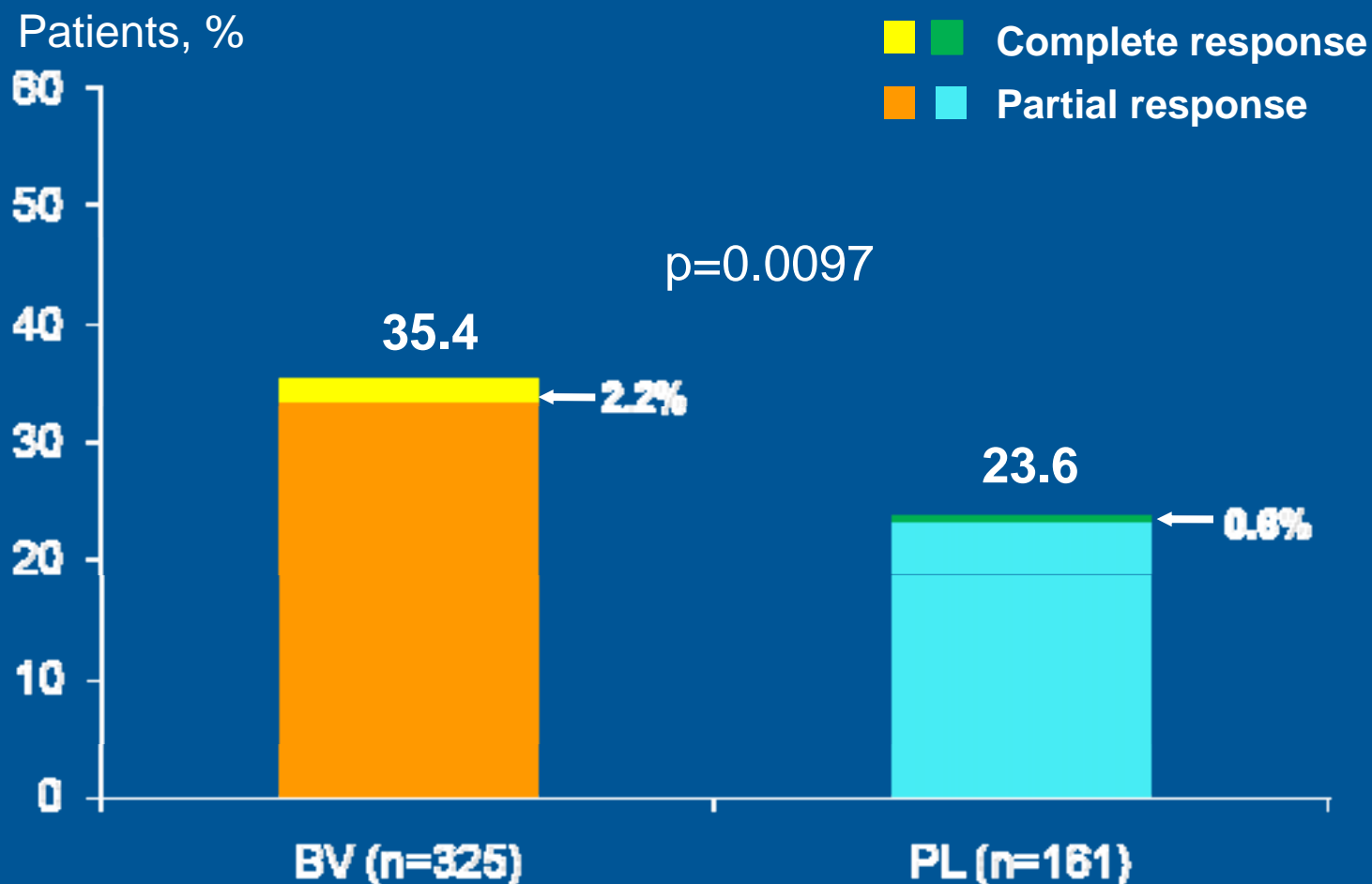


*Stratified analysis

NJ Robert, JCO 2011

Robert et al. ASCO 2009

Objective Response Rate*: Capecitabine Cohort



*Patients with measurable disease at baseline

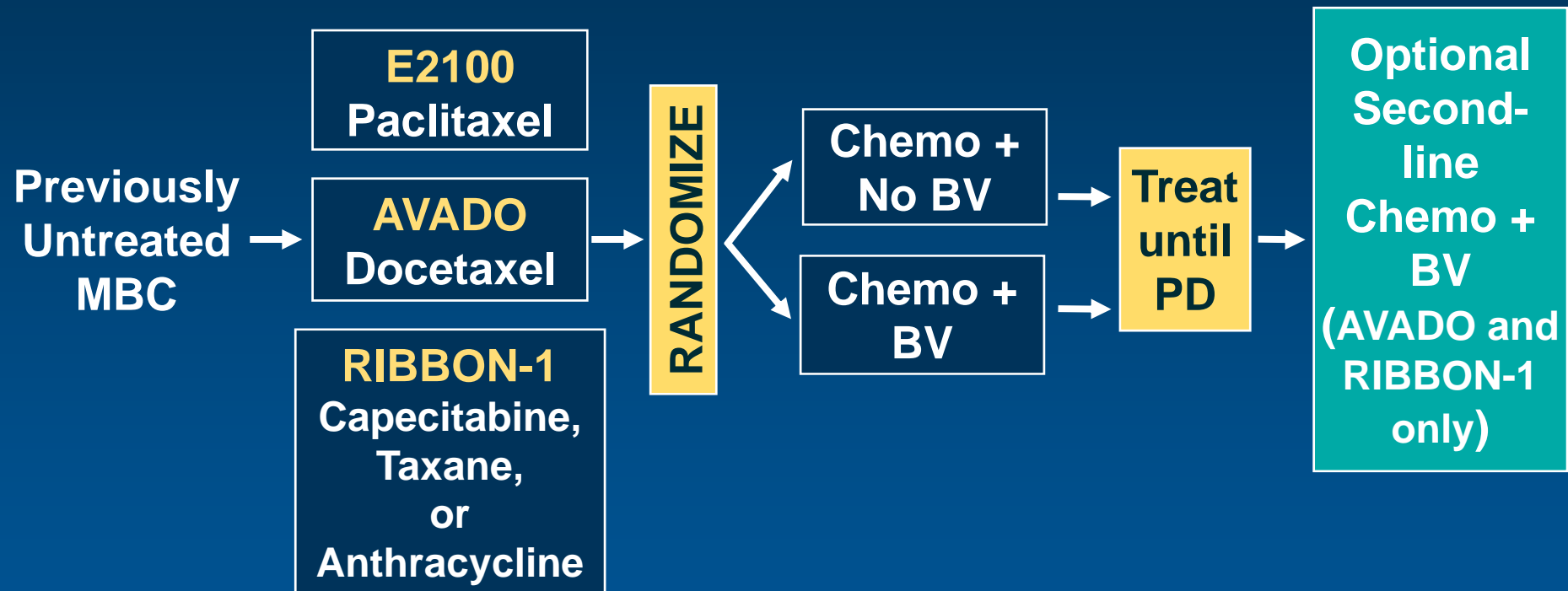
NJ Robert, JCO 2011
NJ Robert, JCO 2011

A Meta-Analysis of Overall Survival Data from Three Trials of Bevacizumab and First-Line Chemotherapy as Treatment for Patients with Metastatic Breast Cancer

Joyce O'Shaughnessy, David Miles, Robert Gray,
Véronique Diéras, Edith A. Perez, Robin Zon, Javier Cortés,
Xian Zhou, See-Chun Phan, Kathy Miller

Baylor-Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX; Mount Vernon Cancer Centre, London, England; Dana-Farber Cancer Institute, Boston, MA; Institut Curie, Paris, France; Mayo Clinic, Jacksonville, Florida; Michiana Hematology Oncology, South Bend, IN; Vall d'Hebron University Hospital, Barcelona, Spain; BioOncology, Genentech, S San Francisco, CA; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

General Study Designs



Comparison of the Studies

	E2100	AVADO*	RIBBON-1*
No. of patients	722	488	1237
Geography	US (90%)	Ex-US	US (50%)
Randomization ratio (BV:PL)	1:1	1:1	2:1
Chemotherapy	Paclitaxel weekly	Docetaxel	Capecitabine, Docetaxel/nab-Paclitaxel, Doxorubicin/Epirubicin
Primary Endpoint	PFS [†]	PFS	PFS
Key Secondary Endpoints	OS, ORR	OS, ORR, 1-yr survival	OS, ORR, 1-yr survival

BV=bevacizumab, PL=placebo, PFS=progression-free survival, ORR=objective response rate, OS=overall survival.

* Permitted continuing on BV or crossing over to BV.

[†]Analyses based on IRF assessments.

Overview of Efficacy Results from the Individual Studies in the Pooled Analysis

	E2100		AVADO		RIBBON-1 (Cape)		RIBBON-1 (Tax/Anthra)	
	Non-BV	BV	Non-BV	BV*	Non-BV	BV	Non-BV	BV
Median PFS, mo	5.8	11.3	7.9	8.8	5.7	8.6	8.0	9.2
Stratified HR (95% CI)	0.48 (0.39–0.61)		0.62 (0.48–0.79)		0.69 (0.56–0.84)		0.64 (0.52–0.80)	
p-values	p<0.0001		p=0.0003		p=0.0002		p<0.0001	

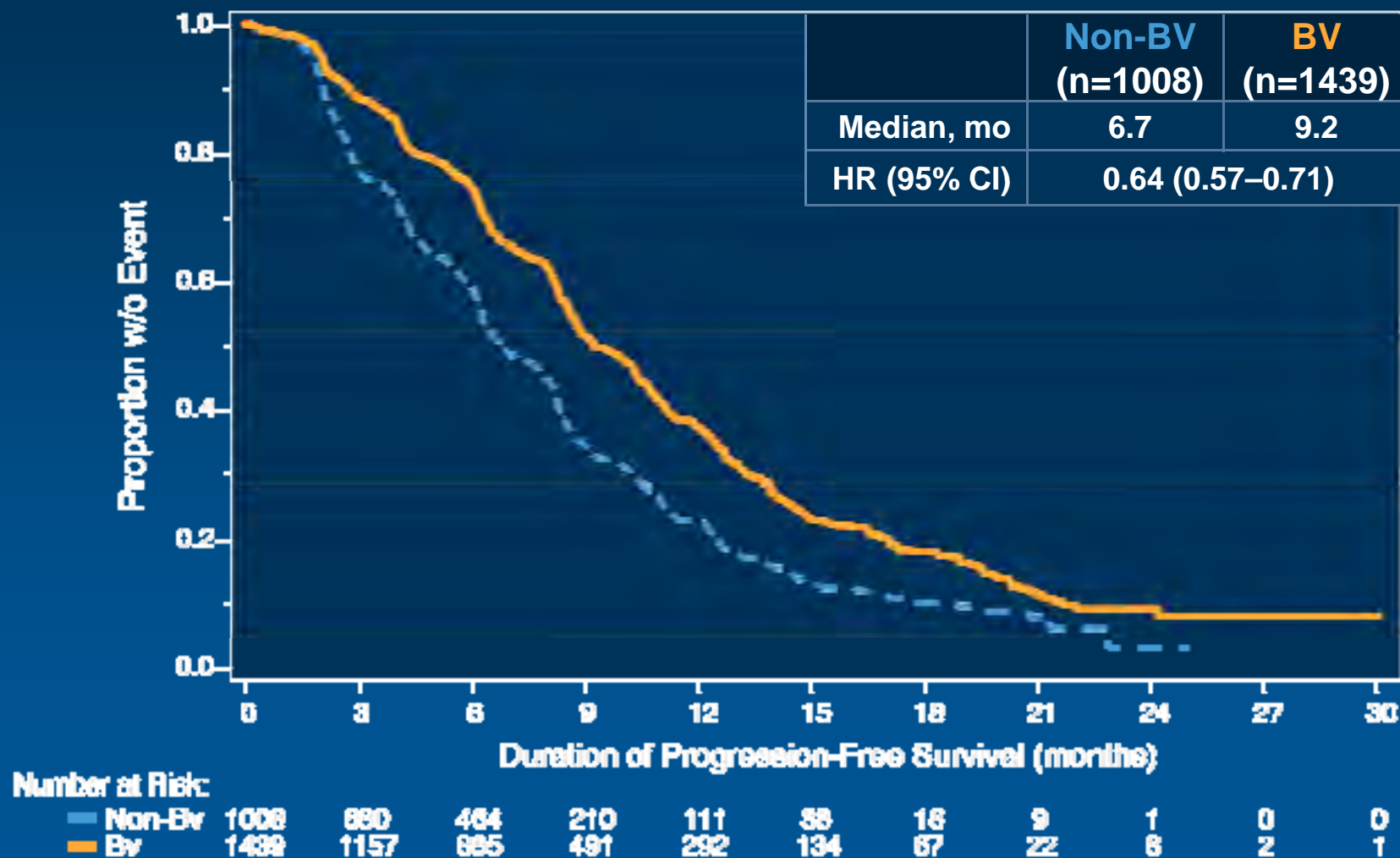
BV=bevacizumab, Cape=capecitabine, Tax/Anthra=taxane/anthracycline.

* 15 mg/kg cohort.

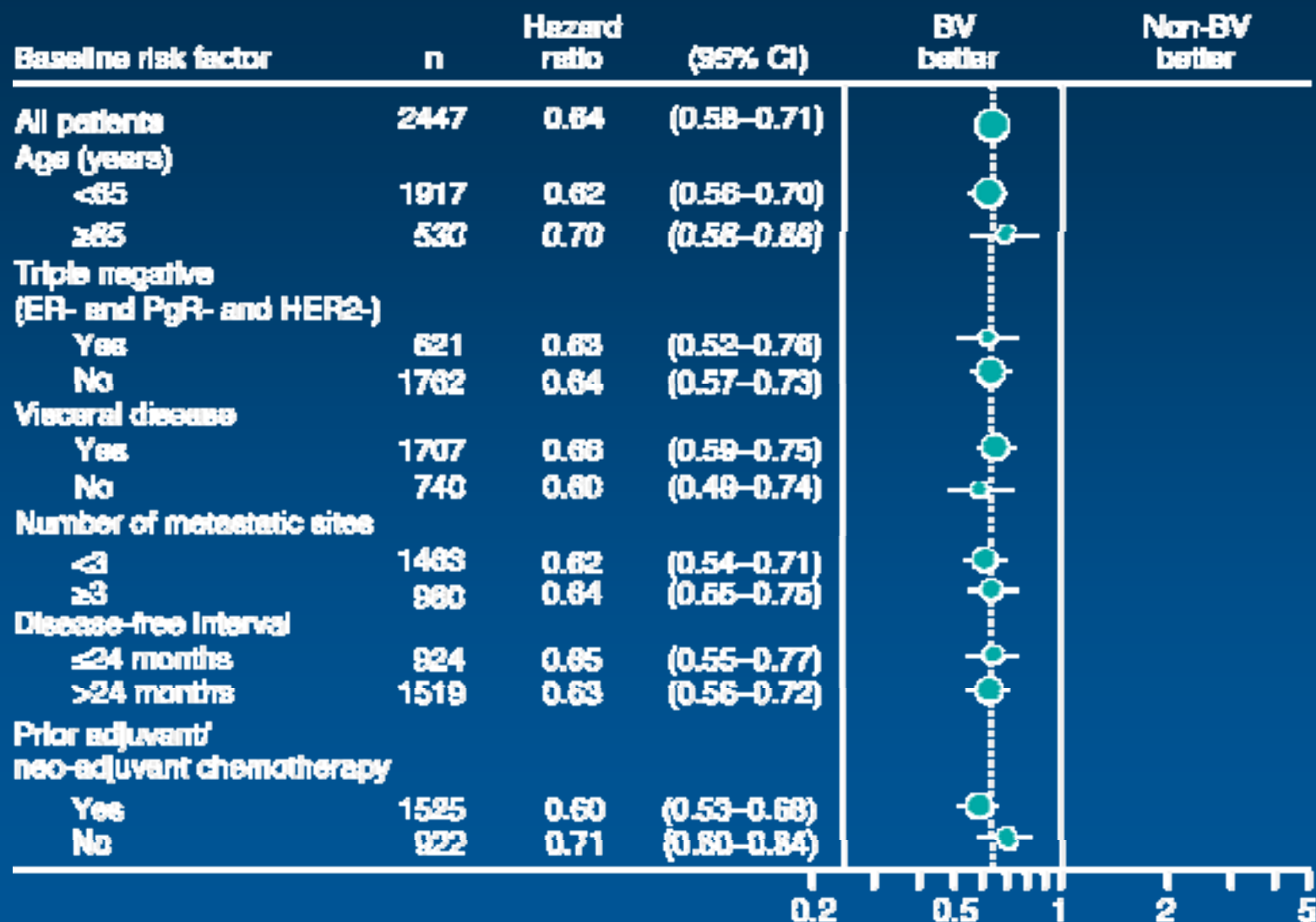
Patient Characteristics, Pooled Population

	Non-BV (n=1008)	BV (n=1439)
Age, median	55 yr	56 yr
Triple-negative disease, %	26	25
Disease-free interval (≤ 24 mo), %	39	37
Prior adjuvant chemo, %	64	62
Taxane	22	24
Anthracycline	52	48
Visceral disease, %	71	69
≥ 3 metastatic sites, %	38	41

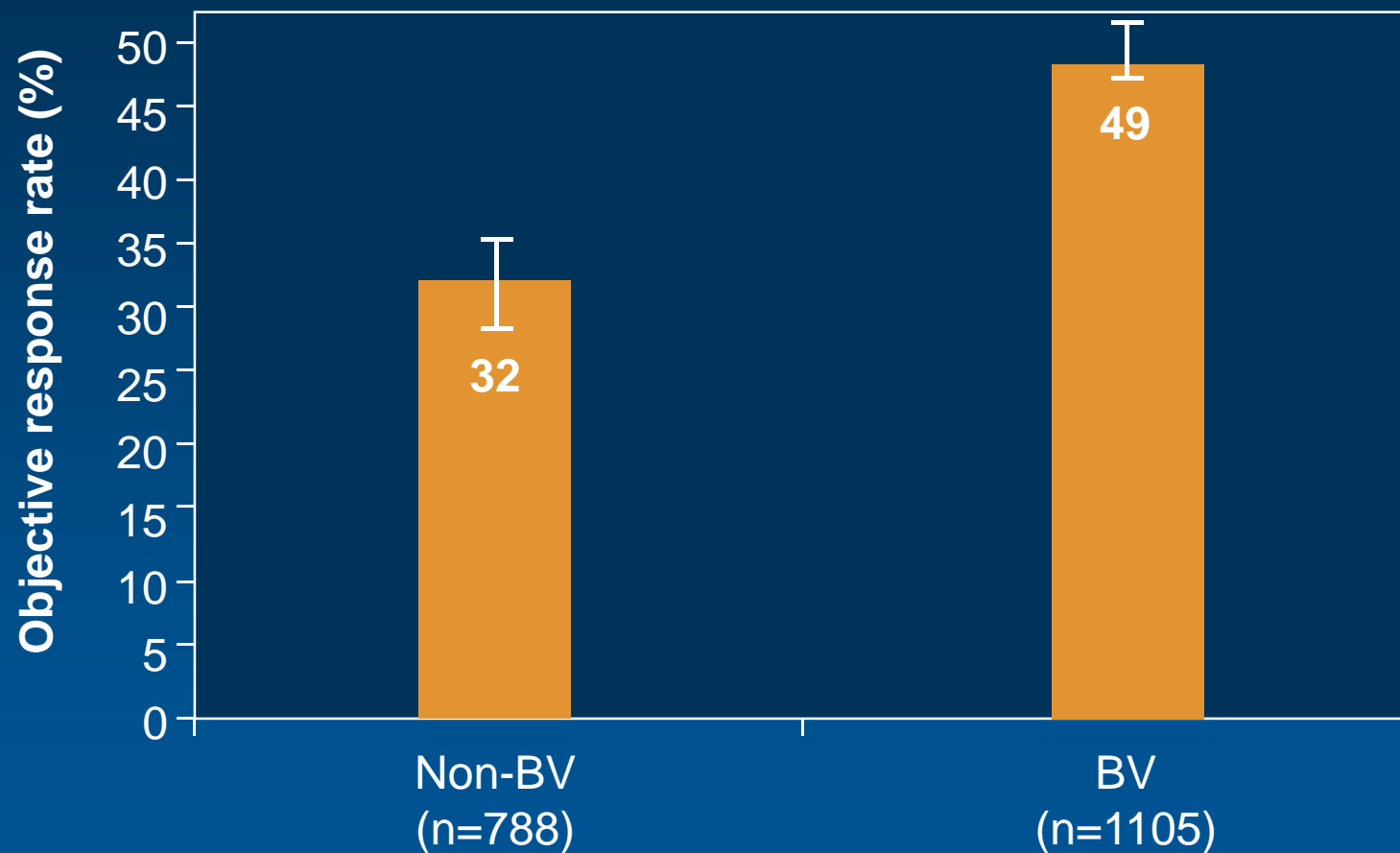
Progression-Free Survival, Pooled Population



Analysis of PFS by Subgroups

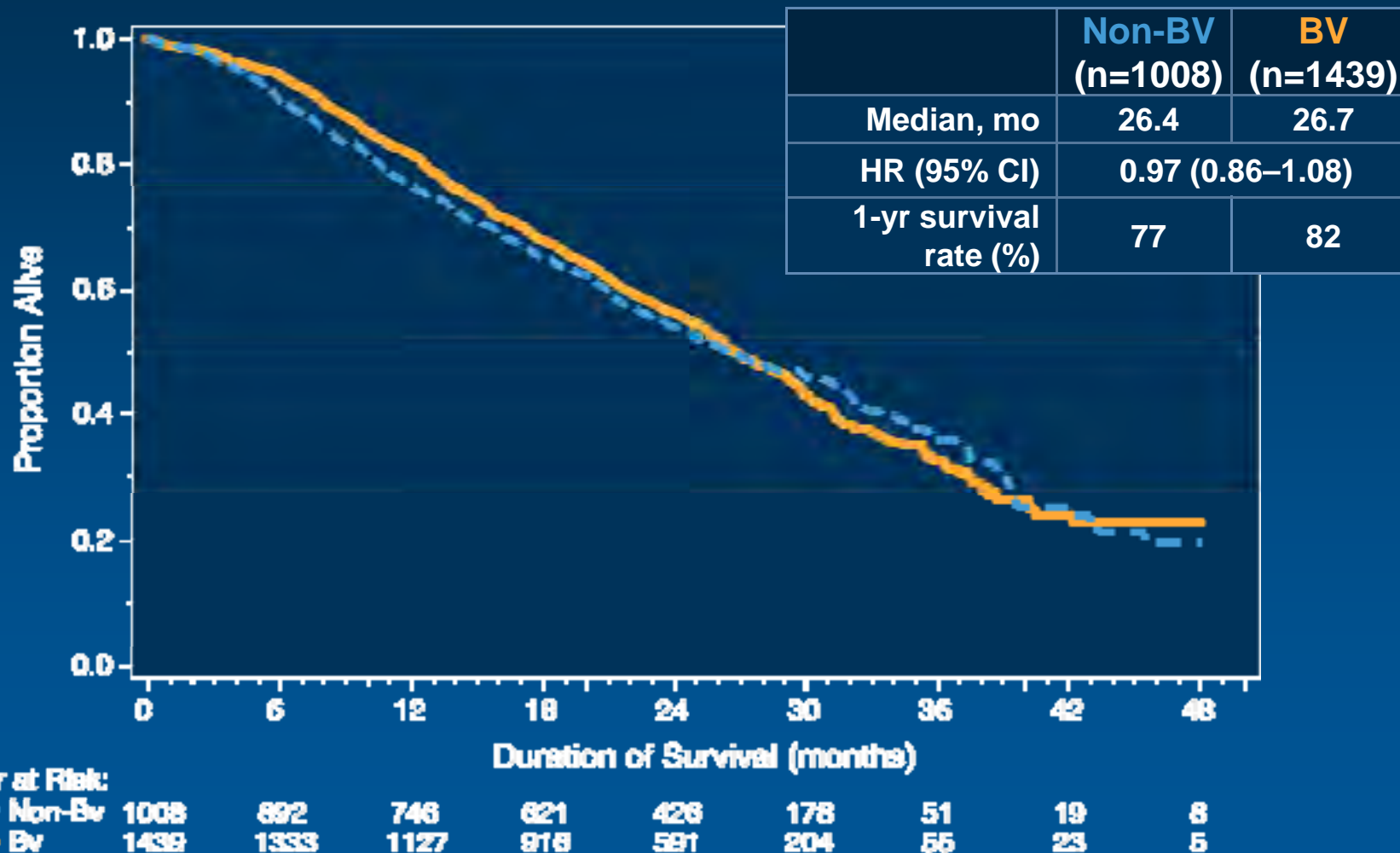


Objective Response Rate*



*Includes only patients with measurable disease at baseline.

Overall Survival, Pooled Population



Use of Subsequent Systemic Therapies in AVADO and RIBBON-1 Studies*

%	Non-BV (n=654)	BV (n=1071)
Any chemotherapy	71	65
Bevacizumab	51	40
Any hormonal therapy	25	23
# of subsequent anti-cancer agents		
≥4	27	23
3	15	12
2	27	26
1	10	15

*Data not available from E2100.

Conclusions

- Significant PFS advantage but no OS difference with BV across 3 first-line studies and in pooled analysis
 - In MBC, the ability of Phase III trials to demonstrate treatment effect upon OS depends on the duration of survival post-progression (SPP)
 - Higher chance of affecting OS in populations with short SPP (20 month PPS in these 3 first-line trials)
- Patients with adverse prognostic features benefit from BV as do patients with more indolent disease
- Low incidence of treatment-related deaths with BV
- Safety profile consistent with previous BV experience

A look at TNBC

Meta-analysis of First-line Bevacizumab Plus Chemotherapy in Triple-Negative Breast Cancer

	Bevacizumab/ Chemo (n = 363)	Chemo (n = 258)	HR (95% CI)	P Value
Median Progression-Free Survival	8.1 months	5.4 months	0.649 (0.538-0.783)	< .0001
Overall Response Rate	42%	23%	NR	< .0001
Median Overall Survival	18.9 months	17.5 months	0.959 (0.790-1.164)	.6732
1-Year Overall Survival Rate	71%	65%	NR	.1140

- This meta-analysis represents the largest reported population of patients randomized to treatment for metastatic TNBC.
- The addition of bevacizumab significantly improved PFS but not OS.

O'Shaughnessy et al. SABCS 2010; abstract P6-12-03

PRESENTED AT: ASCO Annual Meeting



PHYSICIANS
EDUCATION
RESOURCES

RIBBON-2 trial design

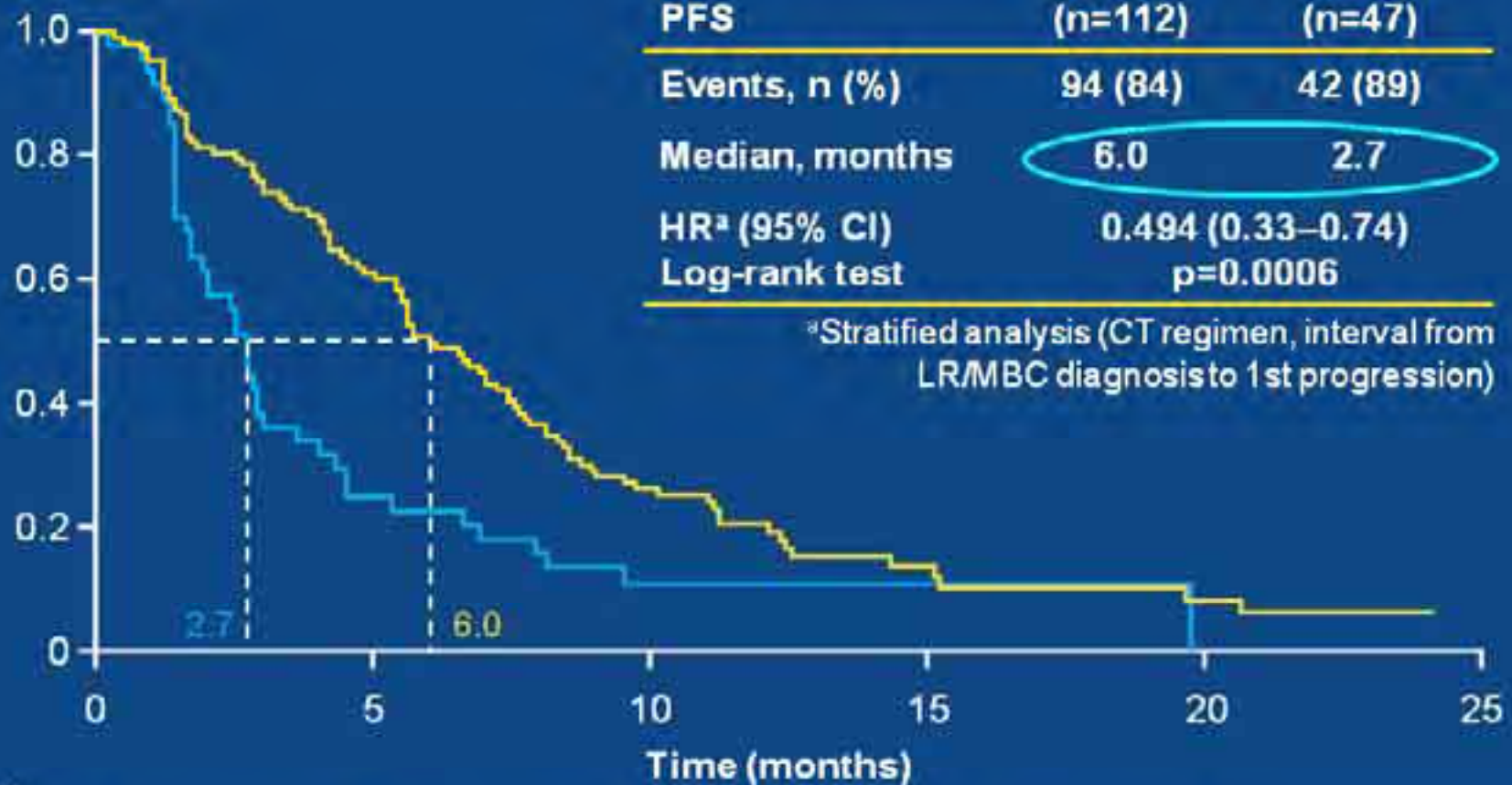


- Taxane (paclitaxel 90 mg/m² d1, 8, 15 q4w or paclitaxel 175 mg/m², nab-paclitaxel 260 mg/m², or docetaxel 75–100 mg/m² q3w)
- Gemcitabine (1250 mg/m² d1, 8 q3w)
- Capecitabine (1000 mg/m² bid d1–14 q3w)
- Vinorelbine (30 mg/m² d1, 8, 15 q3w)
- BEV or PLA (15 mg/kg q3w or 10 mg/kg q2w, depending on CT regimen)
- Stratification factors: CT regimen; interval from LR/MBC diagnosis to 1st progression; ER and PgR status

ER = estrogen receptor, PgR = progesterone receptor, PLA = placebo, R = randomization

TNBC population (23% of all): PFS

Estimated probability



No. at risk:

BEV + CT 112
Placebo + CT 47

65
11

26
4

8
2

4

Facts and Prejudices

- **Regrowth/Rebound**
- **Toxicity**
- **Age**
- **Biomarkers**
- **Cost**

Regrowth/Rebound

From discontinuation to death

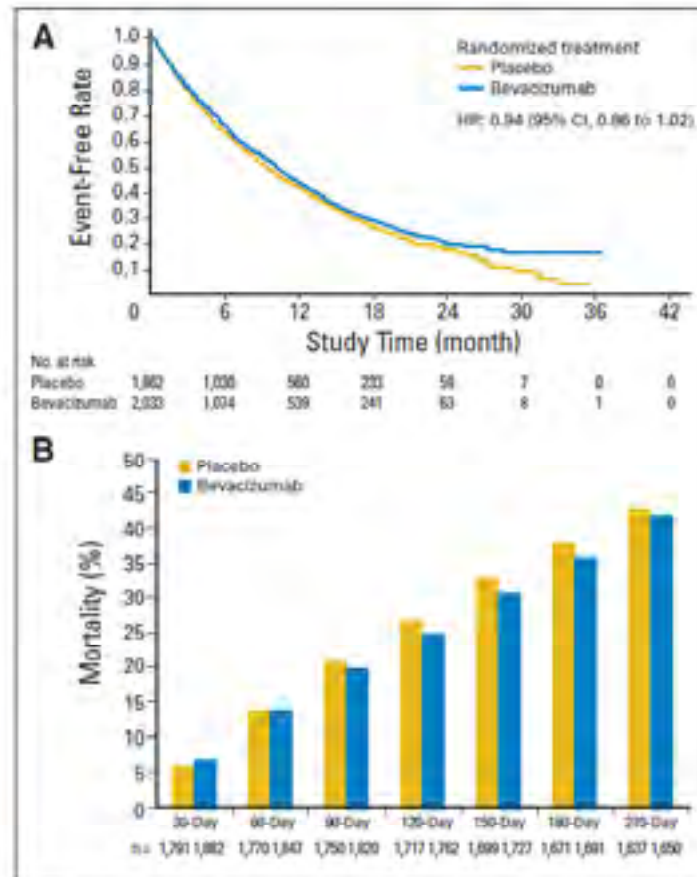


Fig 3. Outcomes in patients who discontinued treatment for any reason. (A) Time from treatment discontinuation to death in patients who discontinued bevacizumab/placebo for any reason in the pooled analysis. (B) Mortality at 30, 60, 90, 120, 150, 180, and 210 days after discontinuation of bevacizumab or placebo in the pooled analysis. HR, hazard ratio.

Toxicity

Treatment-Related Mortality With Bevacizumab in Cancer Patients

A Meta-analysis

Vishal Ranpura, MD

Sanjaykumar Hapani, MD

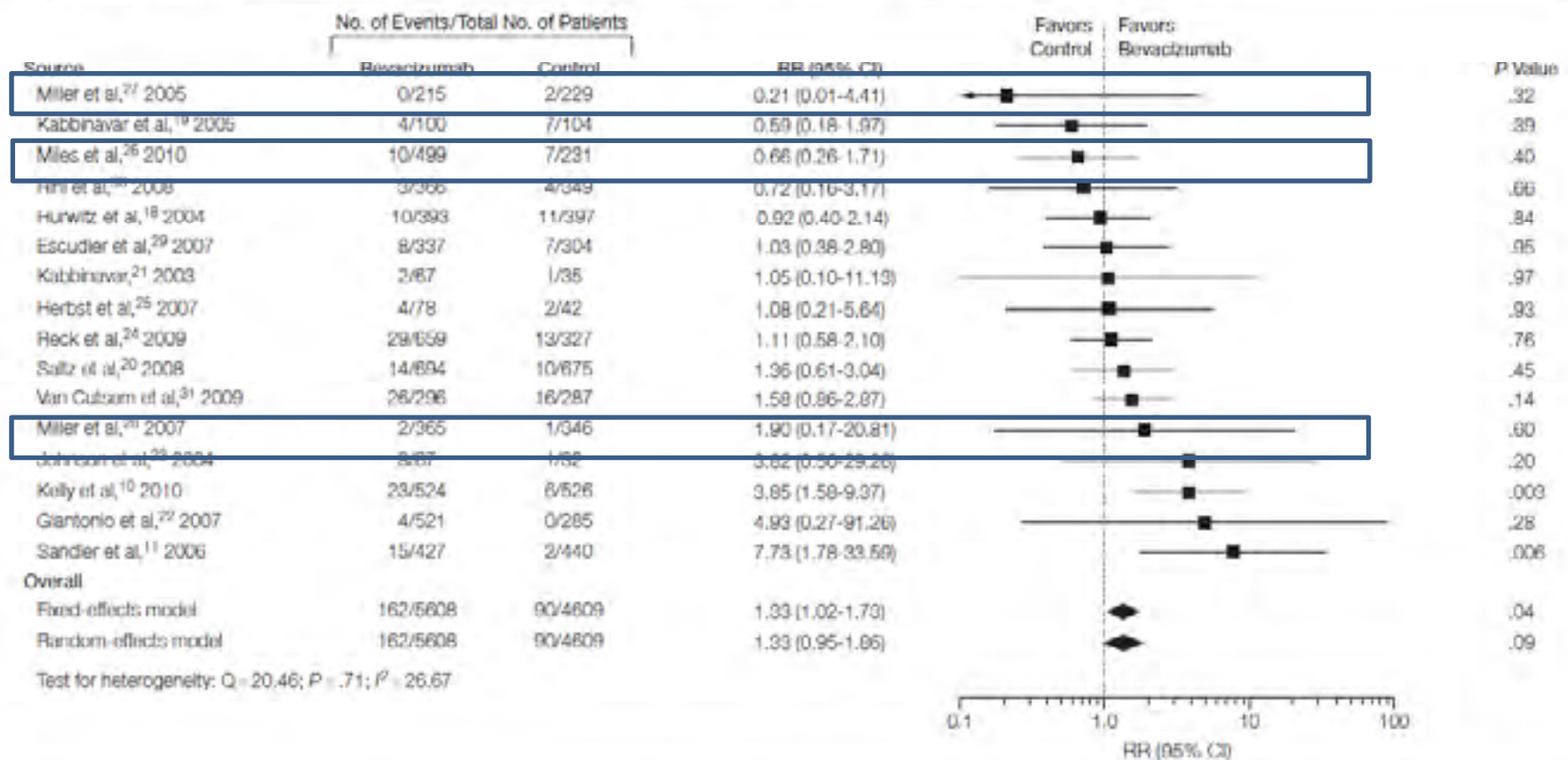
Shenhong Wu, MD, PhD

Data Synthesis A total of 10 217 patients with a variety of advanced solid tumors from 16 RCTs were included in the analysis. The overall incidence of FAEs with bevacizumab was 2.5% (95% CI, 1.7%-3.9%). Compared with chemotherapy alone, the addition of bevacizumab was associated with an increased risk of FAEs, with an RR of 1.46 (95% CI, 1.09-1.94; $P=.01$; incidence, 2.5% vs 1.7%). This association varied significantly with chemotherapeutic agents ($P=.045$) but not with tumor types ($P=.13$) or bevacizumab doses ($P=.16$). Bevacizumab was associated with an increased risk of FAEs in patients receiving taxanes or platinum agents (RR, 3.49; 95% CI, 1.82-6.66; incidence, 3.3% vs 1.0%) but was not associated with increased risk of FAEs when used in conjunction with other agents (RR, 0.85; 95% CI, 0.25-2.88; incidence, 0.8% vs 0.9%). The most common causes of FAEs were hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal tract perforation (7.1%).

Conclusion In a meta-analysis of RCTs, bevacizumab in combination with chemotherapy or biological therapy, compared with chemotherapy alone, was associated with increased treatment-related mortality.

Bevacizumab and FAEs

Figure 2. Relative Risk (RR) of Fatal Adverse Events Associated With Bevacizumab vs Control



Overall summary risk of fatal adverse events was calculated using fixed- and random-effects models. For studies with 0 events in a cell, 0.5 was added to the cell frequency before calculation of the relative risk. CI indicates confidence interval.

Bevacizumab and FAEs

Table 3. Incidence and Relative Risk (RR) of Specific FAEs With Bevacizumab^a

FAEs	No. of Studies	No. of FAEs/ Total No. of Participants		Incidence of FAEs, % (95% CI)		RR (95% CI)
		Bevacizumab	Control	Bevacizumab	Control	
Specified	13	67/4219	28/3503	2.1 (1.7-2.7)	1.0 (0.5-2.1)	1.76 (1.10-2.82)
Unspecified	12	95/3878	62/3167	2.6 (1.7-3.8)	2.5 (2.0-3.2)	1.09 (0.73-1.62)
Hemorrhage	7	23/2403	3/1737	1.3 (0.6-2.9)	0.5 (0.1-1.7)	2.77 (1.07-7.16)
Pulmonary hemorrhage	5	14/1568	0/1145	1.3 (0.4-4.2)	0.3 (0.1-1.2)	3.96 (1.03-15.25)
Gastrointestinal tract perforation	5	7/2318	1/2039	0.3 (0.9-1.7)	0.2 (0-1.0)	2.45 (0.63-9.51)
Neutropenia	3	12/1154	3/803	1.1 (0.6-1.9)	0.6 (0.1-2.7)	2.37 (0.61-9.18)
Gastrointestinal hemorrhage	2	6/733	1/741	0.9 (0.3-2.3)	0.2 (0-1.0)	3.71 (0.58-23.63)
Pulmonary embolism	5	5/1133	4/1111	0.7 (0.3-1.5)	0.6 (0.2-1.4)	1.10 (0.34-3.10)
Cerebrovascular accident	2	5/733	1/741	0.7 (0.3-1.7)	0.2 (0-1.1)	3.60 (0.59-22.02)
Overall	16	162/5608	90/4609	2.9 (2.0-4.2)	2.2 (1.4-3.2)	1.33 (1.02-1.73)

Abbreviations: CI, confidence interval; FAE, fatal adverse event.

^a The incidences and RRs were calculated from trials included in this meta-analysis as described in the "Methods" section of the text. Other rare causes of bevacizumab-associated FAEs include wound dehiscence, liver failure, lung abscess, chronic obstructive pulmonary disease, aspiration pneumonia, septic shock, and respiratory failure.

Bevacizumab and ATE

Table 2. Incidence of an arterial thromboembolic event in the pooled population by treatment, type of event, baseline risk factors, and aspirin use*

Group	Control patients (n = 782)	Bevacizumab-treated patients (n = 963)	P†
Overall			
Incidence No. (%)	13 (1.7)	37 (3.8)	
Difference in incidence (95% CI)		2.1 (0.7 to 3.7)	
Follow-up, py	419	673	
Rate per 100 py (95% CI)	3.1 (1.8 to 5.3)	5.5 (4.0 to 7.6)	
Ratio of rate per 100 py (95% CI)		1.8 (0.94 to 3.33)	.076
HR‡ (95% CI)		2.0 (1.06 to 3.75)	.031
By type of event, No. (%)			
Stroke/TIA	4 (0.5)	16 (1.7)	
MI/angina	8 (1.0)	14 (1.5)	
Other	1 (0.1)	8 (0.8)	
All	13 (1.7)	37 (3.8)	
By baseline risk factors, % (No. of events/No. of patients)			
Age ≥65 y	2.5 (7/279)	7.1 (24/339)	
History of ATE	3.4 (2/59)	15.7 (14/89)	
Age <65 y and no history of ATE	1.0 (5/490)	1.8 (11/602)	
Age <65 y and history of ATE	7.7 (1/13)	9.1 (2/22)	
Age ≥65 y and no history of ATE	2.6 (6/233)	4.4 (12/272)	
Age ≥65 y and history of ATE	2.2 (1/46)	17.9 (12/67)	
By baseline risk factors and aspirin use, % (No. of events/No. of patients)			
Aspirin nonusers	1.7 (12/698)	3.6 (30/827)	.027
Age <65 y and no history of ATE	1.1 (5/462)	2.0 (11/552)	.315
Age <65 y and history of ATE	0.0 (0/7)	6.7 (1/15)	>.999
Age ≥65 y and no history of ATE	3.0 (6/200)	4.4 (10/225)	.459
Age ≥65 y and history of ATE	3.4 (1/29)	22.9 (8/35)	.033
Aspirin users	1.2 (1/84)	5.1 (7/136)	.159
Age <65 y and no history of ATE	0.0 (0/28)	2.0 (1/51)	>.999
Age <65 y and history of ATE	16.7 (1/6)	0.0 (0/6)	>.999
Age ≥65 y and no history of ATE	0.0 (0/34)	4.3 (2/47)	.607
Age ≥65 y and history of ATE	0.0 (0/16)	12.5 (4/32)	.286

Bevacizumab and CHF

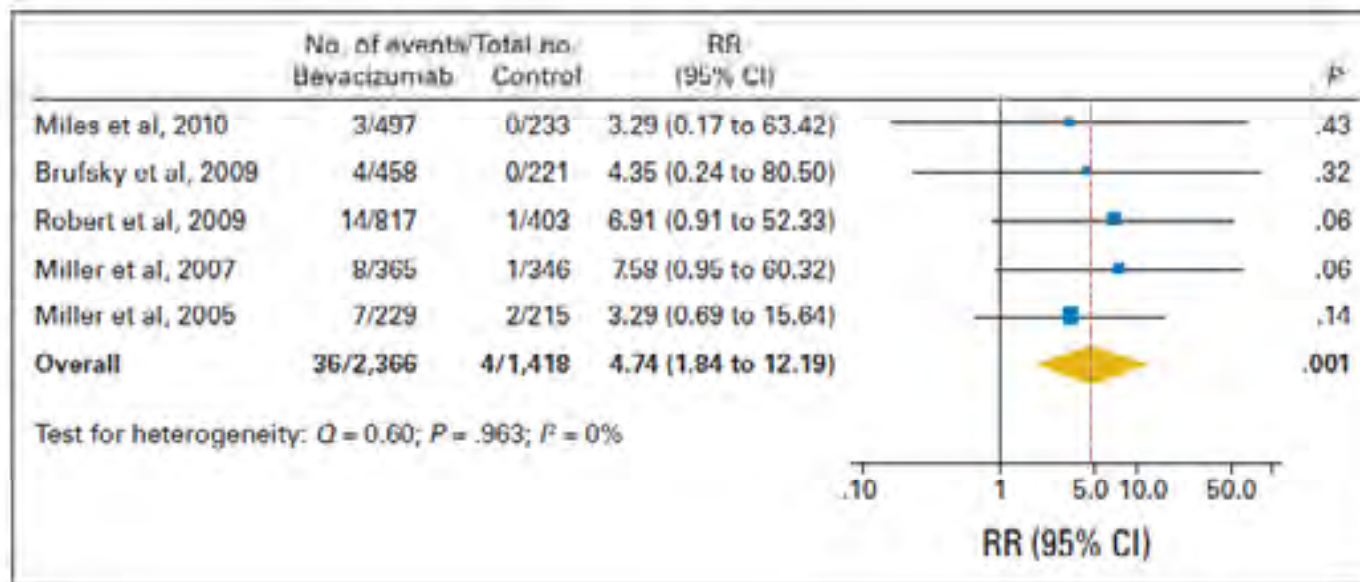


Fig 2. Relative risk of high-grade congestive heart failure events associated with bevacizumab versus control among patients with breast cancer. RR, relative risk.

Safety, Causes of Death*

%	Non-BV (n=982)	BV (n=1679)
Total deaths	55.8	51.3
MBC	51.5	47.4
Treatment-related	1.8	2.1
Other	1.4	1.5
Missing	1.0	0.3

*Safety evaluable patient population.

Grade ≥ 3 Selected Adverse Events (AEs), Pooled Population

%	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

RPLS=Reversible posterior leukoencephalopathy syndrome.

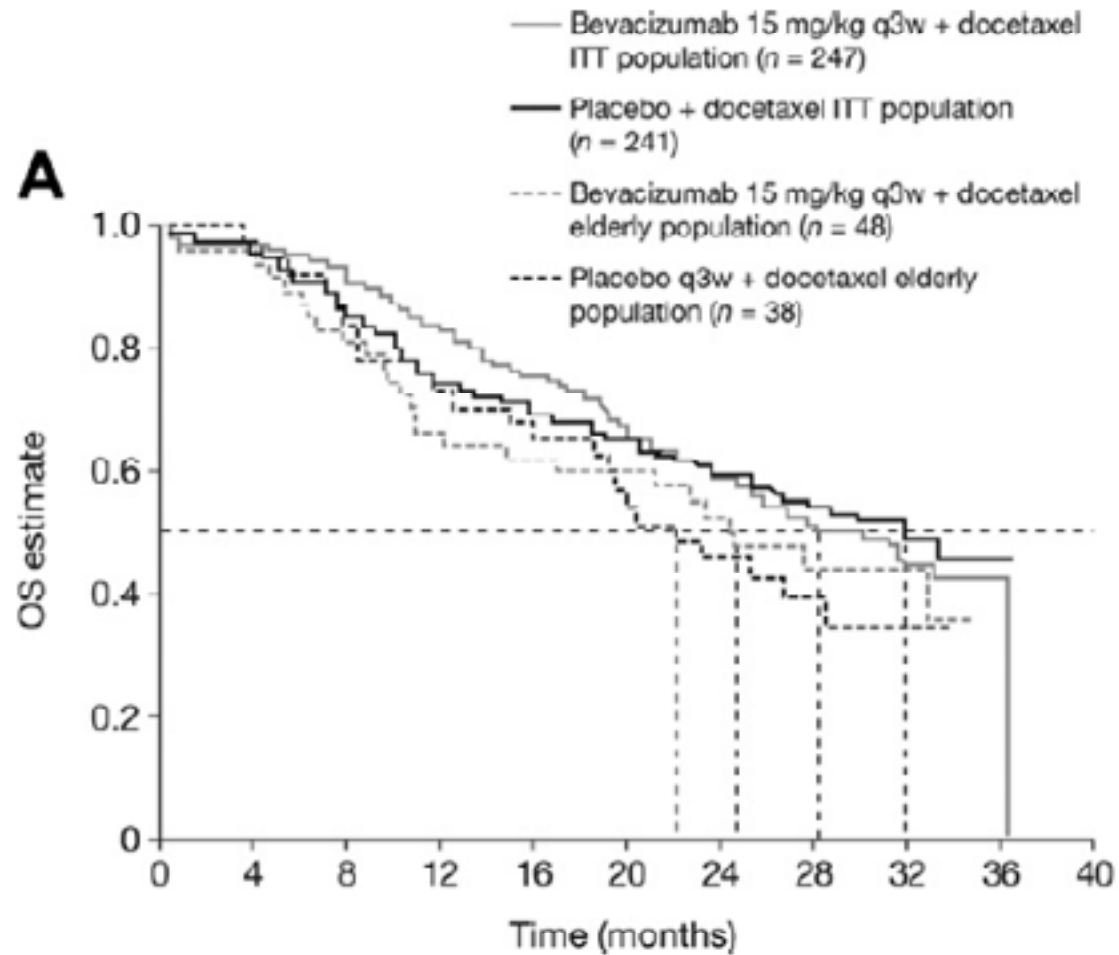
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Hypertension	1.2	9.0
Febrile neutropenia	3.5	6.5
Venous thromboembolic event	3.8	2.8
Proteinuria	0	2.3
Arterial thromboembolic event	0.3	1.6
Bleeding	0.4	1.5
Left ventricular systolic funct.	0.2	1.5
Wound dehiscence	0.3	0.8
Fistula	0.3	0.5
GI perforation	0.3	0.5
RPLS	0	<0.1

RPLS=Reversible posterior leukoencephalopathy syndrome.

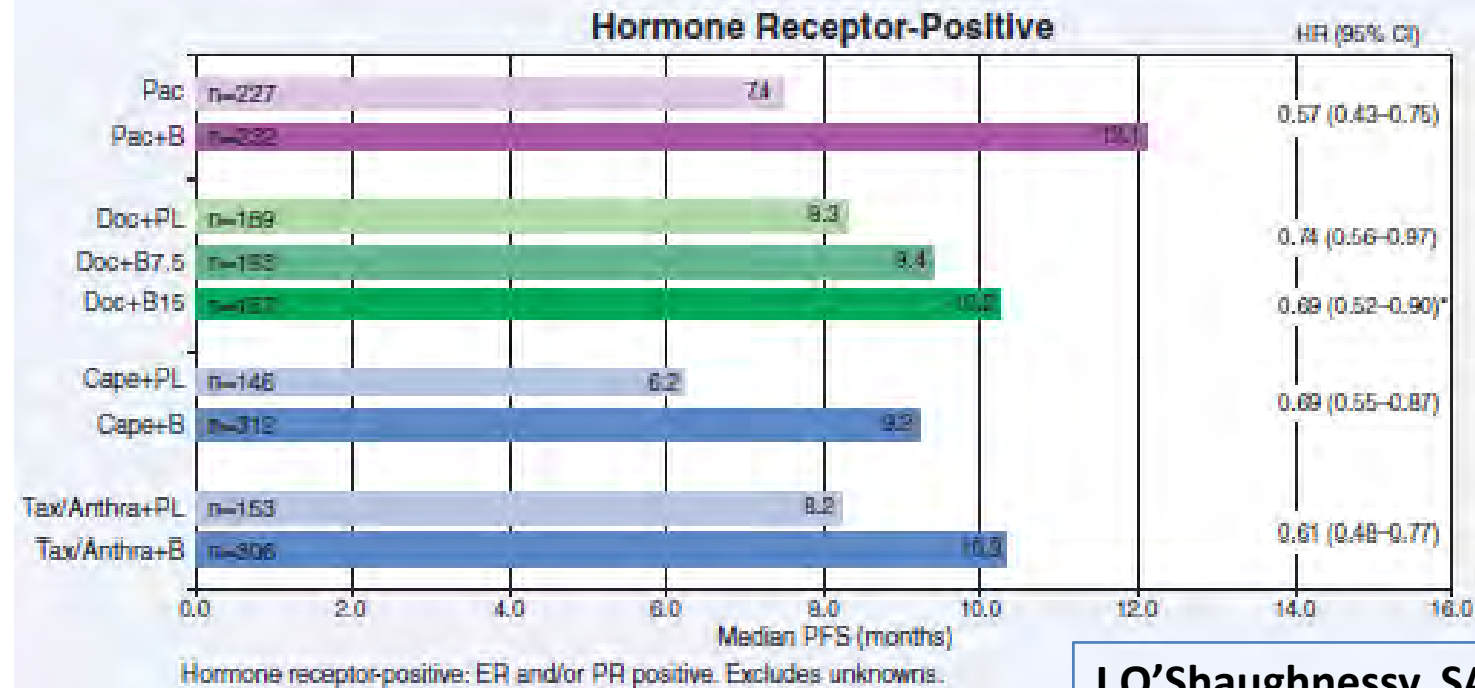
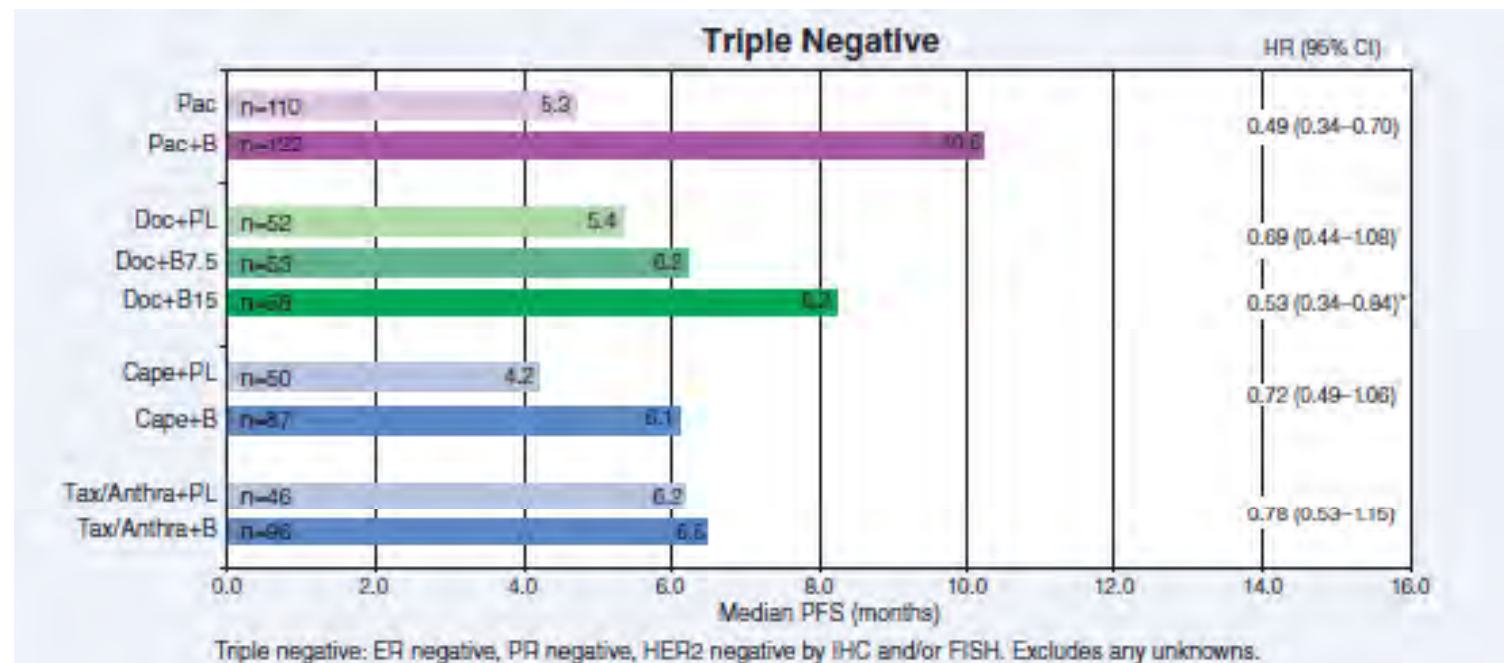
Age

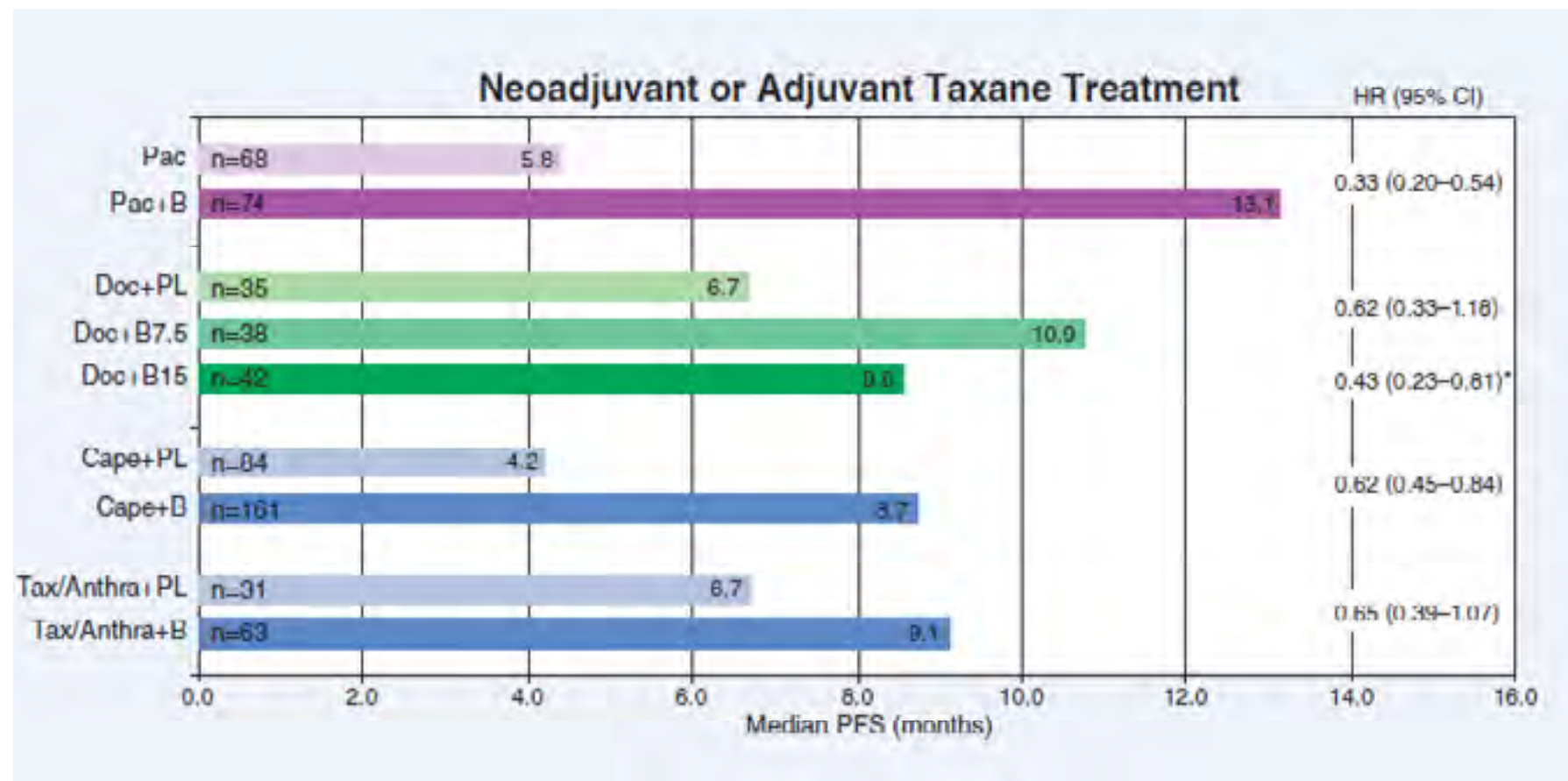
ElderlyPatients



X Pivot, EJC 2011

(Bio)Markers





Biomarkers

- **Imaging**
- **Hypertension**
- **InfiltratingMyeloidCells**
- **CirculatingBiomarkers**
- **Polymorphisms in the VEGF pathway**
- **In situ Biomarkers**

Candidate Biomarkers of Response and Resistance to Antiangiogenic Rx

	Baseline	Dynamic	Escape
Physiologic		Hypertension	
Tumor Tissue	MVD, VEGF, VEGFR2, CD31, PDGFR β	Interstitial fluid pressure, MVD	
Gene Level	VEGF & IL-8 polymorphisms		
Imaging		Vascular MRI parameters (K-trans); FDG-PET	
Circulating	Plasma VEGF, PlGF, VEGFR2, VCAM-1, sICAM1, sVEGFR2	CTCs, Collagen IV	CPCs, SDF1 α , bFGF, IL6

PROGRESS - ON

Adapted from Jain R K et al. (2009) *Nat Rev Clin Oncol*

Table 1. Summary of functional magnetic resonance (MR) imaging techniques, the quantitative parameters derived, and their biological correlates*

Functional imaging technique	Principles of MR measurements	Biological property on which imaging is based	Commonly derived quantitative imaging parameters	Pathophysiological correlates
DCE-MRI (5)	T ₁ -weighted MR imaging at high temporal sampling after gadolinium contrast administration; mathematical modeling of acquired data	Contrast medium uptake rate in tissues, which is influenced by transfer rates and extracellular volume; plasma volume fraction	IAUGC; Transfer and rate constants (K^{trans} , k_{ep}); leakage space fraction (v_p); fractional plasma volume (v_p)	Vessel density; vascular permeability; perfusion; extravascular space; plasma volume
DW-MRI (6,7)	Single-shot echo-planar DW-MRI acquisition; contrast agent not required	Diffusivity of water	ADC	Tissue architecture: cell density, extracellular space tortuosity, gland formation, cell membrane integrity, necrosis
¹ H-MRS (8,9)	Single voxel or three-dimensional chemical shift imaging; metabolite assignment based on proton chemical shift effects	Cell membrane turnover and replacement of normal tissues	Quantified ratios of metabolites including choline, creatine, lipids, citrate, lactate	Tumor grade; proliferation index
BOLD-MRI(10)	T ₂ *-weighted imaging performed at different echo times to detect susceptibility effects	Deoxyhemoglobin shows higher relaxivity than oxyhemoglobin; measurements reflect blood volume, perfusion and intrinsic composition of tissues	Intrinsic tissue relaxation rates ($R_2^* = 1/T_2^*$)	Ferromagnetic properties of tissues; level of tissue oxygenation

*ADC = apparent diffusion coefficient; BOLD-MRI = blood oxygenation level-dependent MRI; DCE-MRI = dynamic contrast-enhanced MRI; DW-MRI = diffusion-weighted MRI; IAUGC = initial area under gadolinium curve; ¹H-MRS = ¹H-MR spectroscopic imaging.

DW - MRI

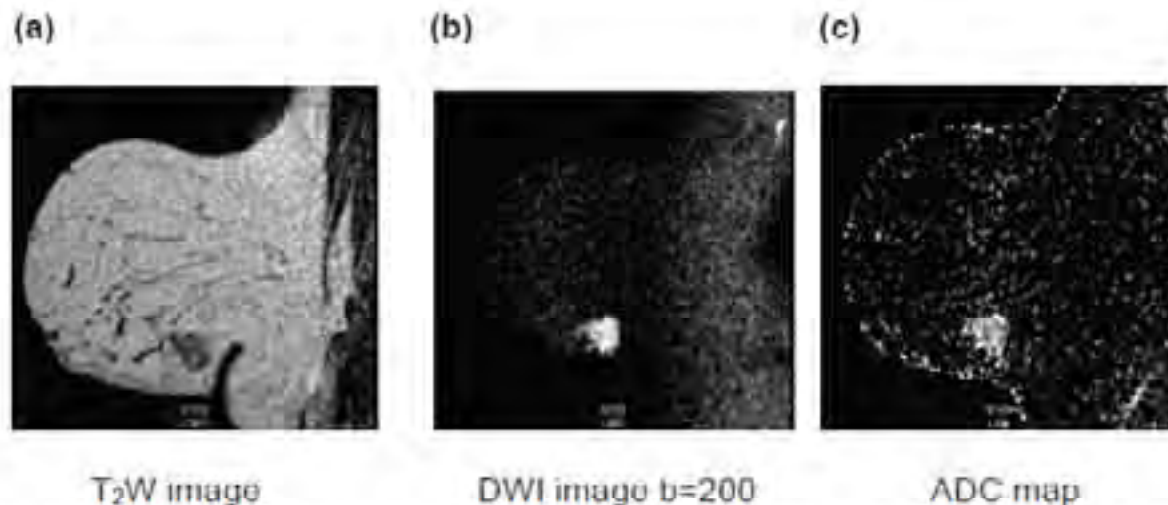
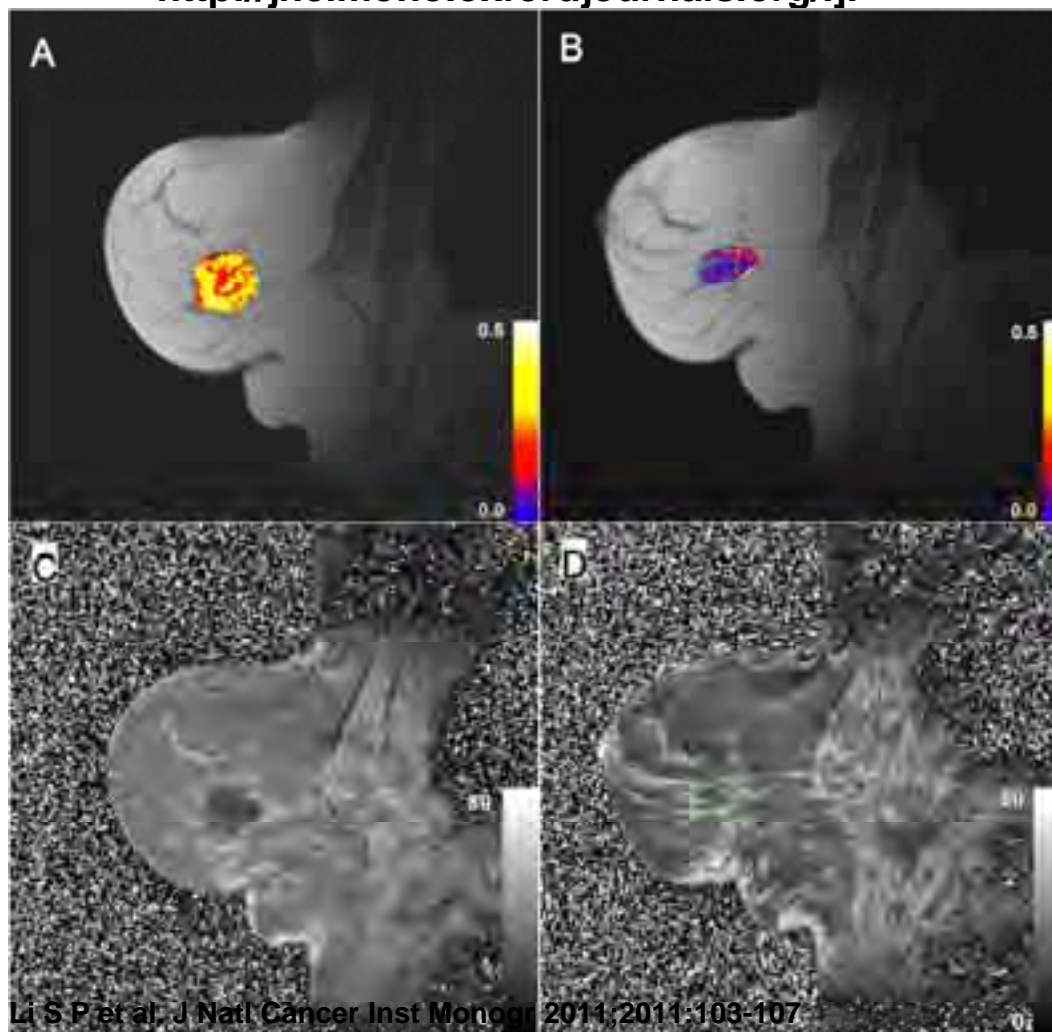


Figure 5. Diffusion weighted images of a breast tumour. (a) Sagittal T₂W image through the breast shows a well-defined lobulated mass inferiorly. (b) This appears as a bright area of restricted diffusion on the corresponding diffusion weighted MRI (DW-MRI) image (b = 200). (c) The calculated apparent diffusion coefficient (ADC) map shows the heterogeneity of diffusion coefficient values within the tumour.

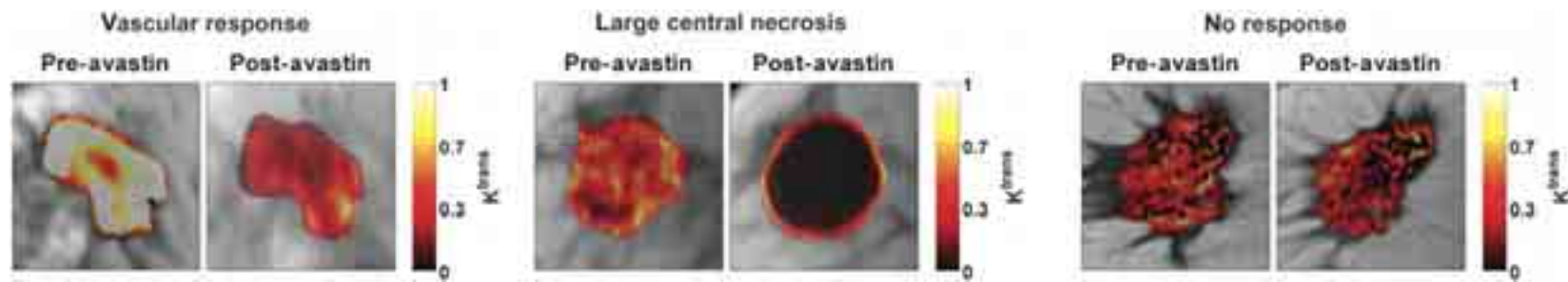
Representative magnetic resonance images (MRI) of a grade 3 invasive ductal breast carcinoma (T2N1M0) with regions of interest outlined: A) Ktrans (min⁻¹) before and B) after 2 cycles of neoadjuvant chemotherapy and on bold oxygenation level-dependent MRI, corresponding R2* (s⁻¹) images C) before and D) after 2 cycles of neoadjuvant chemotherapy on blood oxygenation level-dependent MRI. [For color image please see <http://jncimono.oxfordjournals.org/>].



Before and
After 2
cycles of
NACT

Li S P et al. J Natl Cancer Inst Monogr 2011;2011:103-107

DCE-MRI images of representative patients showing three patterns of response to bevacizumab. [For color image please see <http://jncimono.oxfordjournals.org/>].



**Before and after 1
cycle of Bevacizumab**

Mehta S et al. J Natl Cancer Inst Monogr 2011;2011:71-74

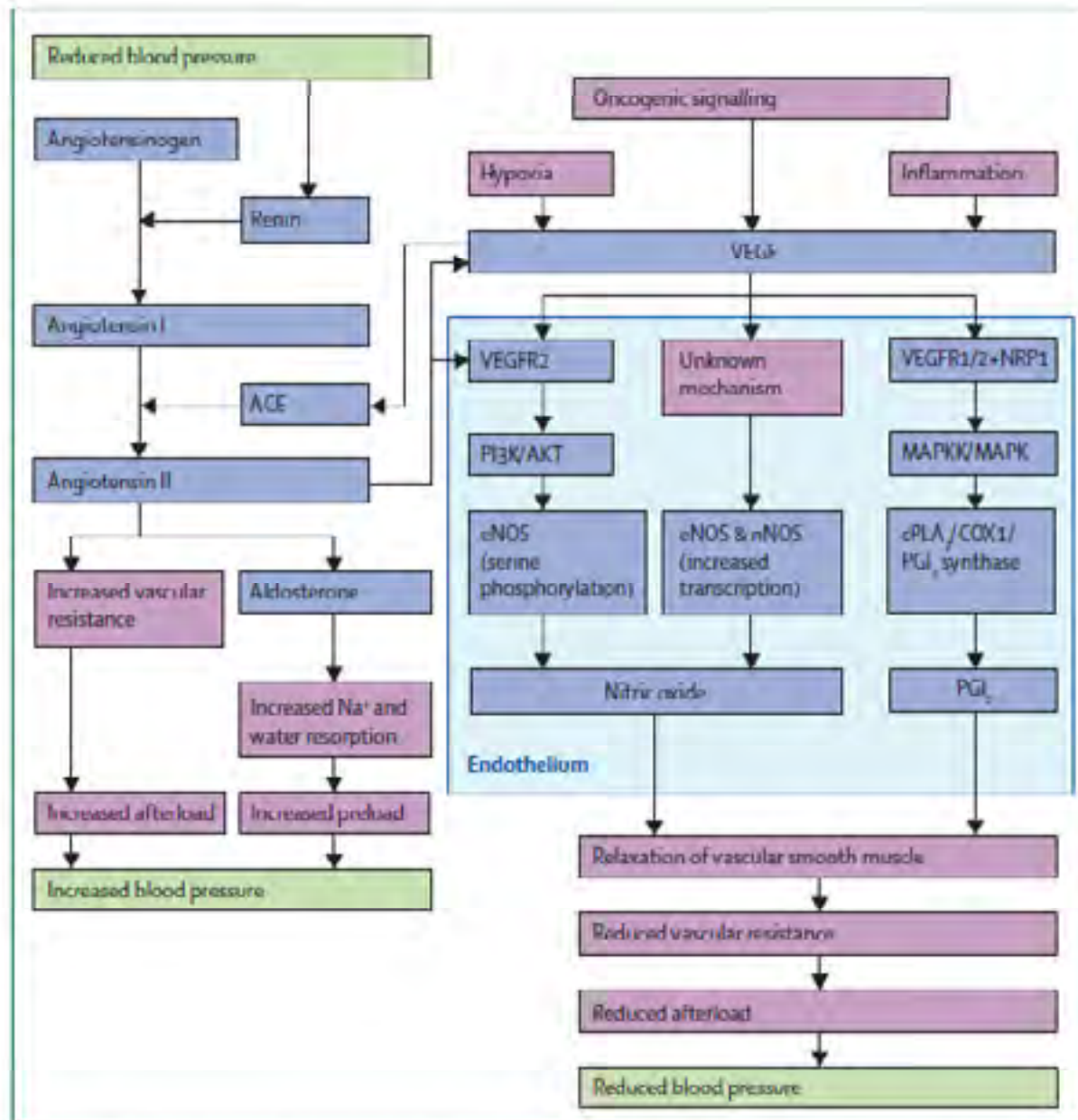
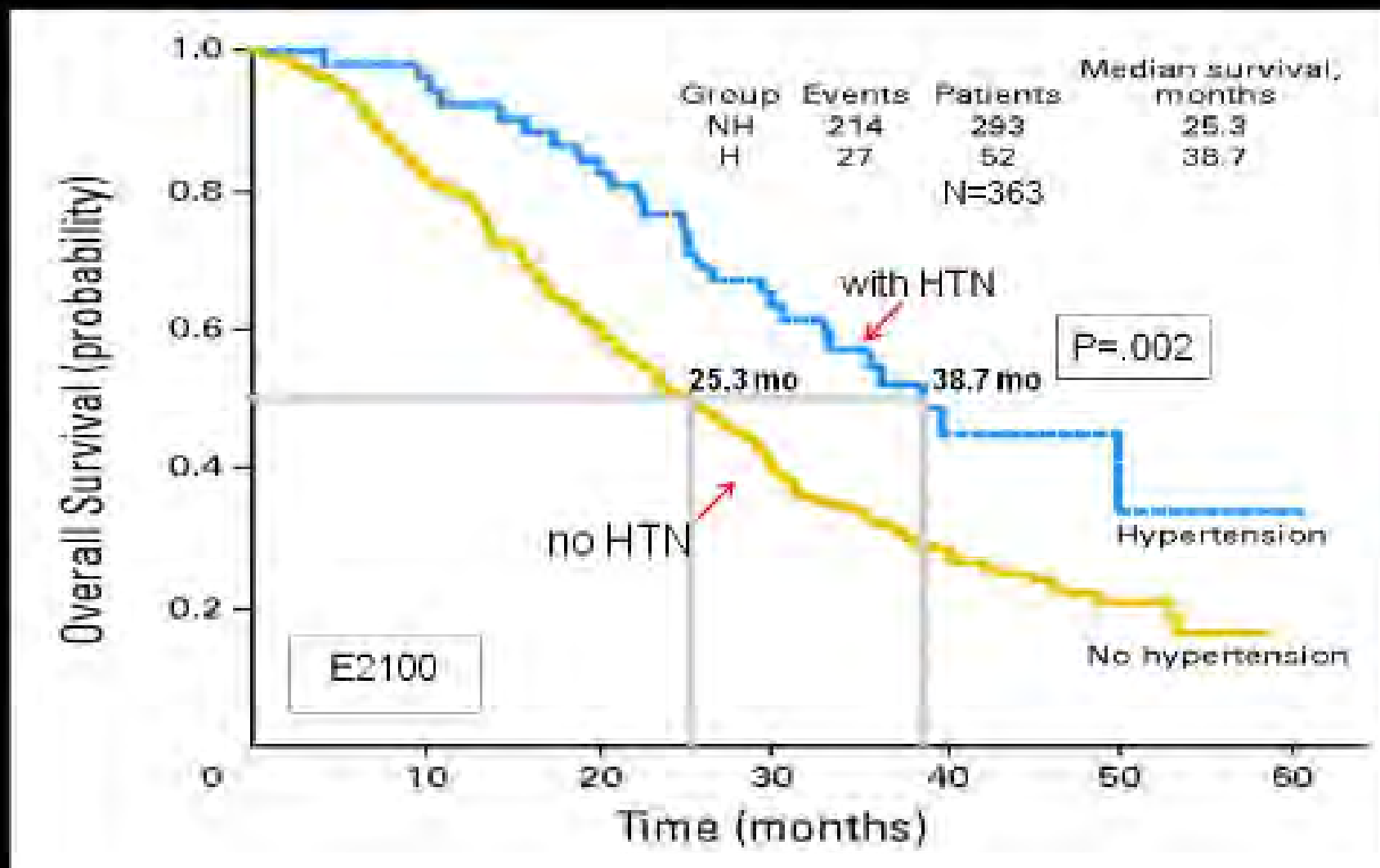


Figure 2: Biochemical and physiological pathways linking VEGF signalling with blood pressure homeostasis

In E2100, ↑ OS for Bev Pts With Grade 3/4 HTN



Schneider, B. P. et al. J Clin Oncol; 26:4672-4678 2008

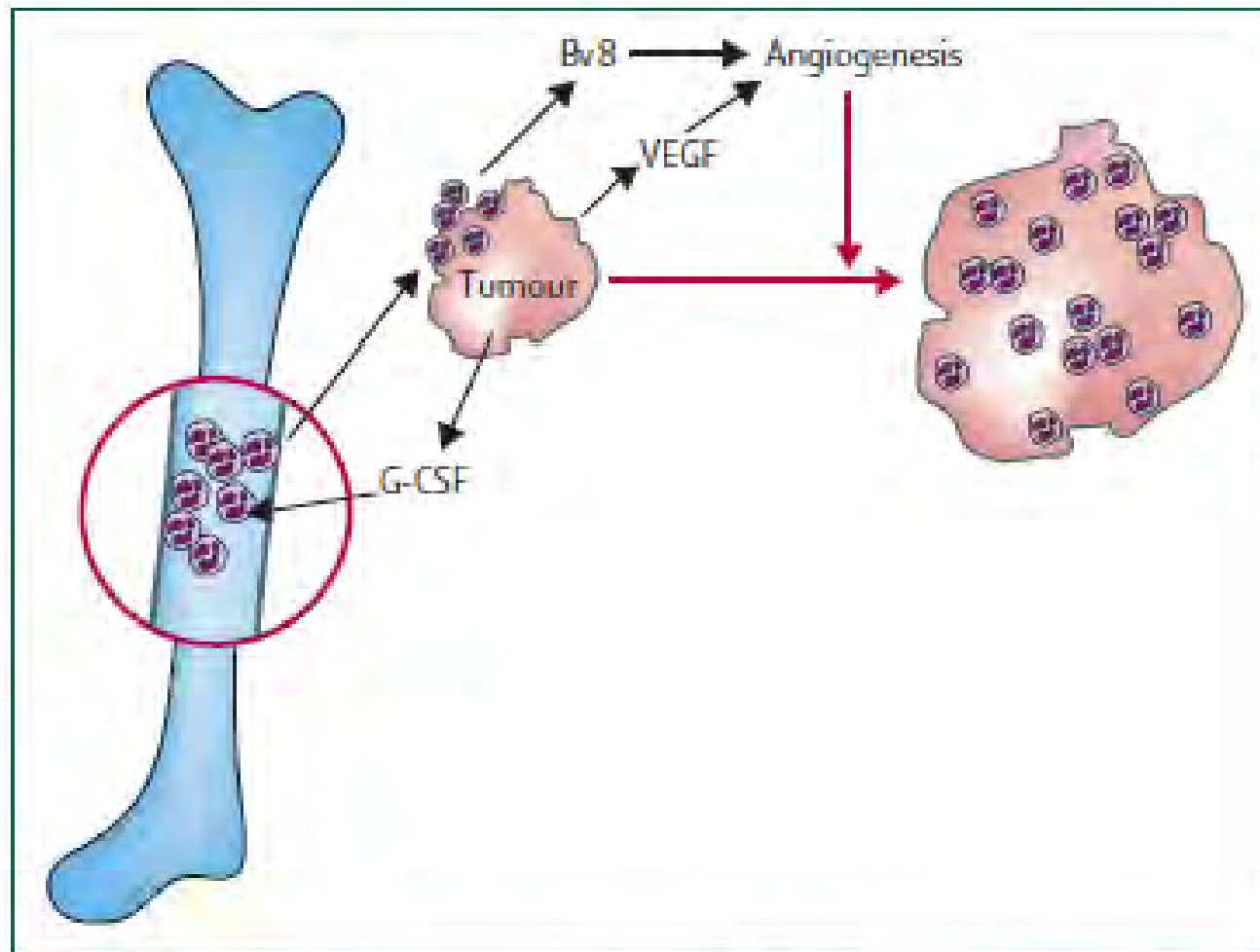
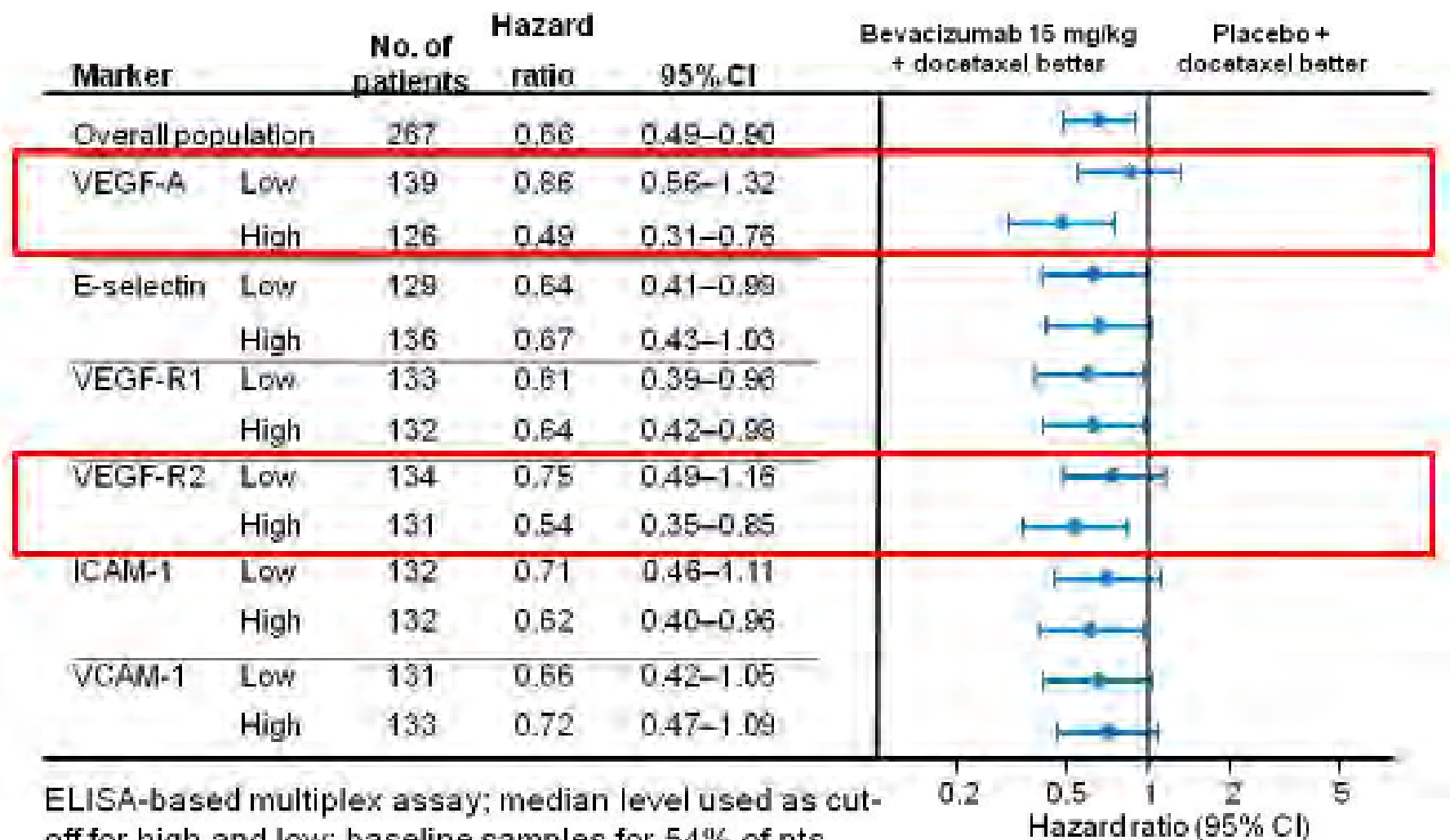


Figure 3: Simplified putative mechanism of action for myeloid cell mediated resistance to antiVEGF therapy

↑ Baseline Plasma VEGF-A & VEGFR2 *May* Predict Benefit in AVADO



DW Miles et al., SABCS 2010

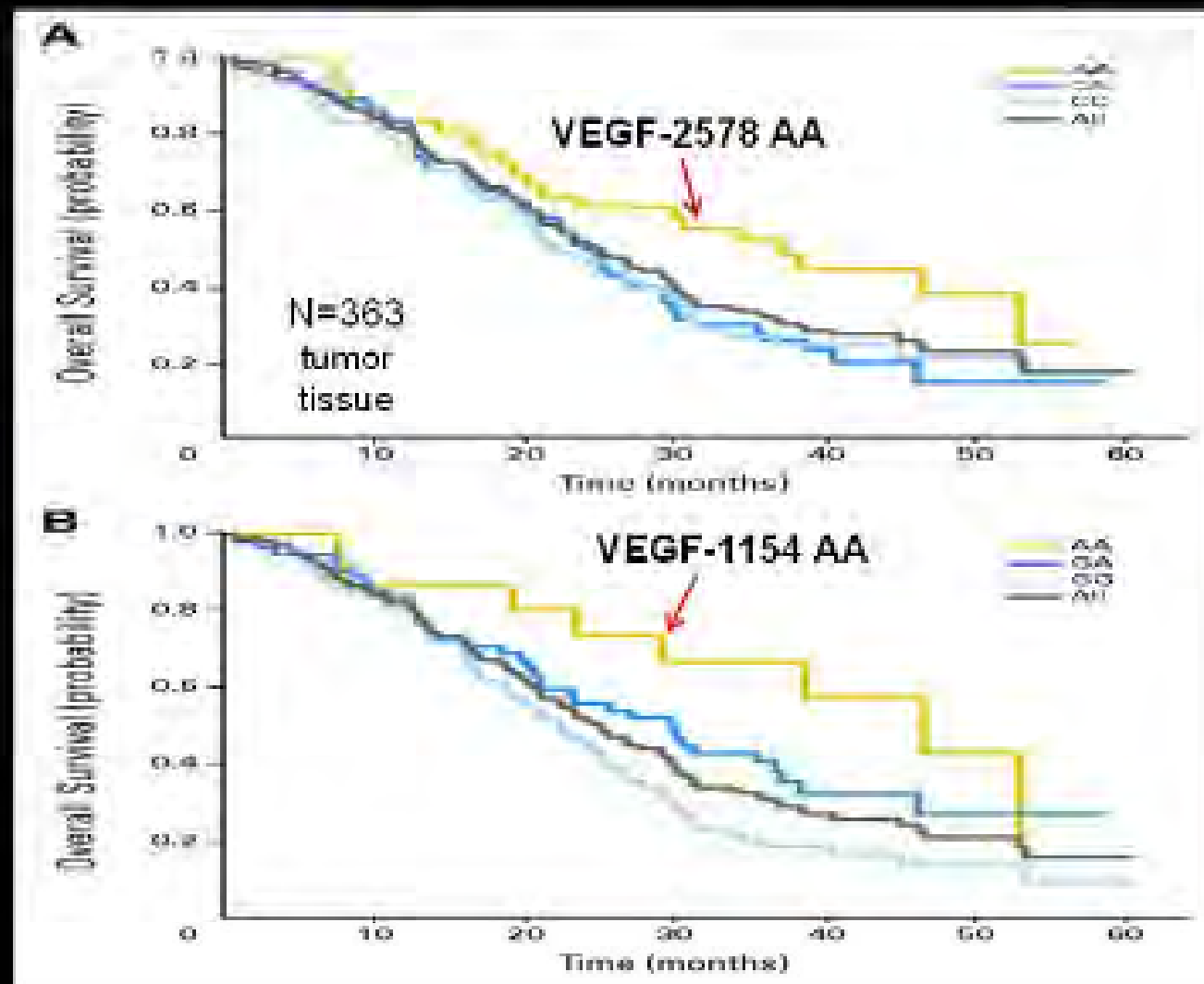
In E2100 Bev Arm, Improved Survival by Genotype

AA Genotype at VEGF-2578 and -1154 Confers OS Advantage

VEGF-2578

E2100

VEGF-1154



	Setting	Trial	Markers	Concentration changed with therapy	Positive associations with clinical endpoints
Baar et al ¹⁵	Neoadjuvant locally advanced breast carcinoma	Randomised, phase 2	MVD	None	NR
Cohen et al ¹⁶	Previously treated metastatic squamous cell carcinoma of the head and neck	Single arm, phase 1/2 (including erlotinib)	Phosphorylated AKT, AKT, phosphorylated EGFR, EGFR, phosphorylated MAPK, MAPK, phosphorylated VEGFR2* and VEGFR2*	NR	Tumour cell phosphorylated VEGFR2/VEGFR2* and phosphorylated EGFR/EGFR associated with response
Foerzler et al ^{17†}	First-line metastatic colorectal cancer	Phase 3 (NO16966)	VEGF-A, VEGFR2†, VEGFR1, HER2, EGFR, and NRP1	NR	Not predictive of PFS benefit
Ince et al ¹⁸	First-line metastatic colorectal cancer	Phase 3 (AVF2107g)	P53	NR	No association with OS benefit
Jubb et al ¹⁹	First line metastatic colorectal cancer	Phase 3 (AVF2107g)	VEGF, MVD, and THBS2	NR	No association with OS benefit
Sathornsumetee et al ²⁰	Malignant astrocytoma	Single arm, phase 2	VEGF, CD31, VEGFR2, CA9, and HIF2α	NR	CA9 associated with OS
Schneider et al ²¹	First-line advanced breast carcinoma	Phase 3 (E2100)	VEGF and VEGFR2	NR	Outcomes not defined
Wedam et al ²²	Neoadjuvant locally advanced and inflammatory breast carcinoma	Single arm, phase 2	VEGF, MVD, antigen Ki67, phosphorylated VEGFR2*, VEGFR2*, and TUNEL assay	Ki67, phosphorylated VEGFR2*, VEGFR2*, and TUNEL	VEGF associated with response
Willett et al ²³	Neoadjuvant rectal cancer	Single arm, phase 1/2 (NC15642)	MVD and vascular maturation	MVD and vascular maturation	NR
Xu et al ²⁴	Neoadjuvant rectal cancer	Single arm, phase 1/2 (NC15642)	SDF1α, CXCR4, CXCL6, DLL4, GM-CSF, ANG1, ANG2, HIF1α, PIGF, NRP1, CXCL5, IL8, bFGF, TGF-β-1, TNFAIP2, MIF, NRP2, VEGF, VEGFR1, VEGFR2*, VEGFC, and VEGFR3	SDF1α, and CXCR4	NR
Yang et al ²⁵	Neoadjuvant locally advanced and inflammatory breast carcinoma	Single arm, phase 2	CD31, PDGFRβ, VEGF, phosphorylated VEGFR2*, MVD, antigen Ki67, TUNEL, ER, HER2, and P53	CD31	CD31, PDGFRβ, and VEGF associated with response

Adherence to REMARK criteria could not be assessed in all cited articles. MVD=diphosphomevalonate decarboxylase. NR=not reported. AKT=Ser-Thr protein-kinase B. EGFR=endothelial growth factor receptor. MAPK=mitogen-activated protein kinase. VEGFR=vascular endothelial growth factor receptor. HER2=receptor tyrosine-protein kinase erbB-2. NRP1=neuropilin-1. P53=cellular tumour antigen p53. VEGF=vascular endothelial growth factor. THBS2=thrombospondin-2. CA9=carbonic anhydrase 9. HIF=hypoxia-inducible factor. TUNEL=terminal deoxynucleotidyl transferase dUTP nick end labelling. SDF-1α=stromal-cell-derived factor 1α. CXCR4=chemokine receptor 4. CXCL6=chemokine ligand 6. DLL4=δ-like protein 4. GM-CSF=granulocyte-macrophage-colony-stimulating factor. ANG=angiopoietin. PIGF=phosphatidylinositol-glycan biosynthesis class F protein. IL8=interleukin 8. bFGF=basic fibroblast growth factor. TGF-β-1=transforming growth factor β-1. MIF=macrophage migration inhibitory factor. VEGFC=vascular endothelial growth factor C. PDGFRβ=platelet-derived growth factor receptor β. ER=oestrogen receptor. REMARK=REporting recommendations for tumour MARKer prognostic studies.

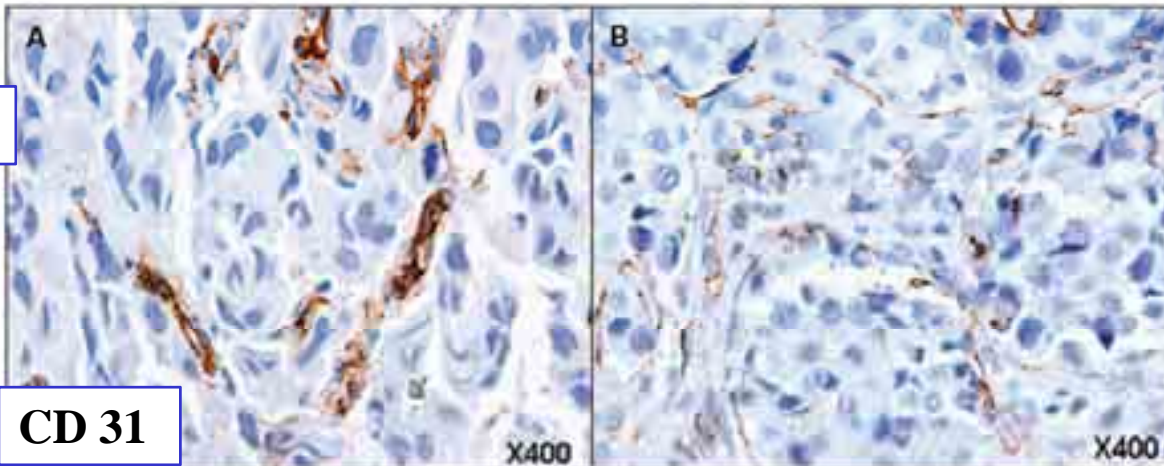
*The specificity of VEGFR2 antibodies has been called into question. †Presented in abstract form only.

Table 3: Clinical trials assessing in-situ biomarkers in relation to the activity or efficacy of bevacizumab

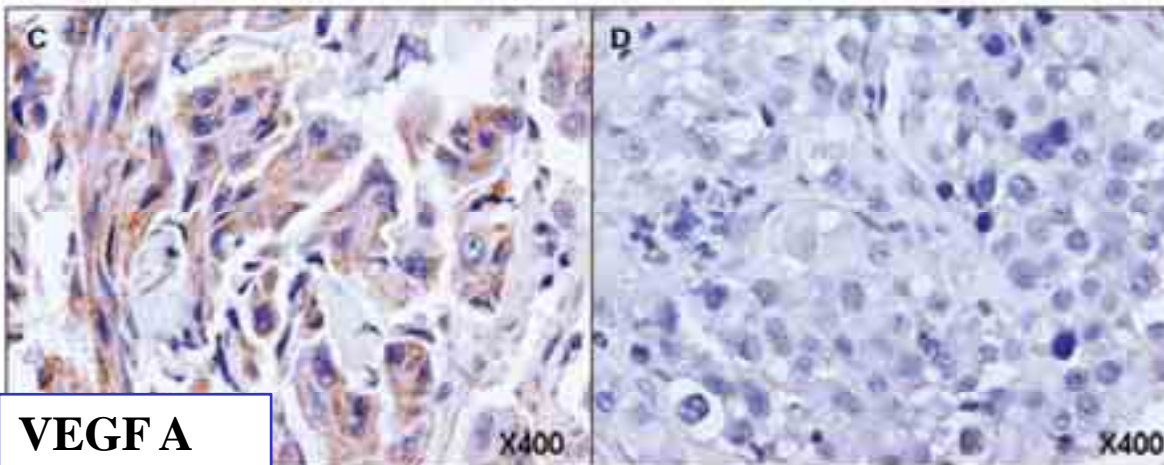
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SD

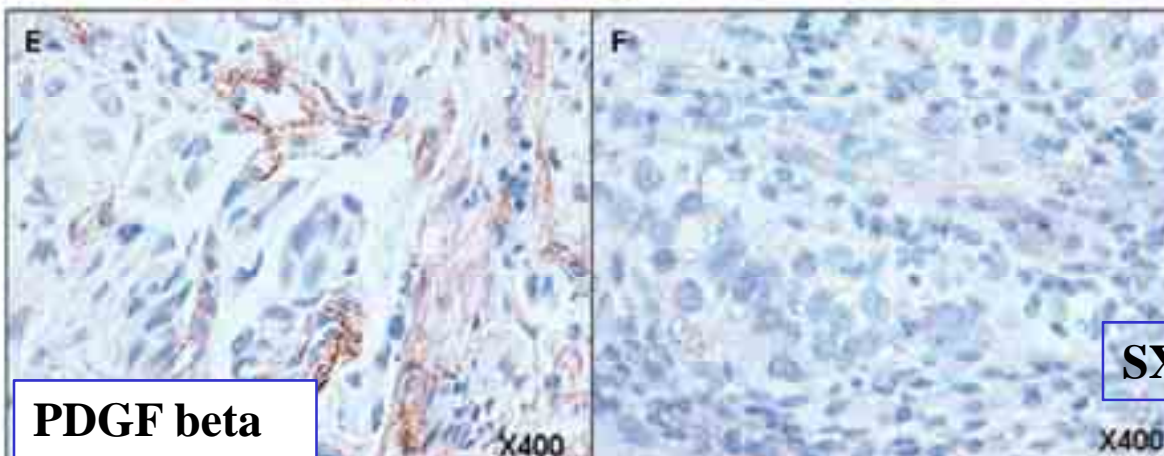
CD 31



VEGF A



PDGF beta



SX Yang, CCR 2008

Gene Ontology

Table 2. GO categories which discriminate the responders from nonresponders

GO category	GO term	GO description	No. of genes*	Average log permutation <i>P</i>	Kolmogorov-Smirnov permutation <i>P</i>
0005581	CC	Collagen	25	1e-05	0.0001194
0044420	CC	Extracellular matrix part	47	1e-05	9.66e-05
0006817	BP	Phosphate transport	39	0.0003932	0.0016308
0005201	MF	Extracellular matrix structural constituent	39	0.0006586	1e-05
0030934	CC	Anchoring collagen	5	0.0009974	0.0078597
0015698	BP	Inorganic anion transport	50	0.0010409	0.0044008
0005819	CC	Spindle	11	0.0014625	0.0074051
0006820	BP	Anion transport	60	0.0015095	0.0098402
0005021	MF	VEGFR activity	5	0.0017757	0.0183713
0005001	MF	Transmembrane receptor protein tyrosine phosphatase activity	9	0.001975	0.0776652
0019198	MF	Transmembrane receptor protein phosphatase activity	9	0.001975	0.0776652
0007185	MF	Transmembrane receptor protein tyrosine phosphatase signaling pathway	5	0.0025524	0.1774075
0031072	MF	Heat shock protein binding	18	0.0025617	0.0271924
0007167	BP	Enzyme linked receptor protein signaling pathway	54	0.0033393	0.1507051
0015662	MF	ATPase activity, coupled to transmembrane movement of ions, phosphorylative mechanism	11	0.003359	0.0396246
0050767	BP	Regulation of neurogenesis	6	0.003614	0.0041765
0005813	CC	Centrosome	15	0.0046869	0.0427838
0051094	BP	Positive regulation of development	6	0.0060322	0.0041765
0030693	MF	Caspase activity	8	0.0066096	0.001746
0042623	MF	ATPase activity, coupled	74	0.0239713	0.0031284
0006928	BP	Cell motility	80	0.0376735	0.0048878
0040011	BP	Locomotion	80	0.0376735	0.0048878
0051674	BP	Localization of cell	80	0.0376735	0.0048878
0016887	MF	ATPase activity	84	0.0419617	0.0036955
0007389	BP	Pattern specification	6	0.1218883	0.0033214
0000226	BP	Microtubule cytoskeleton organization and biogenesis	14	0.1229871	0.0011392

Abbreviations: CC, cellular component; MF, molecular function; BP, biological process.

*All the genes from the 26 GO categories are listed in Supplementary Table S1.

Cost

Annual direct costs for cancer care are projected to rise — from \$104 billion in 2006¹ to over \$173 billion in 2020 and beyond.² This increase has been driven by a dramatic rise in both the cost of therapy³ and the extent of care.⁴ In the United States, the sales of anticancer drugs are now second only to those of drugs for heart disease, and 70% of these sales come from products introduced in the past 10 years. Most new molecules are priced at \$5,000 per month or more,⁵ and in many cases the cost-effectiveness ratios far exceed commonly accepted thresholds.⁶ This trend is not sustainable.^{7,8}

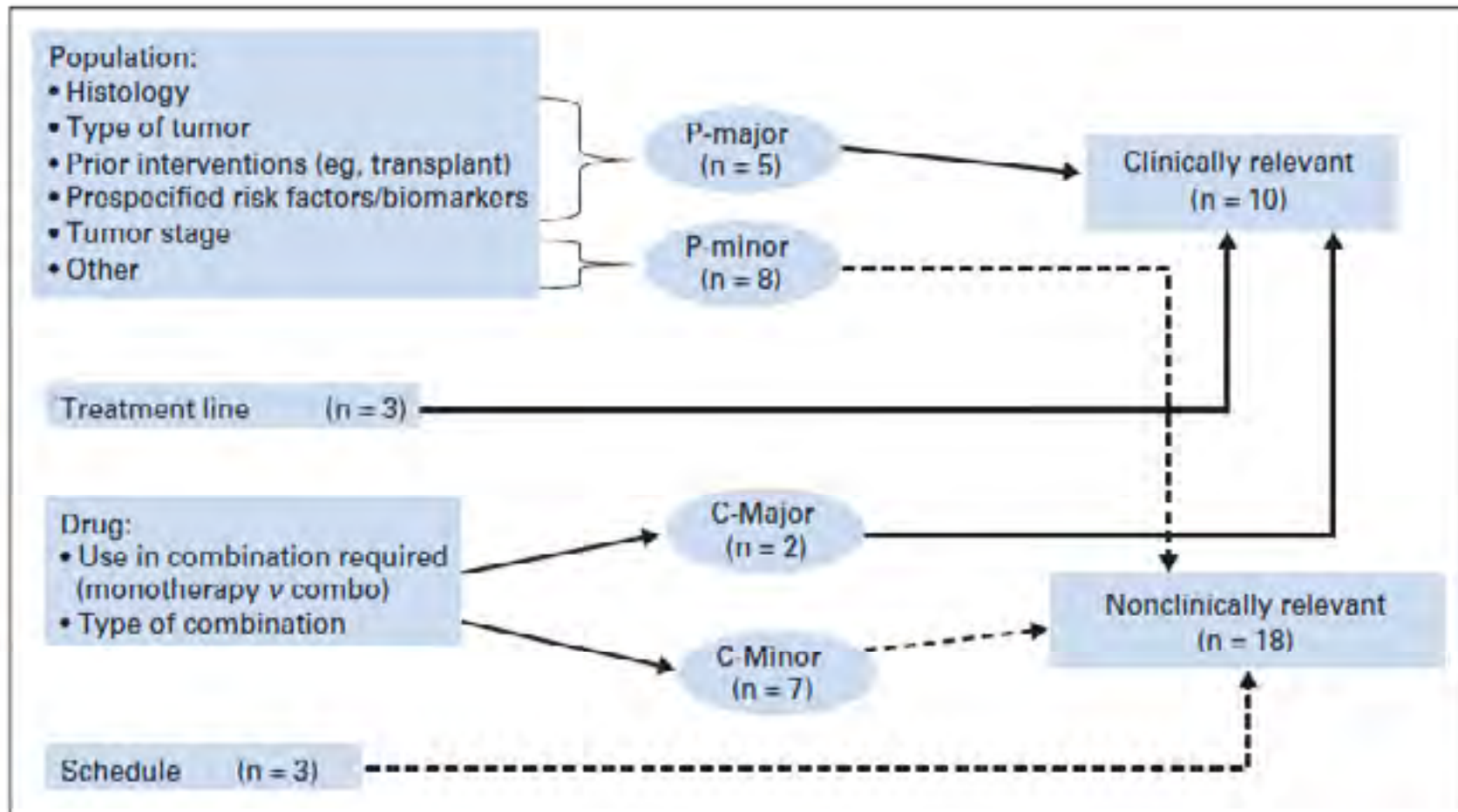
We must find ways to reduce the costs of everyday care to allow more people and advances to be covered without bankrupting the health care system.

TJ Smith, & BE Hillner, NEJM 2011

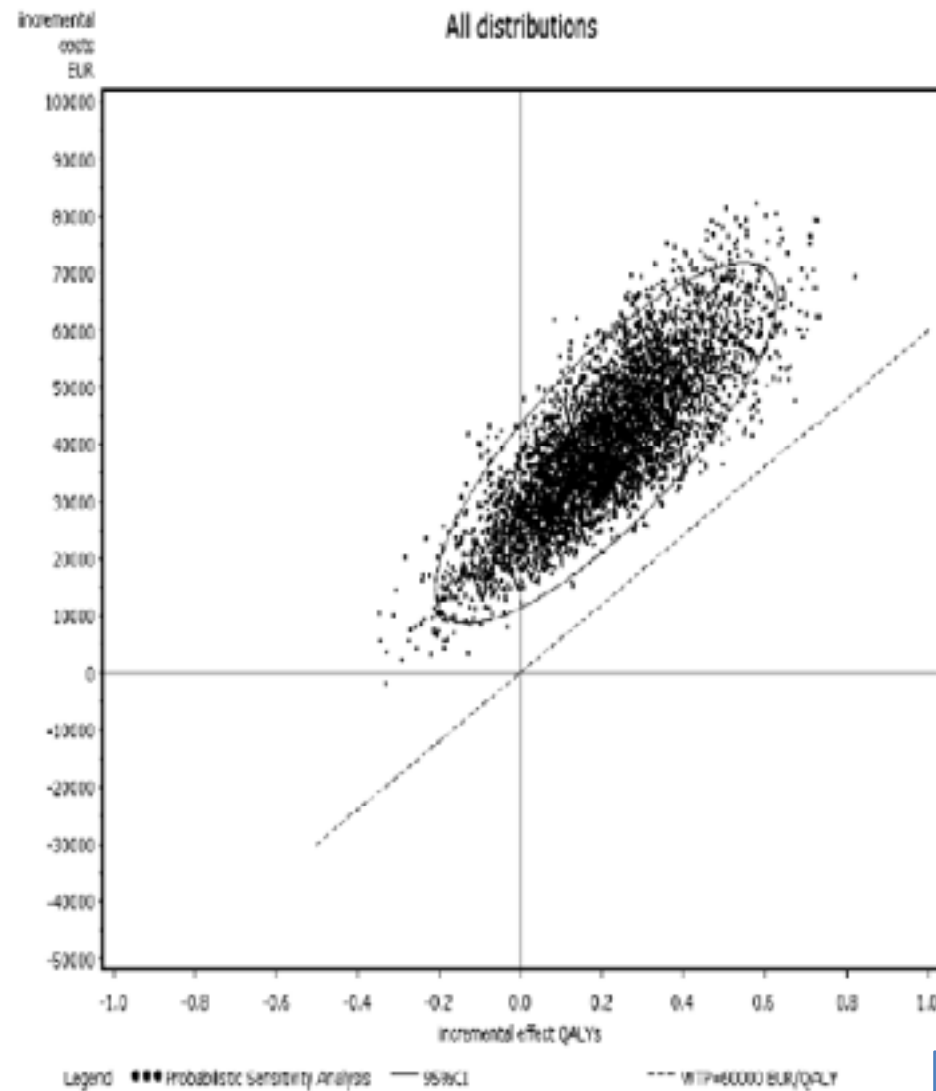
On the Regulatory Front in MBC

- In 2007, ODAC voted 5:4 against Bev approval
- FDA opted to grant accelerated approval - contingent upon data from ongoing RCTs:
 - Confirmation of the magnitude of the PFS benefit
 - No evidence of detrimental effect on OS
- 2 RCTs + meta-analysis subsequently reported:
 - Less robust PFS benefit
 - No improvement in OS
- In July, 2010, ODAC voted 12:1 to recommend withdrawal of Bev label → process initiated by FDA
- EMA has limited use of Bev to combo with paclitaxel or capecitabine (when use of A or T not appropriate)
- Await hearing granted to sponsor for June 28-29, 2011

FDA vs EMA

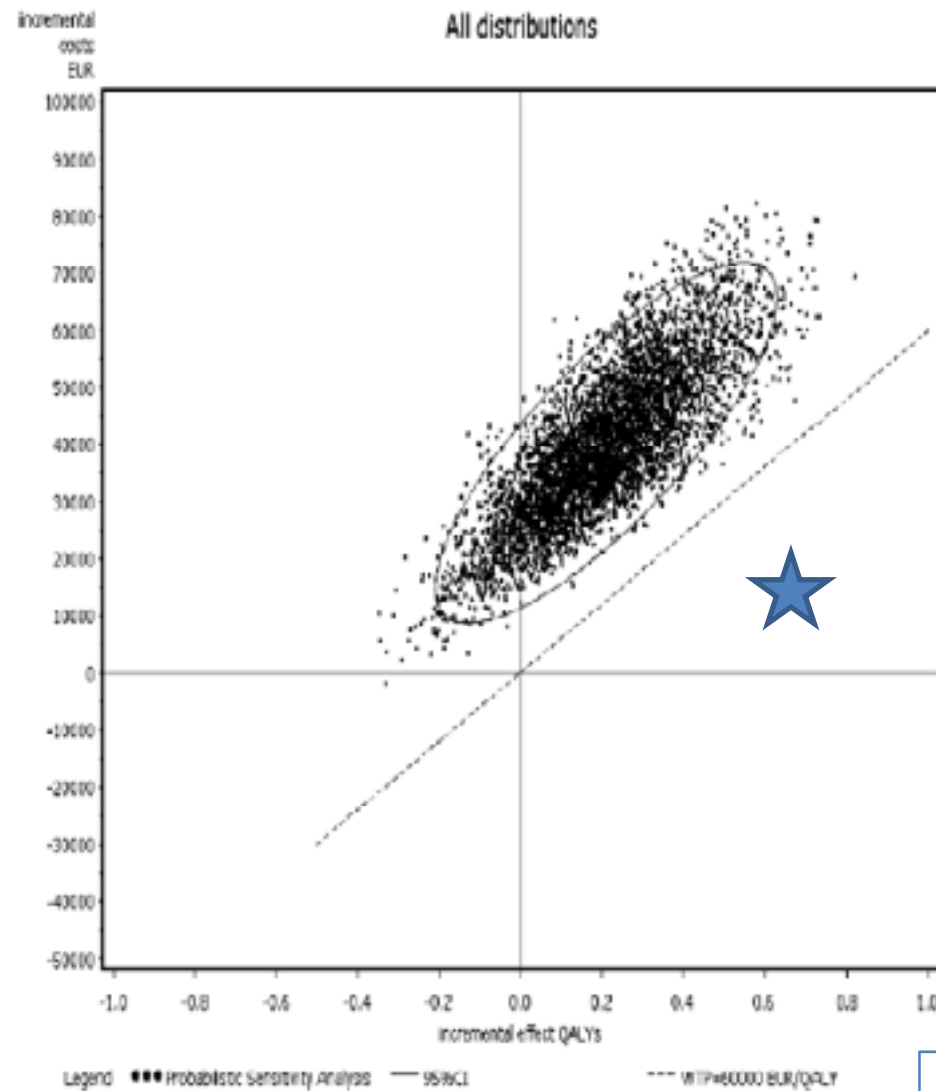


Cost-Effectiveness

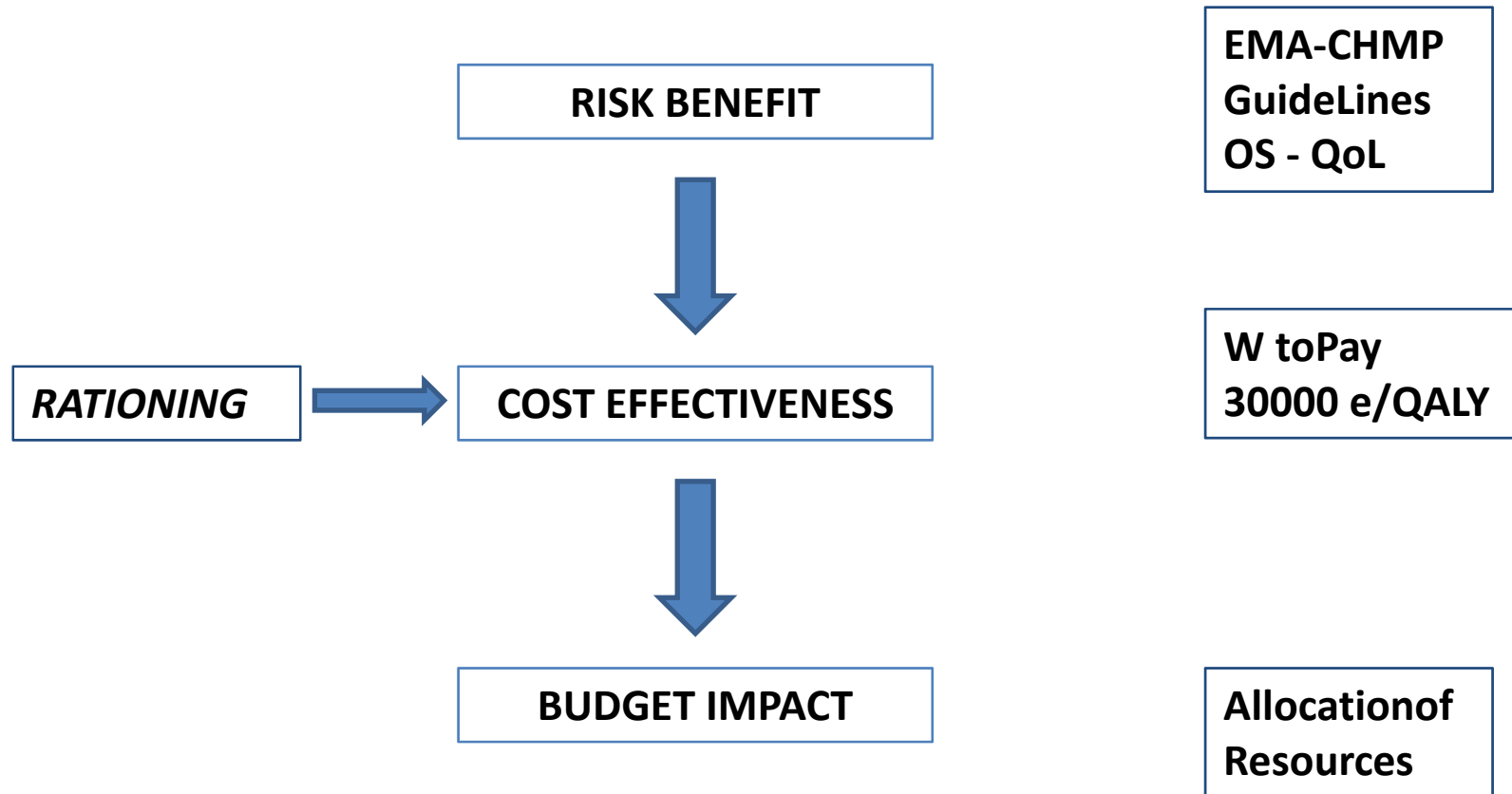


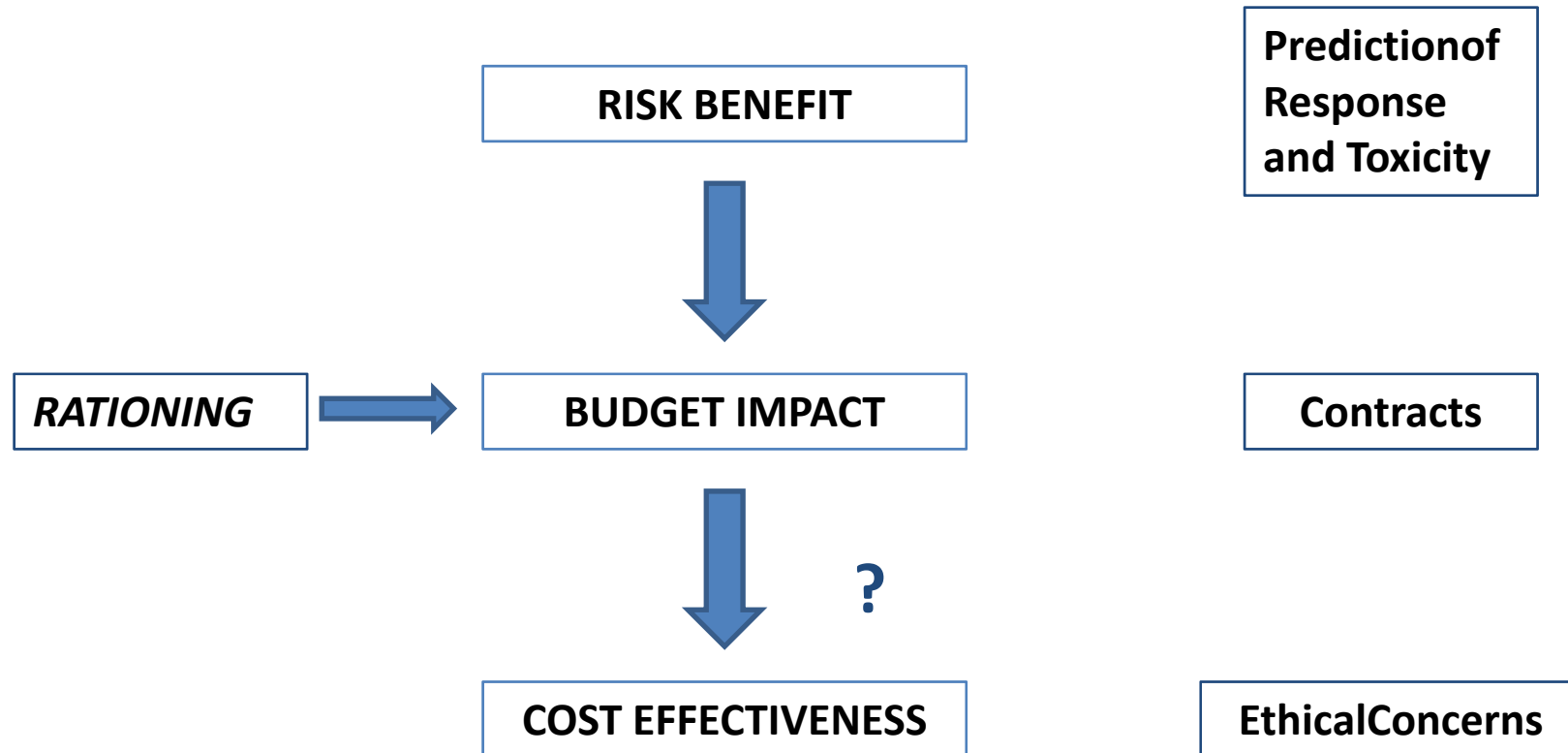
KJ Dedes, EJC 2009

Cost-Effectiveness



KJ Dedes, EJC 2009





Breast: PFS as a surrogate for OS

Burzykowski et al JCO 2008

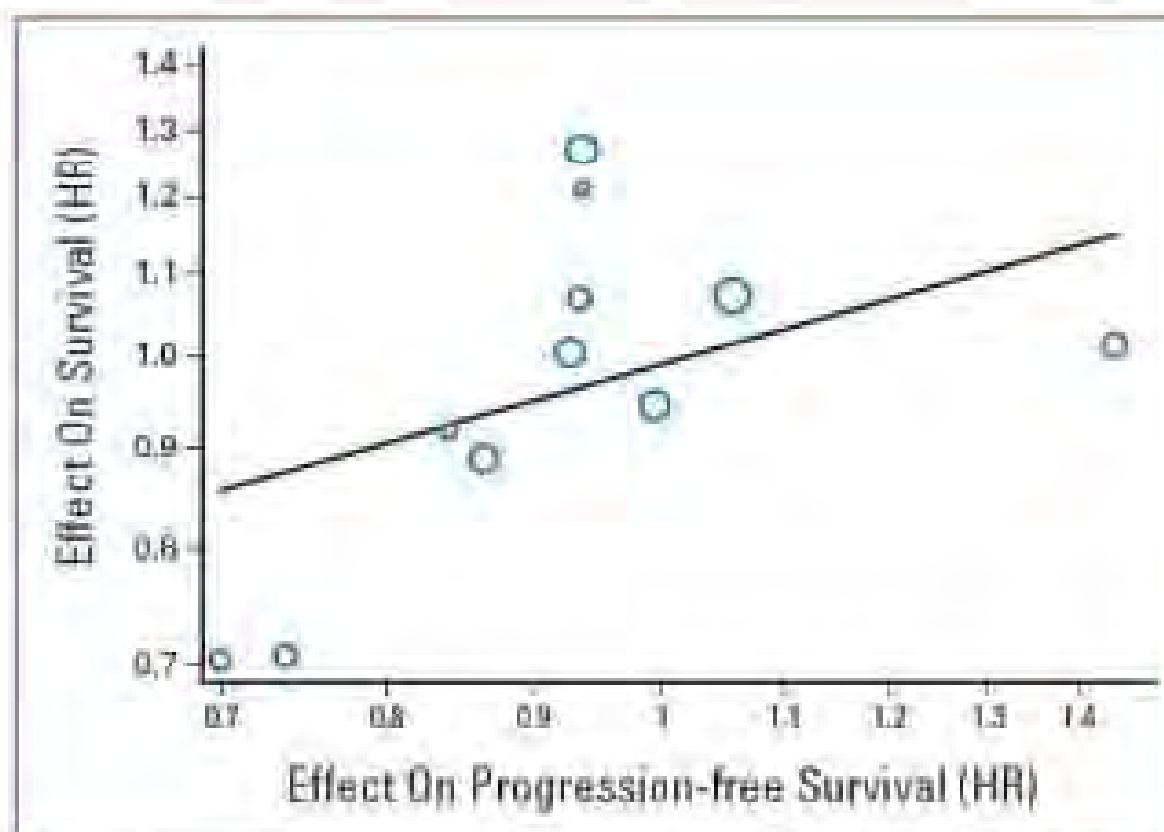
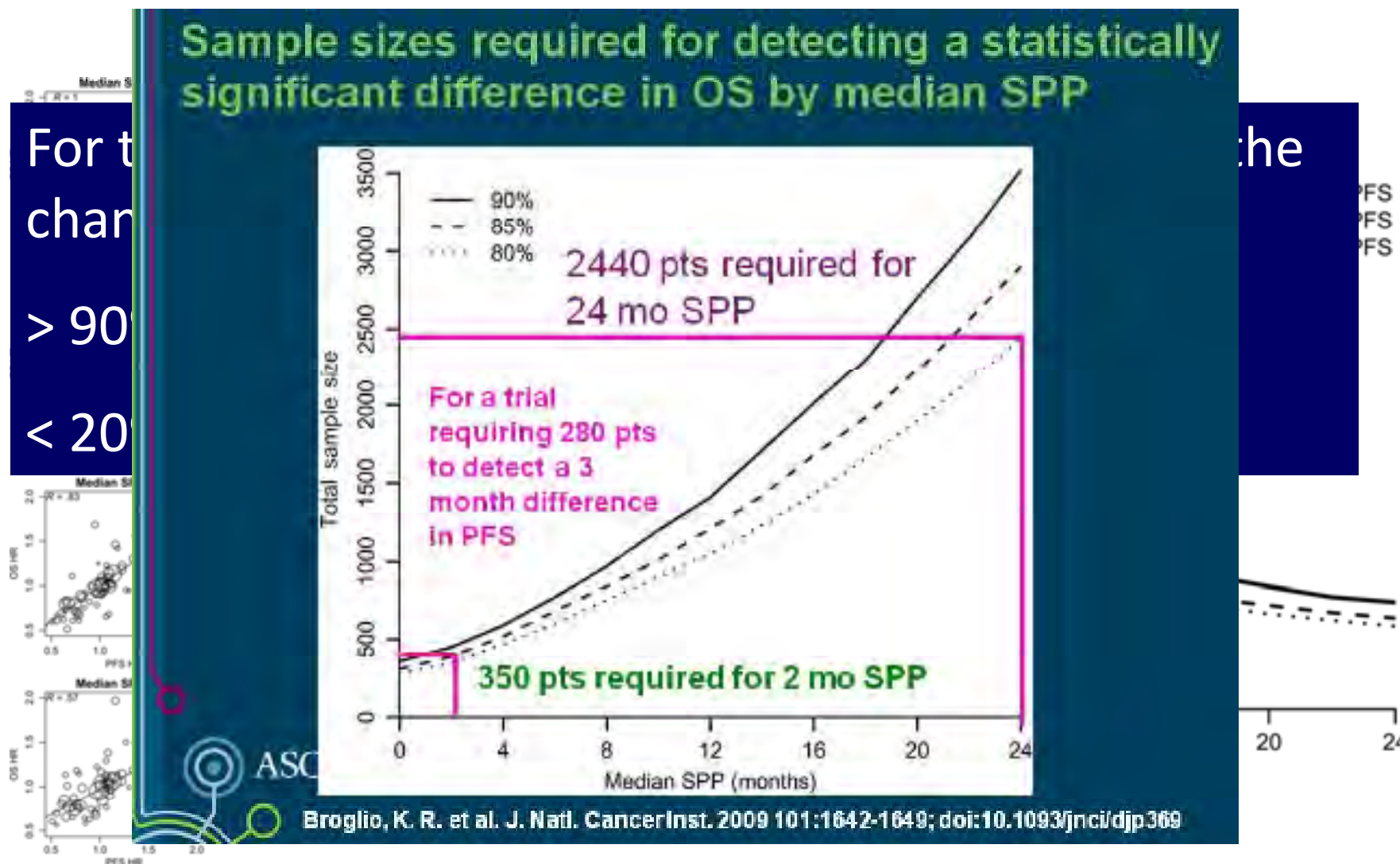


Fig 3. Correlation between treatment effects on progression-free survival and on survival. Each circle represents a trial, and the surface area of the circle is proportional to the size of the corresponding trial. HR: hazard ratio; OR, odds ratio.

Probability of statistically significant differences in overall survival (OS) as a function of median survival postprogression (SPP)

For t
chan
> 90
< 20



Is PFS a Clinical Benefit Endpoint?

Opinion: Pro

- **"I have no problem accepting that, in a lethal disease such as metastatic cancer, delaying progression is a clinical benefit in itself, provided that the magnitude of the benefit is sufficient and the side-effect profile acceptable."**

R Pazdur, NCI Cancer Bulletin May 13, 2008

http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051308/page7

Conclusions

Patient Profiling

- 45 years old
- 2006: FEC → D + Tam (pT2N1 G2 HER2- HR+)
- 2.2011: Symptomatic Bone and Liver Mts
- 11.2011. In Response (Objective and Symptomatic) with Paclitaxel and Bevacizumab

Conclusions

- **Neo-Angiogenesis is obviously important also in Breast Cancer**
- **Addition of Bevacizumab to CT results in a clear advantage in RR and PFS**
- **The advantage may be clinically very relevant in some situations (ie TNBC)**
- **Toxicity is manageable**
- **Age and other factors are little relevant**
- **Cost issues should be scientifically faced**

The debate that rages around antiangiogenic therapy for breast cancer will likely continue for the next few years as additional data from the adjuvant setting comes forth. There are many patients and physicians who are frustrated by the likely loss of a class of drugs with clear benefit for some patients. While the correct bar for success is unclear in an unselected population, the identification of the proper patients, tumors, or clinical settings has the potential to eradicate this ambiguity. While the road to successfully identifying these subgroups is long and winding, we are obligated to approach biomarkers with the same meticulous methodology, enthusiasm, effort, and resources that we do for drug development itself.