

Anti-angiogenic therapy in breast cancer: First results



Nadia Harbeck

Frauenklinik der

Technischen Universität München



Frauenklinik und Poliklinik der
Technischen Universität München
Klinikum rechts der Isar
Direktorin: Prof. Dr. M. Kiechle



VEGF is an independent prognostic factor in invasive breast cancer

Table 7
Prognostic value of determination of VEGF in human invasive breast cancer, published studies^a

Author	Number of patients	Nodal status	Method	Univariate analysis		Multivariate analysis	
				RFS	OS	RFS	OS
Toi [135]	103	N- /N+	ICA	<0.01	ND	0.039	ND
Toi [140]	230	N- /N+	ICA	0.01	ND	NS	ND
Obermaier [141]	89	N- /N+	IMA	NS	ND	ND	ND
Gasparini [137]	260	N-	IMA	<0.001	<0.001	<0.001	<0.001
Relf [142]	64	N- /N+	Rnase	0.03	ND	ND	ND
Eppenberger [143]	305	N- /N+	ICMA	<0.001	ND	0.01	ND
	190	N-	ICMA	0.02	ND	0.04	ND
Linderholm [144]	525	N-	ELISA	ND	0.001	ND	0.03
Gasparini [139]	353	N+	IMA	<0.01	0.05	<0.05	<0.05
Linderholm [145]	362	N+	ELISA	ND	<0.0001	ND	<0.05
Linderholm [146]	302	N-	ELISA	<0.01	<0.01	<0.01	<0.01
Corradini [147]	212	N-	ELISA	0.06	ND	0.07	ND

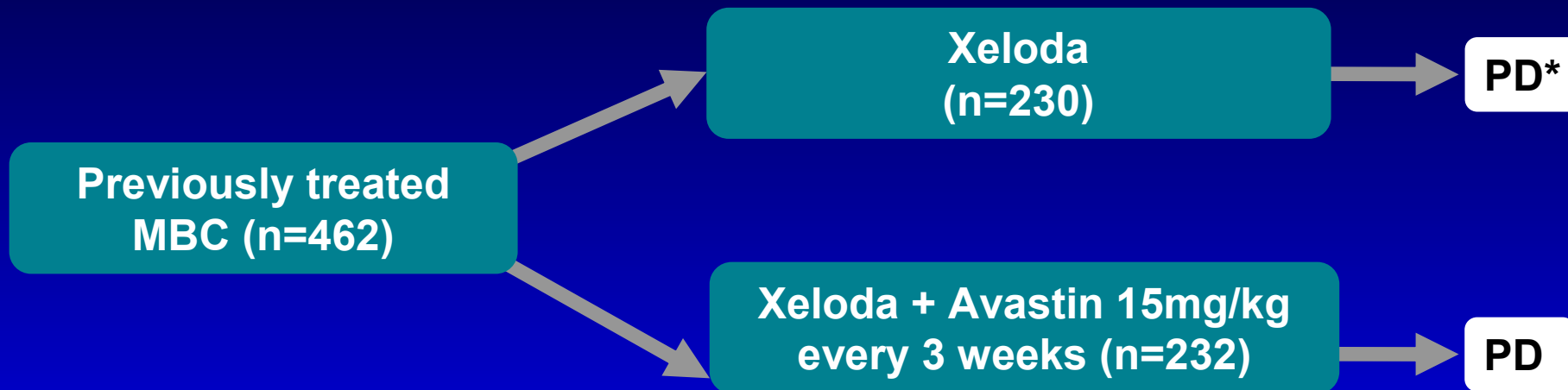
^a Abbreviations, N, nodal status; - negative, + positive; ND, not done; NS, not significance; IMA, immunometric assay; ICA, immunohistochemical assay; Rnase, Rnase protection analysis; ICMA, immunochemiluminescence assay; RFS, relapse-free survival; OS, overall survival.

Early phase clinical studies of Avastin

- **Two phase I trials in solid tumours**
 - Avastin monotherapy¹
 - Avastin in combination with doxorubicin, carboplatin/paclitaxel or 5-FU/LV²
- **Results of phase I trials in solid tumors showed**
 - no grade 3/4 toxicities attributed to Avastin
 - no increase in incidence of chemotherapy related adverse events
 - no evidence of toxicity related to long-term therapy with Avastin
- **Efficacy and safety data of phase I / II trials in metastatic breast cancer suggest further investigations**
 - Phase I/II dose-escalation trial of Avastin monotherapy³: 10mg / kg
 - Avastin + weekly docetaxel⁴ (n=21): 56 % response rate (all PR)
 - Avastin + vinorelbine⁵ (n=56): 30 % response rate, 45 % SD

¹Gordon MS, et al. JCO 2001;19:843–50; ²Margolin K, et al. JCO 2001;19:851–6; ³Cobleigh MA, et al. Semin Oncol 2003;30(5 Suppl. 16):117–24; ⁴Ramaswamy B, et al. BCRT 2003;81 (Abstract 224); ⁵Burstein HJ, et al. BCRT 2002;76 (Abstract 446)

Phase III trial of Avastin plus Xeloda in MBC (AVF2119g)



- Primary endpoint: progression-free survival
- Secondary endpoints: overall response rate, duration of response, overall survival
- More than 80 % of patients > 1st line; about 50 % ER positive; 20 % HER2 positive.
- Treatment administration
 - Avastin 15mg/kg i.v. every 3 weeks
 - Xeloda 2,500mg/m² orally daily for 2 weeks of a 3-week cycle

*No cross over was permitted

Xeloda ± Avastin: Grade 3/4 toxicities

Adverse event	Incidence (%)	
	Xeloda (n=215)	Xeloda + Avastin (n=229)
Hypertension*	0.5	17.9
Proteinuria*	0	0.9
Thrombosis	3.7	5.6
Hand-foot syndrome*	24.2	27.5
Bleeding*	0.5	0.4
CHF/cardiomyopathy	1.0	3.0
Nausea*	1.9	2.6

*No grade 4

Xeloda ± Avastin: Efficacy

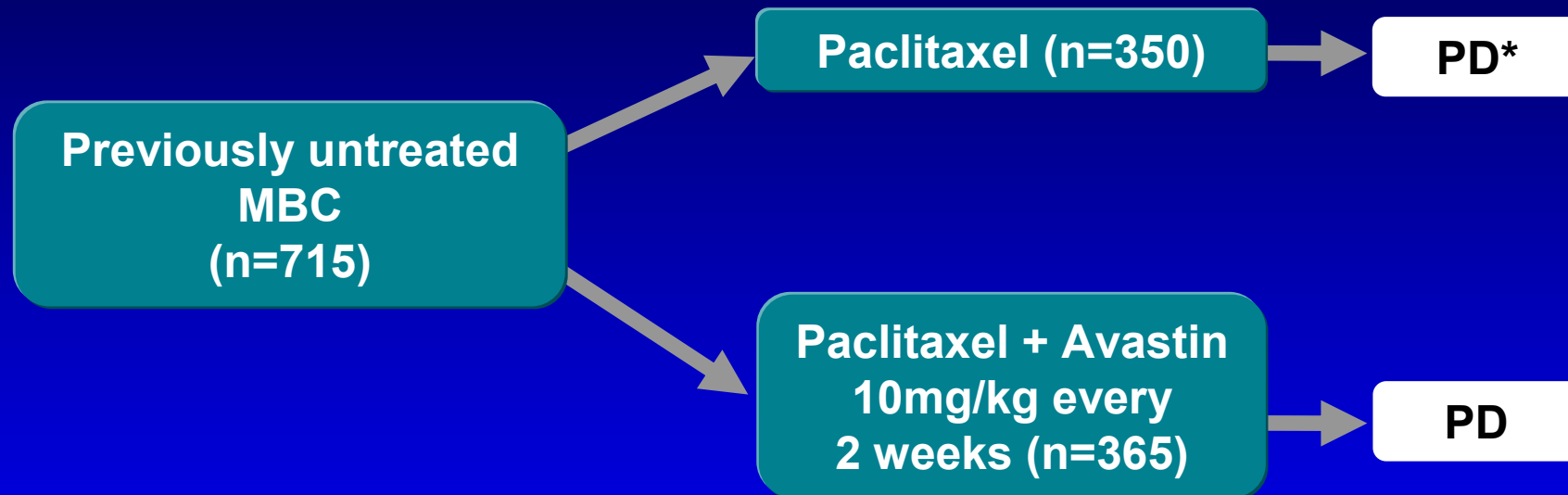
	Rate (%)	
	Xeloda (n=230)	Xeloda + Avastin (n=232)
Overall response rate (Inv)	19.1	30.2 (p=0.006)
Overall response rate (IRF)	9.1	19.8 (p=0.001)

Inv = investigator

IRF = independent review facility

Miller KD, et al. JCO 2005;23:792-9

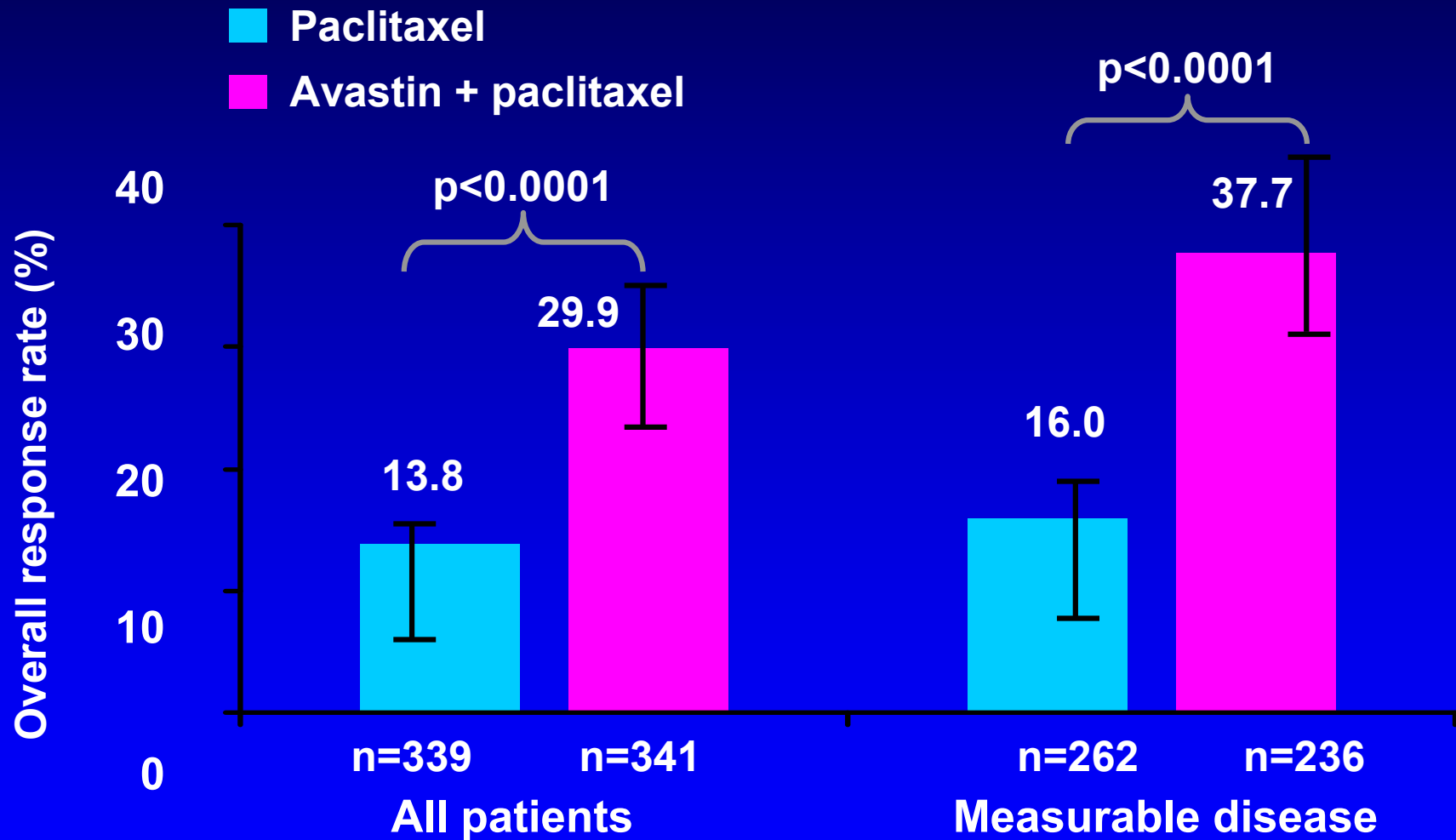
Phase III MBC trial of first-line Avastin and paclitaxel (E2100)



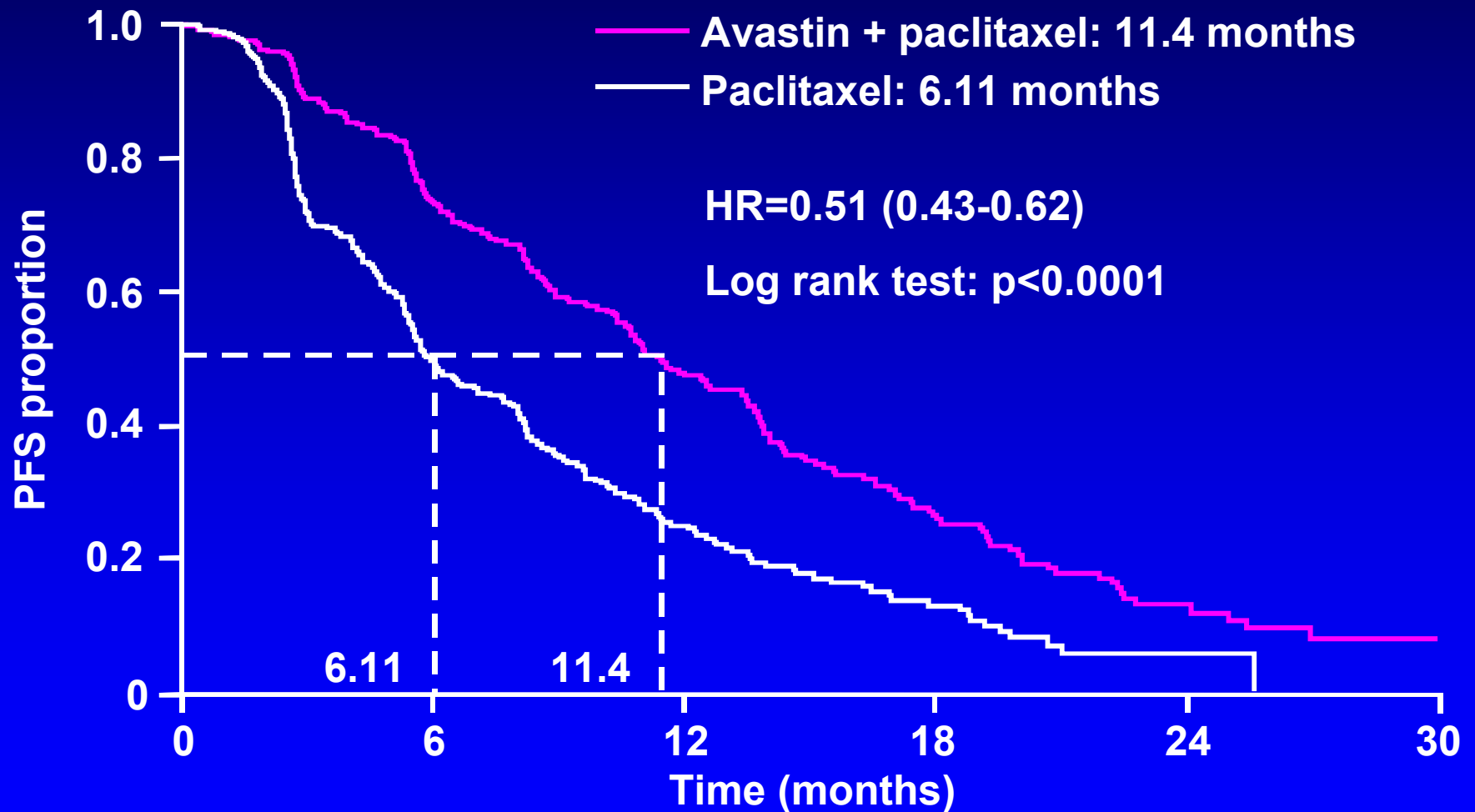
- Primary endpoint: progression-free survival
- About 60 % adjuvant chemotherapy (18 % taxane-containing)
- 28-day cycle
 - Paclitaxel 90mg/m² days 1, 8 and 15
 - Avastin 10mg/kg days 1 and 15

*No cross over was permitted

Phase III MBC trial of first-line Avastin (E2100): Response rate

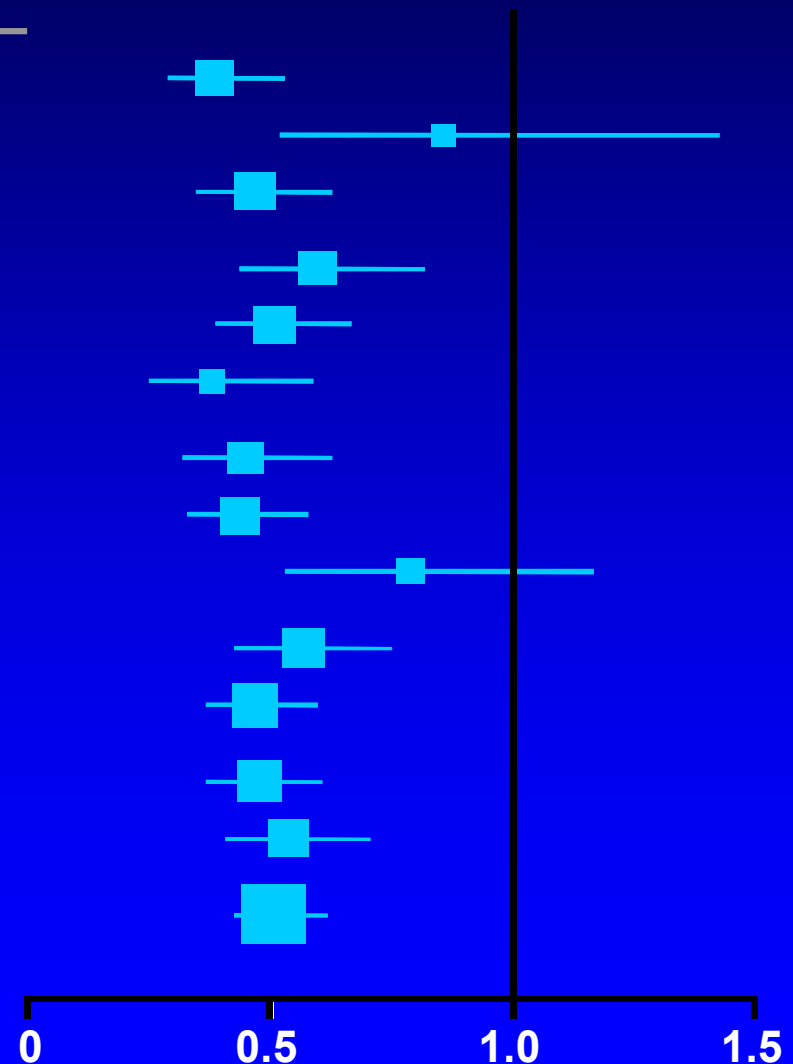


Phase III MBC trial of first-line Avastin (E2100): Progression-free survival

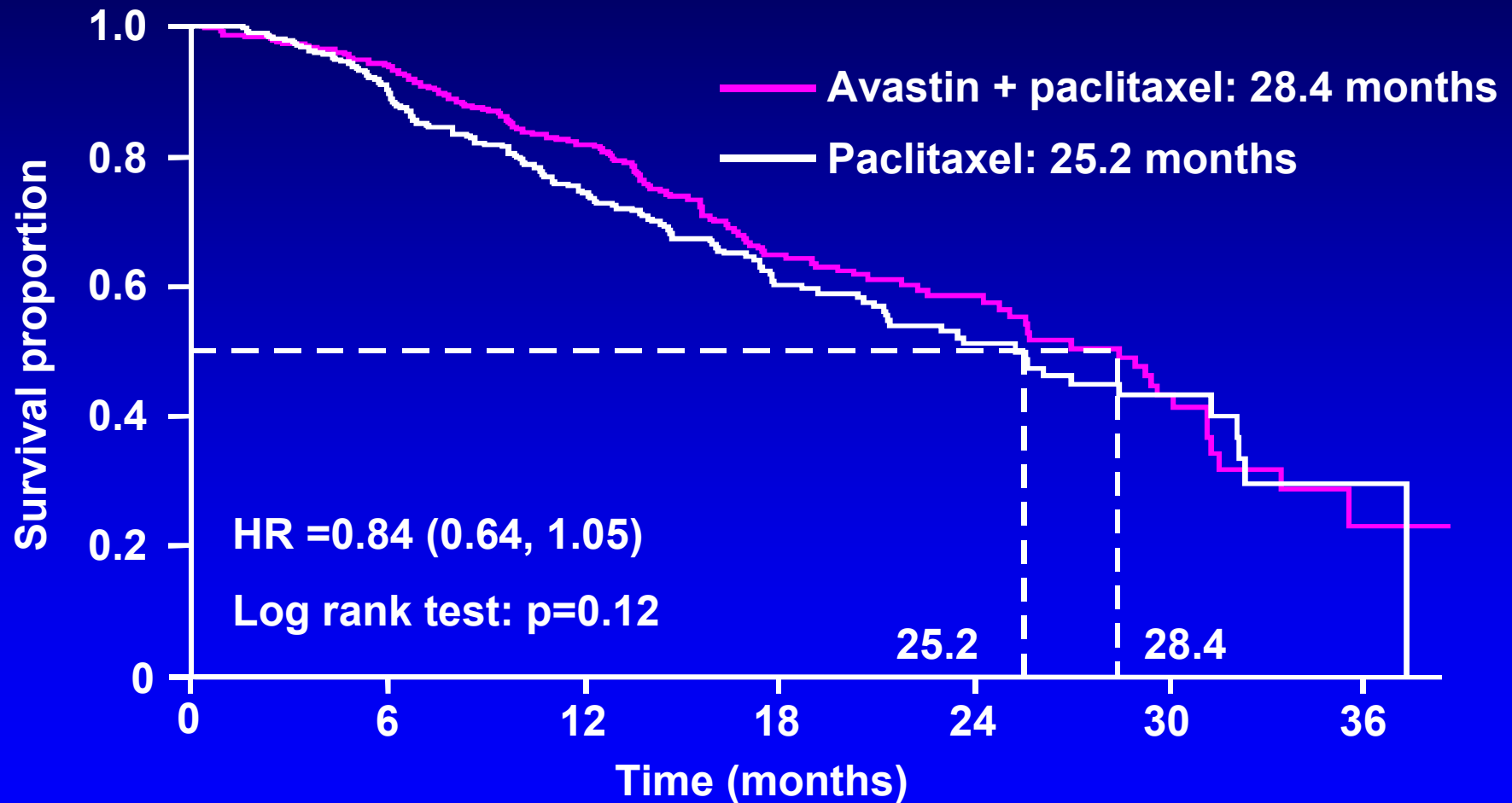


Phase III MBC trial of first-line Avastin (E2100): Progression-free survival

Group	Ratio	95% CI
ER+, PR+	0.39	(0.29, 0.53)
ER+, PR-	0.86	(0.52, 1.43)
ER-, PR-	0.47	(0.35, 0.63)
No adj chemo	0.60	(0.44, 0.82)
Non-taxane	0.51	(0.39, 0.67)
Taxane	0.38	(0.25, 0.59)
Age 27-49	0.45	(0.32, 0.63)
Age 50-64	0.44	(0.33, 0.58)
Age 65-85	0.79	(0.53, 1.17)
DFI 0-24 months	0.57	(0.43, 0.75)
DFI >24 months	0.47	(0.37, 0.60)
<3 sites	0.48	(0.37, 0.61)
≥3 sites	0.54	(0.41, 0.71)
Overall	0.51	(0.43, 0.62)



Phase III MBC trial of first-line Avastin (E2100): Overall survival



Phase III MBC trial of first-line Avastin (E2100): Grade 3/4 toxicities

	Paclitaxel (n=332)		Avastin + paclitaxel (n=350)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hypertension* (%)	2	0	15	<1
Thromboembolic events (%)	2	2	2	0
Bleeding [†] (%)	0	0	2	<1
Proteinuria [‡] (%)	0	0	1	1
Neuropathy (%)	17	1	22	1
Fatigue [§] (%)	4	<1	8	<1
Neutropenia (%)	NR	3	NR	4
↓LVEF (%)	0	0	<1	0

National Cancer Institute-Common Toxicity Criteria, worst per patient *p<0.0001; †p=0.02; ‡p=0.002; §p=0.05

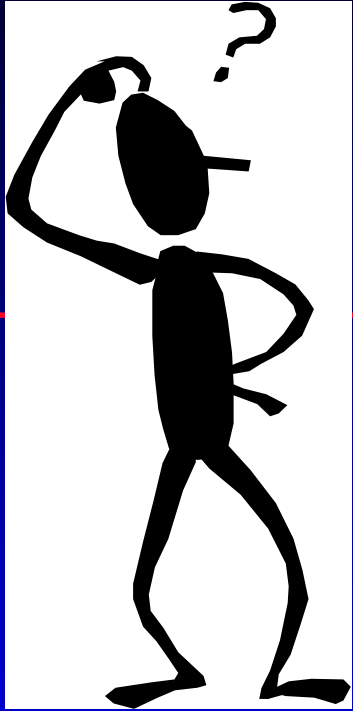
NR = not reported

LVEF = left ventricular ejection fraction

Miller KD, et al. BCRT 2005;94 (Abstract 3)

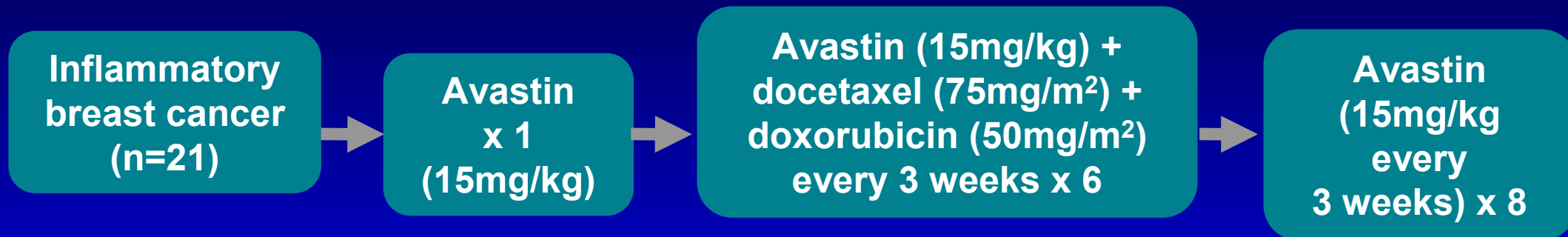
Phase III MBC trial of first-line Avastin (E2100): Summary

- Addition of Avastin to paclitaxel
 - significantly increased progression-free survival, the primary trial endpoint
 - significantly increased response rate in all patients and in patients with measurable disease
- Combination of Avastin and paclitaxel was well tolerated
- No difference in quality of life was observed between study arms
- Longer follow-up is required to assess impact on overall survival



Where are we going from here

Pilot study of Avastin in inflammatory and locally advanced breast cancer (n=21)



- Response: Overall response rate was 66.7% (14 partial responses), five patients (23.8%) had stable disease, 2 patients had progressive disease.
- Safety: neutropenia was the only grade 4 toxicity, hypertension (38.1%) was the most frequent grade 3 toxicity
- DCE-MRI: reduced K^{trans} , k_{ep} and v_e (pharmacokinetic parameters of vascular permeability and flow)
- Molecular markers: decrease in phosphorylated VEGF receptor-2 & endothelial cell proliferation, increase in apoptosis

DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging

VEGF = vascular endothelial growth factor

Wedam SB, et al. JCO 24: 769-777, 2006

Pilot study of Avastin in inflammatory and locally advanced breast cancer (n=21)

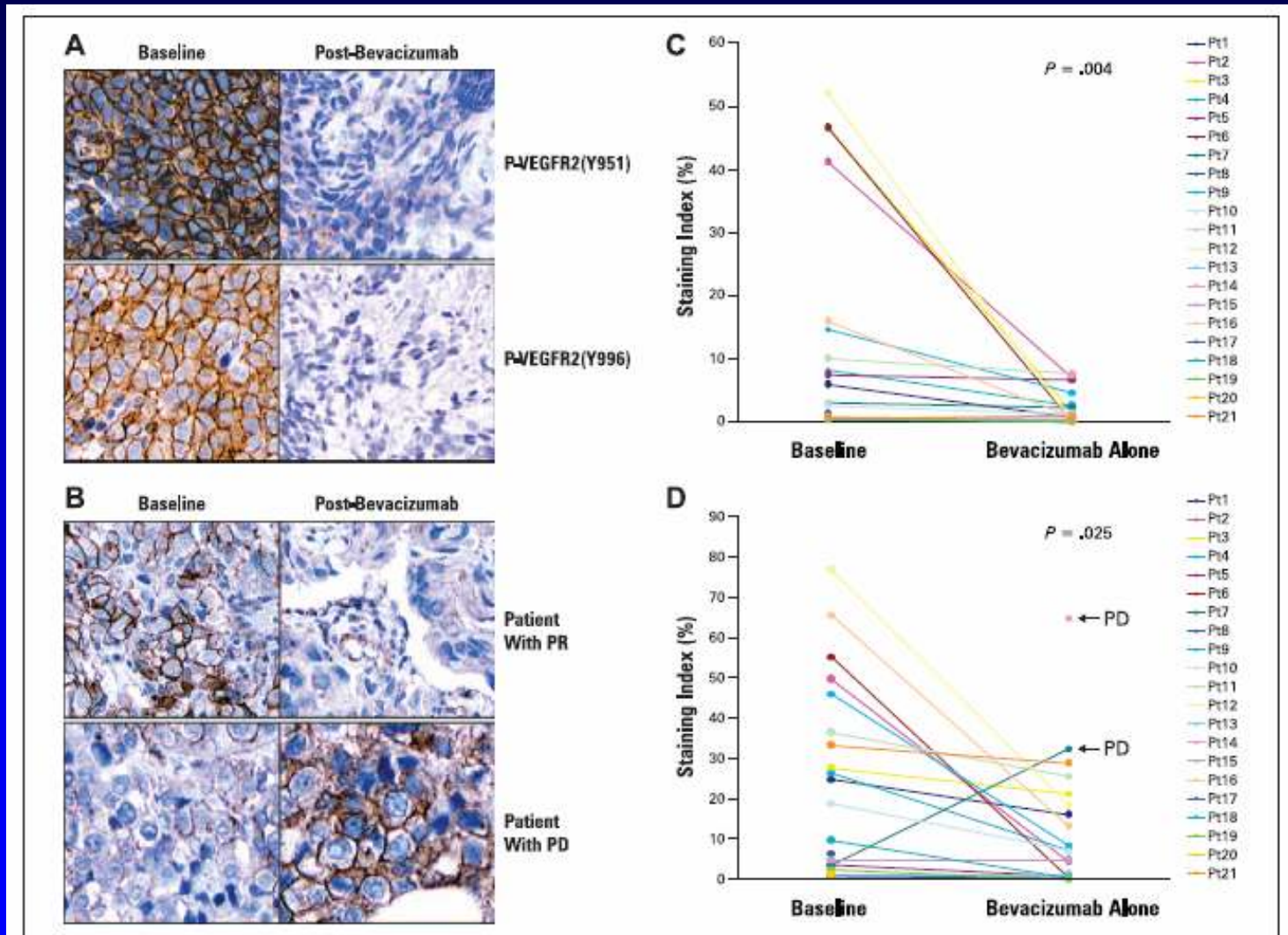
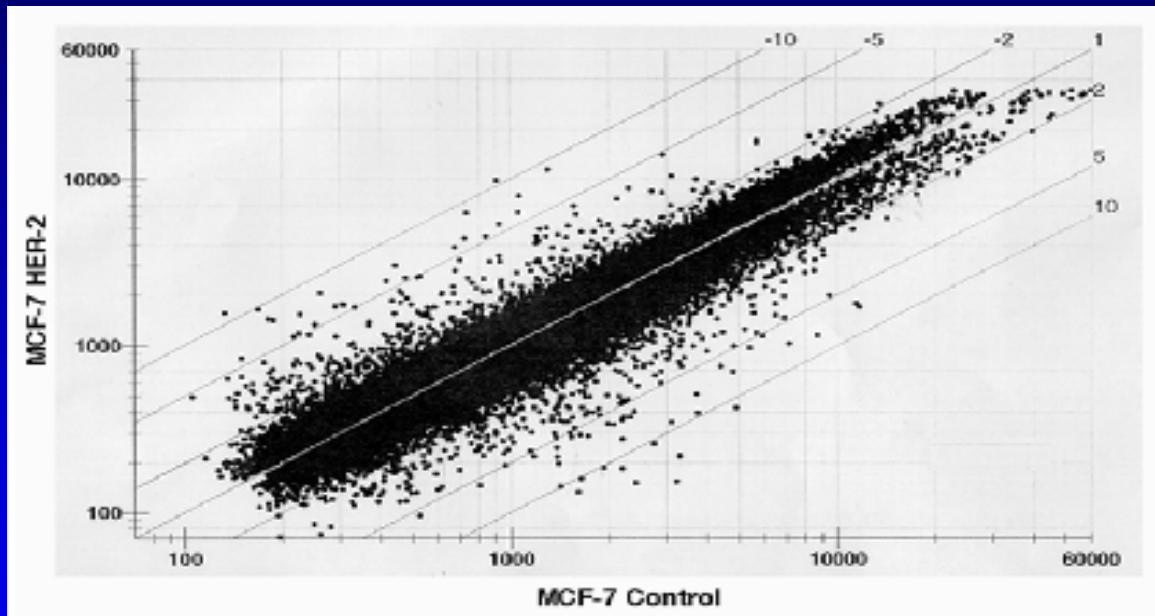
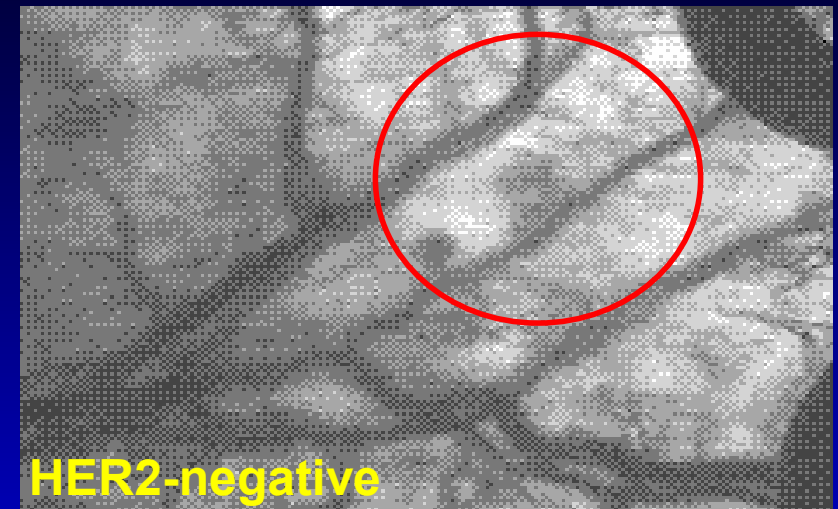


Fig 3. Phosphorylated vascular endothelial growth factor receptor 2 (p-VEGFR2) by immunohistochemistry. (A) p-VEGFR2 at Y951 and Y996 at baseline on left and post-cycle 1 on right. (B) p-VEGFR2 at Y951 in a patient (pt) with partial response (PR) on top and in a patient with progressive disease (PD) at bottom. (C) Changes in p-VEGFR2 (Y951) and (D) p-VEGFR2 (Y996) in all patients.

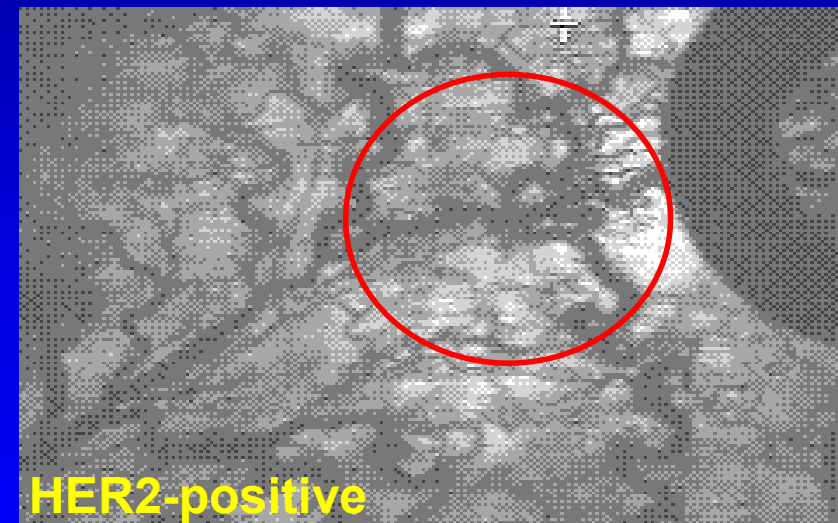
Rationale for combining Avastin and Herceptin®



Upregulation of VEGF by HER2
Confirmed at transcript and protein level



HER2-negative

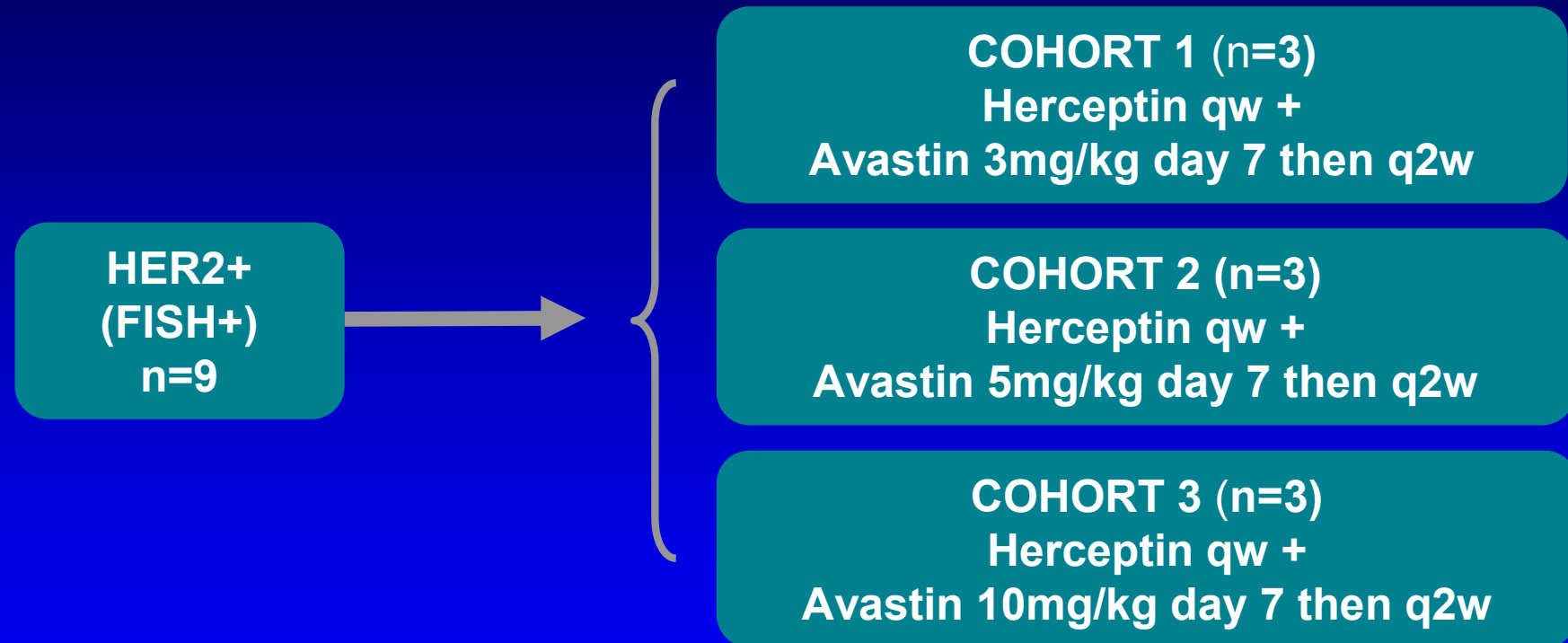


HER2-positive

Increased number of vessels

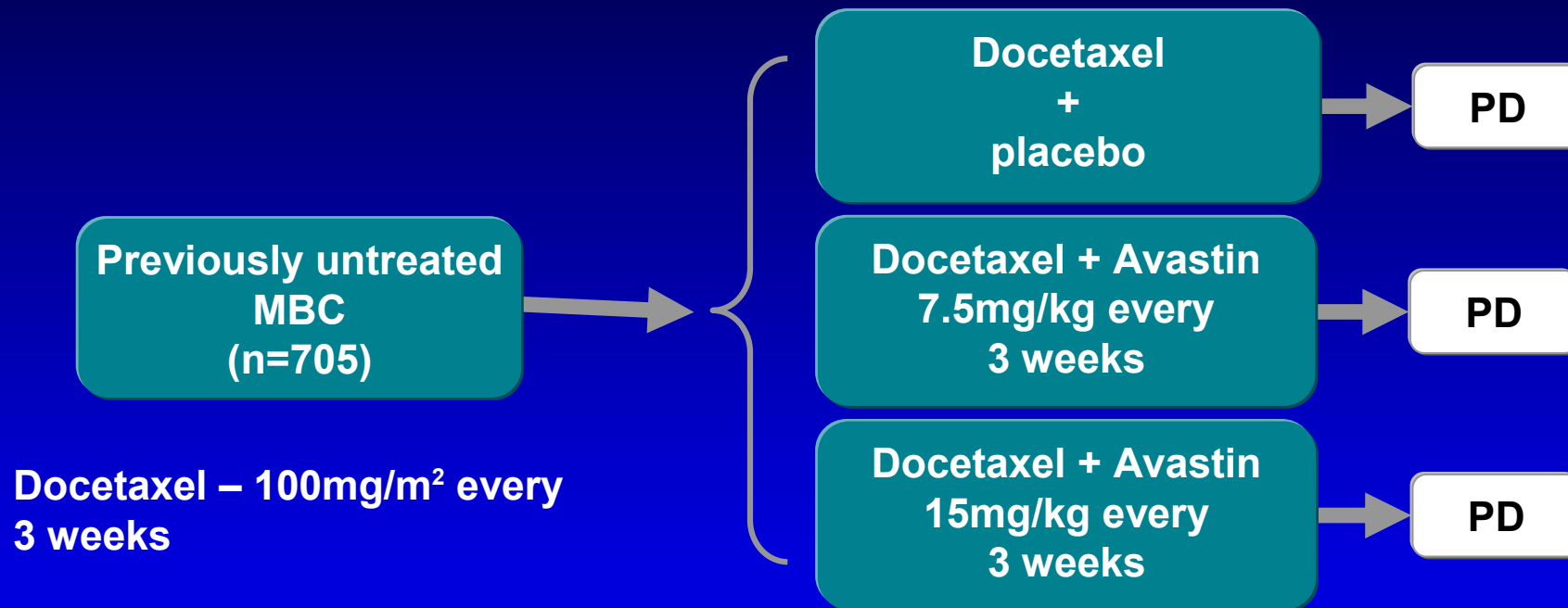
- vessel dilation
- vessel tortuosity

Phase I/II trial of Herceptin + Avastin in relapsed/MBC



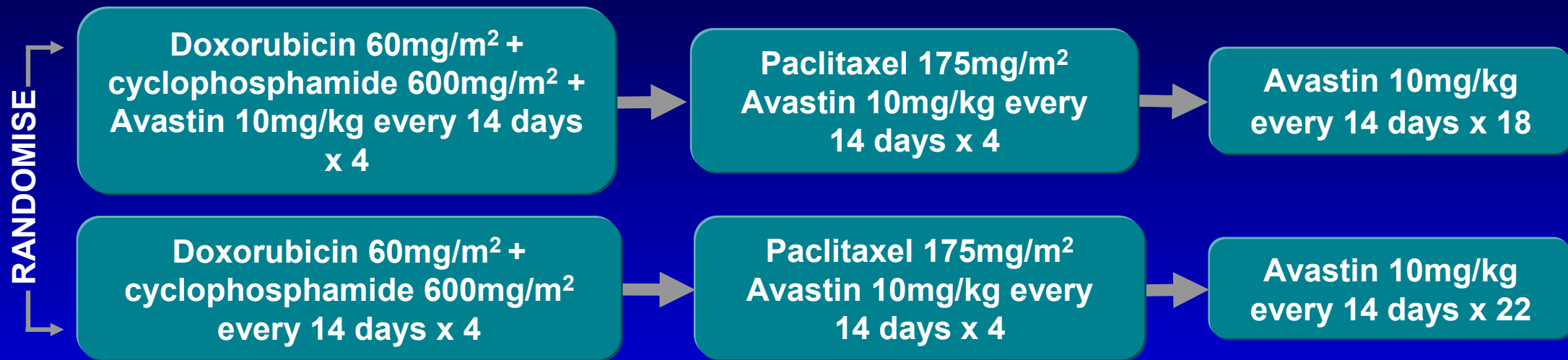
- Investigator-initiated, investigator held IND
- First report of two humanised MAb in human subjects
- Primary endpoints: safety, PK

Future trials of Avastin in breast cancer: **AVADO (BO17708)**



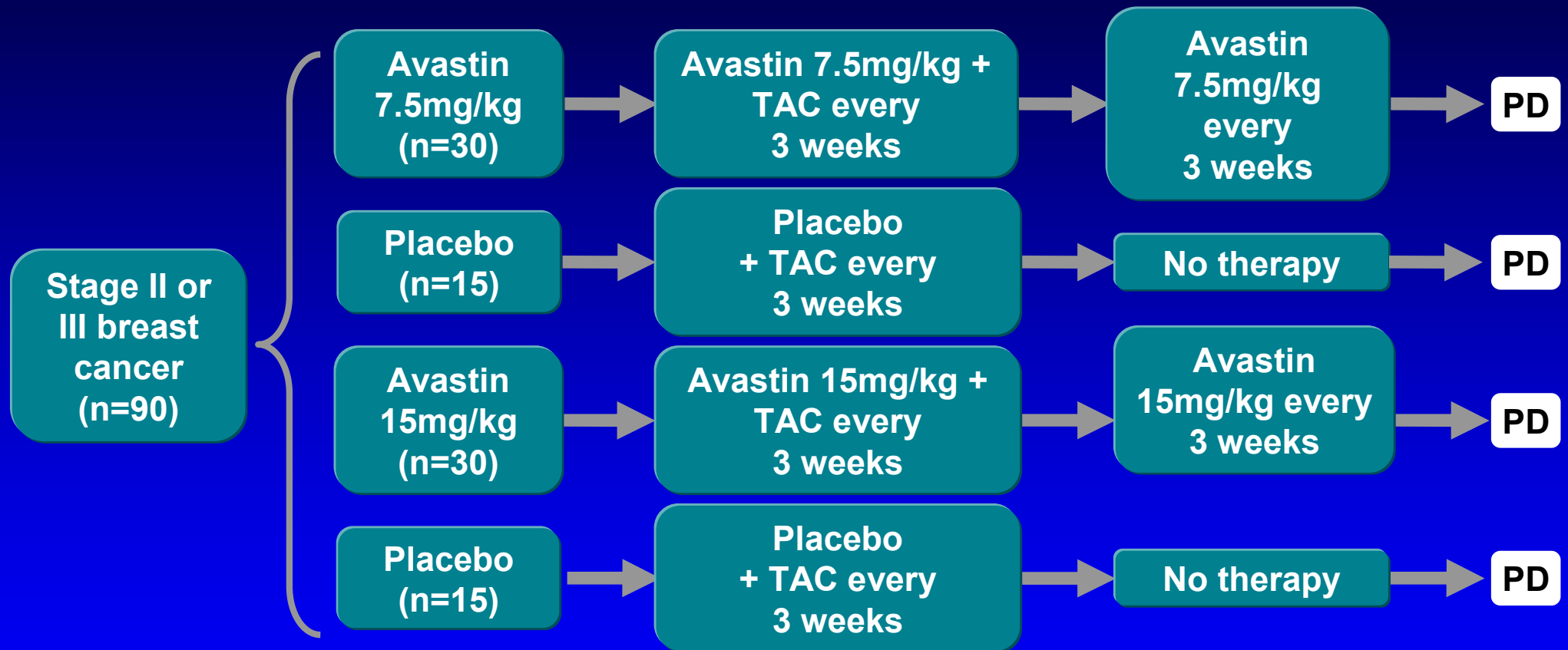
- Randomised, double-blind, placebo-controlled, multicentre, phase III trial
- Primary endpoint: progression-free survival
- Secondary endpoints: overall response rate, duration of response, time to treatment failure, overall survival, safety, quality of life
- Recruitment to commence March 2006

Ongoing trials of Avastin in breast cancer: E2104



- Phase II trial of adjuvant Avastin with a therapeutic regimen containing an anthracycline and a taxane (n=204)
- Primary endpoint: incidence of clinically apparent cardiac dysfunction
- Secondary endpoints: incidence of non-cardiac toxicity, changes in LVEF

Avastin in the neoadjuvant setting in breast cancer: TORI-B-02



- Randomised, double-blind, placebo-controlled phase II trial of Avastin
- Primary endpoint: safety

TAC = docetaxel, doxorubicin and cyclophosphamide

Translational Oncology Research International (TORI) trial protocol B-02

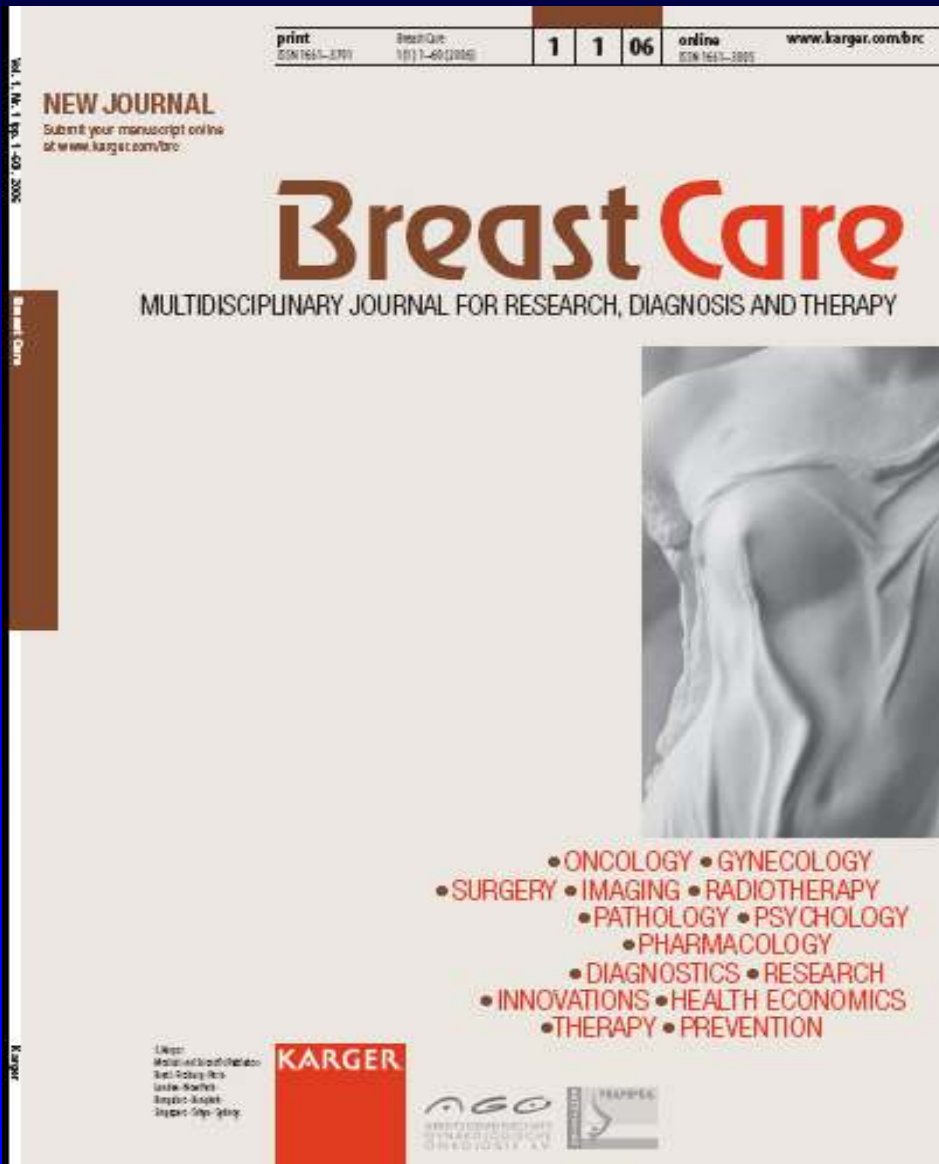
Conclusions

- Avastin is the first anti-angiogenic agent to have proven clinical benefit in breast cancer
- Avastin is well tolerated in patients with breast cancer, with manageable side-effects
- Avastin significantly improves progression-free survival and response rate in patients with locally recurrent or MBC when used in combination with paclitaxel

Conclusions (cont'd)

- Avastin provides greater clinical benefit when used in breast cancer patients who have not been heavily pretreated
- Ongoing studies in the neoadjuvant, adjuvant and metastatic settings are investigating Avastin in combination with other agents and further establish the role of Avastin in breast cancer

Evidence-based breast cancer therapy



AGO (DKG, DGGG)
www.ago-online.org

www.karger.com/brc



In breast cancer, Avastin has demonstrated clinical activity in phase III studies

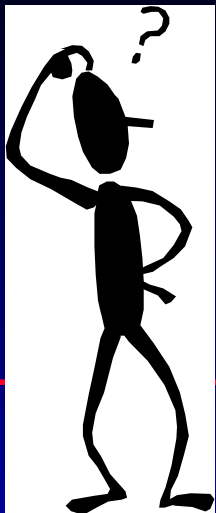
1. In the metastatic setting
2. In the adjuvant setting
3. In the neoadjuvant setting



In breast cancer, hypertension is the most commonly observed grade 3/4 side effect in about

1. 10 – 15 %
2. 15- 20 %
3. 20 – 25 %
4. 30- 35 %
5. more than 50 %

of all patients as documented in the available phase III studies



Interesting papers on Avastin therapy in breast cancer

1. Bevacizumab in the treatment of breast cancer: Rationale and current data. Rugo HR. *The Oncologist* 2004 (suppl 1): 43-49, 2004.
2. Randomized Phase III Trial of Capecitabine Compared With Bevacizumab Plus Capecitabine in Patients With Previously Treated Metastatic Breast Cancer. Miller KD. Et al. *JCO* 23:792-799, 2005.
3. Antiangiogenic and antitumoreffects of bevacizumab in patients with inflammatory and locally advanced breast cancer. Wedam SB, et al. *JCO* 24: 769-777, 2006.