Anti-angiogenic therapy for metastatic breast cancer

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- **Bevacizumab**

  first-line: phase III E2100, AVADO, RIBBON-1
  second-line: phase III RIBBON-2

- **Sorafenib**

  2 randomized phase II with paclitaxel and capecitabine

- **Sunitinib**

  phase III vs capecitabine

- **Motesanib**

  randomized phase II vs placebo

Three randomised trials of first-line bevacizumab-based therapy in advanced breast cancer

			RIBBON-1[3]	
	E2100[1]	AVADO[2]	Xeloda	Taxane/ anthracycline
Placebo controlled	No	Yes	Yes	
Chemotherapy	Weekly paclitaxel	3-weekly docetaxel	Xeloda	3-weekly docetaxel/ nab-paclitaxel or AC/FAC/EC/FEC
Bevacizumab dose	10 mg/kg q2w	7.5 or 15 mg/kg q3w	15 mg/kg q3w	
Primary endpoint	PFS (inv)	PFS (inv)	PFS (inv)	

[1]Miller et al. NEJM 2007; [2]Miles et al. ASCO 2008; [3]Robert et al. ASCO 2009

Consistent benefit: significant improvement in PFS & ORR

	E2100[1,2a]		AVADO[3b]		RIBBON-1[4]			
					Xeloda		Taxane/ anthracycline	
	Pacl	BEVA + pacl	Placebo + doce	BEVA[c] + doce	Placebo + Xeloda	BEVA +Xeloda	Placebo + T/A	BEVA + T/A
ORR, %	22	50	46	64	24	35	38	51
	p<0.0001		p=0.0003[d]		p=0.0097		p=0.0054	
Median PFS, months	5.8	11.3	8.1	10.0	5.7	8.6	8.0	9.2
HR for PFS	0.48 p<0.0001		0.67 p=0.0002[d]		0.69 p=0.0002		0.64 p<0.0001	

[a]IRF assessment; [b]PFS censored for non-protocol therapy before disease progression; [c]15 mg/kg q3w; [d]Exploratory p value

[1]Klencke et al. ASCO 2008; [2]Gray et al. JCO 2009; [3]Miles et al. SABCS 2009; [4]Robert et al. ASCO 2009

Secondary Endpoint: Overall Survival

	E2100[1]		AVADO[2]		RIBBON-1[3]			
					Xeloda		Taxane/ anthracycline	
	Pacl	BEVA + pacl	Placebo + doce	BEVA[a] + doce	Placebo + Xeloda	BEVA + Xeloda	Placebo + T/A	BEVA + T/A
Median OS, months	**24.8**	**26.5**	**31.9**	**30.2**	**21.2**	**29.0**	**23.8**	**25.2**
HR for OS	**0.87**		**1.03**		**0.85**		**1.03**	
	p=0.14		**p=0.85**		**p=0.27**		**p=0.83**	
1-year OS rate, %[b]	**74**	**81**	**76**	**84**	**74**	**81**	**83**	**81**
	p=0.017		**p=0.02**		**p=0.076**		**p=0.44**	

[a]15 mg/kg q3w

[1]Cameron EJC Suppl 2008; [2]Miles et al. SABCS 2009; [3]Robert et al. ASCO 2009

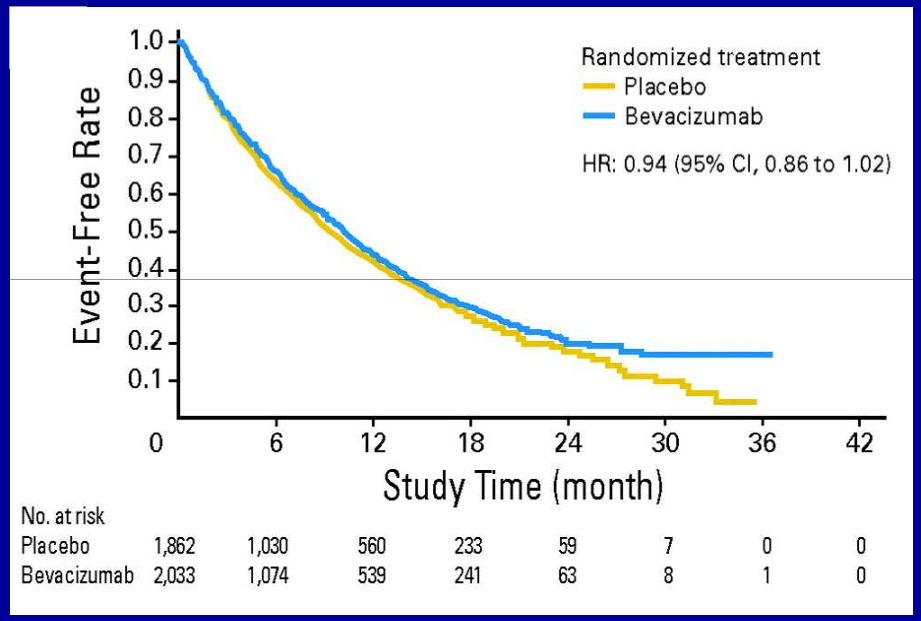
Two meta-analyses investigating bevacizumab effects on overall survival

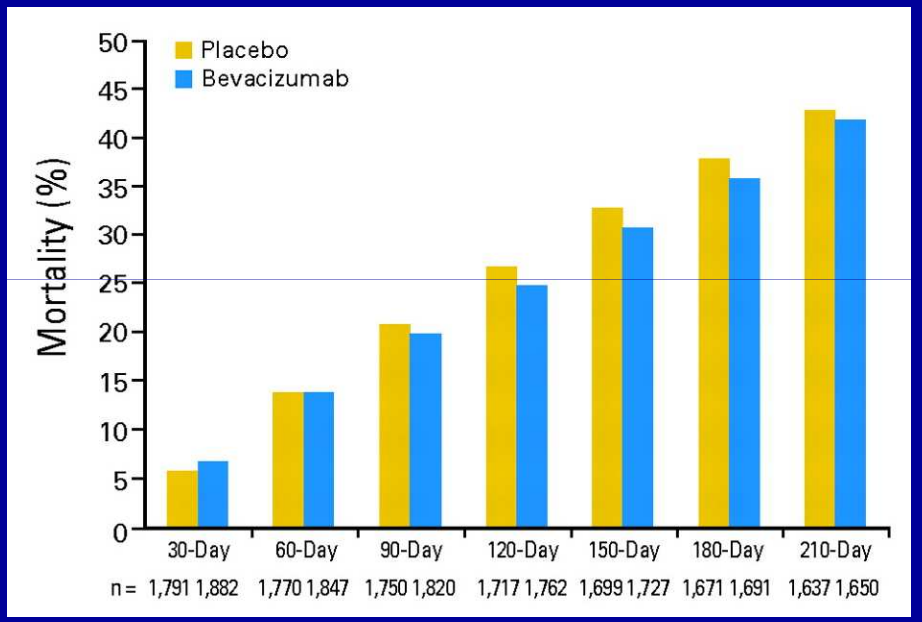
CT vs. CT + bevacizumab

Abstracted data*	Individual patient data**
N = 3,163 pts (5 trials)	N = 2,447 pts (3 trials)
HR = 0.90	HR = 0.97
95% CI = 0.80 – 1.03	95% CI = 0.86 – 1.08
p = 0.119	p = 0.56

* Valachis A et al, Breast Cancer Res Treat 2010; ** O'Shaughnessy J et al, proc ASCO 2010

Bevacizumab withdrawal is not correlated with an increase in disease aggressiveness





Miles D et al, J Clin Oncol 29: 83-88, 2011

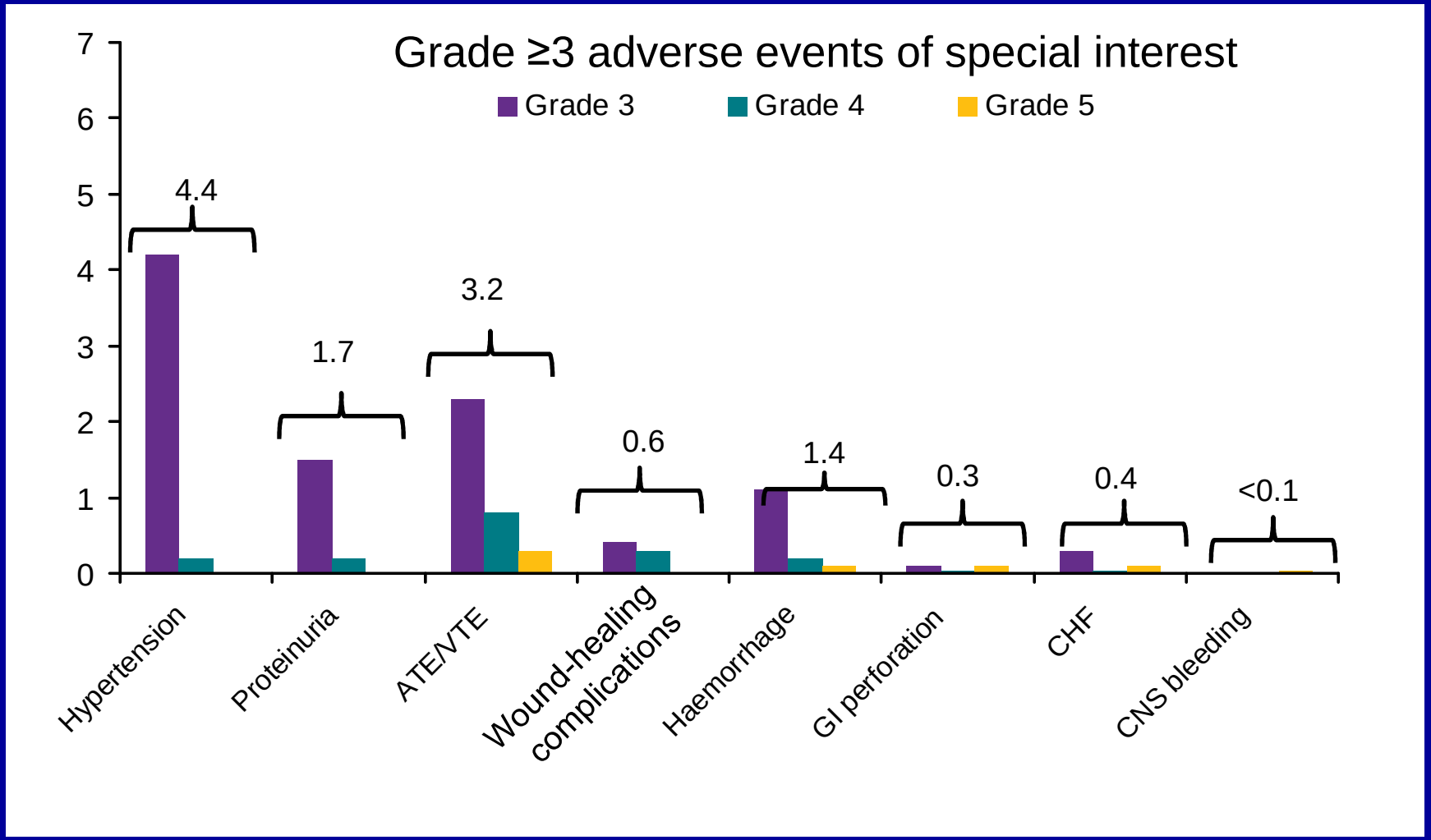
E2100: safety data

Selected grade 3/4 adverse events[a], %	Paclitaxel (n=348)		BEVA + paclitaxel (n=363)	
	Grade 3	Grade 4	Grade 3	Grade 4
Sensory neuropathy	**17.5**		**24.2**	
Fatigue	**5.2**		**10.7**	
Neutropenia with or without infection	**8.0**		**17.4**	
Hypertension	**1.4**	**0**	**15.4**	**0.6**
Arterial thromboembolic events	**0**		**3.6**	
Venous thromboembolic events	**4.3**		**3.0**	
Bleeding	**0.3**	**0**	**1.7**	
Proteinuria	**0**	**0**	**1.9**	
Left ventricular dysfunction	**0.3**		**2.2**	

[a]Includes NCI AdEERS mandatory collection in the Avastin + paclitaxel arm only, which does not allow a valid comparison between the two arms

Miles EJC Suppl 2008; Robert et al. SABCS 2009

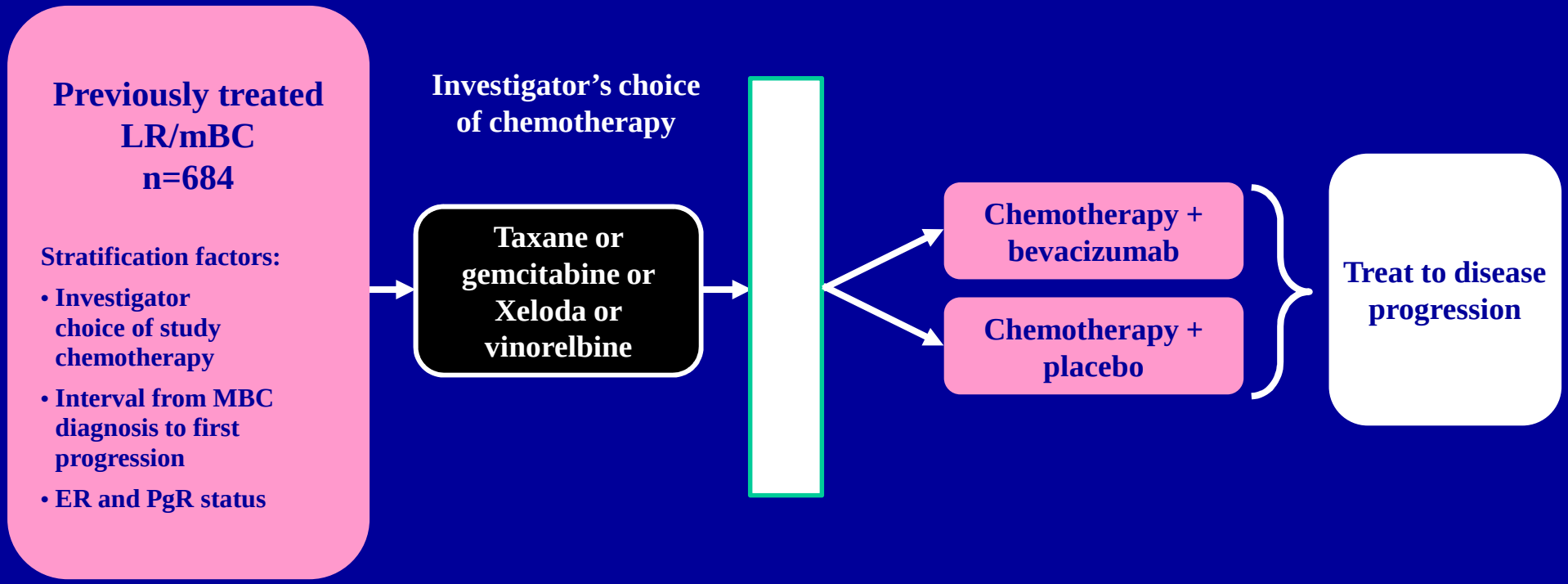
ATHENA (n=2251) : safety profile in routine oncology practice consistent with data from randomised trials



ATE = arterial thromboembolism; VTE = venous thromboembolism; CHF = congestive heart failure

Cortes-Funes et al. ECCO-ESMO 2009

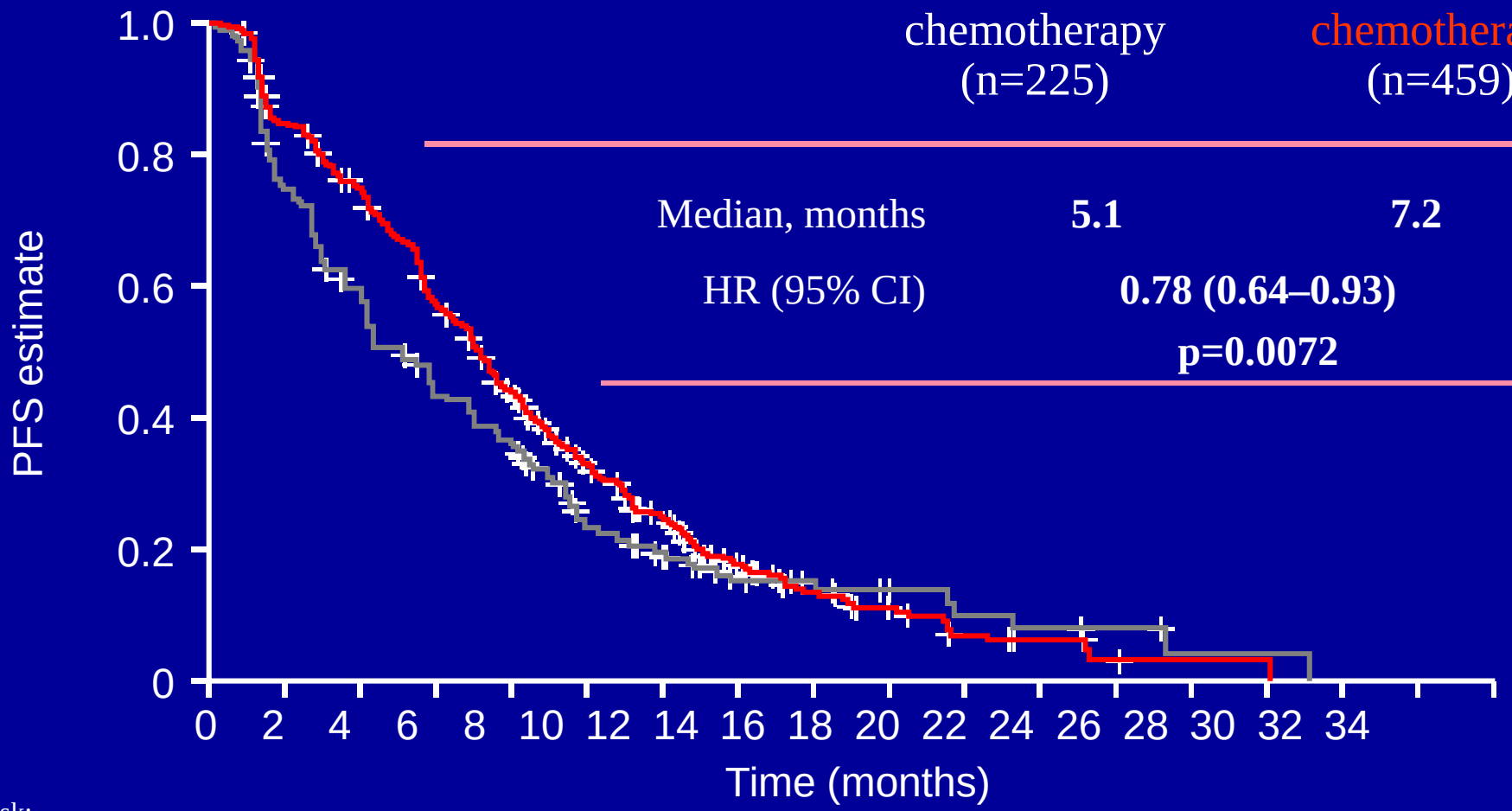
RIBBON-2: Trial Design



- Taxane (paclitaxel 90 mg/m^2 d1, 8, 15 q4w OR paclitaxel 175 mg/m^2, nab-paclitaxel 260 mg/m^2 or docetaxel 75–100 mg/m^2 q3w)
- Gemcitabine (1250 mg/m^2 d1, 8 q3w)
- Xeloda (1000 mg/m^2 bid d1–14 q3w)
- Vinorelbine (30 mg/m^2 d1, 8, 15 q3w)
- Bevacizumab or placebo (15 mg/kg q3w or 10 mg/kg q2w, depending on chemotherapy regimen)

Brufsky et al. SABCS 2009

Ribbon 2: Efficacy data

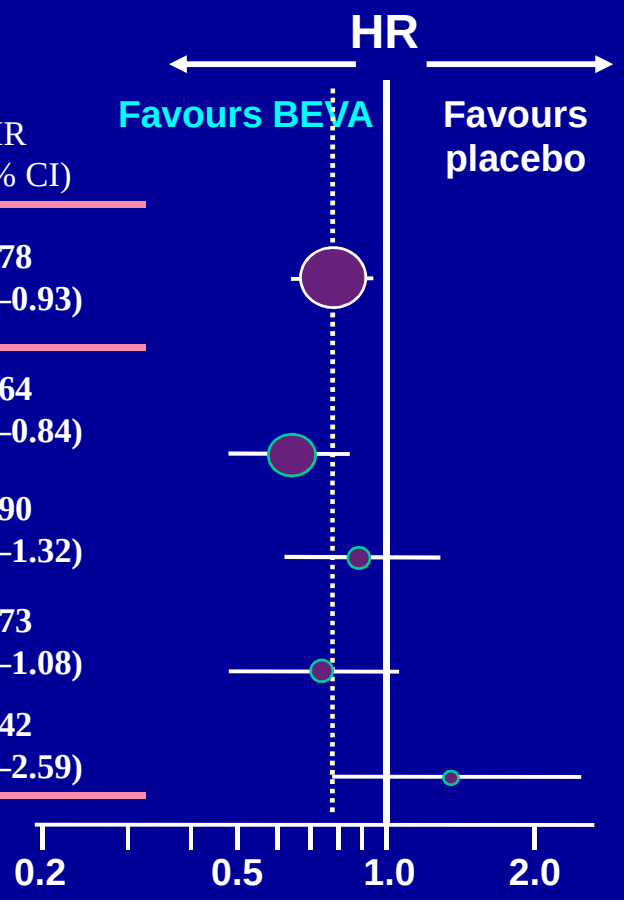


Number at risk:

Placebo + chemo	225	165	129	93	77	44	33	19	12	8	5	4	3	1	1	0	0	0
BEVA + chemo	459	381	334	254	190	130	87	47	27	18	9	5	2	1	1	0	0	0

RIBBON-2: PFS in Chemotherapy Subgroups

Cohort	Total (n)	BEVA + chemotherapy (n=459) Events	BEVA + chemotherapy (n=459) Median (months)	Placebo + chemotherapy (n=225) Events	Placebo + chemotherapy (n=225) Median (months)	HR (95% CI)
All subjects	**684**	**372/459**	**7.2**	**184/225**	**5.1**	**0.78 (0.64–0.93)**
Taxane	**304**	**151/201**	**8.0**	**84/103**	**5.8**	**0.64 (0.49–0.84)**
Gemcitabine	**160**	**84/108**	**6.0**	**43/52**	**5.5**	**0.90 (0.61–1.32)**
Xeloda	**144**	**87/97**	**6.9**	**39/47**	**4.1**	**0.73 (0.49–1.08)**
Vinorelbine	**76**	**50/53**	**5.7**	**18/23**	**7.0**	**1.42 (0.78–2.59)**



Brufsky et al. SABCS 2009

Selected grade ≥3 adverse events

Patients, %	Placebo + chemotherapy (n=221)	BEVA + chemotherapy (n=458)
Neutropenia	**14.5**	**17.7**
Hypertension	**0.5**	**9.0**
Sensory neuropathy	**5.9**	**6.3**
Proteinuria	**0.5**	**3.1**
Febrile neutropenia	**2.7**	**2.2**
Bleeding events	**0**	**1.7**
Left ventricular systolic dysfunction	**0**	**0.9**
Arterial thromboembolic event	**1.4**	**0.7**
Wound dehiscence	**0**	**0.7**
GI perforation	**0**	**0.4**
RPLS	**0**	**0**

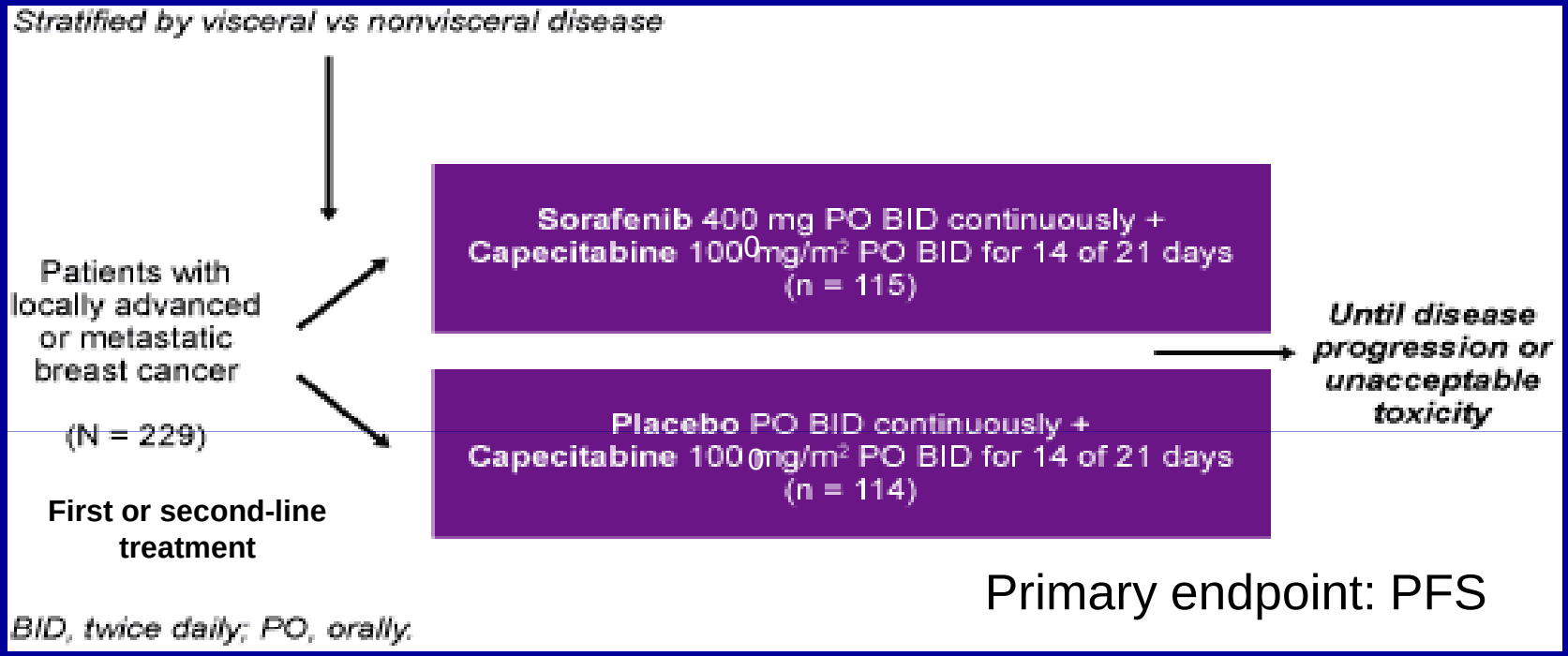
RPLS = reversible posterior leucoencephalopathy syndrome

Brufsky et al. SABCS 2009

Summary on Bevacizumab

- **Well proven benefit on objective response rate and progression-free survival when combined with chemotherapy as 1st-line treatment**
- **Lack of benefit on overall survival. Mandatory requirement in advanced disease?**
- **Specific toxicity profile. Manageable side-effects**
- **Uncertainty on dose/schedule and elevated costs may represent an issue**
- **Good option for 1st line treatment as an alternative to polychemotherapy**

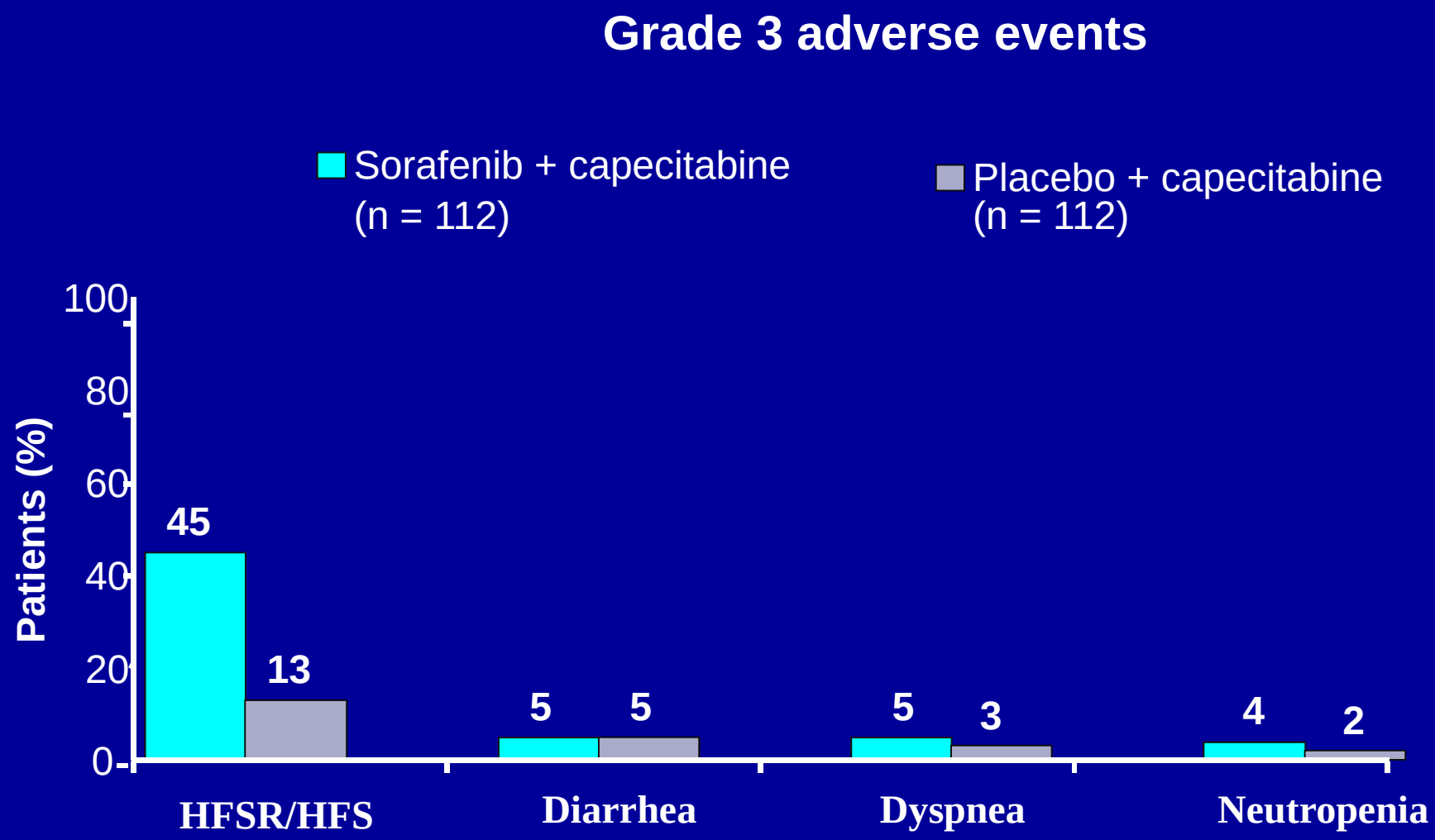
SOLTI-0701: randomized phase II study of sorafenib plus capecitabine



- Median PFS significantly longer with addition of sorafenib vs placebo (6.4 vs 4.1 months, respectively) HR: 0.576 (95% CI: 0.410-0.809; *P* = .0006)
- No significant improvement in response rate with addition of sorafenib vs placebo

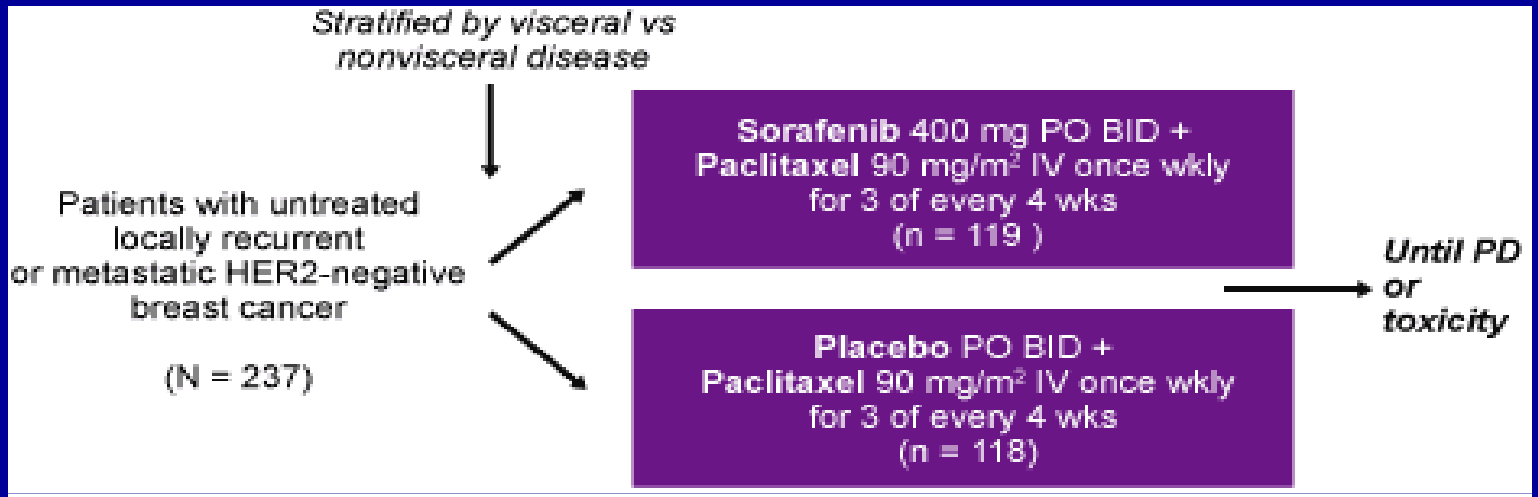
Baselga et al. SABCS 2009

Safety



Baselga J, et al. SABCS 2009

Randomized phase II study of first-line sorafenib in combination with paclitaxel



Primary endpoint: PFS

Outcome (Intent toTreat)	S+P (n = 119)	PL+P (n = 118)	HR (95%CI)	*P* Value*
Median PFS, mos	6.9	5.60	.79 (0.56-1.11)	.0857
Median TTP, mos	8.1	5.60	.67 (0.46-0.98)	.0171
ORR, %	67.0	54.0	--	.0234
Median duration of response, mos	5.63	7	--	.0079†

*One-sided *P* value; †Responder only *P* value; S, sorafenib, P, paclitaxel, PL, placebo

Gradishar et al. SABCS 2009

Safety

Treatment-Related Adverse Events,* %	Sorafenib +Paclitaxel (n = 115)		Placebo + Paclitaxel (n = 118)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hand-foot skin reaction	55	30	7	3
Diarrhea	37	3	55	3
Physical weakness	29	7	21	3
Vomiting	28	3	14	0
Neutropenia	24	13	19	7
Anemia	22	11	19	6
Stomatitis	16	3	31	0
Peripheral neuropathy	16	6	9	7
Headache	15	3	11	2
Fatigue	14	3	20	2
Neuropathy	10	5	14	1

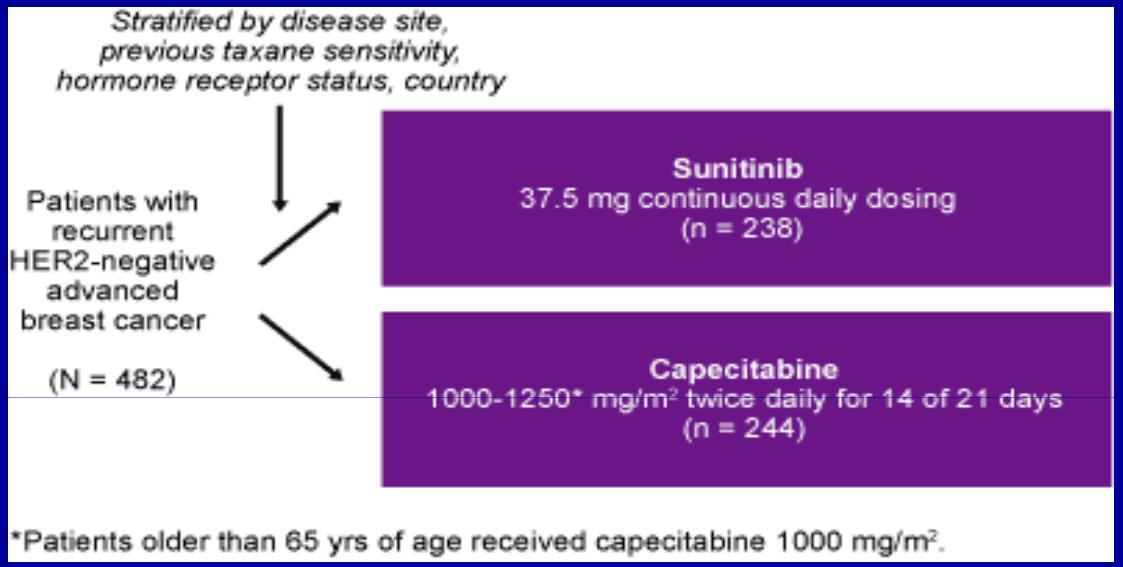
*Any grade adverse event occurring in ≥ 15% of patients and grade 3/4 adverse event occurring in ≥ 5% of patients in either treatment arm reported

Sorafenib/paclitaxel: n=2 deaths due to treatment-related adverse event: (malaria and liver failure)

Summary of Sorafenib

- **Preliminary evidence of activity when combined with chemotherapy as 1st or 2nd-line (↑ ORR and PFS)**
- **Toxicity may be an issue (HFS, diarrhea, neutropenic fever)**
- **Doses lower than 400 mg bid may be more tolerable and still active**
- **Ongoing Phase III trials in combination with capecitabine will define its role in advanced disease**

Sunitinib Associated With Shorter Median PFS Than Capecitabine in Previously Treated HER2 negative advanced breast cancer



Phase III study

Failure of previous therapy with taxane and anthracycline (T only allowed)

1 previous CT regimen allowed

Primary endpoint: PFS

- Independent data and safety monitoring committee recommended discontinuation of enrollment at first interim analysis based on futility of reaching primary endpoint (S>X)
- Median PFS significantly longer with X vs S (4.2 vs 2.8 months, respectively) HR: 1.47 (95% CI: 1.16-1.87; *P* = .002)

S, sunitinib; X, capecitabine

Barrios et al. SABCS 2009

Safety

Grade3-4 Adverse Events in ≥5% of patients, %	Sunitinib (n = 238)	Capecitabine (n = 240)
Neutropenia	11	4
Thrombocytopenia	8	1
HFS	8	16
Fatigue	7	1
Diarrhea	6	5

Sunitinib associated with higher rates of grade 3/4 fatigue, hypertension, neutropenia, thrombocytopenia

Summary on Sunitinib

- **Negative results**
  - **sunitinib vs. capecitabine**
  - **sunitinib + capecitabine vs. capecitabine**
  - **sunitinib vs. other cytotoxics in triple negative disease**
  - **sunitinib + docetaxel vs. docetaxel**
- **No further development in breast cancer**

Conclusions

- **Overall positive results although clinical impact less dramatic than initially expected based on biological/pre-clinical considerations**
- **Current efforts: treatment individualization based on prediction of sensitivity/toxicity (polymorphisms under current investigation).**