

Metastatic Breast Cancer Following Adjuvant Anthracycline and Taxane: Best Choice of Therapy?

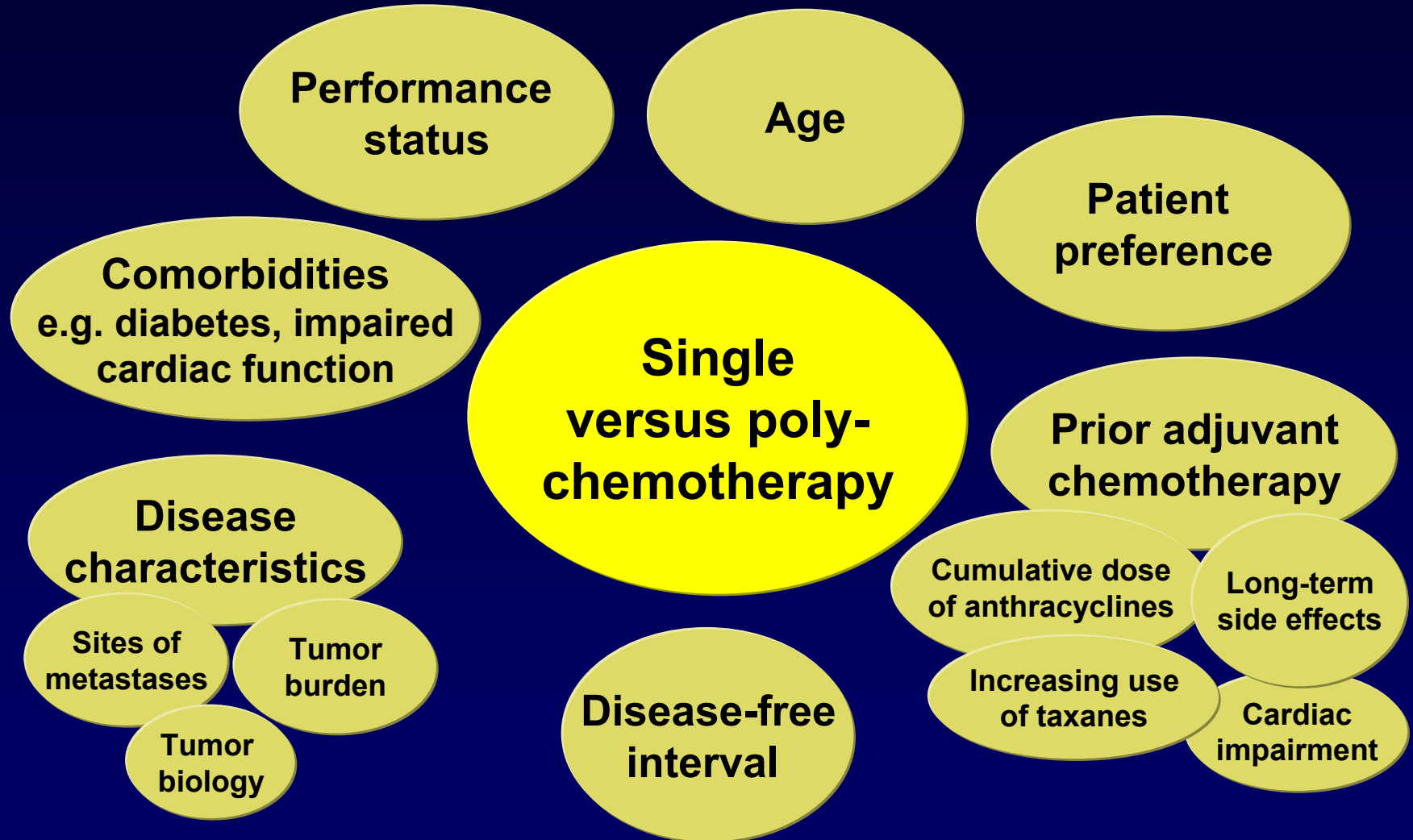
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London**

Management of Advanced Breast Cancer: Efficacy Versus Toxicity



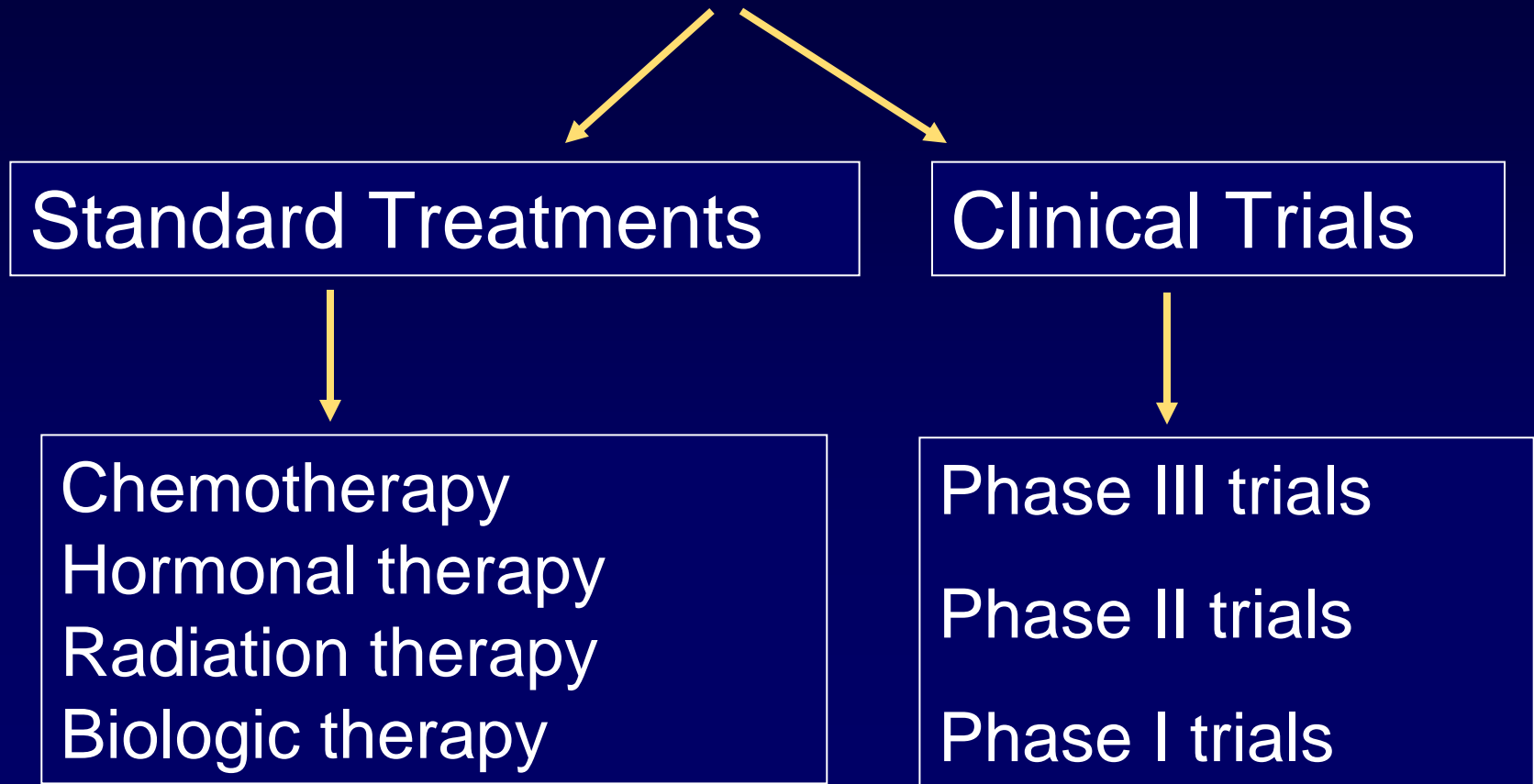
Patient and Disease Characteristics Influence Treatment Decisions



What are the aims of treatment for this patient?

- Improved overall survival?
- Improved progression free survival?
- Improved response rate?
- Symptom control?
- Quality of life?

Treatment Options Stage IV Breast Cancer



What treatment option would you advise?

- **Hormonal treatment**
- **Single agent chemotherapy**
- **Combination chemotherapy**
- **Chemotherapy and a biological agent**

Chemotherapy for MBC: Simultaneous or Sequential? The Issue

- **Patients with MBC receive multiple cytotoxic agents during their disease**
- **Do combinations of two or more drugs given simultaneously give better results than each single agent given until progression and then the others given sequentially?**
- **Is there a role for maintenance treatment?**

Simultaneous vs Sequential Combinations: Advantages and Disadvantages

Simultaneous

- Higher response rate
- Higher complete response rate
- Longer time to progression
- Covers multiple mechanisms of resistance
- Exploits synergistic interactions
- Generates more adverse events

Sequential

- Avoids additive or overlapping toxic effects
- Simpler scheduling
- Lower response rate
- Shorter time to progression
- Equivalent median survival

Metastatic Breast Cancer: First Line Chemotherapy – Cochrane Overview

Single Agent vs Combination

Outcome	No of studies	No of Participants	Effect size (odds ratio)
Overall survival	29	5099	0.88 (0.83-0.94)
TTP	16	3377	0.78 (0.73-0.83)
Overall response	33	5539	1.32 (1.18-1.48)

Metastatic Breast Cancer: Chemotherapy Cochrane Overview

Single Agent vs Combination: Toxicity

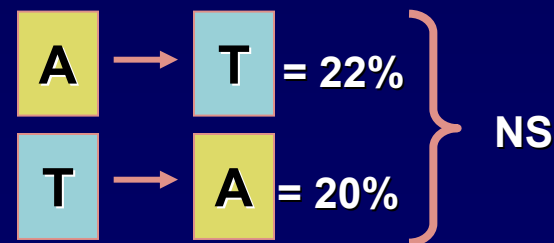
Outcome	No of studies	No of Participants	Effect size (odds ratio)
Emesis	27	5754	1.65 (1.41-1.93)
White blood cells	28	5340	1.45 (1.28-1.65)
Alopecia	15	2859	1.55 (1.32-1.81)

Combination vs Sequential Therapy: ECOG 1193

	Doxorubicin 60 mg/m ²	Paclitaxel 175 mg/m ² /24 hr	Doxorubicin + Paclitaxel 50/150 mg/m ² /24 hr
Response	36%	34%	47%*
Median TTF	6 mos.	6 mos.	8 mos.*
Median Survival	19 mos.	22 mos.	22 mos.
QOL	=	=	=

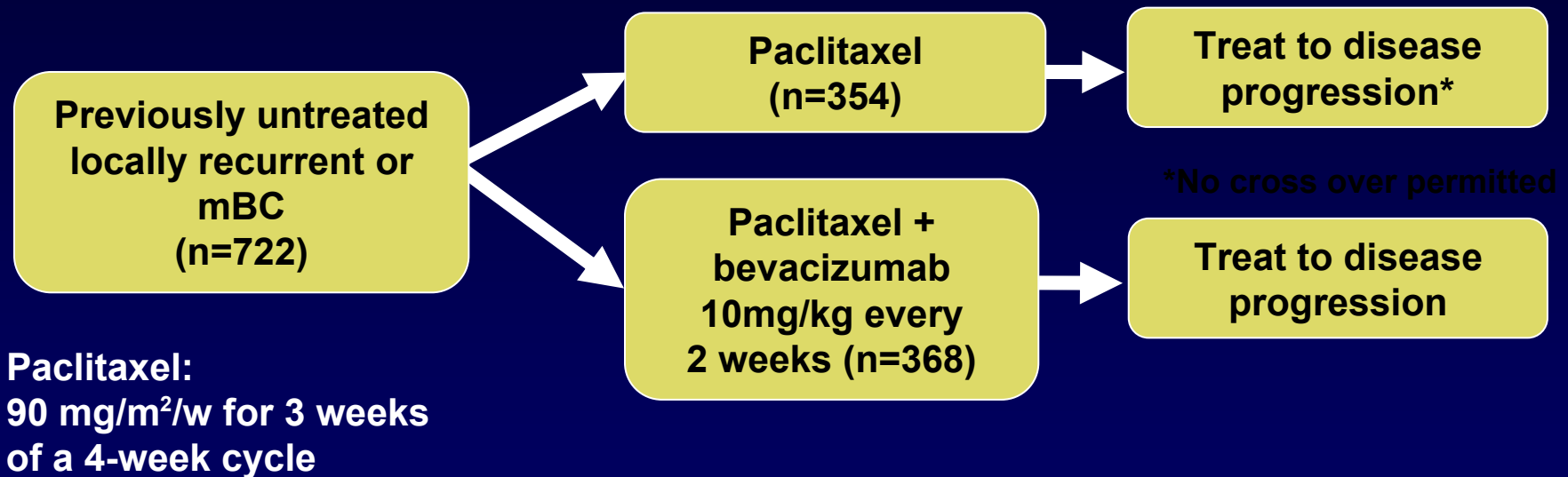
Primary Endpoint was Response Rate

Crossover Responses:



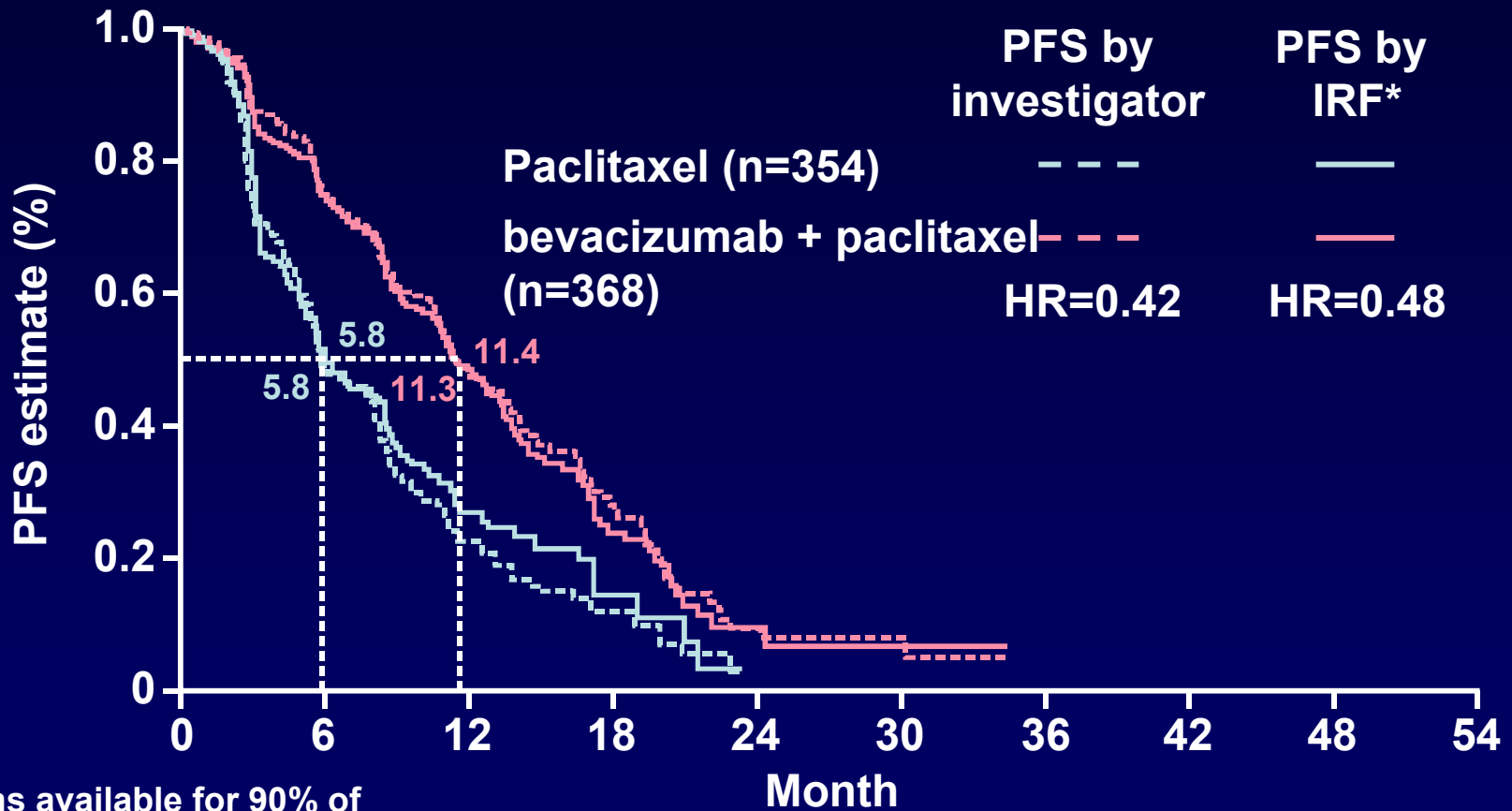
* Statistically Significant

Phase III Trial of Bevacizumab + Paclitaxel in First-line MBC (E2100)



- **Primary endpoint: progression-free survival**
 - other endpoints: overall response rate, overall survival, quality of life

E2100: Progression-free Survival

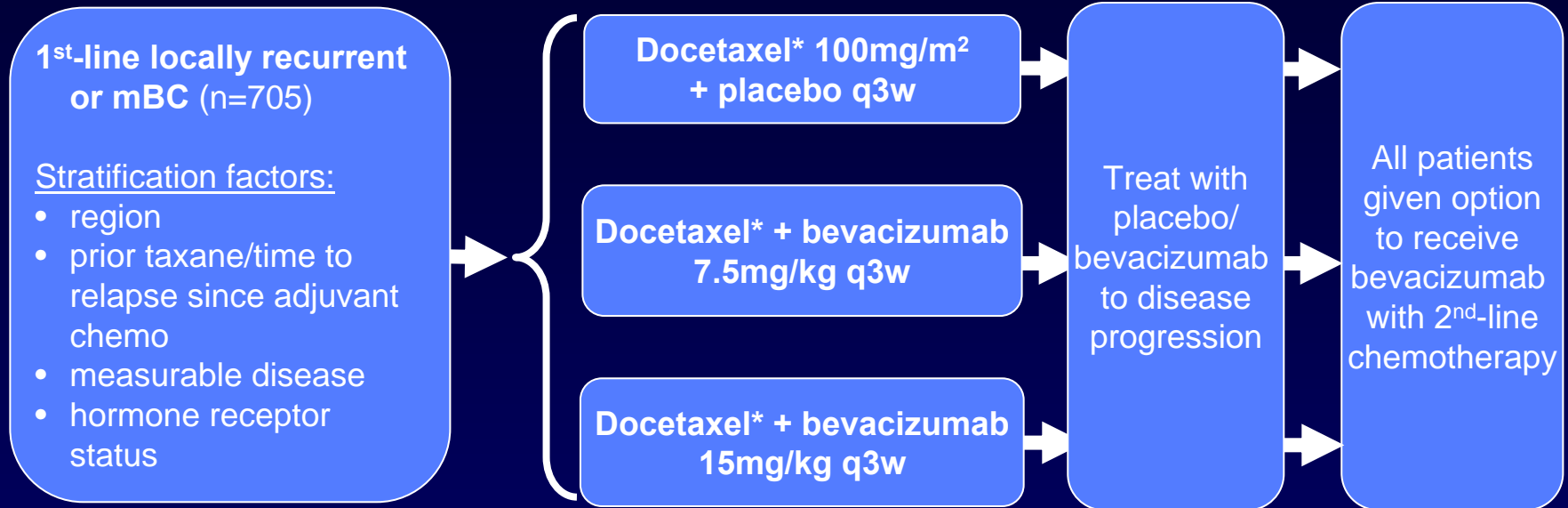


*Scans available for 90% of patients;

PFS = progression-free survival;
HR = hazard ratio

Cameron D. EJC Suppl. 2008.
 Adapted with permission from Elsevier
 Roche data on file submitted to regulatory authority in 2007

Phase III Trial of Bevacizumab plus Docetaxel in First-line mBC (AVADO)



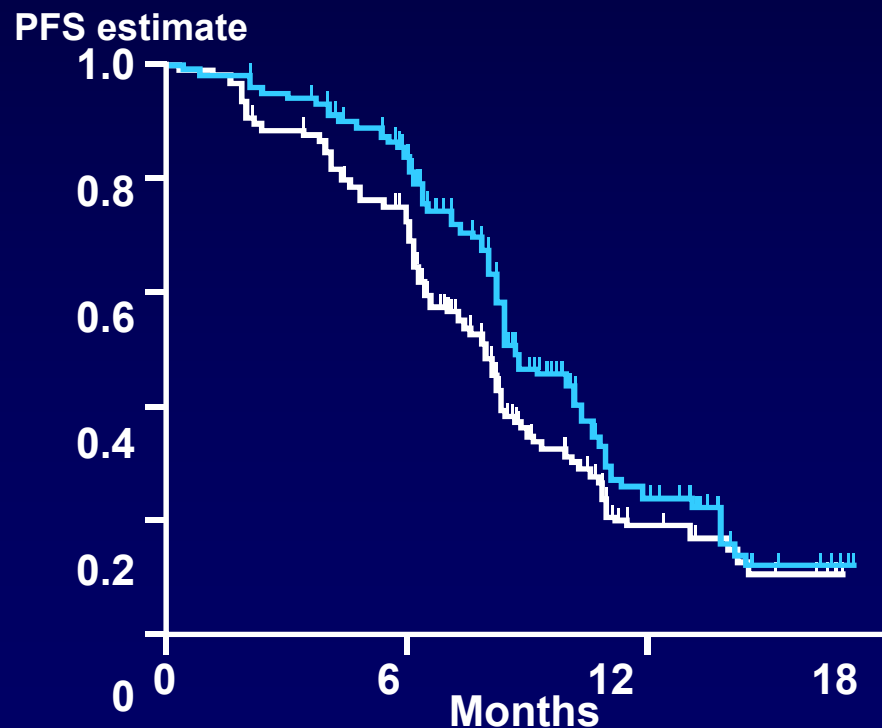
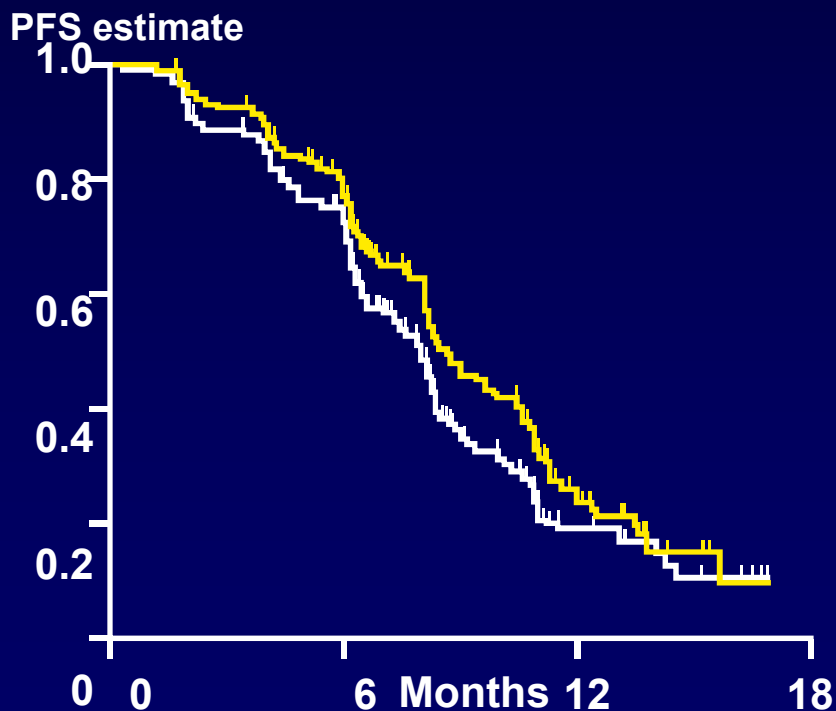
***Docetaxel was administered for a maximum of 9 cycles, but earlier discontinuation was permitted**

- **Primary endpoint: progression-free survival**
- **Secondary endpoints: overall response rate, duration of response, time to treatment failure, overall survival, safety, quality of life**

AVADO: Progression-free Survival

	Placebo + docetaxel (n=241)	Bev 7.5 + docetaxel (n=248)
HR + 95% CI (unstratified)		0.79 (0.63–0.98) p=0.0318
HR + 95% CI (stratified*)		0.69 (0.54–0.89) p=0.0035
Median	8.0	8.7

	Placebo + docetaxel (n=241)	Bev 15 + docetaxel (n=247)
HR + 95% CI (unstratified)		0.72 (0.57–0.90) p=0.0099
HR + 95% CI (stratified*)		0.61 (0.48–0.78) p<0.0001
Median	8.0	8.8



How Realistic is this Option?

- **Data from clinical trials in fit patients**
- **Toxicity profile**
- **Availability**
- **Cost**

Which systemic single agent treatment option would you select for this patient?

- Taxane either weekly or 3 weekly
- Pegylated liposomal doxorubicin
- Capecitabine
- Vinorelbine
- Gemcitabine
- Ixabepilone
- Other

Active Single Agents in Breast Cancer

- **Taxanes**
 - Docetaxel, paclitaxel
- **Anthracyclines**
 - Doxorubicin, epirubicin, liposomal doxorubicin
- **Alkylating agents**
- **Fluoropyrimidines**
 - 5-FU, capecitabine
- **Gemcitabine**
- **Epothilones**
- **Platinums**

Capecitabine: Activity in Taxane-pretreated MBC

Study ¹	Response rate (%)	Tumor control (%)	Median TTP (months)	Median OS (months)
Blum (n=162)	20	63	3.0	11.6
Blum (n=74)	26	57	3.2	12.2
Reichardt (n=136)	15	62	3.3	10.4
Fumoleau (n=126)	28	63	4.9	15.2

- Capecitabine is more effective than other monotherapies, $p=0.005^2$

¹Leonard R et al. *Semin Oncol* 2004;31(Suppl. 10):21–8

²Miles D et al. *Clin Breast Cancer* 2004;5:273–8

Capecitabine: First-line Monotherapy in Patients ≥ 65 years

	Capecitabine 1250mg/m ² (n=30)	Capecitabine 1000mg/m ² (n=43)
Median age (years)	73 (range: 65–89)	
ORR (%)	37	35
CR	3	2
PR	33	32
Disease control (ORR + stable disease) (%)	70	81
Median TTP (months)	3.9	4.1
Median overall survival (months)	10.0	16.0

ORR = overall response rate

CR = complete response

PR = partial response



Navelbine As Single Agent

Metastatic 1st line

OR: 40% to 60%

AUTHOR		No. PTS	OR (%)
FUMOLEAU P.	<i>JCO 93</i>	145	41
BRUNO S.	<i>Am. JCO 95</i>	63	44
GARCIA-CONDE J.	<i>Ann. Oncol. 94</i>	50	50
ROMERO A.	<i>JCO 94</i>	44	41
CANOBBIO L.	<i>J. Libbey 91</i>	25	60
RANUZZI M.	<i>ASCO 96</i>	34	47
TERENZIANI/BONADONNA	<i>Br.C.Res.T. 96</i>	27	59

Gemcitabine in Metastatic Breast Cancer

- 6 Phase II trials, total # 205 patients
- 1st, 2nd, or 3rd line metastatic disease
- Most patients had received prior anthracycline or taxane
- Response rates 14 to 37%
- Median Survival 11.5 to 18.6 months
- Common Toxicity
 - Neutropenia, thrombocytopenia, anaemia
 - Occasional 'flu-like' symptoms N/V, dyspnoea, ↑ LFTs

Single Agent PLD for MBC in Heavily Pretreated Patient – Phase II Studies

	No of pts	Schedule	ORR (%)
Ranson (JCO 1997)	71	45-50 mg/m ² q 3-4 w x 6	31
Lyass (Cancer 2000)	45	35-70 mg/m ² q 3-6 w	33
Schmid (SABCS 2004)	24 (19)*	25 mg/m ² q 2 w	5 (CB = 21%)
Mlineritsch (Onkologie 2004)	30	45 mg/m ² q 4 w	31

* Evaluable

Toxicity	Range (%)
Neutropenia (Grade 3/4)	0-27 (up to 3% FN)
Mucositis	0-32
Hand Foot Syndrome (HFS) (Grades 1-3) (schedule dependent)	13-30% no grade 4

PLD vs Conventional Doxorubicin in First-line Treatment of MBC: Phase III Trial

Study Design

- 1st-line MBC (Stages IIIB/IV)
- Open-label, multicenter

Stratification

- Prior adjuvant anthracycline
- Cardiac risk factor
- Bone only mets

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- N = 509
- 68 international sites

PLD 50 mg/m² q 4 wks*

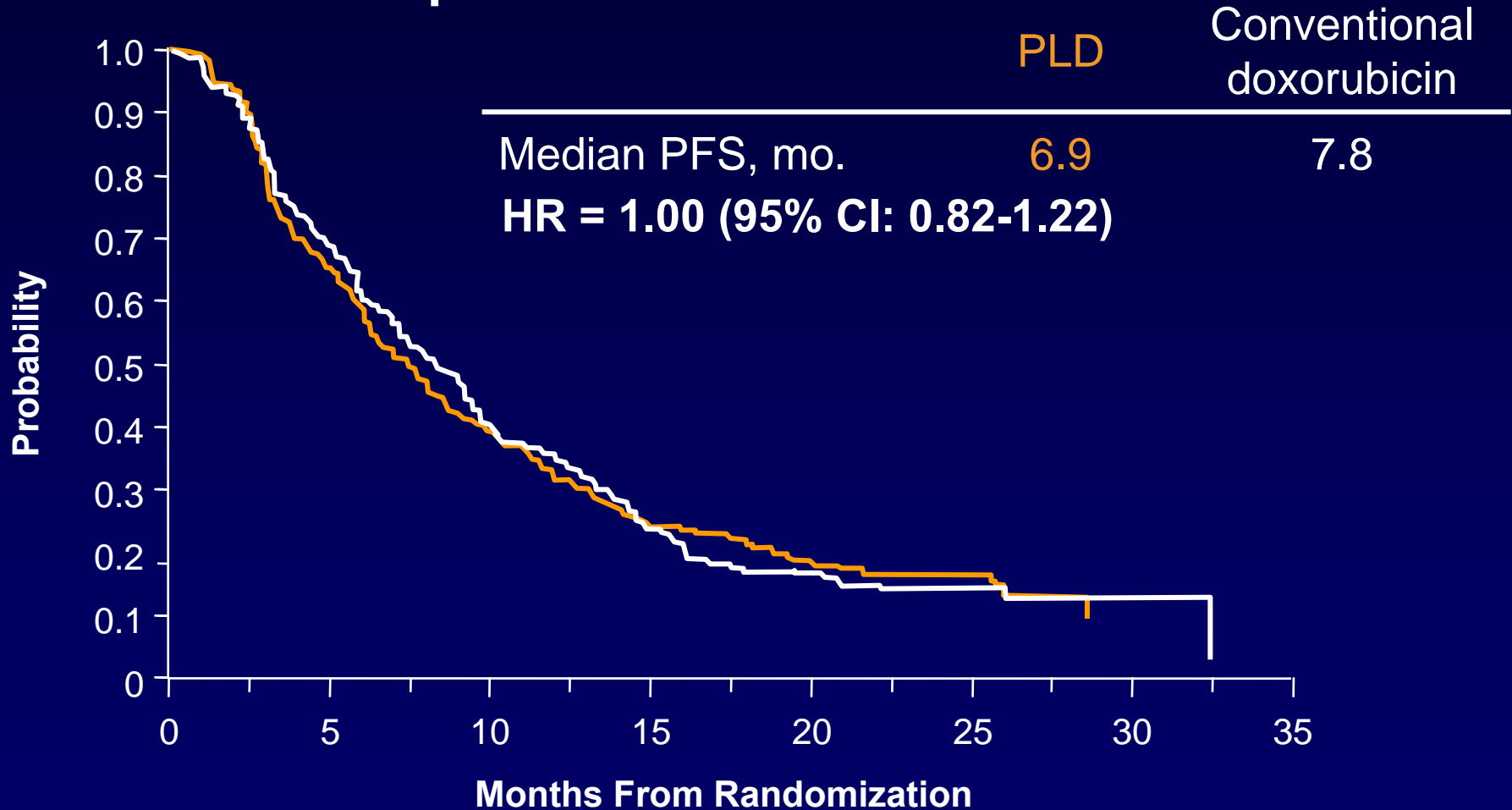
Conventional doxorubicin
60 mg/m² q 3 wks[†]

*Until PD or unacceptable toxicity.

†Until PD or cumulative anthracycline dose of 550 mg/m².

PLD vs Doxorubicin Progression-Free Survival (PFS)

Intent-to-Treat Population



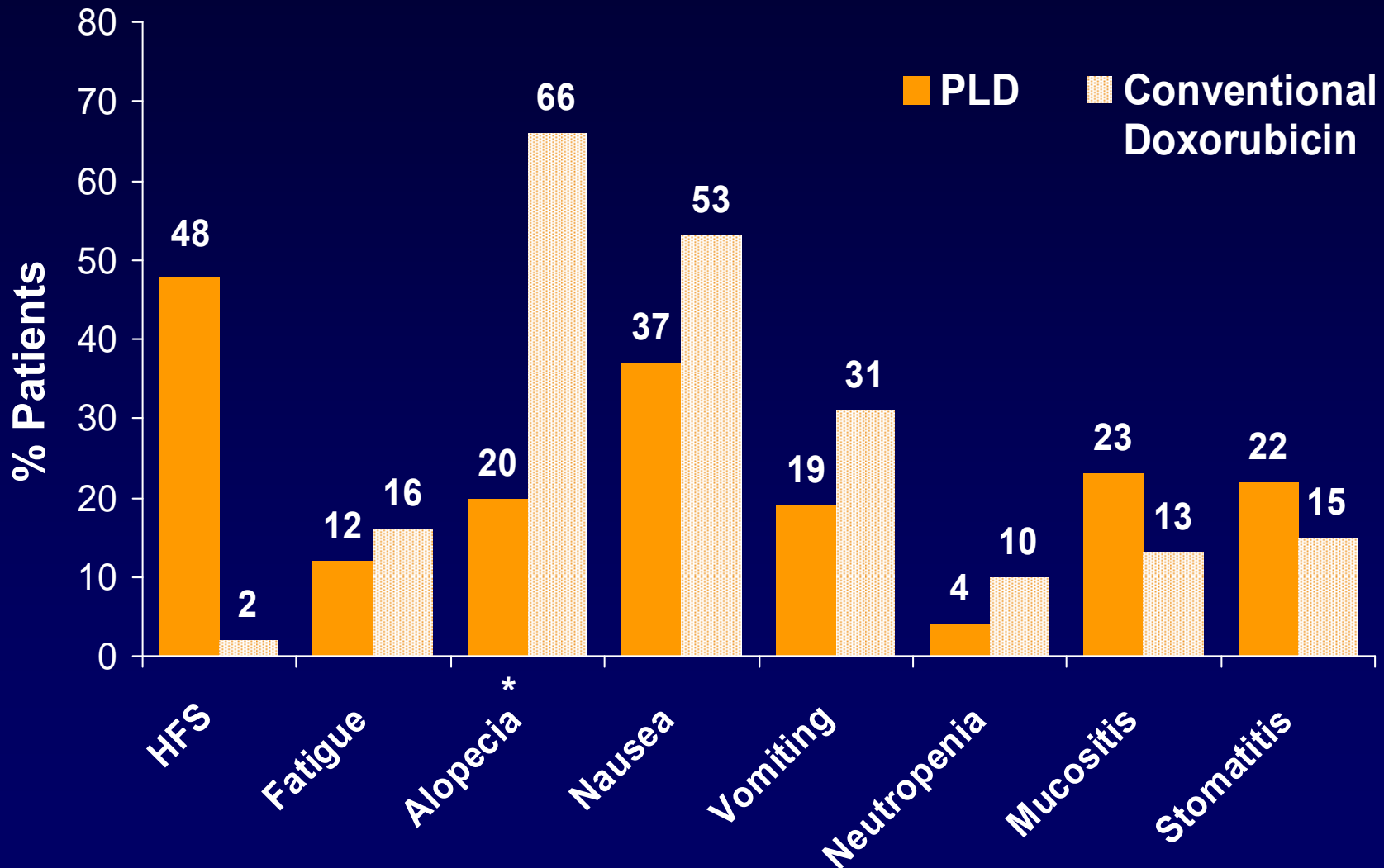
PLD vs Doxorubicin Response Rates*

	PLD (N=209)	Conventional Doxorubicin (N=201)
Overall response rate (CR + PR)	33%	38%
Complete response (CR)	3%	4%
Partial response (PR)	29%	34%
Stable disease (SD)	25%	25%
Progressive disease (PD)	18%	11%
Median duration of response	7.3 mo	7.1 mo
Median overall survival	21 mo	22 mo

*Measurable disease (n=410); 25% in each group had no radiographic assessment of response.

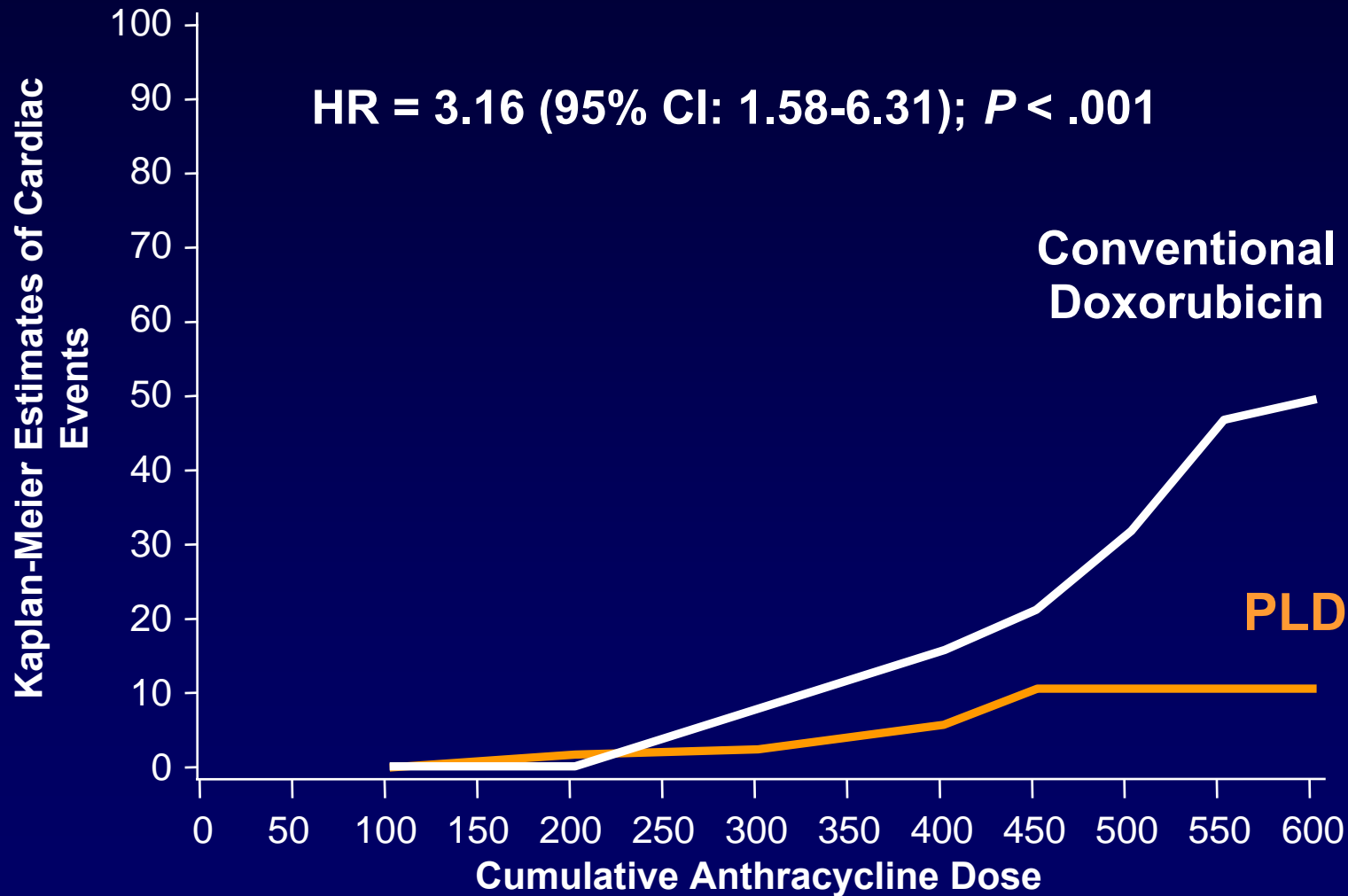
O'Brien et al. *Ann Oncol.* 2004;15:440-449.

Treatment-Related Adverse Events All Grades



PLD vs Doxorubicin

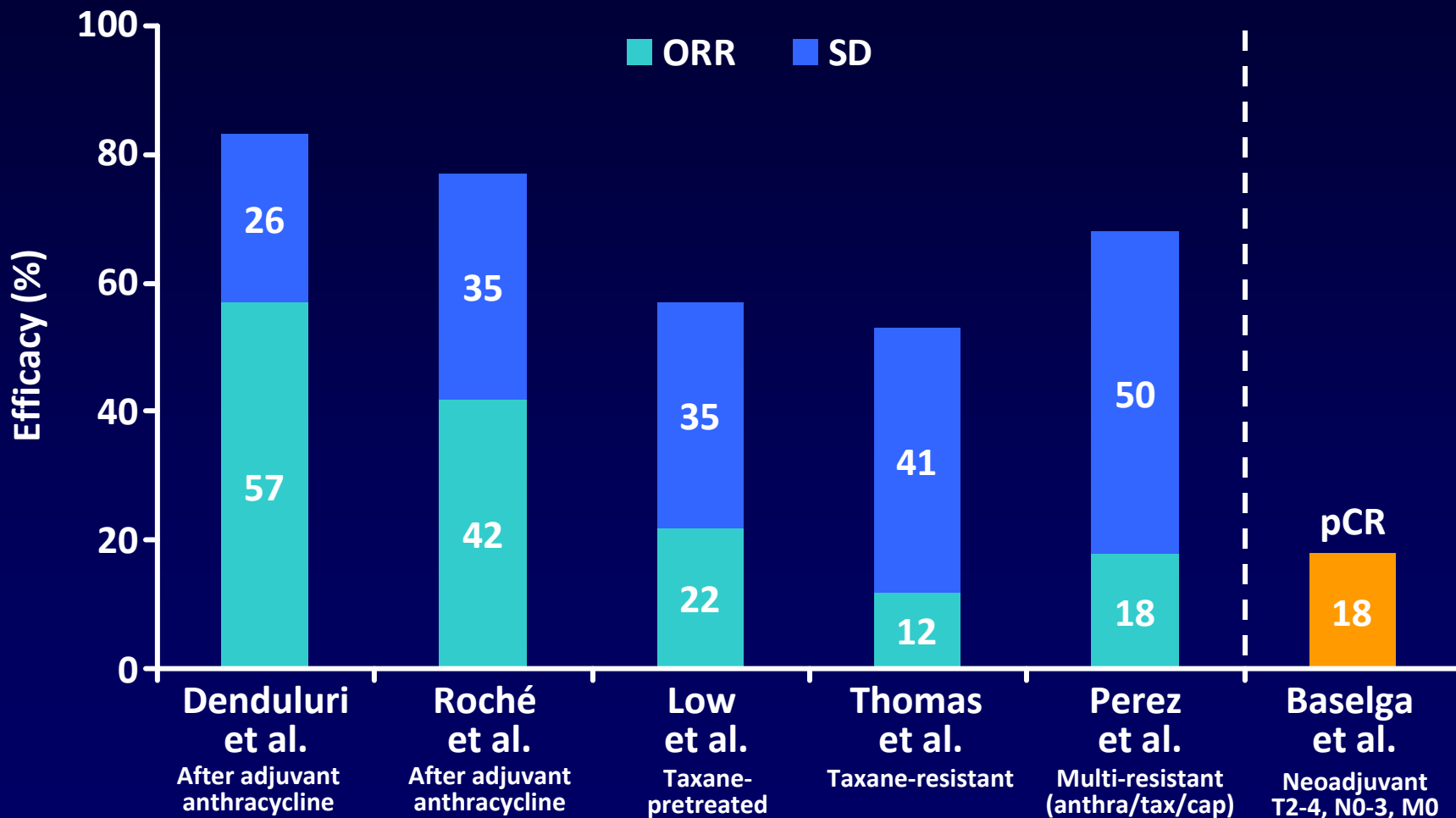
Cardiac Events vs Cumulative Dose



Ixabepilone: Epothilone B Analog

- **1st approved agent in a new class of antineoplastics, the epothilones**
- **Novel microtubule-stabilizing agent with tubulin-binding mode distinct from other agents**
- **Low susceptibility to tumor resistance mechanisms**
 - **MRP-1 and P-gp efflux pumps**
 - **β (III) tubulin overexpression**
 - **β tubulin mutations**

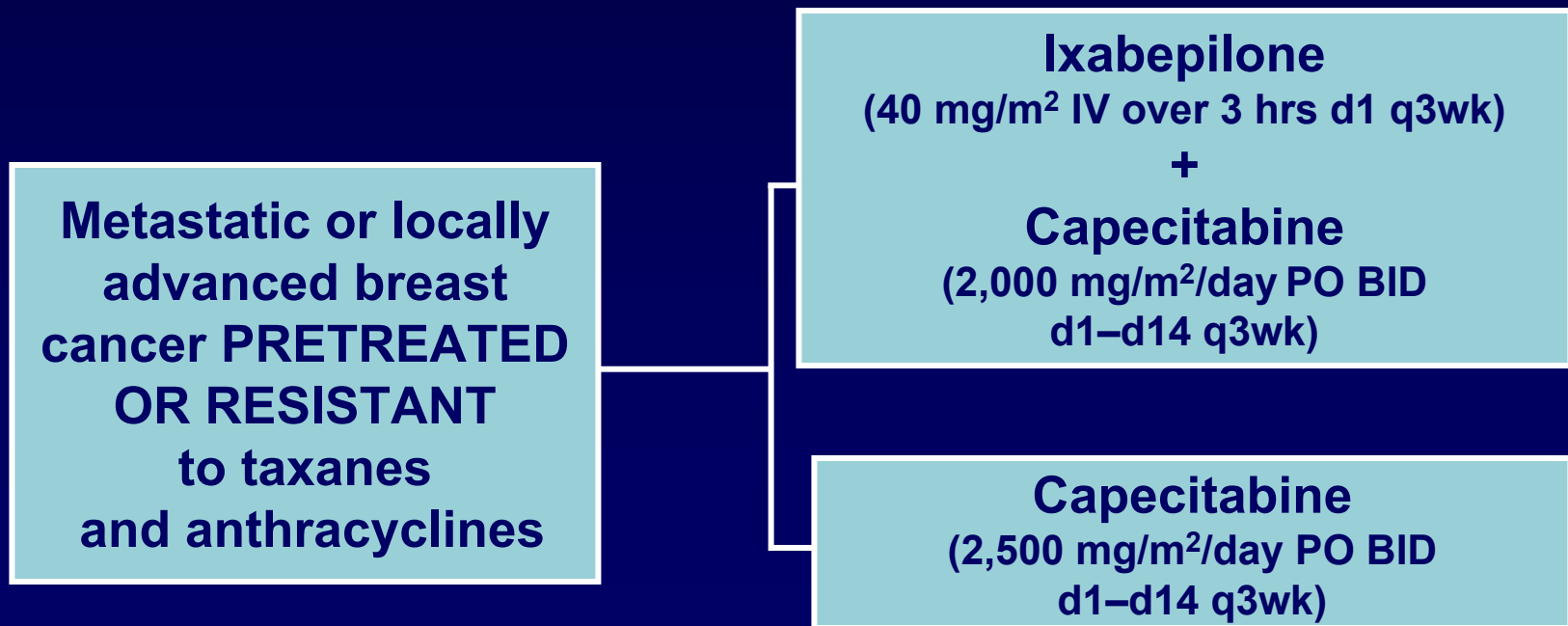
Ixabepilone clinical activity in advanced breast cancer: phase II studies



Denduluri et al. J Clin Oncol 2007;25:3421-7; Roché et al. J Clin Oncol 2007;25:3415-20
Low et al. J Clin Oncol 2005;23:2726-34; Thomas et al. J Clin Oncol 2007;25:3399-406
Perez et al. J Clin Oncol 2007;23:3407-14; Baselga et al. Breast Cancer Res Treat 2005;94:S31 (Abstract 305)

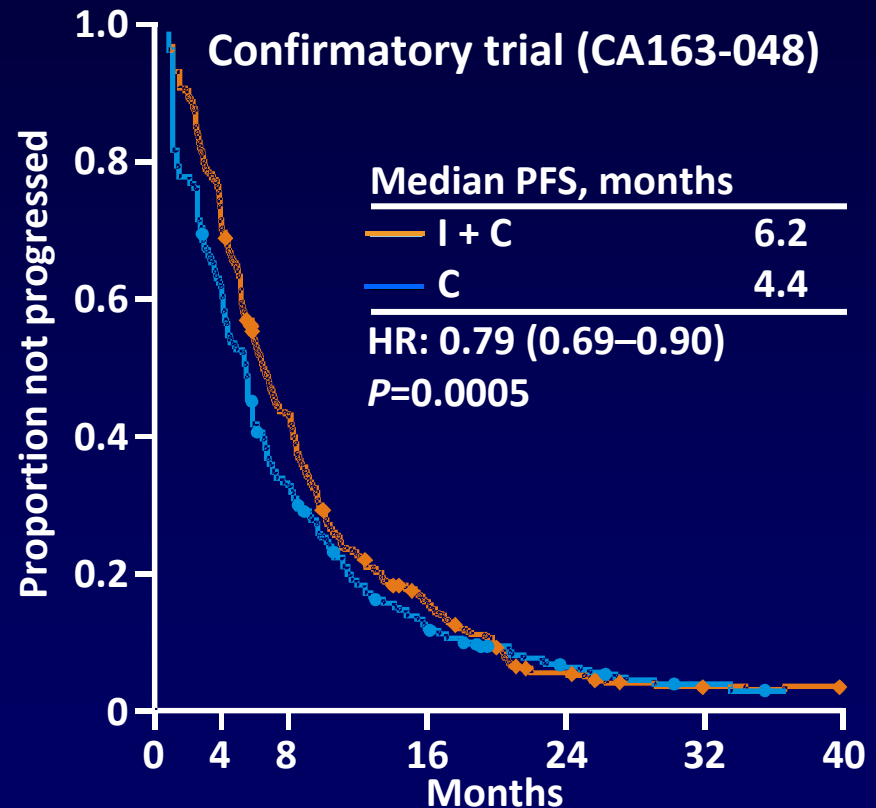
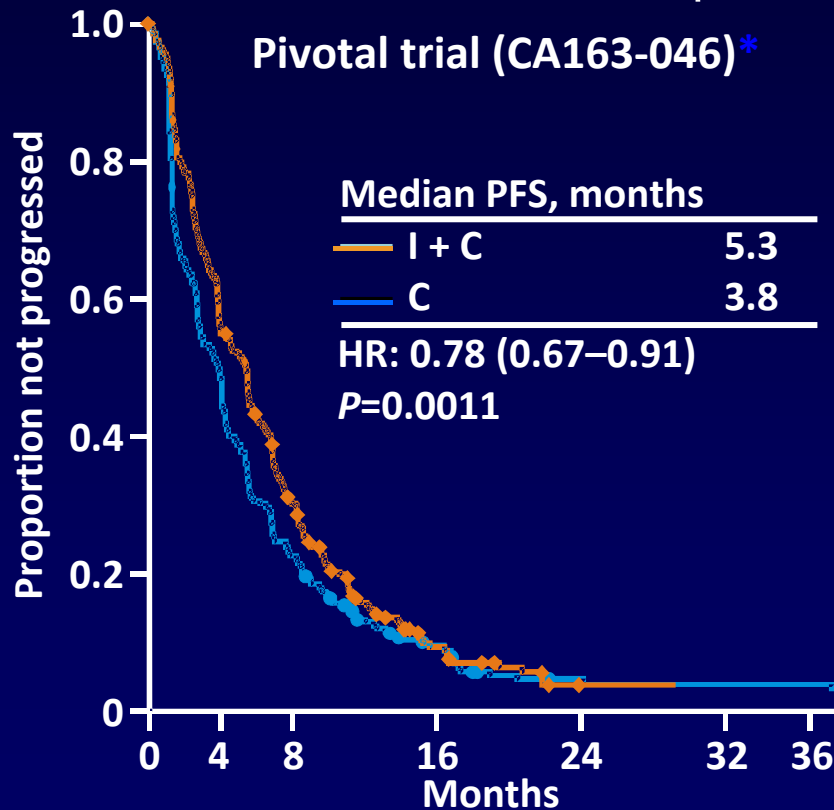
Ixabepilone + capecitabine phase III trials: study design (CA163-046 and CA163-048)

- Two international, randomised, open-label, phase III trials
 - CA163-046: pivotal trial of patients with resistance to anthracyclines and taxanes; **primary endpoint PFS**
 - CA163-048: confirmatory trial of patients pretreated OR resistant to anthracyclines and taxanes; **primary endpoint OS**



Ixabepilone + capecitabine phase III trials: progression-free survival

- Consistent superiority in prolonging PFS with ixabepilone combination over capecitabine alone in both phase III studies



*Primary endpoint

~40% increase in PFS

Ixabepilone + capecitabine phase III trials: grade 3/4 treatment-related toxicities

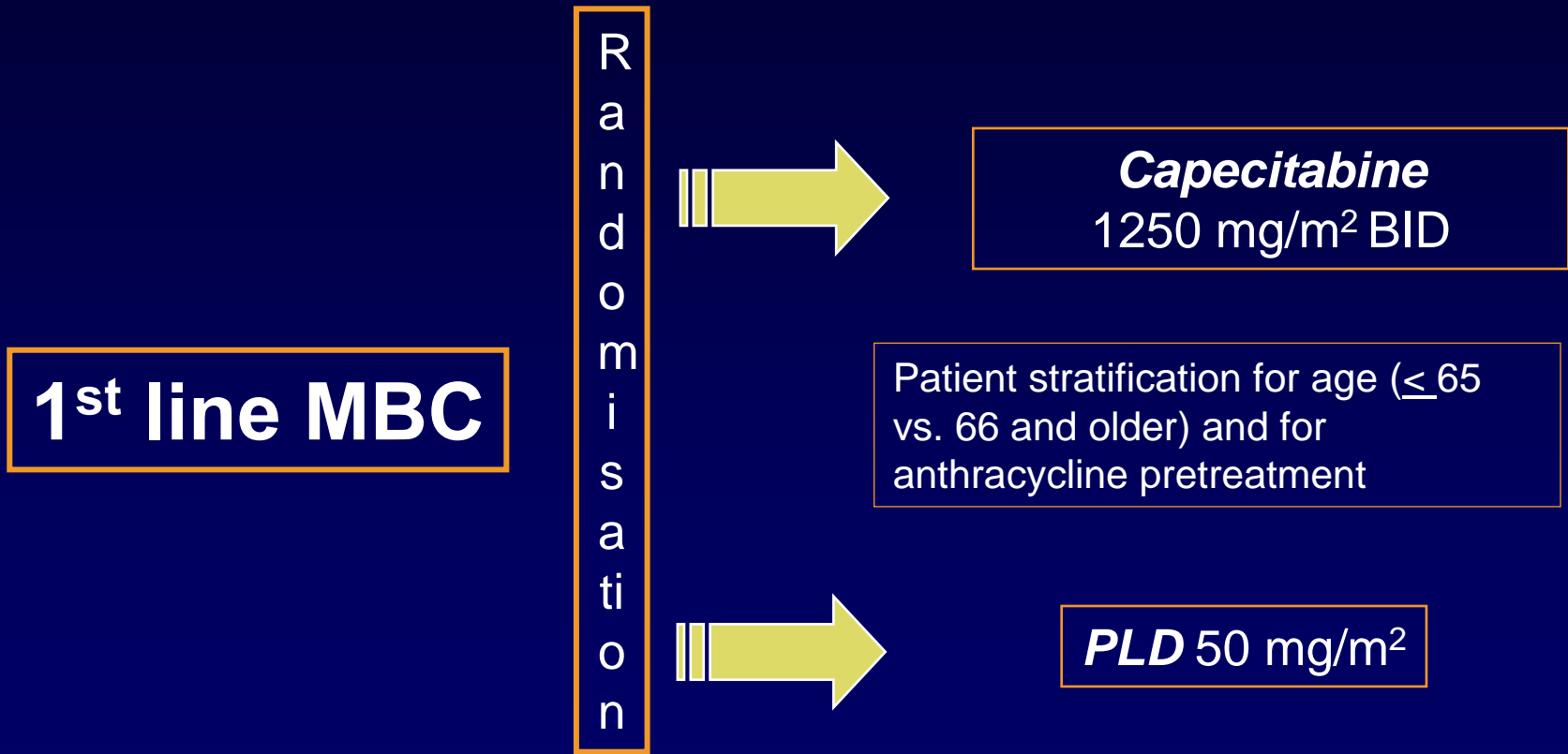
Adverse event	Pivotal trial (CA163-046)		Confirmatory trial (CA163-048)	
	I + C, % (N=369)	C, % (N=368)	I + C, % (N=595)	C, % (N=603)
Neutropenia	68	11	73	8
Febrile Neutropenia	4	1	4	2
Peripheral neuropathy	23	0	24	1
Resolution of neuropathy*, median wks (range)	6.0 (4.6–7.6)	NA	6.2 (5.0–8.7)	NA
Hand-foot syndrome	18	17	21	20
Diarrhoea	6	9	7	9
Myalgia	8	<1	5	0
Stomatitis	1	1	2	1

*Defined as the time from onset of worst grade to baseline or grade 1; NA: neuropathy not seen

What are the realistic options for this patient given her comorbidities?

- Capecitabine
- Pegylated Liposomal Doxorubicin

PELICAN Trial: PLD vs Capecitabine Study Design



Cycles in both arms will be repeated as scheduled until disease progression or unacceptable toxicity