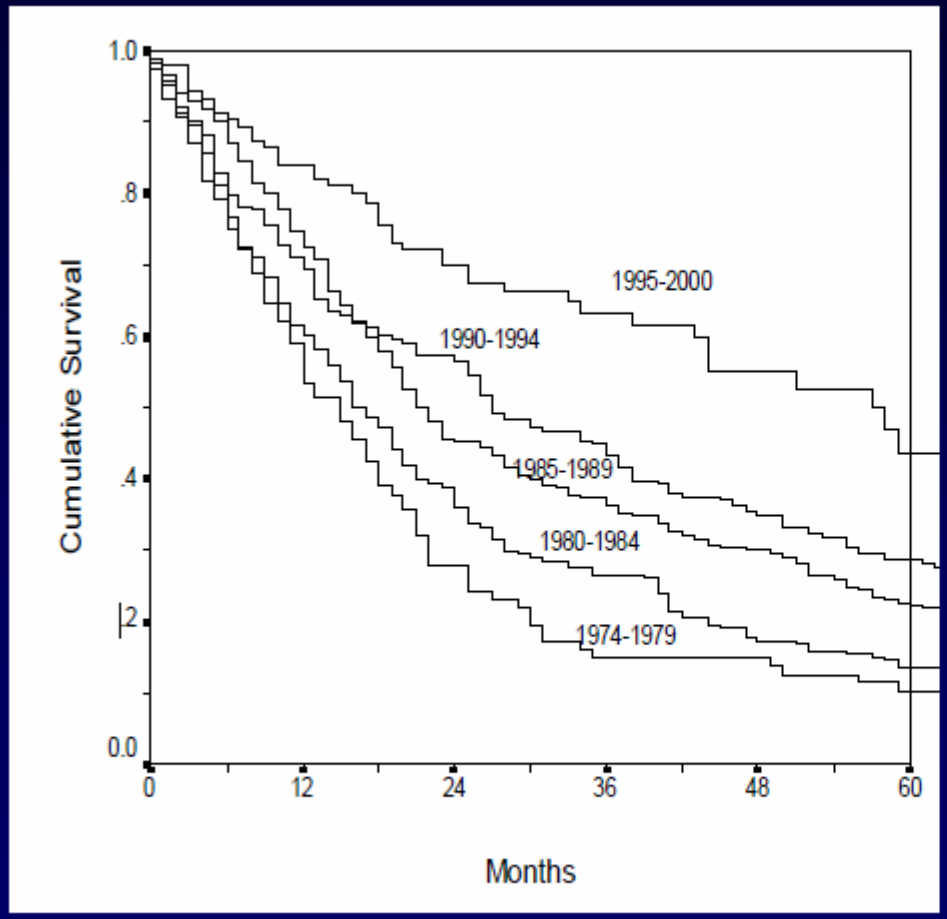
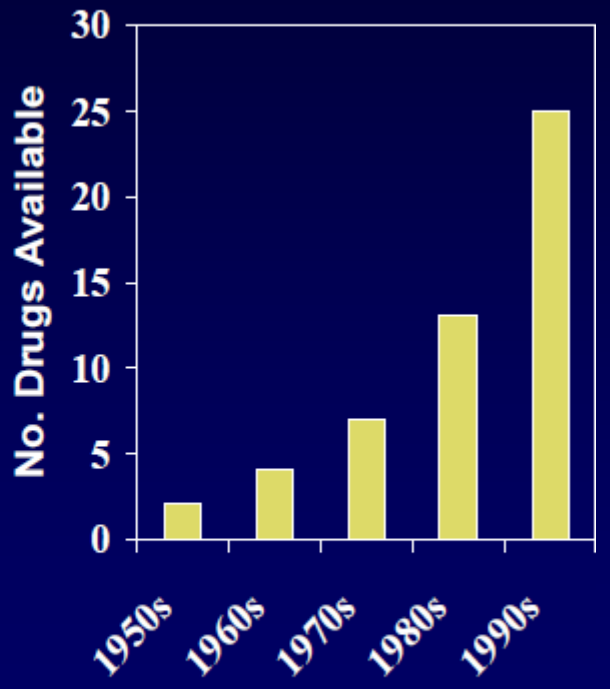
New chemotherapy drugs in metastatic breast cancer

Guy Jerusalem, MD, PhD

MBC Patients' survival over time





Giordano SH, et al. *Cancer.* 2004;100(1):44-52.

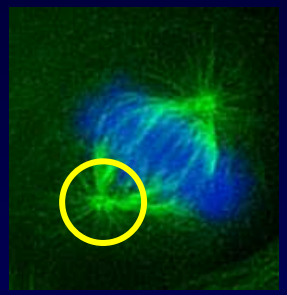
Median survival increases over time, but is still measured in months

This is not yet a chronic disease

New chemotherapy drugs in metastatic breast cancer

- Erubiline
- Nab-paclitaxel
- Etirinotecan pegol (NKTR-102)

Eribulin Inhibits Microtubule Dynamics in the Mitotic Spindle



Eribulin

1. Inhibits microtubule growth

Tubulin Polymerization

Growing microtubule

3. Generation of nonproductive tubulin aggregates

Eribulin

Spindle Pole

Tubulin Depolymerization

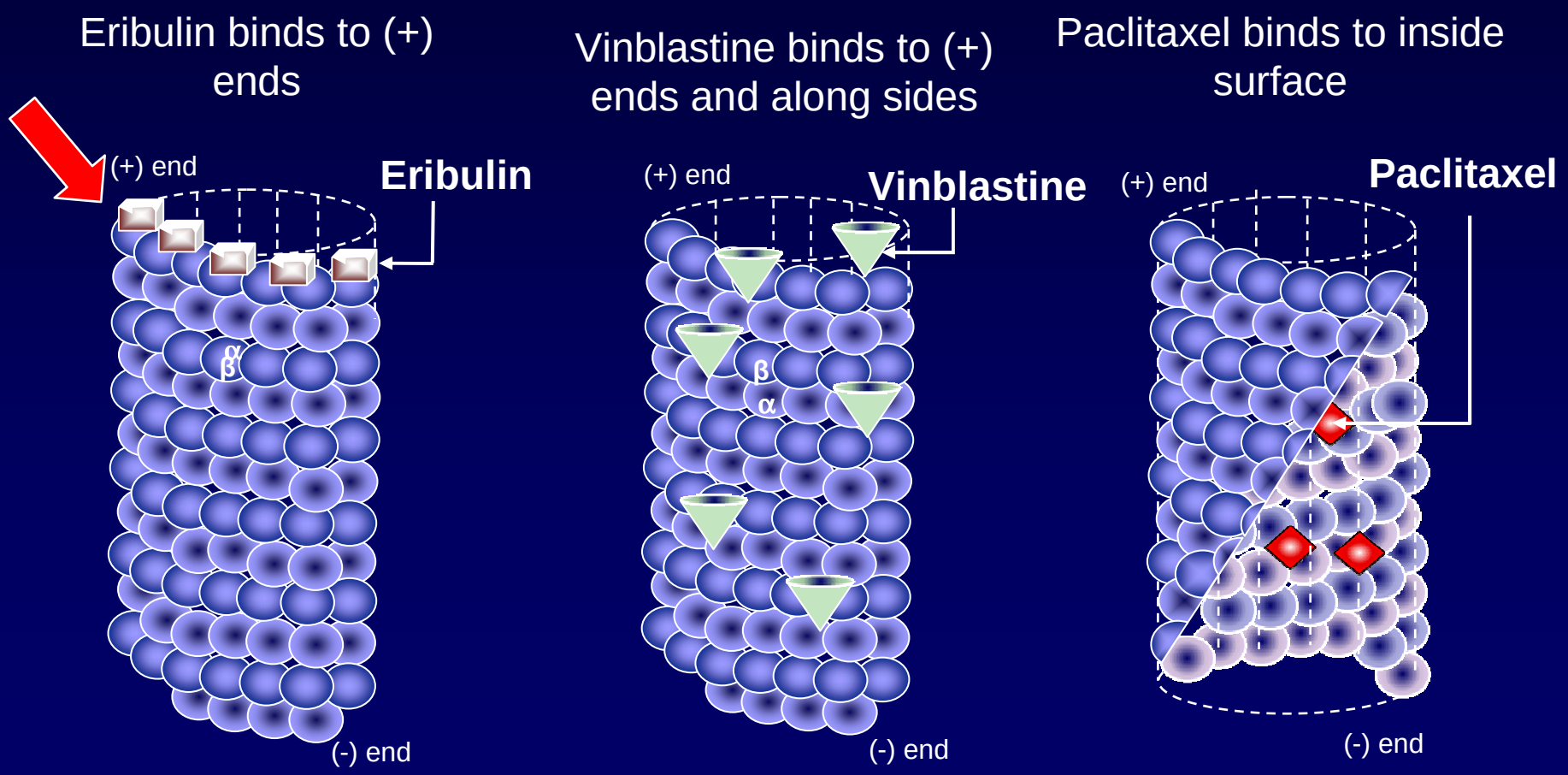
Shortening microtubule

Nonproductive tubulin aggregates

2. No measurable effect on shortening (at relevant concentrations)

Adapted from Jordan MA et al. *Mol Cancer Ther* 2005; 4:1086-1095.

Eribulin Blocks Microtubule Growth by Binding to Microtubule Ends



Modified from Jordan MA and Wilson L, Nat RevCancer. 2004;4:253-65, and Smith JA, Biochemistry, 2010:49, 1331-1337

EMBRACE: Randomized, Open-Label Phase III Trial Primary Endpoint: Overall Survival

Randomized 2:1; stratified by geographic region, previous capecitabine treatment, HER2/*neu* status

Patients with heavily pretreated locally recurrent or metastatic breast cancer

(N = 762)

Eribulin Mesylate
1.4 mg/m^2 2-5 min IV on Days 1, 8
q3w
(n = 508)

Treatment of Physician's Choice (TPC)
Any monotherapy approved for cancer treatment (chemotherapeutic, hormonal, or biologic)*, or supportive care only†
(n = 254)

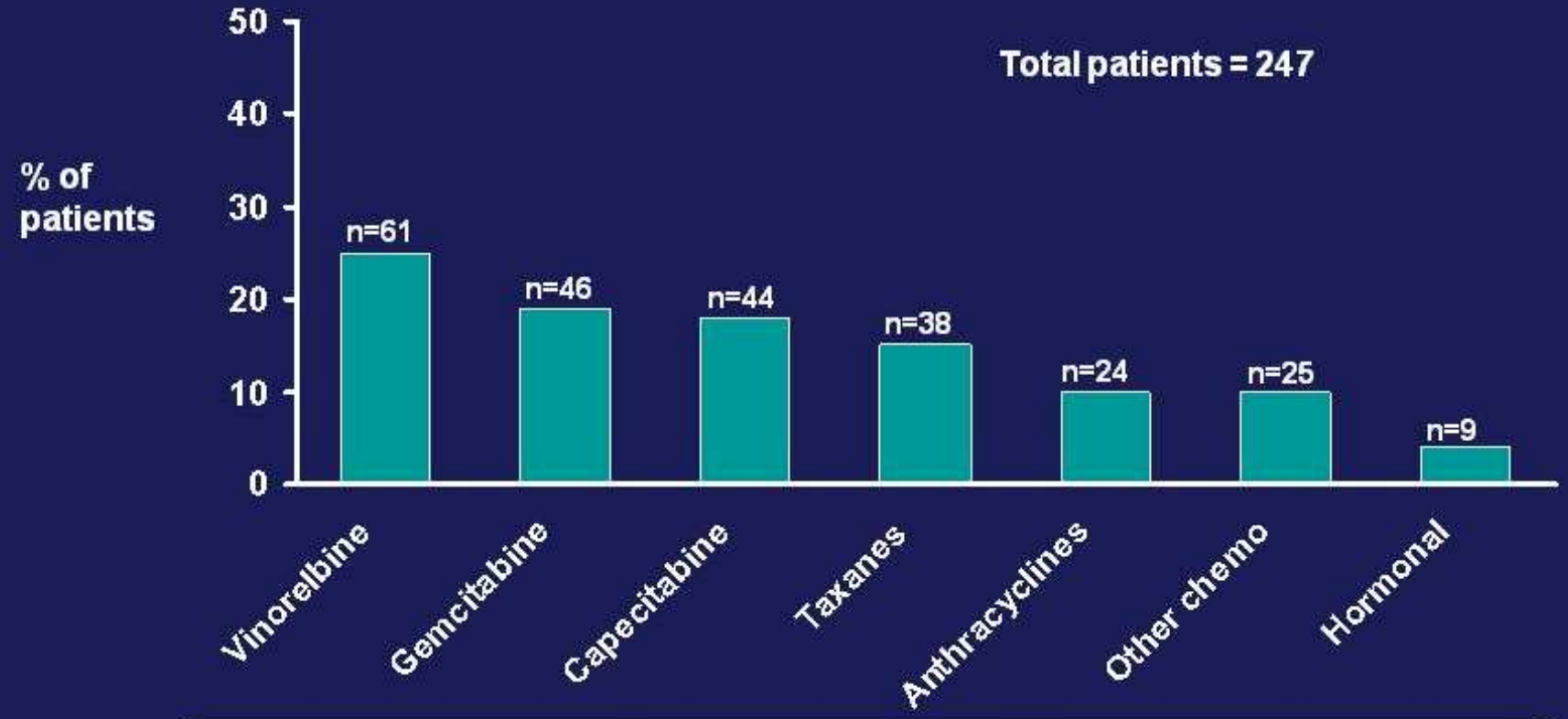
- **96% of patients in TPC arm received chemotherapy**

*Approved for treatment of cancer administered according to local practice.
†Palliative treatment or radiotherapy according to local practice.

Cortes J, et al. *Lancet.* 2011;377(9769):914-923.

TPC treatment received

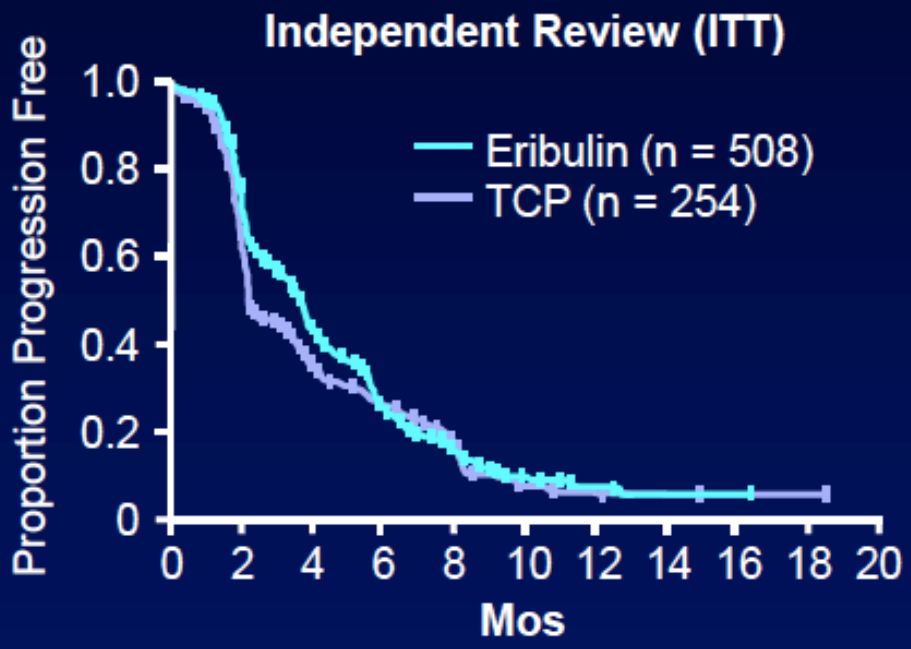
96% of patients treated with chemotherapy



No patient received best supportive care or "biological" therapies only

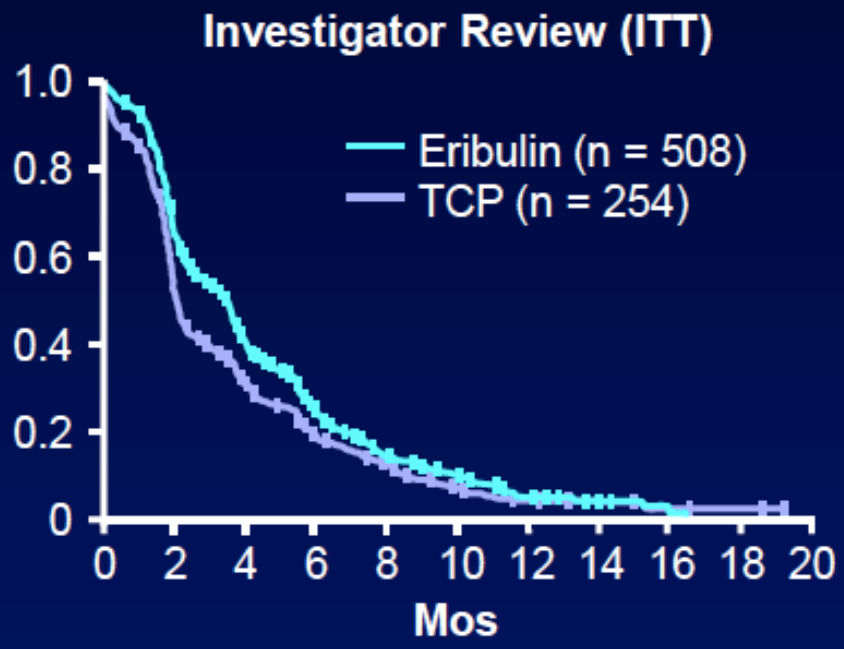
ITT population; Taxanes: paclitaxel, docetaxel, abraxane, (ixabepilone)
Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone

EMBRACE: Progression-free survival



Median, Mos
Eribulin 3.7
TCP 2.2

HR: 0.87 (95% CI: 0.71-1.05; *P* = .14)



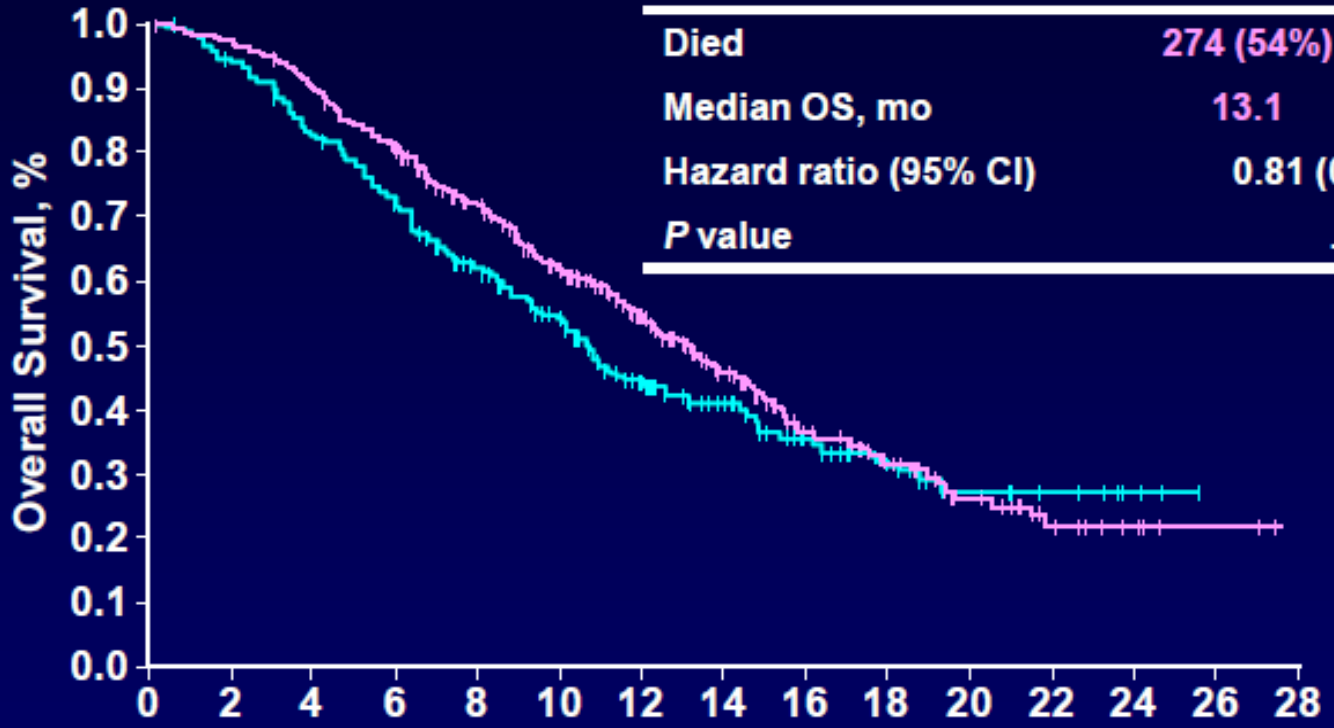
Median, Mos
Eribulin 3.6
TCP 2.2

HR: 0.76 (95% CI 0.64-0.90; *P* = .002)

Twelves C, et al. ASCO 2010. Abstract CRA1004.

EMBRACE: Overall Survival

	Eribulin N = 508	TPC N = 254
Died	274 (54%)	148 (58%)
Median OS, mo	13.1	10.6
Hazard ratio (95% CI)	0.81 (0.66-0.99)	
P value	.041	



Number at risk															
Eribulin	508	491	451	401	320	255	179	116	69	51	23	11	4	2	0
TPC	254	237	206	176	139	111	74	53	34	24	11	7	3	0	0

Tick marks indicate censored data
TPC = treatment of physician's choice

Cortes J, et al. *Lancet.* 2011;377(9769):914-923.

Grade 3 and 4 AEs*:

	Grade 3		Grade 4	
	Eribulin (n=503)	TPC (n=247)	Eribulin (n=503)	TPC (n=247)
Hematologic events, %				
Neutropenia	21.1	14.2	24.1	6.9
Leukopenia	11.7	4.9	2.2	0.8
Anemia	1.8	3.2	0.2	0.4
Febrile neutropenia	3.0	0.8	1.2	0.4
Non-hematologic events, %				
Asthenia / fatigue	8.2	10.1	0.6	0
Peripheral neuropathy†	7.8	2.0	0.4	0
Nausea	1.2	2.4	0	0
Dyspnea	3.6	2.4	0	0.4
Mucosal inflammation	1.4	2.0	0	0
Hand-foot syndrome	0.4	3.6	0	0

*≥2% incidence; †Neuropathy peripheral, neuropathy, paresthesia, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy

Study design

- Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)

Locally advanced or MBC

- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m^{2†} 2- to 5-min IV
Day 1 & 8 q21 days

Randomization 1:1

Capecitabine
1250 mg/m^2 BID orally
Days 1-14, q21 days

Co-primary endpoint

- OS and PFS

Secondary endpoints

- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

- Stratification:
  - Geographical region, HER2 status

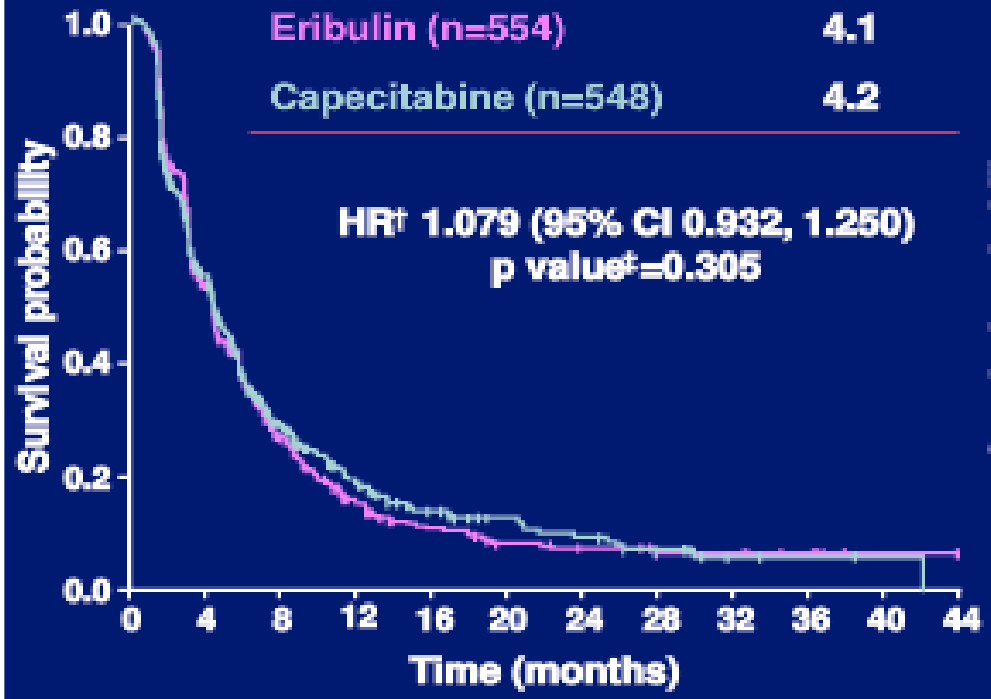
†Equivalent to 1.23 mg/m^2 eribulin

Progression-free survival

Independent Review

	Median (months)
Eribulin (n=554)	4.1
Capecitabine (n=548)	4.2

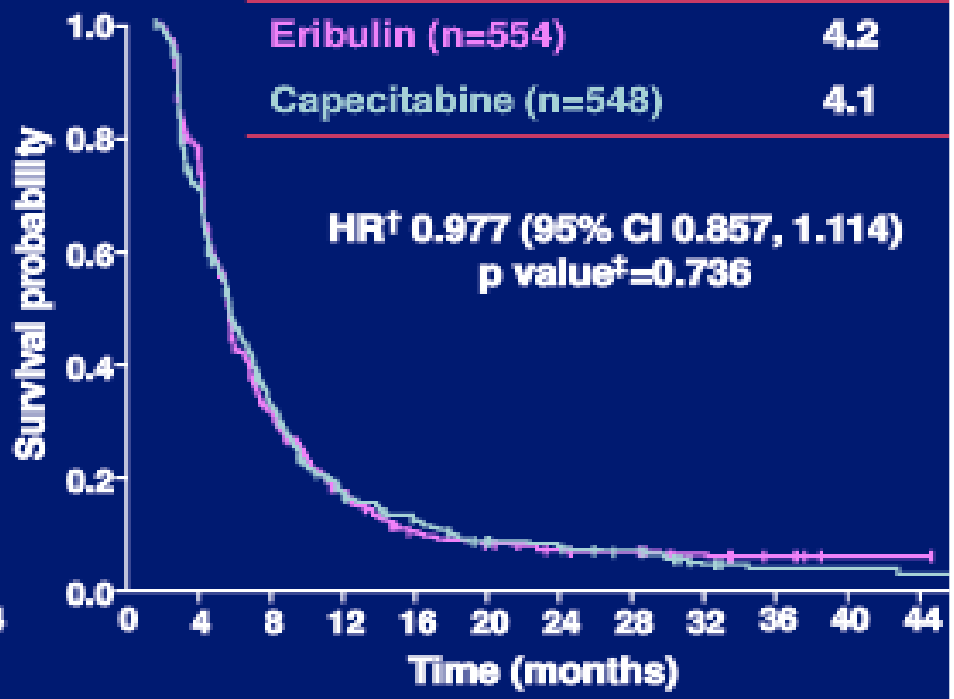
HR† 1.079 (95% CI 0.932, 1.250)
p value‡=0.305



Investigator Review

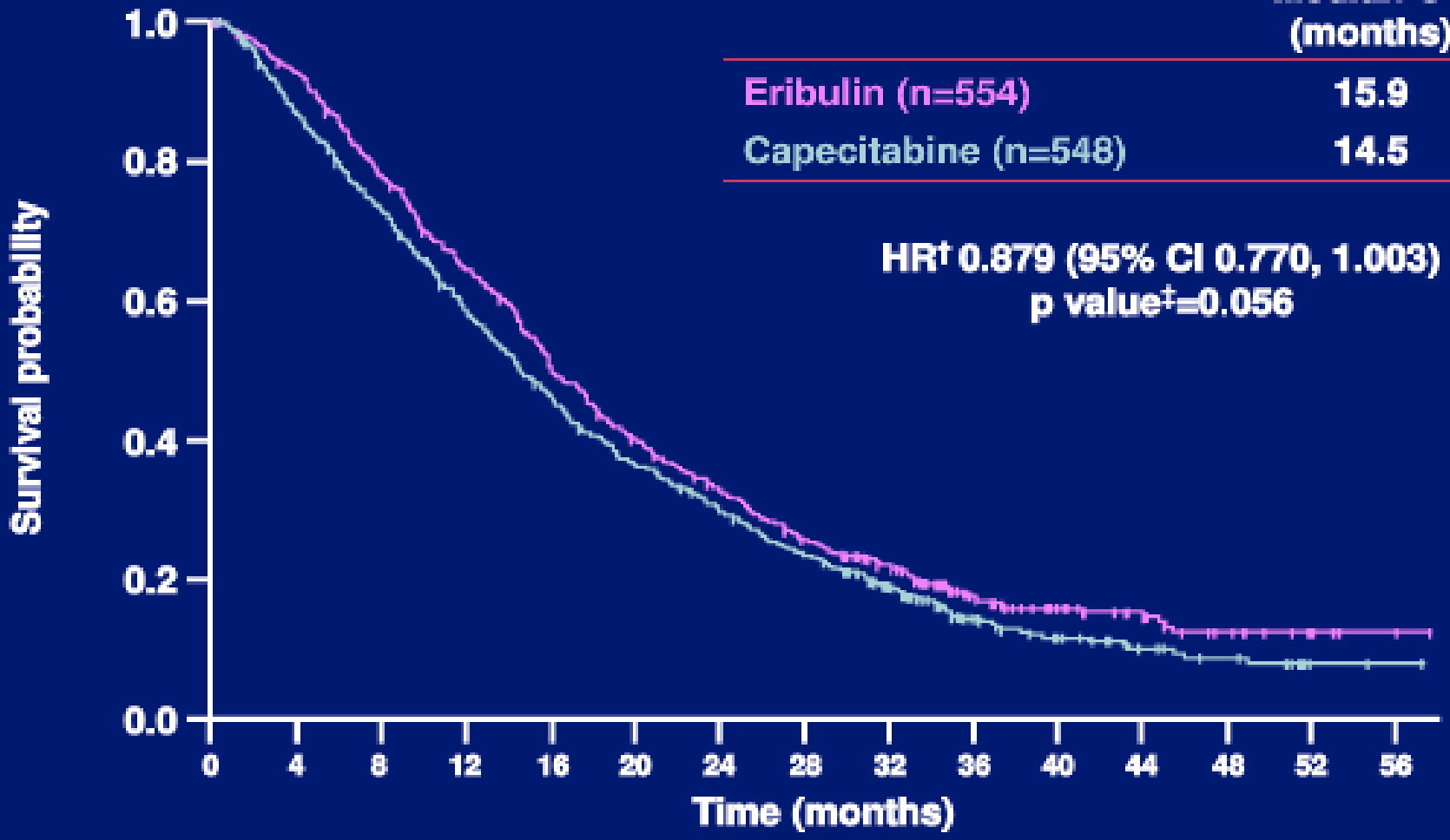
	Median (months)
Eribulin (n=554)	4.2
Capecitabine (n=548)	4.1

HR† 0.977 (95% CI 0.857, 1.114)
p value‡=0.736



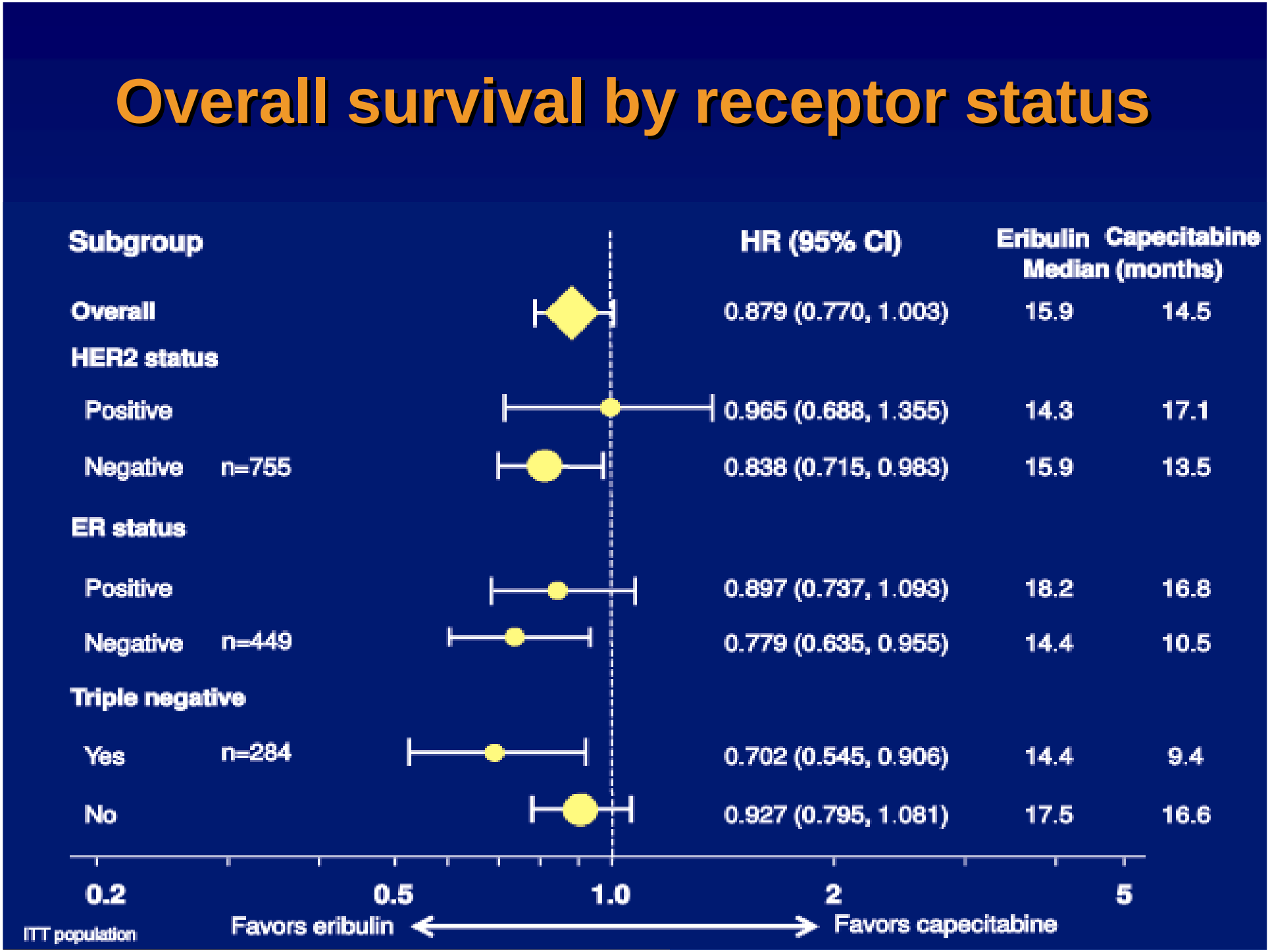
ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

Overall survival



ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

Overall survival by receptor status



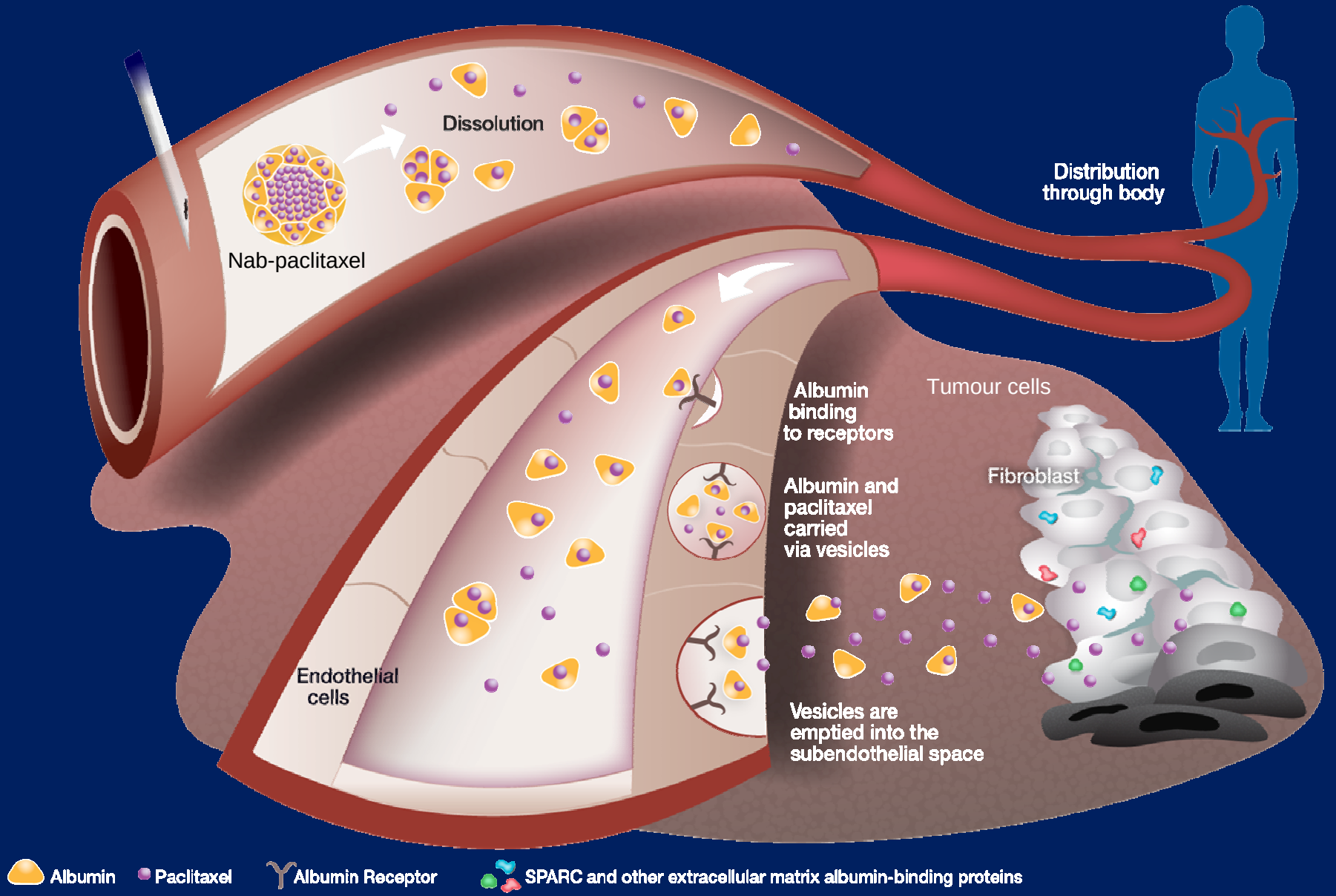
nab Paclitaxel

- **Paclitaxel bound to albumin in a nanoparticle**
  - **Increases drug selectivity for tumor cells (albumin intake mechanisms)**

- **No routine steroid or antihistamine premedication required, no toxic solvents**

Gradishar W et al. J Clin Oncol. 2005;23:7794-7803

Nab-paclitaxel: Proposed mechanism of action



Desai. Drug Delivery Report 2007/8:16th Ed, 37-41; Desai et al. CCR 2006;12:1317-24

nab Technology Platform: Harnessing Endogenous Albumin Pathways Through Two Mechanisms of Action

1. Active receptor-mediated transport (transcytosis) by gp60 and caveolae
2. Active binding of albumin–drug complex by SPARC in tumor

Injection into circulation

Dissociation into individual albumin-bound paclitaxel complexes at concentration below threshold

Albumin
Paclitaxel
SPARC

Albumin–paclitaxel complex

gp60 receptors

Caveolae and vesicles

Tumor blood vessel endothelial cells

Tumor interstitium

Albumin–paclitaxel accumulation with SPARC binding

SPARC

Paclitaxel-induced tumor cell apoptosis

Tumor cells

Phase III Trial
Albumin-Bound Paclitaxel vs. Paclitaxel in MBC

Albumin-bound paclitaxel: 260 mg/m^2 q3w; Paclitaxel:175 mg/m2 q3w

	Albumin-Bound Paclitaxel N=229	Paclitaxel N=225	*P*-Value
Overall Response Rate	33%	19%	.001
Time to Progression	23.0 wk	16.9 wk	.006
Grade 4 Neutropenia	9%	22%	<.001
Grade 3 Sensory Neuropathy	10%*	2%	<.001

* Median time to improvement: 22 days

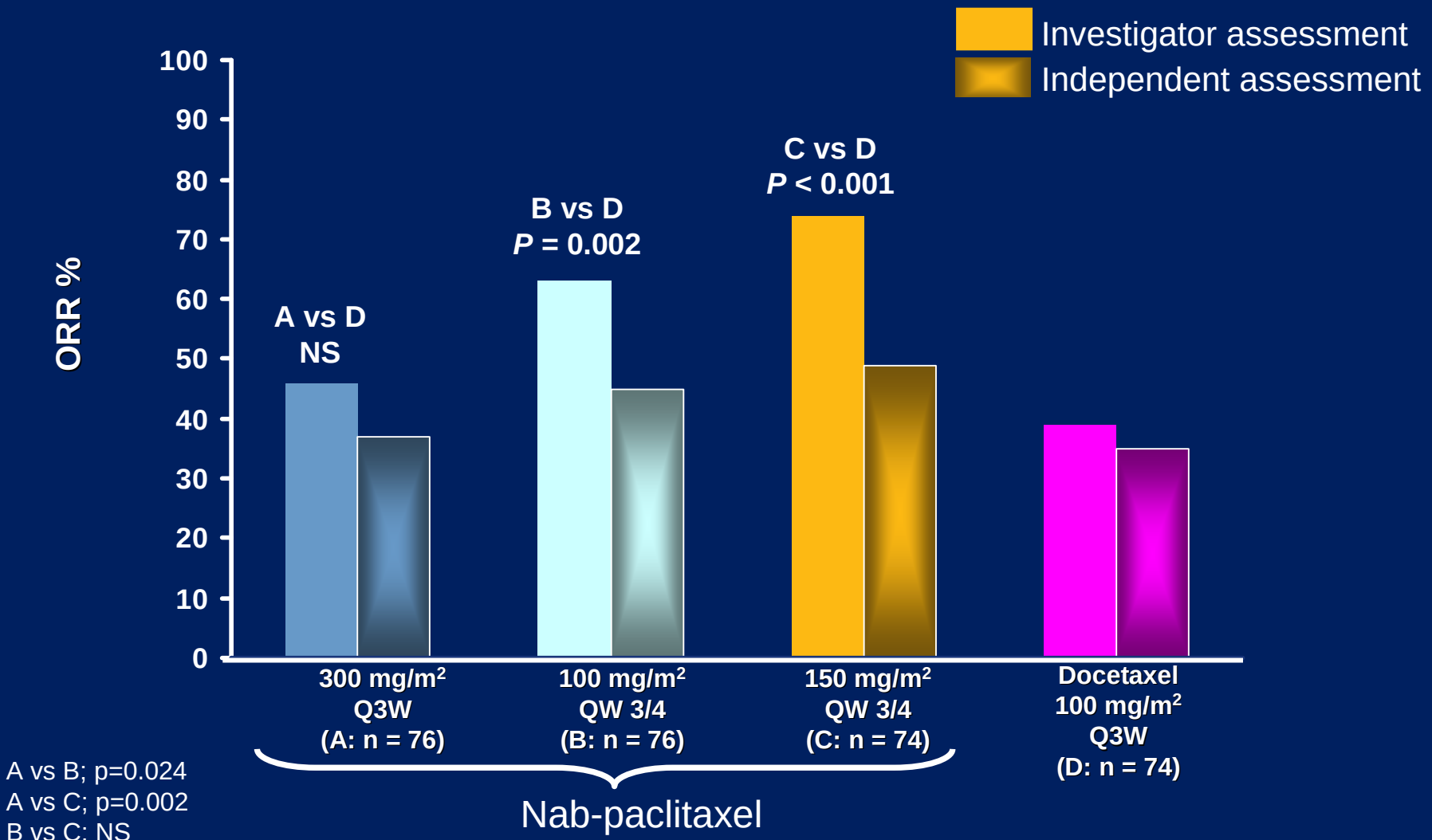
Gradishar W et al. J Clin Oncol. 2005;23:7794-7803

Approval/indication in Europe

Based on the results of the Phase III study, nab-paclitaxel received EMA approval at a dose of 260 mg/m^2 Q3W for the treatment of MBC in adult patients who have failed 1st-line treatment for metastatic disease and for whom standard, anthracycline-containing therapy is not indicated

Gradishar W et al. JCO 2005;23:7794-803
ABRAXANE® SPC. Available at:
http://www.medicines.org.uk/emc/document.aspx?documentid=21384&docType=SPC

Randomized Phase II study: Nab-paclitaxel Q3W vs QW vs docetaxel in 1st-line MBC

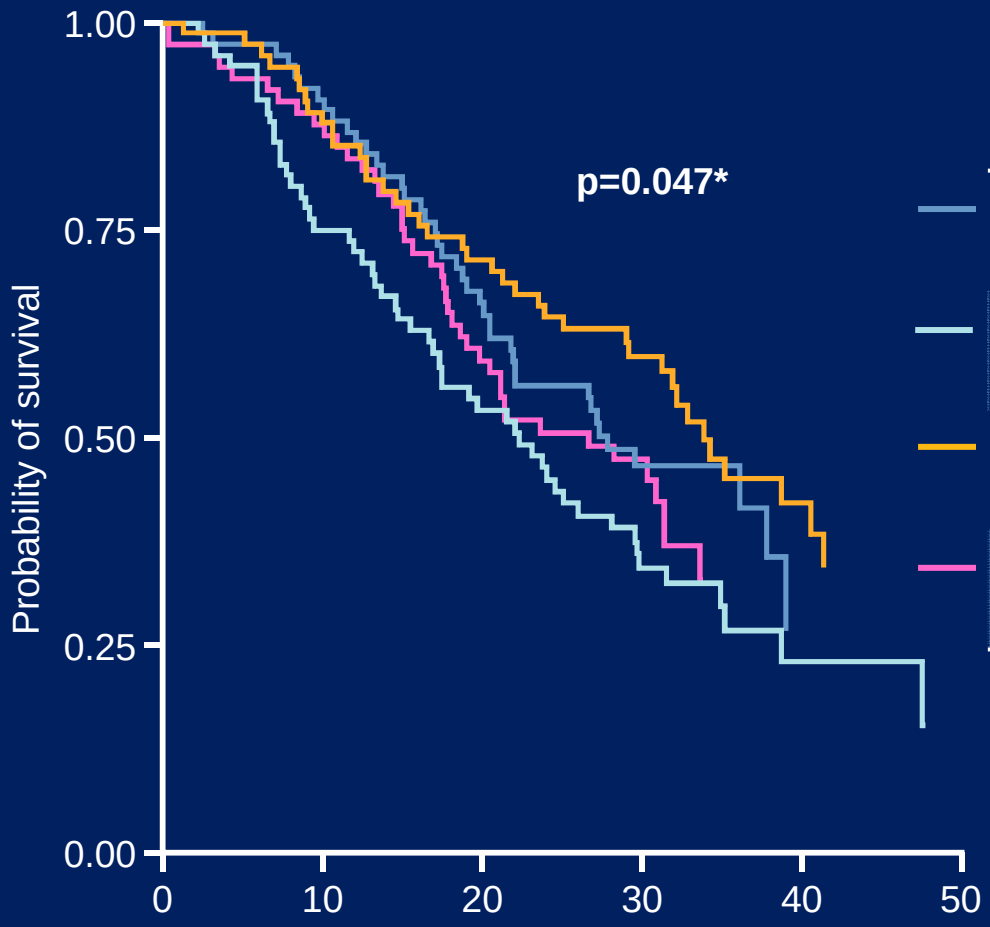


A vs B; p=0.024
A vs C; p=0.002
B vs C; NS

P values are for investigator assessment

Gradishar W et al. JCO 2009;27:3611-9

Randomized Phase II study: OS



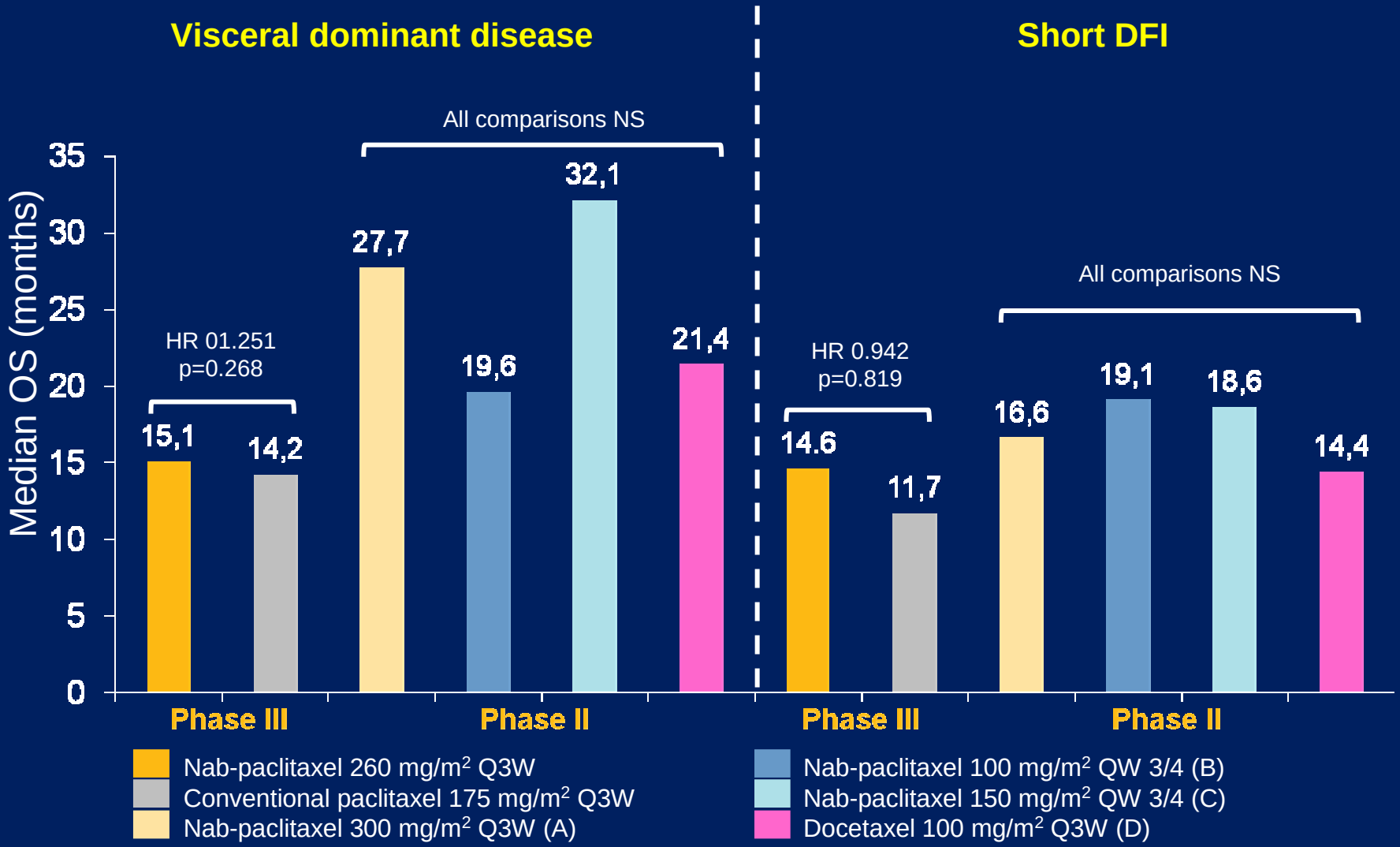
Regimen	Median OS (months)	vs docetaxel
A. Nab-paclitaxel 300 mg/m² Q3W	27.7	–
B. Nab-paclitaxel 100 mg/m² QW 3/4	22.2	–
C. Nab-paclitaxel 150 mg/m² QW 3/4	33.8	HR 0.688
D. Docetaxel 100 mg/m² Q3W	26.6	–

C vs B: p=0.008; HR 0.575

*3 degrees of freedom test for overall difference
No p value is reported where a treatment difference is not detected by stepdown methodology

Gradishar W et al. Clin Breast Cancer. 2012;12:313-21

Nab-paclitaxel improves OS vs traditional taxanes in patients with poor prognostic factors*



*Most comparisons did not reach statistical significance due to small sample sizes

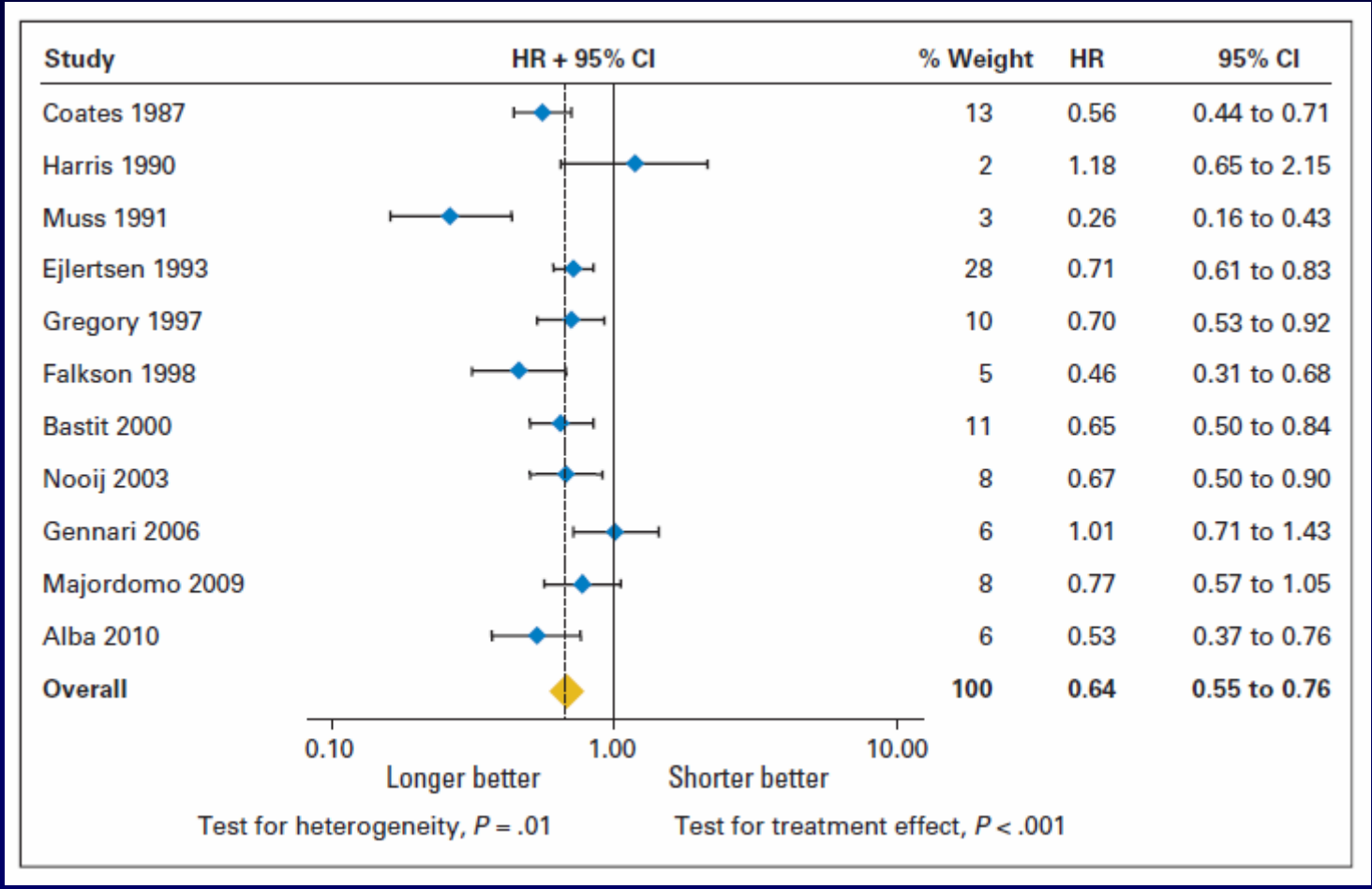
O'Shaughnessy et al BCRT 2013, April 6 [epub ahead of print]

Key ongoing trials evaluating nab-paclitaxel in breast cancer

Setting	Study ID	Description	No of pt
1st line MBC	SNAP NCT01746225	Randomized phase II study evaluating different nab-paclitaxel schedules in patients with HER2-/HR- (or + resistant) MBC	240
1st line MBC	tnAcity NCT01881230	Randomized phase II/III study evaluating nab-paclitaxel + gem or carb vs gem + carb in patients with TNMBC	240 (ph 2) 550 (ph 3)
Neoadjuvant	GEPARSEPTO NCT01583426	Randomized phase III trial comparing nab-paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer	1200
Neoadjuvant	GEICAM NCT01565499	Phase II, open-label, non-randomized study of nab-paclitaxel for patients with stage II and III luminal breast cancer as neoadjuvant therapy	78
Neoadjuvant	ETNA NCT01822314	Randomized phase III trial comparing nab-paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with HER2-negative high-risk breast cancer	632
Neoadjuvant/ adjuvant	ADAPT NCT01781338	Adjuvant Dynamic marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early cancer	4936
Adjuvant	GAIN-2 NCT01690702	Phase III trial to compare intense dose-dense adjuvant treatment with EnPC to dose-dense, tailored therapy with dtEC-dtD for patients with high risk primary breast cancer	2960
Adjuvant	ICE-II NCT01204437	A randomized Phase II study of EC/CMF vs nab-paclitaxel plus capecitabine as adjuvant chemotherapy for elderly patients with an increased risk for relapse of a primary carcinoma of the breast	1458

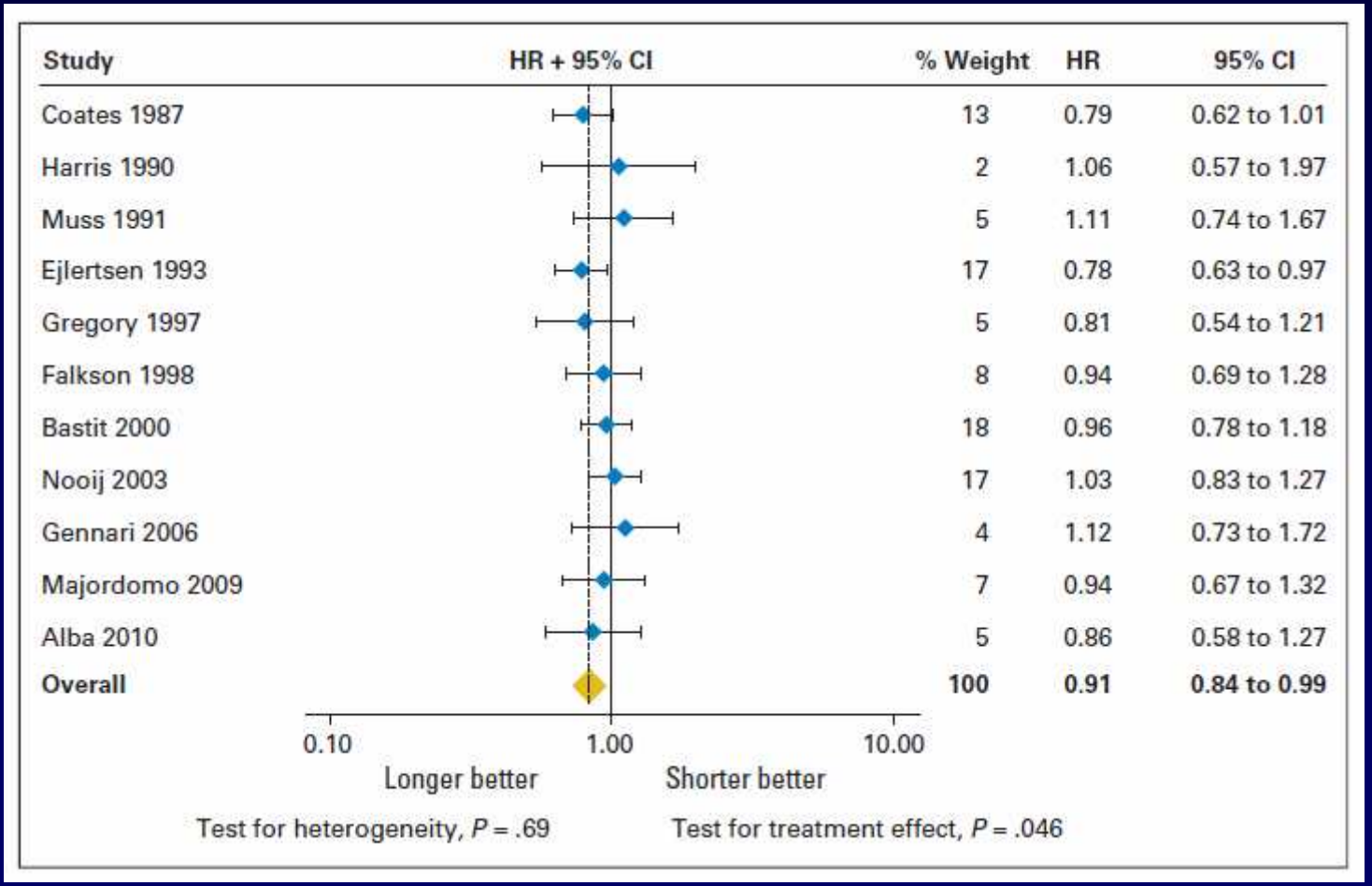
www.clinicaltrials.gov

Longer first-line chemotherapy duration: Substantially longer PFS (HR:0.64)



Gennari et al. J Clin Oncol,2011,29:2144-2149

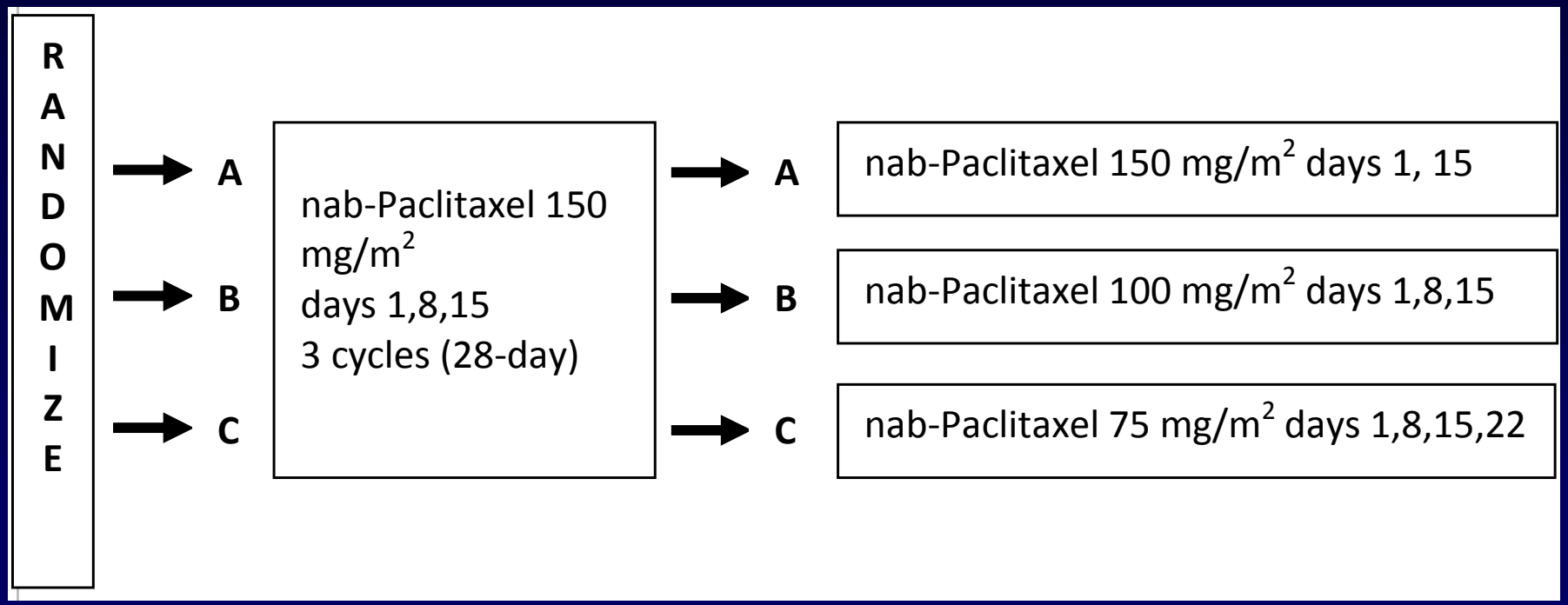
Longer first-line chemotherapy duration: Marginal effect on overall survival (HR:0.91)



Gennari et al. J Clin Oncol,2011,29:2144-2149

SNAP trial

First line chemotherapy for metastatic breast cancer

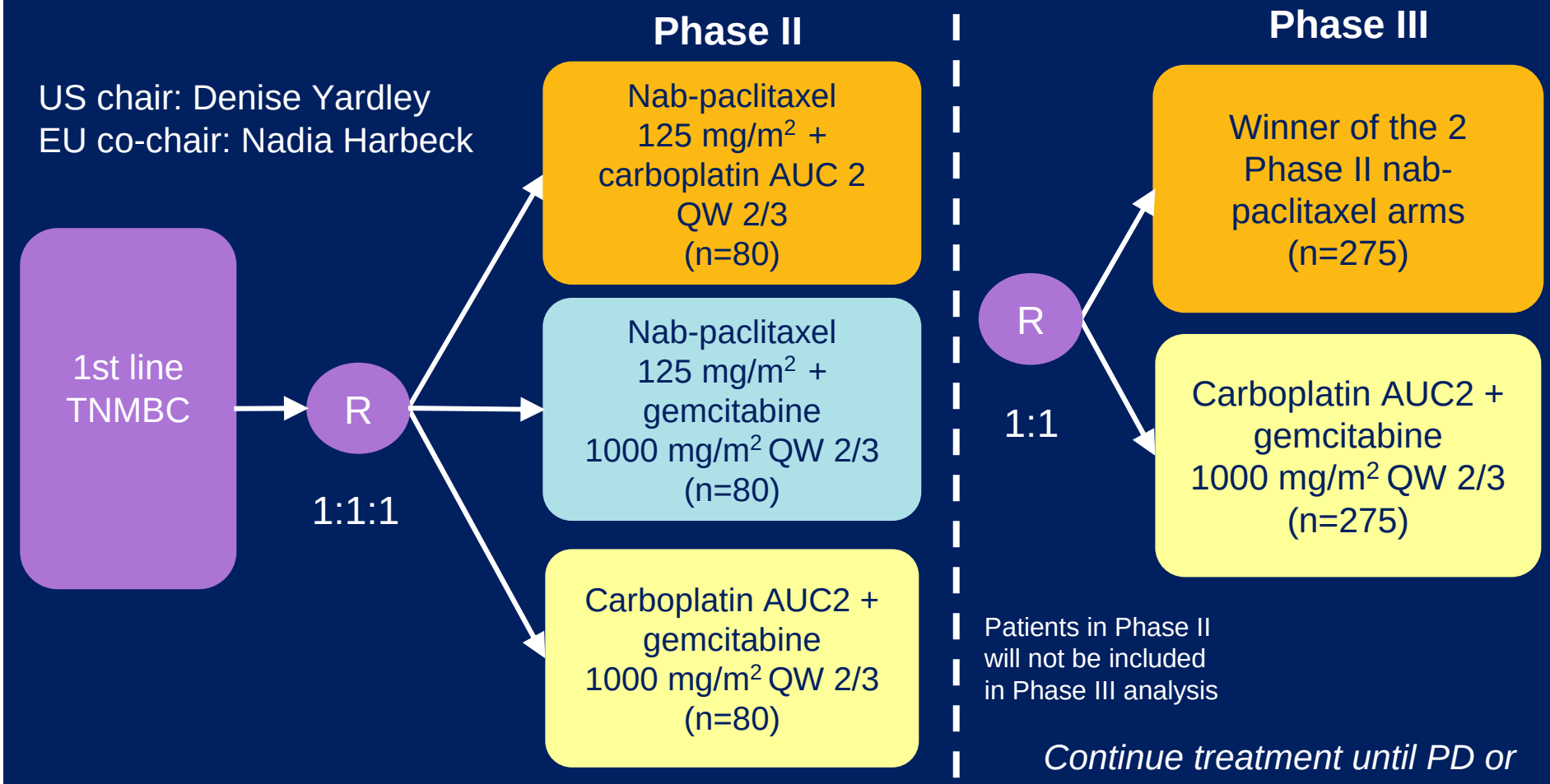


In case of toxicity, dose reductions and delays are preferred to dose discontinuation

SNAP Accrual and Study Duration

- **Target Accrual: 240 patients**
  - **(Arm A: 80, Arm B: 80, Arm C: 80)**
  - **88% power if median PFS of any arm is at least 10 mos. compared with reference 7 mos.**
- **Study Duration**
  - **Randomization during 30 months**
  - **Additional 12 months of follow-up after the last patient entered**
- **BIG Supporter Trial: IBCSG (coordinating), SOLTI, ICORG, EORTC**

tnAcity: Study design



Phase II Study start: June 2013
Phase II estimated completion (primary analysis): June 2015
Phase III 'go/no go' decision : Sep 2015

tnAcity: Study endpoints

Phase II

- Primary:
  - PFS (investigator assessment)
- Secondary
  - ORR
  - % of pts initiating cycle 6
  - OS
  - Safety

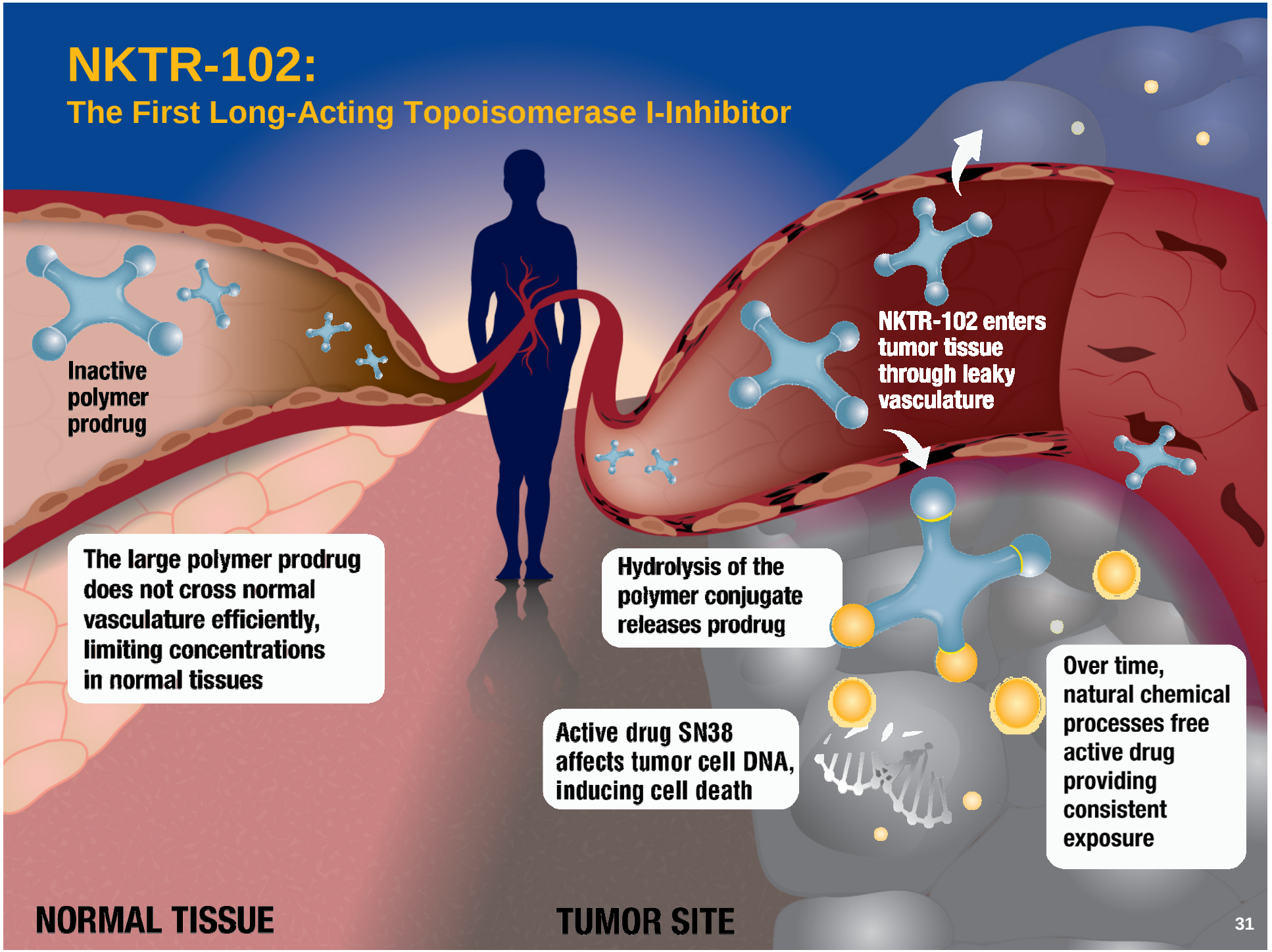
Phase III

- Primary:
  - PFS (central assessment)
- Secondary
  - ORR
  - OS
  - DCR
  - DoR
  - Safety

NKTR-102: Etirinotecan pegal

- NKTR-102 is the first long-acting topoisomerase I-inhibitor
- Targets tumor tissue through Enhanced Permeability and Retention (EPR) effect
- Optimized pharmacokinetic profile with continuous tumor exposure but with reduced peak exposures
- High response rates in advanced disease and poor prognosis tumors

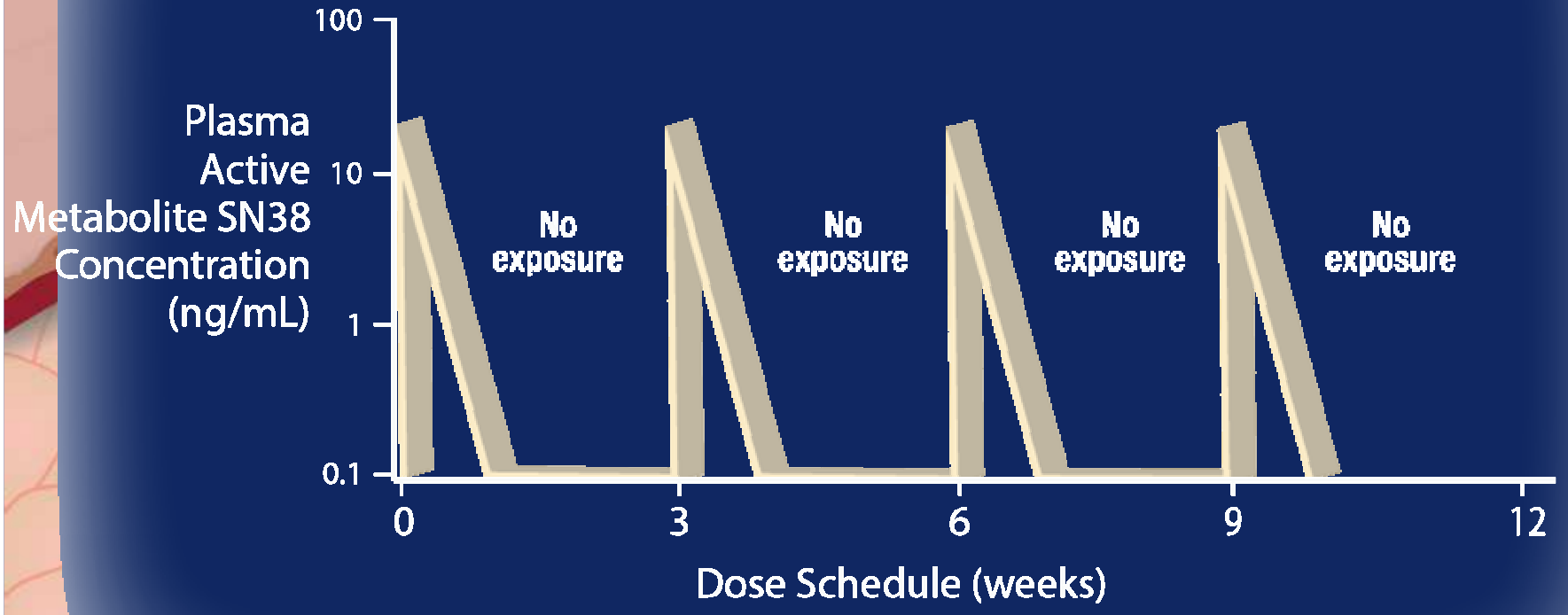
The unique profile of NKTR-102 is expected to improve efficacy, while offering a more tolerable therapy for women with metastatic breast cancer.


NKTR-102:
The First Long-Acting Topoisomerase I-Inhibitor
Inactive polymer prodrug
NKTR-102 enters tumor tissue through leaky vasculature
The large polymer prodrug does not cross normal vasculature efficiently, limiting concentrations in normal tissues
Hydrolysis of the polymer conjugate releases prodrug
Active drug SN38 affects tumor cell DNA, inducing cell death
Over time, natural chemical processes free active drug providing consistent exposure
NORMAL TISSUE
TUMOR SITE

NKTR-102:

Mechanism of Action:

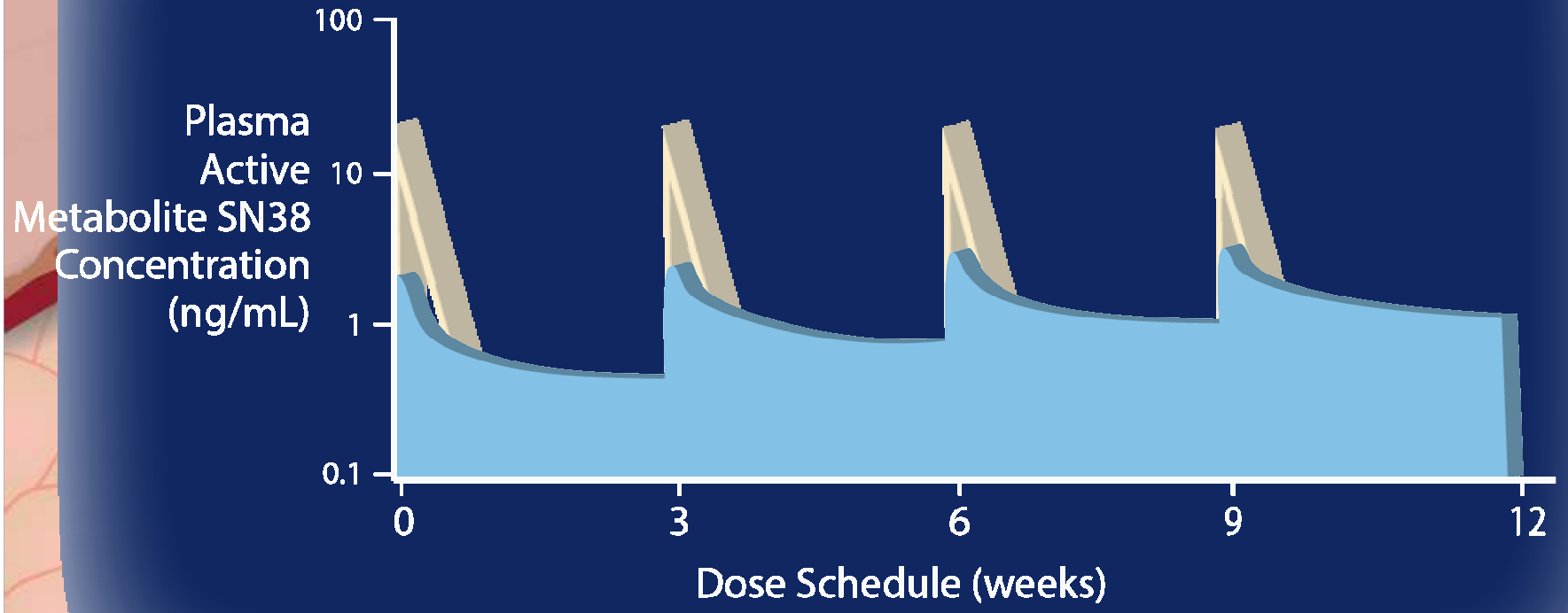
First-generation topoisomerase I-inhibitors have a high initial peak concentration and short half-life



NKTR-102:

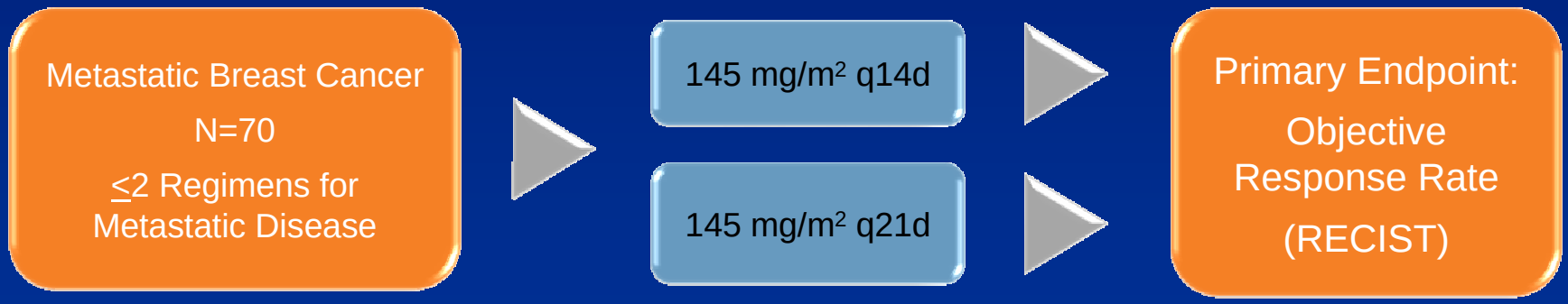
Mechanism of Action:

NKTR-102's design results in a lower initial peak concentration of active topoisomerase I-inhibitor in the blood



Phase 2 Study Design:
Randomized to 2 Schedules of NKTR-102

- **Primary Efficacy Objective:**
  - Determine the objective response rate (ORR) by RECIST v 1.0
  - Determine the optimal schedule of NKTR-102 in breast cancer
- **Secondary Objectives: PFS, OS and safety**



Statistical Hypotheses:

H_0 ORR (RECIST version 1.0) ≤ 5% and H_a ORR ≥ 20%. (Type 1 error = 0.029; type 2 error = 0.145)

Demographics in Phase 2 Study

	NKTR-102 145 mg/m² q14 days N=35	NKTR-102 145 mg/m² q21 days N=35
Age, median yr (range)	53 (33-83)	56 (37-77)
Women, No. (%)	34 (97)	35 (100)
Ethnic origin, No. (%)		
White	31 (89)	33 (94)
Black	2 (6)	2 (6)
Asian	1 (3)	0
Other	1 (3)	0
ECOG PS, No. (%)		
0	15 (43)	13 (37)
1	20 (57)	22 (63)
Postmenopausal, No. (%)	24 (71)*	29 (83)
Time from initial diagnosis to first dose, median yr (range)	4 (0-15)	5.4 (1-19)
Time from initial diagnosis to metastatic disease, median yr (range)	1.5 (0-7)	2 (0-12)
Receptor status		
ER+	21 (60)	20 (57)
PR+	11 (31)	13 37)
HER2+	3 (9)	2 (6)
ER-/PR-/HER2- (triple-negative)	11 (31)	10 (29)
Visceral disease	28 (80)	32 (91)

*Out of women only (n=34).
ECOG PS; Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Awada A, et al. *Lancet Oncol.* 2013;14:1216-1225

Demographics in Phase 2 Study (cont.)

	NKTR-102 145 mg/m^2 q14 days N=35	NKTR-102 145 mg/m^2 q21 days N=35
Previous cytotoxic regimens in metastatic setting, median No.(range)	1 (0-3)	2 (0-2)
Any previous cytotoxic regimens in the metastatic setting, No. (%)	34 (97)	34 (97)
1 previous cytotoxic regimen	17 (49)	9 (26)
2-3 previous cytotoxic regimens	17 (49)	25 (71)
Previous systemic treatments*, No. (%)		
Taxane	35 (100)	35 (100)
Anthracycline	31 (89)	31 (89)
Capecitabine	9 (26)	10 (29)
Anthracycline/taxane	23 (66)	21 (60)
Anthracycline/taxane/capecitabine	8 (23)	10 (29)
Previous cytotoxic (neo)adjuvant therapy	27 (77)	24 (69)
Previous adjuvant anthracycline	15 (43)	17 (49)
Previous adjuvant taxane	9 (26)	5 (14)
Previous adjuvant anthracycline and/or taxane	19 (54)	18 (51)

*In adjuvant or metastatic setting.

Awada A, et al. *Lancet Oncol.* 2013;14:1216-1225

NKTR-102:

Metastatic Breast Cancer Phase 2 Final Results

- **Single-agent NKTR-102 demonstrated a 29% ORR in heavily pretreated (median 2 prior lines of therapy) advanced metastatic breast cancer**
  - PFS: 4.7 months
  - Median OS: 10.3 months
  - Progression-free at 6 months: 35.5%
- **ORR was maintained in heavily pretreated and poor prognosis subsets**
  - A/T/C pre-treated: 33%
  - Triple negative: 33%
  - Visceral disease: 30%
- **Activity in the 3 main subtypes: TNBC, HER2+, Hormone+**

NKTR-102:

Metastatic Breast Cancer Phase 2 Final Results

- **Most common Grade 3/4 toxicity was diarrhea (21%)**
  - Typically occurring after approximately 3 months of therapy for both schedules
- **21-day schedule better tolerated and more efficacious**
  - ORR: 29%; PFS: 5.6 months, OS: 13.1 months
  - Selected for Phase 3 BEACON study

Summary of Treatment-emergent Adverse Events (TEAEs)

Most Common TEAEs (≥ 15%), No. (%)	NKTR-102 145 mg/m² q14 days n=35		NKTR-102 145 mg/m² q21 days n=35	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Diarrhea	24 (69)	7 (20)	22 (77)	8 (23)
Nausea	25 (71)	2 (6)	26 (74)	1 (3)
Fatigue	15 (43)	5 (14)	18 (51)	3 (9)
Vomiting	19 (54)	3 (9)	14 (40)	2 (6)
Decreased appetite	14 (40)	1 (3)	12 (34)	0
Constipation	14 (40)	0	9 (26)	0
Abdominal pain	7 (20)	1 (3)	8 (23)	0
Blurred vision	9 (26)	0	6 (17)	0
Dehydration	7 (20)	3 (9)	6 (17)	4 (11)
Neutropenia	6 (17)	4 (12)	7 (20)	4 (11)
Alopecia	7 (20)	0	4 (11)	0
Anemia	6 (17)	1 (3)	4 (11)	1 (3)
Decreased weight	3 (9)	0	7 (20)	0
Dyspnea	6 (17)	1 (3)	3 (9)	0

- 2 possible treatment-related deaths occurred (both in q14 day): sepsis and acute renal failure following diarrhea.

Awada A, et al. *Lancet Oncol*. 2013;14:1216-1225.

NKTR-102:
New Mechanism of Action in Metastatic Breast Cancer

The Challenge of Treating Metastatic Breast Cancer:

Overlapping Toxicities and Resistance with Existing Treatments

- **Most therapies used in MBC disrupt microtubules and have overlapping toxicities**
- **In Phase 2, NKTR-102 had activity as single agent in breast cancer patients with poor prognosis**
  - Primary toxicity is diarrhea
  - Low rates of neutropenia
  - No neuropathy
  - Little alopecia
  - No cardiac toxicity

Currently no other topoisomerase I inhibitors in development or approved for the treatment of breast cancer

Time Course of Diarrhea and Neutropenia

	NKTR-102 145 mg/m^2 q14 days N=35	NKTR-102 145 mg/m^2 q21 day N=35
Diarrhea (≥ Grade 3)		
Cycle 1 and/or 2	9%	3%
Cycle 3 and/or 4	0%	6%
Cycle 4+	11%	14%
Onset, median days (range) [# cycle]	88 (1-121) [6]	90 (8-107) [5]
Duration, median days (range)	8.5 (1-16)	16 (2-39)
Neutropenia (≥ Grade 3)	3%	3%
Cycle 1 and/or 2	0%	6%
Cycle 3 and/or 4	9%	3%
Cycle 4+	98 (15-188) [6.5]	60 (28-140) [3]
Onset, median days (range) [# cycle]	12 (6-15)	9.8 (6-14)
Duration, median days (range)		

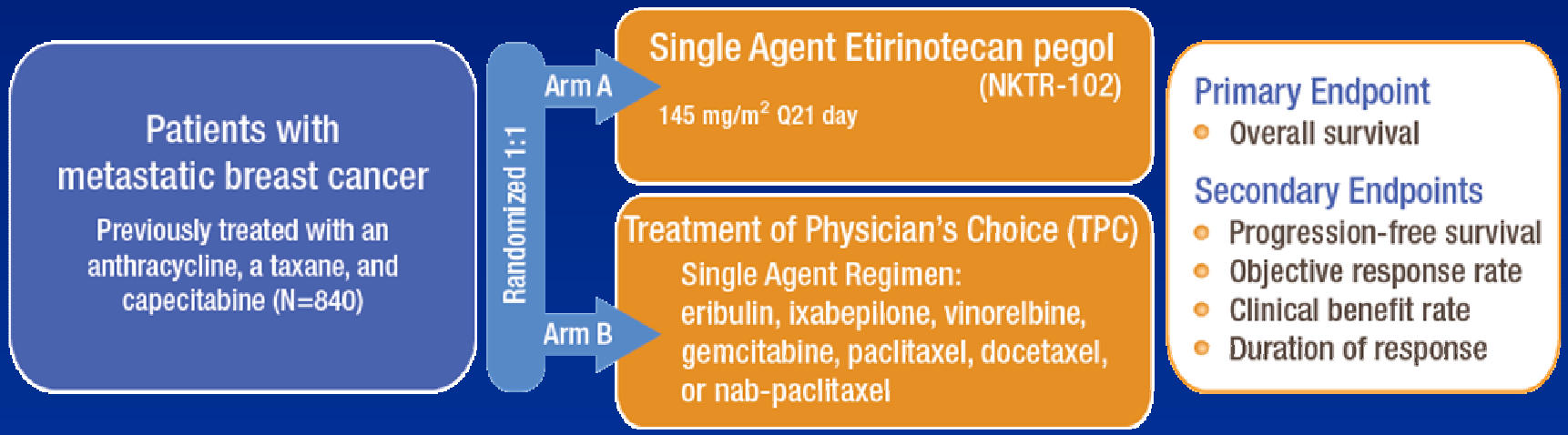
Anti-diarrheals given therapeutically; no prophylactic anti-diarrheals administered

Source: Data as of 09May2011

BEACON Phase 3 Registration Study of NKTR-102 in Metastatic Breast Cancer

BEACON

BREAST CANCER OUTCOMES WITH NKTR-102



Global enrollment completed ahead of schedule in August 2013;

Topline data expected end of 2014 or early 2015

Single Agent Chemotherapy Outcomes in Refractory MBC

Author	Agent	Prior Therapy			RR	PFS (mo.)
		A	T	C		
Perez JCO 2007	Ixabepilone	x	x	x	11%	3.1
Cortes JCO 2010	Eribulin	x	x	x	9%	2.6
Cortes Lancet 2011	Eribulin	x	x	x / –	13%	3.7
Awada Lancet Oncology 2013	NKTR-102 (q14d + q21d)	x	x	x / –	**29%**	**4.7**
	NKTR-102 (q21d only)	x	x	x / –	**29%**	**5.6**

A = Adriamycin T = Taxane C = Capecitabine

New chemotherapy drugs in metastatic breast cancer

- Erubiline
- Nab-paclitaxel
- Etirinotecan pegol (NKTR-102)