

Case # 8: Current Management of Recurrent Triple-Negative Breast Cancer: What's the Best Approach?

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43-Year-Old Liver and Lung Meastases. No Comorbidities. PS = 1. Triple Negative. BRCA 1 Carrier

Options

Anthra and/or taxane-based chemotherapy

“Hair saving” chemotherapy (capecitabine and/or vinorelbine)

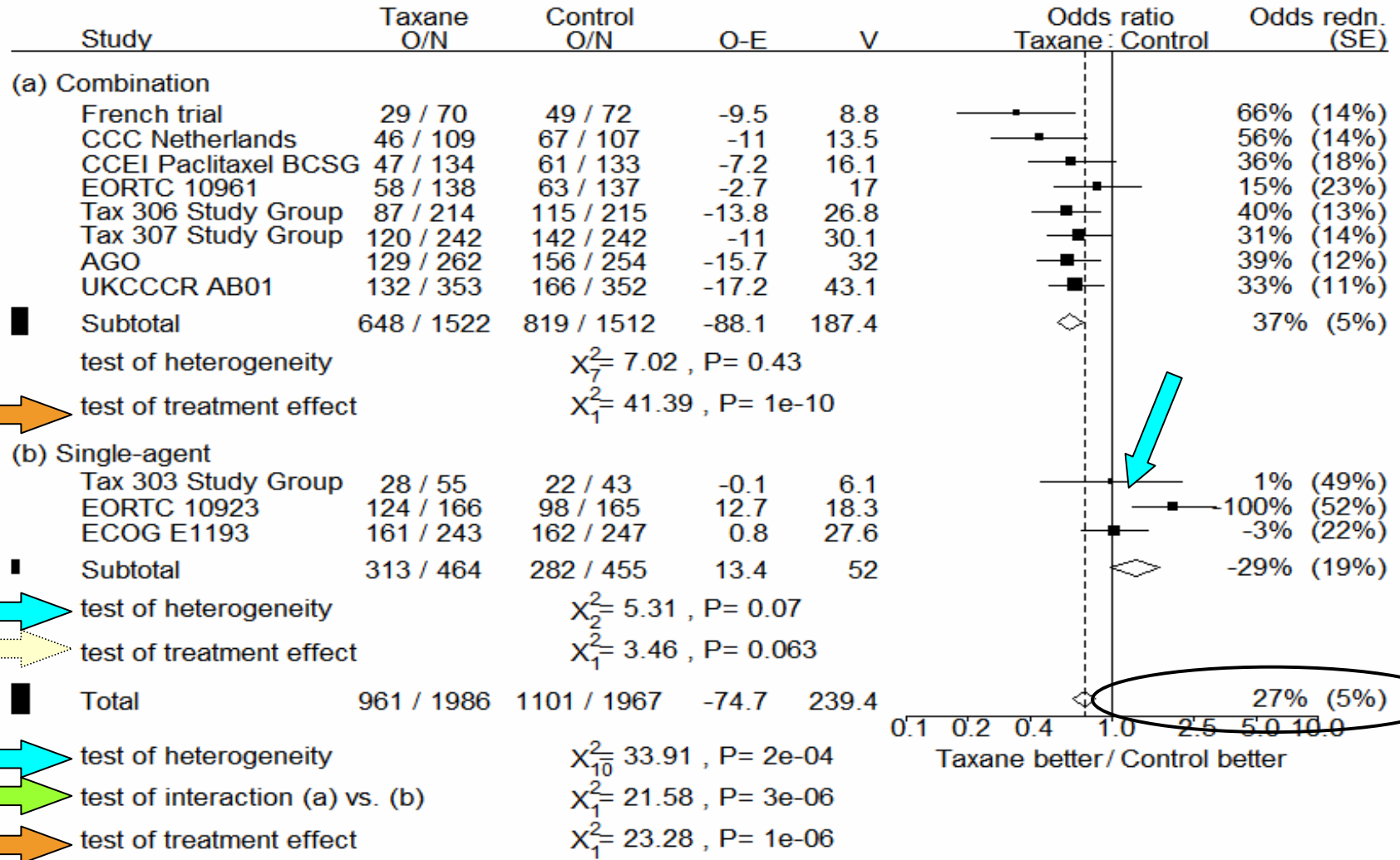
Platinum-based chemotherapy

Taxane in combo with bevacizumab

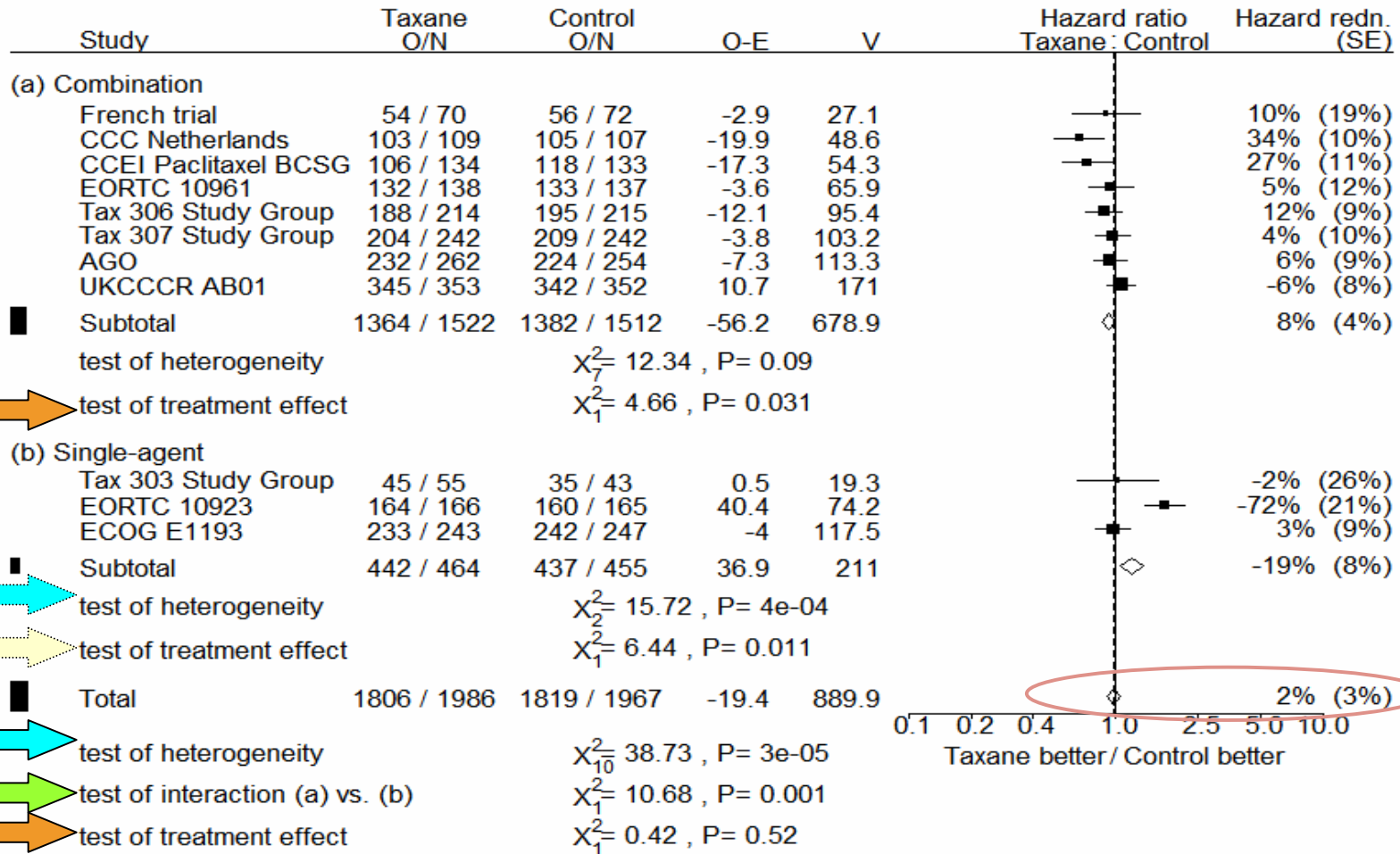
Option 1: Anthracyclines and/or Taxane–Based Chemotherapy

- **Time elapsed from the end of adjuvant EC → paclitaxel = 1.5 years**
- **No relevant impact on time to progression and survival**
- **Increased risk of neutropenic fever**

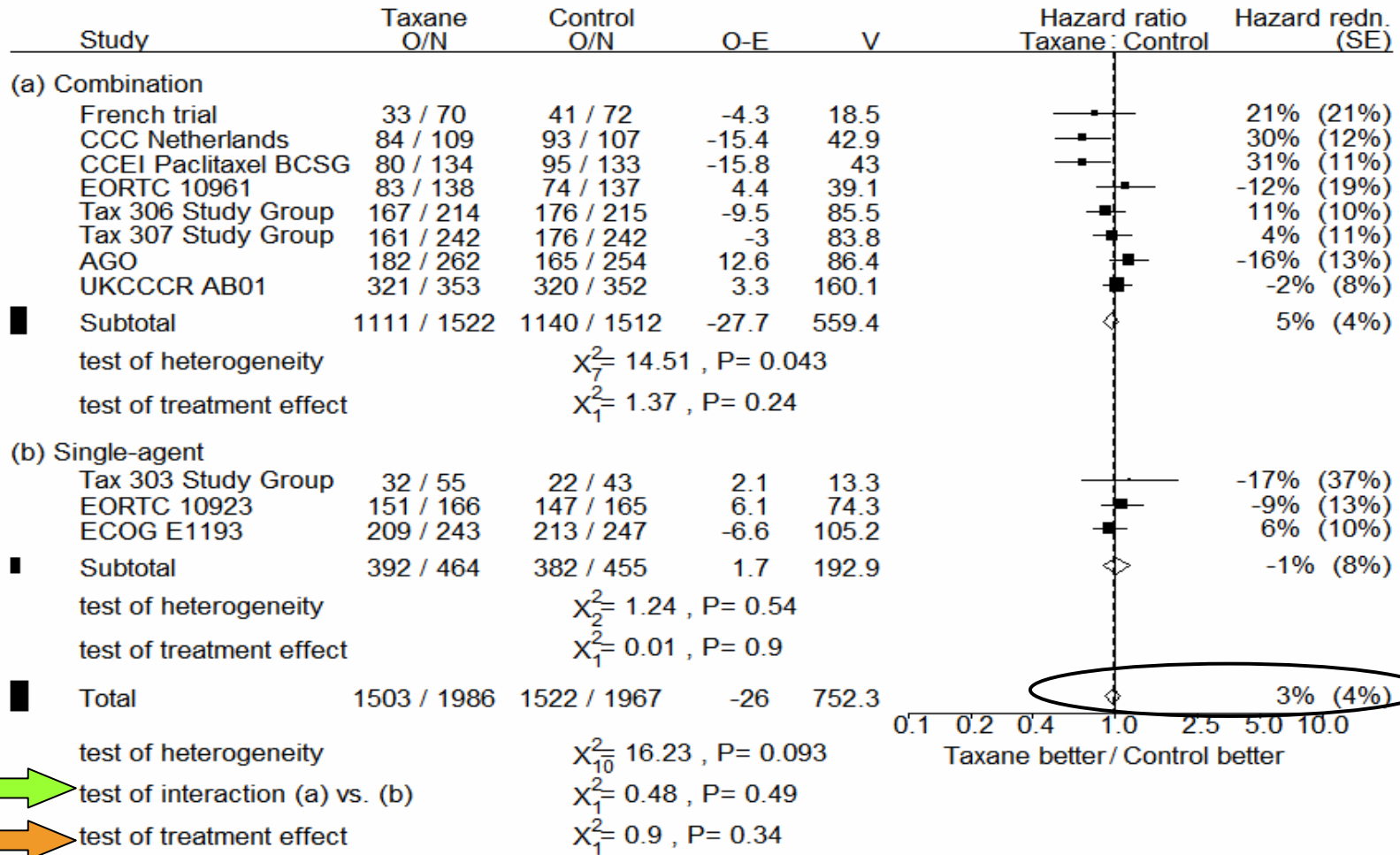
Failure to Respond Odds Ratios



Progression-Free Survival Hazard Ratios



Overall Survival Hazard Ratios



Option 2: Capecitabine and/or Vinorelbine

Patient characteristics: 44 patients, median age 53 years, adjuvant only 66%, visceral involvement 77%, ≥ 3 sites 36%

Activity: 3 CR + 15 PR (OR 41%), clinical benefit 50%

Grade 3 toxicity: constipation 0.3%, diarrhea 0.6%, vomiting 0.6%, desquamation 0.6%, fatigue 0.9%, abdominal pain 0.3%, alopecia G2 4.6%

Recommended doses

- N 60 mg/m² d1 and 8 + X 2250 mg/m² d1-14 q 3 wks
- N 80 mg/m² d1 and 8 + X 2000 mg/m² d1-14 q 4 wks

Option 3: Platinum-Based Chemotherapy— Rationale

**Triple-negative disease
(± 20% of breast cancer cases)**

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graph TD; A["Triple-negative disease  
(± 20% of breast cancer cases)"] --> B["Basal-like phenotype  
(50% to 80% of triple-negative)"]; B --> C["BRCA 1 loss-of-function  
(±80% of basal-like)"];
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**Basal-like phenotype
(50% to 80% of triple-negative)**

**BRCA 1 loss-of-function
(±80% of basal-like)**

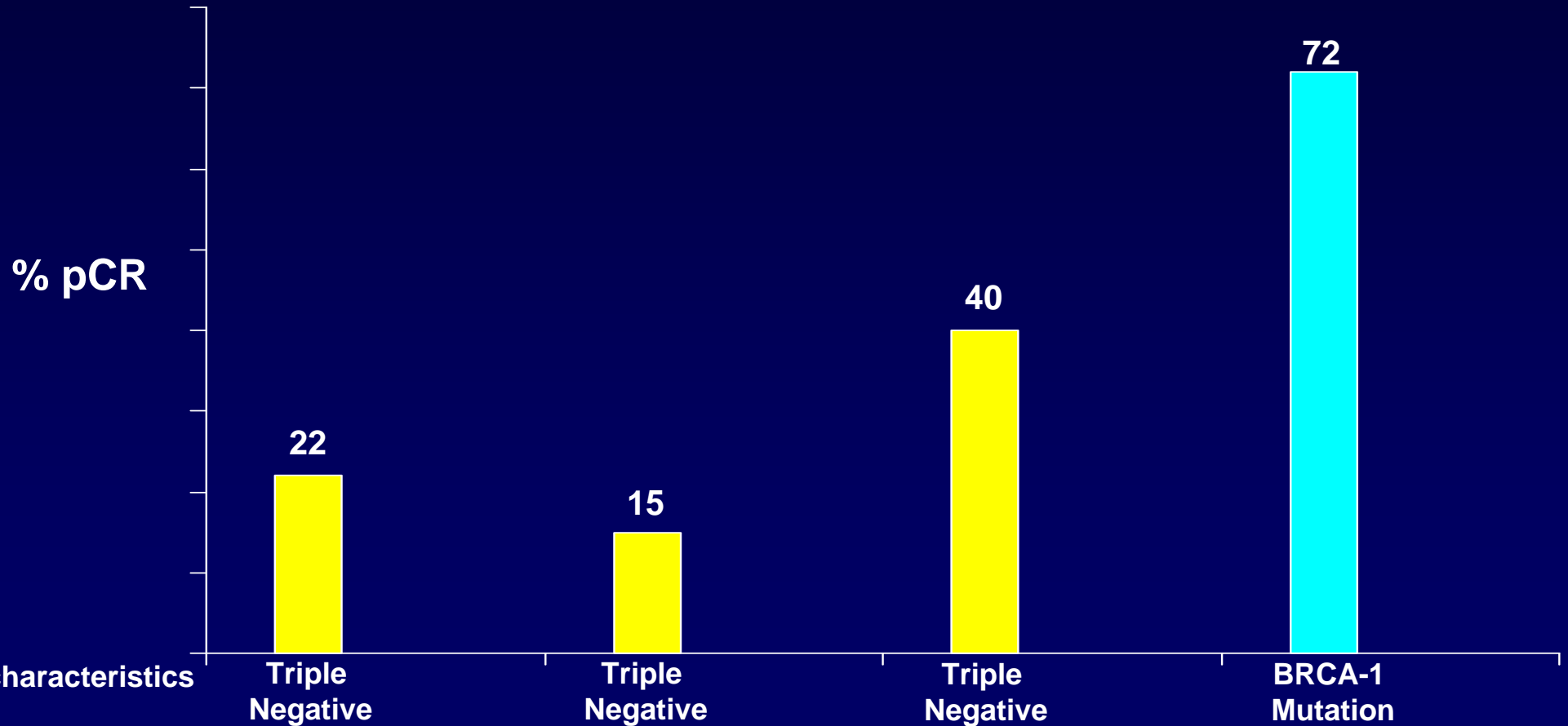
Neoadjuvant Chemotherapy with Platinum-Compounds: Phase II Trials

Garber JE
2006
CDDP → Sx
N = 28

Ryan PD
2009
CDDP + BEV → Sx
N = 51

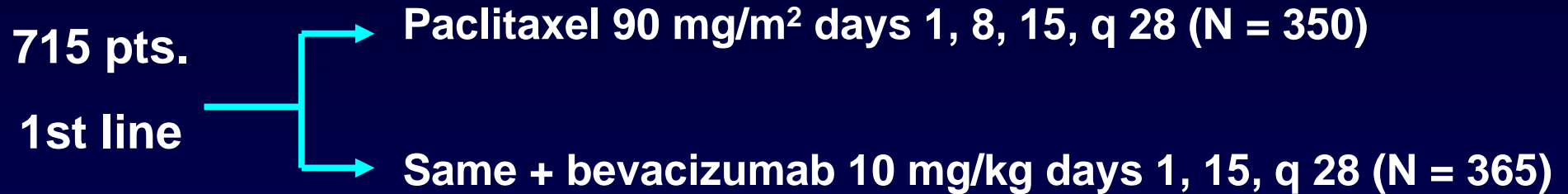
Torrise R
2008
ECF → P → Sx
N = 30

Gronwald J
2009
CDDP → Sx
N = 25



CDDP = cisplatin, Sx = surgery, BEV = bevacizumab, ECF = epirubicin-cisplatin-5FU, P = paclitaxel

Option 4: Taxane in Combination with Bevacizumab—The E2100 trial



: progression free survival curve

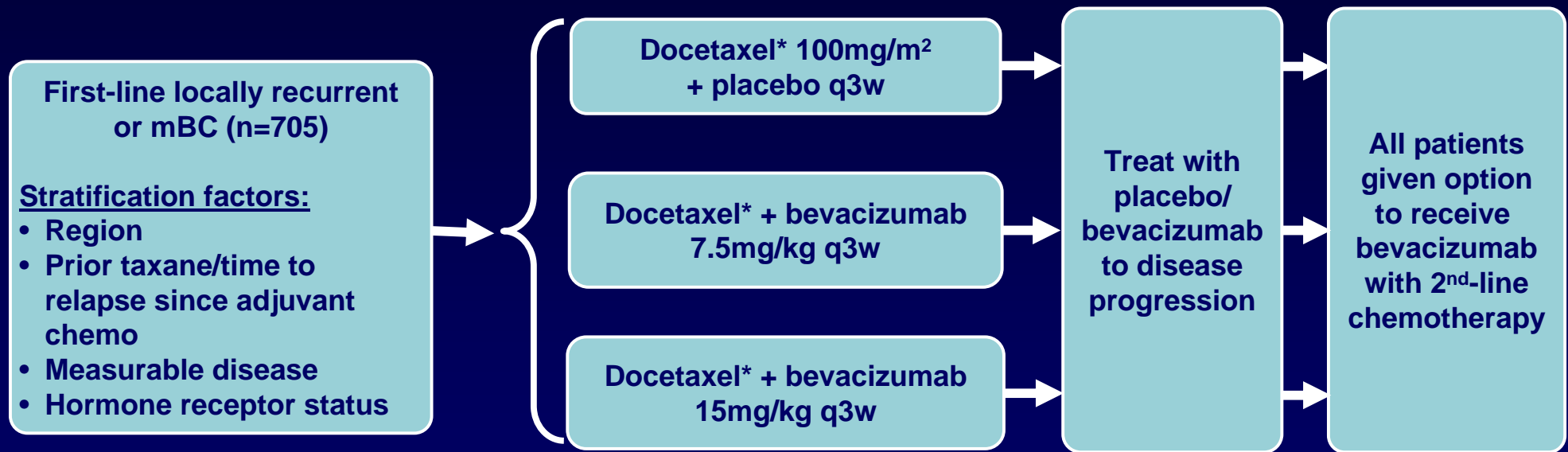
: overall survival curve

E2100 vs Previous Trials Testing Weekly Paclitaxel: Objective Response Rates

TRIAL	E2100	M. D. Anderson	CALGB 9840	MSKCC
No. patients	350	75	350	39
Previous therapy for M+	NO	NO	≤ 1	≤ 3
Weekly regimen	90 mg/m ² days 1, 8, 15, q 28	80 mg/m ² weekly	80 mg/m ² weekly	90 mg/m ² weekly



AVADO: Double-Blind, Placebo-Controlled Trial



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

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

AVADO: Response (patients with measurable disease), %

	Placebo + docetaxel (n=207)	Bev 7.5 [†] + docetaxel (n=201)	Bev 15 [†] + docetaxel (n=206)
Overall response rate	44	55	63
p value (vs control)	–	0.0295	0.0001
Best response			
CR	1	3	1
PR	44	52	62
SD	39	35	25
PD	12	5	4

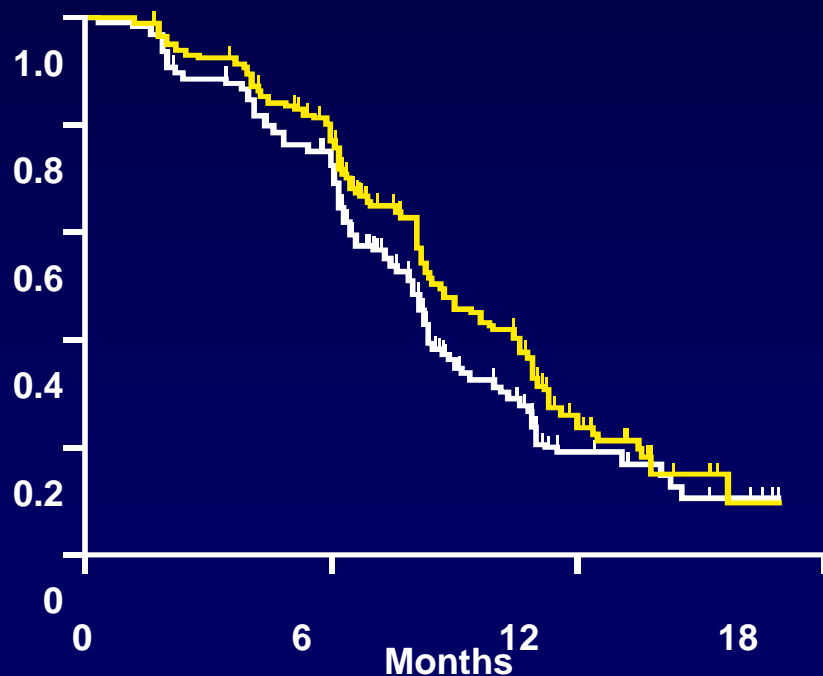
[†]mg/kg q3w

AVADO: Progression-Free Survival (ITT population)

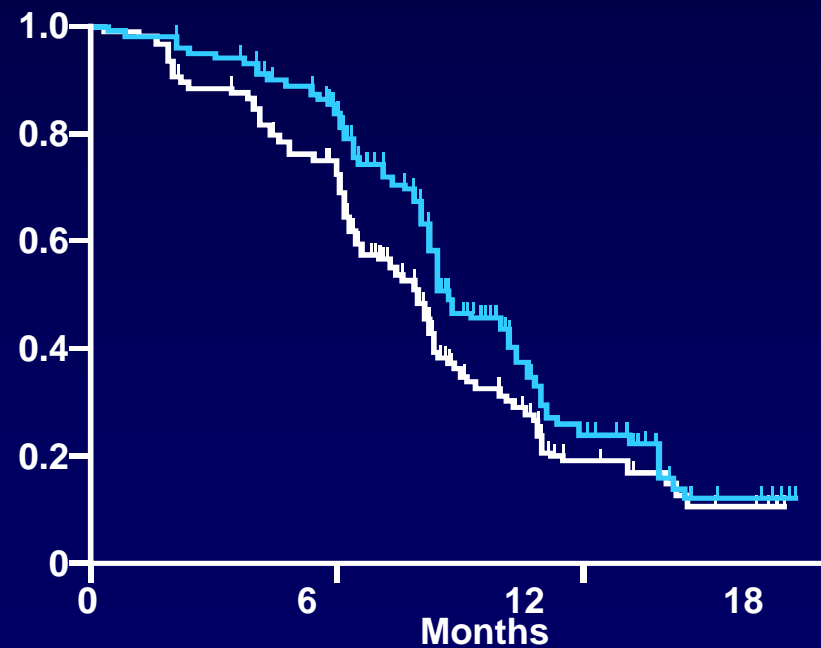
	Placebo + Docetaxel (n = 241)	Bev 7.5 [†] + docetaxel (n = 248)
HR + 95% CI (unstratified)		0.79 (0.63–0.98) P = .0318
HR + 95% CI (stratified*)		0.69 (0.54–0.89) P = .0035
Median	8.0	8.7

	Placebo + Docetaxel (n = 241)	Bev 15 [†] + Docetaxel (n = 247)
HR + 95% CI (unstratified)		0.72 (0.57–0.90) P = .0099
HR + 95% CI (stratified*)		0.61 (0.48–0.78) P < .0001
Median	8.0	8.8

PFS estimate



PFS estimate



[†]mg/kg q3w;

*Data censored for non-protocol therapy before PD

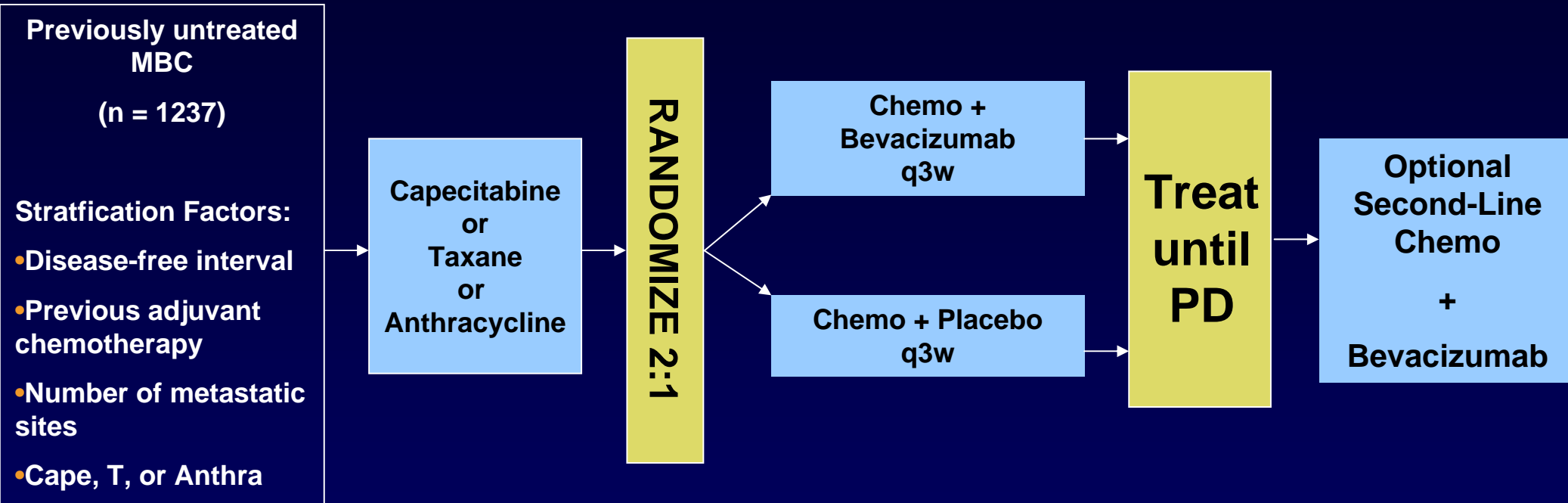
AVADO: Overall Survival* (ITT Population)

	Placebo + Docetaxel (n = 241)	Bev 7.5 [†] + Docetaxel (n = 248)	Bev 15 [†] + Docetaxel (n = 247)
Deaths, n (%)	50 (21)	49 (20)	37 (15)
Median overall survival, months	NR	NR	NR
Hazard ratio (95% CI)	–	0.92 (0.62–1.37)	0.68 (0.45–1.04)
1-year survival, %	73	78	83
Patients still at risk, n	63	73	79

Cut-off for final survival analysis 24 months after last patient recruited (April 2009)

*Unstratified analysis; [†]mg/kg q3w; NR = not reached

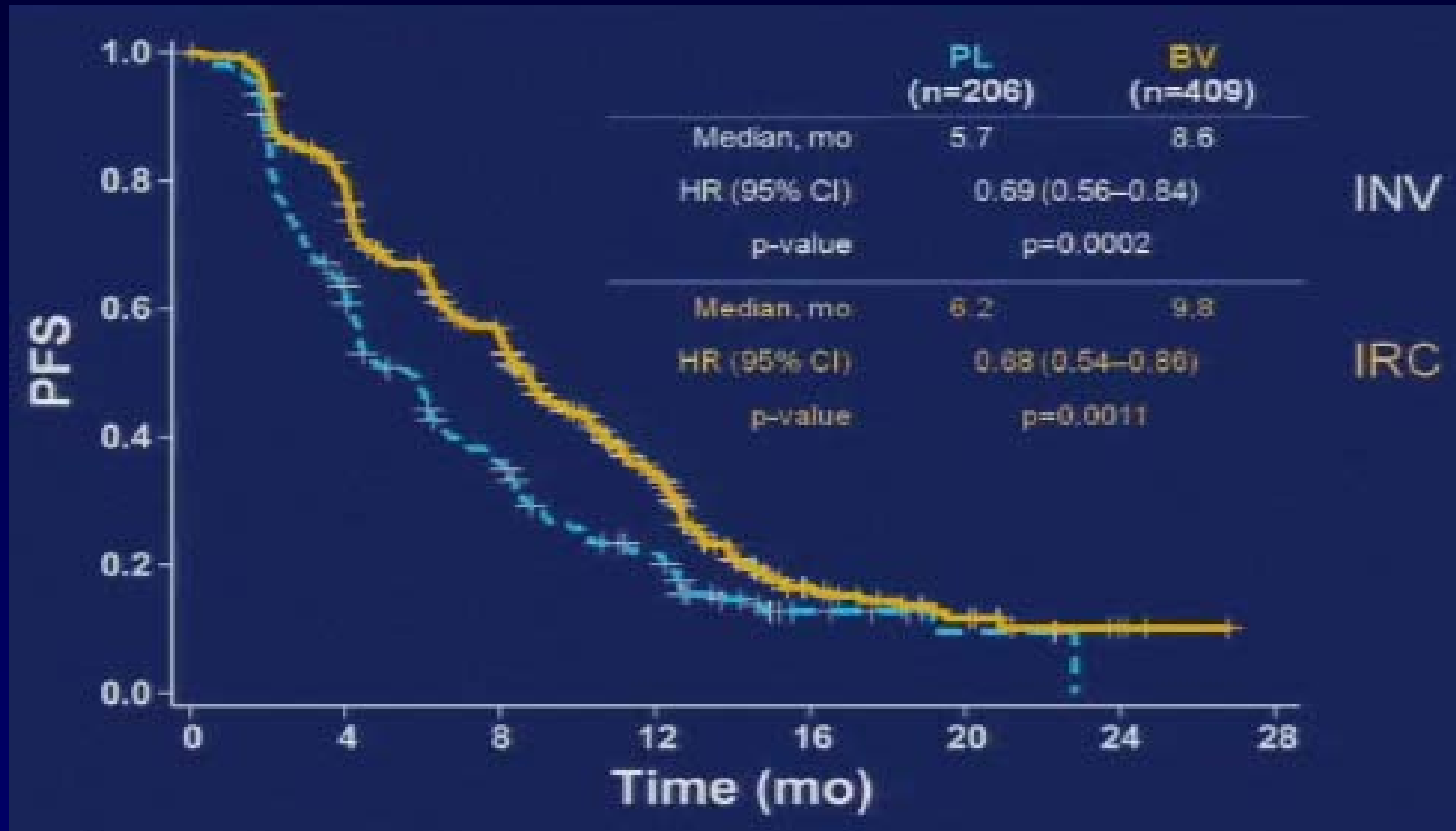
RIBBON-1 Study Design



- Capecitabine (1000 mg/m² BID x 14d)
- Taxane (docetaxel q3w or protein-bound paclitaxel q3w)
- Anthracycline-based chemotherapy (AC, EC, FAC, FEC)
- Placebo or bevacizumab (15 mg/kg q3w)

RIBBON 1

Capecitabine: Progression Free Survival



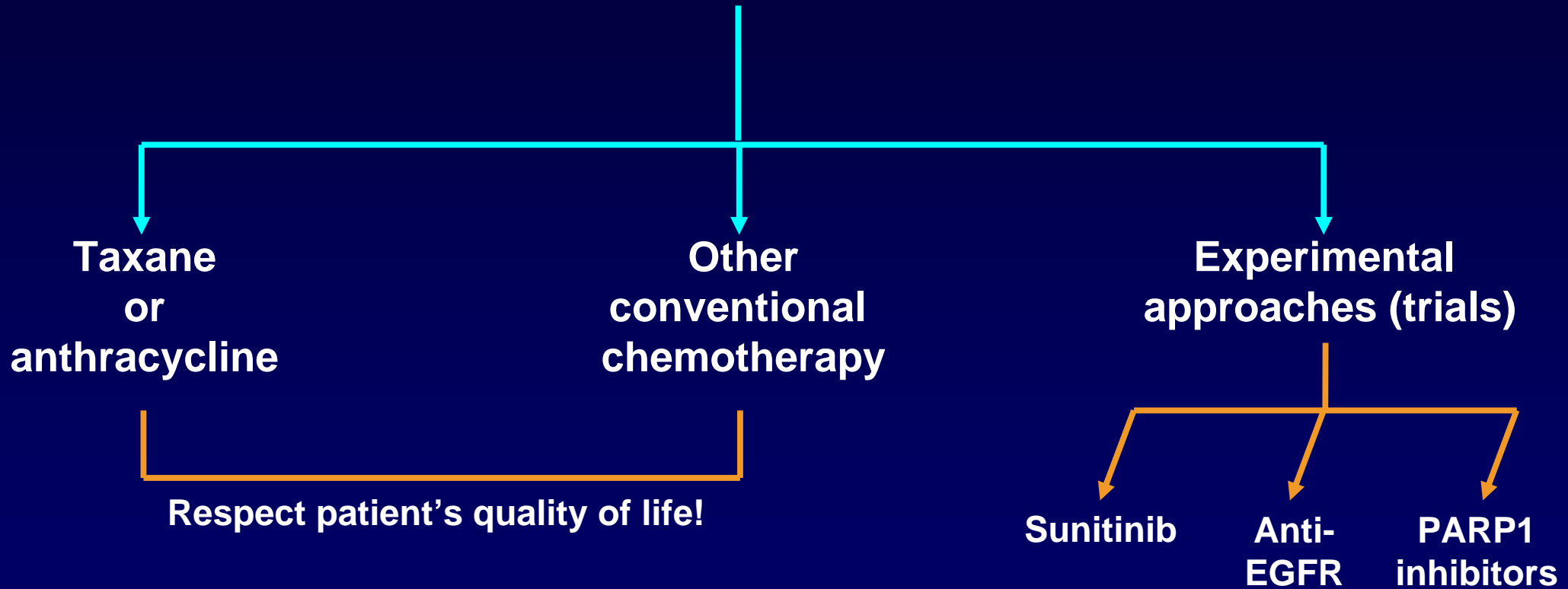
My Choice

Discuss with the patient → understanding of her treatment expectations

- **Platinum-based chemotherapy**
- or**
- **Capecitabine plus vinorelbine**

Treatment After Progression to First-Line Therapy

Options



Phase II Trial of Sunitinib Single-Agent in Advanced Breast Cancer Patients Previously Treated with Anthracyclines and Taxanes (Part 1)

N = 64 patients

42% ER neg

19% HER2+

31% Triple negative

83% Visceral disease

50 mg/daily, 4 weeks on – 2 weeks off

Treatment delivered

Median no. of days = 70 (1 - 336)

Median RDI = 84% (3.6% to 107%)

Dose interruption/reduction = 52% / 39% of patients

Phase II Trial of Sunitinib Single-Agent in Advanced Breast Cancer Patients Previously Treated with Anthracyclines and Taxanes (Part 2)

Response

ORR = 11% (7 PRs)
CBR = 16% (10 patients/64)
Median response duration/TTP = 19/10 weeks

Clinical (% Patients)

Fatigue = 14

Dyspnea = 9

Hand/foot = 9

Nausea/vomiting = 8/6

Diarrhea = 6

Hypertension = 6

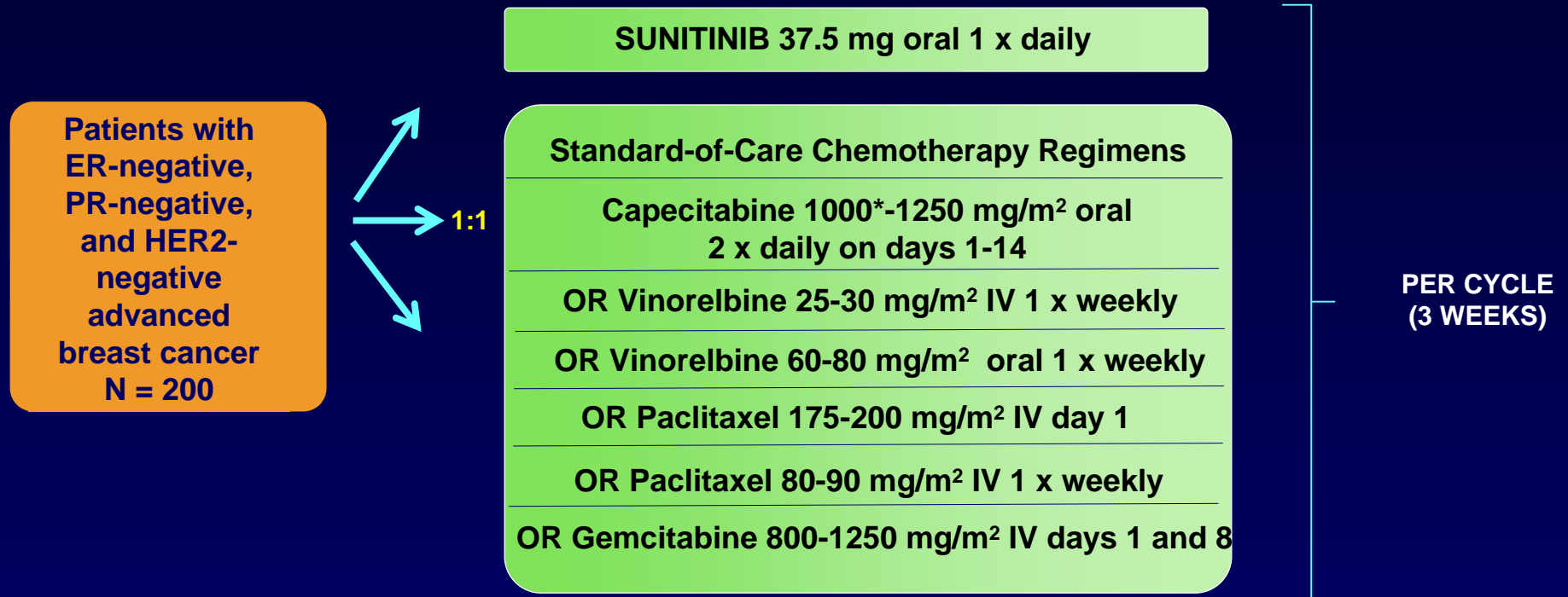
Hemato-chemistry (% Patients)

G4 chemistry abnormalities
(hyperuricemia, ALT and AP↑) = 5

G3 platelets/ANC = 14/33

Safety
(Grade 3 > 5%
patients)

SUN 1077: Sunitinib Malate vs Standard-of-Care in Triple-Negative Advanced Breast Cancer



Trial Design	Endpoints	Study Sites	Indication	FPFV
Multinational, multi-center, randomized, open label	Primary: PFS Secondary: safety, ORR, OS, QoL, PK, biomarker	US, EU	2 nd line (Triple -)	Enrolling

* Patients >65 years of age

EGF 30001: Lapatinib (L) + Paclitaxel (P) Versus Paclitaxel as First-Line Treatment for Patients with MBC

Key Inclusion

- Incurable Stage III/IV
- No prior treatment for M+
- **HER-2 negative (0, 1+, 2+ FISH, or FISH-) or untested**

Stratification

- Disease site
- Disease stage

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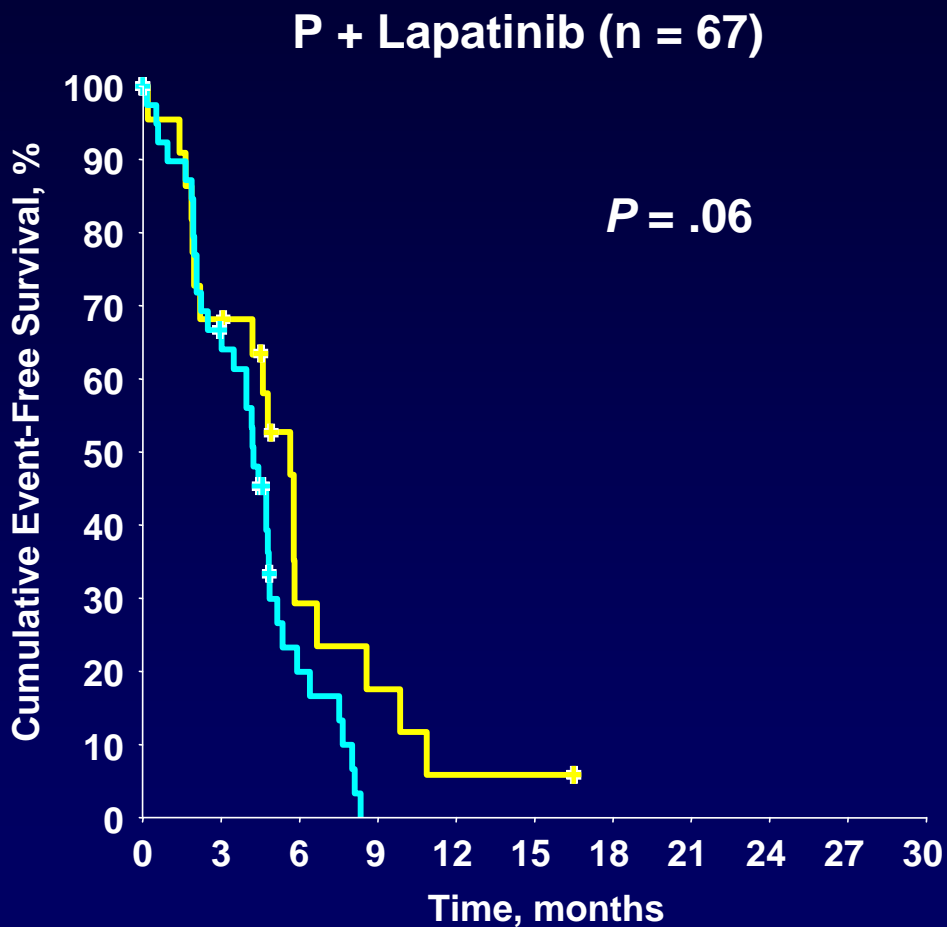
Paclitaxel 175 mg/m² q3w
Lapatinib 1500 mg po QD

Paclitaxel 175 mg/m² q3w
Placebo po QD

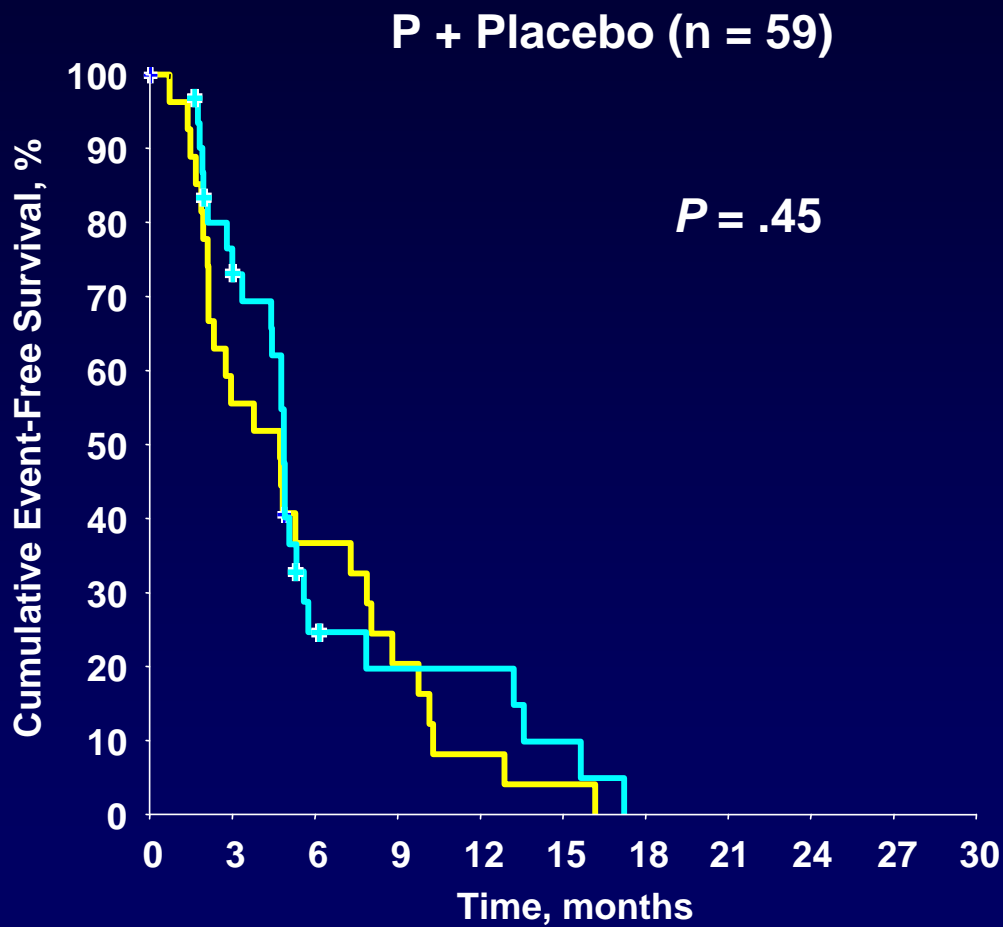
EGF30001-Biomarker Analysis Methods

- ER, PR, HER2, and EGFR staining and scoring performed centrally under blinded conditions (N = 492)
- Calculation of H-score for ER and PR (N = 454)
 - $H = (\% 1+ \times 1) + (\% 2+ \times 2) + (\% 3+ \times 3)$
 - Negative, H = 0
 - “Weak”, H = 1-50
 - “Strong”, H > 50
- HER2+: amplified by FISH or 3+ IHC if FISH not available (N = 86)
- EGFR status by IHC scored as 0, 1+, 2+, 3+ (N = 443)
- Subgroups analyzed by hormone receptor status and benefit of lapatinib

No Significant Benefit in “Triple Negative” Breast Cancer That Is EGFR+

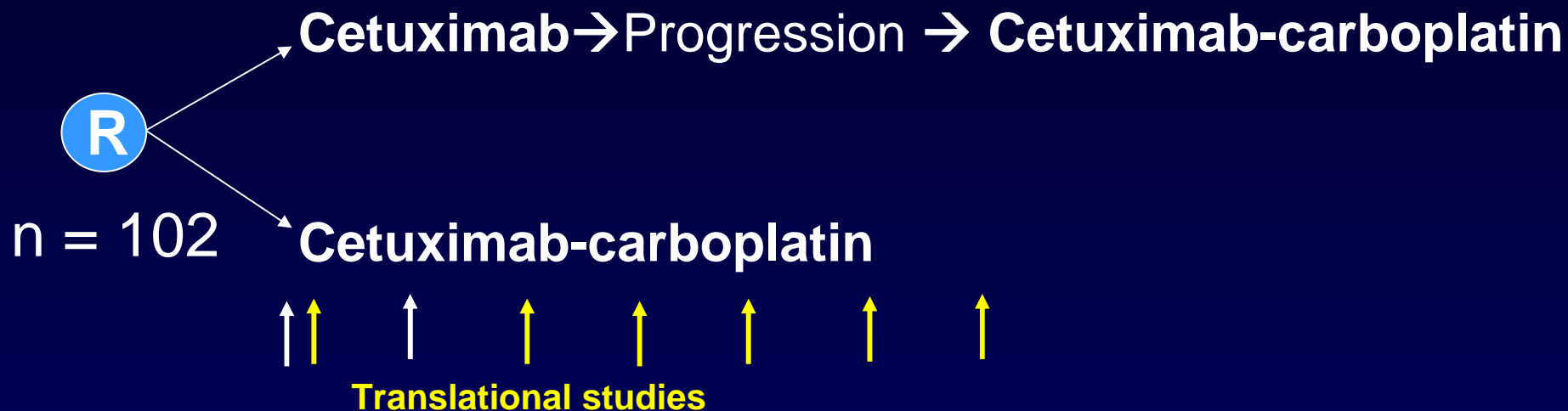


— EGFR IHC = 0 (n = 25)
— EGFR IHC = 1+, 2+, 3+ (n = 42)



— EGFR IHC = 0 (n = 28)
— EGFR IHC = 1+, 2+, 3+ (n = 31)

Cetuximab - Carboplatin

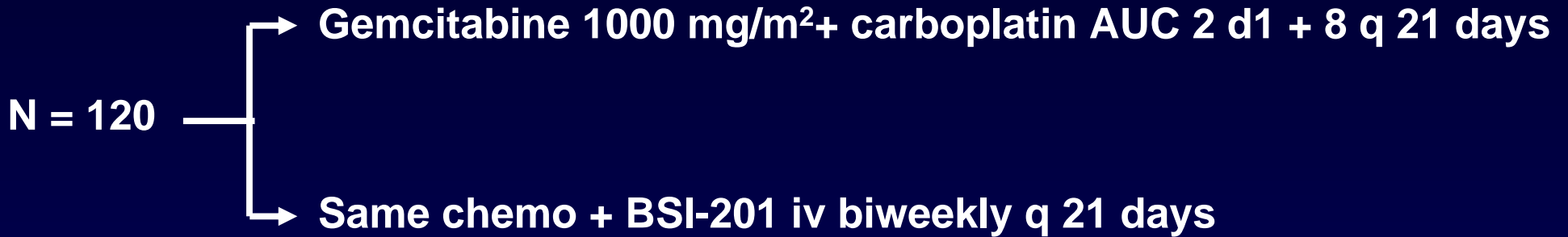


	Arm 1		Arm 2
	Cetuximab (n = 31)	Cetuximab/ Carboplatin (n = 24)	Cetixumab/ Carboplatin (n = 71)
ORR, %	6	17	17
Clinical benefit, %	10	25	31

Poly (ADP-ribose) Polymerase-1 (PARP 1) as a Treatment Target in Triple-Negative Breast Cancer

- **Nuclear enzyme involved in DNA base excision repair**
- **Upregulated in majority of triple negative breast cancers**
- **Key-role in BRCA-1 deficient cell lines***

A Phase II Randomized Trial Testing a PARP 1 Inhibitor in Triple-Negative Metastatic Breast Cancer Patients



	Chemo	Chemo + PARP inh.	HR (95% CI)	P Value
% Clinical benefit rate	21	62	-	.0002
Median PFS, months	3.3	6.9	.034 (0.20-0.58)	.0001
Median OS, months	5.7	9.2	0.34 (0.18-0.64)	.0005

No increase in toxicity in the PARP inhibitor arm

A Phase II Trial Testing Olaparib (a PARP 1 inhibitor) in BRCA-Deficient Advanced (Heavily Pre-Treated) Breast Cancer

Cohort 1 : N = 27 Olaparib 400 mg po bid

Cohort 2 : N = 27 Olaparib 100 mg po bid

	Cohort 1 400 mg	Cohort 2 100 mg
% Overall response rate	41	22
% Complete/partial response rate	4/37	0/22

Main G3 side-effects : fatigue (6 patients), nausea (5 patients), vomiting (3 patients)

Open Questions on PARP 1 Inhibitors

- **Clinical activity of PARP 1 inhibitors in combination with cisplatin in BRCA deficient tumors**
- **Combination of PARP 1 inhibitors with other DNA damaging agents (ie, cyclophosphamide, anthracyclines, doublets or triplets)**
- **Clinical activity of PARP 1 inhibitor in non–triple-negative or non-BRCA deficient tumors**

My Choice

- **If clinical trial accessible → I would recommend patient's participation**
- **Alternatively, chemotherapy options respecting patient's quality of life**