Question #1: Selection of Therapy for High Volume, Recurrent HER2-Negative Metastatic Breast Cancer

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Which of the following outcomes do you feel is the most important when selecting therapy for a "fit" patient who suffers recurrent HER2-negative breast cancer with significant visceral organ involvement but adequate hepatic and renal function?

1. **Rapid response rate**
2. **Improved progression-free survival**
3. **Improved overall survival**
4. **Least toxicity**

Which of the following outcomes do you feel is the most important when selecting therapy for a "fit" patient who suffers recurrent HER2-negative breast cancer with significant visceral organ involvement but adequate hepatic and renal function?

1. Rapid response rate

33.3%

2. Improved progression-free survival

24.4%

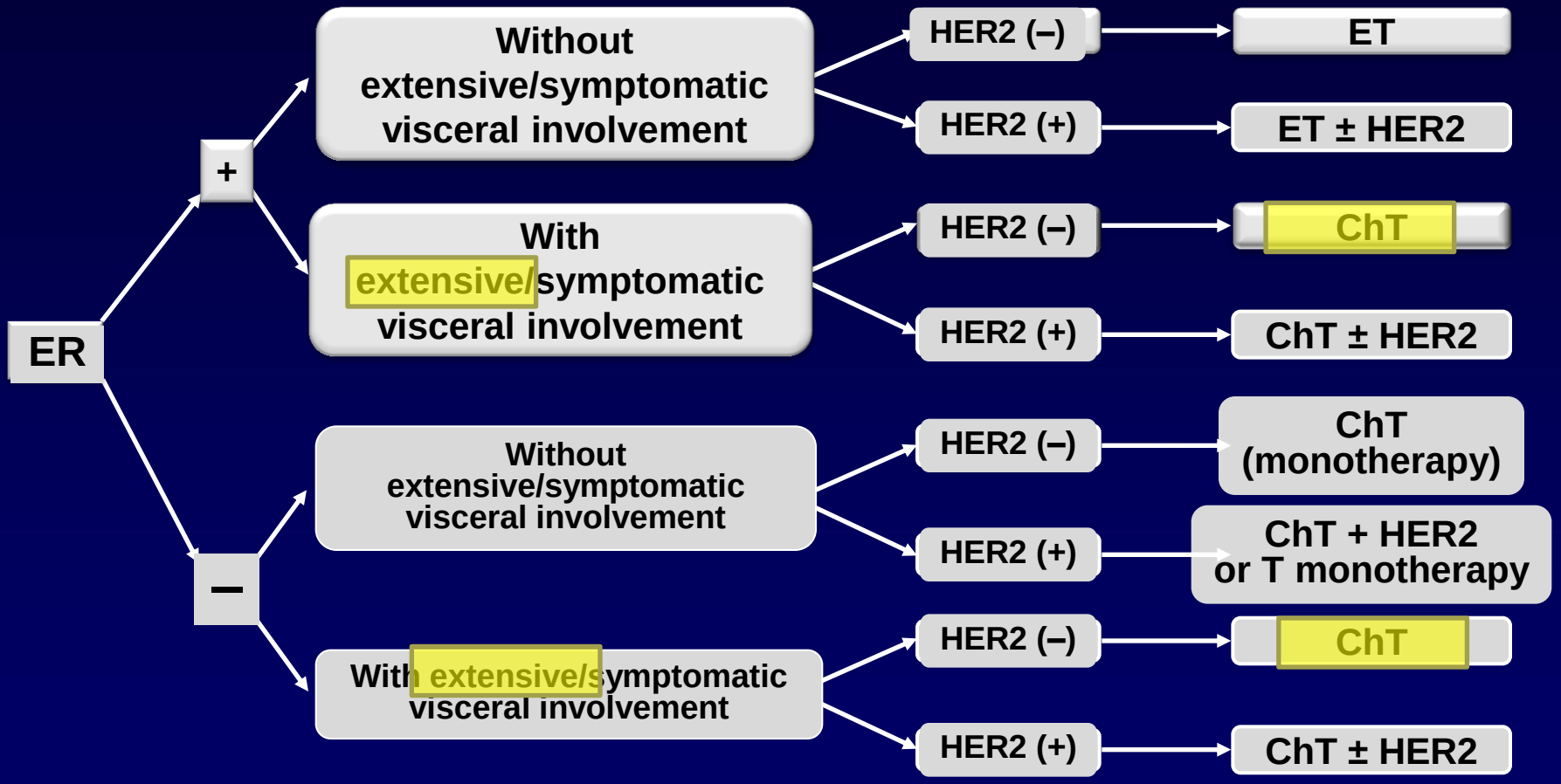
3. Improved overall survival

33.3%

4. Least toxicity

8.9%

ESMO Guidelines: First-Line Therapy in Advanced Breast Cancer



ChT, chemotherapy; ET, endocrine therapy; T, trastuzumab

Adapted from Cardoso F, et al. Ann Oncol. 2012;23 Suppl 7:vii11-9.

Chemotherapy for Metastatic Breast Cancer

- **Sequential single agents (at MTD) preferred for most patients**
  - **Variety of options—no single 'gold standard'**
  - **Limited toxicity regimens are generally preferred**
- **Combinations appropriate for rapidly progressive, symptomatic disease**
  - **Reduction in disease symptoms outweighs potential toxicity**
  - **May not be a candidate for subsequent therapy if rapid progression continued**

MTD, maximum tolerated dose

Individualized Therapy and Personalized Medicine

Individualized therapy: Estrogen and progesterone receptor status, HER2 status, other targets probably in the near future

Personalized medicine: Comorbidities, age, opinion of the patient

Single-Agent Versus Polychemotherapy in Patients With Advanced Breast Cancer

- Meta-analysis from abstracted data presented by the Cochrane Breast Cancer Group
- 43 trials identified up to November 2008
- 9742 women (55% of them received treatment as first-line therapy)

Carrick S, et al. *Cochrane Database Syst Rev.* 2009;(2):CD003372.

Single-Agent Versus Polychemotherapy in Patients With Advanced Breast Cancer

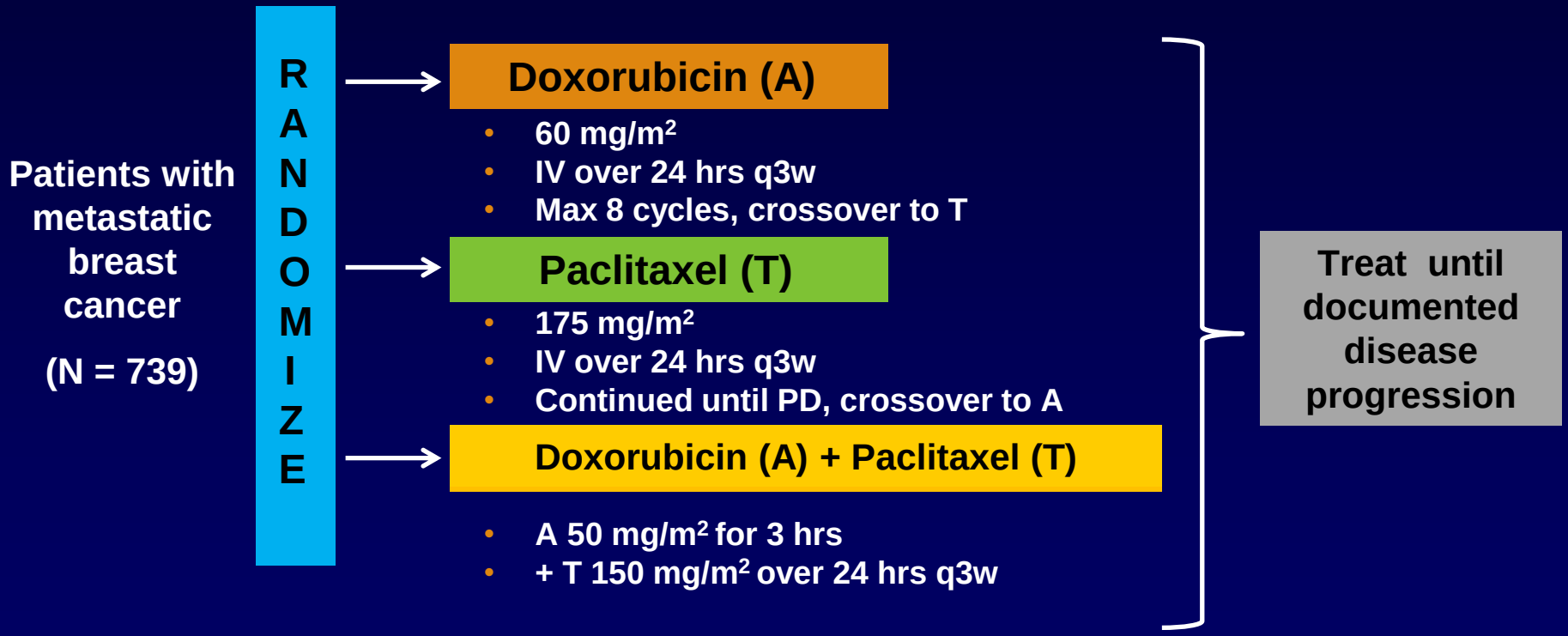
Polychemotherapy is better than single agent in terms of:

- **Response rates (HR = 1.29, 95% CI 1.14-1.45, *P*<.0001)**
- **Time to progression (HR = 0.78, 95% CI 0.74-0.82, *P*<.00001)**
- **Overall survival (HR = 0.88, 95% CI 0.83-0.93, *P*<.00001)**
- **More toxicity with polychemotherapy (nausea, vomiting, leukopenia, alopecia)**

An unresolved question is whether combination regimens are more effective than single agents given sequentially.

Carrick S, et al. *Cochrane Database Syst Rev.* 2009;(2):CD003372.

Doxorubicin vs Paclitaxel vs Doxorubicin/Paclitaxel (ECOG 1193 Phase III Study)



Sledge GW, et al. *J Clin Oncol*. 2003;21:588-592.

ECOG 1193: First-Line Treatment of MBC

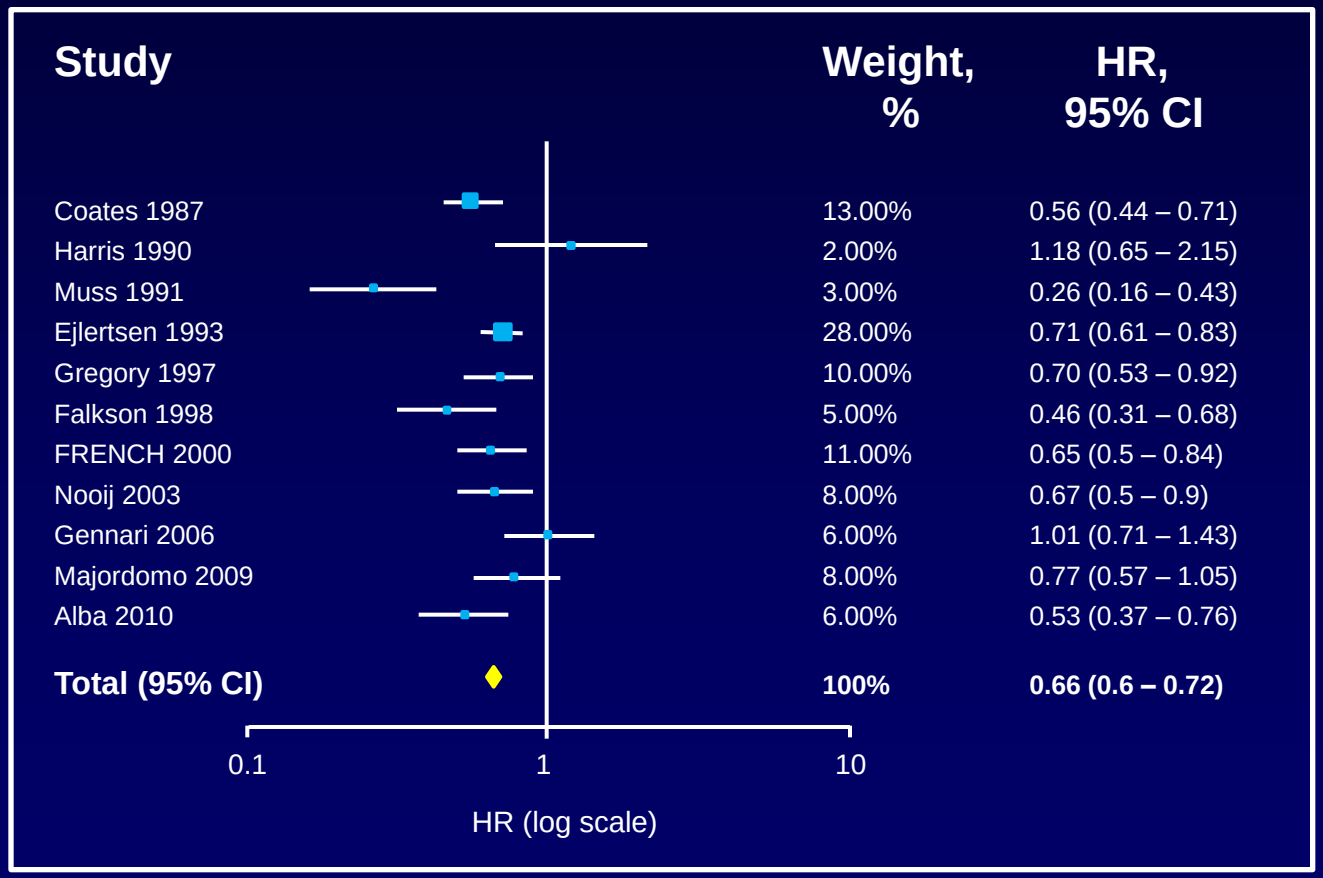
- ORR
  - Doxorubicin: 36%
  - Paclitaxel: 34%
  - Doxorubicin→Paclitaxel: 47%
- TTF
  - Doxorubicin: 5.8 months
  - Paclitaxel: 6.0 months
  - Doxorubicin→Paclitaxel: 8.0 months
- Median OS
  - Doxorubicin: 18.9 months
  - Paclitaxel: 22.2 months
  - Doxorubicin→Paclitaxel: 20 months
- Responses observed in 20% of patients crossing over from doxorubicin to paclitaxel; 22% crossing over from paclitaxel to doxorubicin (*P = NSS)*

Sledge GW, et al. *J Clin Oncol*. 2003;21:588-592.

Chemotherapy for Metastatic Breast Cancer

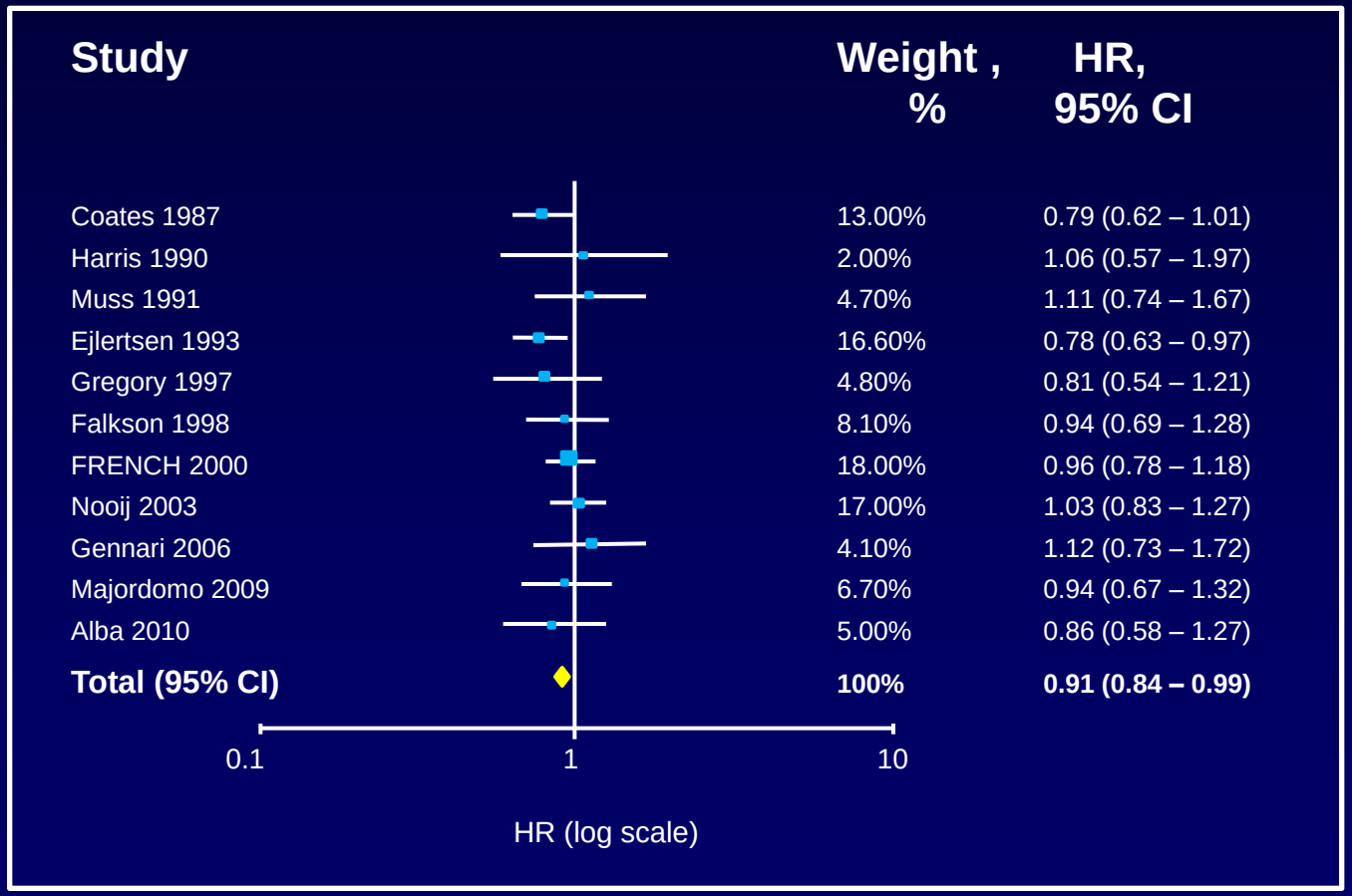
- Sequential single-agent chemotherapy preferred for most patients
- Limits toxicity
- Combinations may be preferred for rapidly progressive symptomatic disease
  - Reduction in symptoms outweighs toxicity
  - Not a candidate for subsequent therapy if continued progression

Longer First-Line Chemotherapy Duration: Substantially Longer PFS (HR: 0.64)



Gennari A, et al. *J Clin Oncol.* 2011;29(16):2144-2149.

Longer First-Line Chemotherapy Duration: Marginal Effect on OS (HR: 0.91)



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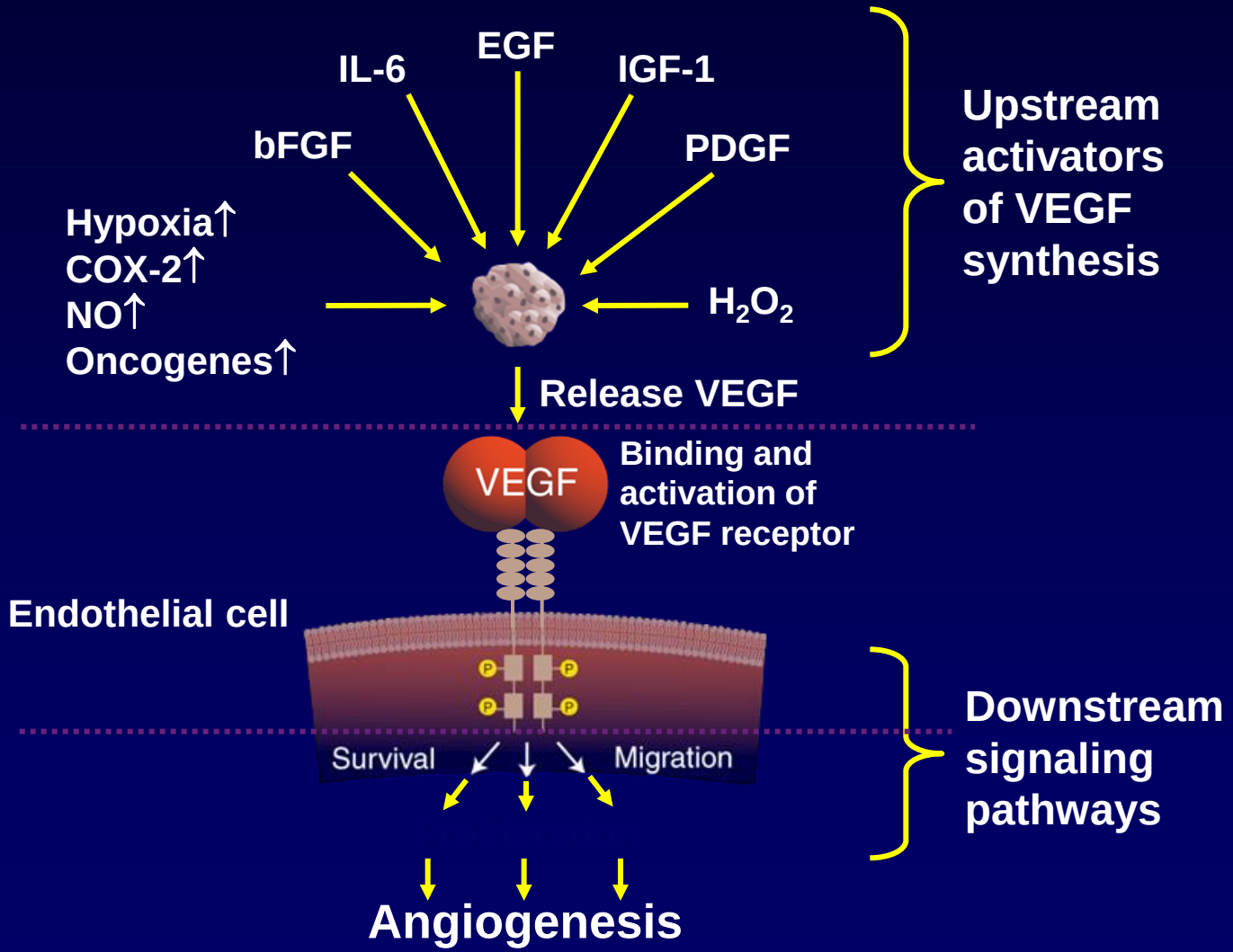
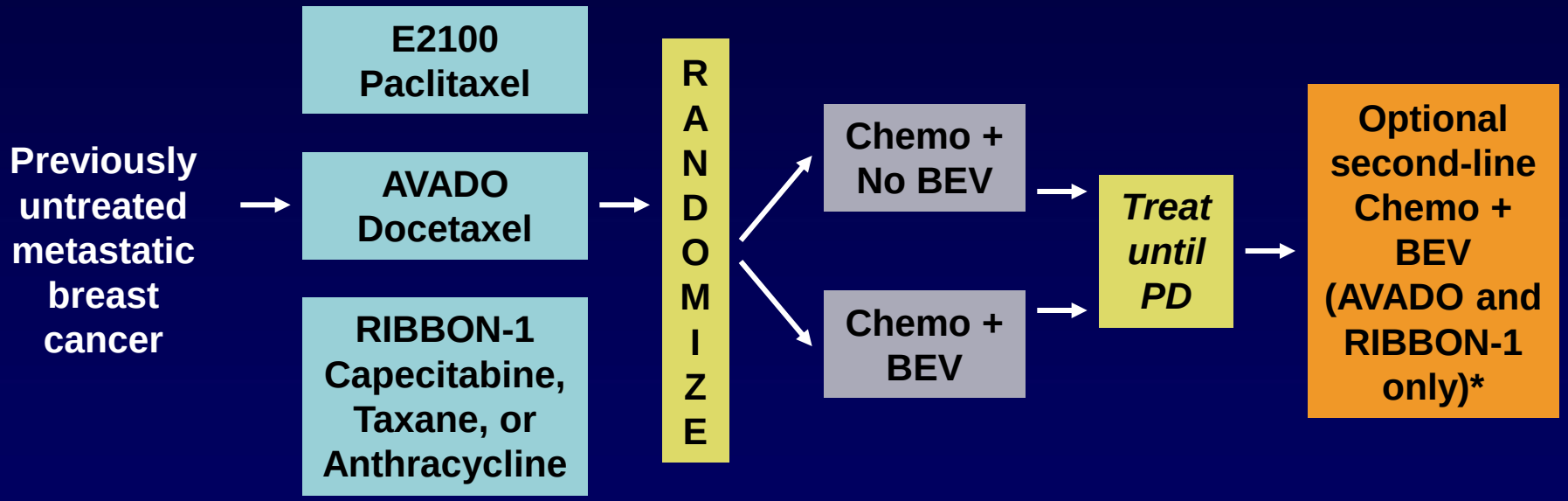
Do We Have an Alternative to Polychemotherapy?

VEGF Is a Key Mediator of Angiogenesis



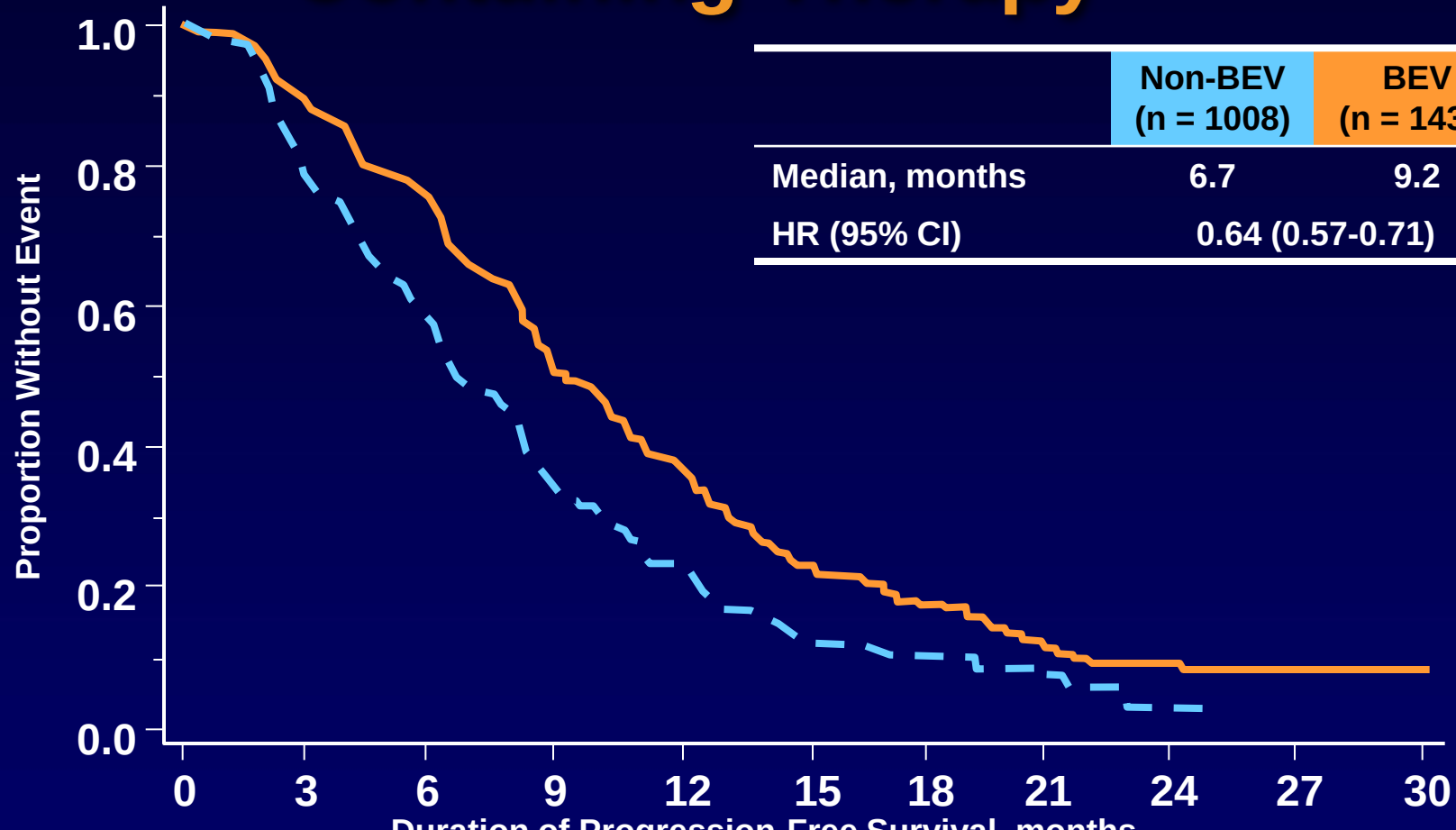
Meta-Analysis of 3 Phase III Trials of Bevacizumab (BEV) in Previously Untreated Metastatic Breast Cancer



*~50% of patients received bevacizumab at crossover

Miles DW, et al. *Ann Oncol*. 2013;24(11):2773-2780.

Meta-Analysis: PFS With Bevacizumab-Containing Therapy



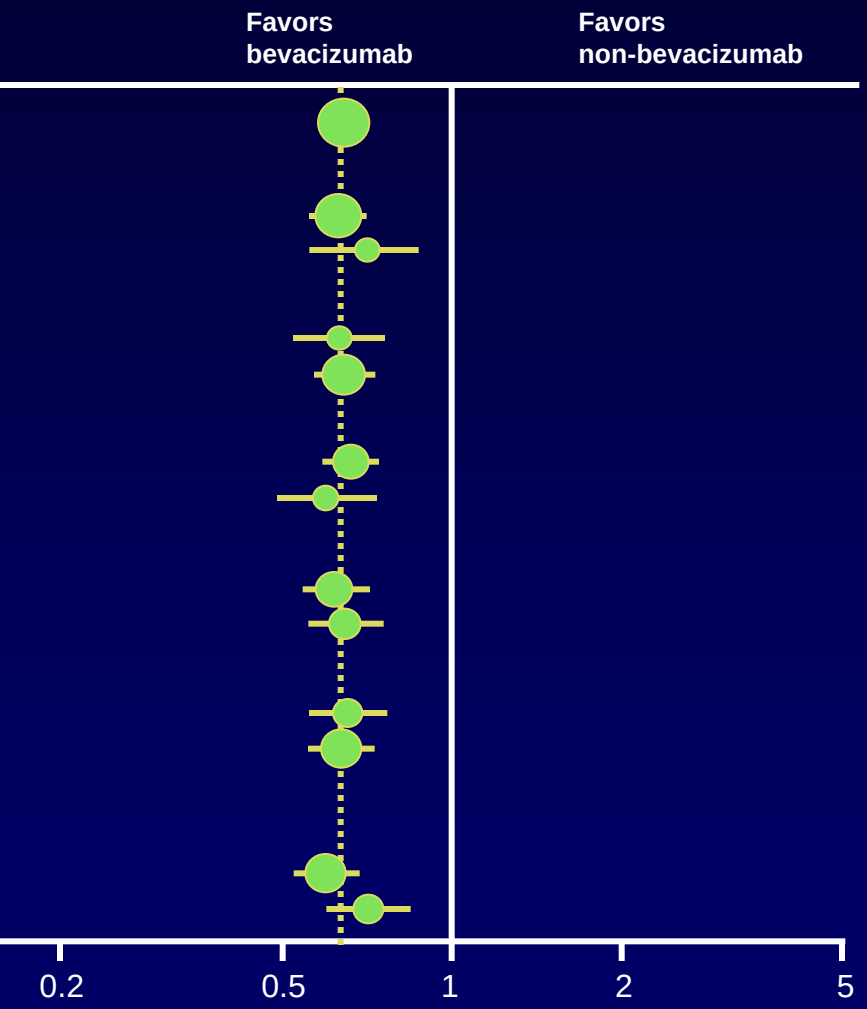
	Non-BEV (n = 1008)	BEV (n = 1439)
Median, months	6.7	9.2
HR (95% CI)	0.64 (0.57-0.71)	

No. at risk											
Non-BEV	1008	680	464	210	111	38	18	9	1	0	0
BEV	1439	1157	885	491	292	134	67	22	8	2	1

Miles DW, et al. *Ann Oncol*. 2013;24(11):2773-2780.

Meta-Analysis: PFS in Clinically Relevant Subgroups

Baseline risk factor	Total n	HR	(95% CI)
All patients	2447	0.64	(0.58–0.71)
Age, years			
<65	1917	0.62	(0.56–0.70)
≥65	530	0.70	(0.56–0.88)
Triple-negative disease			
Yes	621	0.63	(0.52–0.76)
No	1762	0.64	(0.57–0.73)
Visceral disease			
Yes	1707	0.66	(0.59–0.75)
No	740	0.60	(0.49–0.74)
No. of metastatic sites			
<3	1463	0.62	(0.54–0.71)
≥3	980	0.64	(0.55–0.75)
Disease-free interval, months			
≤24	924	0.65	(0.55–0.77)
>24	1519	0.63	(0.56–0.72)
Prior (neo)adjuvant chemotherapy			
Yes	1525	0.60	(0.53–0.68)
No	922	0.71	(0.60–0.84)



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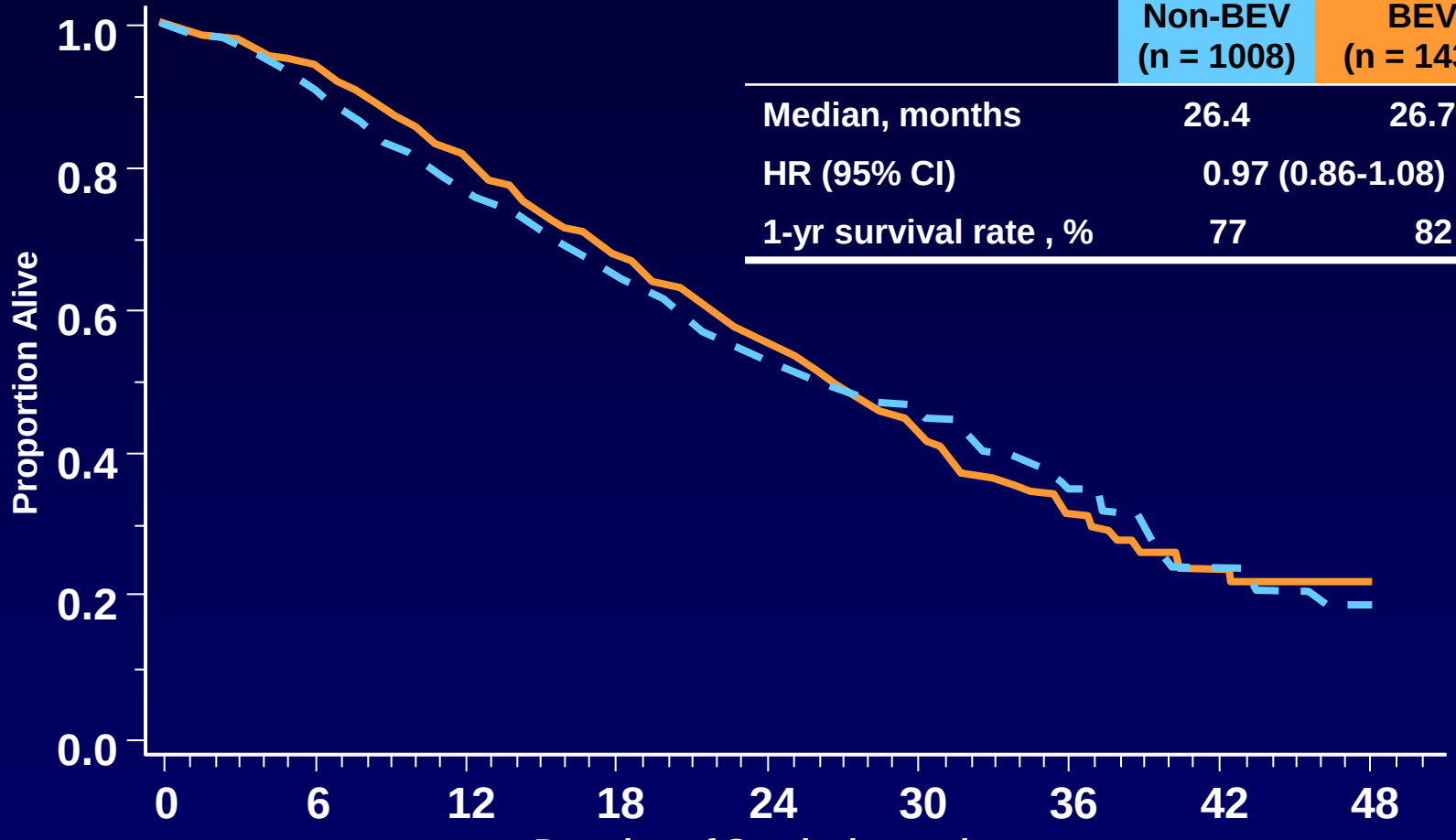
Bevacizumab Meta-Analysis: OS



	Non-BEV (n = 1008)	BEV (n = 1438)
Median, months	26.4	26.7
HR (95% CI)	0.97 (0.86-1.08)	
1-yr survival rate , %	77	82

No. at risk									
Non-BEV	1008	892	746	621	426	178	51	19	8
BEV	1439	1333	1127	916	591	204	55	23	5

Miles DW, et al. *Ann Oncol*. 2013;24(11):2773-2780.

My Opinion

Which of the following outcomes do you feel is the most important when selecting therapy for a "fit" patient who suffers recurrent HER2-negative breast cancer with significant visceral organ involvement but adequate hepatic and renal function?

1. **Rapid response rate**
2. **Improved progression-free survival**
3. **Improved overall survival**
4. **Least toxicity**

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions