Avastin Combined with Chemotherapy in HER2$^-$ Negative First Line Metastatic Breast Cancer (MBC)

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Avastin Combined with Chemotherapy in HER2-Negative MBC

Objective

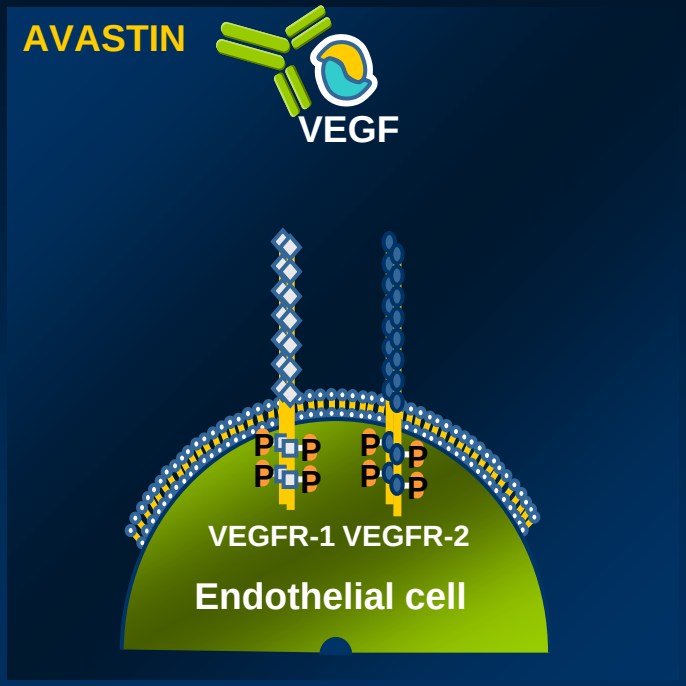
- Conversion from accelerated to full approval based on:
  - RIBBON1 (AVF3694g)
  - AVADO (BO17708)
  - FDA's accelerated approval conditions
- Revised labeling to be based on efficacy supplements from these studies

Avastin Combined with Chemotherapy in HER2-negative MBC

Key Elements

1. **Reliable, consistent, and significant improvement in PFS**
   - 31% - 52% reduction in risk of disease progression or death
   - Observed in key subgroups, multiple chemotherapies
2. **Safety well characterized and known to physicians**
   - No impairment in overall survival
   - Hypertension and proteinuria account for majority of AEs, typically asymptomatic, infrequent discontinuation (0.7% - 2.9%)
3. **Important option for physicians and patients**
   - Choice informed by largest dataset ever submitted in 1st-line mBC - > 2400 patients, 3 RCT, 4 fully-powered cohorts

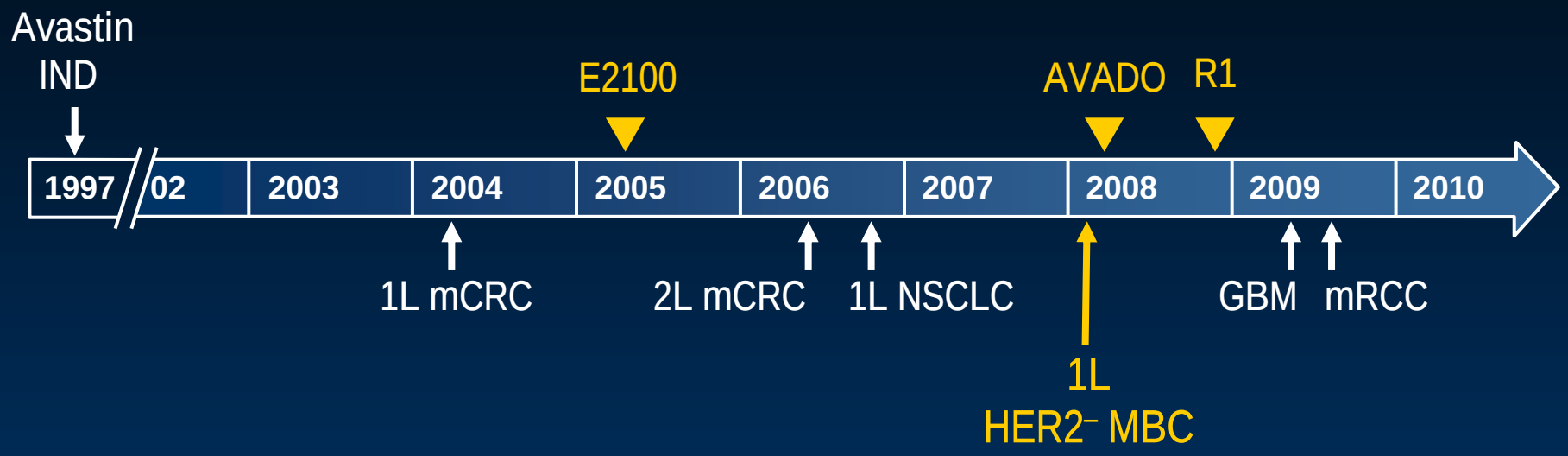
Mechanism of Action of Avastin



- Highly specific, IgG1 antibody binds and neutralizes VEGF
- Combines with multiple CT agents
- Complements CT
  - Enhances vascular damage
  - Prevents new vessels
  - “Normalizes” vessels, limits tumor spread

Avastin: anti-vascular, anti-angiogenic, and potential anti-metastatic actions

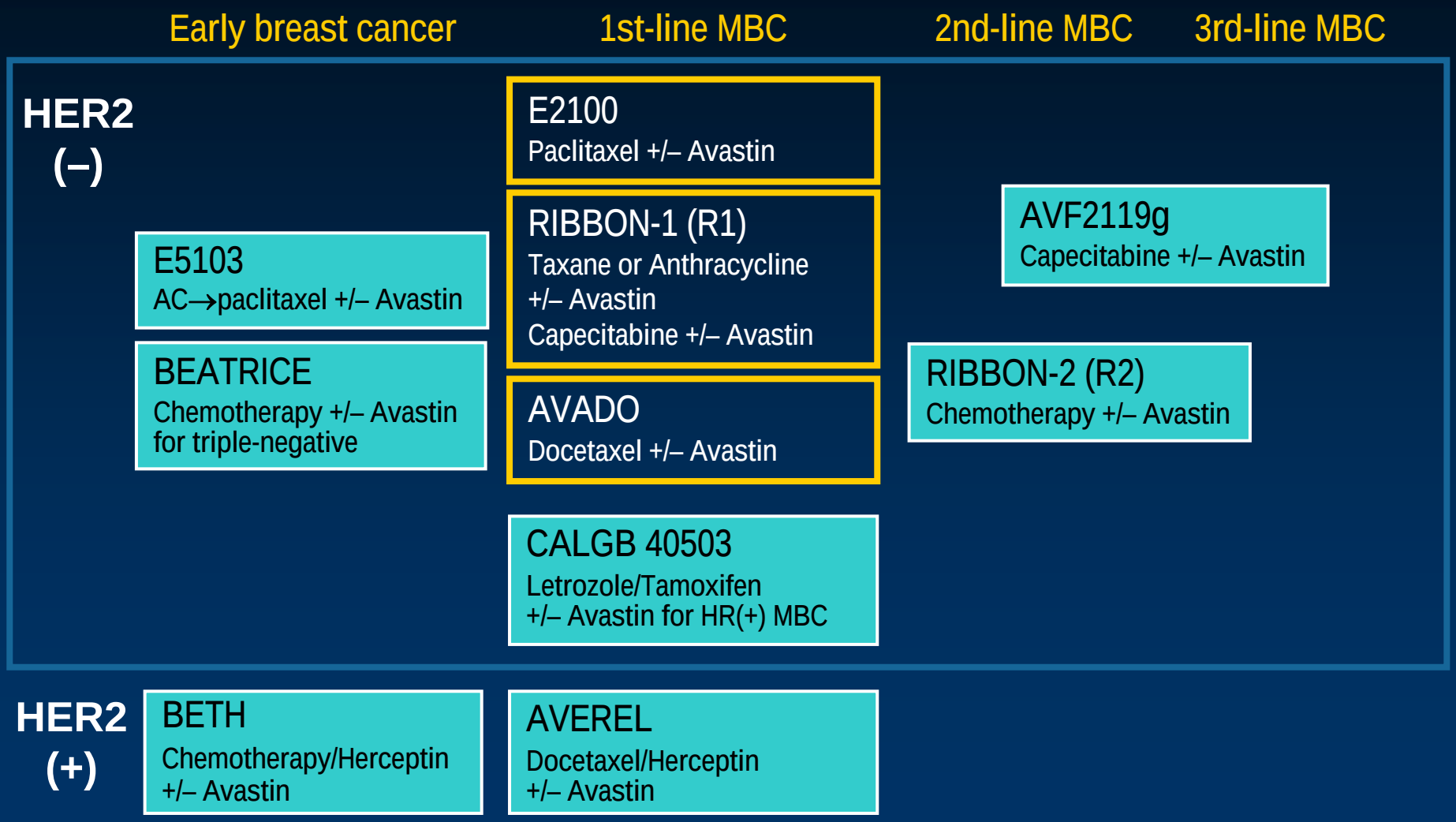
Avastin: Extensive Experience in Oncology



- **Approved in 6 indications; survival, PFS benefits**
- **Combined with 5FU, irinotecan, oxaliplatin, carboplatin, paclitaxel, IFN**
- **Data from > 13,000 patients in completed trials**
- **> 812,000 patients treated; > 90,000 MBC**

GBM = Glioblastoma multiforme; mBC = Metastatic breast cancer; mCRC = Metastatic colorectal cancer.
NSCLC = Non-small cell lung cancer; mRCC = Metastatic renal cell carcinoma

Avastin Phase III Clinical Trials in Breast Cancer



AVF2119g also enrolled a small group of HER2-positive and/or first-line patients.

Avastin Regulatory History
Conversion to Full Approval

Approval Letter 2/22/08

Submit efficacy supplement to further define the degree of clinical benefit with data from

- **RIBBON1 (AVF3694g)**
- **AVADO (BO17708)**

Type B Meeting 2/26/09; FDA Minutes

FDA confirmed that the basis for conversion to full approval will be demonstrated improvement in progression-free survival and evidence that survival is not impaired.

Proposed Indication Statement

Avastin®, in combination with taxane-based, anthracycline-based or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

Avastin in HER2$^-$ Negative First Line mBC

Today's Discussion

- PFS benefit
  - Statistically persuasive, consistent
  - Use of all data to define magnitude
- Risk
  - Distinguish among type and frequency of AEs
  - Relationship to chemotherapy backbone
  - Physicians' experience and management
- Clinical relevance
  - Importance of Avastin as a treatment option in mBC
  - Why observed benefit is meaningful

Today's Agenda

See Phan, MD Genentech	**Efficacy and Safety Results from E2100, RIBBON1, AVADO**
James Reimann, PhD Genentech	**Measures and Magnitude of Avastin PFS Benefit**
Gabriel Hortobagyi, MD MD Anderson Cancer Center	**Metastatic Breast Cancer: State of the Art**
Sandra Horning, MD Genentech	**Concluding Remarks**

Results from Studies E2100, RIBBON1, and AVADO

See Phan, MD

Senior Medical Director
Genentech

First-Line Metastatic Breast Cancer Trial Endpoints

- Progression-free survival as primary endpoint
  - Captures clinical objective of treatment
  - Direct measure of immediate treatment effect
  - Equals time to progression or death
    - If no event, censored at last tumor assessment or at start of non-protocol therapy (NPT)
- Secondary endpoints include ORR, OS, 1-year survival rate, safety

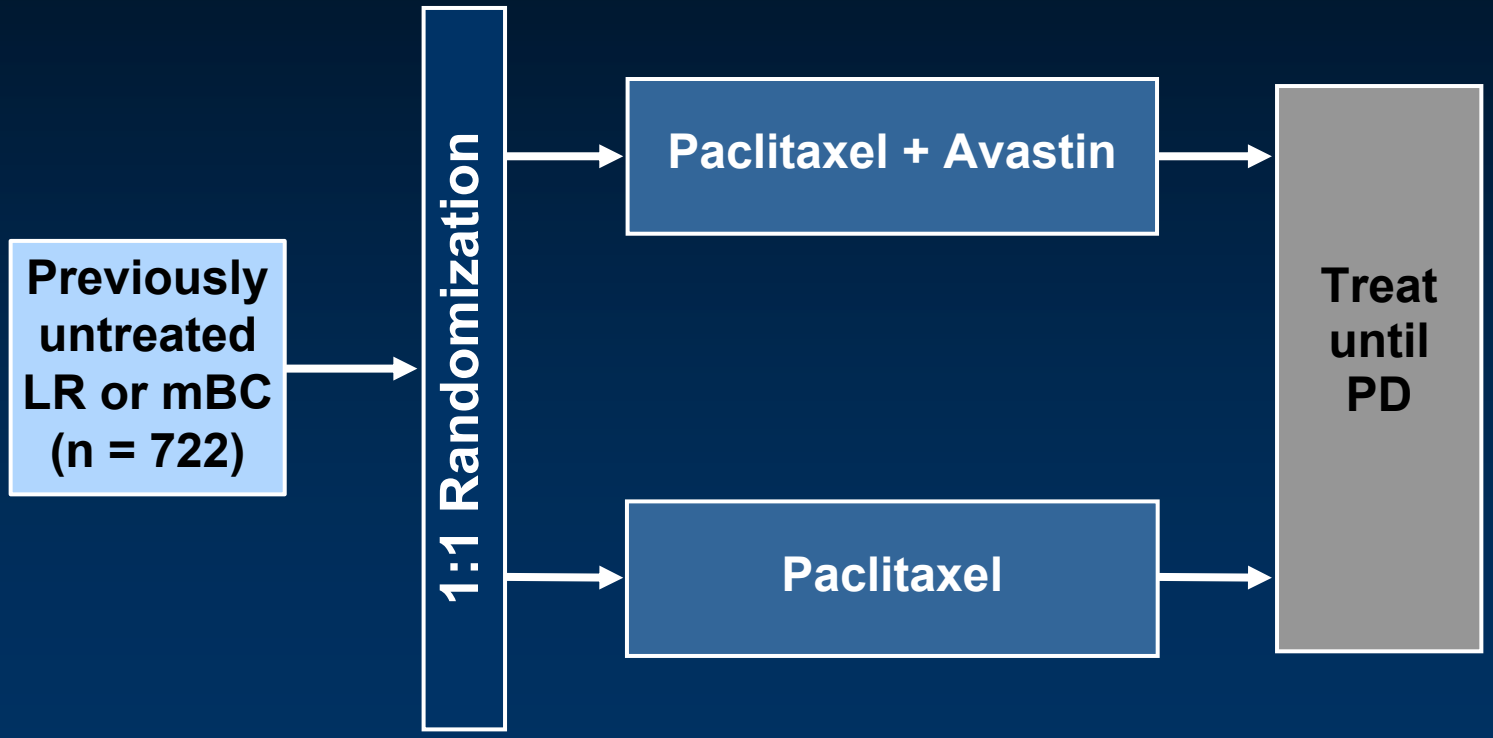
Patient Characteristics

	E2100 n = 722	R1-Cap n = 615	R1-T/Anth n = 622	AVADO n = 736
Median age, yr	55	56	55	55
Triple negative	32	22	24	22
Disease-free ≤ 24 mo	41	33	42	35
Adj chemotherapy	66	72	46	66
≥ 3 metastatic sites	29	44	45	47
Visceral disease	66	69	70	71

- **In each study, characteristics balanced between treatment arms**

All data are %, unless otherwise noted.

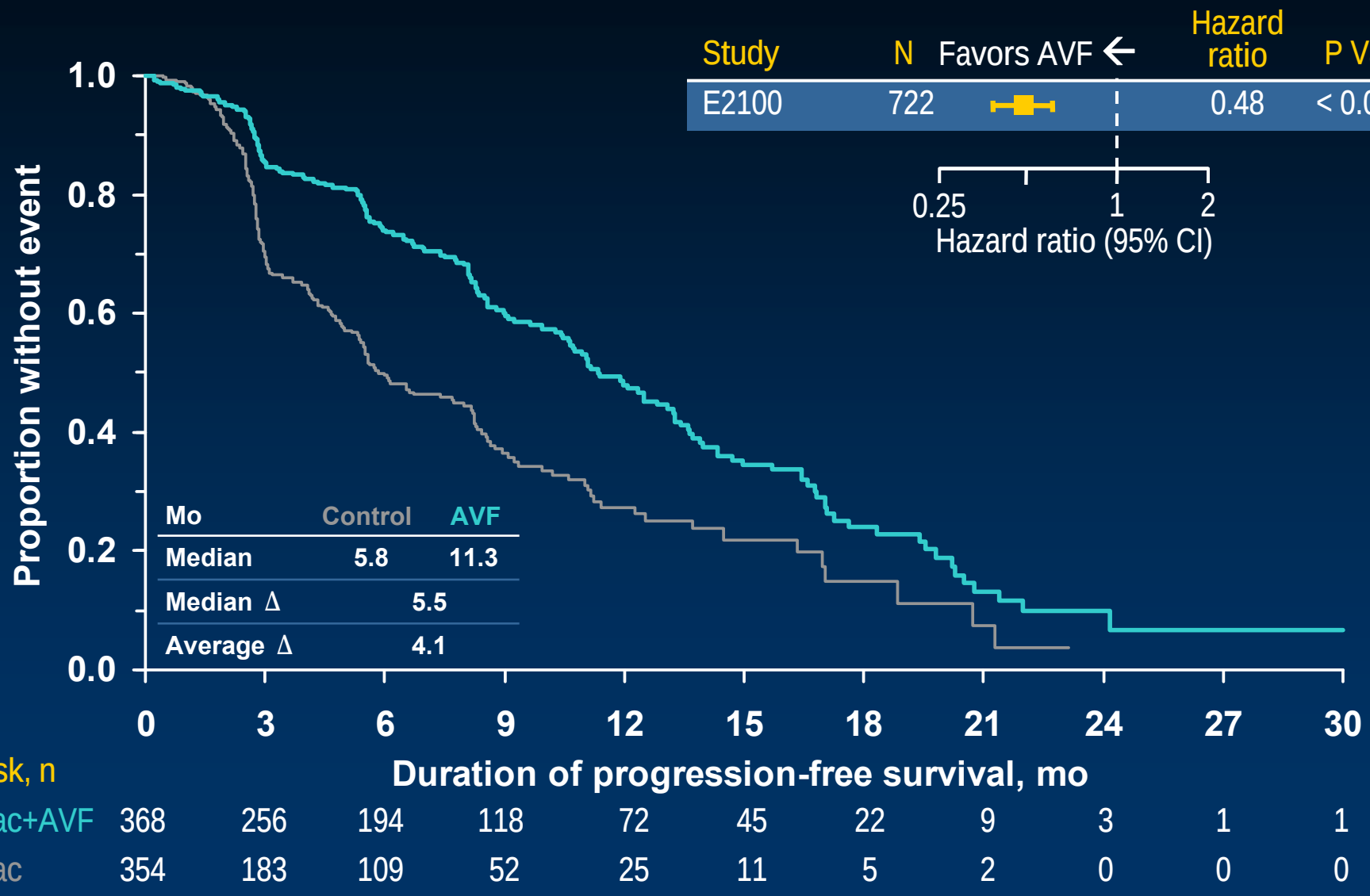
E2100 Study Design



Paclitaxel 90 mg/m^2 qwk, 3 of 4 wk
Avastin 10 mg/kg q2wk

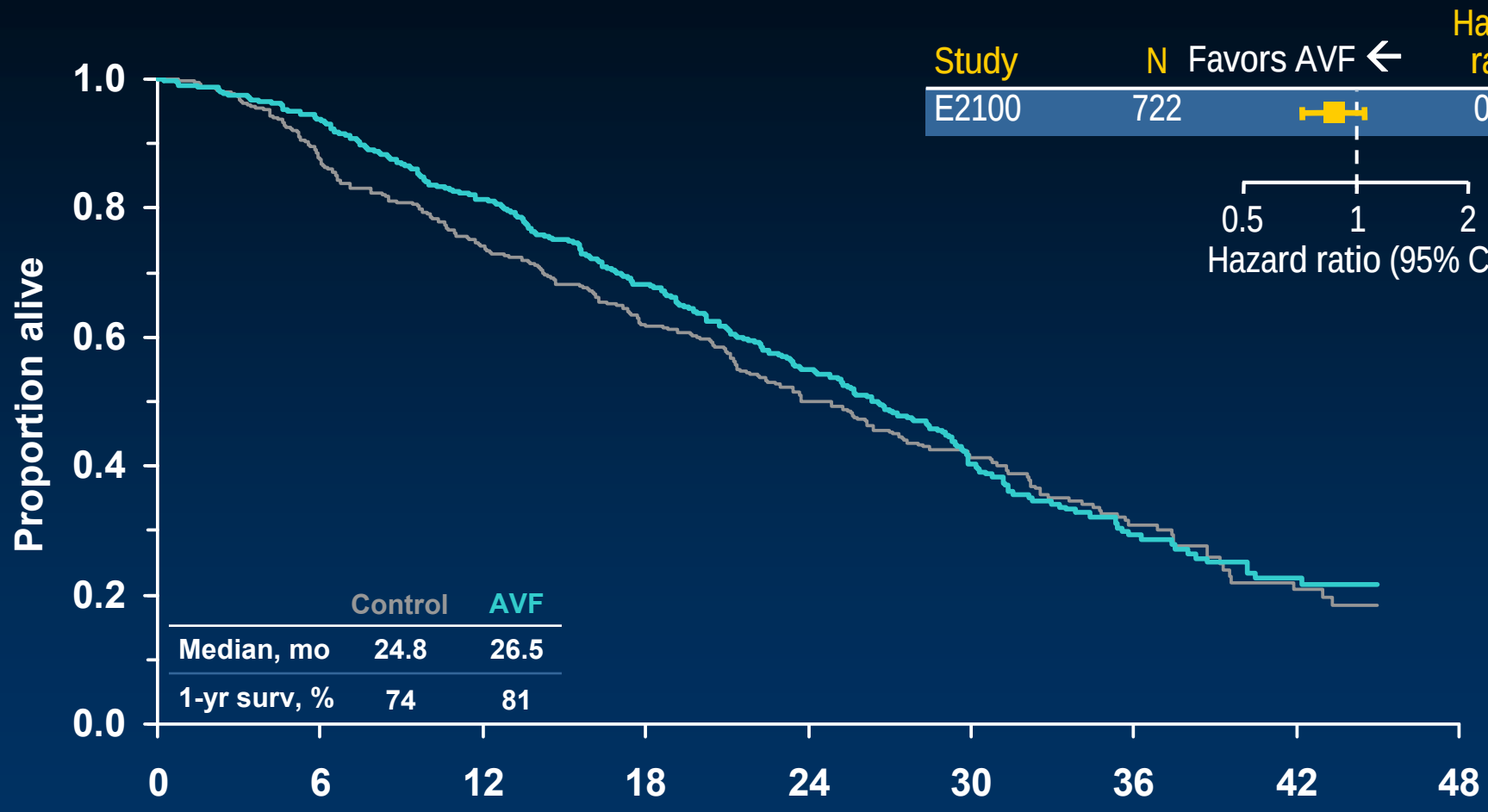
LR = Locally recurrent; mBC = Metastatic breast cancer; PD = Progressive disease.

Progression-Free Survival
E2100



AVF = Avastin; CI = Confidence interval; Pac = Paclitaxel; Mo = months

Overall Survival
E2100



At risk, n									
— Pac+AVF	368	344	297	249	193	104	48	23	0
— Pac	354	307	258	215	165	103	48	19	0

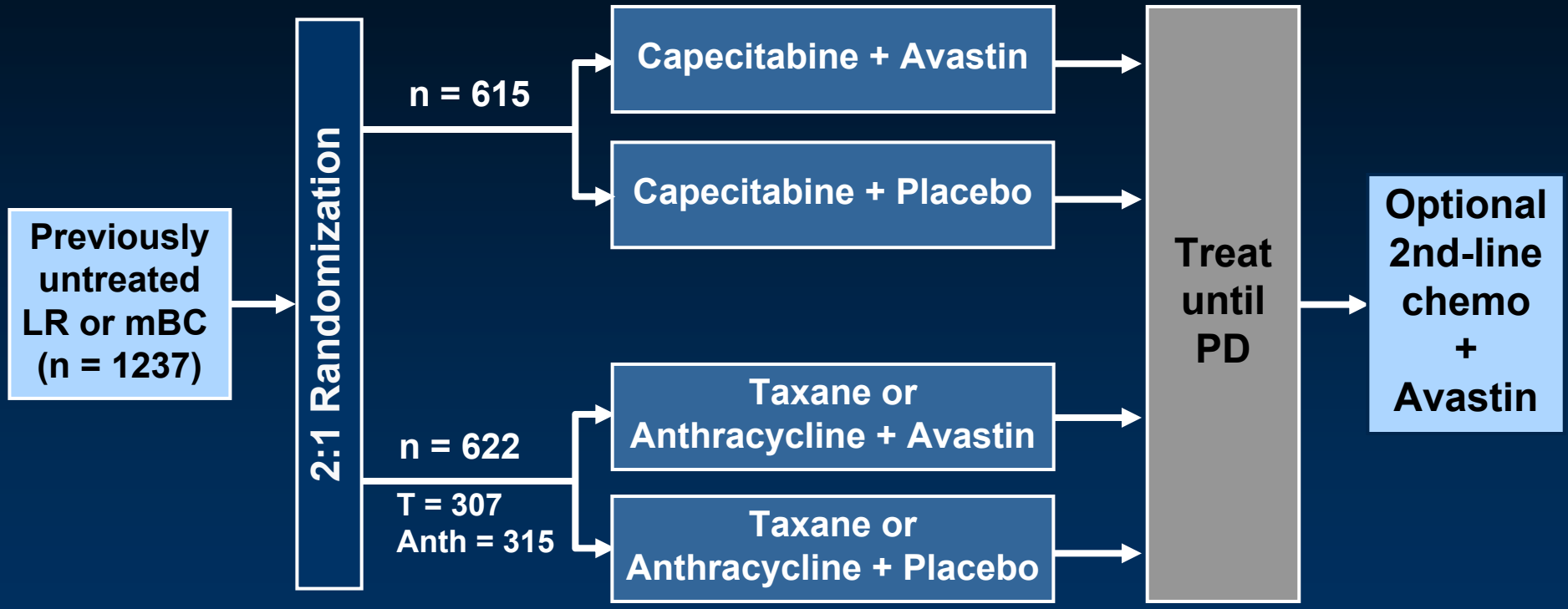
AVF = Avastin; CI = Confidence interval; Pac = Paclitaxel; mo = months

E2100: Gr ≥ 3 Select Adverse Events

	Pac n = 348, %	Pac+AVF n = 363, %
Common AVF-assoc. AEs		
Hypertension*	1.4	16.0
Proteinuria	0	3.0
Other AVF-assoc. AEs		
ATE	0	3.6
VTE	4.3	3.0
Bleeding	0.3	2.2
Fistula	0	0.6
GI perforation	0	0.6
Wound dehiscence	0	0.8
Chemotherapy-assoc. AEs		
Neutropenia	4.0	8.0
Febrile neutropenia	0	1.7
Sensory neuropathy**	18.1	24.8
LV systolic dysfunction	0.3	2.2

*NCI CTC v2 **No difference after adjusting for paclitaxel exposure

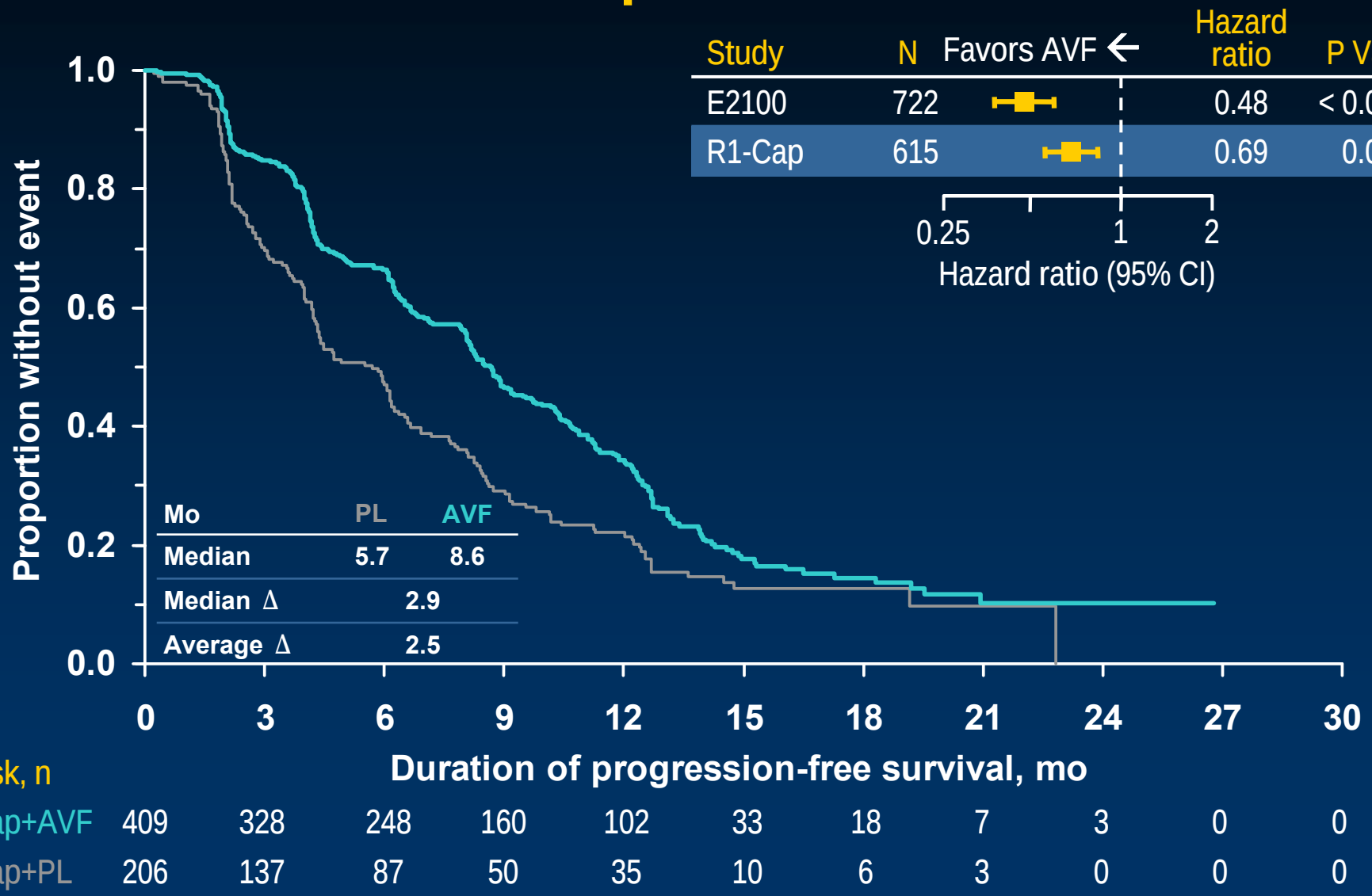
RIBBON1 Study Design



Taxane (T) = Docetaxel or Abraxane
Anthracycline (Anth) = Doxorubicin or Epirubicin
with cyclophosphamide or cyclophosphamide/5-FU
Avastin 15 mg/kg q3wk

LR = Locally recurrent; mBC = Metastatic breast cancer; PD = Progressive disease.

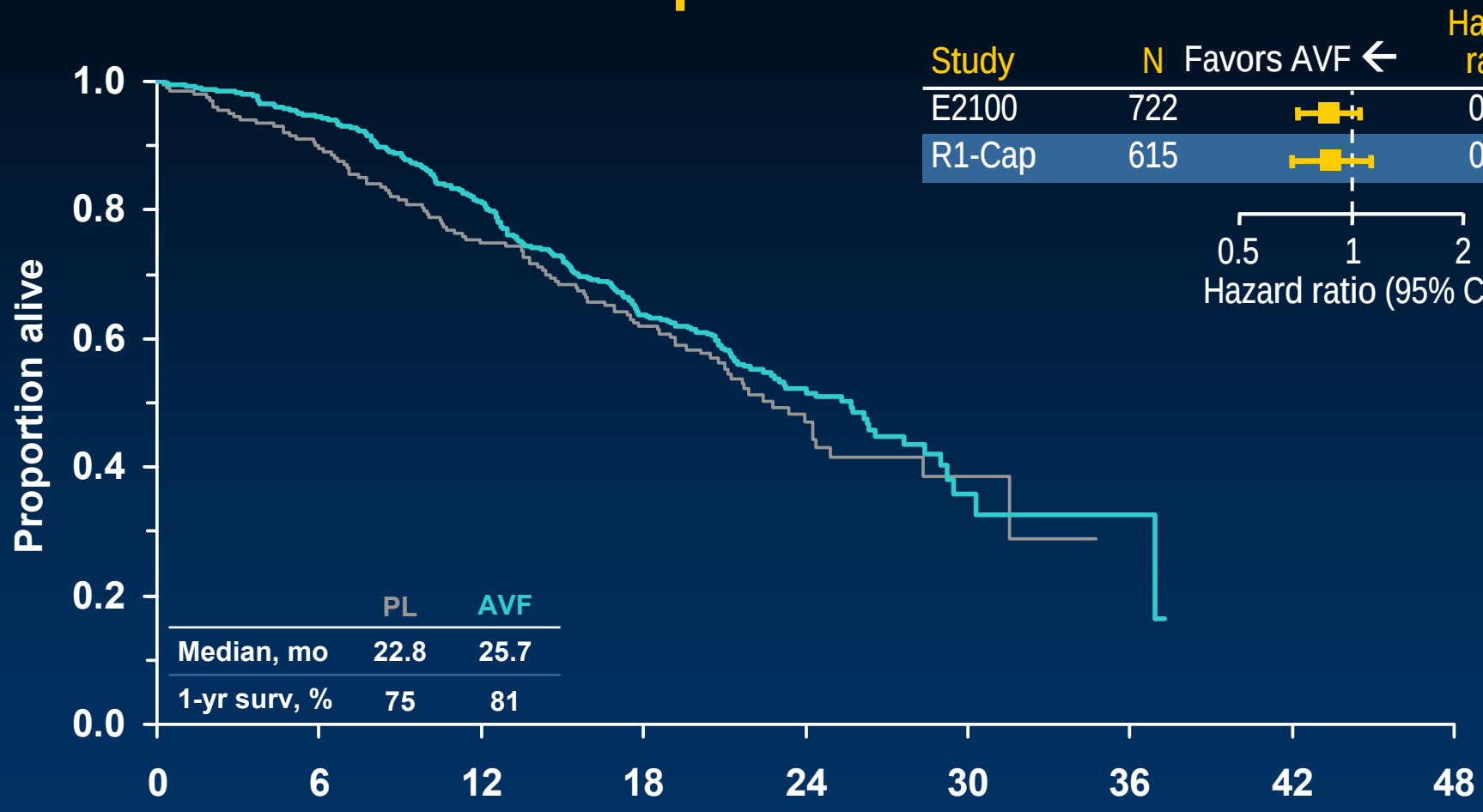
Progression-Free Survival
R1-Capecitabine



At risk, n											
— Cap+AVF	409	328	248	160	102	33	18	7	3	0	0
— Cap+PL	206	137	87	50	35	10	6	3	0	0	0

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; PL = Placebo; Mo = months

Overall Survival
R1-Capecitabine



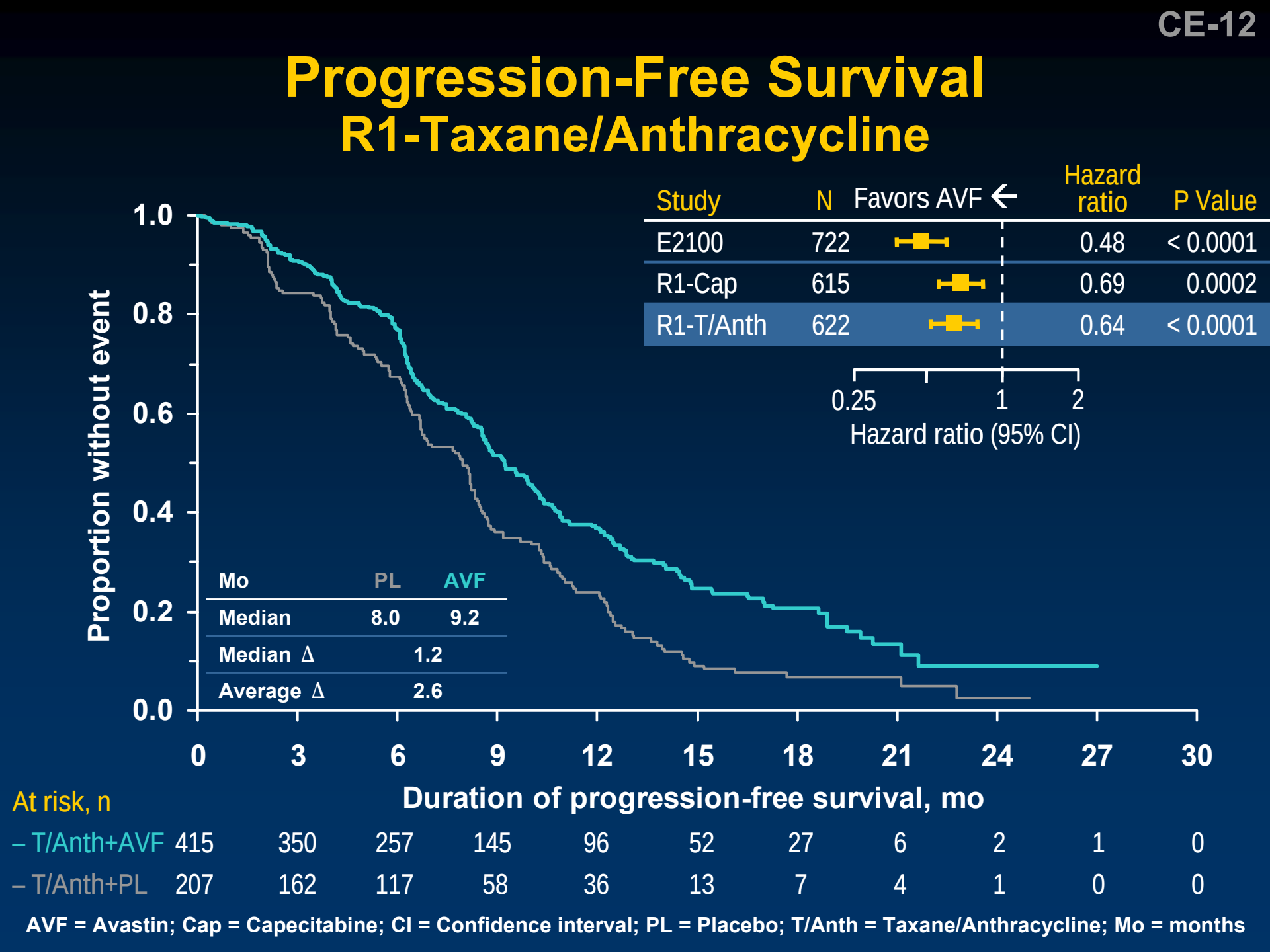
At risk, n									
— Cap+AVF	409	375	312	231	86	15	2	0	0
— Cap+PL	206	178	144	109	38	6	0	0	0

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; PL = Placebo; mo = months

R1-Cap: Gr ≥ 3 Select Adverse Events

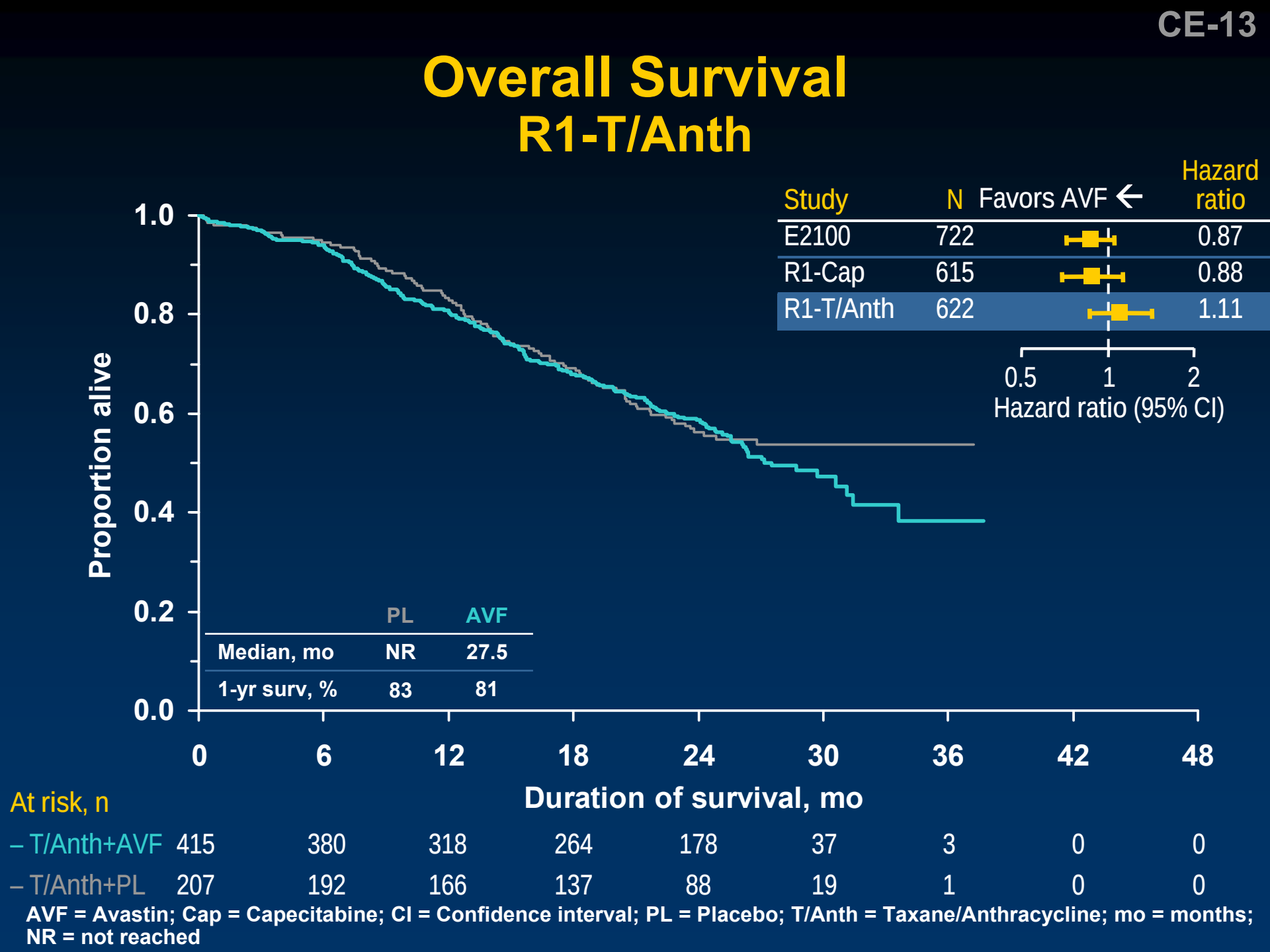
	Cap+PL n = 201, %	Cap+AVF n = 404, %
Common AVF-assoc. AEs		
Hypertension	1.0	9.9
Proteinuria	0	2.2
Other AVF-assoc. AEs		
ATE	1.0	2.0
VTE	3.5	4.7
Bleeding	0.5	0.2
Fistula	0.5	0.2
GI perforation	0	0
Wound dehiscence	0	0.7
Chemotherapy-assoc. AEs		
Neutropenia	1.0	1.2
Febrile neutropenia	0	0
Sensory neuropathy	0.5	3.0
LV systolic dysfunction	0.5	1.0

Progression-Free Survival
R1-Taxane/Anthracycline



AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; PL = Placebo; T/Anth = Taxane/Anthracycline; Mo = months

Overall Survival
R1-T/Anth



At risk, n									
– T/Anth+AVF	415	380	318	264	178	37	3	0	0
– T/Anth+PL	207	192	166	137	88	19	1	0	0

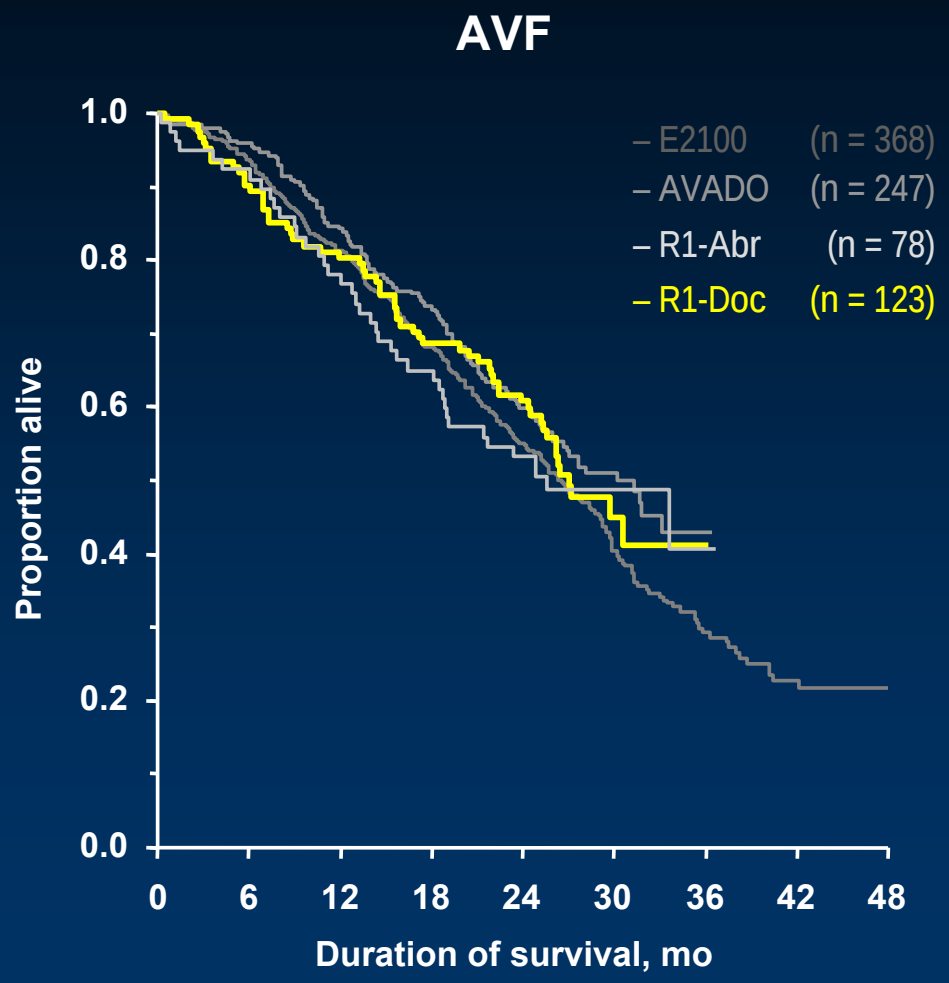
AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; PL = Placebo; T/Anth = Taxane/Anthracycline; mo = months; NR = not reached

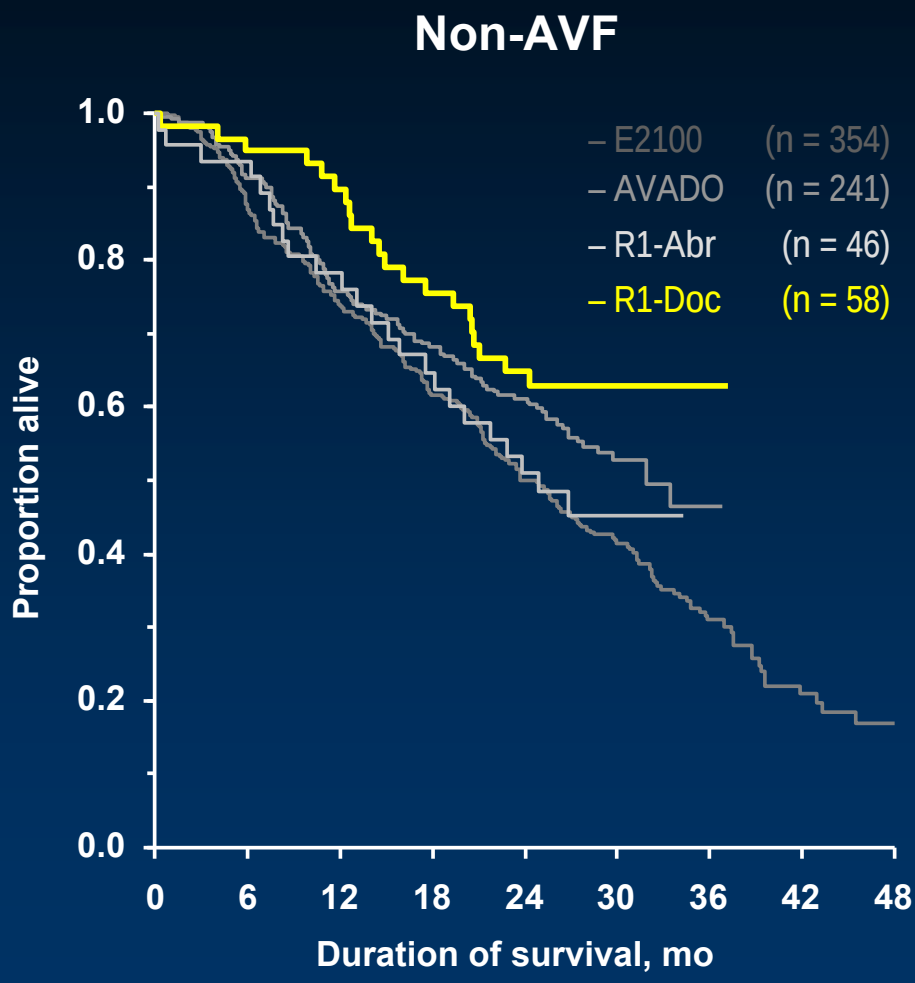
R1 Exploratory Analyses of Anthracycline and Taxane Treated Subgroups

	Anthracycline		Taxane	
	PL n = 103	AVF n = 212	PL n = 104	AVF n = 203
PFS				
HR (95% CI)	0.55 (0.40, 0.74)		0.75 (0.56, 1.01)	
OS				
HR (95% CI)	0.97 (0.67, 1.41)		1.24* (0.87, 1.77)	

* R1-Docetaxel subgroup, OS HR = 1.45 (0.88, 2.40), n = 181

Kaplan-Meier Curves for OS Taxane-Treated Patients



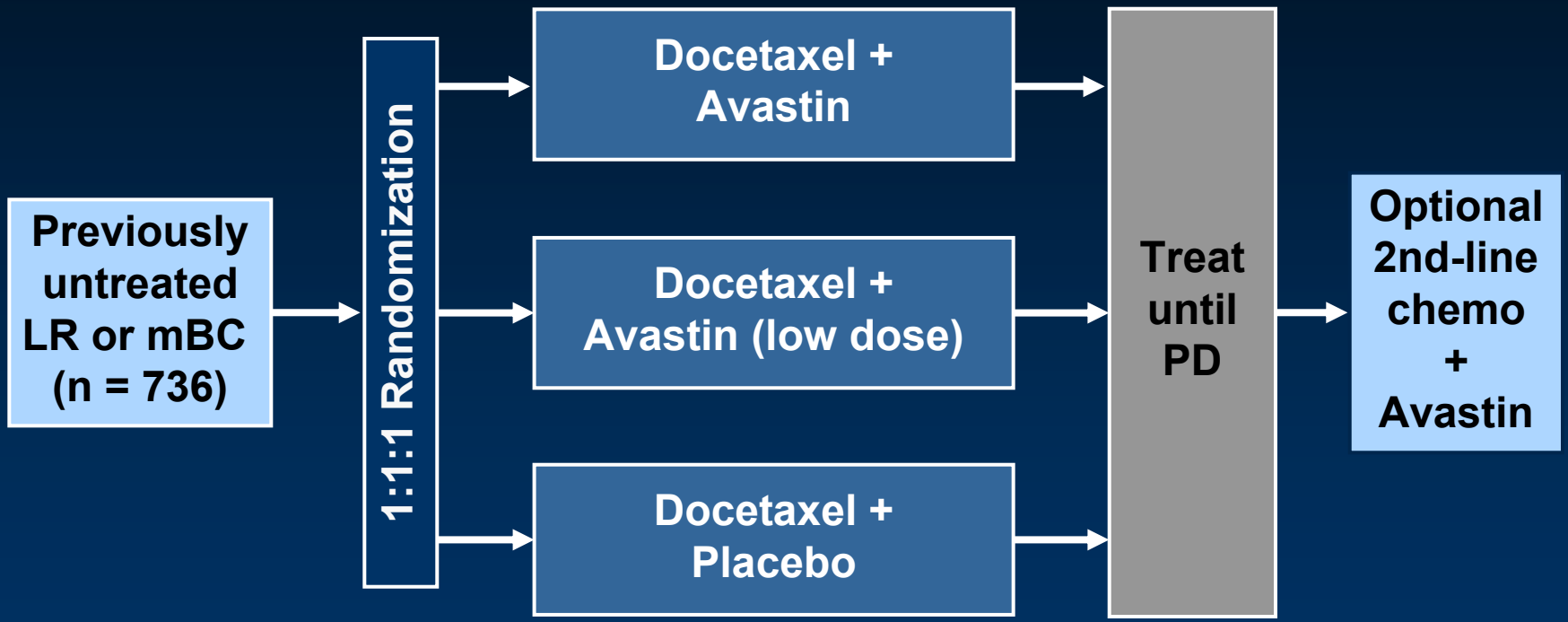


Abr = Abraxane; AVF = Avastin; Doc = Docetaxel; mo = months; OS Overall survival.

Grade ≥ 3 Select Adverse Events
R1

Adverse event category	Anth+PL n = 100, %	Anth+AVF n = 210, %	Tax+PL n = 102,%	Tax+AVF n = 203, %
Common AVF-assoc. AEs				
Hypertension	0	10.0	2.0	9.4
Proteinuria	0	1.9	0	3.9
Other AVF-assoc. AEs				
ATE	0	1.4	0	0.5
VTE	2.0	2.9	4.9	2.0
Bleeding	0	0	0	5.4
Fistula	0	0	1.0	0.5
GI perforation	0	0	1.0	2.0
Wound dehiscence	0	1.0	1.0	1.5
Chemotherapy-assoc. AEs				
Neutropenia	4.0	4.3	4.9	9.4
Febrile neutropenia	5.0	3.8	2.0	7.9
Sensory neuropathy	0	0.5	8.8	8.4
LV systolic dysfunction	0	2.9	0	2.0

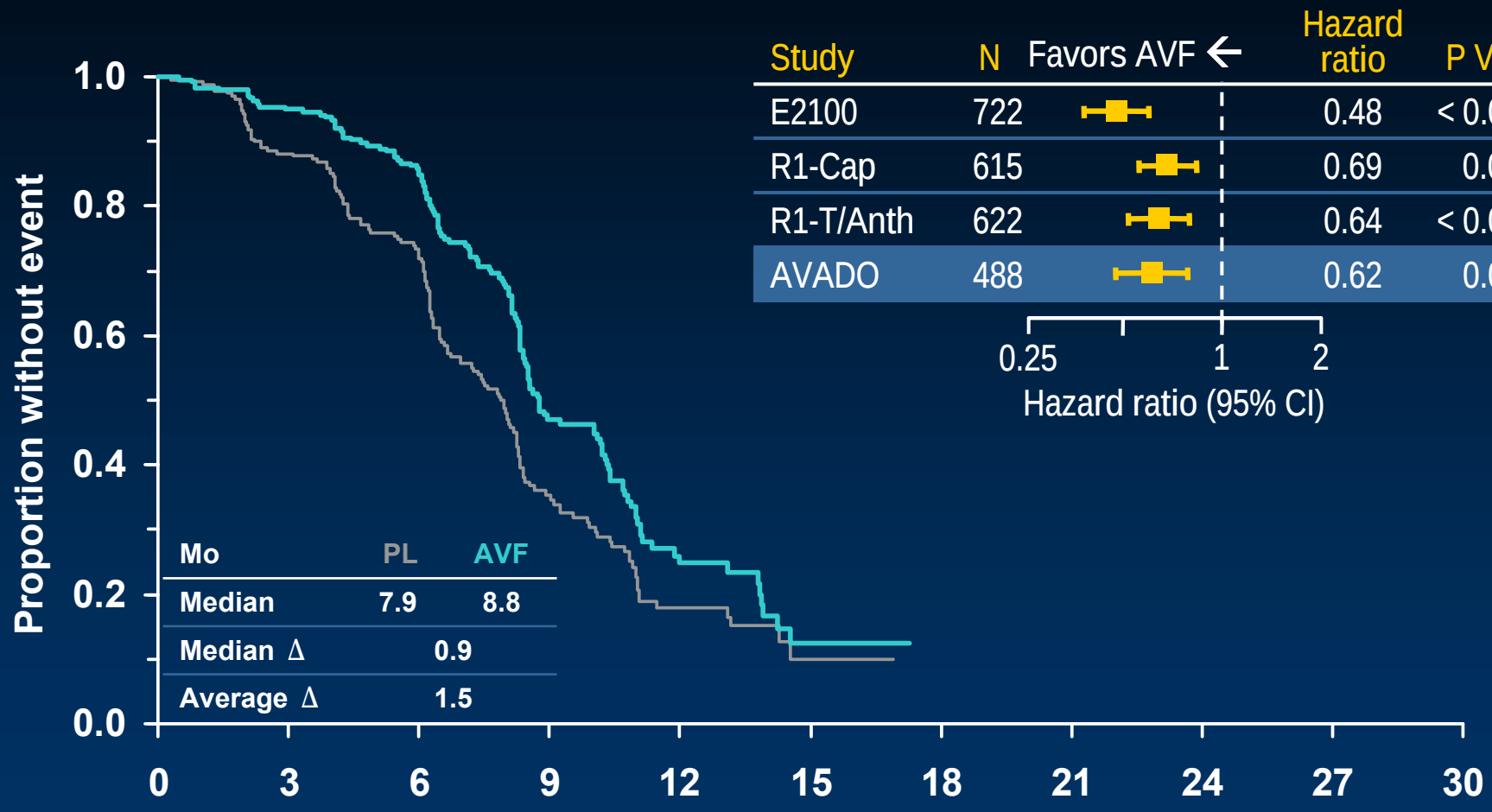
AVADO Study Design



Docetaxel 100 mg/m^2 q3wk, max 9 cycles
Avastin 15 or 7.5 mg/kg q3wk

LR = Locally recurrent; mBC = Metastatic breast cancer; PD = Progressive disease.

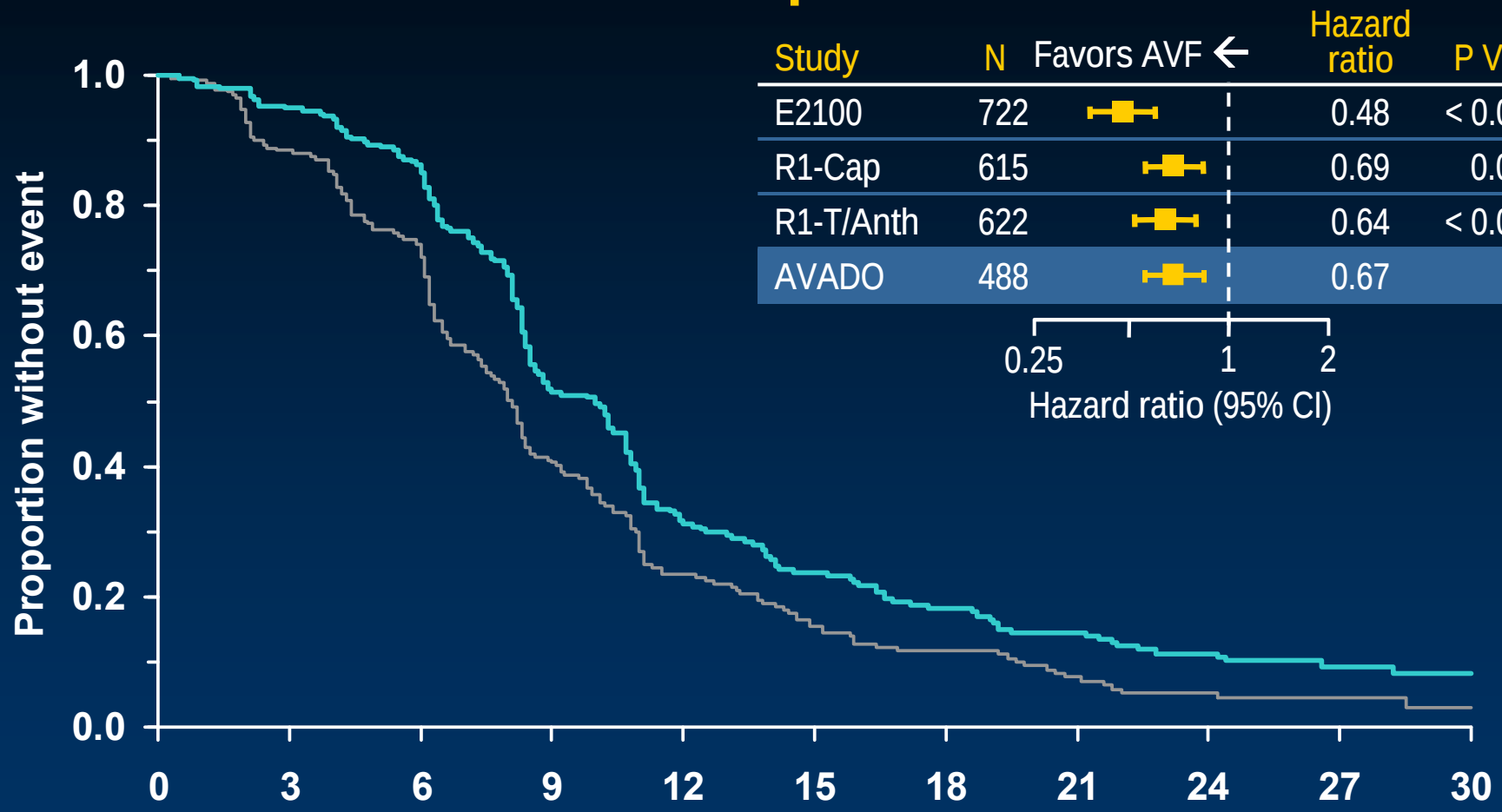
Progression-Free Survival
AVADO



At risk, n											
— Doc+AVF	247	223	186	68	22	4	0	0	0	0	0
— Doc+PL	241	198	151	50	15	4	0	0	0	0	0

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; Doc = Docetaxel; Mo = months; PL = Placebo.

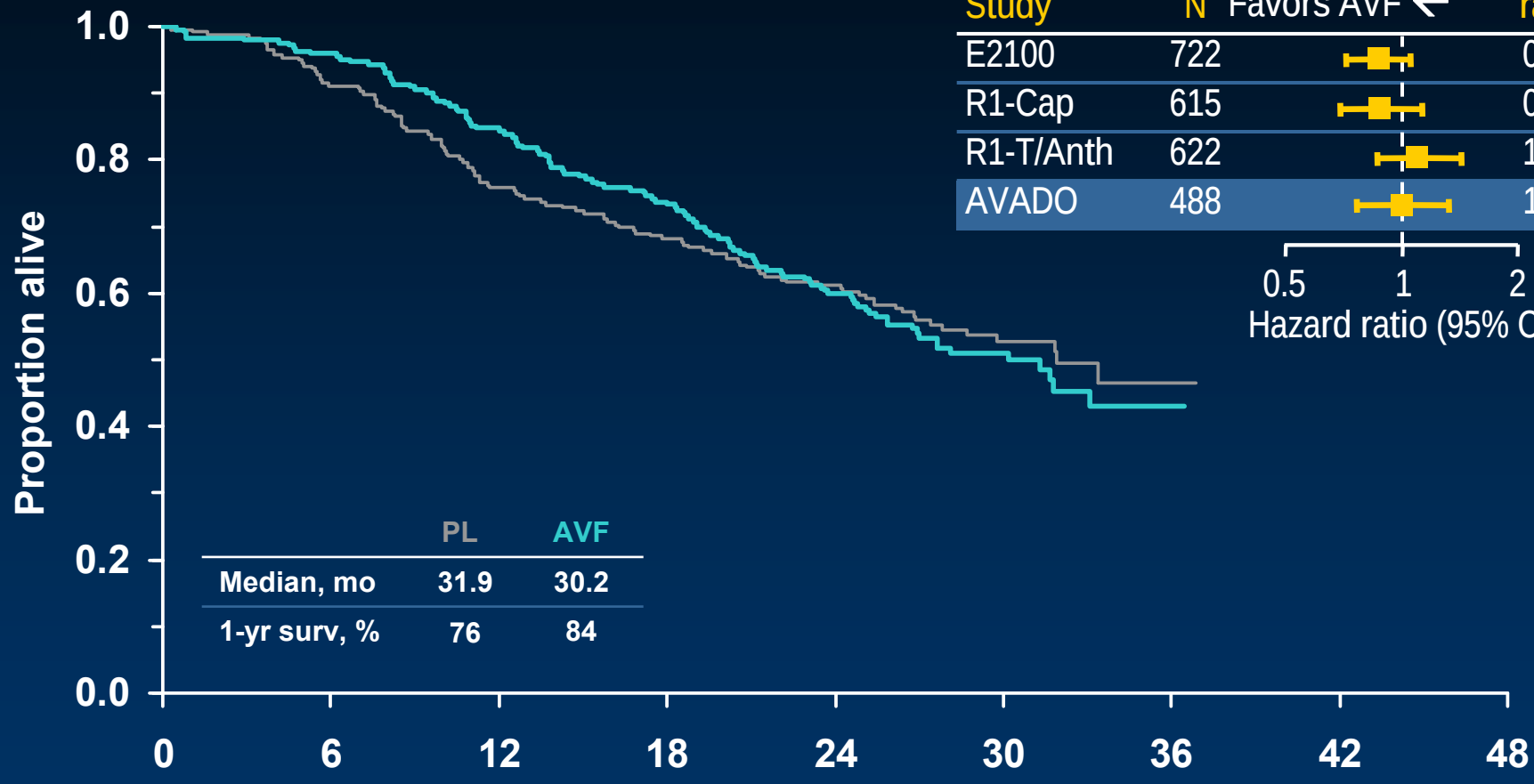
Progression-Free Survival
AVADO Updated



At risk, n											
— Doc+AVF	247	223	195	113	69	48	35	28	20	11	4
— Doc+PL	241	203	161	86	47	30	21	13	7	4	2

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; Doc = Docetaxel; Mo = months; PL = Placebo.

Overall Survival
AVADO



	PL	AVF
Median, mo	31.9	30.2
1-yr surv, %	76	84

Study	N	Favors AVF ←	Hazard ratio
E2100	722		0.87
R1-Cap	615		0.88
R1-T/Anth	622		1.11
AVADO	488		1.00

0.5 1 2
Hazard ratio (95% CI)

At risk, n								
— Doc+AVF	247	234	200	172	134	48	2	0	0
— Doc+PL	241	215	178	160	135	50	2	0	0

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; Doc = Docetaxel; PL = Placebo; mo = months

AVADO: Gr ≥ 3 Select Adverse Events

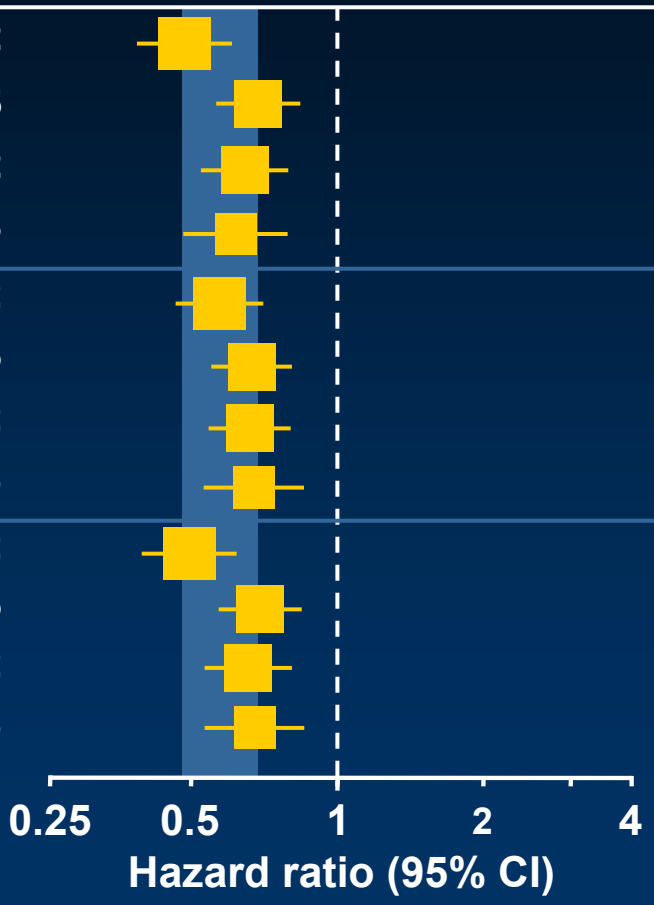
	Doc+PL n = 231, %	Doc+AVF n = 247, %
Common AVF-assoc. AEs		
Hypertension	1.3	4.5
Proteinuria	0	2.0
Other AVF-assoc. AEs		
ATE	0.4	0.8
VTE	3.5	1.2
Bleeding	0.9	1.2
Fistula	0.4	0.8
GI perforation	0.9	0.4
Wound dehiscence	0.9	0.4
Chemotherapy-assoc. AEs		
Neutropenia	19.5	21.1
Febrile neutropenia	11.7	16.6
Sensory neuropathy	4.3	7.7
LV systolic dysfunction	0	0

Summary of Efficacy

- Sensitivity analyses
- Clinical subgroups
- Objective response rate

PFS Robust in Sensitivity Analyses

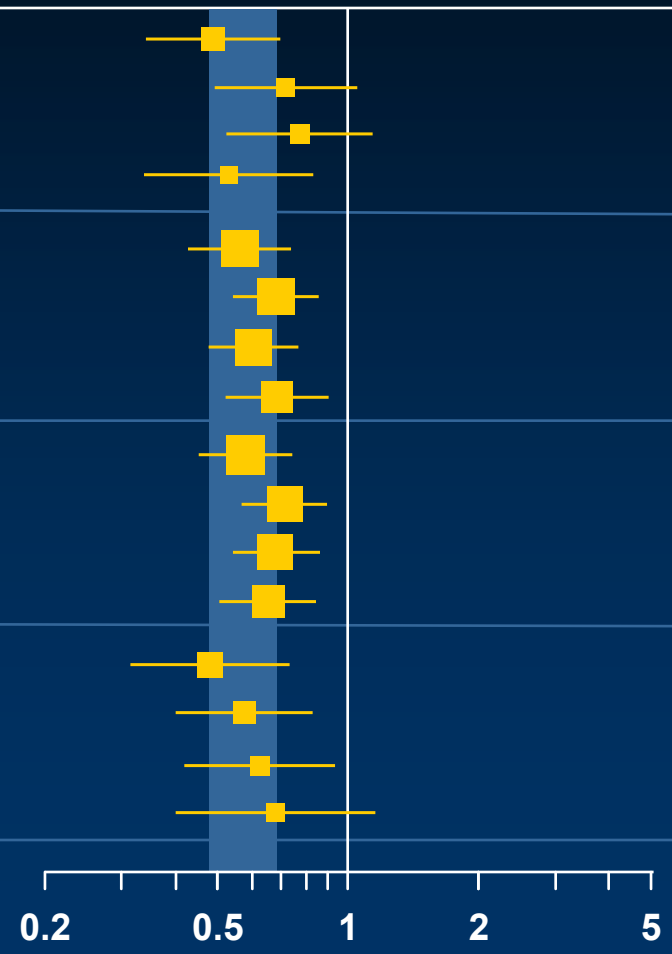
Analysis	Study	N	Hazard ratio
Primary	E2100	722	0.48
	R1-Cap	615	0.69
	R1-T/Anth	622	0.64
	AVADO	488	0.62
Without censoring NPT	E2100	722	0.57
	R1-Cap	615	0.66
	R1-T/Anth	622	0.66
	AVADO	488	0.67
Missing tumor assessment	E2100	722	0.49
	R1-Cap	615	0.69
	R1-T/Anth	622	0.65
	AVADO	488	0.67



AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; NPT = Non-protocol therapy; T/Anth = Taxane/Anthracycline.

PFS Consistent in Subpopulations

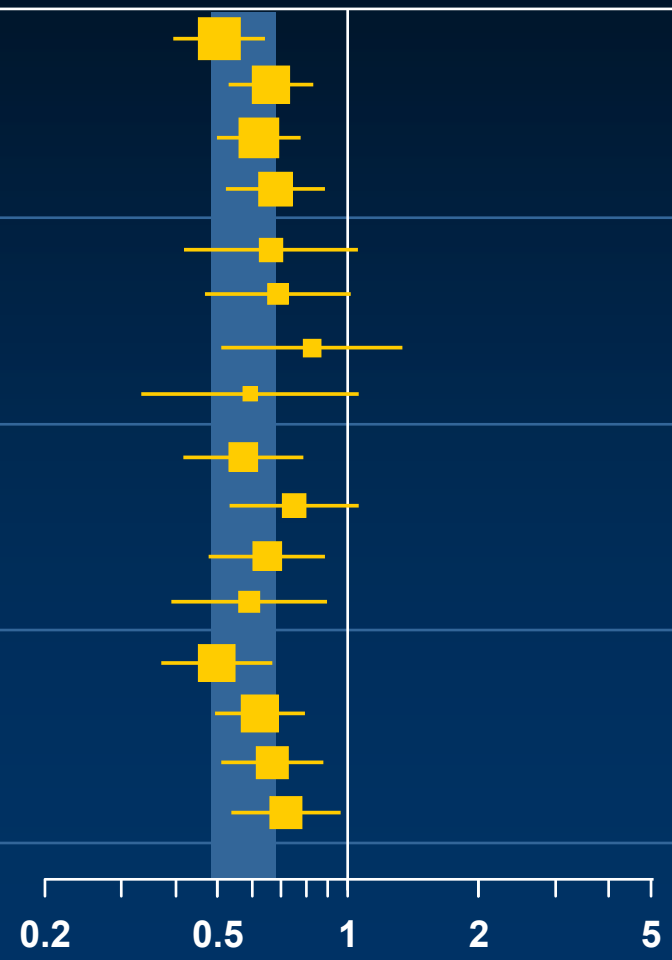
Risk factor	Study	N	Hazard ratio[1]
Triple Neg Yes	E2100	232	0.49
	R1-Cap	137	0.72
	R1-T/Anth	142	0.78
	AVADO	110	0.53
No	E2100	464	0.56
	R1-Cap	462	0.68
	R1-T/Anth	459	0.61
	AVADO	377	0.69
Visceral Involved	E2100	480	0.58
	R1-Cap	423	0.72
	R1-T/Anth	438	0.68
	AVADO	366	0.65
Non-involved	E2100	242	0.48
	R1-Cap	192	0.58
	R1-T/Anth	184	0.63
	AVADO	122	0.68



Cap = Capecitabine; T/Anth = Taxane/Anthracycline.
1. Based on unstratified analysis

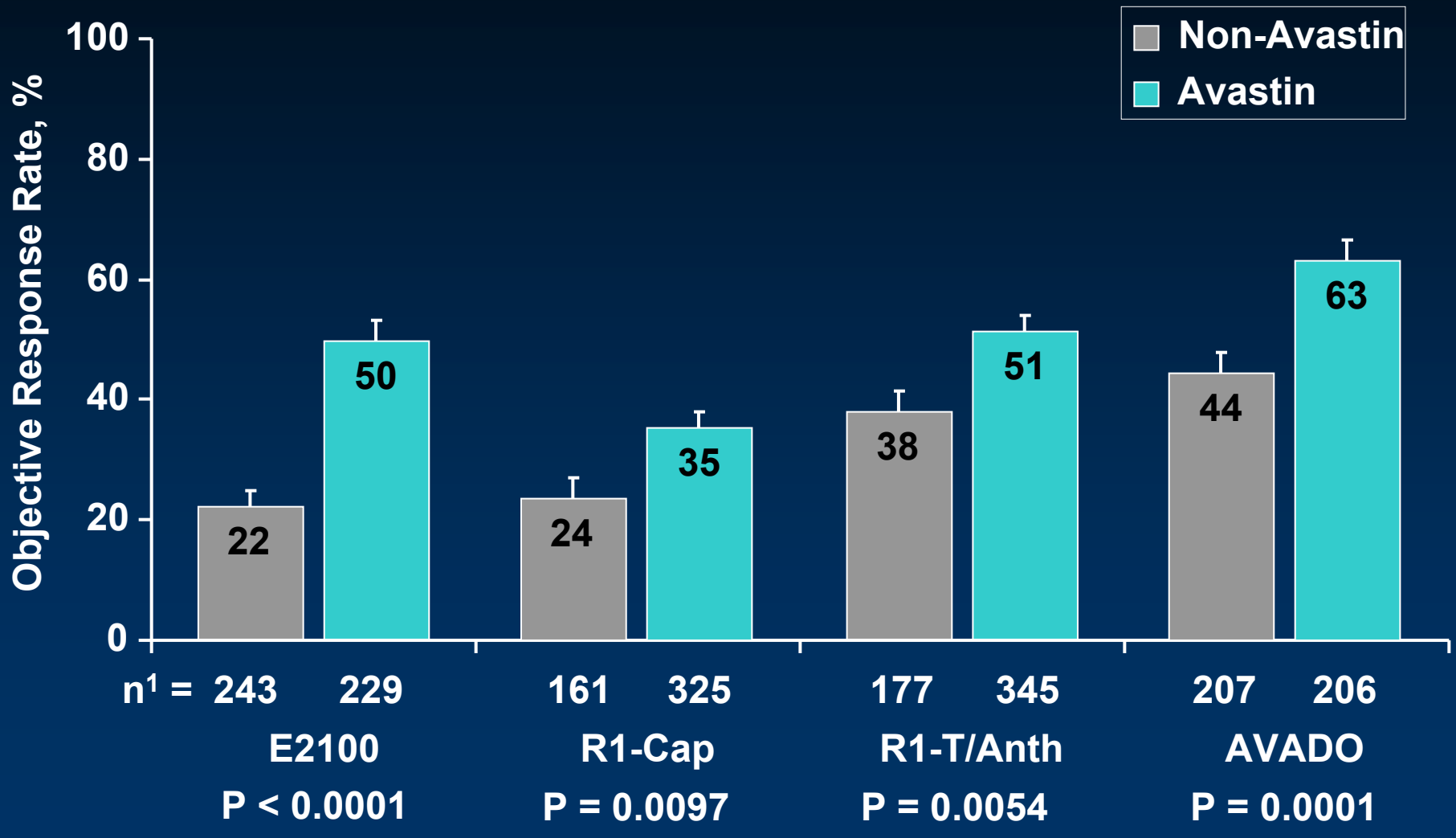
PFS Consistent in Subpopulations

Risk factor	Study	N	Hazard ratio[1]
Age, yr <65	E2100	555	0.51
	R1-Cap	462	0.67
	R1-T/Anth	498	0.63
	AVADO	402	0.68
≥65	E2100	167	0.67
	R1-Cap	153	0.69
	R1-T/Anth	124	0.83
	AVADO	86	0.60
DFI, mo ≤24	E2100	296	0.58
	R1-Cap	205	0.76
	R1-T/Anth	262	0.65
	AVADO	161	0.60
>24	E2100	426	0.50
	R1-Cap	408	0.63
	R1-T/Anth	358	0.67
	AVADO	327	0.72



Cap = Capecitabine; T/Anth = Taxane/Anthracycline.
1. Based on unstratified analysis

Objective Response Rate



Cap = Capecitabine; T/Anth = Taxane/Anthracycline.

1. Patients with measurable disease at baseline only. Error bar represents the standard error.

Summary of Safety

- Grade 3-5 AEs
- Dose intensity
- Treatment related mortality
- Pooled survival

Grade ≥ 3 Select AEs
Pooled (E2100, R1, AVADO)

	Chemo ± PL n = 982, %	Chemo + AVF n = 1427, %	Difference
Cumulative	**23.1**	**36.4**	**13.3**
Common AVF-assoc. AEs	**1.2**	**12.5**	**11.3**
Hypertension	1.2	10.4	
Proteinuria	0	2.6	
Other AVF-assoc. AEs	**5.3**	**8.2**	**2.9**
ATE	0.3	1.9	
VTE	3.8	3.0	
Bleeding	0.4	1.6	
Fistula	0.3	0.4	
GI perforation	0.3	0.5	
Wound dehiscence	0.3	0.8	
Chemotherapy-assoc. AEs	**18.2**	**21.9**	**3.7**
Neutropenia	7.1	8.0	
Febrile neutropenia	3.5	5.0	
Sensory neuropathy	8.5	9.7	
LV systolic dysfunction	0.2	1.5	

Duration and Dose Intensity of Chemotherapy Exposure

	Median dose intensity, %		Difference in Median chemo exposure, mo
	Non-AVF	AVF	
E2100	95	86	2.2
R1-Cap	96	88	2.0
R1-Anth	100	99	0.4
R1-Tax	99	98	–0.3
AVADO	95	89	0.6

Overall dose intensity is calculated as the actual dose received divided by the intended dose x 100%.

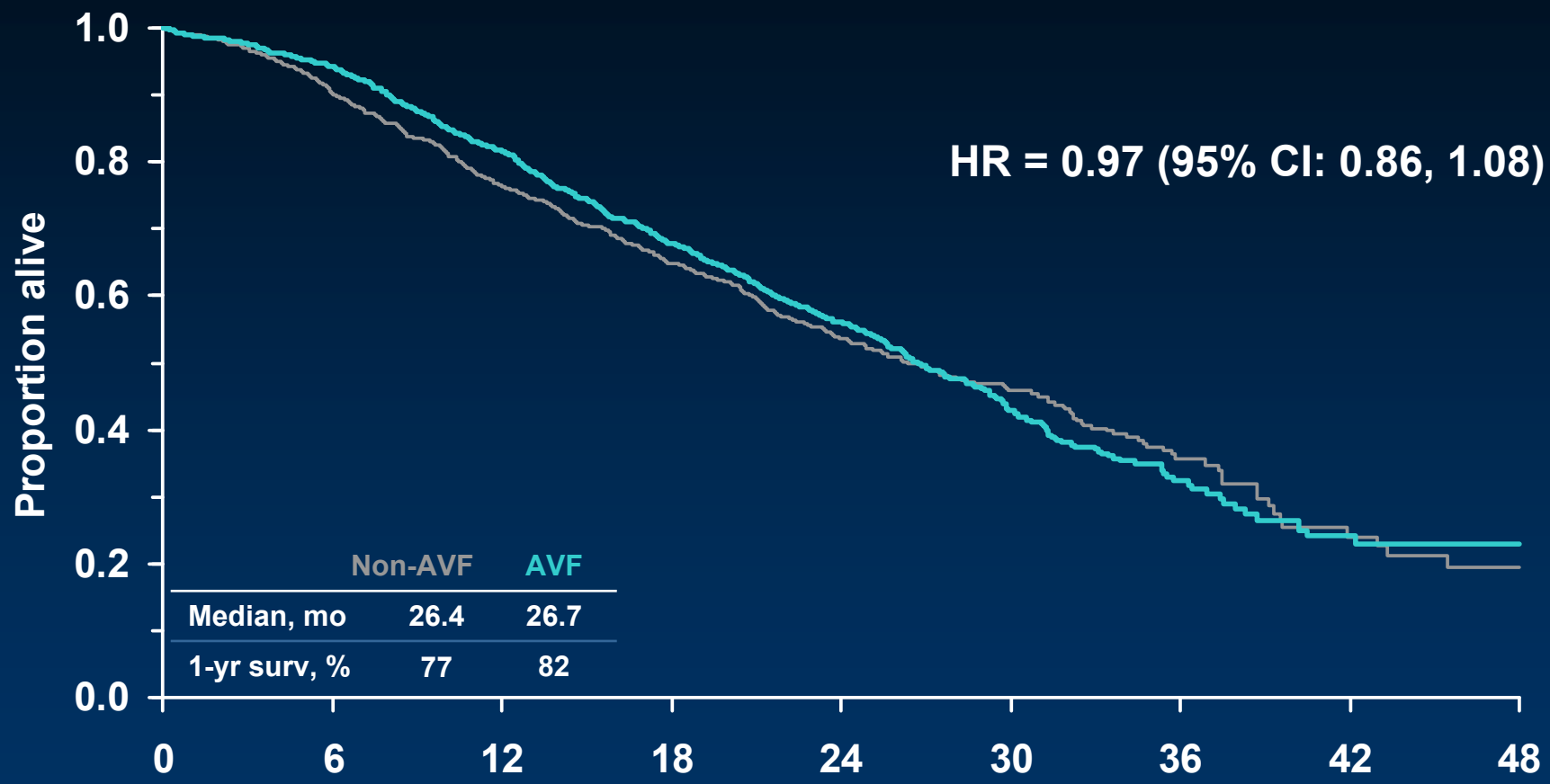
Study Mortality
Pooled (E2100, R1, AVADO)

Cause of mortality, %	Non-AVF n = 982	AVF n = 1427
Deaths	55.8	52.0
mBC	51.5	48.1
Adverse event or protocol therapy	1.8	1.8
Other	1.4	1.8
Missing/unknown	1.0	0.3

Treatment-related Mortality by Study

	Non-AVF, %	AVF, %
E2100 (paclitaxel)	0.3	1.7
R1-Capecitabine	2.5	1.5
R1-Anthracyclines	3.0	1.0
R1-Taxanes	2.9	2.5
AVADO (docetaxel)	2.6	2.8

Overall Survival
Pooled



At risk, n									
— AVF	1439	1333	1127	916	591	204	55	23	5
— Non-AVF	1008	892	746	621	426	178	51	19	8

AVF = Avastin; mo = months

Efficacy and Safety Conclusions

- 3 RCTs, 4 efficacy comparisons, show treatment effect
  - Improved PFS (31% - 52% risk reduction)
  - Increased ORR (11% - 28% more responses)
  - Reliable and robust measures of PFS
  - Consistent treatment effect in key clinical subpopulations
- Safety of chemotherapy + Avastin well characterized
  - Increase in AEs primarily due to hypertension and proteinuria
  - Other AEs low incidence, consistent with experience
- No impairment in overall survival
  - No increase in treatment-related mortality
  - HR < 1 for pooled OS

Measures and Magnitude of Avastin PFS Benefit

James Reimann, PhD

Director, Biostatistics

Genentech

Statistical Design

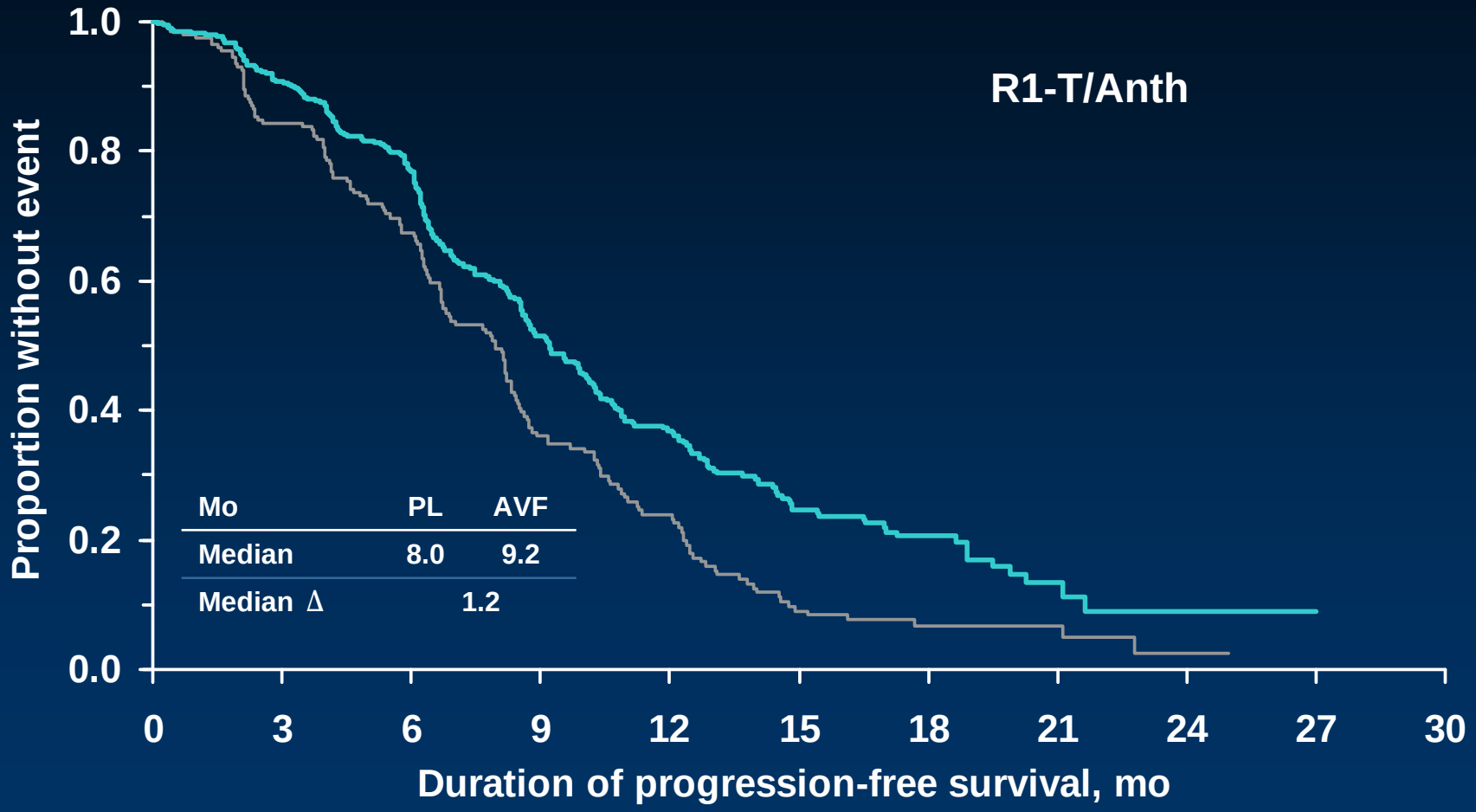
	E2100	R1-Cap	R1-T/Anth	AVADO[1]
Sample size	685	600	600	705
PFS events	546	415	405	435
Power (%)	85	80	90	80
Effect in HR				
Targeted	0.75	0.75	0.70	0.70
Observed	0.48	0.69	0.64	0.62
P value	< 0.0001	0.0002	< 0.0001	0.0003

Cap = Capecitabine; HR = Hazard ratio; PFS = Progression-free survival; T/Anth = Taxane/anthracycline.
1. Sample size and PFS events include information from all 3 treatment arms. Effected size and p-value refer to the comparison between placebo and the standard dose.

Hazard Ratio

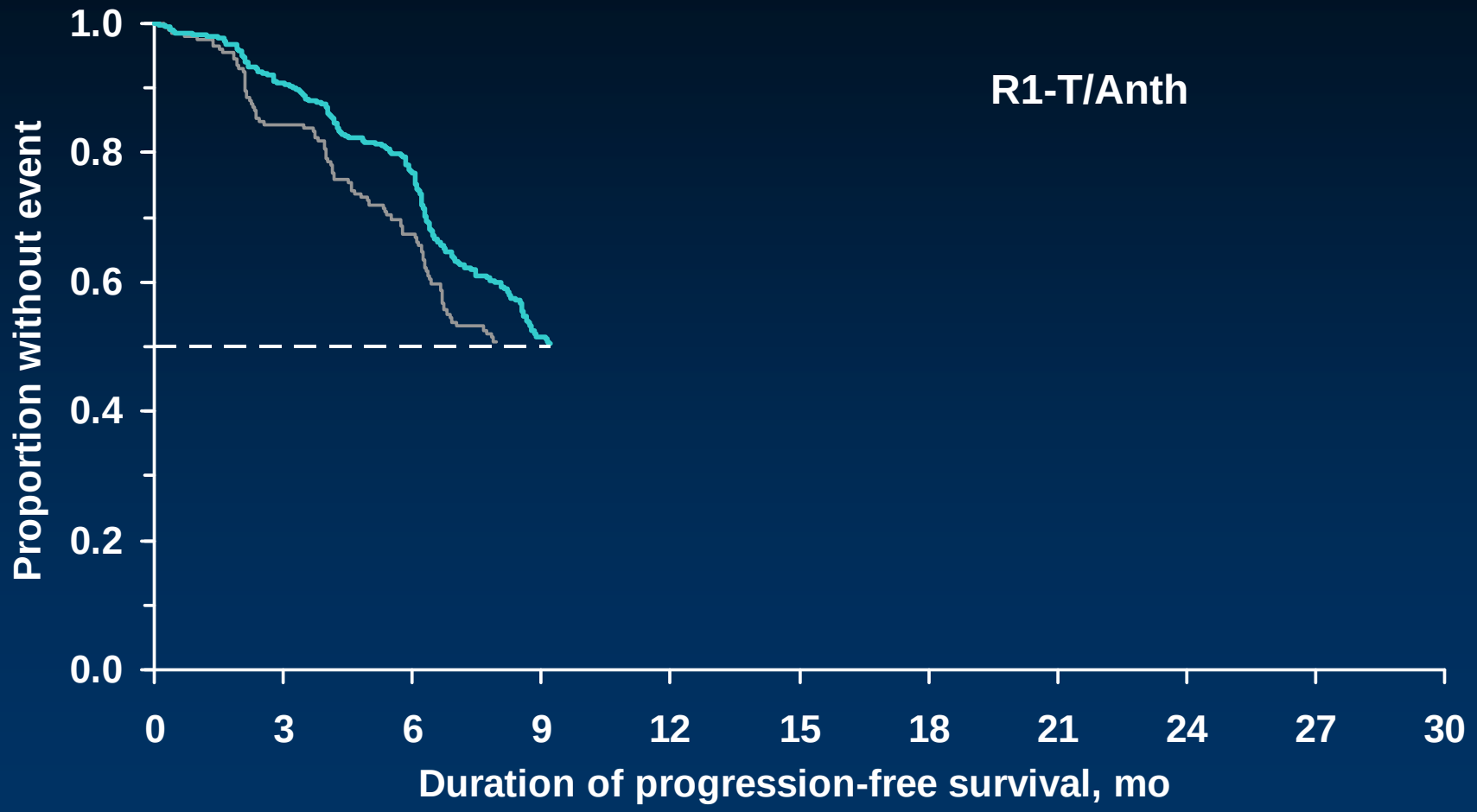
- Conventional way to describe PFS improvement
  - Risk of progression in one arm relative to the other, averaged over time
- Advantages
  - Uses all data
  - Related to log-rank test
- Limitation
  - No direct translation to time

Median PFS
May Misrepresent Benefit



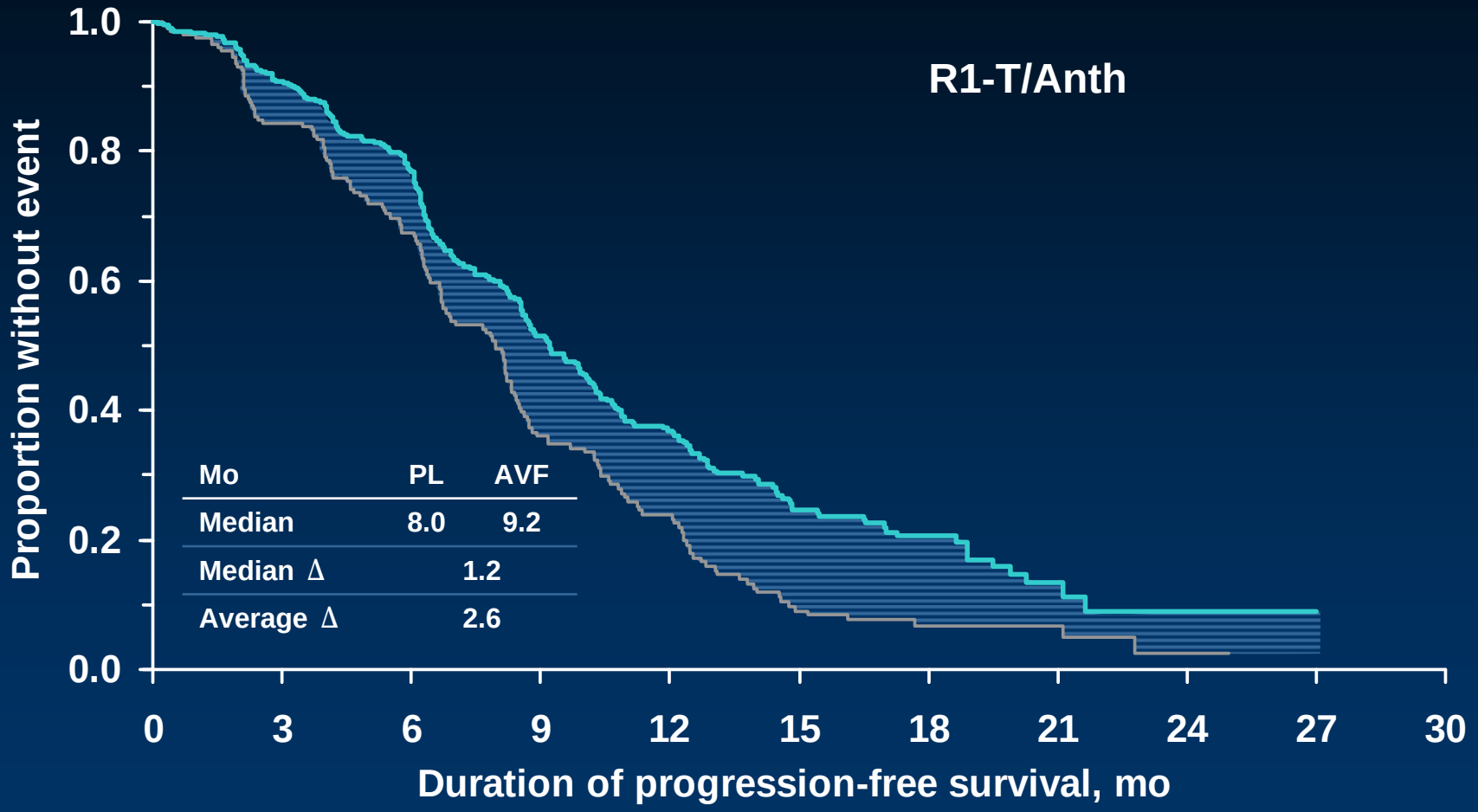
AVF =Avastin; mo = Month; PFS = Progression-free survival; T/Anth = Taxane/anthracycline.

Median PFS
Does Not Use All Data



mo = Month; PFS = progression-free survival; T/Anth = Taxane/anthracycline.

Average PFS
Average Time Between Curves

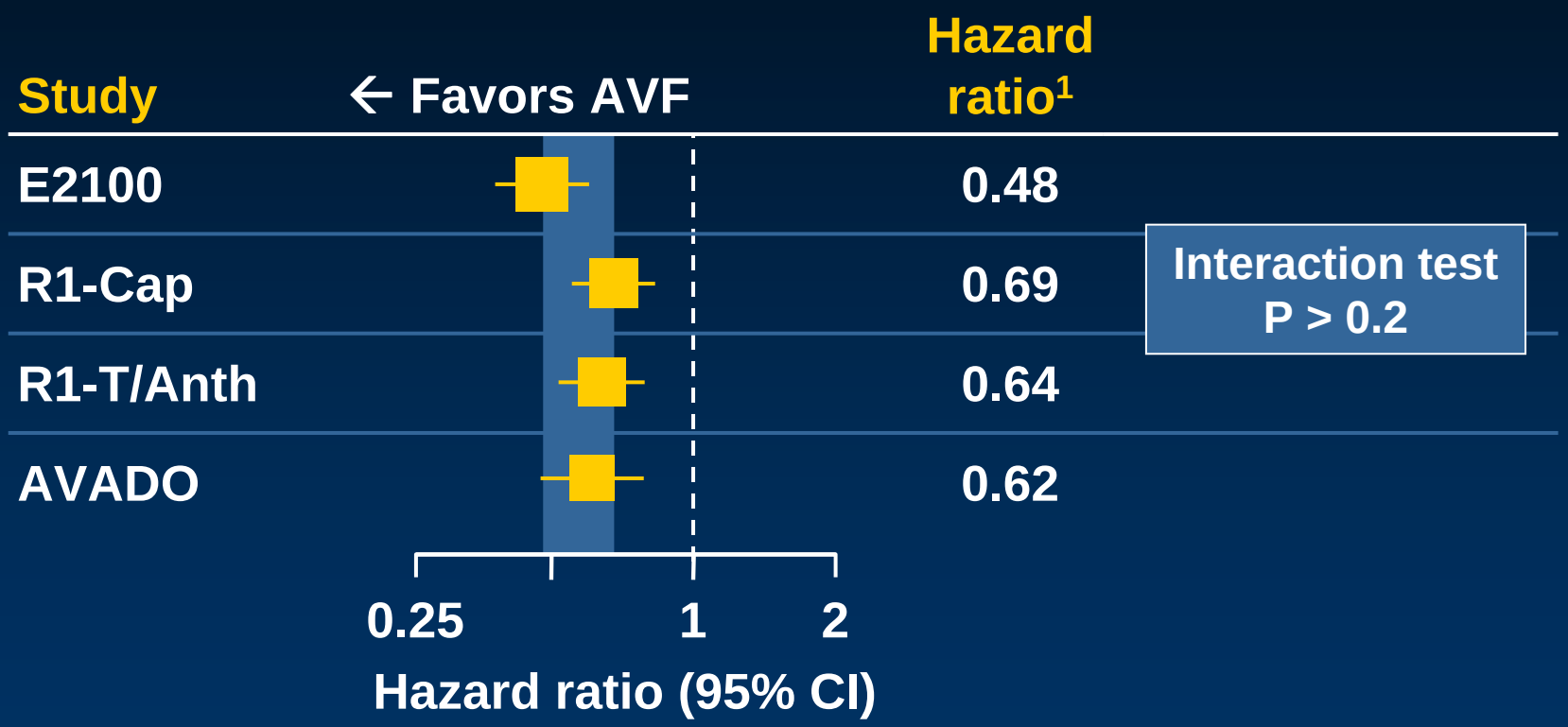


AVF = Avastin; mo = Month; PFS = Progression-free survival; T/Anth = Taxane/anthracycline.

Comparison of PFS Measures

Criteria	Hazard ratio	Δ Median	Δ Average
Clinical research standard	✓		
All data used	✓		✓
Commonly reported	✓	✓	
Uses time scale		✓	✓
Intuitive			✓

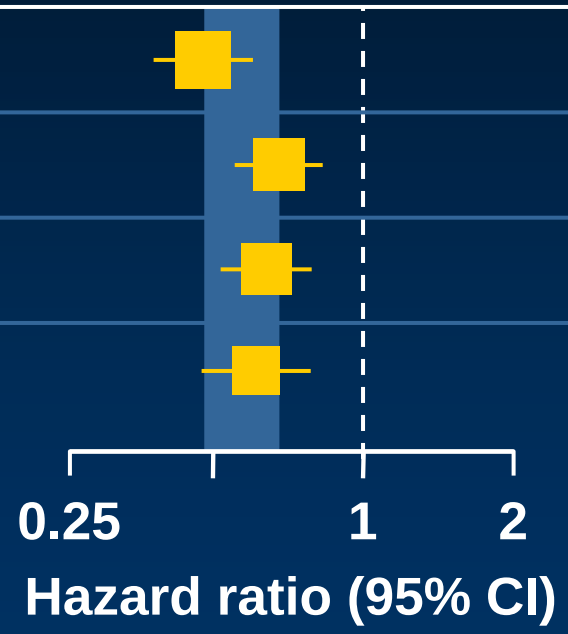
Magnitude of Benefit for All Studies



AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; T/Anth = Taxane/anthracycline.
1. Hazard ratio based on stratified analysis.

Magnitude of Benefit for All Studies

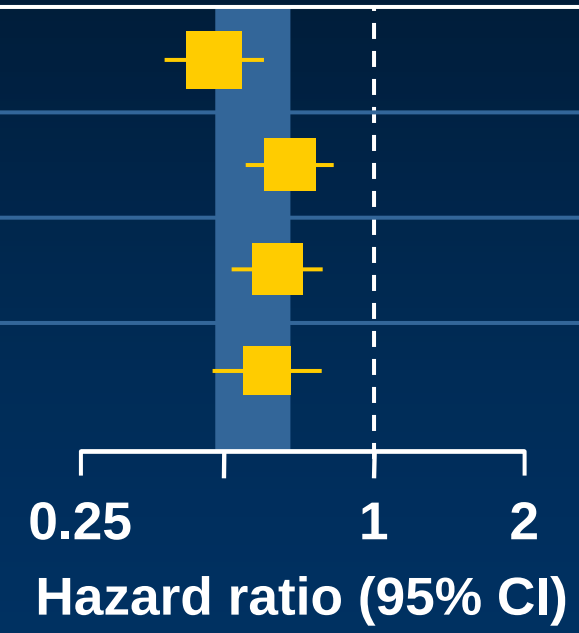
Study	Hazard ratio[1]	Improvement, mo	
		Median	Average
E2100	0.48	5.5	4.1
R1-Cap	0.69	2.9	2.5
R1-T/Anth	0.64	1.2	2.6
AVADO	0.62	0.9	1.5



AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; T/Anth = Taxane/anthracycline.
1. Hazard ratio based on stratified analysis.

Magnitude of Benefit for All Studies

Study	Hazard ratio[1]	Improvement, mo	
		Median	Average
E2100	0.48	5.5	4.1
R1-Cap	0.69	2.9	2.5
R1-T/Anth	0.64	1.2	2.6
AVADO	0.62	0.9	1.5
	0.67	*1.9*	*2.5*



AVADO 24-mo update

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; T/Anth = Taxane/anthracycline.
1. Hazard ratio based on stratified analysis.

Metastatic Breast Cancer State of the Art

Gabriel N. Hortobagyi, MD FACP

Professor of Medicine

Nellie B. Connally Chair in Breast Cancer

Director, Breast Cancer Research Program

The University of Texas

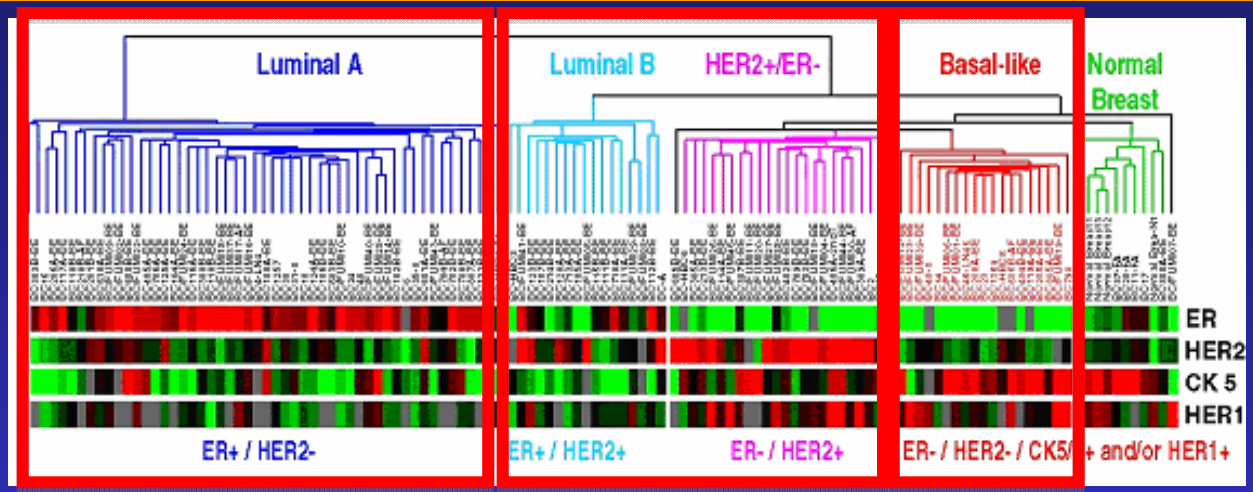
M D Anderson Cancer Center

Washington, July 20, 2010

Goals of Therapy in MBC

- **Maintain or improve quality of life**
- **Maintain disease control**
- **Minimize, prevent, or delay symptoms of disease**
- **Minimize toxicity from treatment**
- **Prolong overall survival**

Outcome of Modern Treatment by Disease Subtypes



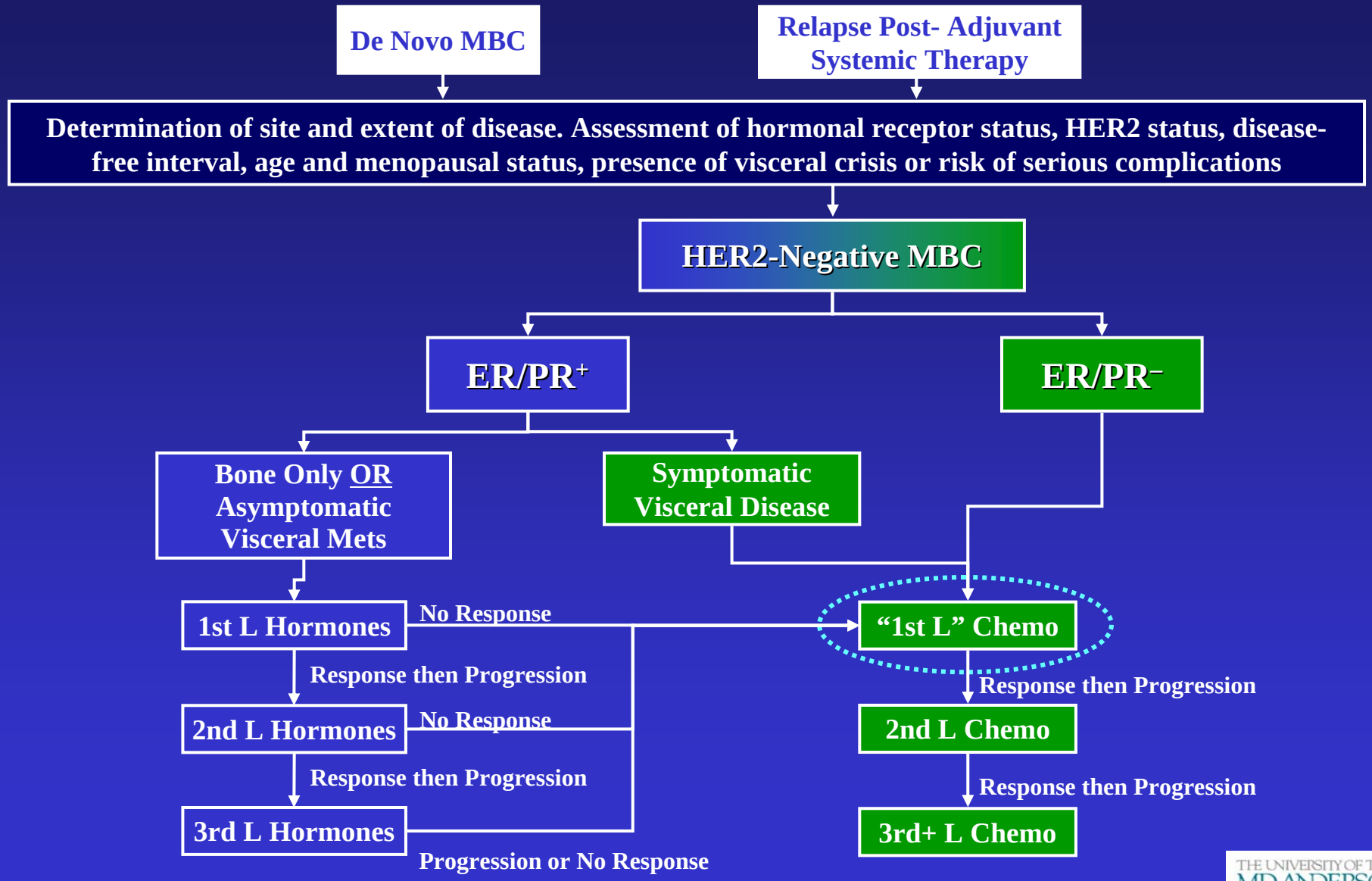
HER2^{+} tumors: intermediate survival

- Median survival ranges from 2 to 3 years

HER2^{-} tumors:

- Patients with ER/PR^{+} tumors tend to live longest
  - Median survival ranges from 3 to 5 years.
- Triple-negative tumors confer a short survival
  - Median survival ranges from 1 to 1 ½ years.

NCCN HER2-Negative MBC Treatment Algorithm



Source: NCCN guidelines.

Conceptual Changes in Managing Metastatic Breast Cancer

- Major emphasis on disease control and clinical benefit
- Increased use of sequential single-agent therapy or rational combinations
- Continuous vs intermittent therapy
- Careful attention to benefit:risk ratio
- Need for multiple treatment options

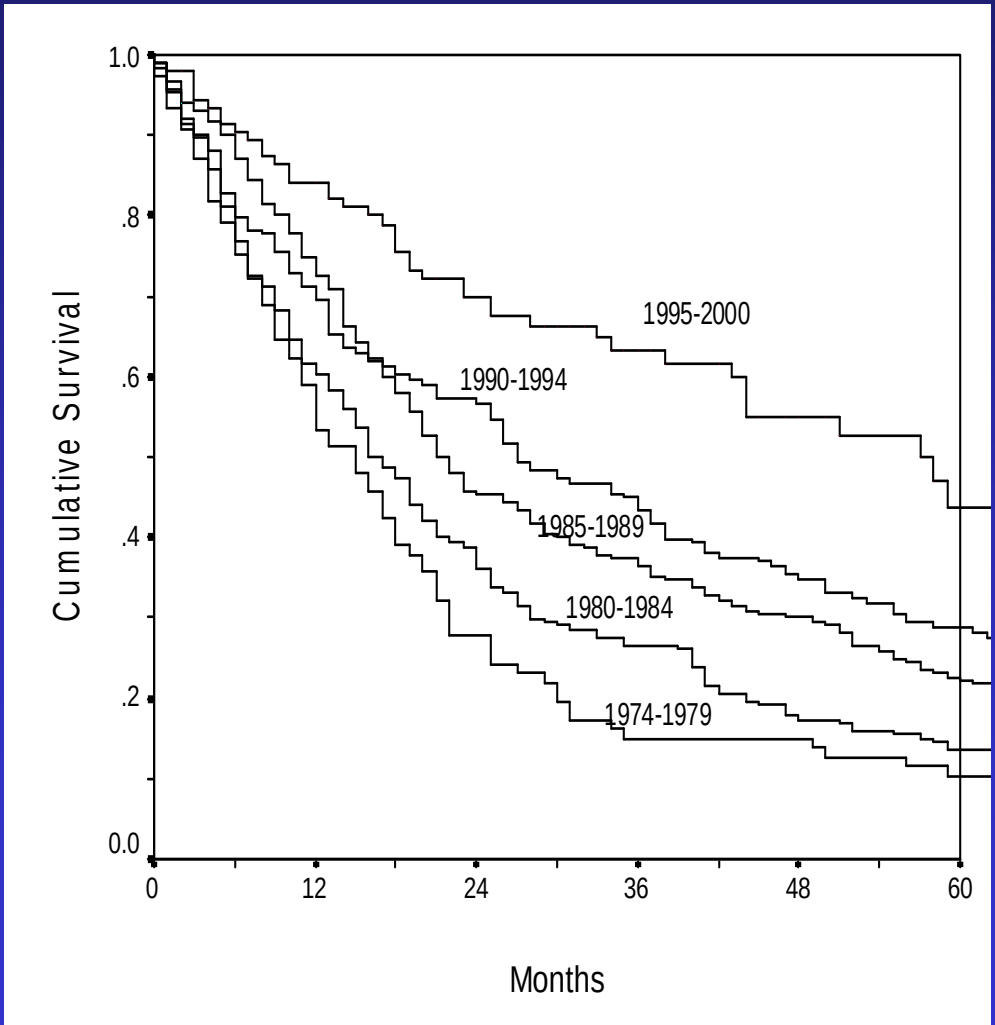
Overall Survival as a Treatment Endpoint in Metastatic Breast Cancer

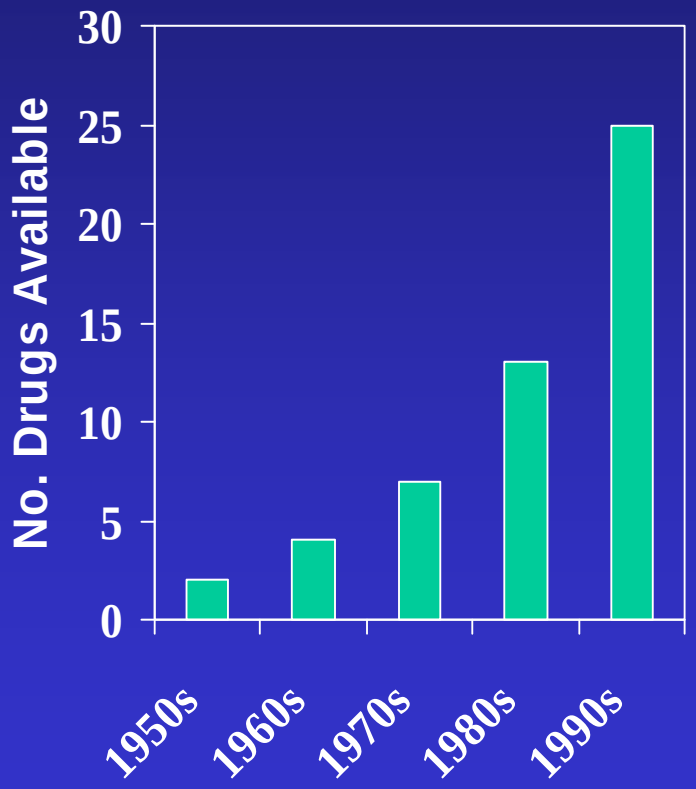
- Overall Survival (OS) is a hard and reliable endpoint

However,

- Prolongation of OS not expected despite better PFS because of
  - Long median OS for 1st-line MBC patients
  - Multiple subsequent treatment regimens
  - Cross-over designs attenuate/obscure effect of 1st-line treatment
- OS is most likely to be affected by treatment regimens closest to the end of life

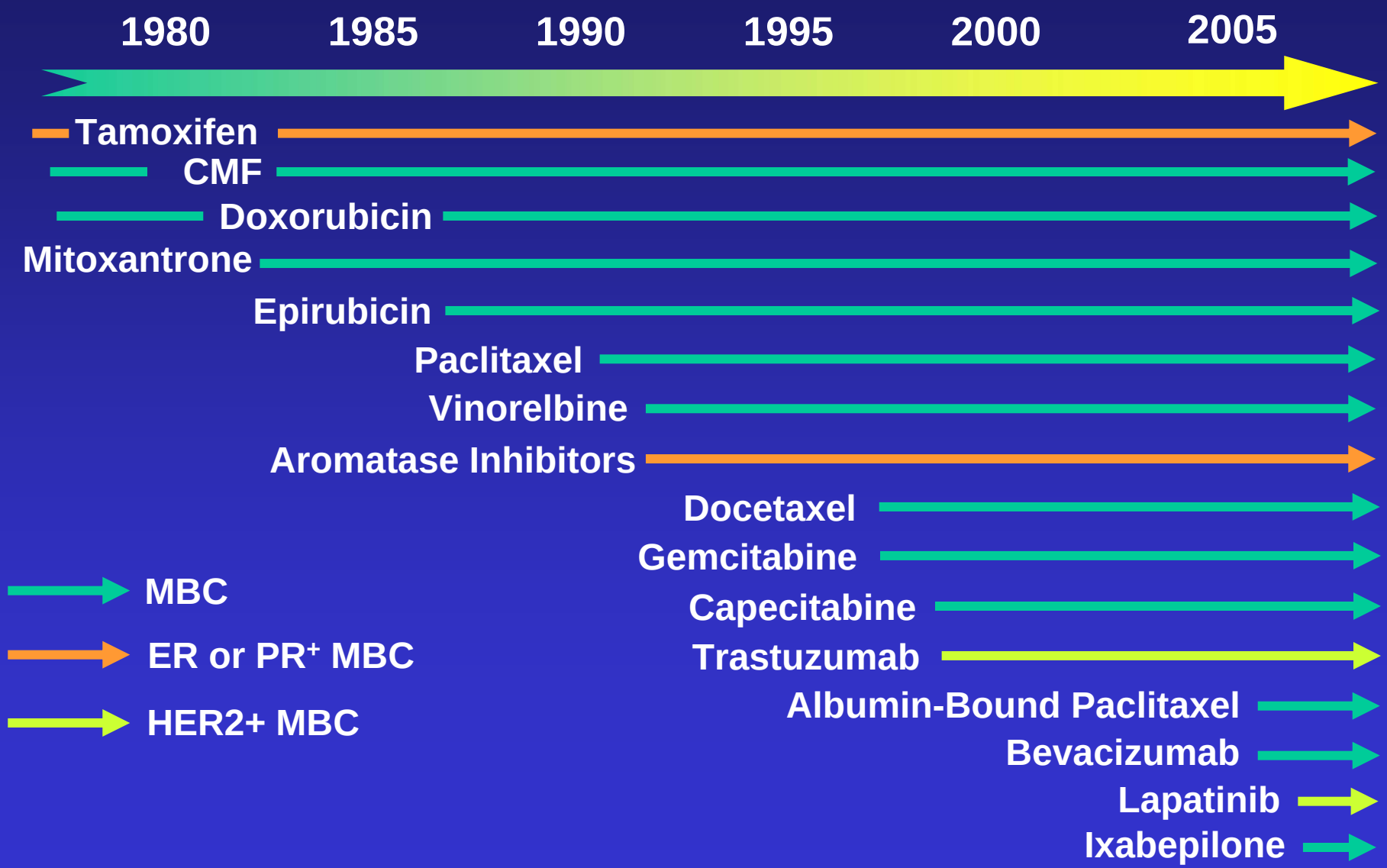
Survival of Patients With Metastatic Breast Cancer 1974 - 2000





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

Progress in Systemic Treatment of MBC



Is Prolonging Progression-Free Survival Meaningful for Patients?

- Improvements in progression-free survival
  - Delay the onset of disease-related symptoms and the side effects from a new therapy
  - Avoid the psychological consequences (anxiety, fear) and inconvenience associated with disease progression and changing therapy
  - Eliminate the uncertainty as to whether new treatment will be effective

Yes, prolonging progression-free survival can be highly meaningful!

What Is a Meaningful Prolongation of PFS?

- Prolongation of disease control without symptoms
- Prolongation of disease control without toxicity that impairs quality of life
- Defined by benefit relative to individual patient circumstances

Clinical Value of Treatment Options

- Different treatments might offer different therapeutic benefits
- Various treatments
  - have different safety patterns or toxicity profiles
  - offer different levels of convenience of administration
  - might be associated with different levels of compliance
- The psychological benefit of having choices should not be underestimated

Patient Study 1

- 45-yr–old pre-menopausal African-American woman
  - Presents c/o 1 month history of abdominal pain and loss of appetite
  - PE reveals palpable 3-cm R breast lump and liver edge
  - Mammogram shows 2.5-cm spiculated mass in R breast
  - CT reveals multiple liver metastases in L and R lobes
  - Biopsy reveals triple-negative breast cancer

- Treatment choice
- No prior treatment
- Poor prognosis
- Requires high response rate
- Treatment with Avastin + taxane

Patient Study 2

- 58-yr–old post-menopausal Caucasian woman
  - Stage IIB ER^+/PR^+, HER2- IDC in L breast
  - Initial AC - T adjuvant chemotherapy
  - After 4 yr of anastrozole, has 2 mo of dry cough
  - CXR and CT show multiple nodules in L lung; bone scan + T and L spine
  - Biopsy confirms recurrence

- Treatment choice
- First and foremost, endocrine therapy (exemestane or fulvestrant);
- When endocrine refractory:
- "1st line" will really be 2nd+ line
- Capecitabine appropriate given prior anthracycline, taxane
- Discuss benefits and risks of bevacizumab

RCTs Since 2000 Referenced by NCCN Guidelines for Non-HER2$^+$ MBC

	Treatment	TTP/PFS HR	Median Δ, mo	OS
Ackland*	CEF vs CMF	0.73	2.4	NS
Langley*	EP vs EC	1.07 (NS)	0.1	NS
Nabholz*	AT vs AC	0.76	1.3	NS
Albain*	T vs GT	0.70	2.2	NS
Gradishar*	Abraxane vs P	0.75[2]	1.4	NS
Gradishar*	Abraxane vs D	0.50/0.57[2]	5.4/6.8	—
O'Shaughnessy	D vs XD	0.65	1.9	0.78
O'Brien	Doxil vs A	1.00[1]	-0.9	NS

*1st Line MBC trial.
[1]Non-inferiority study.
[2]Primary endpoint = ORR, non-inferiority study.
[3]IRC/Investigator determined.

In This Context, What Do the Bevacizumab Data Mean?

- The combination of bevacizumab and chemotherapy results in
  - Substantial improvement in progression-free survival (HR: 0.48-0.69)
  - Significant improvement in response rate (P=0.0097 - <0.0001)
  - Modest additional toxicity for the majority of patients
- These results are consistent across three large multicenter randomized trials using commonly employed drugs (taxanes, anthracyclines and capecitabine)
- Analysis by subgroups shows benefit in all key prognostic categories, including the most unfavorable groups

In This Context, What do the Bevacizumab Data Mean?

- Well-characterized safety profile
  - Tolerable in combination with key chemotherapies
  - Severe adverse events are infrequent
  - Hypertension and proteinuria are manageable adverse events
  - Awareness of potential adverse events and proactive management results in well-tolerated treatment with bevacizumab
- **Bevacizumab provides an important treatment option for patients with metastatic breast cancer**

Thank You!

Concluding Remarks

Sandra Horning, MD

Senior Vice President,
Clinical Hematology/Oncology
Genentech

Avastin Regulatory History
Conversion to Full Approval

Approval Letter 2/22/08

Submit efficacy supplement to further define the degree of clinical benefit with data from

- RIBBON1 (AVF3694g)
- AVADO (BO17708)

Type B Meeting 2/26/09; FDA Minutes

FDA confirmed that the basis for conversion to full approval will be demonstrated improvement in progression-free survival and evidence that survival is not impaired.

R1-Capecitabine Summary

Clinical use	Important option for patients who have received adjuvant chemotherapy or to avoid toxicity of taxanes / anthracyclines; oral
PFS improvement	HR 0.69, median Δ 2.9 mo, average Δ 2.5 mo
Response rate	Δ 12%
Safety*	Increase HTN, proteinuria Neuropathy
Overall survival	HR 0.88
Treatment-related mortality	No increase

*Selected Gr 3-5 ≥2%

R1-T/Anth Summary

Clinical use	**Taxanes standard option; anthracyclinces used if no adjuvant tx**
PFS improvement	**HR 0.64, median Δ 1.2 mo, average Δ 2.6 mo**
Response rate	**Δ 13%**
Safety*	**Increase HTN, proteinuria** **T: Incr bleeding, neutropenia, febr neutropenia** **Anth: Incr LVSD**
Overall survival	**HR 1.11 (T: 1.24; Anth: 0.97)**
Treatment-related mortality	**No increase in taxanes** **No increase in anthracyclines**

*Selected Gr 3-5 ≥ 2%

AVADO Summary

Clinical use	**Docetaxel highly active and neutropenia, neuropathy observed**
PFS improvement	**HR 0.62, median Δ 0.9 mo, average Δ 1.5 mo** **(Updated: HR 0.67, median Δ 1.9 mo, average Δ 2.5 mo)**
Response rate	**Δ 19%**
Safety*	**Increase HTN, proteinuria;** **Increase febr neutropenia, neuropathy**** ***No increase infection***
Overall survival	**HR 1.00 (Updated 0.97)**
Treatment-related mortality	**No increase**

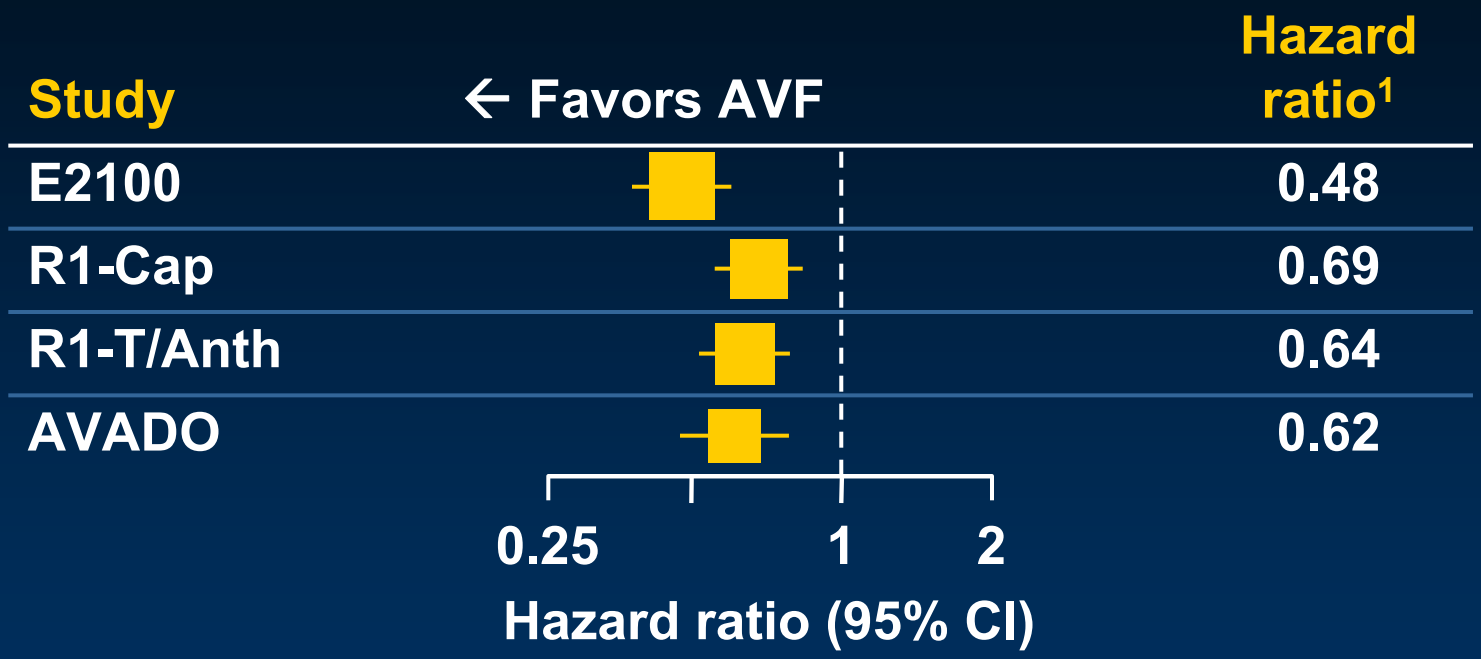
***Selected Gr 3-5 ≥2%** ****No increase after adjustment for docetaxel exposure**

E2100 Summary

Clinical use	**Paclitaxel active, standard treatment**
PFS improvement	HR 0.48, median Δ 5.5 mo, average Δ 4.1 mo
Response rate	Δ 27%
Safety*	Increase HTN, proteinuria;
	Increase ATE, neutropenia, febr neutropenia, neuropathy**
Overall survival	HR 0.87
Treatment-related mortality	1.7% vs 0.3%

*Selected Gr 3-5 ≥2% **No increase after adjustment for paclitaxel exposure

Consistent and Reliable PFS Improvement
Reduction in Risk: 31% - 52%



- HR, median, average differences clinically relevant in this clinical setting: 1st-line HER2-negative mBC

AVF = Avastin; Cap = Capecitabine; CI = Confidence interval; PFS = Progression-free survival; T/Anth = taxane/anthracycline.

1. Hazard ratio based on stratified analysis.

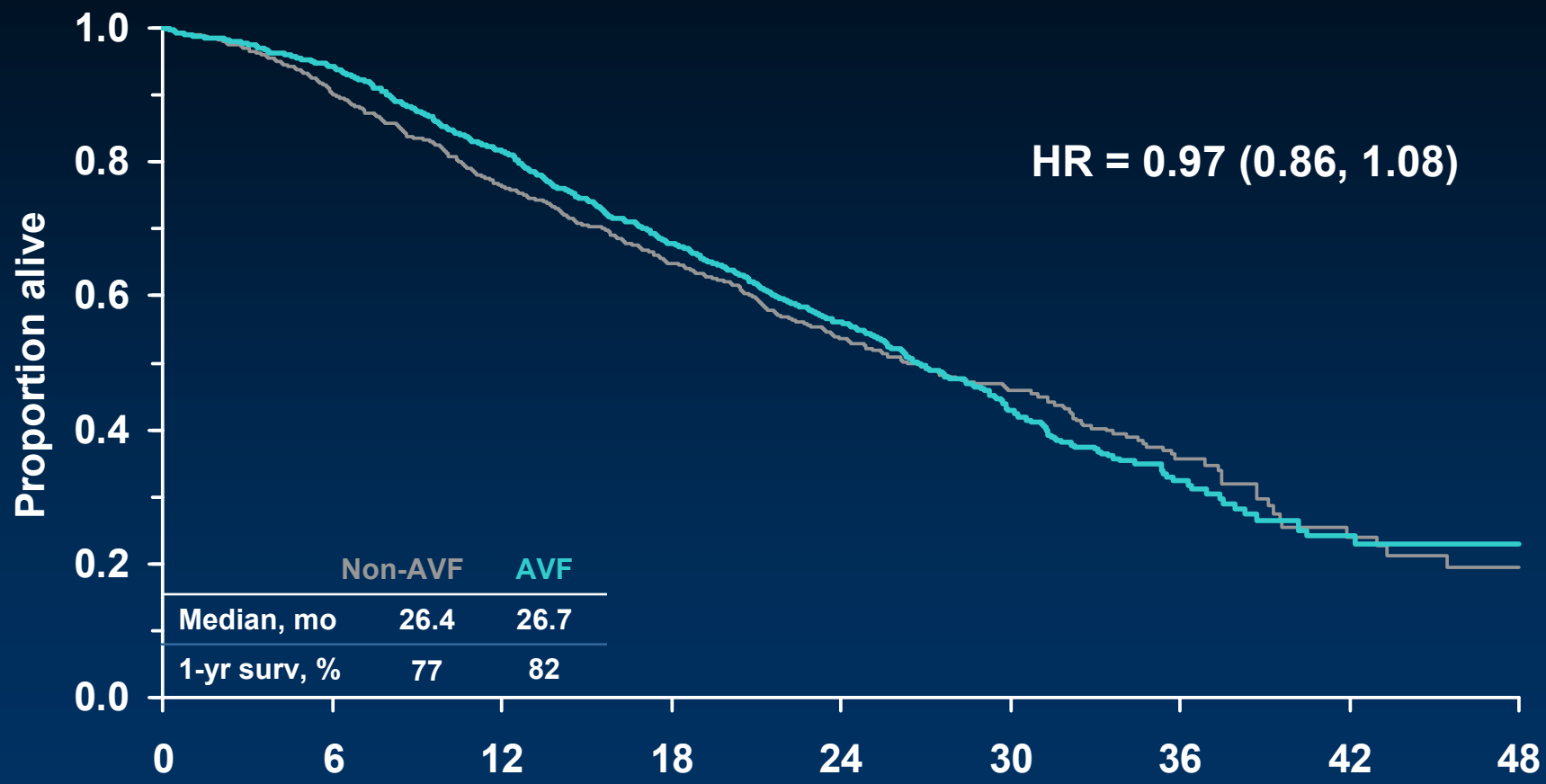
Consistent and Reliable PFS Improvement
Key Prognostic Subgroups

Subgroup	Reduction in risk of progression or death
Visceral disease	28% - 42%
Triple negative	22% - 51%
≥ 3 metastatic sites	26% - 44%
Disease-free interval ≤ 24 mo	24% - 42%

Grade ≥ 3 Select AEs
Pooled (E2100, R1, AVADO)

	Chemo ± PL n = 982, %	Chemo + AVF n = 1427, %	Difference
Cumulative	**23.1**	**36.4**	**13.3**
Common AVF-assoc. AEs	**1.2**	**12.5**	**11.3**
Hypertension	1.2	10.4	
Proteinuria	0	2.6	
Other AVF-assoc. AEs	**5.3**	**8.2**	**2.9**
ATE	0.3	1.9	
VTE	3.8	3.0	
Bleeding	0.4	1.6	
Fistula	0.3	0.4	
GI perforation	0.3	0.5	
Wound dehiscence	0.3	0.8	
Chemotherapy-assoc. AEs	**18.2**	**21.9**	**3.7**
Neutropenia	7.1	8.0	
Febrile neutropenia	3.5	5.0	
Sensory neuropathy	8.5	9.7	
LV systolic dysfunction	0.2	1.5	

No Impairment in Overall Survival
Pooled



At risk, n									
— AVF	1439	1333	1127	916	591	204	55	23	5
— Non-AVF	1008	892	746	621	426	178	51	19	8

AVF = Avastin.

Mortality in E2100, AVADO, R1
No Increase in Toxic Deaths

Cause of mortality, %	Non-AVF n = 982	AVF n = 1427
Deaths	55.8	52.0
mBC	51.5	48.1
Adverse event or protocol therapy	1.8	1.8
Other	1.4	1.8
Missing/unknown	1.0	0.3

Avastin for First-Line HER2– mBC

- Unique mechanism complements multiple chemotherapies
- Consistent, reliable, significant PFS improvement; supported by ORR
- Safety well characterized and known to physicians
- No impairment in OS
- Clinical benefit for 1st-line mBC

Proposed Indication Statement

Avastin®, in combination with taxane-based, anthracycline-based or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

Supportive Slides

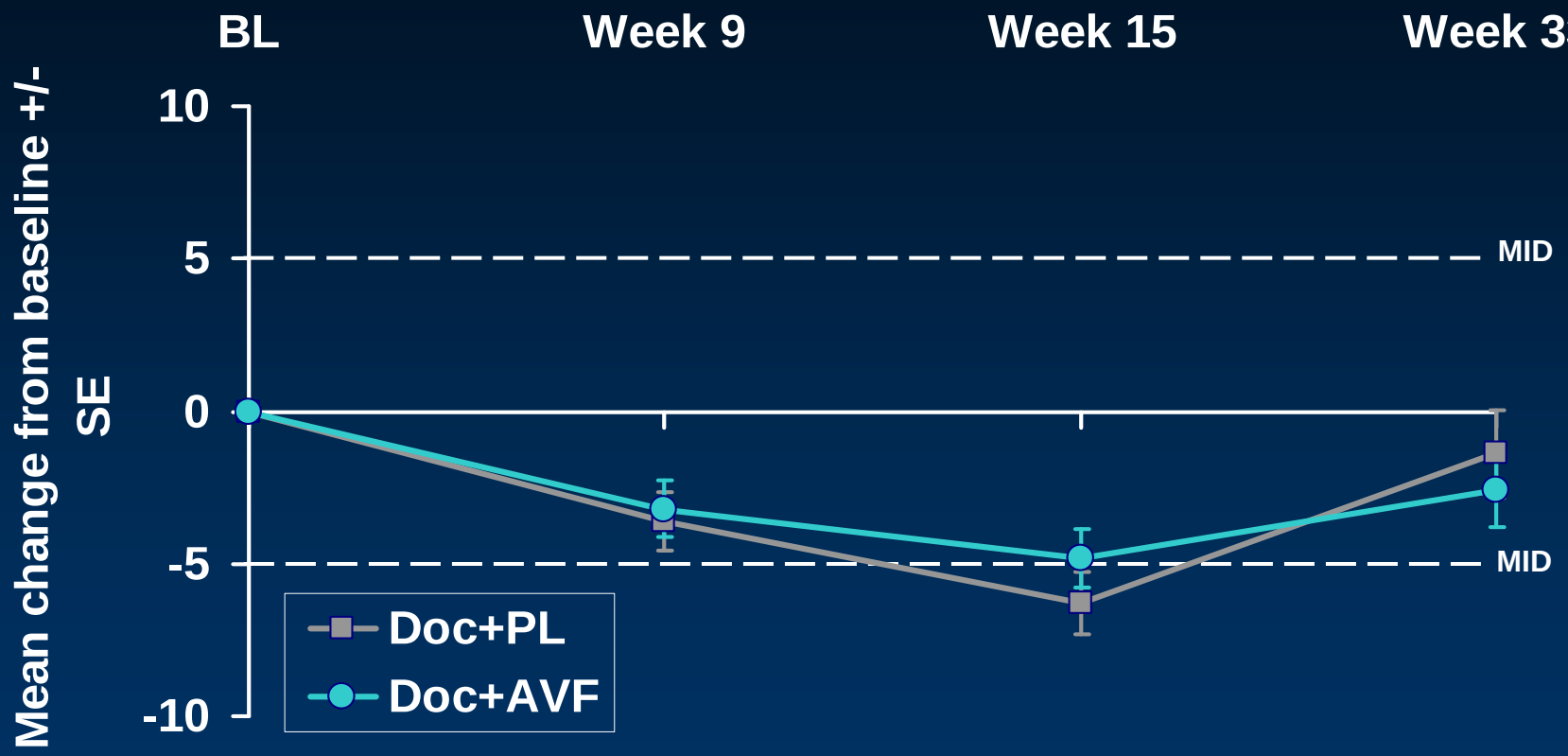
Health-Related Quality of Life (HRQOL)
AVADO

- Standard and validated Instrument:
- Functional Assessment of Cancer Therapy-Breast (FACT-B)
  - Social/family well-being
  - Emotional well-being
  - Physical well-being
  - Functional well-being
  - Breast cancer subscale

Physical well-being, Functional well-being, Breast cancer subscale → Trial Outcome Index (TOI) score

Social/family well-being, Emotional well-being, Trial Outcome Index (TOI) score → FACT-B total score

AVADO: Health-Related Quality of Life
Trial Outcome Index



Treatment	BL	Week 9	Week 15	Week 33
Doc+AVF	n = 211	n = 183	n = 165	n = 105
Doc+PL	n = 206	n = 168	n = 144	n = 75

AVF = Avastin; Doc = Docetaxel; MID = minimally important difference; PL = Placebo; SE = Standard Error

PK-DDI Potential of Avastin

- No relevant PK interactions between monoclonal antibodies and chemotherapy
  - Lack of common clearance pathways with chemotherapies
- No relevant differences in exposure for capecitabine and paclitaxel with Avastin
- Avastin PK-DDI data with other molecules do not show relevant DDI potential

Drug-drug Interaction Evaluations With Avastin

DDI assessments (no effect on backbone therapy)	DDI assessments (no effect on Avastin)
Capecitabine	XELOX
Carboplatin	FOLFOX
Cisplatin	Gemcitabine + Erlotinib
Erlotinib	Trastuzumab
Gemcitabine[1]	Rituximab
Interferon	Bolus-IFL[2]
Irinotecan and SN-38	Interferon
Oxaliplatin	Capecitabine[2]
Paclitaxel	Carboplatin[2]
Rituximab	Cisplatin
Trastuzumab	Doxorubicin[2]
	Erlotinib
	Paclitaxel[2]

1. Inclusive due to high variability.
2. Population PK.

Management of Hypertension of Any Grade
AVADO

	Patients, n (%)	
	Doc+PL n = 231	Doc+AVF n = 247
Any grade hypertension, %	10.4	22.7
AVF/PL discontinued due to hypertension AE	0	5.4
AVF/PL interrupted due to hypertension AE	12.5	12.5
Any treatment given for hypertension as AE	66.7	78.6
No treatment given for hypertension as AE	33.3	21.4

AVF = Avastin; Doc = Docetaxel, PL = Placebo

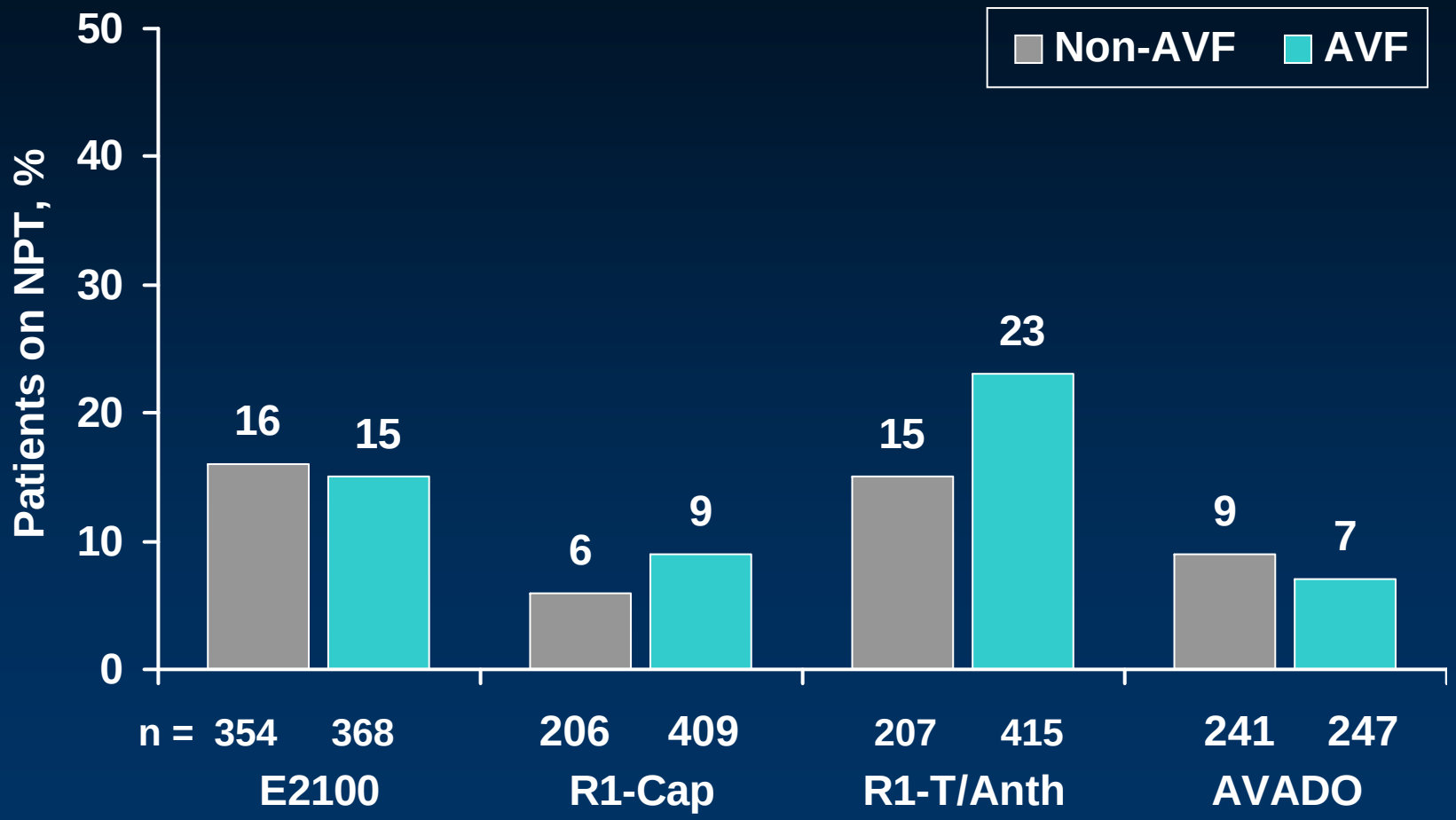
Patient Population in AVF2119g

Patient population	AVF2119g
HER2-positive status	23%
Previously untreated mBC	16%[1]
Previously treated mBC	2L: 44% 3+L: 40%

2% (10/462) patients from AVF2119g met inclusion criteria for R1

mBC = Metastatic breast cancer; 2L = Second-line; 3+L = Third-line or above.
1. mBC treated with prior adjuvant anthracycline and taxane and disease relapsed within 1 year.

Patients on Non-Protocol Therapy

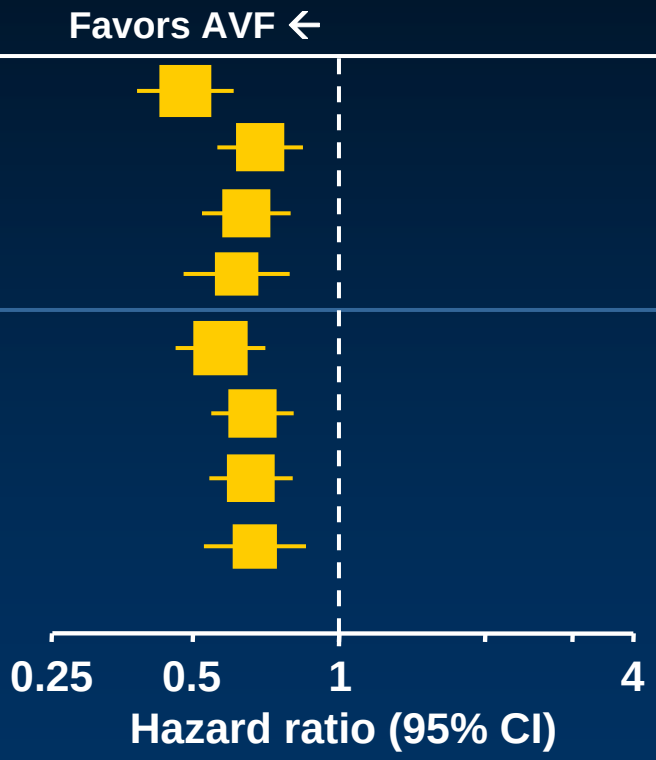


AVF = Avastin; Cap = Capecitabine; NPT = non-protocol specified anti-cancer therapy; T/Anth = Taxane/Anthracycline.

1. NPT administered before IRC assessed disease progression for E2100 and investigator assessed disease progression for R1 abd AVADO.

Sensitivity Analysis of PFS
Without Censoring NPT

Analysis	Study	N	Hazard ratio[1]
Primary	E2100	722	0.48
	R1-Cap	615	0.69
	R1-T/Anth	622	0.64
	AVADO	488	0.62
Without censoring NPT[2]	E2100	722	0.57
	R1-Cap	615	0.66
	R1-T/Anth	622	0.66
	AVADO	488	0.67



1. Based on stratified analysis.
2. NPT was not censored in the analysis of PFS

AVF = Avastin; Cap = capecitabine; CI = confidence interval; NPT = non-protocol specified anti-cancer therapy; PFS = progression-free survival ; T/Anth = taxane/anthracycline.

AVADO Safety Summary

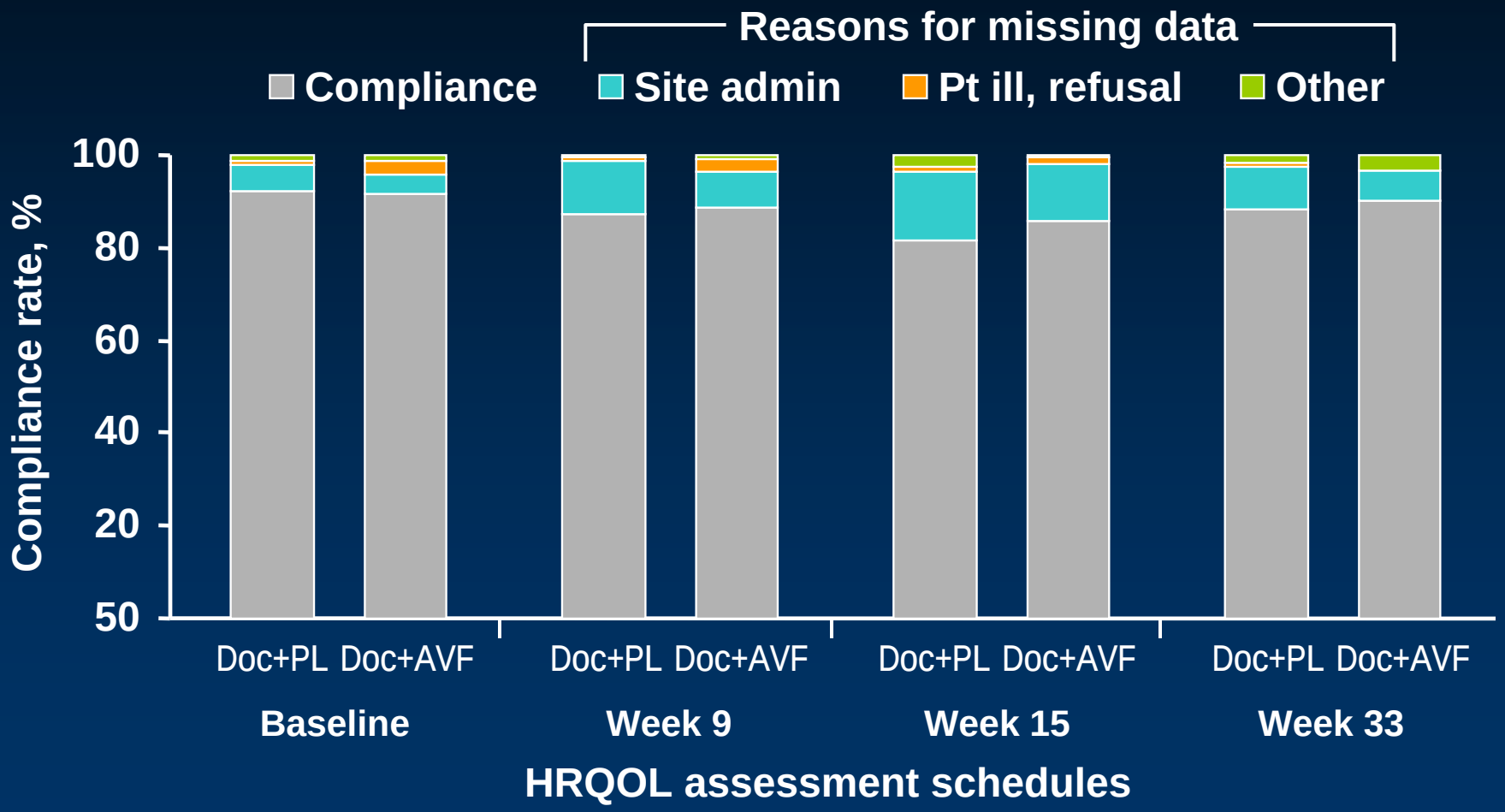
	Patients, %	
	Doc + PL n = 231	Doc + AVF n = 247
All AEs	99.6	99.6
Grade 3 – 5 AEs	67.5	75.3
Serious AEs	32.5	42.9
AEs leading to study drug discon	11.7	13.8
AEs leading to docetaxel discon	24.7	24.3

Incidence of Sensory Adjusted for Person-years of Exposure
AVADO

	Doc+PL n = 231	Doc+AVF n = 247
Any grade sensory neuropathy, n (%)	144 (62.3)	142 (57.5)
Person-years of exposure, n	84	94
Any grade sensory neuropathy event rate per 100 person-years	172.1	150.6

AVF = Avastin; Doc = Docetaxel; PL = Placebo.

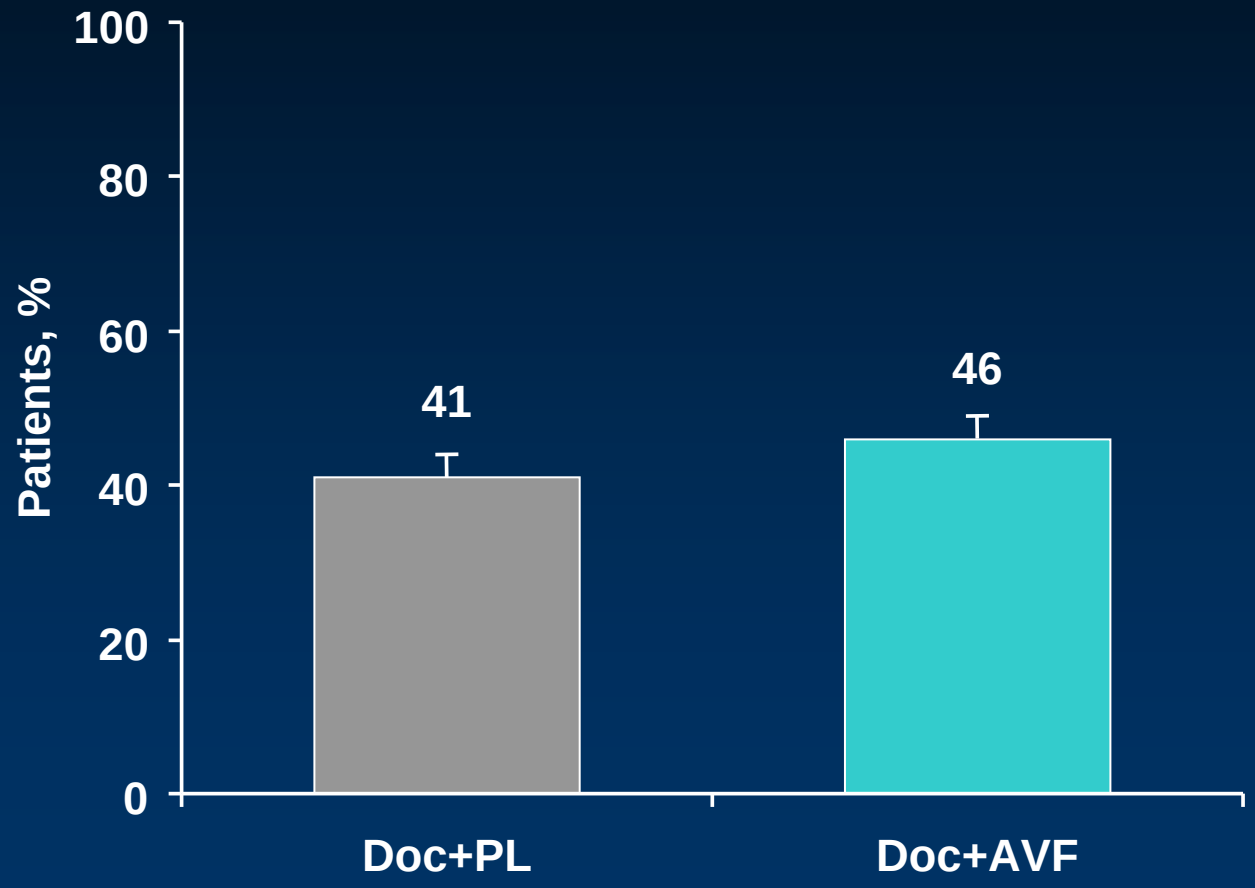
Compliance for On-Study HRQOL Data Collection AVADO



Percent of patients who had non-missing scores for FACT-B or TOI at the protocol-specified assessment schedule.

AVF = Avastin; Doc = docetaxel; FACT-B = Functional Assessment of Cancer Therapy-Breast; HRQOL = Health-Related Quality of Life; PL = placebo; Pt = patient.

Patients With Stable or Improved ECOG Performance Status Scores - AVADO



Error bars represent standard errors.
AVF = Avastin; Doc = docetaxel; ECOG = Eastern Cooperative Oncology Group; PL = placebo.

Efficacy Results
RIBBON-2

	Chemo+PL n = 225	Chemo+AVF n = 459
Progression-free survival		
Stratified HR (95% CI)	0.78 (0.64, 0.93)	
Median, mo	5.1	7.2
P value	0.0072	
Overall survival		
Deaths, %	48	45
Stratified HR (95% CI)	0.90 (0.71, 1.14)	
Median, mo	16.4	18.0
Objective response rate[1]		
ORR, % (95% CI)	29.6 (23.0, 36.7)	39.5 (34.4, 44.7)

1. Patients with measurable disease at baseline

AVF = Avastin; Chemo = Chemotherapy (taxane (Abraxane, docetaxel, paclitaxel), capecitabine, gemcitabine,vinorelbine.); CI = Confidence interval; PL = Placebo; HR = Hazard ratio; ORR = Objective response rate; mo = month

Prior Breast Cancer Treatment

	% Patients			
	E2100 n = 722	R1-Cap n = 615	R1-T/Anth n = 622	AVADO n = 736
Prior adjuvant/neo-adjuvant				
Chemotherapy	66	72	46	66
Taxane	20	40	15	16
Anthracycline	50	63	30	55
Hormone therapy	48	51	38	54
Prior hormone therapy for LR or mBC	36	45	26	30

Cap = Capecitabine; LR = Locally recurrent; mBC = Metastatic breast cancer; T/Anth = Taxane/Anthracycline.

Patient Characteristics

	E2100		R1-Cap		R1-T/Anth		AVADO	
	Non-AVF (n=354)	AVF (n=368)	Non-AVF (n=206)	AVF (n=409)	Non-AVF (n=207)	AVF (n=415)	Non-AVF (n=241)	AVF (n=247)
Median age, yr	55	56	57	56	55	55	55	55
Triple negative,%	31	33	24	21	22	23	22	24
DFI ≤ 24 mo,%	41	41	31	35	45	41	37	30
Adjuvant chemotherapy,%	65	66	76	70	47	45	65	68
≥ 3 Metastatic sites,%	29	29	45	43	45	45	41	50
Visceral disease,%	69	64	71	68	73	69	73	77

AVF = Avastin; DFI = disease-free interval; mo = month; yr = year.