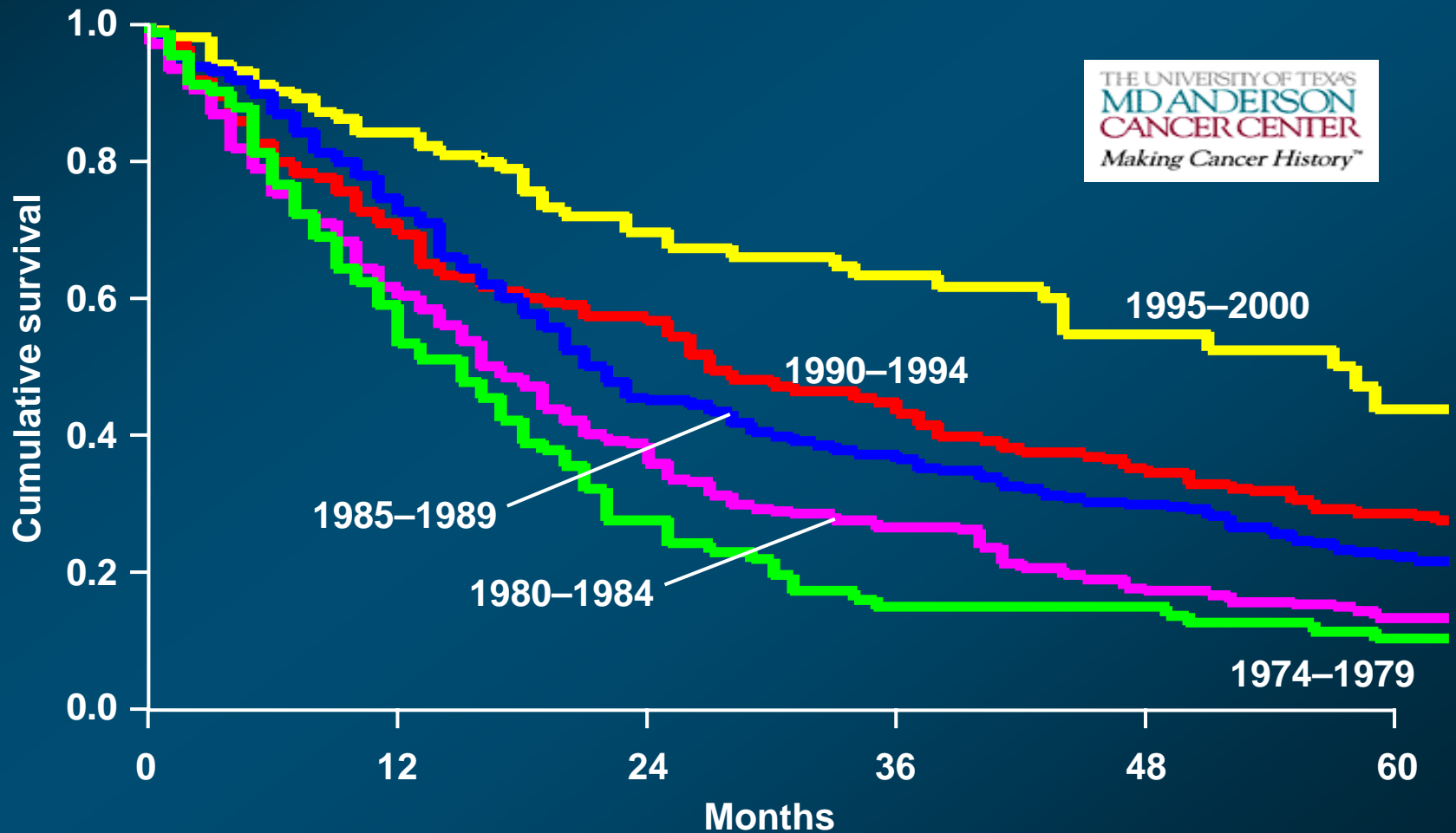


**Advanced Breast Ca.  
Cases discussion**

**Heba El-Zawahry M.D.  
Prof. Medical Oncology  
National Cancer institute, Cairo  
University**

**ASCO SEMCO Meeting  
Cairo, April 5<sup>th</sup> 2007**

# Metastatic breast cancer: improved survival over time



# Therapy for MBC

## Low predictive factors :

- Postmenopausal status
- Years between primary disease and first metastasis
- Loco-regional disease (skin/ LN)
- Good P.S (0-1)
- Hormonal responsive tumor (ER /PR+ve) for met. or recurrent disease.
- Isolated bone metastasis.
- Her2Neu negative (-ve) metastatic disease.

# Therapy for MBC

## High predictive factors :

- Premenopausal status.
- Months between primary disease and first metastasis.
- Visceral metastasis ( 2 sites or more).
- Bad P.S (2,3,4).
- Hormonal non-responsive tumor (ER/PR-ve) for met. or recurrent disease.
- Her2Neu over expression of metastatic disease.

# Treatment choices in metastatic breast cancer

		Aggressive case		Non-aggressive case	
		HER2 status			
		-	+	-	+
HR status	-		+ HER	CT	CT + HER HER
	+	→ HT	+ HER → HT	HT	HT HT + HER

# Case No. 1

- Postmenopausal Female patient 55 years old had
- In the year 2001 she had T2 N3 M0 Left breast ca, GII, ER+ve/ PR-ve and HER 2Neu -ve.
- Lt MRM was done followed by 6 cycles of FEC<sub>75</sub> followed by local radiotherapy then Tamoxifen 20 mg/day for 3years.
- In the year 2004 her work up revealed multiple hepatic focal deposits 3 in No. largest 3x5cm. Her mammography and chest X ray were free....

# Case No. 1

**Q1 what are the other investigations needed for proper evaluation of the case...?**

1- CT chest?

2-Tumor marker?

3-Bone scan?

4- Re-evaluation of ER and PR??

5- Retesting for HER2Neu , may be with FISH??

**•55 years ,T2 N3 M0  
Left breast ca, GII,  
ER+ve/ PR-ve and  
HER 2Neu -ve.  
•6 cycles of CEFthen  
Tamoxifen 3years.  
•In the year 2004,  
multiple hepatic  
focal deposits**

# Case No. 1

**Q1 what are the other investigations needed for proper evaluation of the case...?**

- 1- CT chest showed small lt upper pneumonic patche 2x2cm that may be pulmonary nodule for close follow up.
- 2-Tumor marker ca15.3 was 112.
- 3-Bone scan was free
- 4- Re-evaluation of ER and PR proved ER+ve PR-ve
- 5- Retesting for HER2*Neu* result in –ve result by I H C.

•55 years ,T2 N3  
M0 Left breast ca,  
GII, ER+ve/ PR-ve  
and HER 2*Neu* -ve.  
•6 cycles of CEF  
then Tamoxifen  
3years.  
•In the year 2004,  
multiple hepatic  
focal deposits

# Case No. 1

**Q2**

**what is the suggested line of treatment for this lady?**

**1-Taxenes;as single agent e.g Docetaxel vs Paclitaxel in 3ws schedules weekly schedule?**

**2- Taxenes in combination; with gemcitabine, capcitabine, platinum ???**

**3- Hormonal treatment AIS?**

**•55 years ,T2 N3 M0  
Left breast ca, GII,  
ER+ve/ PR-ve and  
HER 2Neu -ve.  
•6 cycles of CEF  
3years.  
•In the year 2004,  
multiple hepatic  
focal  
deposits.....**

# Treatment objectives for first-line chemotherapy selection

---

Primary objective

Chemotherapy option

---

Quick response or  
symptom relief

Highly active  
combinations

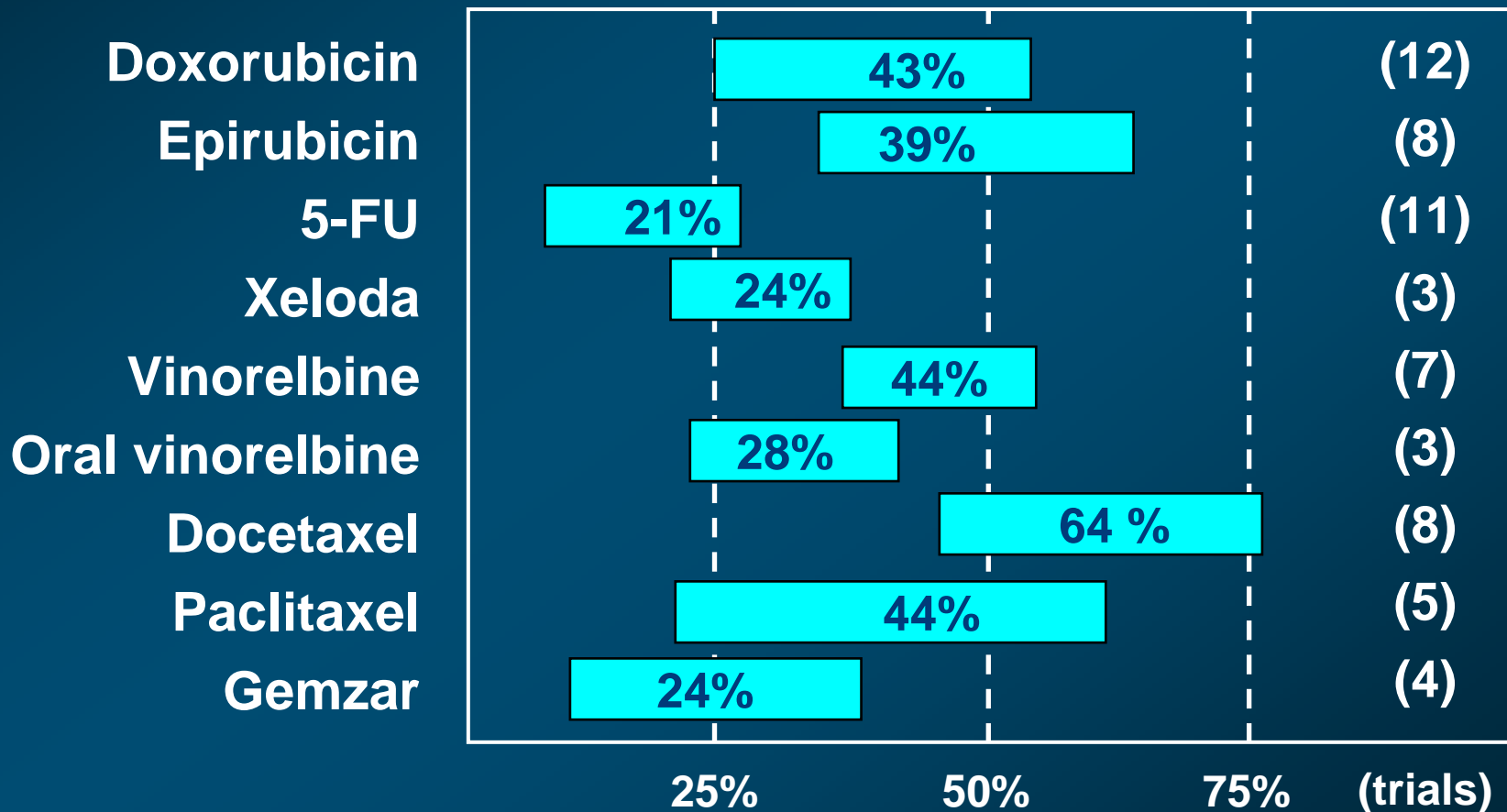
Disease free  
progression or QoL

Single agent,  
sequential therapies or  
low toxic combinations

---

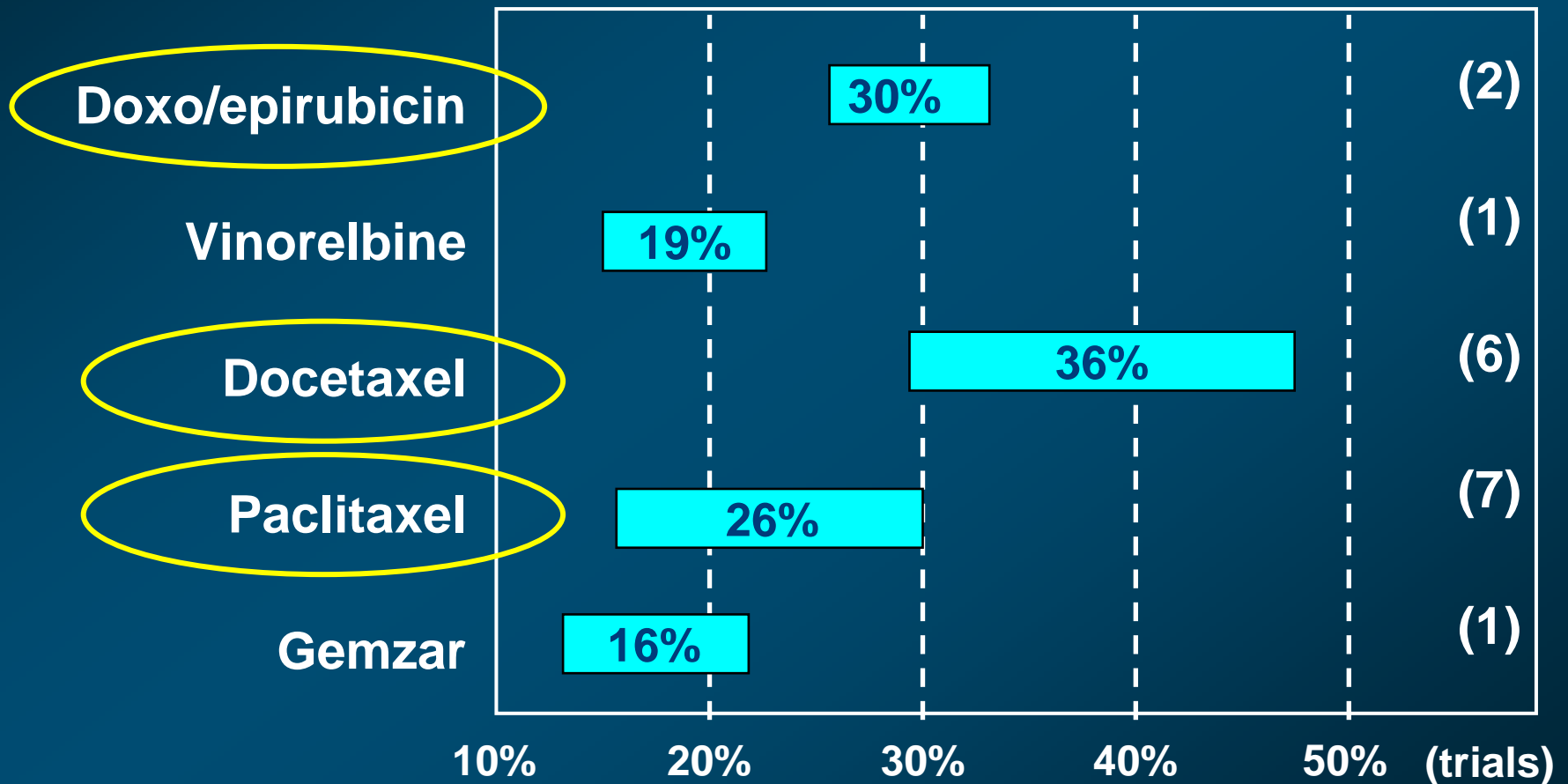
# First-line single agent Phase II trials

## Overall response rates



# First-line single agent Phase III trials

## Overall response rates

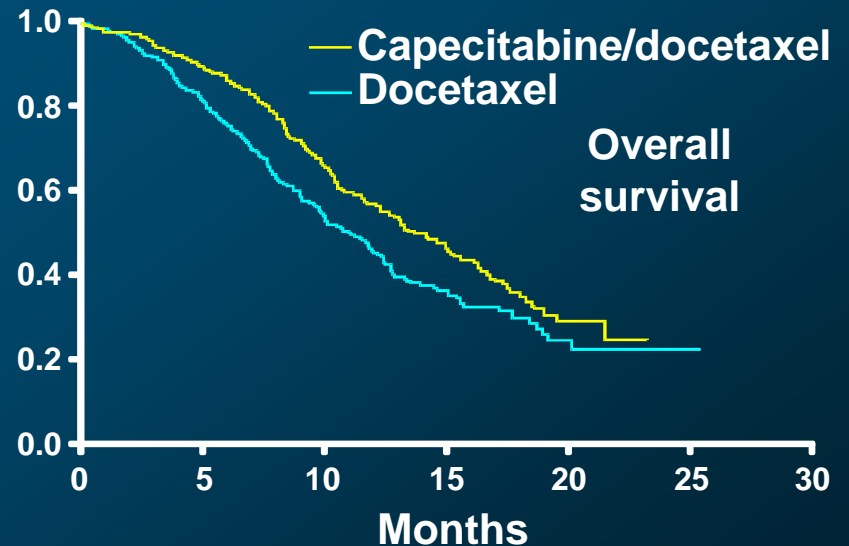
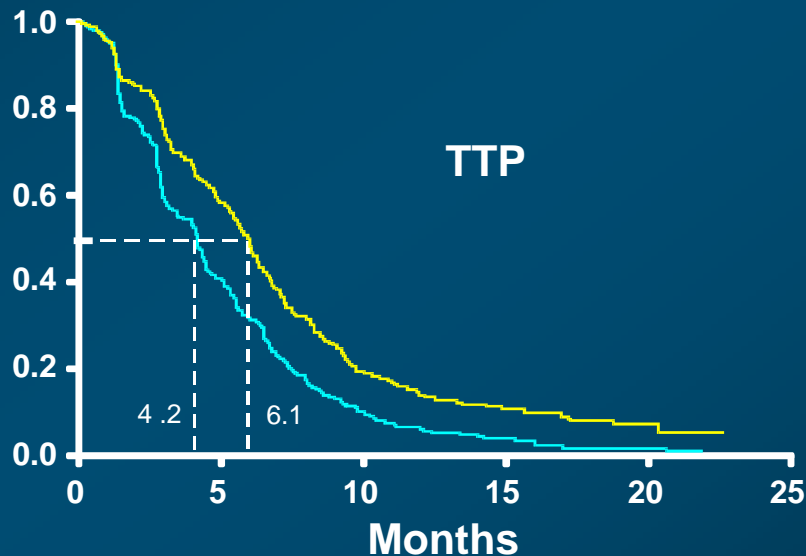


# Docetaxel vs doublets

	n	Prior CT, %	ORR	Median TTP	Overall survival
<b><i>Sjöstrom (EJC 1999)</i></b>	<b>282</b>	<b>100</b>			
<b>Docetaxel 100 mg/m<sup>2</sup></b>			<b>42%</b>	<b>27 wk</b>	<b>10.4 mo</b>
<b>Methotrexate + 5-FU</b>			<b>21%</b>	<b>13 wk</b>	<b>11.1 mo</b>
	<b>p</b>		<b>0.001</b>	<b>0.001</b>	<b>NS</b>
<b><i>Bonneterre (SABCS 1998)</i></b>	<b>175</b>	<b>100</b>			
<b>Docetaxel 100 mg/m<sup>2</sup></b>			<b>33%</b>	<b>24 wk</b>	<b>13 mo</b>
<b>Vinorelbine 25 + 5-FU 750</b>			<b>26%</b>	<b>20 wk</b>	<b>12 mo</b>
	<b>p</b>		<b>0.003</b>	<b>NS</b>	<b>NS</b>

# Docetaxel vs docetaxel + Xeloda

	n	Prior CT, %	ORR	Median TTP	Overall survival
<i>O'Shaughnessy (JCO 2003)</i>	511	100			
Docetaxel 100 mg/m <sup>2</sup>			30%	4.2 mo	11.5 mo
Docetaxel 75 mg/m <sup>2</sup> + Xeloda <sup>®</sup> 2500 mg/m <sup>2</sup> D1-14			42%	6.1 mo	14.5 mo
			<b>p</b>	<b>0.006</b>	<b>0.0001</b>
				<b>0.0001</b>	<b>0.0126</b>



# Case No. 1

**Patients received taxoter as single agent  
100mg/m<sup>2</sup> q21 days for 4 regular cycles with  
tolerable side effect**

1. Tumor marker ca15.3 reduced to 55.
2. Her Ct chest remained the same finding.
3. Triphasic CT revealed increase in the size and No. of hepatic deposits
4. All LFT were with normal
5. Her PS was 1
6. She asked for more effective chemotherapy.

- 55 years ,T2 N3 M0  
Left breast ca, GII,  
ER+ve/ PR-ve and  
HER 2Neu -ve.
- 6 cycles of CAF  
then Tamoxifen 3  
years.
- In the year 2004,  
multiple hepatic  
focal  
deposits.....

# Case No. 1

**Q3**

**what is her better choice now???**

1. Continue same treatment with weekly schedule?
2. Shift to Paclitaxel as single agent
3. Combination of Taxenes with Gemzar/ Xeloda/Platinum?
4. Lipsomal anthracyclines (Calyx)?
5. Navelben plus fluorouracil
6. Non taxenes combinations ?e.g Gemzar plus Platinum/ Xeloda plus Navelben ?
7. Single Agent Xeloda,

**•55 years ,T2 N3  
M0 Left breast ca,  
GII, ER+ve/ PR-ve  
and HER 2Neu -ve.  
•6 cycles of CAF  
then Tamoxifen 3  
years.  
•In the year 2004,  
multiple hepatic  
focal deposits,  
•Received Taxoter  
100mg/m<sup>2</sup>with  
mixed response**

Third generation trials:  
are doublets superior to  
single agent TXNs?

Taxane vs Taxane + Other  
Exploring  
synergistic mechanisms

# Docetaxel + Gemzar vs docetaxel + Xeloda

**RANDOM**  
**(cycle x 3 weeks)**

**Docetaxel 75 mg/m<sup>2</sup> d 1**  
**Xeloda<sup>®</sup> 1250 mg/m<sup>2</sup> x 2**  
**Day d 1–14**

**n = 525**

**Docetaxel 75 mg/m<sup>2</sup> d 1**  
**Gemzar 1250 mg/m<sup>2</sup>**  
**d 1 y d 8**

- First to second line following anthracyclines
- Primary objective: DFS
- Treatment until progression or unacceptable toxicity
- Closed in March 2004

**Toxicity and  
preliminary DFS results  
at ASCO 2005**

# Docetaxel + Gemzar vs docetaxel + Xeloda<sup>®</sup>

Docetaxel 75 mg/m<sup>2</sup> d 1  
Xeloda<sup>®</sup> 1250 mg/m<sup>2</sup> x 2  
Day d 1–14



Gemzar  
1250 mg/m<sup>2</sup>  
D 1 and d 8



**RANDOM**

**Crossover  
at progression**



Docetaxel 75 mg/m<sup>2</sup> d 1  
Gemzar 1250 mg/m<sup>2</sup>  
d 1 y d 8



Xeloda<sup>®</sup>  
1250 mg/m<sup>2</sup> x 2  
Day d 1–14

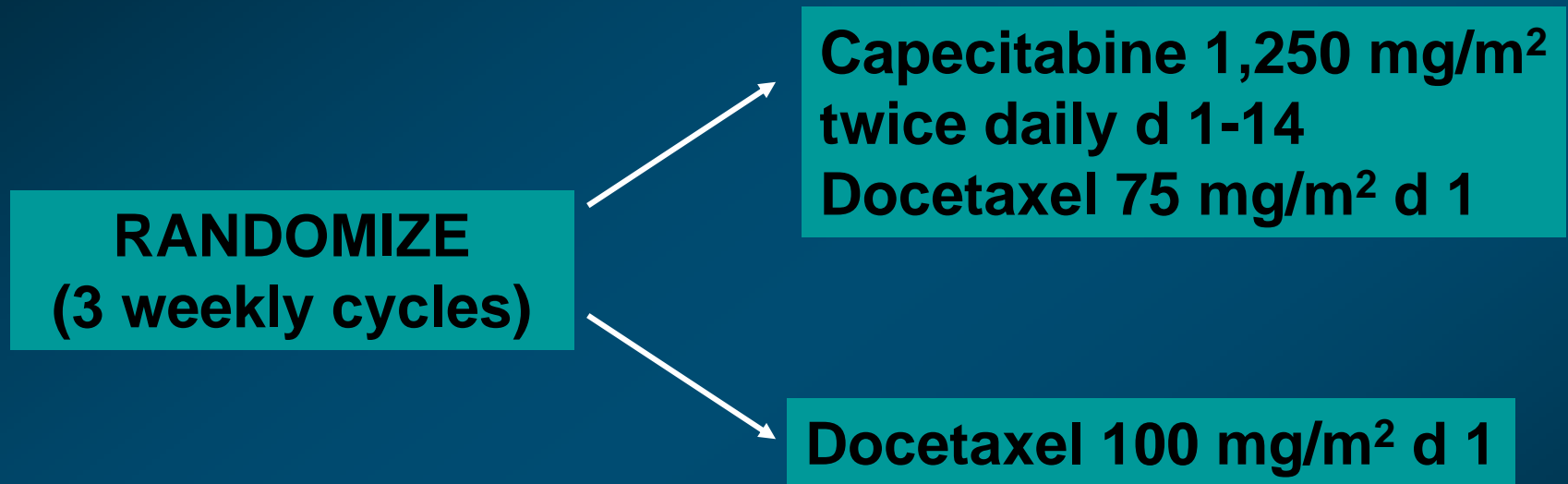
# Phase III Study of Capecitabine (Xeloda) Plus Docetaxel (Taxotere) vs Docetaxel in Patients With Metastatic Breast Cancer

Joyce O'Shaughnessy  
Baylor-Sammons Cancer Center  
US Oncology

# Capecitabine Plus Docetaxel: Rationale in Breast Cancer

- Capecitabine and docetaxel have considerable activity in breast cancer
- Capecitabine and docetaxel have distinct mechanisms of action and no overlap of key toxicities
- Synergistic interaction between capecitabine and docetaxel mediated by taxane-induced upregulation of thymidine phosphorylase

# Capecitabine Plus Docetaxel: Phase III Study Design



Patients responding or with stable disease after 6 weeks of treatment continued until disease progression or unacceptable toxicity

# Capecitabine Plus Docetaxel: Disease Characteristics

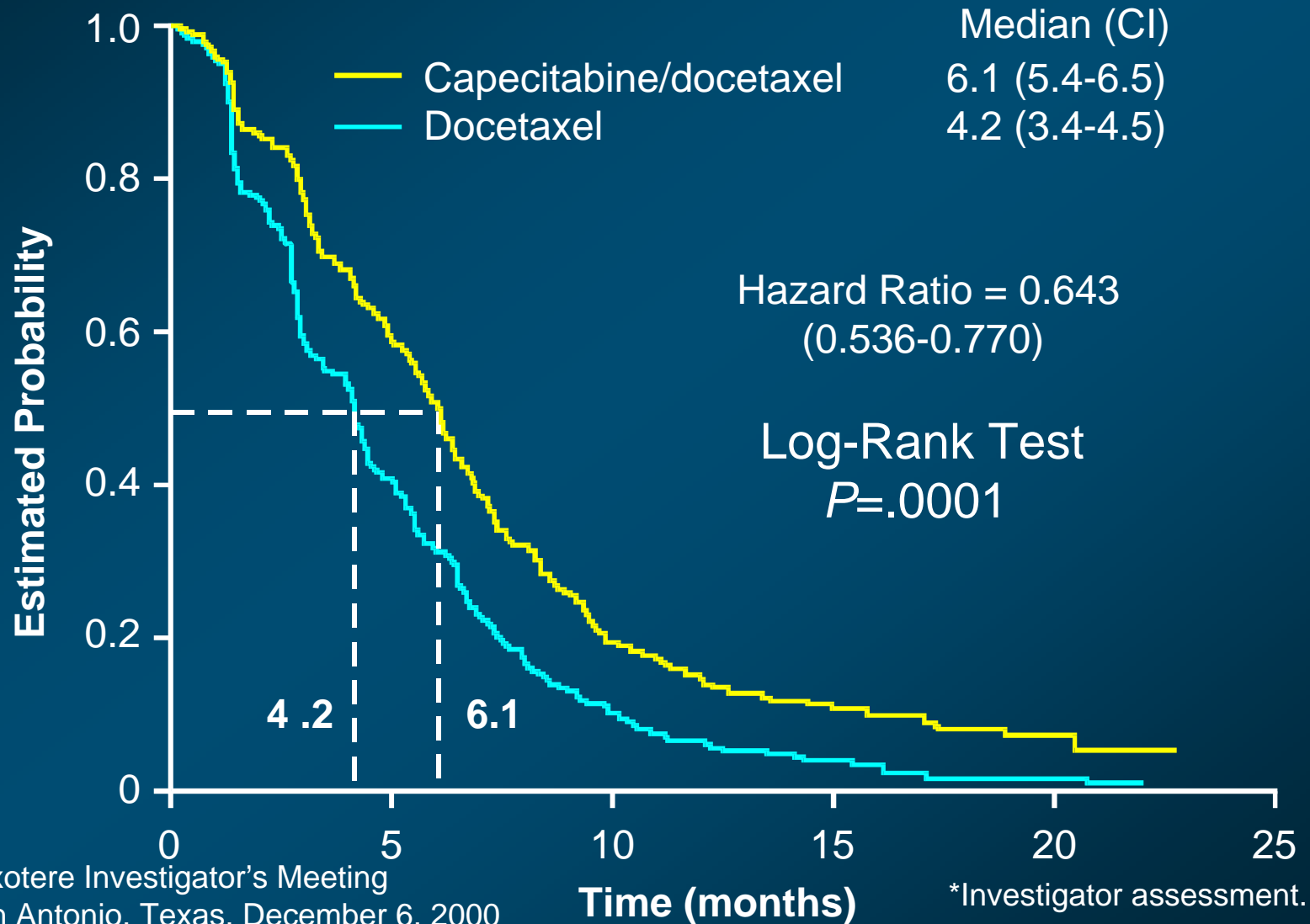
	Capecitabine/ Docetaxel (n=255)	Docetaxel (n=256)
ER/PR, %		
Positive	39	42
Negative	32	28
Unknown	29	30
Metastatic sites, %		
Liver	45	48
Lung	37	39
Bone	42	46
No. of metastatic sites		
1	13	11
2	22	21
≥3	64	69

# Capecitabine Plus Docetaxel: Overall Tumor Response Rates

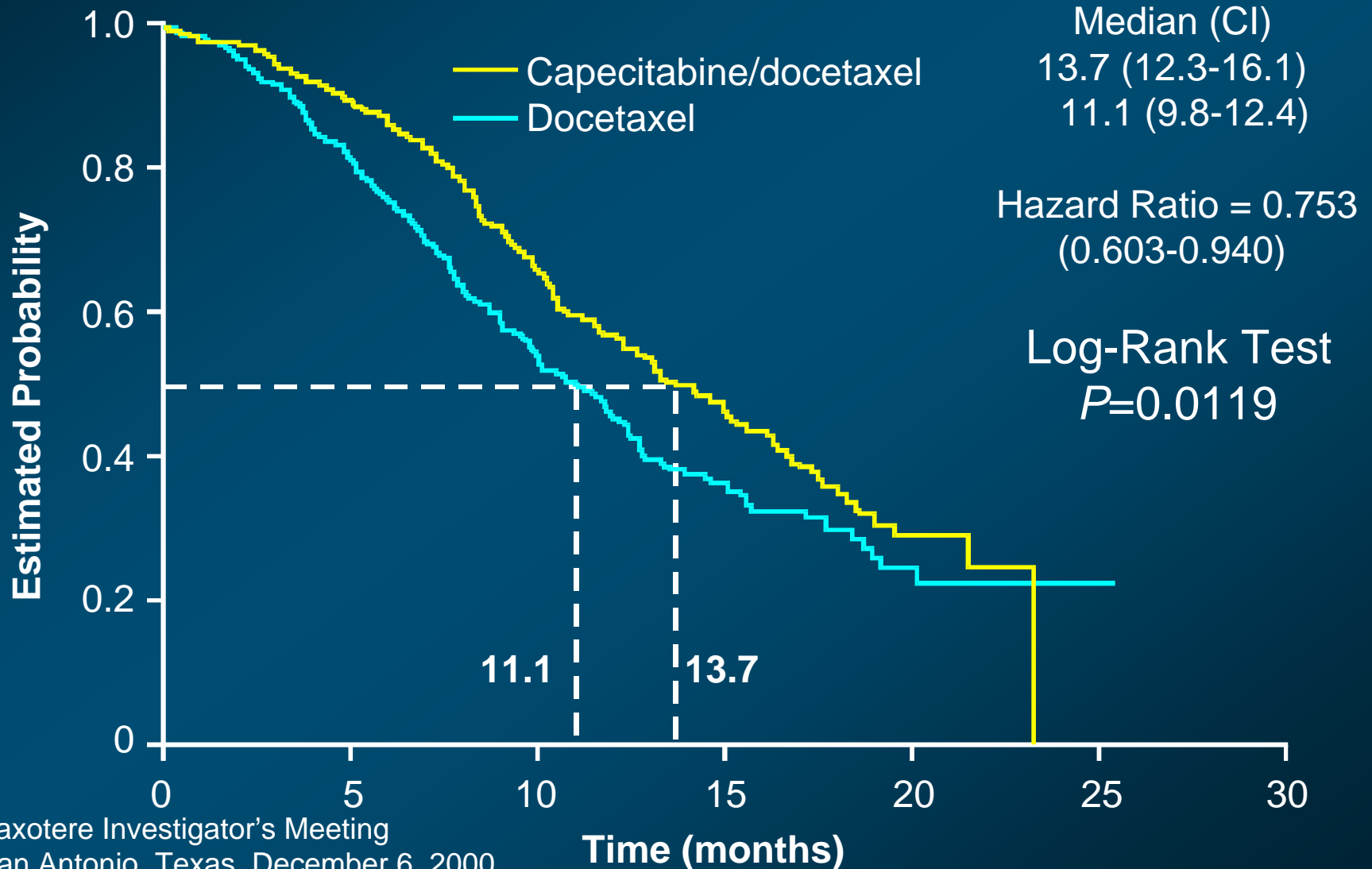
	Capecitabine/ Docetaxel (n=255)	Docetaxel (n=256)	
Investigator			
PR + CR, %	42	30	<i>P</i> =.006
Stable disease, %	38	44	
IRC*			
PR + CR, %	32	23	<i>P</i> =.025
Stable disease, %	46	51	

\*IRC = Independent Review Committee.

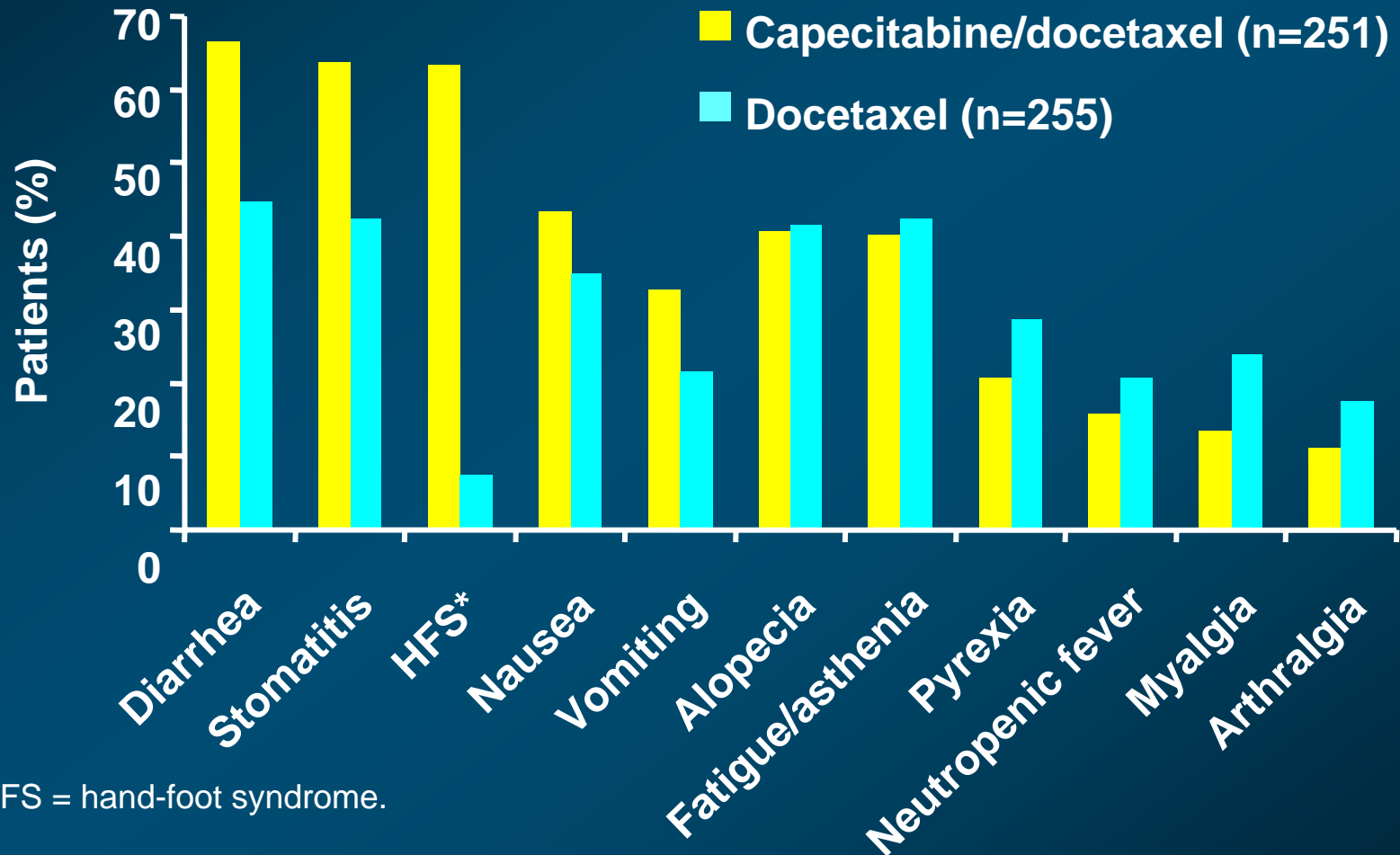
# Capecitabine Plus Docetaxel: Time to Disease Progression\*



# Capecitabine Plus Docetaxel: Overall Survival

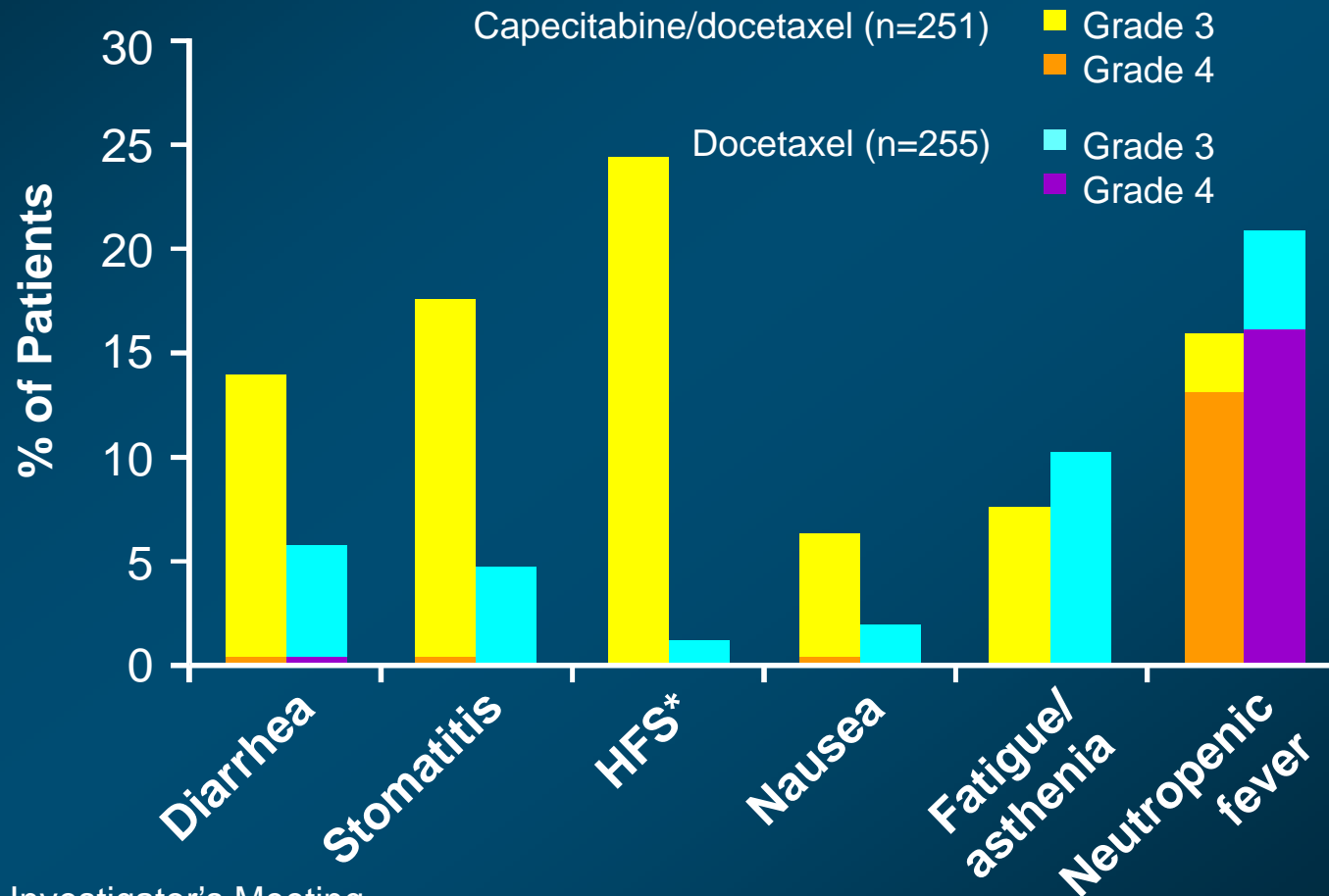


# Capecitabine Plus Docetaxel: Most Common Treatment-Related Clinical Adverse Events (All Grades)



\*HFS = hand-foot syndrome.

# Capecitabine Plus Docetaxel: Most Common Grade 3/4 Treatment-Related Toxicity (>5%)



# Docetaxel vs docetaxel + Xeloda

- Better RR, TTP, survival
- Increased toxicity
  - No adverse effects on QoL
    - As measured in the study
- Retrospective benefit still seen for patients with lower DDI of capecitabine
- Still need to optimize schedule

# Case No. 1

**Patients received 2 cycles of taxoter 75mg/m<sup>2</sup> plus xeloda 1000mg daily with major side effects and mixed results.....**

## Q4

- what is her good options?
- Xeloda single agent?
- BSC?
- Other single agent?

**•55 years ,T2 N3  
M0 Left breast ca,  
GII, ER+ve/ PR-ve  
and HER 2Neu -ve.  
•6 cycles of CAF  
then Tamoxifen 3  
years.  
•In the year 2004,  
multiple hepatic  
focal deposits,  
•Received Taxoter  
100mg/m<sup>2</sup>with  
mixed response**

# CLINICAL EFFICACY OF CAPECITABINE AS FIRST-LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER-HOW LOW CAN YOU GO?

Yap YS, Kendall A, Walsh G, Banerji U,  
Johnston SR, Smith IE, O'brien M.

Royal Marsden Hospital NHS Trust, Downs Road, Sutton SM2 5PT, UK.

Breast. 2007 Mar (internet copy)

- ✓ 63 patients received capecitabine at 1000mg/m<sup>2</sup> twice daily every 2 out of 3 weeks as first-line treatment for advanced disease .
- ✓ 45 patients (71%) had previously received adjuvant or neoadjuvant chemotherapy. .
- ✓ 48 patients had measurable disease with response rate (RR) of 29%. The median time to progression (TTP) was 18(2-122) weeks.
- ✓ 7pat. (11%) had TTP of >1yr, four of whom received more than 10(24-40) cycles of capecitabine.
- ✓ 37% of patients still needed dose reductions.
- ✓ For a subgroup of patients, capecitabine can result in a long TTP with minimal toxicity.
- ✓ The benefit of continuing capecitabine beyond a fixed number of cycles should be investigated further. Schedules using even lower doses of capecitabine for longer periods may also be of same benefit with less toxicity

Thank you