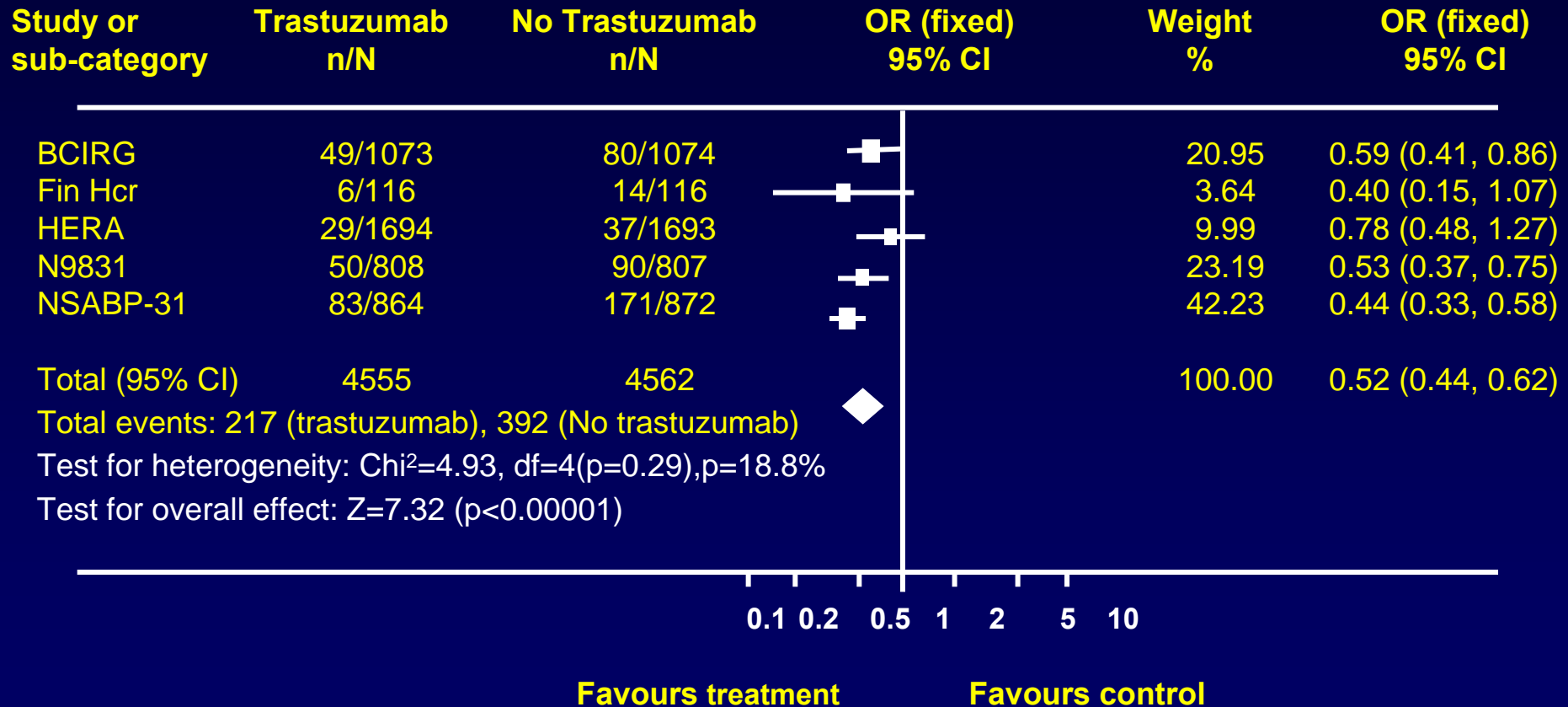


**Optimal Treatment of Recurrent
HER-2 Amplified Breast Cancer (One
Year following Adjuvant
Trastuzumab); Patients Should be
Rechallenged with Trastuzumab-
based Therapy?**

Dr Alison L Jones

**UCLH and Royal Free Hospitals
London, UK**

Meta-analysis of Trastuzumab Adjuvant Trials



¹Viani G et al. *BMC Cancer* 2007;7:153; ² Dahabreh IJ et al. *Oncologist* 2008;13 (6):620

Despite this Women Still Relapse with Metastatic Breast Cancer

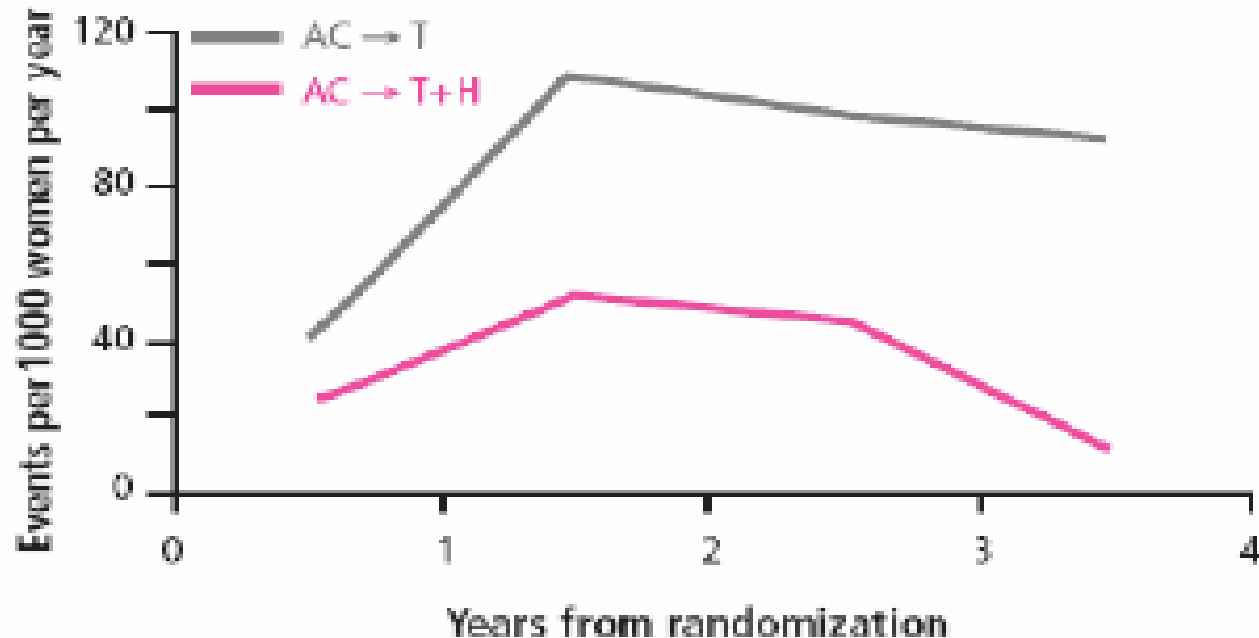
- 15% of women will relapse after adjuvant trastuzumab
- These relapses will occur early
- Relapses may be visceral and/or brain
- This is a real problem for the oncological community

Treatment Duration

Risk of early relapse reinforces importance of one year of Herceptin

- The risk of events is highest in the first three years after surgery ²

Yearly risk of first recurrence in early breast cancer²



Adapted Fig. 4 from Romond et al. Supplementary Appendix on hazard rate for first recurrence, expressed in events per 1000 women at risk per year, in the Joint Analysis.

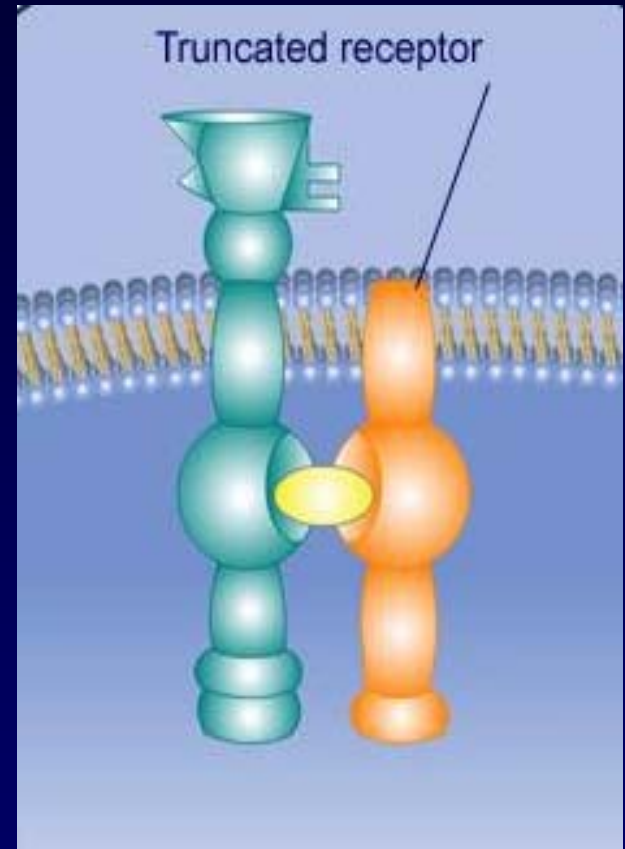
How should we treat patients at relapse?

- Chemotherapy alone?
- Trastuzumab alone?
- Chemotherapy and trastuzumab?
- Chemotherapy and lapatinib?
- Chemotherapy and other HER-2 targeted therapy?
- Chemotherapy and bevacizumab?

Trastuzumab Resistance

Possible mechanisms include:

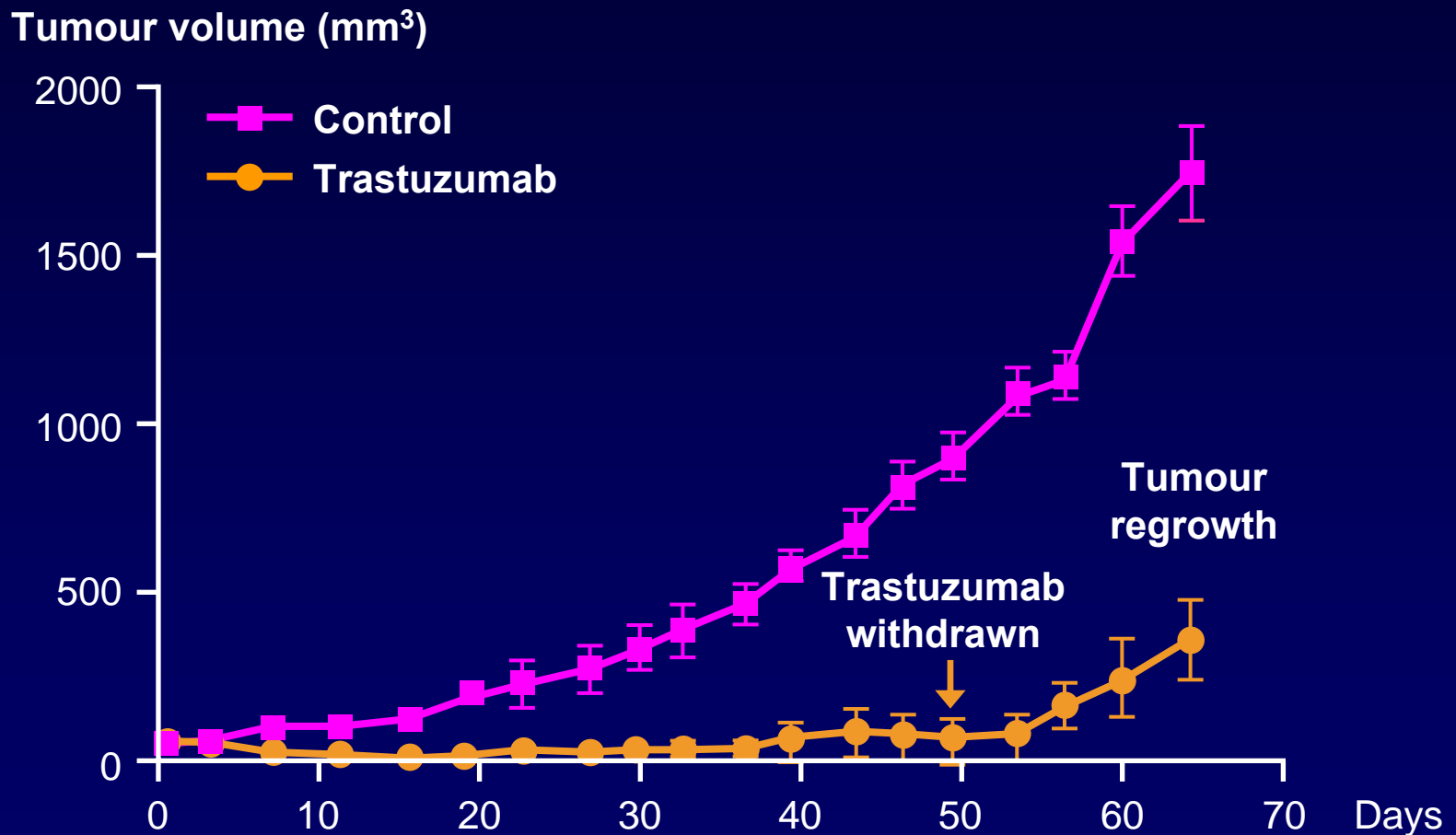
- Altered binding to ErbB2 receptor
 - Truncated ECD (p95 ErbB2)
 - Receptor mutations
 - Binding of other proteins (MUC 4)
- Loss of PTEN function leading to constitutive activation of the PI3K / AKT pathway
- Switching to alternate growth regulatory pathways e.g. IGFR pathway



**Relapse after adjuvant
treatment with trastuzumab
does not equal resistance**

Sustained Levels of Trastuzumab are Required for Tumour Inhibition

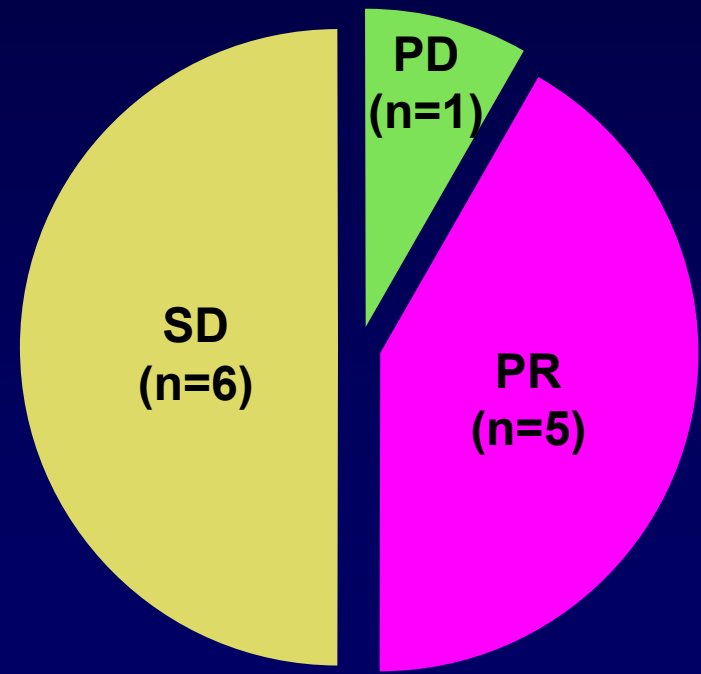
HER2-positive human breast xenograft (MCF-7)



Trastuzumab is Active in Retreatment, as Suggested by Preliminary Data from RHEA

- A non-randomised, open-label, 2-cohort (trastuzumab or trastuzumab + taxane), Phase II trial (n=80)
- Patients with HER2-positive MBC who have relapsed after receiving adjuvant trastuzumab
- Final results expected 2010

Interim analysis (n=12);
early stopping rule surpassed



PD, progressive disease

PR, partial response; SD, stable disease

Most Data However Are Derived From Experience with Trastuzumab Beyond Progression after First-line Treatment

- Non randomised series
- One controlled trial (GBG-26)
- Other approaches to maintain HER-2 suppression (eg lapatinib, pertuzumab)

Clinical Benefits from a 2nd Trastuzumab-based Regimen Have Been Demonstrated by Non-randomised Studies

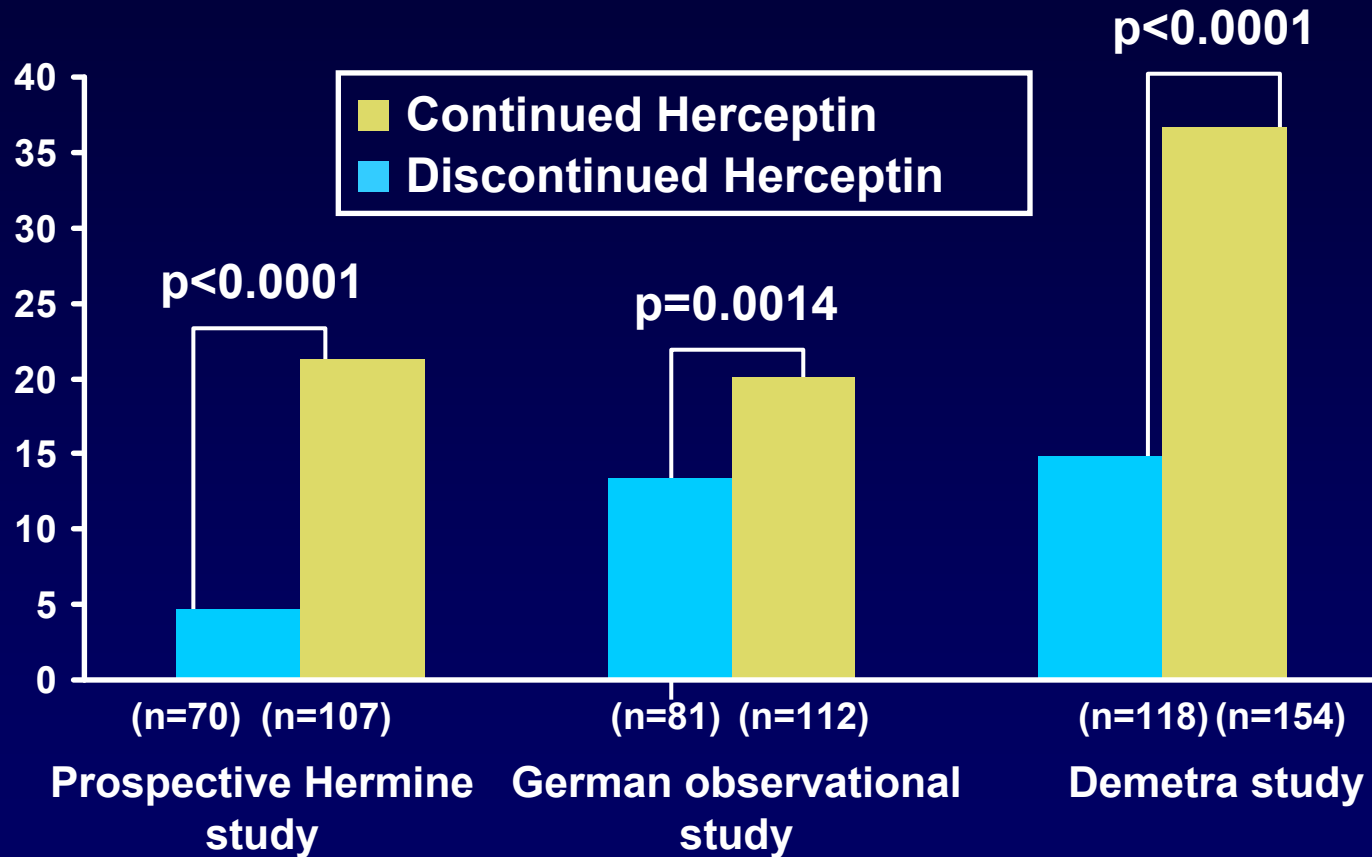
Study	n	ORR, %	TTP, months
Montemurro et al 2006	40	18	6.3
Adamo et al 2007	26	23	9.0
Fountzilas et al 2003	80	24	5.2
Bartsch et al 2006	54	26	6.0
Bachelot et al 2007	17	29	NR
Metro et al 2007	37	29	6.7
Garcia-Saenz et al 2006	47	30	4.0
Gelmon et al 2004	65	32	6.0
Stemmler et al 2005	23	39	NR
Tokajuk et al 2006	14	50	5.1
Hutka et al 2007	12	50	9.0

ORR, overall response rate

TTP, time to progression; NR, not reported

Trastuzumab Improves OS if Continued Beyond Progression

OS (months)



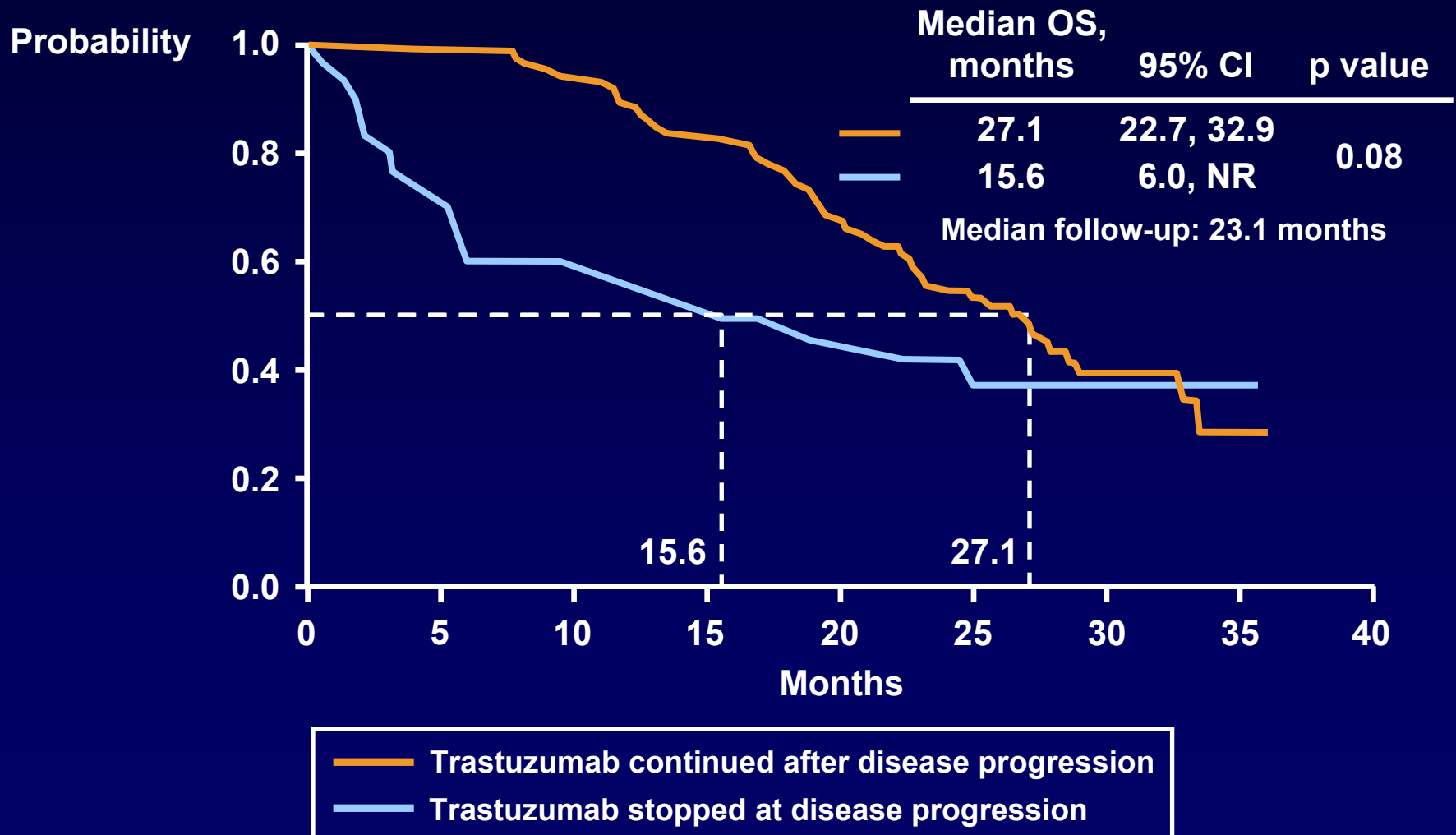
OS, overall survival

Extra J-M et al. *Breast Cancer Res Treat* 2006; 100 (Suppl 1): S102, abs 2064

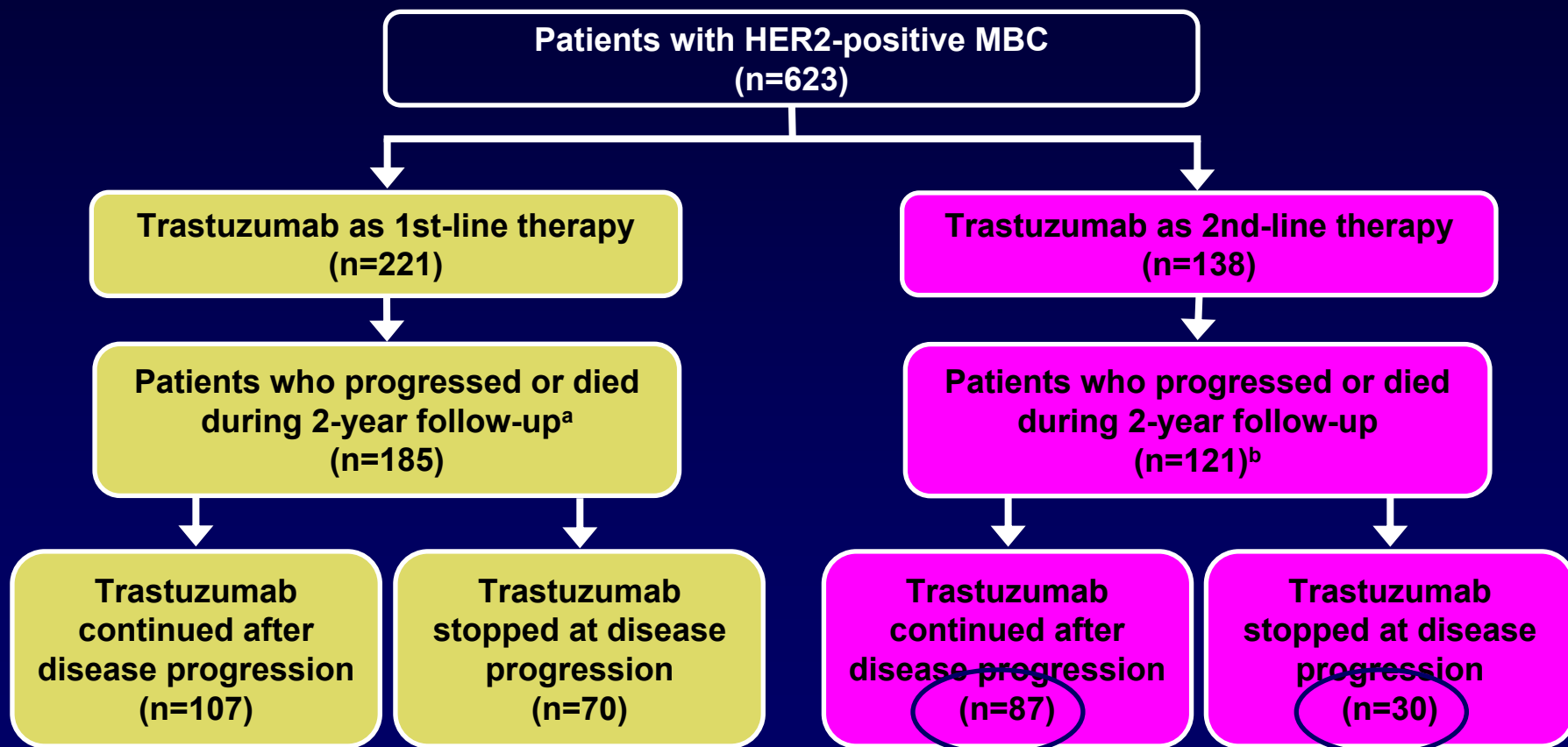
Jackisch C et al. *Breast Cancer Res Treat* 2007; 106 (Suppl 1): S186, abs 4059

Menard S et al. *J Clin Oncol* (Meeting Abstracts) 2008; 26: abs 1062

Impact of Continuing Trastuzumab Beyond Progression on 2nd-line MBC Therapy: OS from Initiation of Treatment

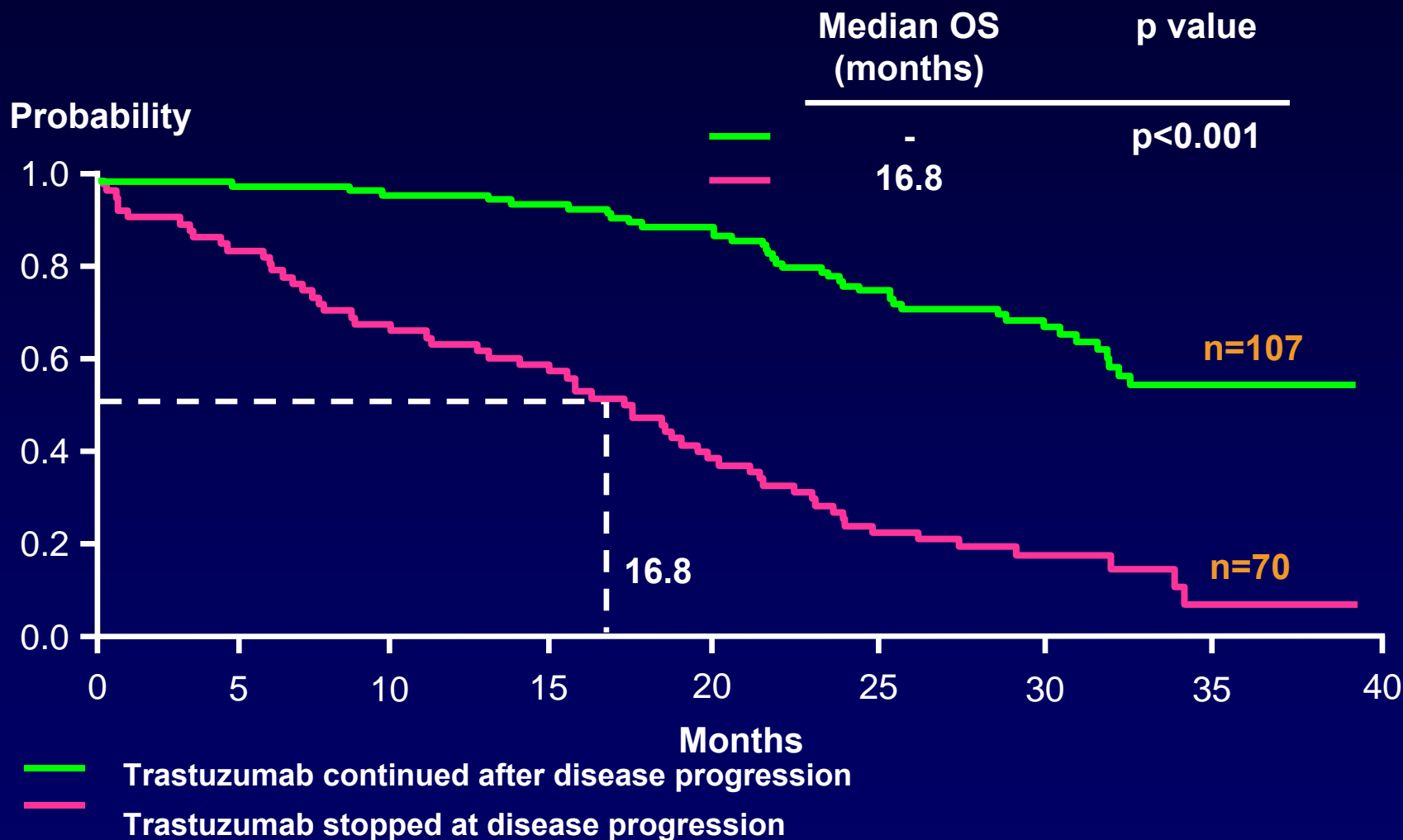


Hermine Cohort Description



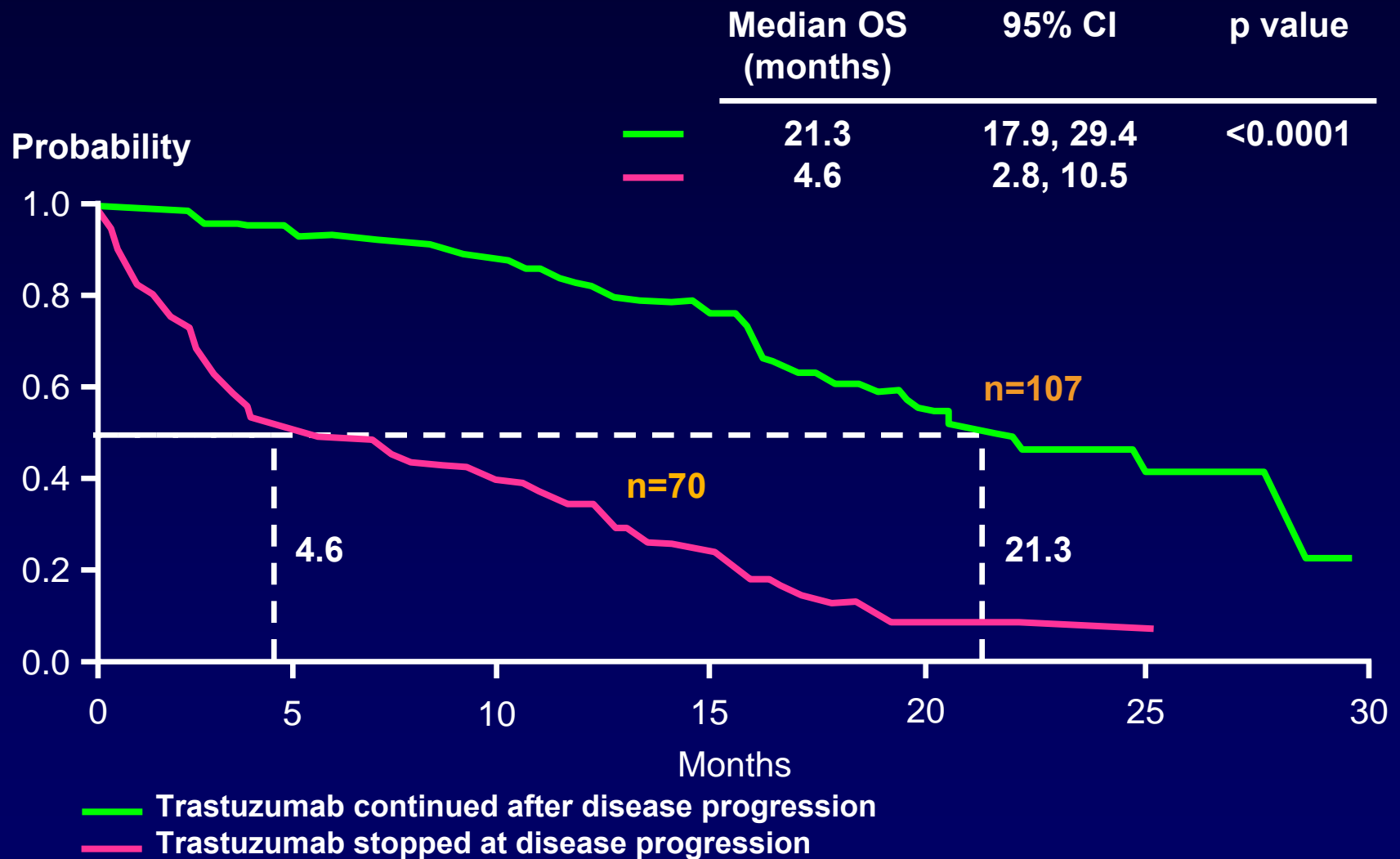
^aData unavailable for 8 patients; ^bData unavailable for 4 patients

French Hermine Study: Overall Survival from Initiation of Trastuzumab Treatment



TTP: 10.2 (range 9.1-11.5) vs 7.1 (range 6.1-7.9)

French Hermine Study: Overall Survival from Date of First Progression



GBG-26 is the First Randomised Phase III Study to Investigate Continuation of Trastuzumab

Progression under trastuzumab-based 1st-line therapy + taxane (n=114)^a
or
progression under trastuzumab monotherapy or non-taxane (n=42)

R

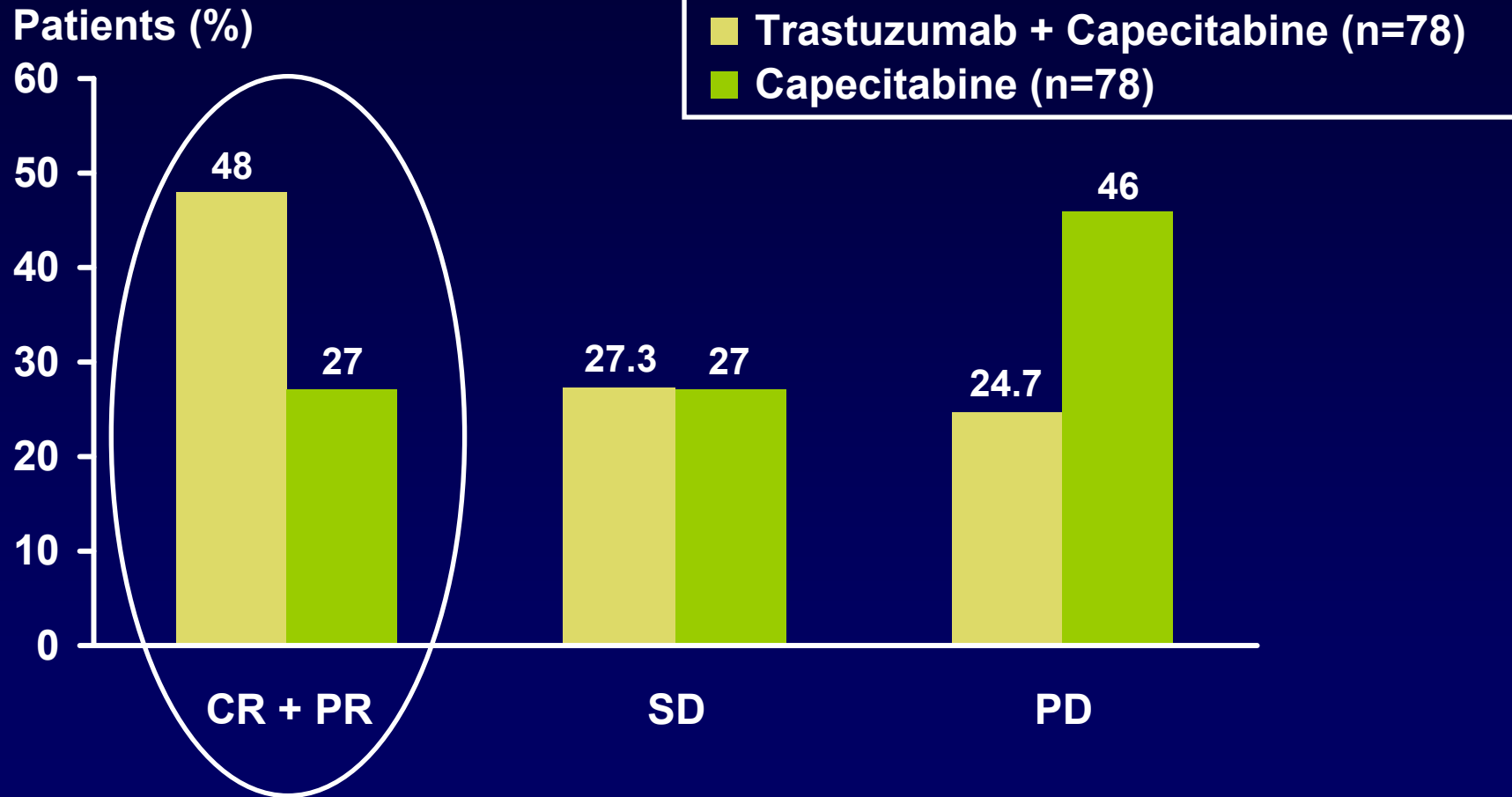
Capecitabine 1,250 mg/m²
bid d1-14 q21d
+
continuation of
trastuzumab 6 mg/kg q3w
(n=78)

Capecitabine 1,250 mg/m²
bid d1-14 q21d
(n=78)

Primary endpoint: TTP

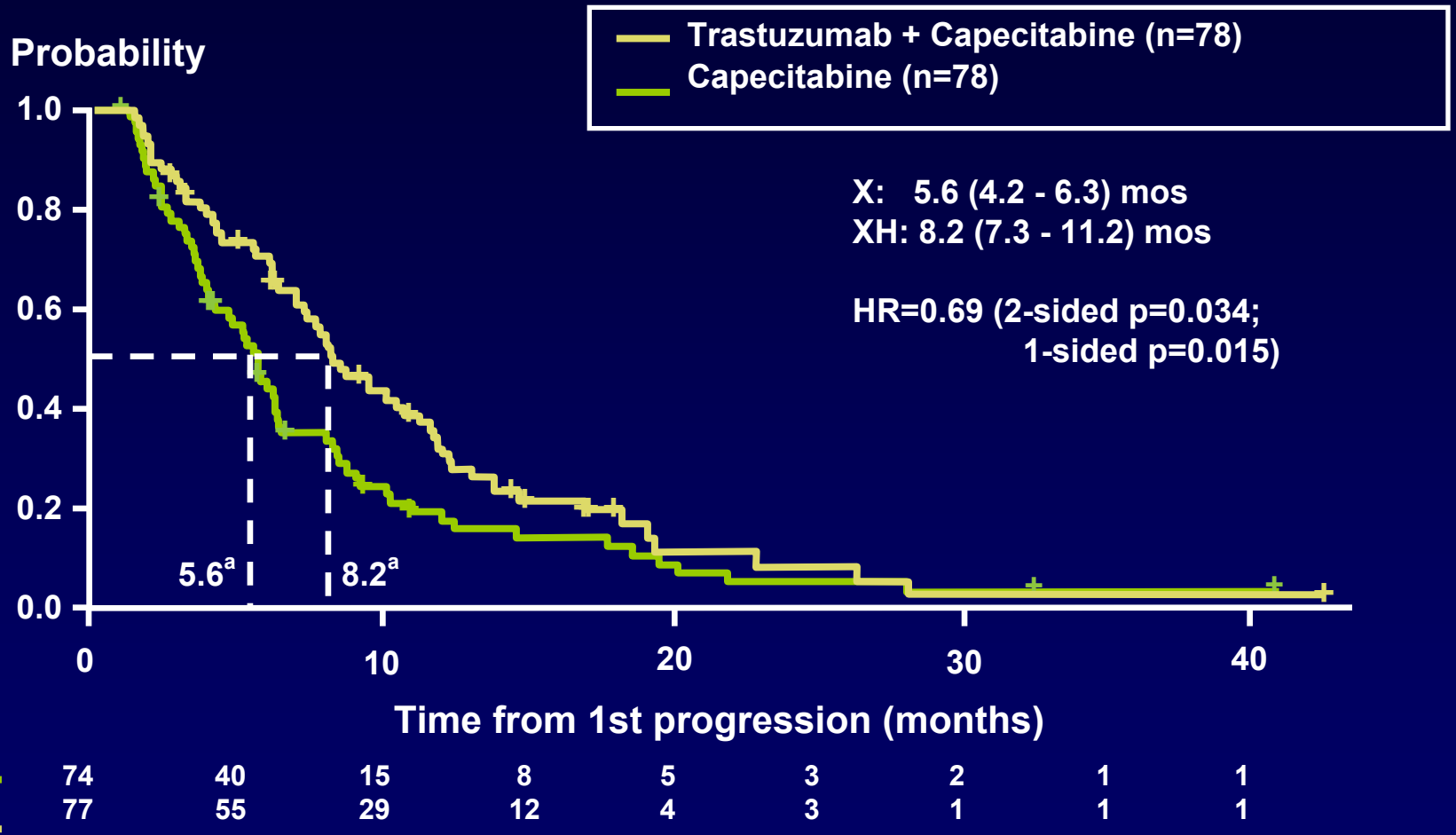
^a Includes 3 patients who received adjuvant Herceptin + taxane
R- randomisation

Continuation of Trastuzumab Doubles Response Rate in the GBG-26 Study



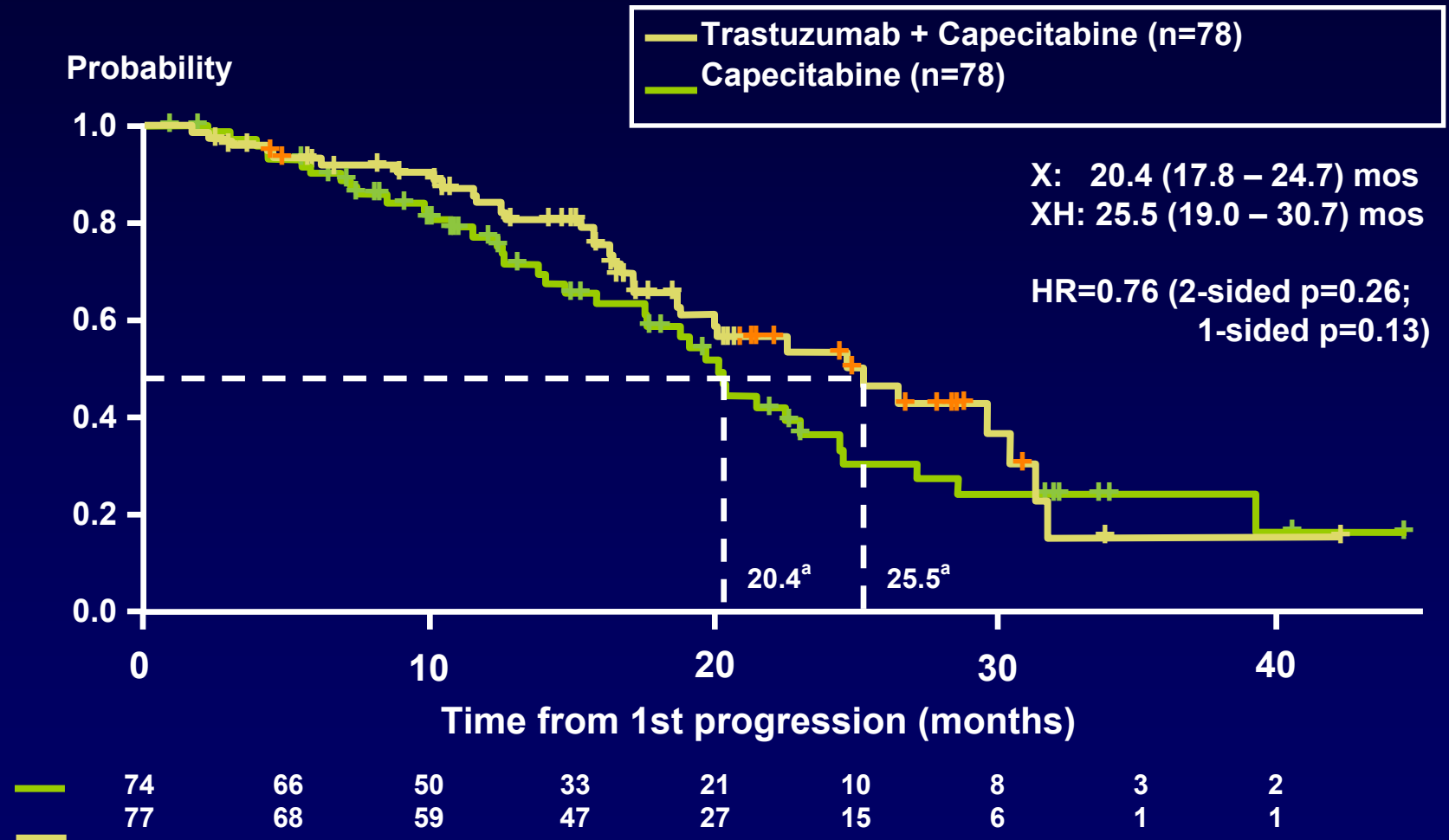
CR, complete response

Continuation of Trastuzumab Prolongs Time to Progression by Nearly 3 Months



^aMedian TTP in months
HR, hazard ratio

Continuation of Trastuzumab Suggests Improvement of Overall Survival



^aMedian survival in months

EGF100151: Study Design (Pivotal Lapatinib Registration Study)

Target N=528

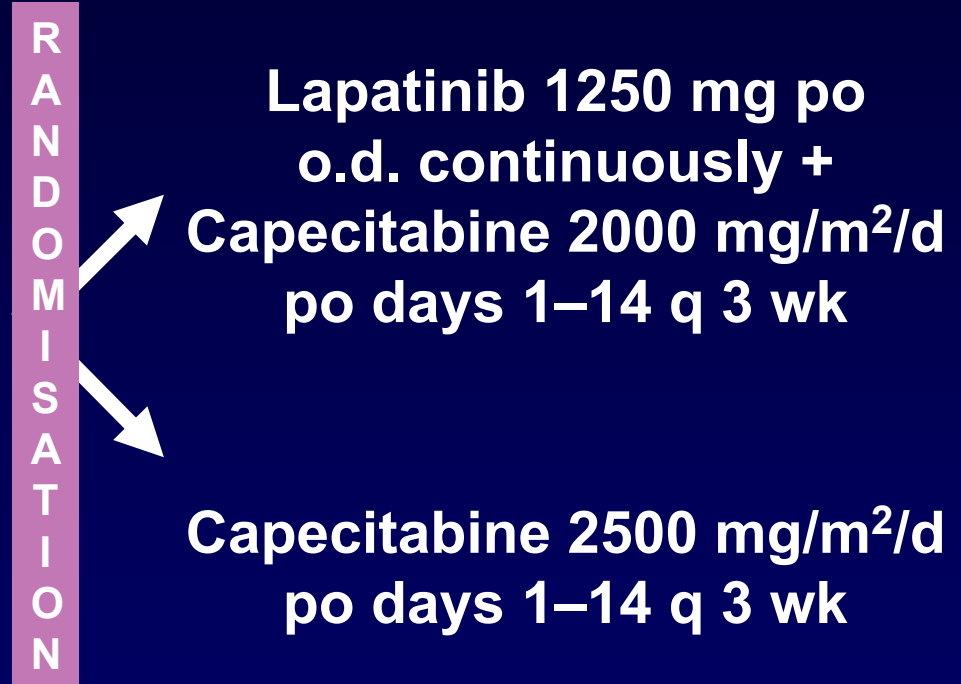
- Progressive, ErbB2+ve MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab^a
- No prior capecitabine
- Measurable disease by RECIST
- LVEF \geq institution LLN

Stratification:

- Disease sites
- Stage of disease

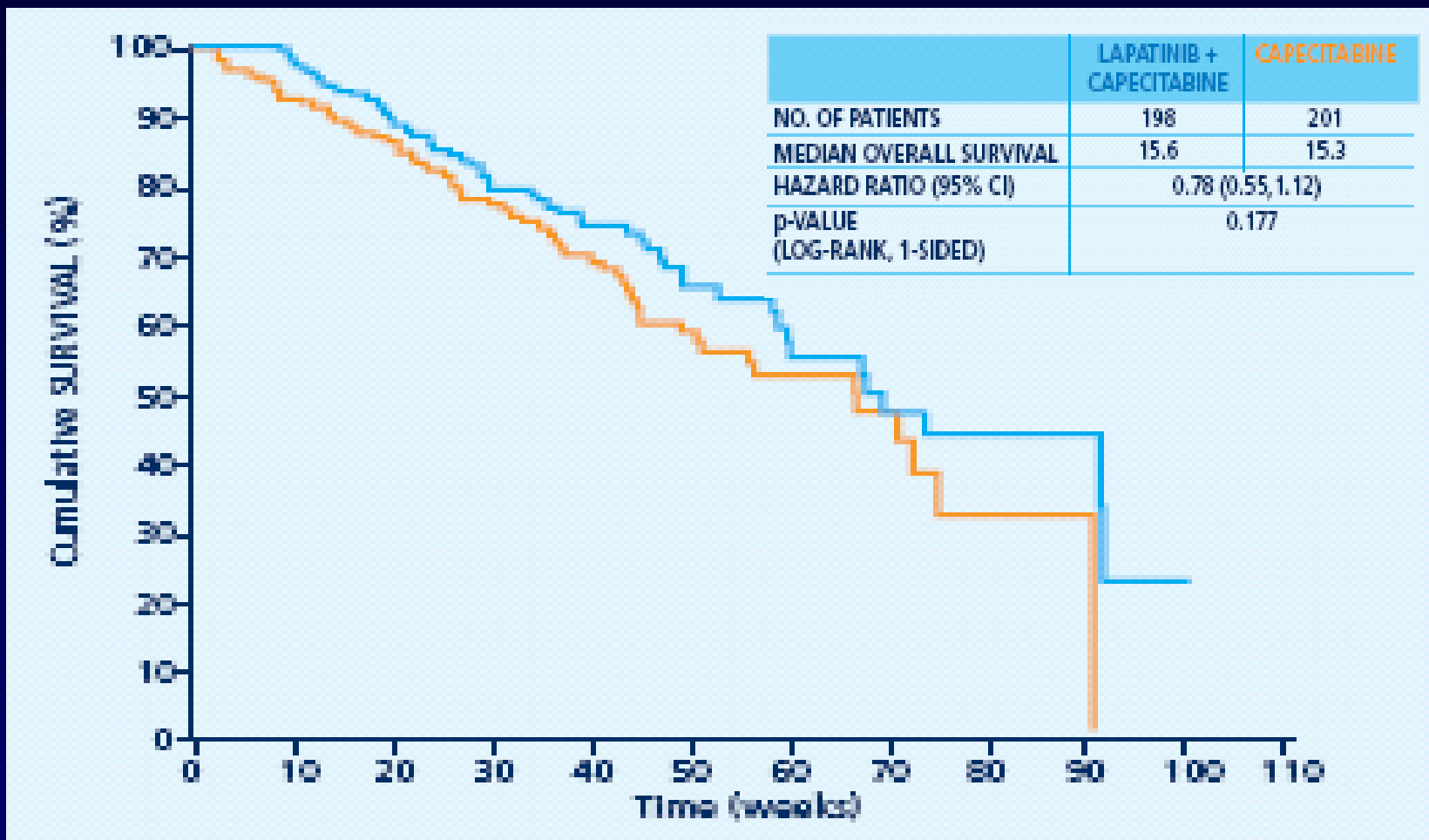
Patients on treatment until progression or unacceptable toxicity, then followed for survival

^aTrastuzumab must have been administered for metastatic disease



Overall Survival (3 April 2006 cut-off)

ITT population, 3 April 2006 cut-off, n=399



What does this trial prove?

- Always keep the brake on Her-2



Trastuzumab is the Drug of Choice for First Line Metastatic Breast Cancer

- The only drug licensed for this indication
- Proven efficacy
- Proven safety
- Acceptable tolerability

What drugs should we use with trastuzumab at metastatic relapse?

- Taxanes?
- Vinorelbine?
- Capecitabine?
- Gemcitabine?
- Other targeted therapies?

Phase III Trials: Trastuzumab Added to Chemotherapy in First-Line MBC

Chemotherapy	No. of Patients	RR, %		TTP, mos	
		C	C + T	C	C + T
Docetaxel ^[1]	186	34	61	6.1	11.7
Paclitaxel ^[2]	188	17	41	3.0	6.9
Paclitaxel ^[3]	124	56	75	9.1	12.3
AC ^[2]	281	42	56	6.1	7.8

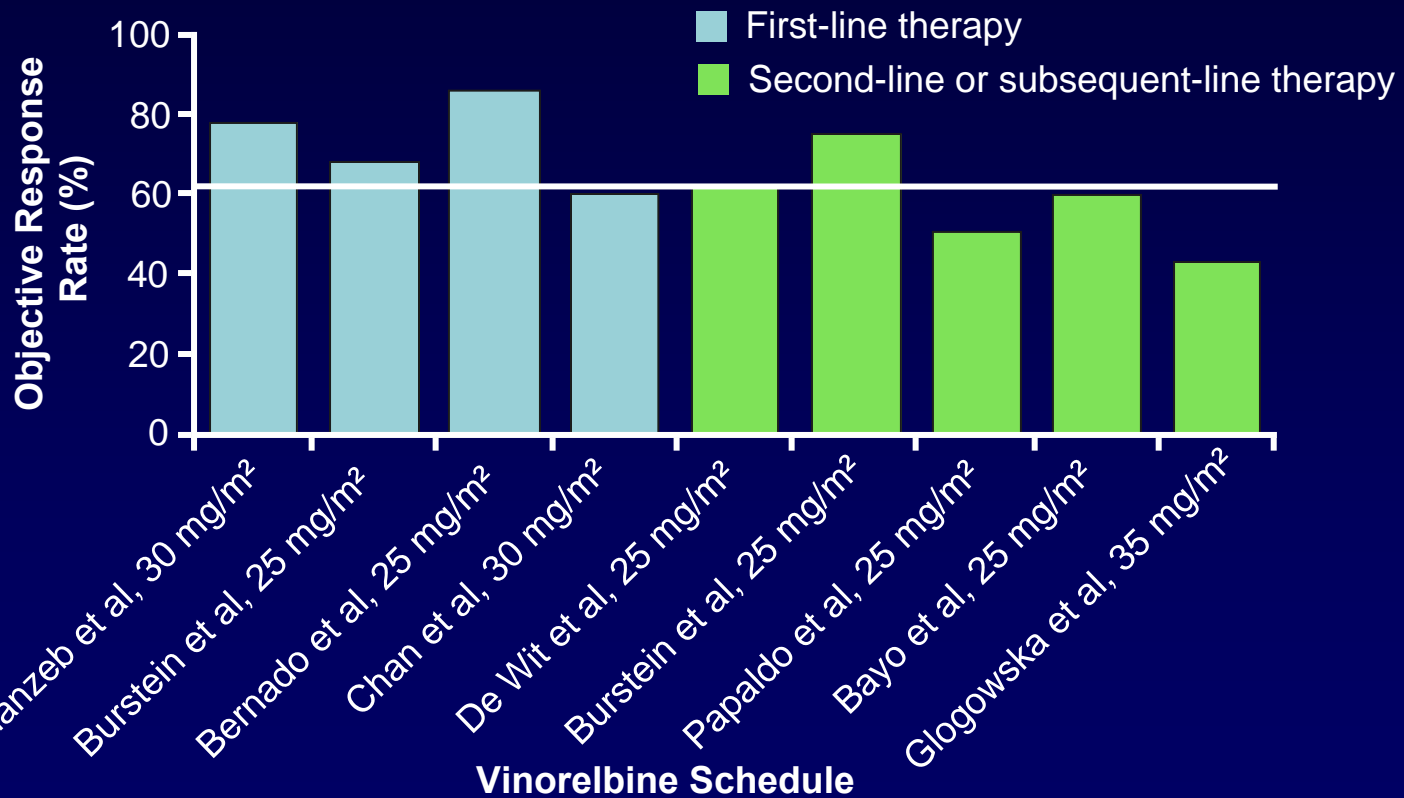
1. Marty M, et al. *J Clin Oncol.* 2005;23:4265-4274.
2. Slamon DJ, et al. *N Engl J Med.* 2001; 344:783-792.
3. Gasparini G, et al. *Breast Cancer Res Treat.* 2007;101:355-365.

Phase II Trials: Trastuzumab Added to Chemotherapy in MBC

Chemotherapy	Line of Therapy	No. of Patients	RR, %	TTP
Vinorelbine ^[1]	1st	54	68	5.6
Vinorelbine ^[2]	1st	69	63	9.9
Vinorelbine ^[3]	1st	40	78	18
Capecitabine ^[4]	1st	43	63	Not reached
Gemcitabine ^[5]	3rd*	64	38	5.8

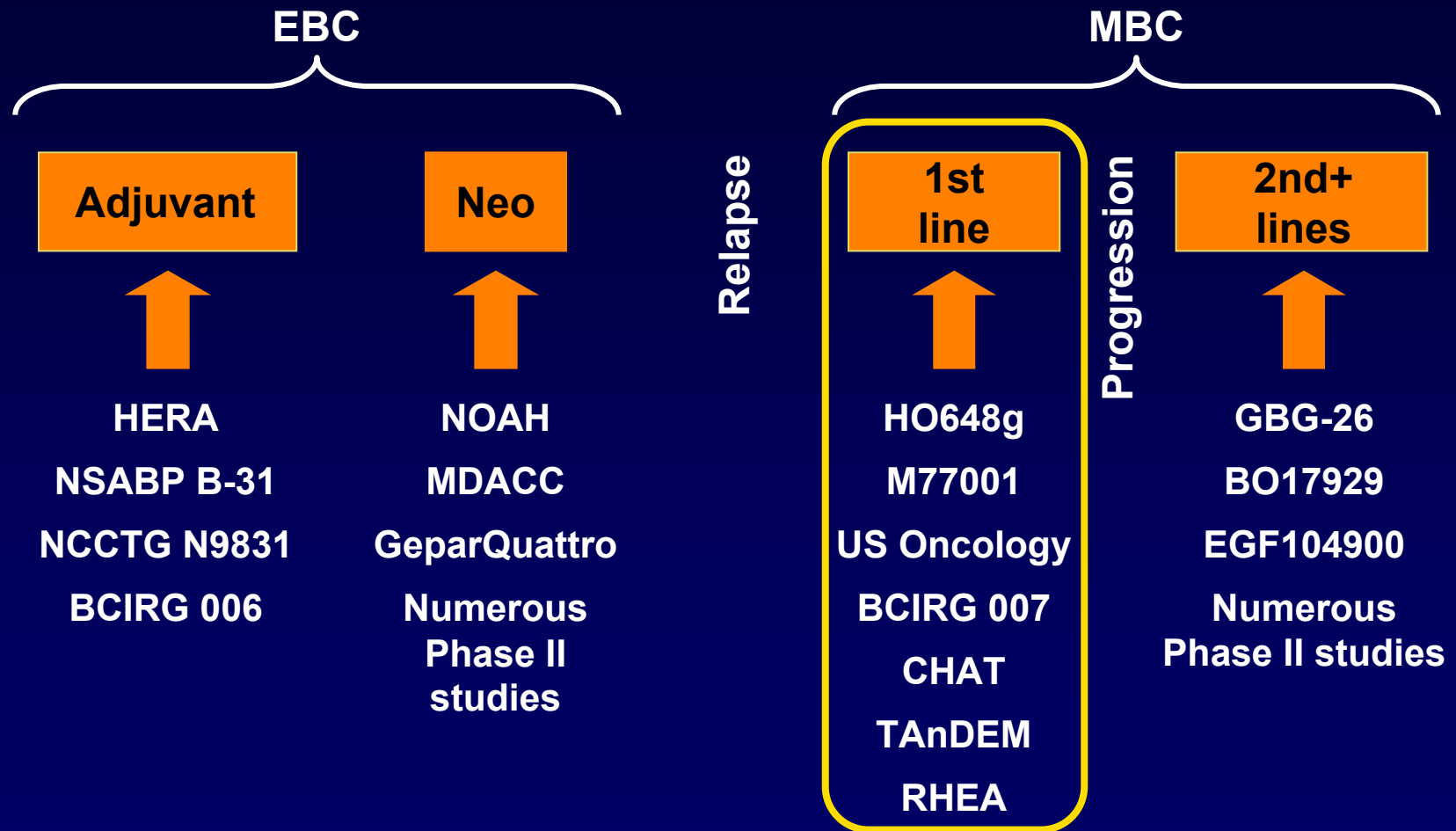
1. Burstein HJ, et al. *J Clin Oncol*. 2003;21:2889-2895. 2. Jahanzeb M, et al. *The Oncologist*. 2002;7:410-417. 3. Burstein HJ, et al. *J Clin Oncol*. 2001;19:2722-2730. 4. Xu L, et al. SABCs 2006. Abstract 2065. 5. O'Shaughnessy JA, et al. *Clin Breast Cancer*. 2004;5:142-147.

Response Rates in Phase II Trials of Trastuzumab + Vinorelbine



At least 50% of the patients benefit

Trastuzumab is the Foundation of Care for Women with HER2-positive Breast Cancer



HER2, human epidermal growth factor receptor 2
EBC, early breast cancer; MBC, metastatic breast cancer

Trastuzumab Beyond Progression: Clinical Implications

“Continuation of Trastuzumab and sequential administration of endocrine therapy, chemotherapy or biologic therapy at the time of progression is the best option for patients with HER2 positive metastatic breast cancer”

HER2 *rules* and sets the rules

- HER2 amplification, when present, results in a dominant phenotype in breast cancer
- In therapy of HER2 + breast cancer whatever approach we choose (hormones or chemotherapy) it has to be given with anti-HER therapy upfront
- Trastuzumab is the current drug of choice for first line metastatic breast cancer

THE END

- Thank you
- Merci
- Obrigada
- Efcharisto
- Gracias

With thanks to Veronique!

