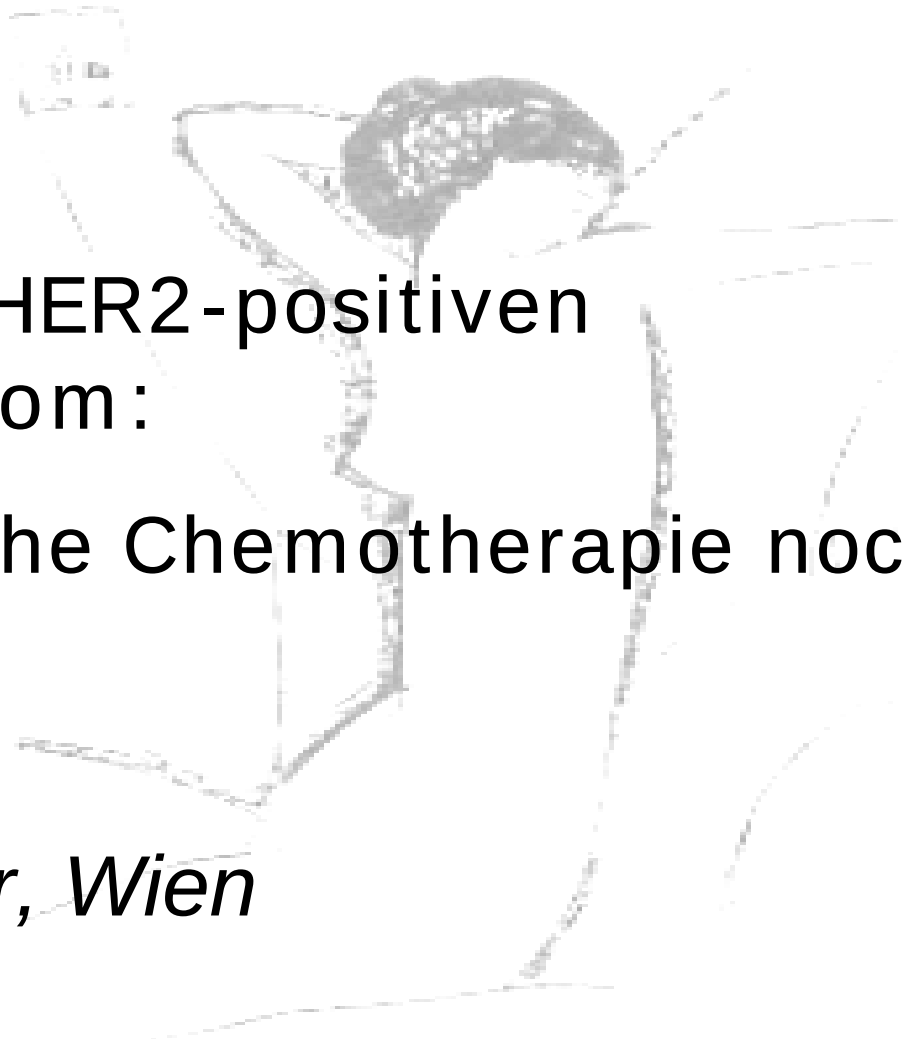


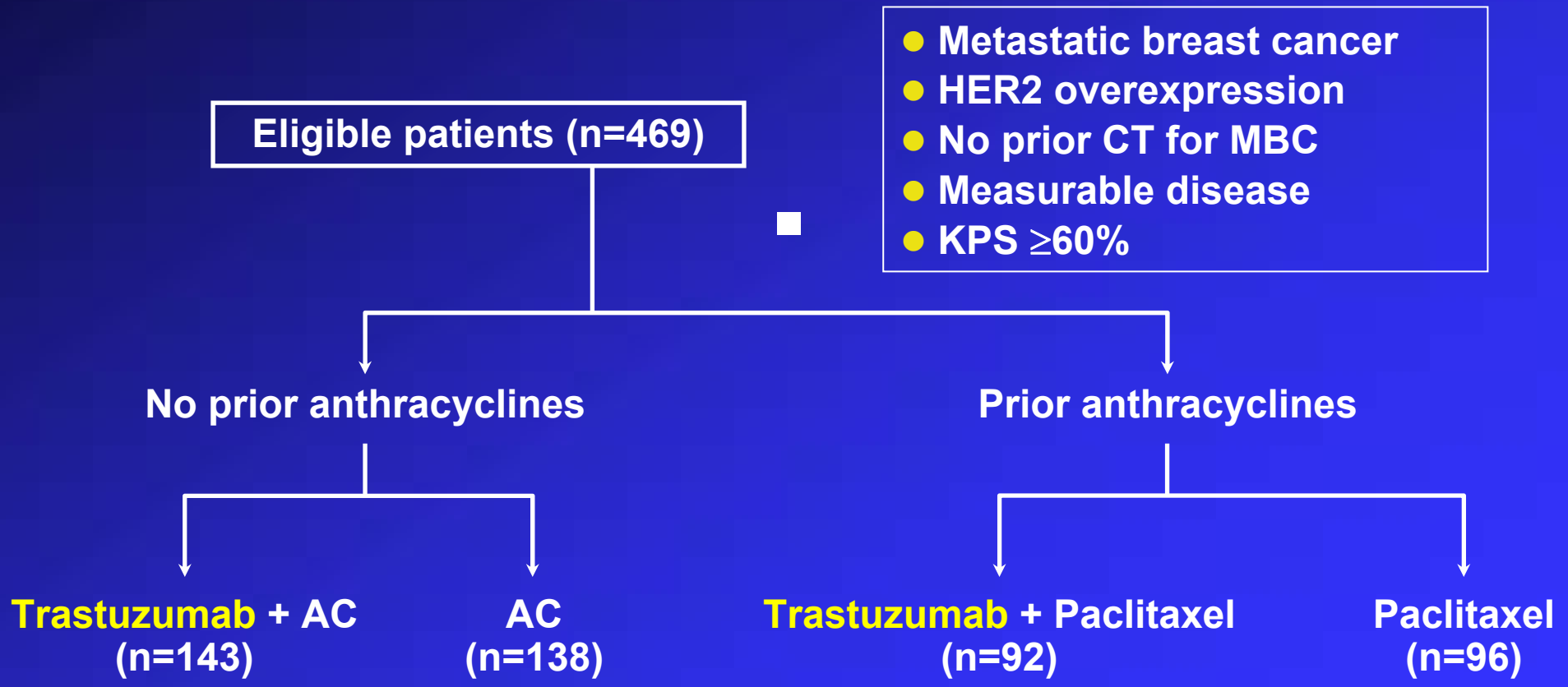
Therapie des HER2-positiven Mammakarzinom:

Ist zytostatische Chemotherapie noch nötig?

Günther Steger, Wien

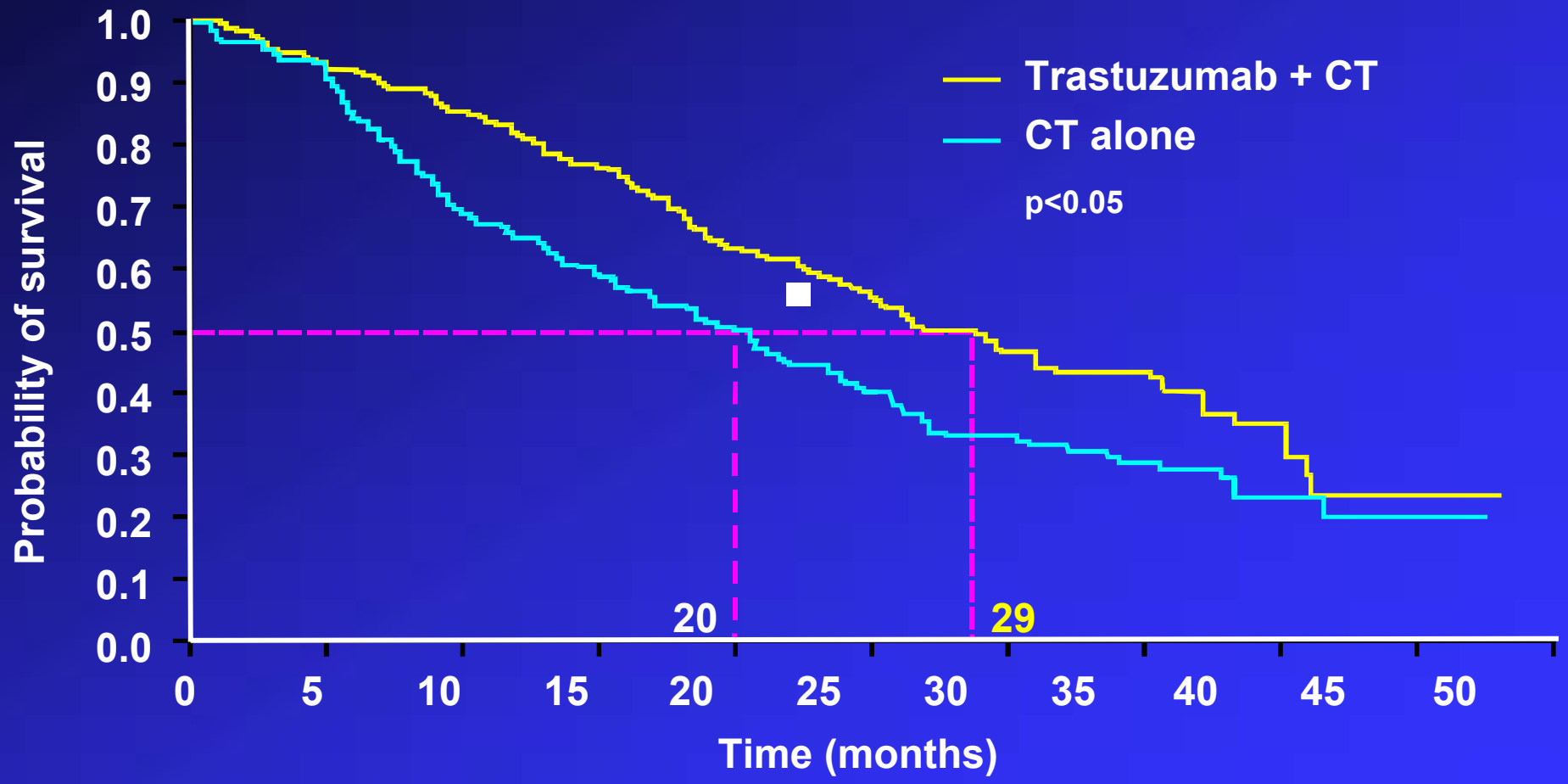
Pivotal phase III trial – Trastuzumab in combination with chemotherapy

Design and enrolment

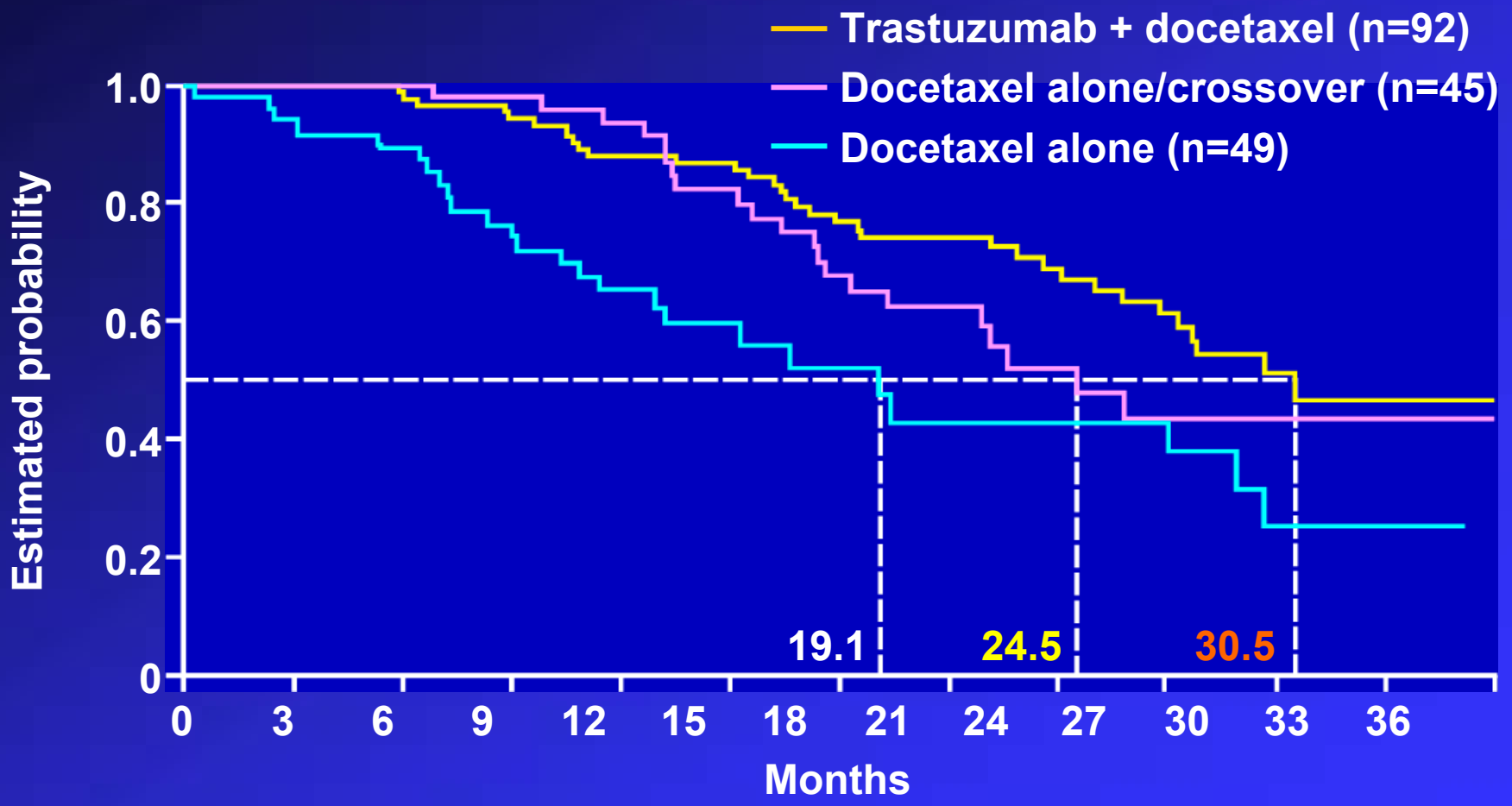


AC = doxorubicin/epirubicin + cyclophosphamide

Overall survival – HER2 3+ patients

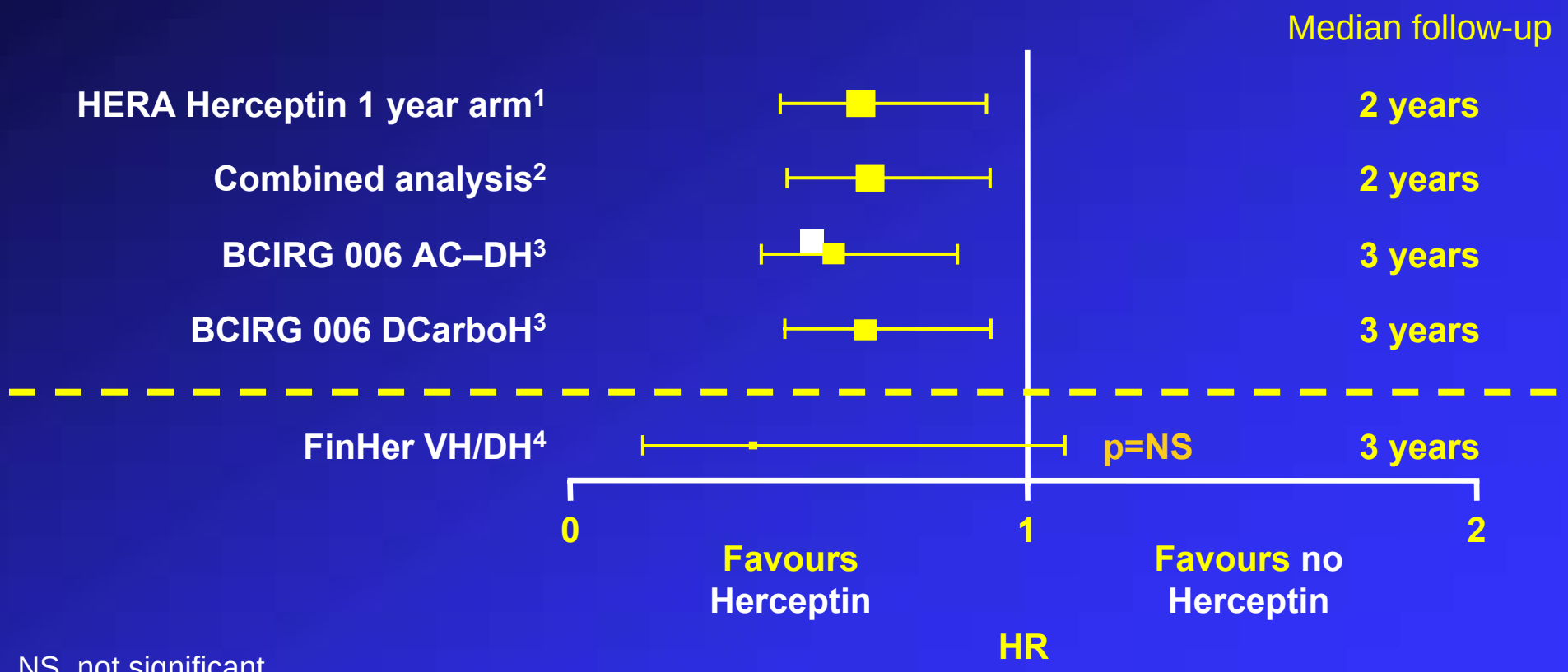


Docetaxel +/- Trastuzumab
Overall Survival II



Intent-to-treat population, 12-month cut-off

Adjuvant trastuzumab trials: summary of Overall Survival data to date



NS, not significant

1. Smith I et al. Lancet 2007;369:29–36; 2. Romond EH et al. N Engl J Med 2005;353(16):1673–84;
3. Slamon D et al. SABCS 2006;Abstract 52; 4. Joensuu H et al. N Engl J Med. 2006;354:809-20

Tumor characteristics & choice of therapy

Advanced Breast Cancer

HER2$^{+++/FISH+}$ (10-15%)	ER+ and/or PgR+ (30-70 %)	HER2^{negativ} & HR^{negativ} (10 - 15%)
Trastuzumab ± Chemotherapy ± Hormonal Tx ???	Hormonal Tx → Chemotherapie ± Bevacizumab	Chemotherapy ± Bevacizumab

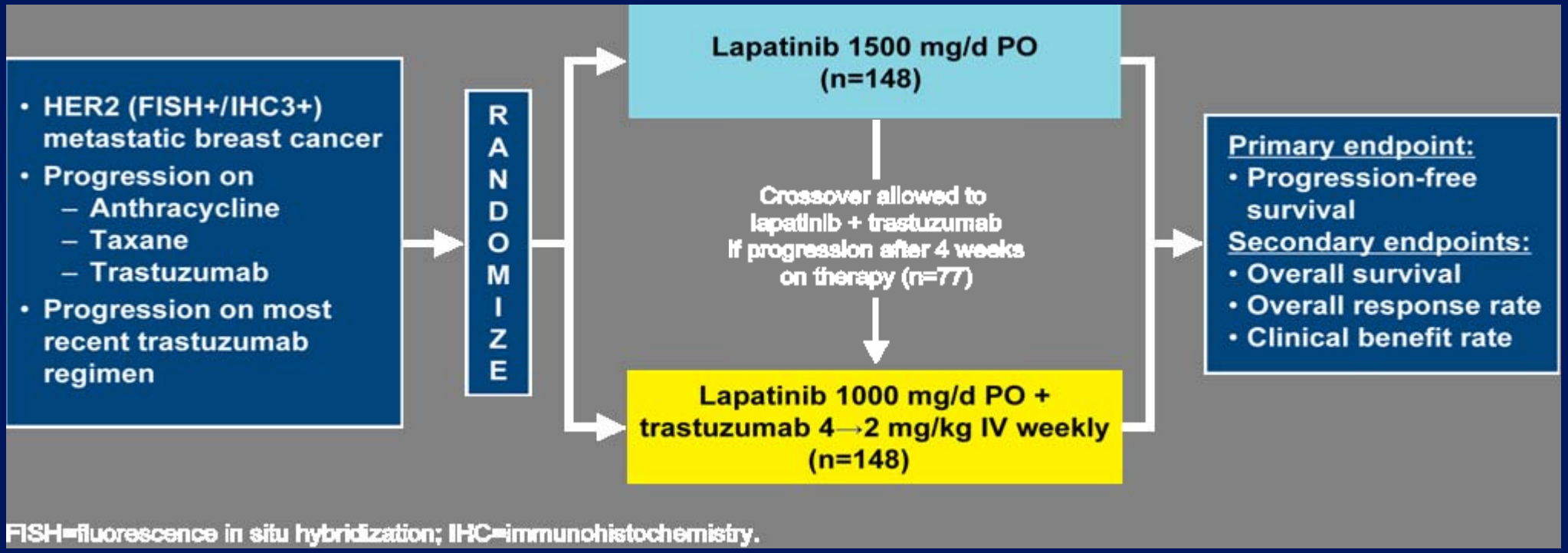
Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy

K Blackwell[1], HJ Burstein[2], G Sledge[3], S Stein[4], C Ellis[4], M Casey[4], J Baselga[5], J O'Shaughnessy[6]

[1]Duke University Medical Center, Durham, NC; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Indiana University Cancer Center, Indianapolis, IN; [4]Medicine Development Center Oncology, GlaxoSmithKline, Collegeville, PA; [5]Vall d'Hebron University Hospital, Barcelona, Spain; [6]Baylor Sammons Cancer Center, Texas Oncology, PA, US Oncology, Dallas, TX

SABCS 2009

EGF104900: Phase III Study Evaluated Dual HER2 Blockade



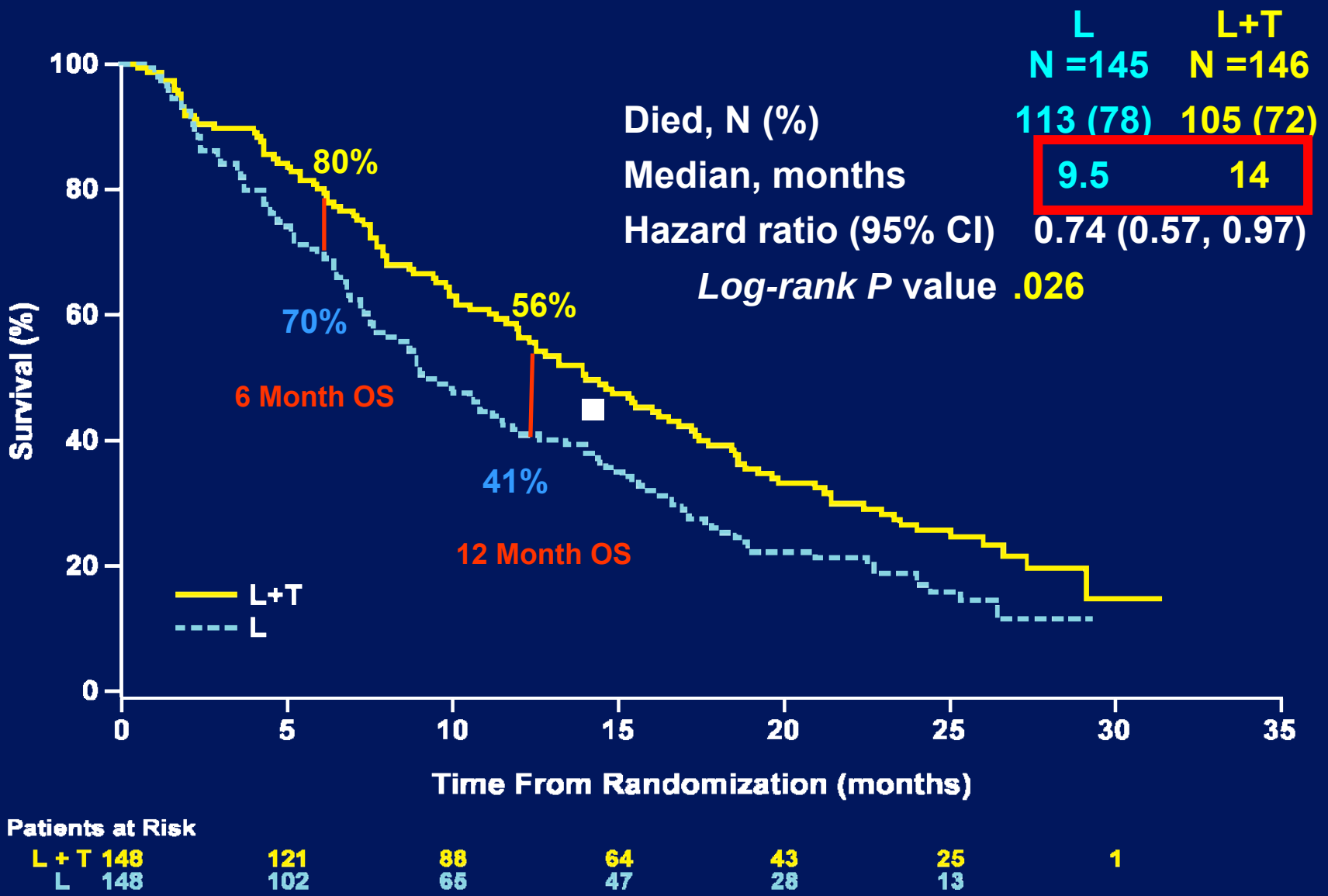
FISH=fluorescence in situ hybridization; IHC=immunohistochemistry.

ASCO 2008 Primary Data Presentation

	Lapatinib N=145	Trastuzumab + lapatinib N=146
Overall Response Rate, %	6.9	10.3
(95% CI)	(3.4, 12.3)	(5.9, 16.4)
Odds Ratio (95% CI)	1.5 (0.6, 3.9)	
	P= .46	
Clinical Benefit Rate, %	12.4	24.7
(95% CI)	(7.5, 18.9)	(17.9, 32.5)
Odds Ratio (95% CI)	2.2 (1.2, 4.5)	
	P= .01	

O'Shaughnessy, et al. ASCO 2008; Blackwell, et al. J Clin Oncol
doi:10.1200/JCO.2008.21.4437

Updated Overall Survival in ITT



ABCSG -31 / ALTTO

Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

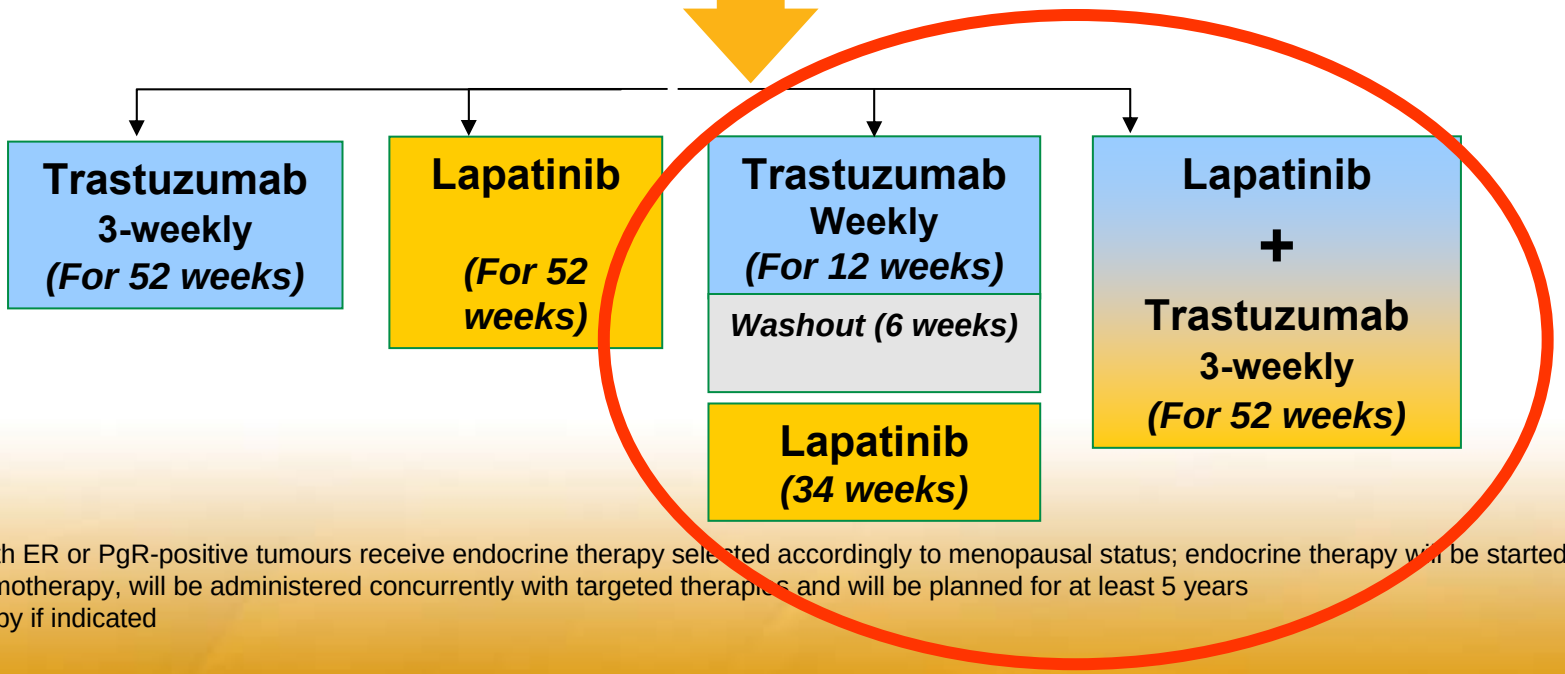
Completion of ALL (neo)adjuvant chemotherapy prior to targeted therapy

Locally-determined HER2-positive invasive breast cancer

Centrally-determined HER2+; ER and PgR

Surgery, complete (neo)adjuvant anthracycline-based chemotherapy
(selected from an approved list)

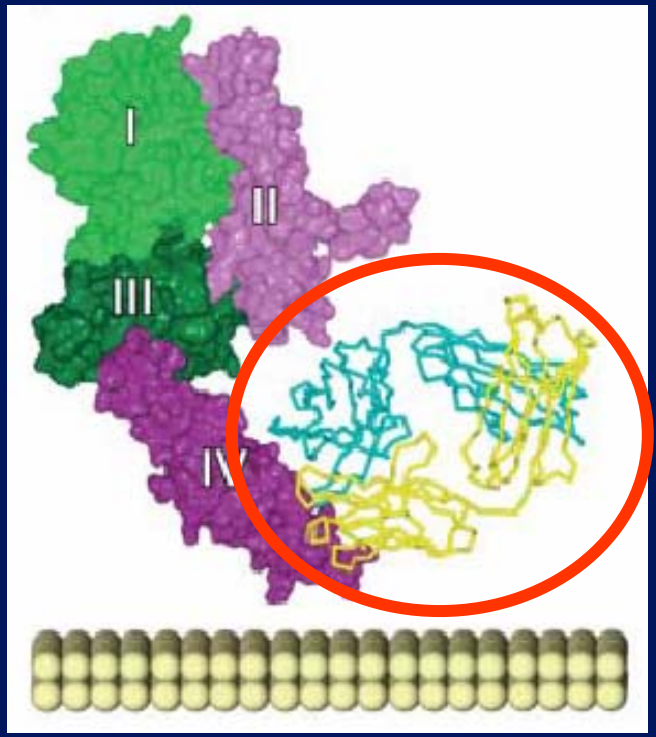
LVEF ≥ 50%



- Patients with ER or PgR-positive tumours receive endocrine therapy selected accordingly to menopausal status; endocrine therapy will be started after the end of chemotherapy, will be administered concurrently with targeted therapies and will be planned for at least 5 years
- Radiotherapy if indicated

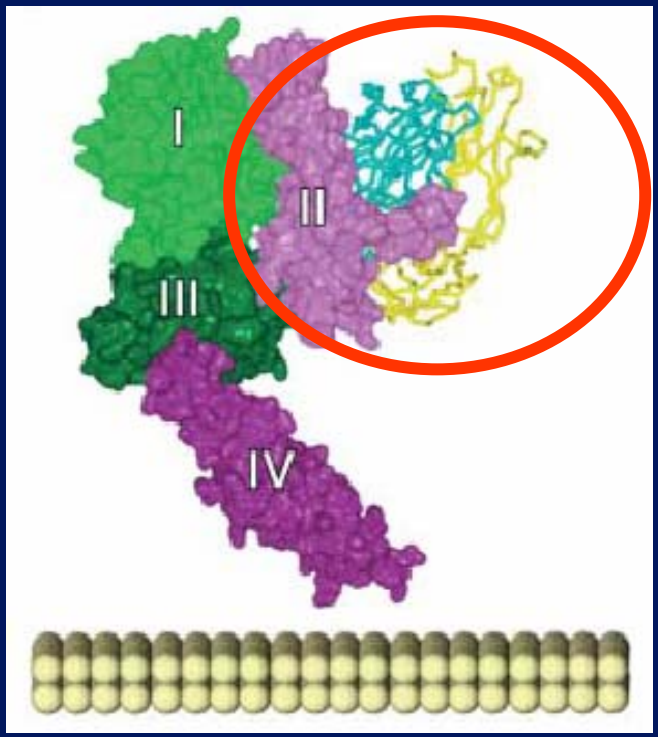
Trastuzumab and pertuzumab bind to distinct epitopes on HER2 extracellular domain

Trastuzumab



- Activates antibody-dependent cellular cytotoxicity
- Inhibits HER2-mediated signalling
- Inhibits shedding and, thus, formation of new p95
- Inhibits HER2-related angiogenesis

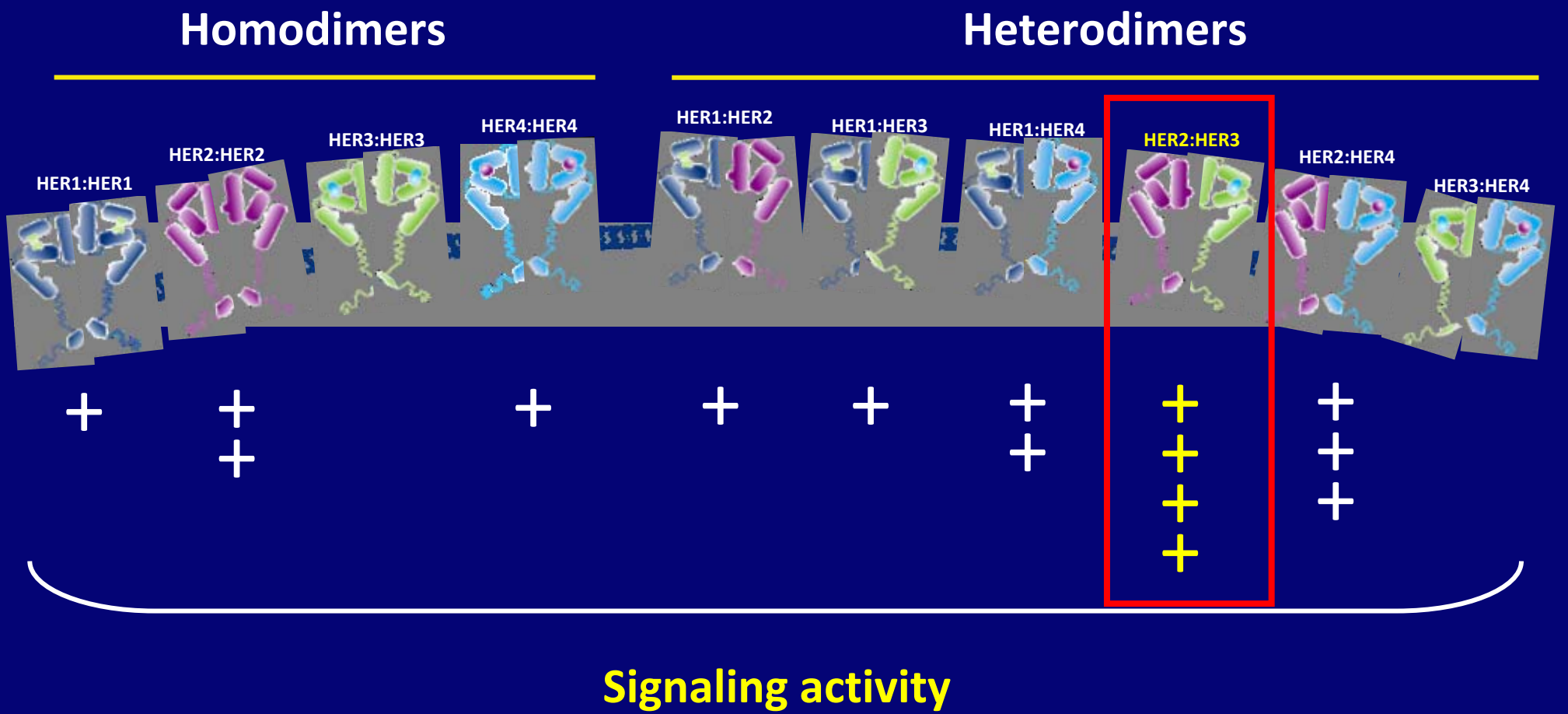
Pertuzumab



- Activates antibody-dependent cellular cytotoxicity
- **Prevents receptor dimerisation**
- Potent inhibitor of HER2/HER2- and HER2/HER3-mediated signalling pathways

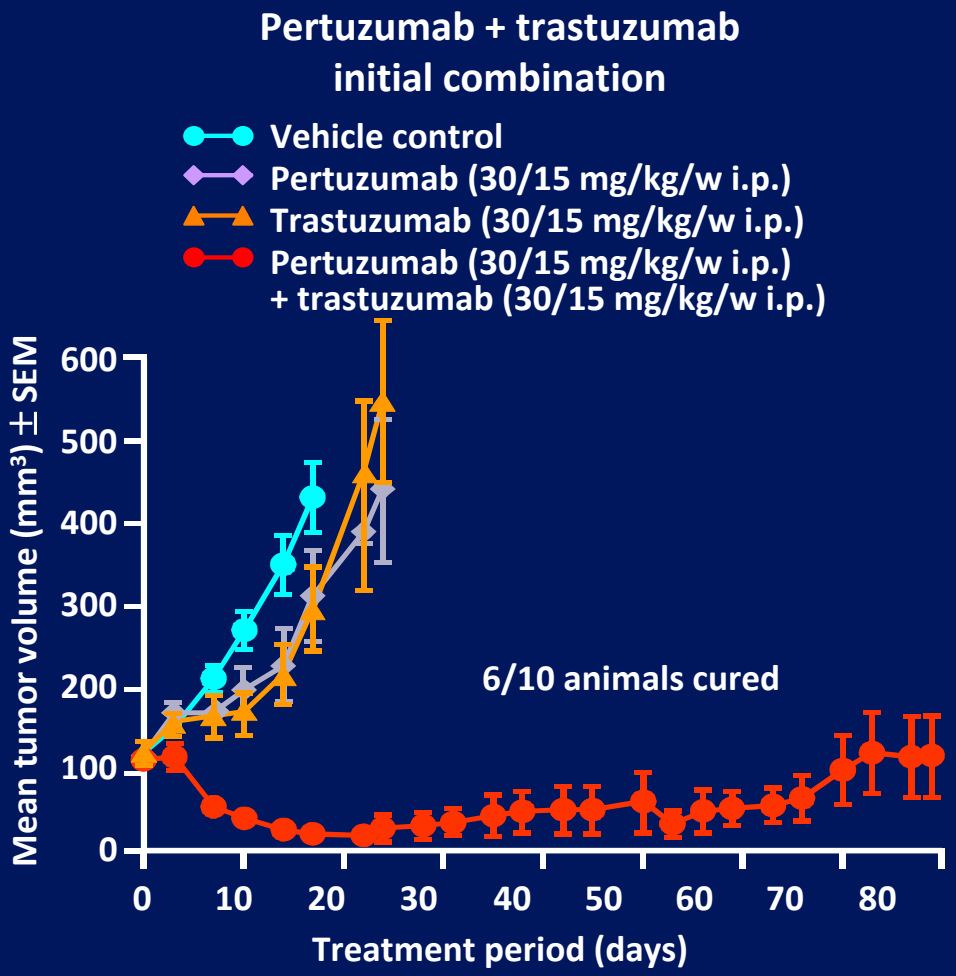
Hubbard 2005

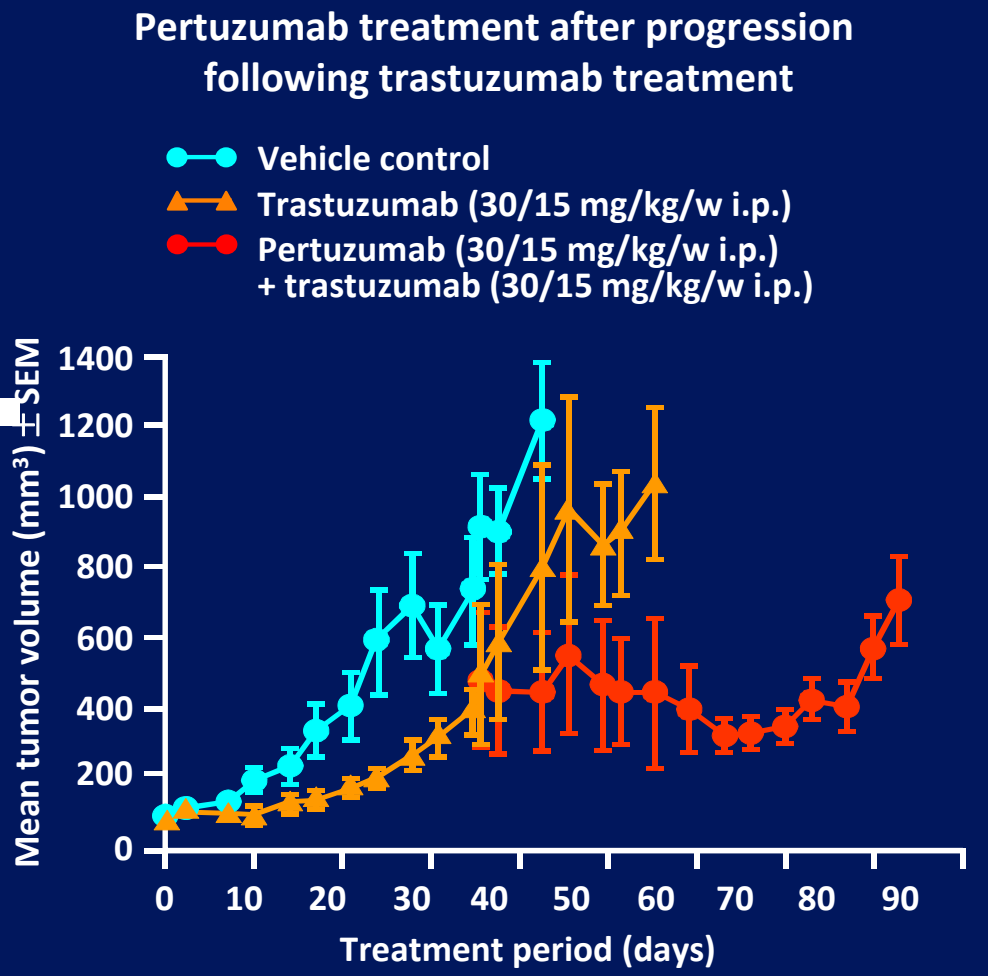
HER2:HER3 dimers may provide an escape mechanism from trastuzumab



Tzahar et al. Mol Cell Biol 1996;
Sergina et al. Nature 2007

In preclinical models, pertuzumab and trastuzumab have a synergistic effect

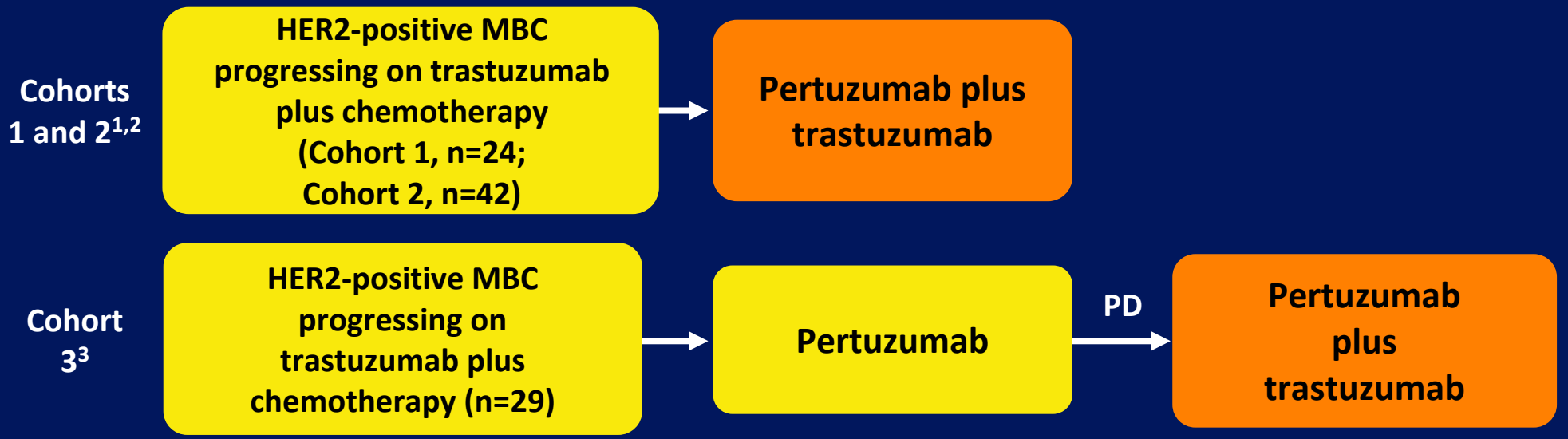




Xenograft model KPL-4
i.p., intraperitoneally; w, week

Scheuer et al, Clin Cancer Research 2009 (in press)

BO17929: a Phase II trial of pertuzumab plus trastuzumab in HER2-positive MBC patients progressing during trastuzumab-based therapy



- Primary objectives
  - Safety (evaluate safety of combined antibody treatment)
  - Efficacy (response rate plus stabilization of disease = clinical benefit rate)
- Heavily pretreated population
  - Median 3 prior lines of therapy in the metastatic setting

[1]Gelmon et al 2008; [2]Baselga et al 2009; [3]Cortés et al 2009; http://www.clinicaltrials.gov/

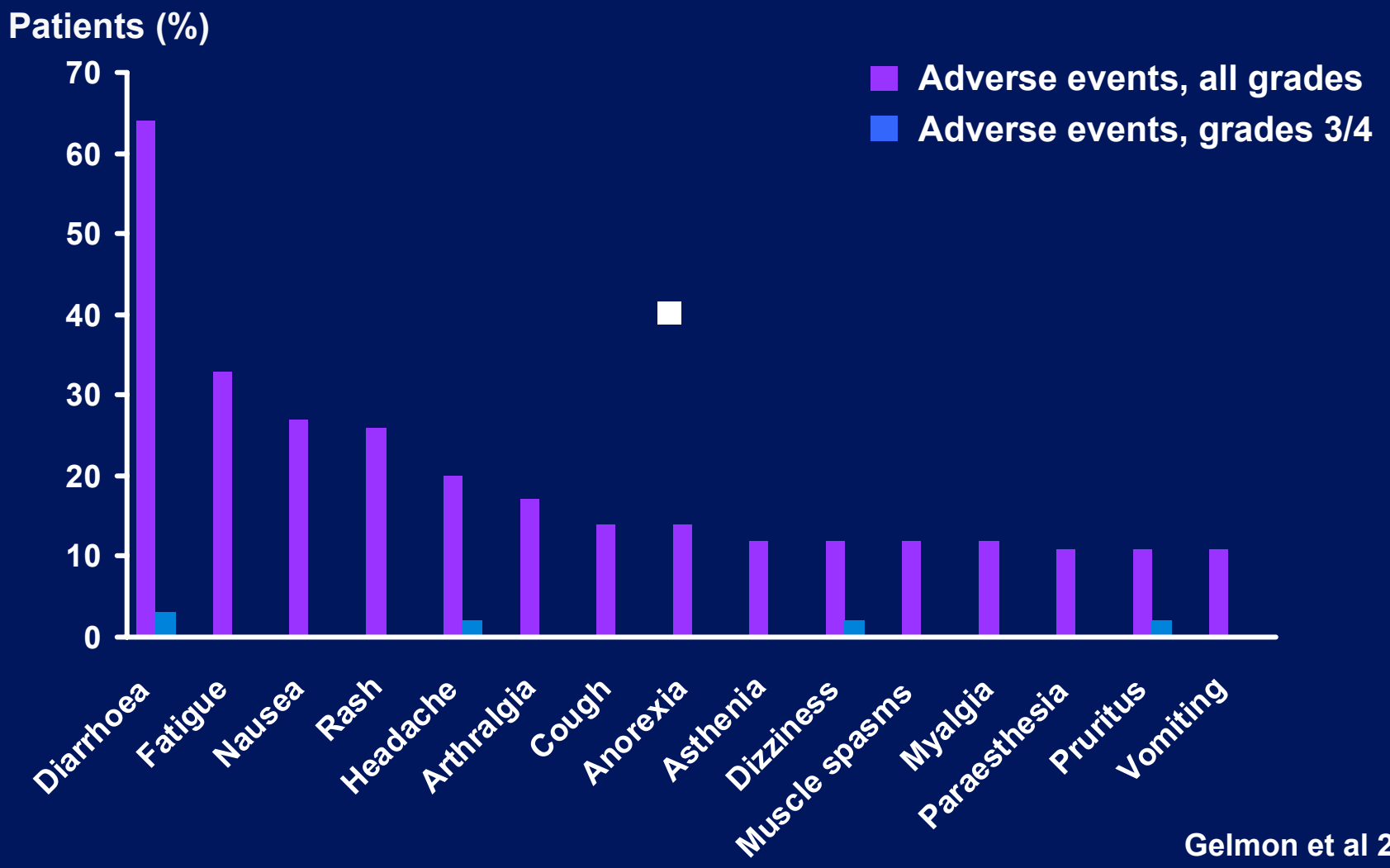
BO17929: pertuzumab plus trastuzumab provides clinical benefit to patients progressing on trastuzumab-based therapy

Response, n (%)	Cohort 1 and 2 n=66
Complete response (CR)*	**5 (7.6%)**
Lymph	4
Lung	1
Partial response (PR)*	**11 (16.7%)**
Lymph	2
Lung	1
Liver	8
Breast	2
Mediastinum	1
ORR	**16 (24.2%)**
Stable disease (SD) for 6 months (≥ cycle 8)	17 (25.8%)
Clinical benefit rate	**33 (50.0%)**
Progressive disease	33 (50.0%)
Median PFS	**24 weeks**

*Sites of target lesions shown for patients with objective response

Baselga et al 2009; Gelmon et al 2008

Trastuzumab + pertuzumab : Toxicity



Gelmon et al 2008

Neoadjuvant Trastuzumab + Pertu
NEOSPHERE

SABCS 2010

FEC, 5-fl uracil, epirubicin, cyclophosphamide

Trastuzumab-DM1: first-in-class antibody–drug conjugate (ADC)

Target expression: HER2

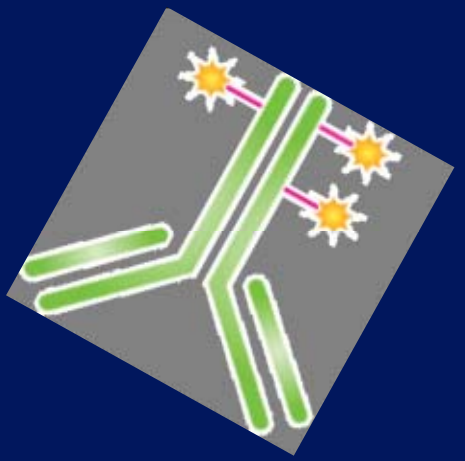
Monoclonal antibody: trastuzumab

Cytotoxic agent: DM1

Highly potent chemotherapy
(maytansine derivative)

Linker

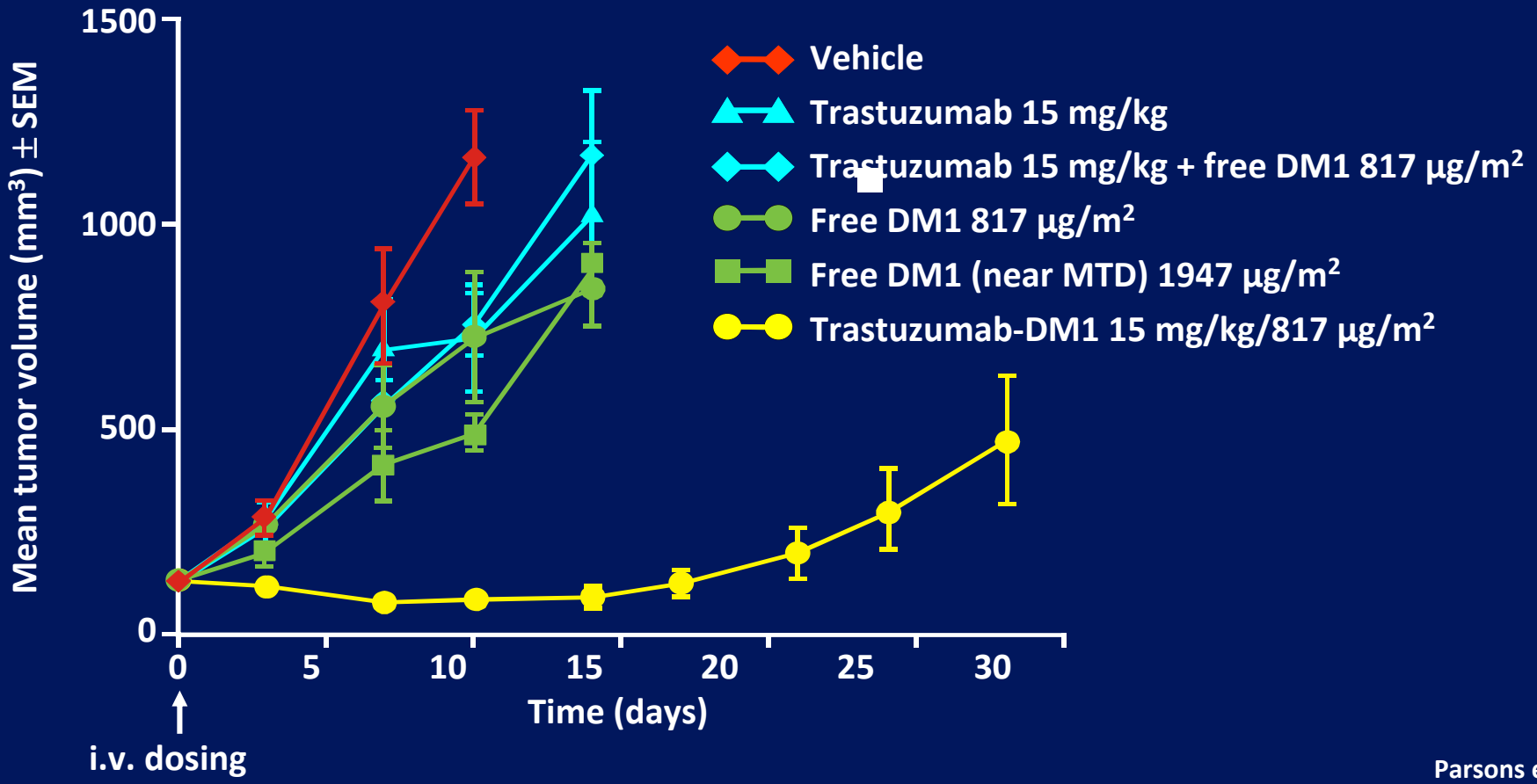
Systemically stable
Breaks down in target cancer cell



T-DM1

Conjugation of T-DM1 components markedly increases efficacy in a preclinical model

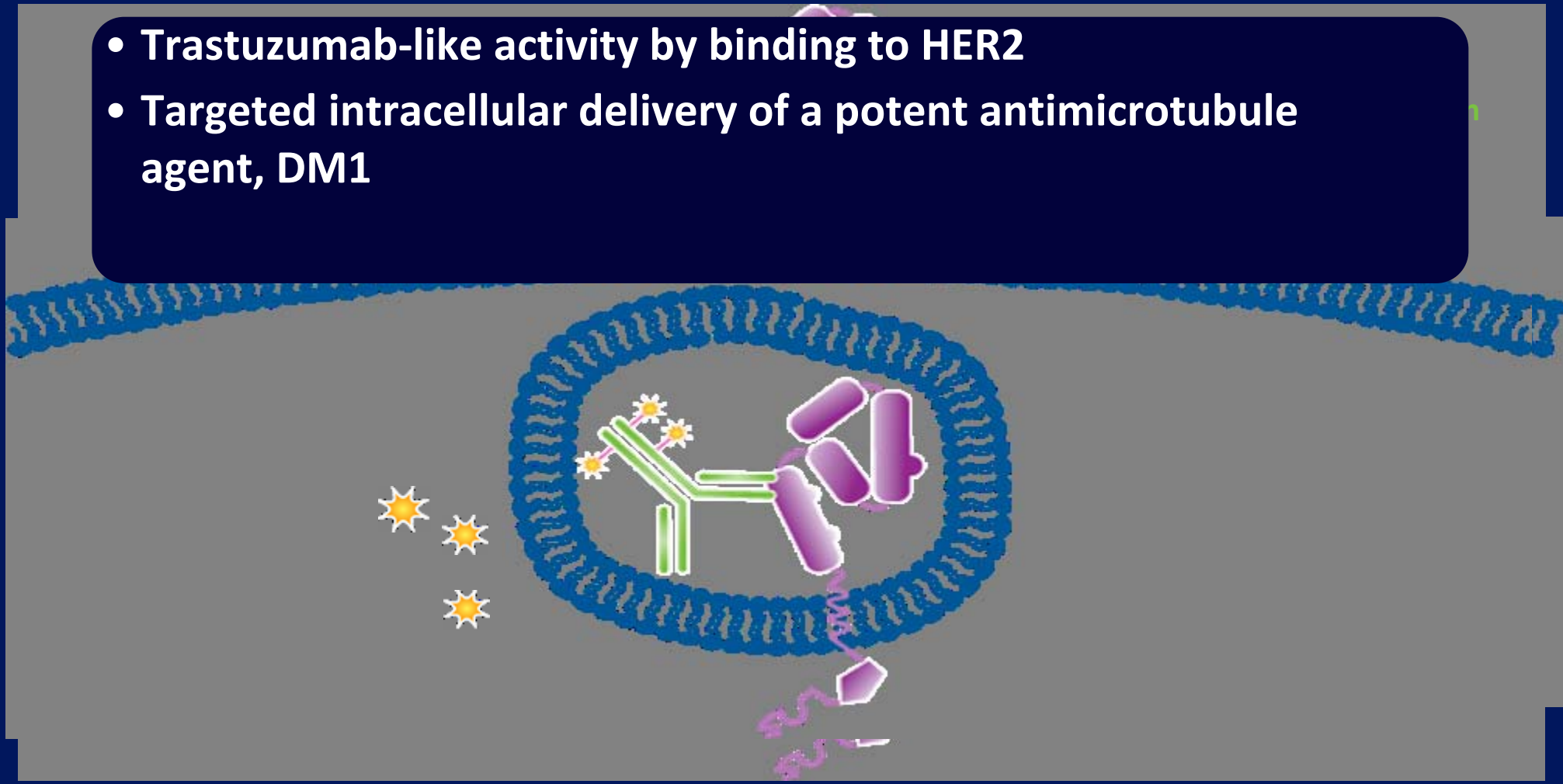
T-DM1 demonstrated a rapid and durable reduction in tumor volume in the Fo5 animal breast cancer model, which was specifically engineered to be insensitive to trastuzumab



Parsons et al. AACR 2007

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumor cells

- Trastuzumab-like activity by binding to HER2
- Targeted intracellular delivery of a potent antimicrotubule agent, DM1



TDM4374g

A Phase II Study of Trastuzumab-DM1 (T-DM1), a Novel HER2 Antibody–Drug Conjugate, in Patients with HER2+ Metastatic Breast Cancer who Were Previously Treated with an Anthracycline, a Taxane, Capecitabine, Lapatinib, and Trastuzumab

Ian Krop,[1] Patricia LoRusso,[2] Kathy D. Miller,[3] Shanu Modi,[4] Denise Yardley,[5] Gladys Rodriguez,[6] Sam Agresta,[7] Michael Lu,[7] Maoxia Zheng,[7] Lukas Amler,[7] Eric Winer,[1] Hope Rugo[8]

[1]Dana Farber Cancer Institute, Boston, MA; [2]Karmanos Cancer Institute, Detroit, MI; [3]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [4]Memorial Sloan-Kettering Cancer Center, New York, NY; [5]Sarah Cannon Research Institute, Nashville, TN; [6]South Texas Oncology/Hematology, San Antonio, TX; [7]Genentech, South San Francisco, California; [8]University of California–San Francisco Comprehensive Cancer Center, San Francisco, CA

Antitumor Activity in Treated Patients by Retrospectively Confirmed HER2 Status

	IRF	INV
Patients centrally confirmed as HER2 +	n=80	n=80
ORR, %	41.3	40.0
Clinical benefit rate, %	55.0	53.8
Patients with unconfirmed HER2 status	n=15	n=14
ORR, %	20.0	13.3
Clinical benefit rate, %	26.7	20.0

IRF - Independent Review Facility
Objective Response = CR or PR determined by two consecutive tumor assessments at least 28 days apart.
Clinical Benefit = objective response or SD maintained for at least 6 months.

TDM4450g

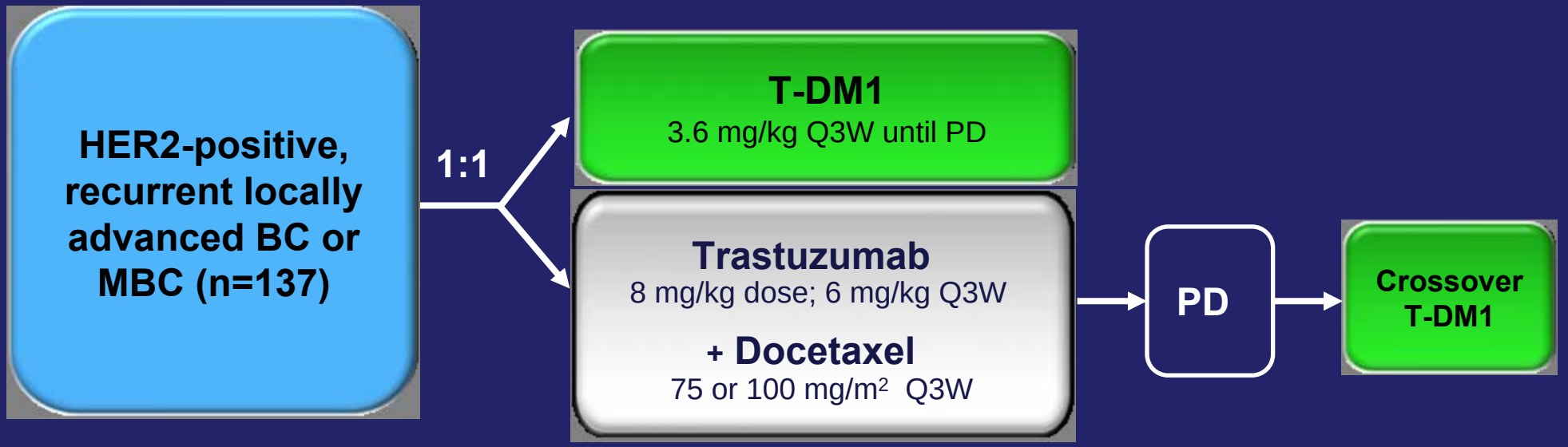
Efficacy and Safety of Trastuzumab-DM1 Versus Trastuzumab plus Docetaxel in HER2-Positive Metastatic Breast Cancer Patients with No Prior Chemotherapy for Metastatic Disease: Preliminary Results of a Randomized, Multicenter, Open-Label Phase 2 Study

EA Perez,[1] L Dirix,[2] J Kocsis,[3] L Gianni,[4] J Lu,[5] J Vinholes,[6] V Ng,[7] C Linehan,[7] S Agresta,[7] S Hurvitz[8]

[1]Mayo Clinic, Jacksonville, FL, USA; [2]Sint-Augustinus Hospital, Antwerp, Belgium; [3]Semmelweis University Hospital, Budapest, Hungary; [4]Istituto Nazionale dei Tumori, Milan, Italy; [5]Division of Hematology and Oncology, State University of New York at Stony Brook, Stony Brook, NY, USA; [6]Clinica de Oncologia de Porto Alegre, Brasil; [7]Genentech, Inc., South San Francisco, CA, USA; [8]UCLA Translational Oncology Research International, Los Angeles, CA, USA

Perez EA, et al. Abstr LBA3. ESMO 2010

Study Design



- Randomized, phase II, international, open-label study
- HER2-positive, measurable disease required
- Stratification factors
  - World region, prior adjuvant trastuzumab therapy, disease-free interval
- Primary endpoints: PFS by INV, safety
- Key Secondary endpoints: ORR, clinical benefit, OS, QOL, symptom control

Perez EA, et al. Abstr LBA3. ESMO 2010

Objective Response by Investigator (ITT)

Randomized Patients

	T-DM1 (n=67)	Trastuzumab + Docetaxel (n=70)
Patients with an Objective Response,* n (%)	**32 (47.8)**	**29 (41.4)**
95% CI	(35.4, 60.3)	(30.2, 53.8)
Patients with Clinical Benefit,† n (%)	**37 (55.2)**	**40 (57.1)**
95% CI	(43.1, 67.2)	(44.8, 68.9)
Objective Responses, n (%)		
Complete Response	3 (4.5)	1 (1.4)
Partial Response	29 (43.3)	28 (40.0)
Stable Disease‡	22 (32.8)	29 (41.4)
Progressive Disease	8 (11.9)	4 (5.7)
Unable to Evaluate	4 (6.0)	4 (5.7)

* Objective response = complete or partial response based on RECIST 1.0 determined on two consecutive tumor assessments at least 4 weeks apart

† Clinical benefit = objective response or maintained stable disease for at least 6 months from start of study treatment

‡ Stable disease includes 11 patients with unconfirmed partial response (5 in T-DM1 arm and 6 in the trastuzumab + docetaxel arm)

Perez EA, et al. Abstr LBA3. ESMO 2010

AE Summary

Safety Evaluable Patients

	T-DM1 (n=67)	Trastuzumab+Docetaxel (n=68)
Any AE, n (%)	63 (94.0)	68 (100.0)
Grade ≥3 AE	**25 (37.3)**	**51 (75.0)**
Serious AE*	13 (19.4)	15 (22.1)
Three most common AEs (any grade) in T-DM1 arm		
Nausea	32 (47.8)	27 (39.7)
Fatigue	31 (46.3)	29 (46.2)
Pyrexia	24 (35.8)	14 (20.6)
Three most common AEs (any grade) in trastuzumab + docetaxel arm		
Alopecia	1 (1.5)	45 (66.2)
Neutropenia	5 (7.5)	39 (57.4)
Diarrhea	7 (10.4)	31 (45.6)

* AEs that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or are congenital anomalies/birth defects

Perez EA, et al. Abstr LBA3. ESMO 2010

Grade ≥3 AEs Occurring with ≥10% Difference in Incidence Between Treatment Arms

Safety Evaluable Patients

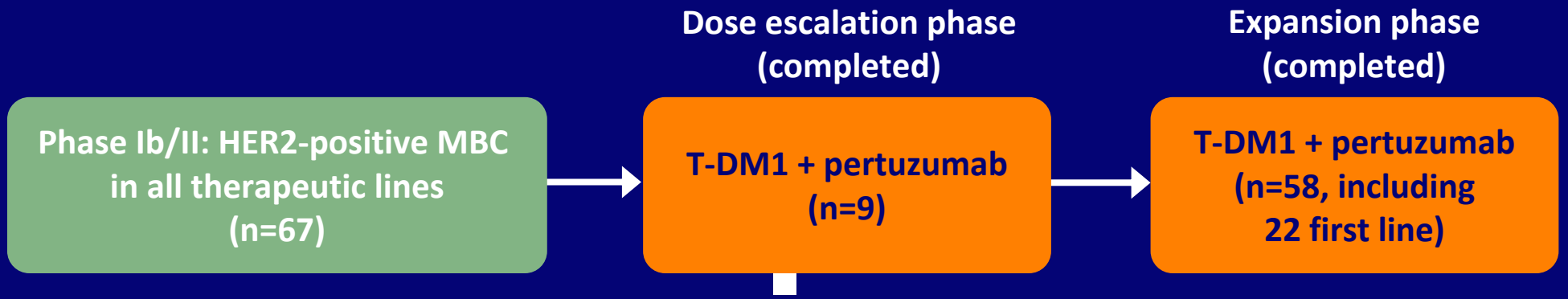
Occurring with ≥10% Difference in Incidence between Arms, n (%)	NCI CTCAE Grade	T-DM1 (n=67)	Trastuzumab + Docetaxel (n=68)
Neutropenia	Total	0	36 (52.9)
	3	0	6 (8.8)
	4	0	30 (44.1)
Leukopenia	Total	0	17 (25.0)
	3	0	12 (17.6)
	4	0	5 (7.4)
Febrile neutropenia	Total	0	7 (10.3)
	3	0	6 (8.8)
	4	0	1 (1.5)

Most common Gr ≥3 AEs in T-DM1 arm (vs. trastuzumab + docetaxel arm)

AST increased (7.5% vs. 0%), thrombocytopenia (6.0% vs. 1.5%), ALT increased (4.5% vs. 0%), fatigue (4.5% vs. 4.4%), and pneumonia (4.5% vs. 1.5%)

Perez EA, et al. Abstr LBA3. ESMO 2010

TDM4373g: a Phase Ib/II trial of T-DM1 + pertuzumab in patients with locally-advanced and MBC who were previously treated with trastuzumab



Primary endpoints:

- Safety
- ORR by RECIST 1.0

Secondary endpoints:

- PFS
- DoR

Phase Ib: 3+3 dose escalation

- Cohort I: T-DM1 3.0 mg/kg; pertuzumab (840 mg loading dose, 420 mg maintenance dose)
- Cohort II: T-DM1 3.6 mg/kg; pertuzumab (840 mg loading dose, 420 mg maintenance dose)

Phase II

- Expansion at dose level established in Phase Ib

Heavily pretreated population:

- Median of 6 prior therapeutic agents in the metastatic setting

Miller et al. ASCO 2010

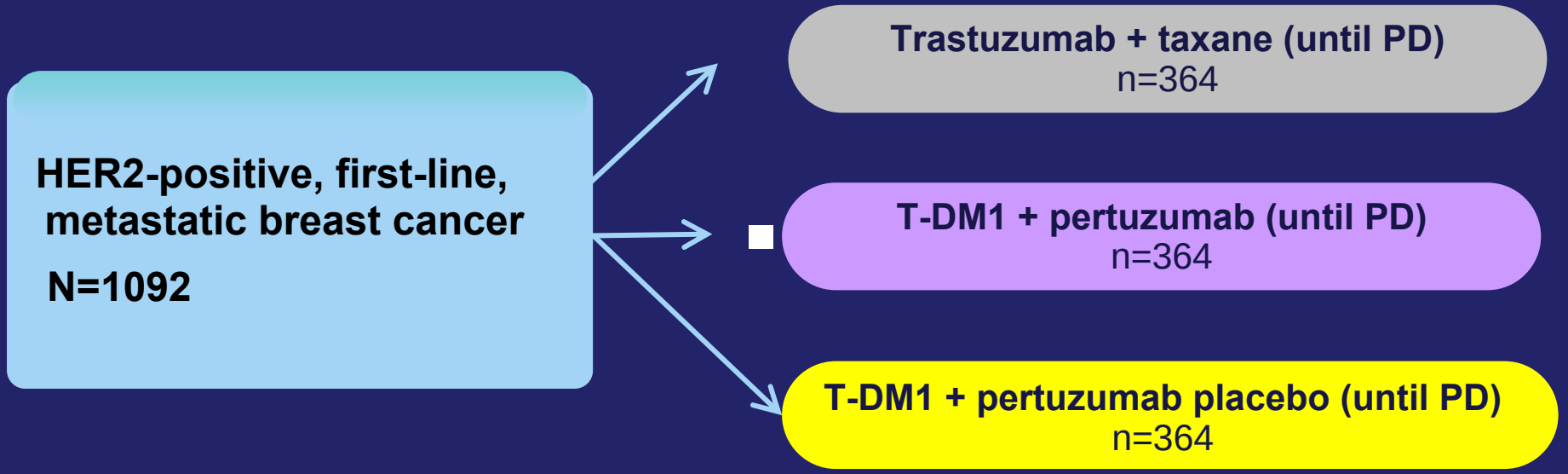
TDM4373g: T-DM1 + pertuzumab shows promising efficacy in patients pretreated with trastuzumab + lapatinib

	Cohort I, n (%) (n=3)	Cohort II, n (%) (n=25)	Total, n (%) (n=28)
PR	2 (66.7)	8 (32.0)	10 (35.7)
SD	1 (33.3)	12 (48.0)	13 (46.4)
PD	0	4 (16.0)	4 (14.3)
Missing	0	1 (4.0)	1 (3.6)

Clinical Benefit Rate: 82.1%

Miller et al. ASCO 2010

1st Line mBC Phase III MARIANNE Study: BO22589/TDM4788g



- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; patient reported outcomes analysis; biomarkers

Therapie des HER2-positiven Mammakarzinoms: ist zytostatische Chemotherapie noch nötig ?

JA

aber nicht mehr lange !

JAHRESTAGUNG DER ÖSTERREICHISCHEN GESELLSCHAFT FÜR SENOLOGIE

www.senologie.at