Targeted Therapy for Metastatic Breast Cancer: HER2+ Disease
轉移性HER2+乳癌標靶治療

Professor Winnie Yeo

MBBS, AKC, MD, FRCP (Lond, Edin, Glasg), FHKCP, FHKAM
Clinical Professor, Chinese University of Hong Kong
Honorary Consultant, Prince of Wales Hospital

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

2015 Dr Stanley Ho Medical Development Foundation Symposium
何鴻燊博士醫療拓展基金會 2015醫學研討會

Breast cancer is a common disease

In Hong Kong:

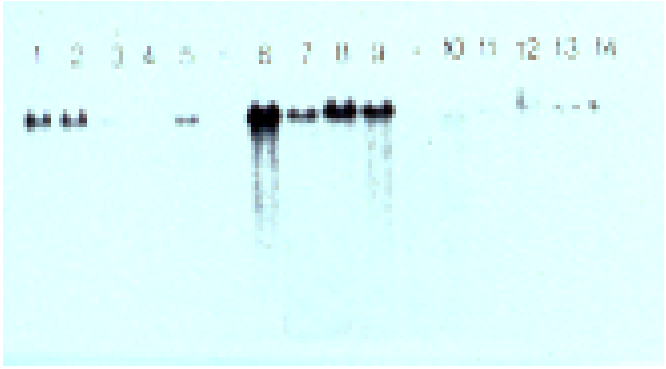
- most frequent non-skin cancer in HK women
- 25.8% of all new cancer cases (3508 new cases of female breast cancer)
- 11.1% of all cancer deaths among women

Data from the Hong Kong Cancer Registry 2011

Biomarkers to guide treatment

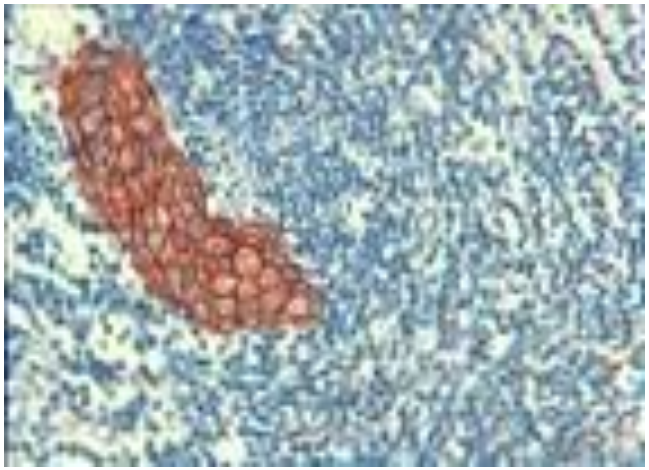
- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Human epidermal receptor 2 (HER2 / Cerb2)
- …

HER2+(Cerb2+) Breast Cancer



HER2 Oncogene Amplification

HER2基因擴增



HER2 Oncoprotein Overexpression

HER2基因表達

Poor prognosis

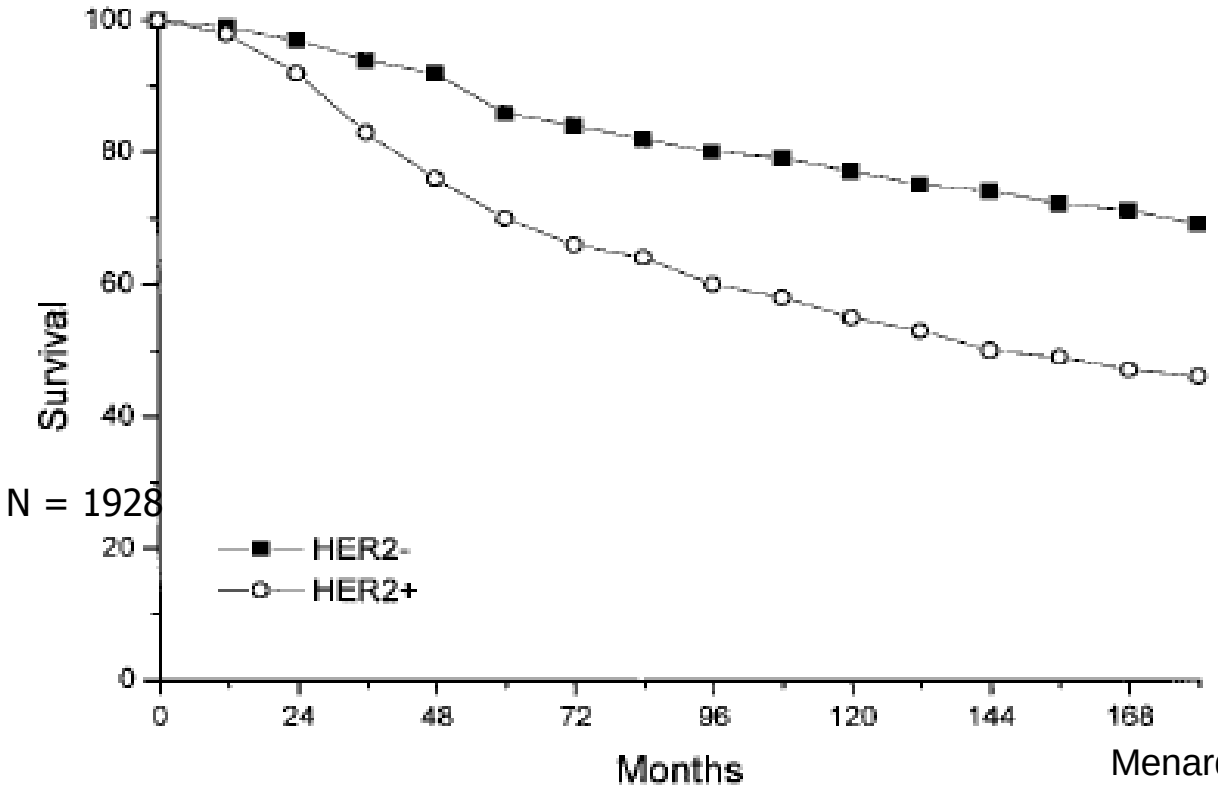
Slamon et al, *Science* 1987

HER2+(Cerb2+) Breast Cancer

- Cytotoxic chemotherapy alone- lower response

Median Survival from First Diagnosis

HER-2 overexpressing	3 yrs
HER-2 normal	6 - 7 yrs



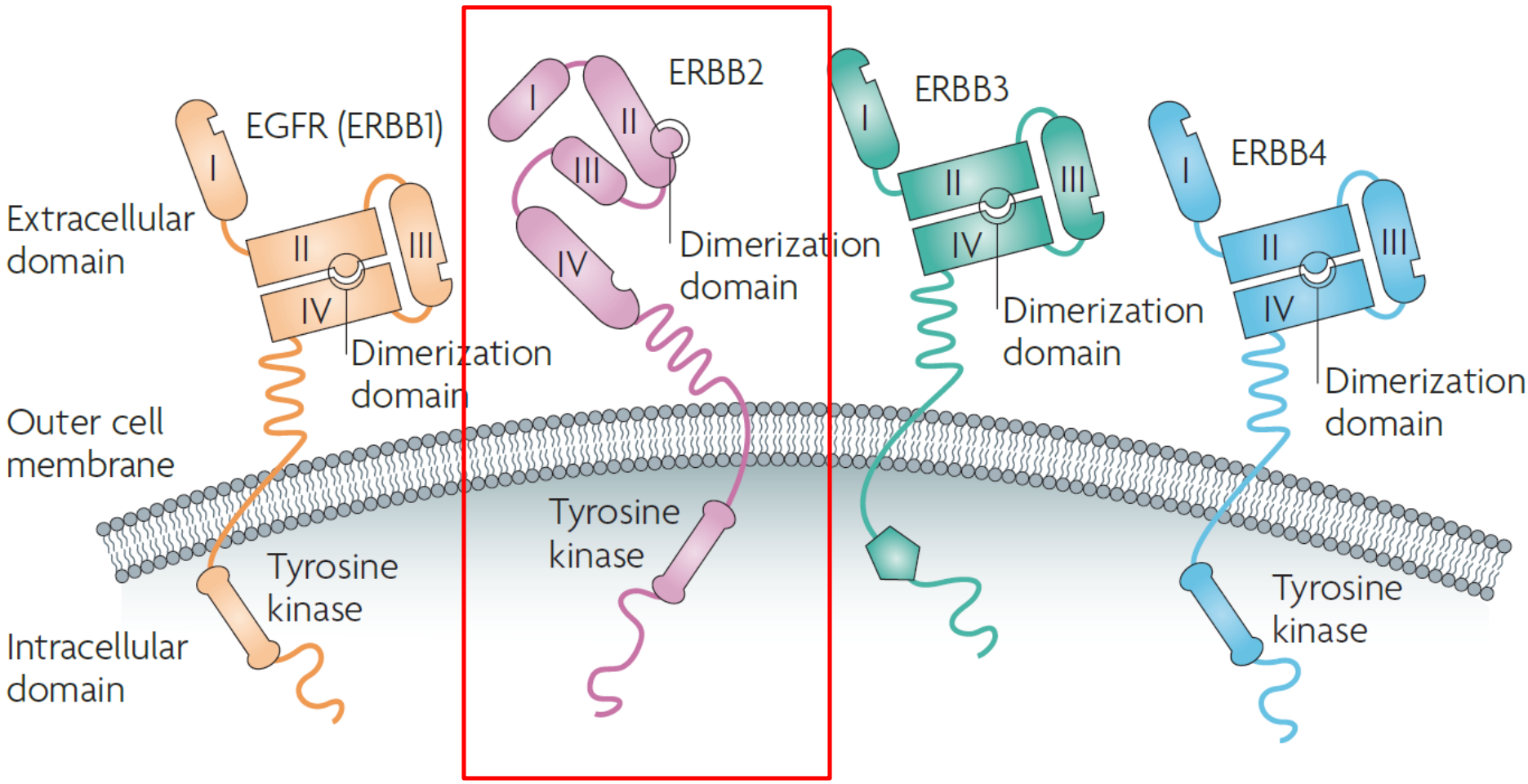
Menard, Clin Can Res 2002

When a patient presents with metastatic breast cancer (MBC)

- Incurable
- Treatment has palliative intent
  - 1st line therapy
  - 2nd line therapy
  - 3rd line therapy
  - ……

How can we tackle HER2+ BC

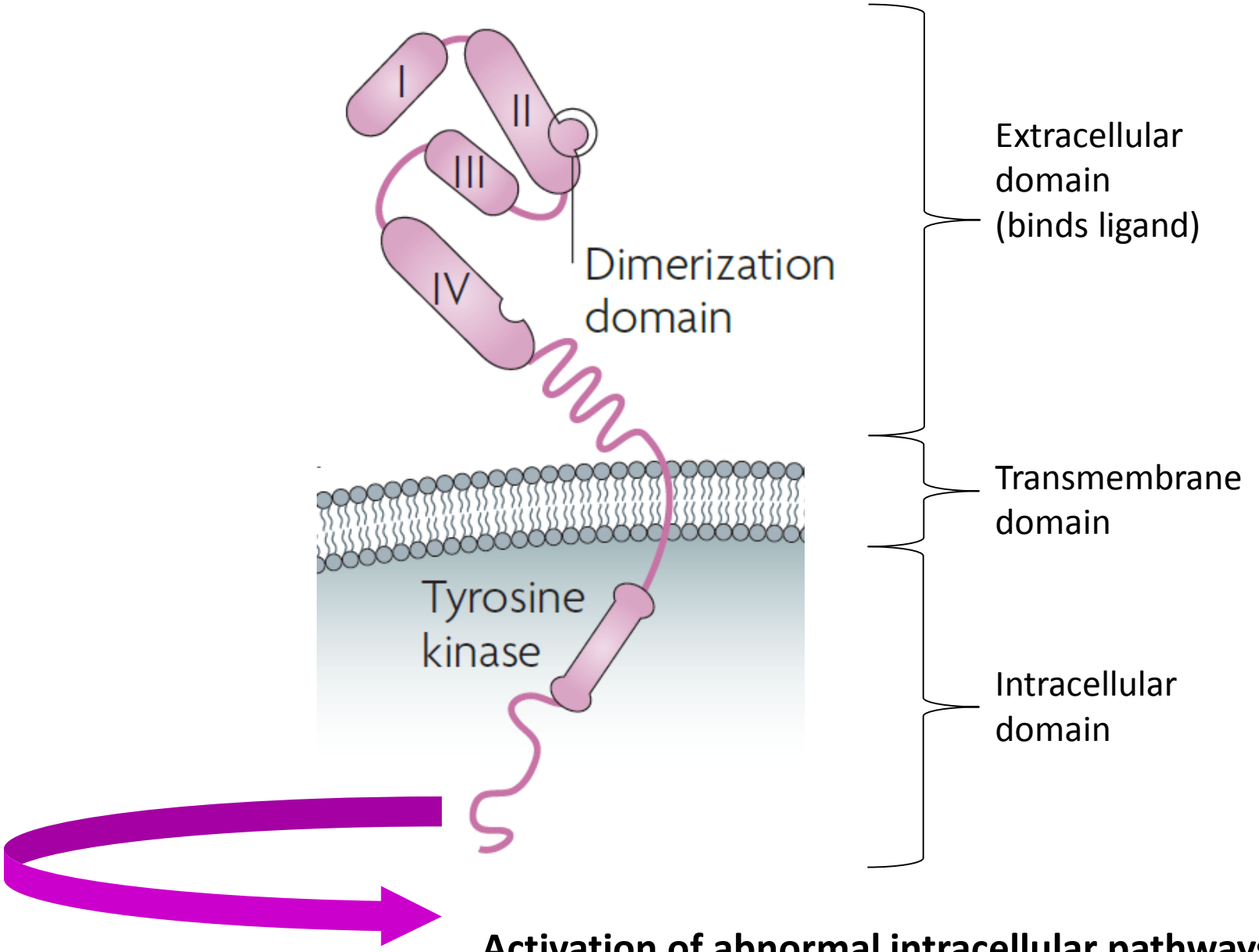
The HER/ ErbB family



Baselga J et al. Nature Reviews 2009; 9: 463 -475.

Berger, M. *FEBS Lett.* **569**, 332–336 (2004).

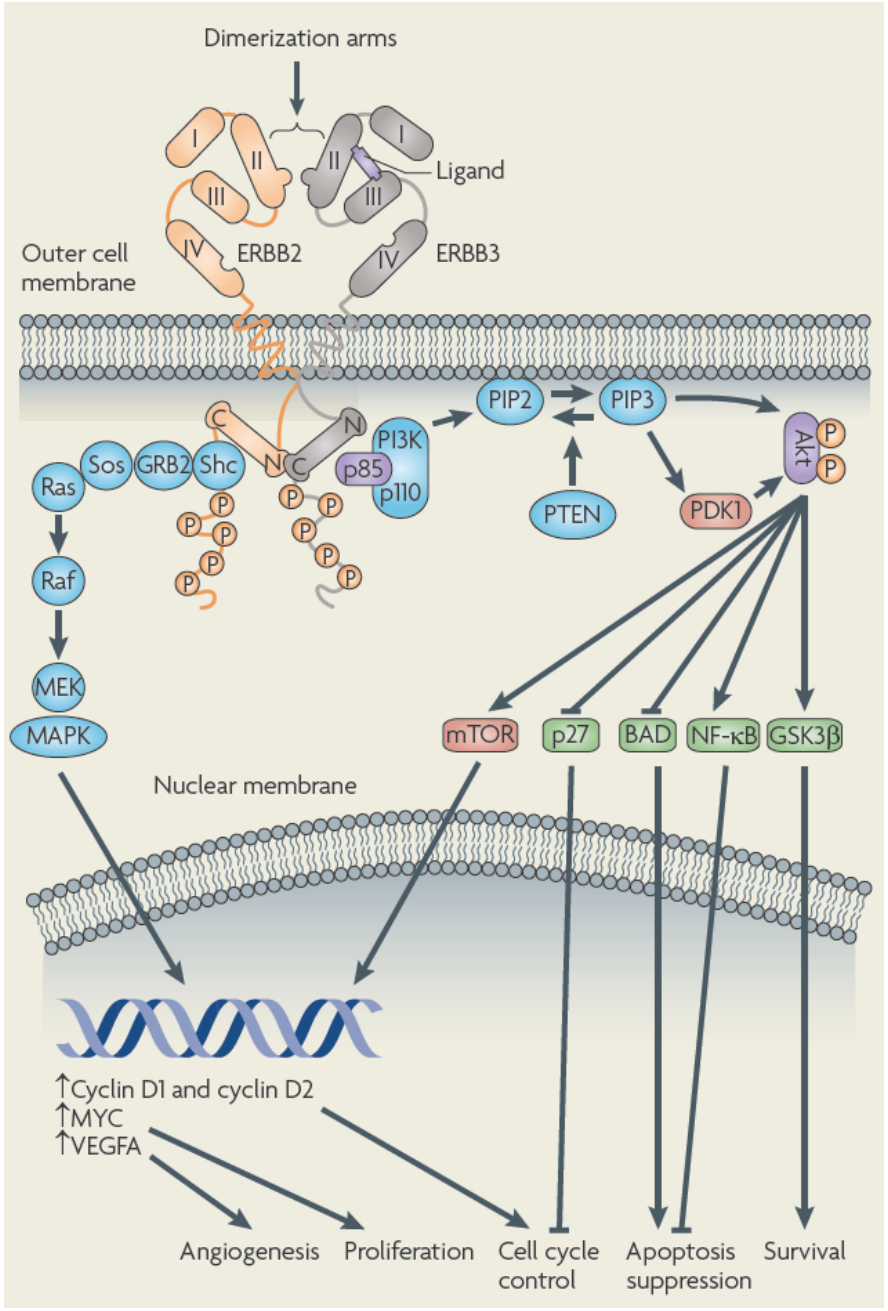
HER2 molecule: ~20-25% of breast cancer patients



Activation of abnormal intracellular pathways

Baselga, 2009

Signalling downstream of HER dimer formation



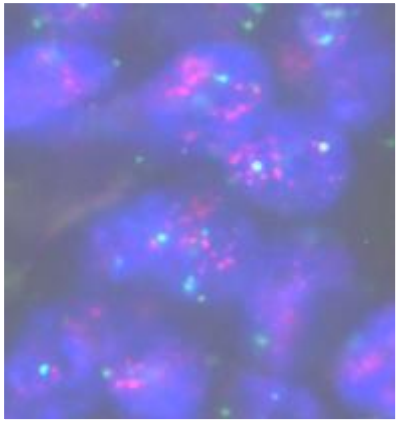
Two key signalling pathways :

1. MAPK pathway, which stimulates proliferation
   激活細胞增殖
2. PI3K–Akt pathway, which promotes tumour cell survival
   激活細胞全活

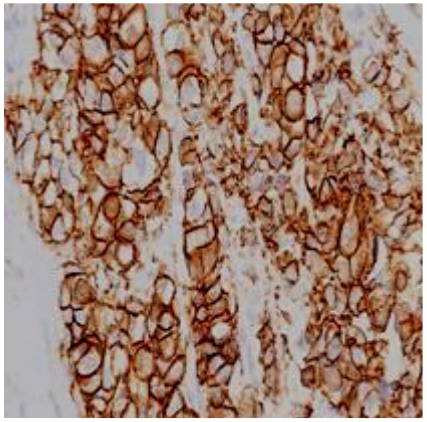
Baselga, 2009

Means to determine HER2+ status

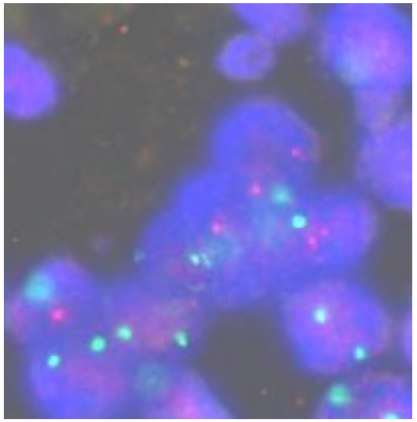
- Determined by IHC or FISH



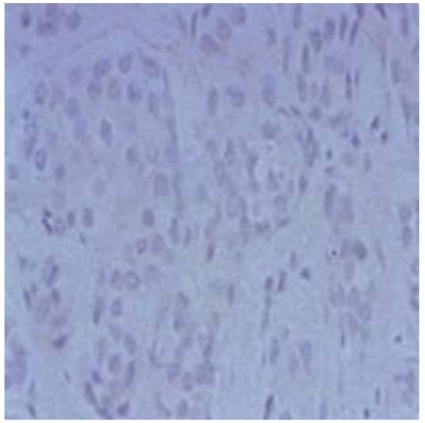
FISH+



IHC+
(HER2 3+)



FISH–



IHC–
(HER2+ 0/1+/2+)

Eligible for anti-HER2 therapy

NO BENEFIT from anti-HER2 therapy

Potential HER2 targets for anticancer therapy

a. **Binds directly to extracellular domain (IV) of HER2**

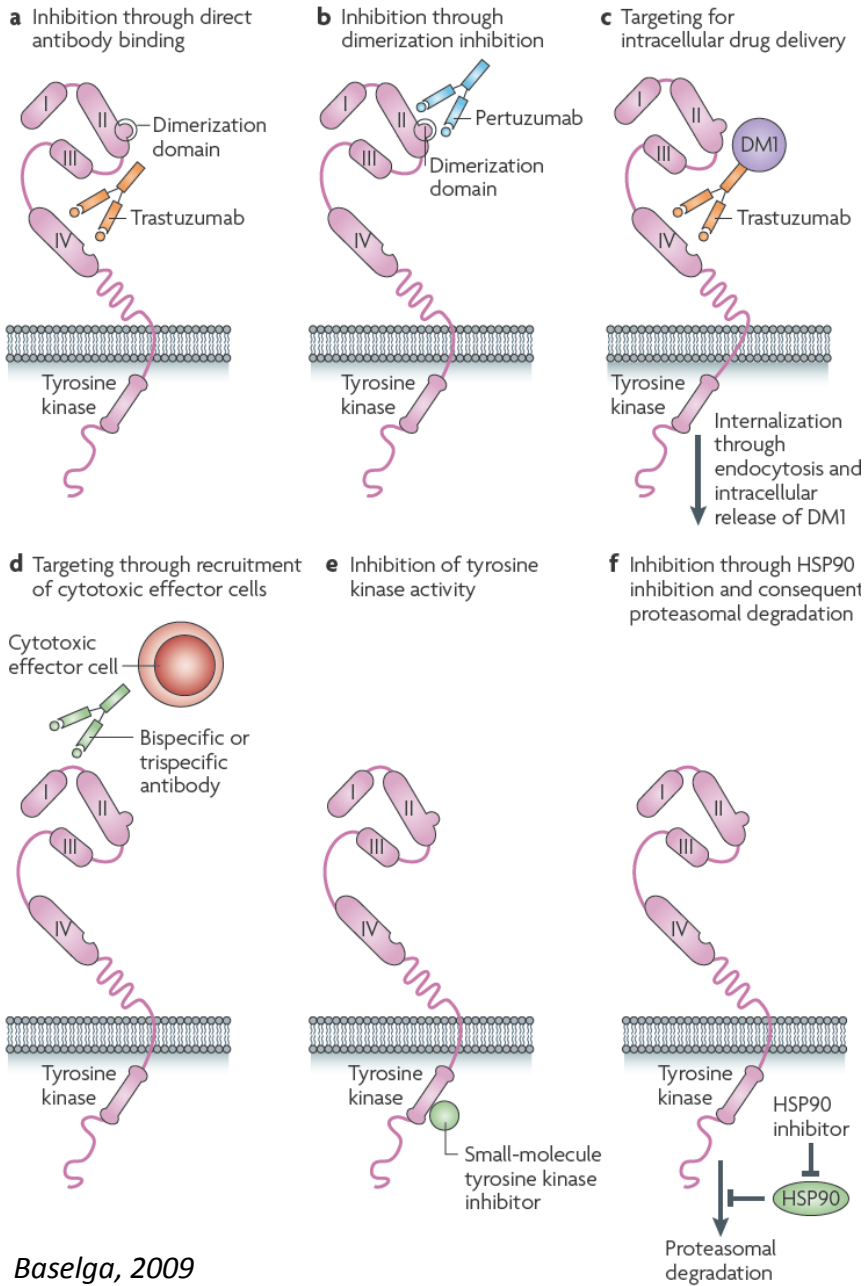
b. **Prevents HER2 dimerization**

c. **Antibody–drug conjugate**

d. **HER2-specific binding by antibodies**

e. **Inhibition of the activity of the HER2 TK domain**

f. **Inhibition of HSP90**



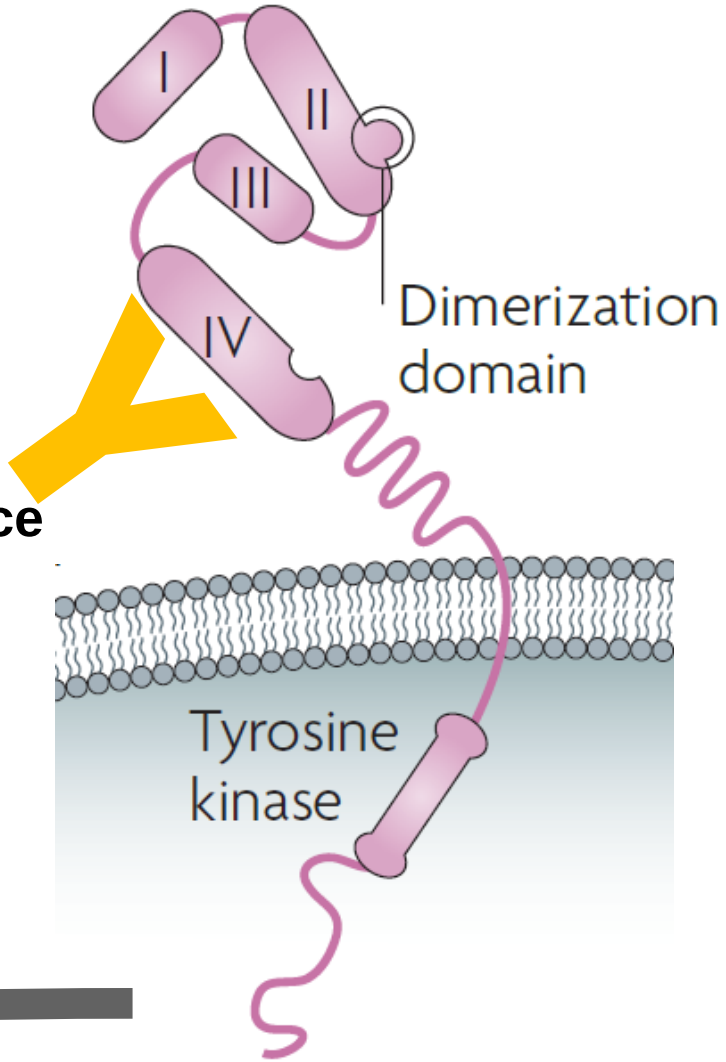
Baselga, 2009

Treatment of HER2+ Metastatic Breast Cancer (MBC)
轉移性HER2+乳癌治療

HER2 targets for anticancer therapy

1. **Binds directly to extracellular domain (IV) of HER2**

Trastuzumab-
a monoclonal antibody against HER2

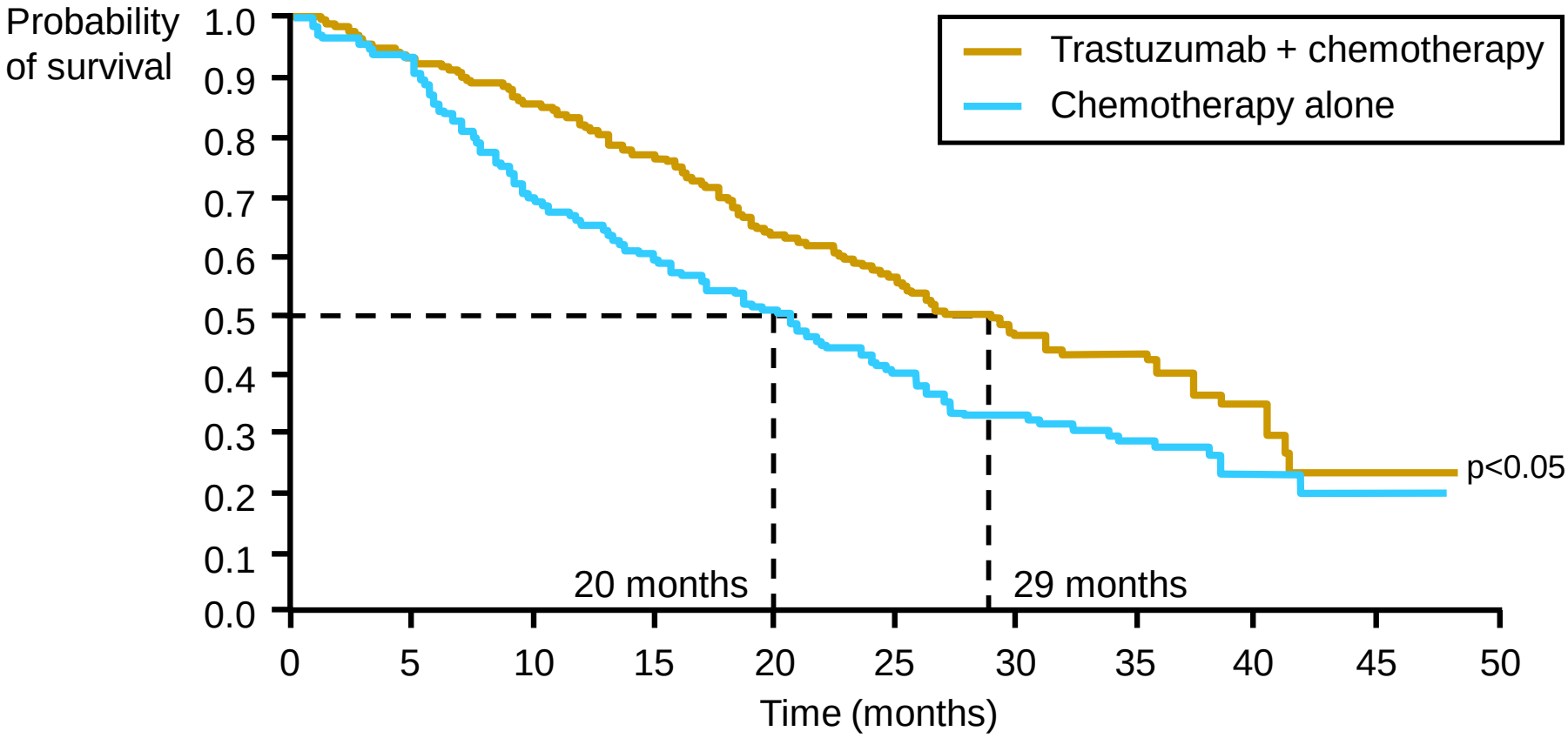


Trastuzumab targets HER2
acts outside the cell surface

Activation of abnormal intracellular pathways

Baselga, 2009

HER2+ MBC 1st line: Trastuzumab + chemotherapy improves OS (HER2 IHC 3+)



OS, overall survival; IHC, immunohistochemistry

Slamon et al 2001

Trastuzumab with Chemotherapy as First-line Therapy for Metastatic Disease

Agent(s) Administered with Trastuzumab	Response Rate (%)	Median Response Duration (months)	Median TTF (months)	Median Survival (months)
Doxorubucin Cyclophos-phamide [1]	56	9.1	7.2	26.8
Paclitaxel [1]	41	10.5	5.8	22.1
Docetaxel [2]	61	11.7	9.8	31.2
Navelbine [3]	68	N/P	5.6	N/P

* N/P = Not Provided

[1] Slamon DJ, Leyland-Jones B, Shak S, et al. *N Engl J Med* 2001;344:783-792

[2] Marty M, Cognetti F, Maraninchi D, et al. *J Clin Oncol* 2005;23:4265-4274

[3] Burstein HJ, Harris LN, Marcom PK, et al. *J Clin Oncol* 2003;21:2889-2895

Active with multiple combination partners

Trastuzumab combination partners in MBC[a]
>110 publications

Trastuzumab + chemotherapy (taxane), e.g.
Trasutuzumab + paclitaxel or
Trasutuzumab + docetaxel

For HER2+ MBC who experienced progression during trastuzumab:

Continuation of anti-HER2 agent + chemotherapy improves clinical outcomes

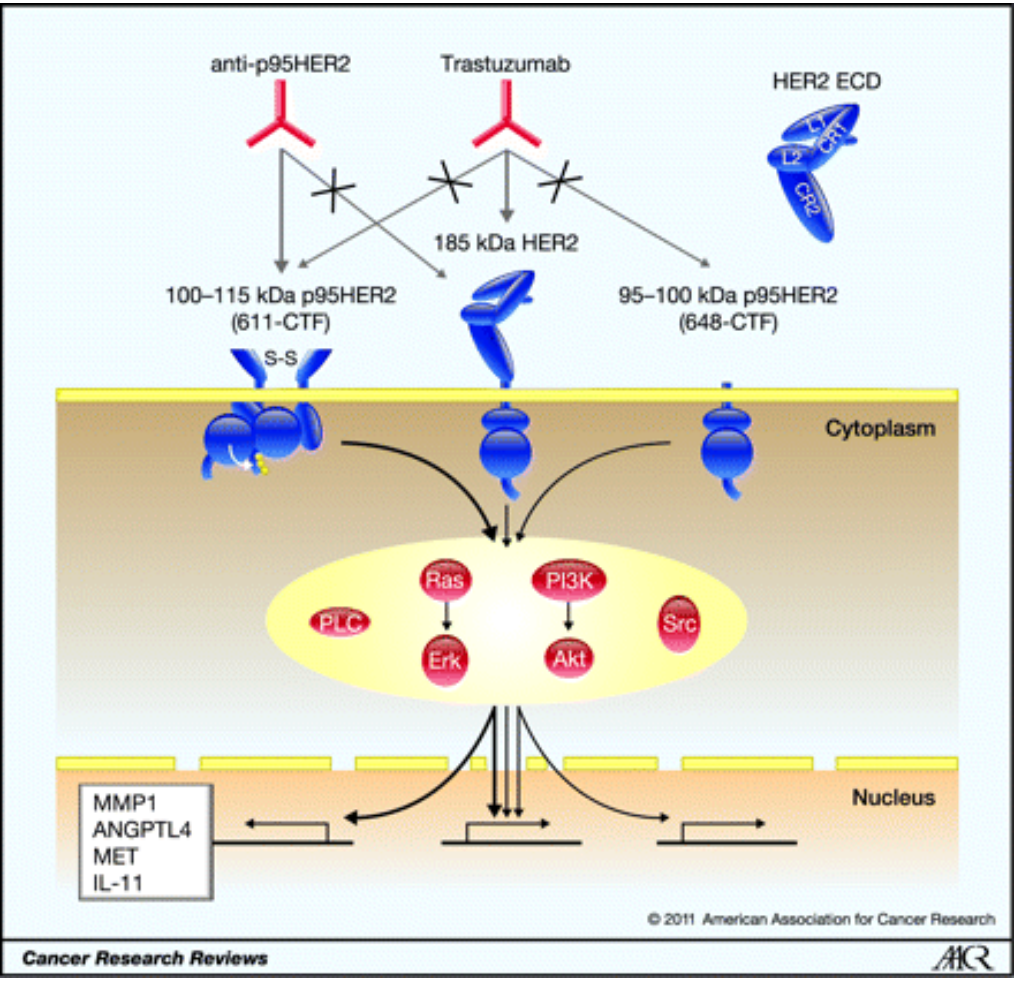
	Chemotherapy + anti-HER2 vs. Chemotherapy
1st line	better outcome with continuation of anti-HER2
2nd line	better outcome with continuation of anti-HER2
3rd line	better outcome with continuation of anti-HER2

Geyer C, et al. NEJM 2006
von Minckwitz, JCO 2009
von Minckwitz, EJC 2011*

Potential Mechanisms of Trastuzumab Resistance

- Altered receptor-antibody interactions
    - Mutations
    - Truncated ECD (p95)- HER2蛋白截短
    - Binding of other proteins (Muc4)
- Increased signaling via the PI3K/Akt pathway
- Increased signaling through alternate growth regulatory pathways (IGF-1R)

Truncated Forms of HER2 Receptor-p95HER2



<u>100- to 115-kDa p95HER2+ tumours</u>

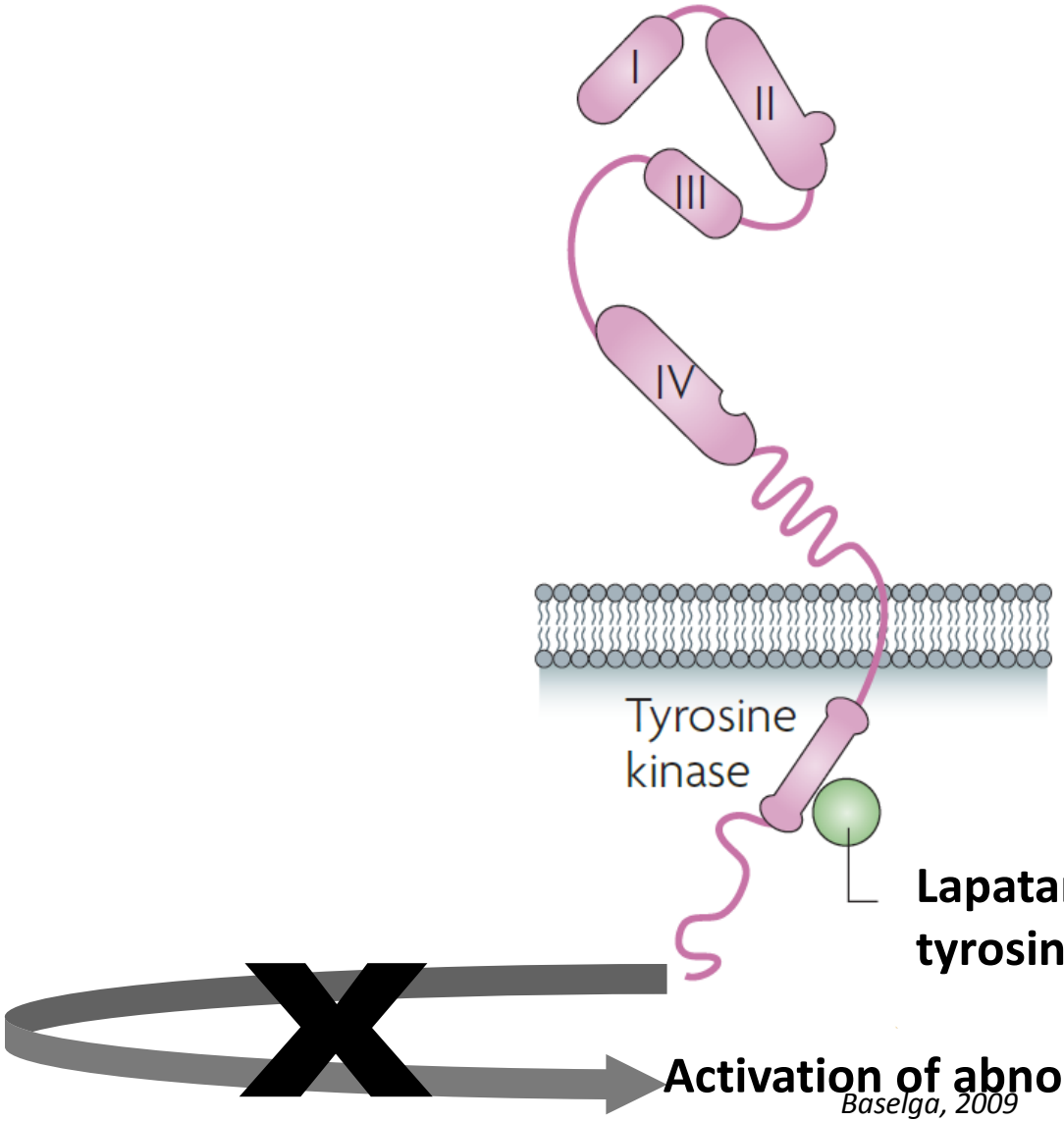
- twice as likely to metastasize to lungs
- specifically regulated genes involved in metastatic progression (MMP1, ANGPTL4, MET, and IL-11)
- significantly shorter PFS and OS when compared to full length HER2
- a more potent activator of the PI3K pathway than HER2-HER3 dimer

Arribas, *Cancer Res* 2011

HER2 targets for anticancer therapy

2. **Inhibition of the activity of the HER2 TK domain**

Lapatinib-
tyrosine kinase inhibitor against HER2



Lapatanib targets intracellular tyrosine kinase HER2 domain

Activation of abnormal intracellular pathways

Baselga, 2009

Treatment response in relation with p95HER2

	Full-length HER2	**p95 HER2**	**P**
Response to trastuzumab* (1st line; n=46)	51.4%	11.1%	0.029
Response to lapatinib (2nd line; n = 68)**	34-35%	29-31%	>0.05

*p95 rate= 19.6%

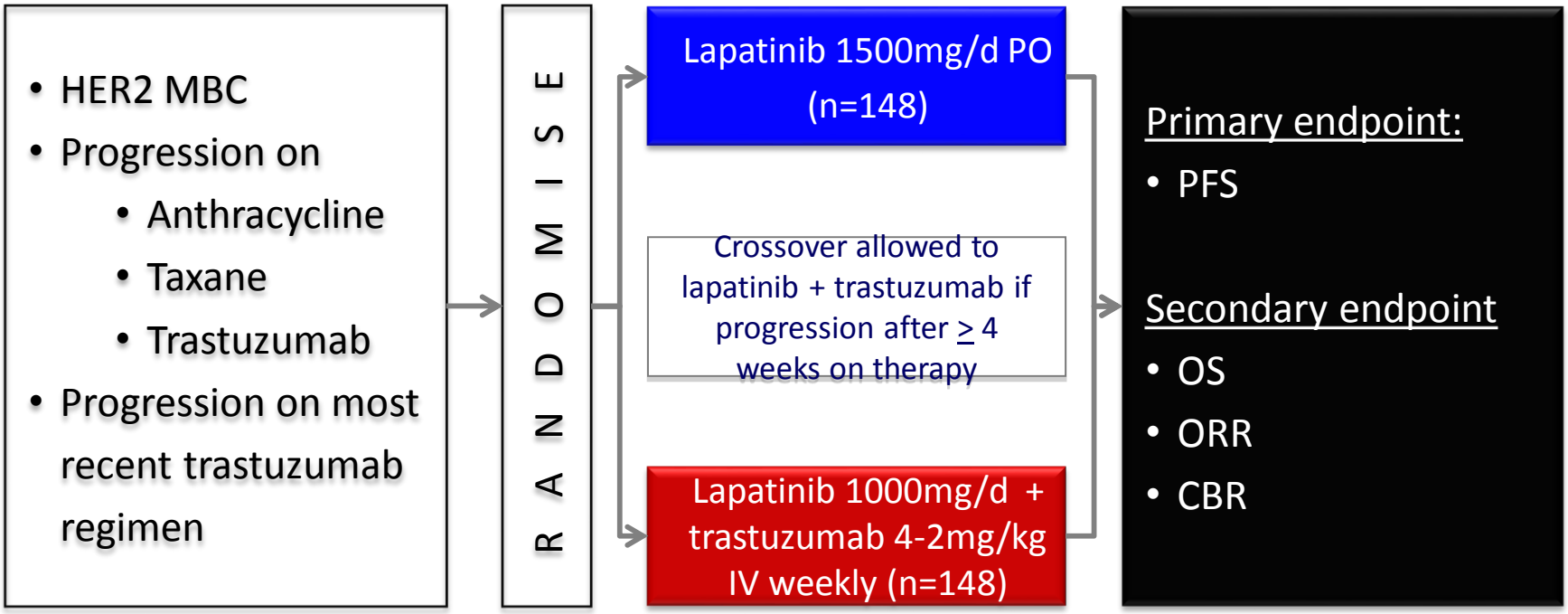
**EGF20009 (n=14; p95 rate= 20.5%) and EGF100151 (n=54; p95 rate= 28.5%)

*Scaltriti , J Natl Cancer Inst 2007

**Scaltriti , Clin Cancer Res; 2010

Refractory HER2+ MBC: Dual blockade

EGF104900- Phase III



Blackwell, et al. J Clin Oncol 2010;28:1124-1130

Efficacy Summary

	L N=145	L + T N=146
Median PFS	8.1 weeks	12.0 weeks
Hazard Ratio (95% CI)	0.73 (0.57, 0.93), p=0.008	
Median OS	9.5 months	14 months
Hazard Ratio (95%CI)	0.74 (0.57, 0.97), p=0.026	
Overall Response Rate, % (95%CI)*	6.9 (3.4, 12.3)	10.3 (5.9, 16.4)
Odds Ratio (95% CI)	1.5 (0.6, 3.9) *P*= 0.46	
Clinical Benefit Rate, % (95%CI)†	12.4 (7.5, 18.9)	24.7 (17.9, 32.5)
Odds Ratio (95% CI)	2.2 (1.2, 4.5) *P*=0.01	

*Confirmed complete (CR) + partial response (PR) †Confirmed CR + PR + stable disease ≥ 6 mo

Blackwell, et al. J Clin Oncol 2010;28:1124-1130

Second Generation TKIs for HER2+ MBC

Neratinib

- HER1/2/4 Receptor TKI
- Irreversible inhibitors
- Orally administered
- Phase III development
- Potential to cross BBB

Afatinib

- HER1/2/4 Receptor TKI
- Irreversible inhibitors
- Orally administered
- Phase III development
- Potential to cross BBB
- Inhibits mutated HER1

HER Receptor TKIs: Efficacy

TKI	1st line Setting ORR; CBR	Pre-treated Setting ORR; CBR	Grade 3 Diarrhea
[1,2]Lapatinib	24%; 31%	4 -7%; 12%	3%
[3]Neratinib	56%; 69%	24%; 33%	30%
[4]Afatinib	N/A	10%; 46%	25%

[1] Blackwell et al, Ann Oncol 2009; [2] Gomez HL, et al, J Clin Oncol 2008; [3] Burstein HJ, et al, J Clin Oncol 2010; [4] Lin NU et al, Breast Can Res Treat 2012

Brain mets in HER2+ MBC

- 30-50% incidence- risk continues over time
- Lapatinib monotherapy: CNS ORR 2-6%
- Lapatinib + capecitabine:
  - CNS ORR 18-36%. PFS 3.6-5.1 months in pre-treated pts
  - CNS ORR 67%, PFS 5.5 months in upfront setting

Olson under review; Brufsky CCR2011, Lin JCO 2008; Lin CCR 2009; Biccardo ASCO 2008; Sutherland BJC 2010; Metro Ann Oncol 2011; Lin Neurooncol 2011; Bachelot ASCO 2011

HER2 Receptor TKIs: On-going trials for Brain mets

TKI	Trials	Patients	Study regimens
Neratinib	[2]TBCRC022	PD after std local Rx Surgical candidate	Neratinib Neratinib→Surgery→Neratinib
Afatinib	[1]LUX-breast 3	Prior T/L	Afatinib vs. Afatinib+vinorelbine vs. TPC

[1]Joensuu, ASCO 2012; [2]Freedman, SABC 2012

HER2 targets for anticancer therapy

3. **Prevents HER2 dimerization**

The HER/ ErbB family

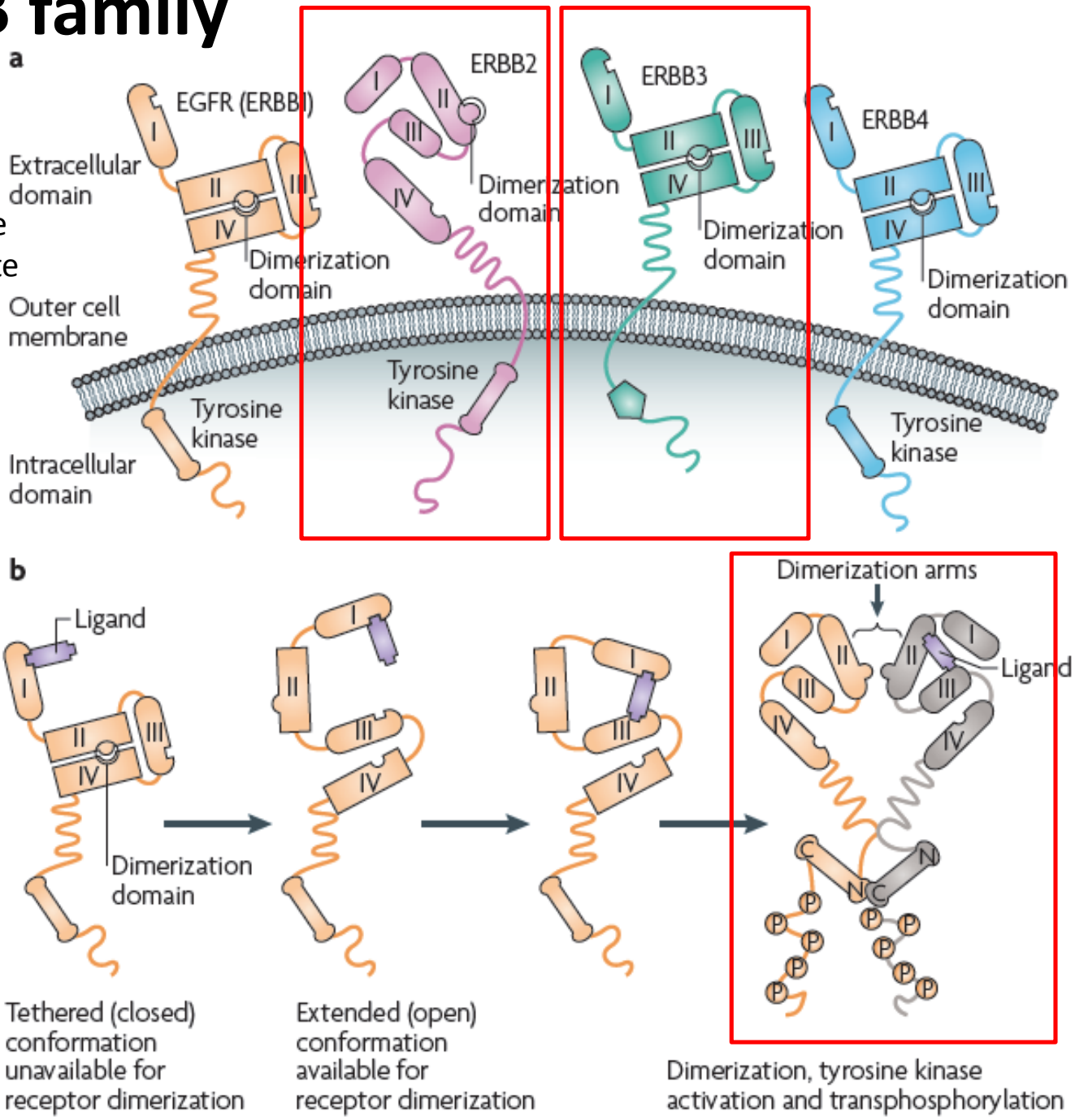
- **HER2**

- Possesses an active TK domain
- no ligand identified exists in the open ('active') conformation state
- available for dimeralization

- **HER3**

- lack intrinsic TK activity
- binds several ligands
- cannot form homo-, and only heterodimers

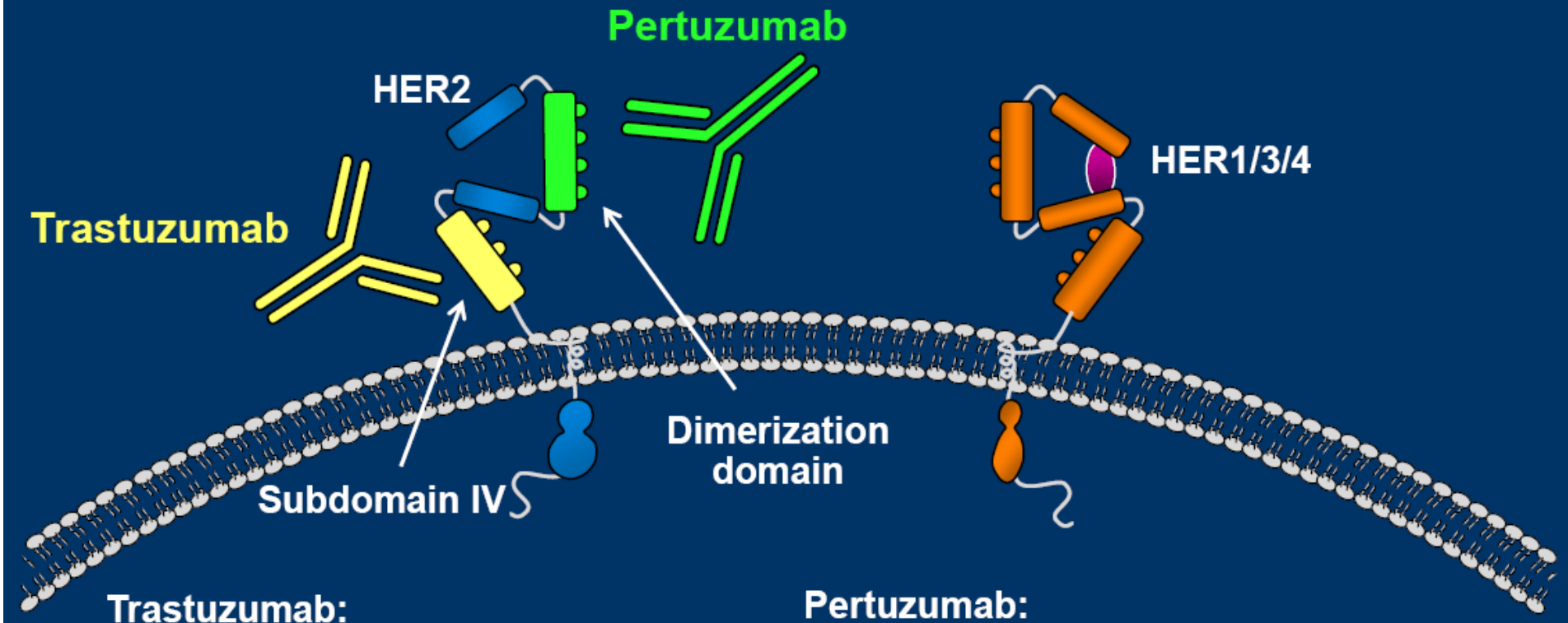
HER2-HER3 dimerization:
- crucial role in activation of intracellular pathways, including PI3K–Akt pathway which drives tumorigenesis



Berger. *FEBS Lett.* **569**, 332–336 (2004).

Baselga J et al. Nature Reviews 2009; 9: 463 -475.

Pertuzumab and trastuzumab have complementary mechanisms of action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

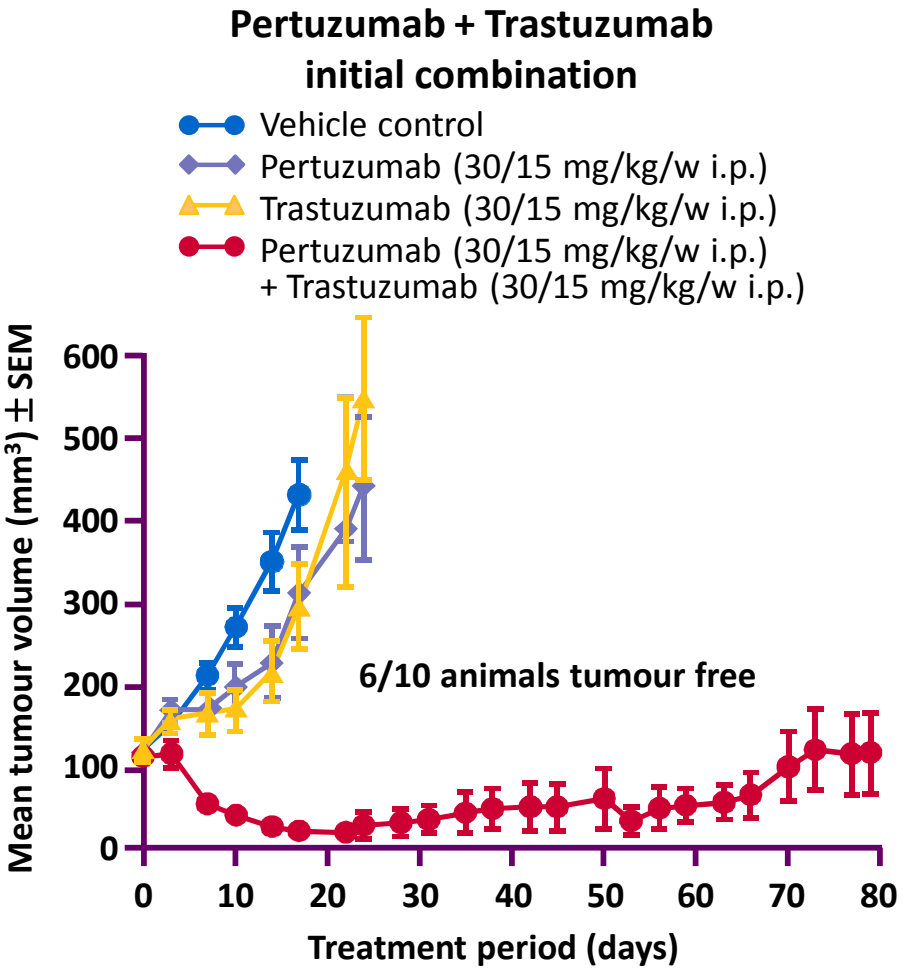
Pertuzumab:

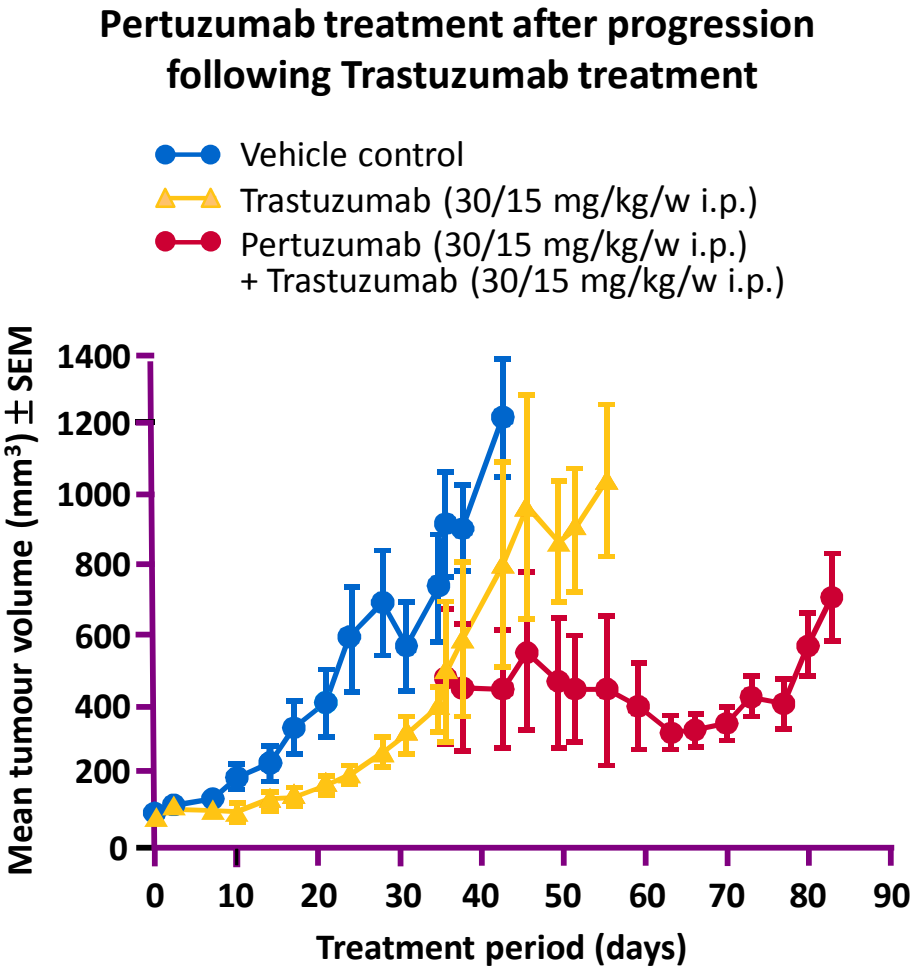
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

ADCC, antibody-dependent cell-mediated cytotoxicity; ECD, extracellular domain

Baselga, 2009

In Preclinical Models, Pertuzumab and Trastuzumab Have a Synergistic Effect



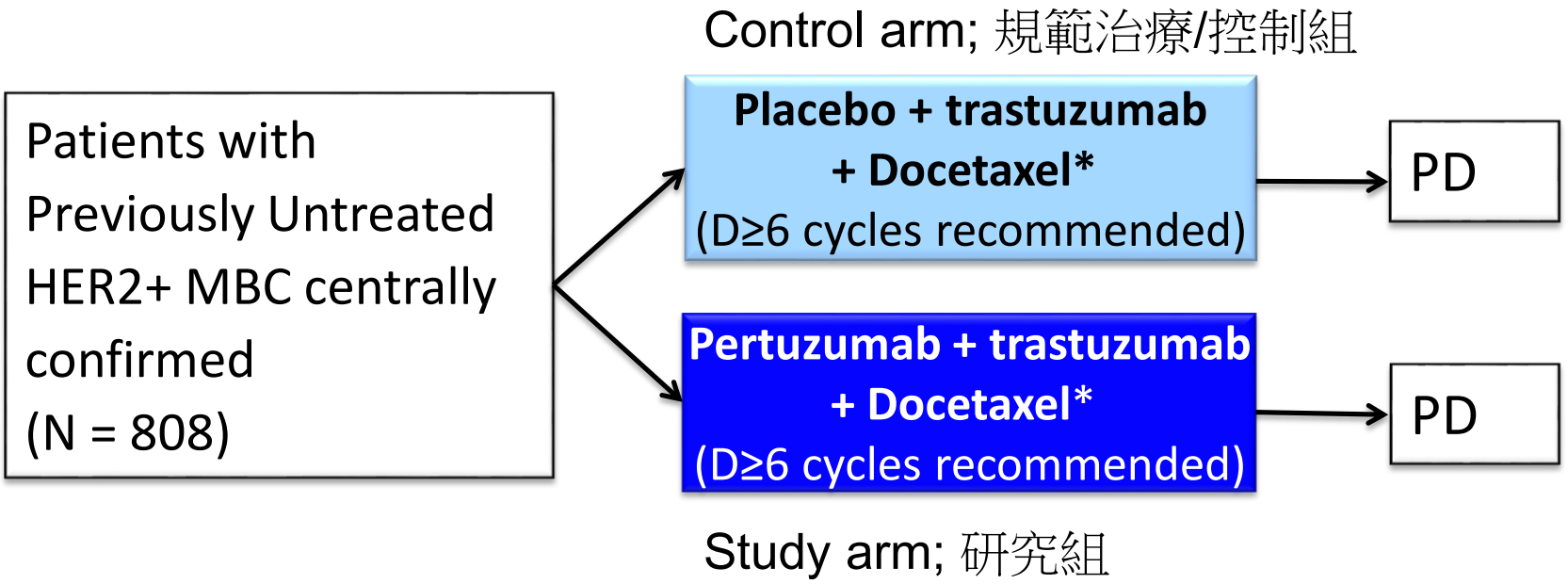


Xenograft model KPL-4; i.p., intraperitoneal; w, week; SEM, standard error of the mean

Scheuer W et al. Cancer Res 2009 , 69: (24) 9330-9336

Pertuzumab: 1st line HER2+ MBC: CLEOPATRA

A Phase III, Randomized, Double-Blind,
Placebo-Controlled Registration Trial



Primary: PFS.
Secondary: OS, RR

Baselga, NEJM 2012

Independently reviewed objective response In patients with measurable disease at baseline

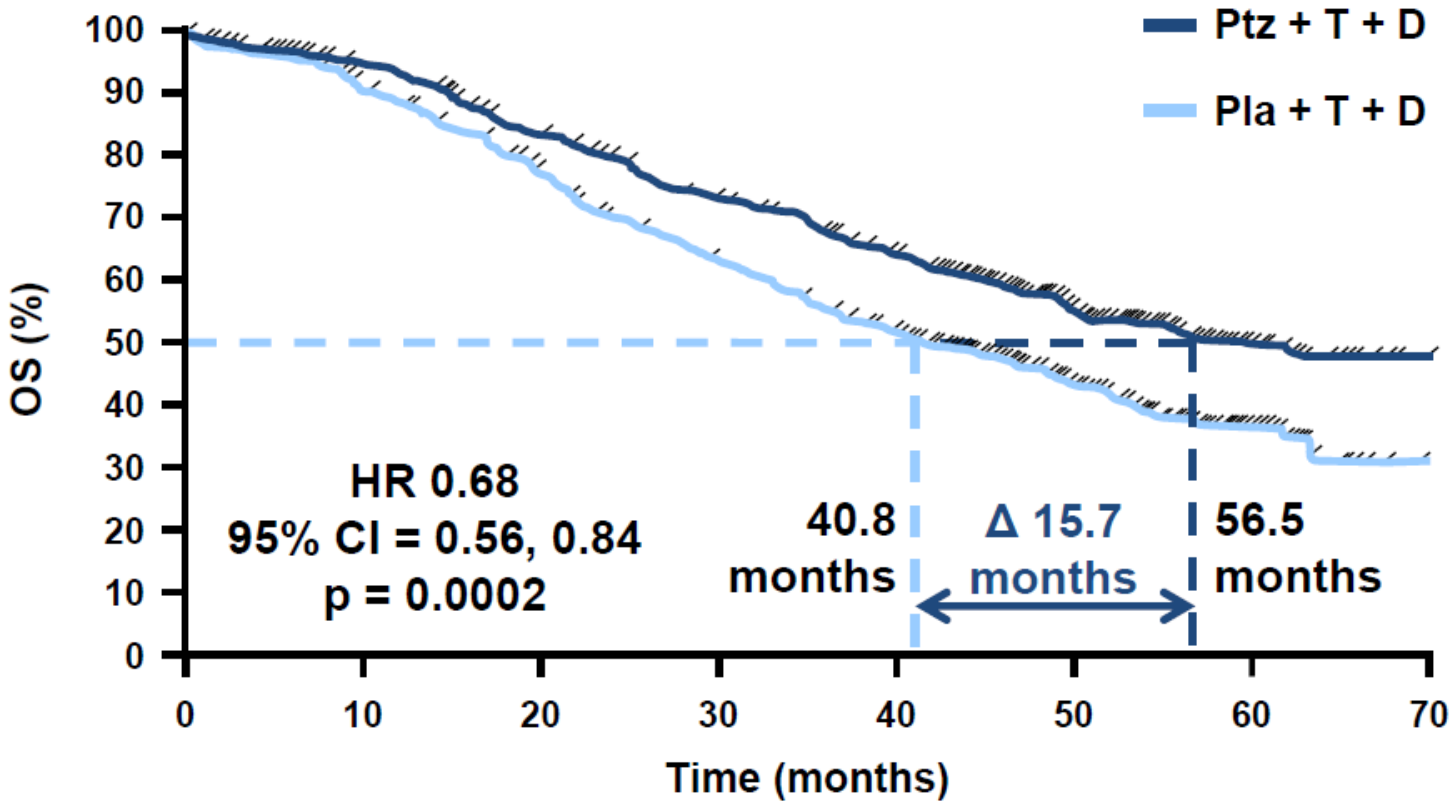
	Placebo + trastuzumab + docetaxel (n = 336)	Pertuzumab + trastuzumab + docetaxel (n = 343)
Objective response rate, n (%)	233 (69.3)	275 (80.2)
Complete response rate, n (%)	14 (4.2)	19 (5.5)
Partial response rate, n (%)	219 (65.2)	256 (74.6)
	p = 0.0011*	
Stable disease, n (%)	70 (20.8)	50 (14.6)
Progressive disease, n (%)	28 (8.3)	13 (3.8)
Unable to assess or no assessment, n (%)	5 (1.5)	5 (1.5)

* The statistical test result is deemed exploratory

Baselga, NEJM 2012

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

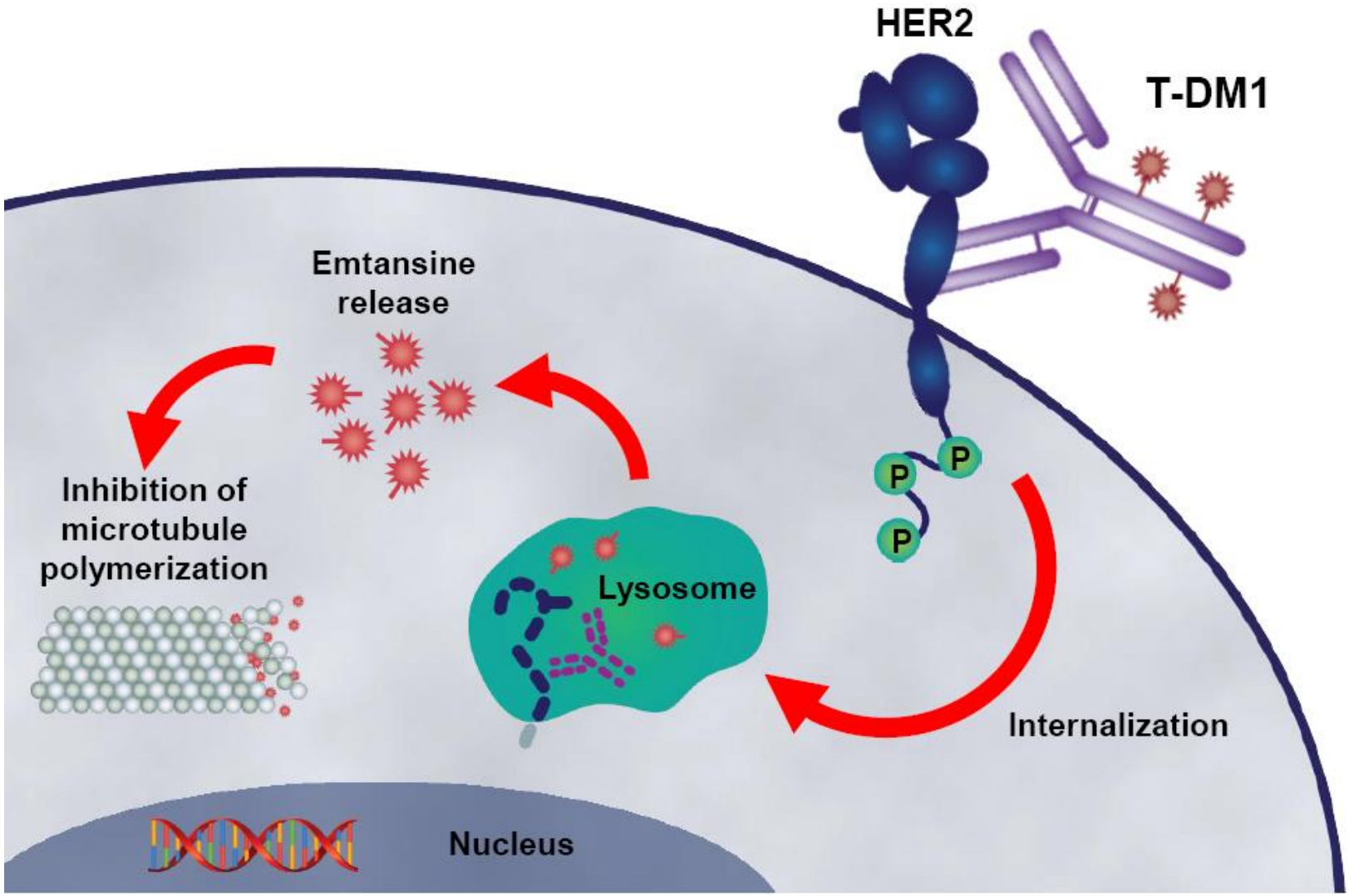
ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain ESMO 2014

HER2 targets for anticancer therapy

4. **Antibody–drug conjugate**

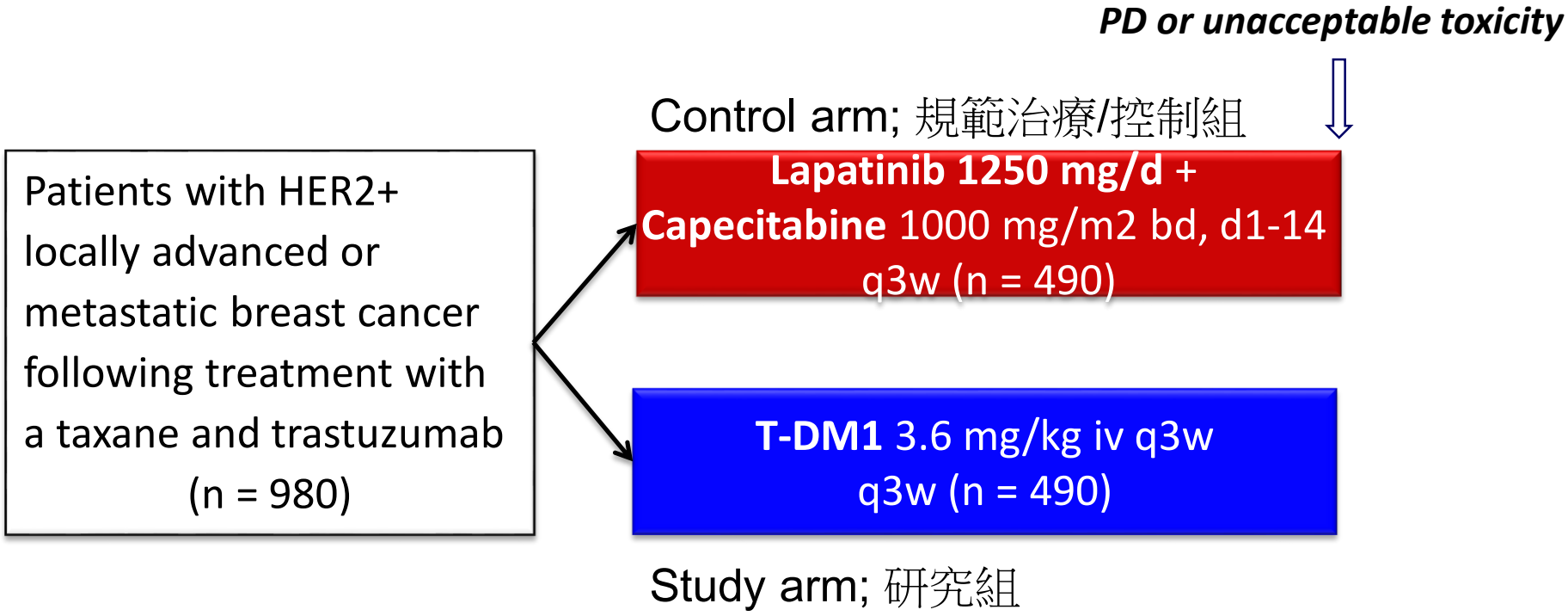
T-DM1: Internalization through endocytosis and intracellular release of DM1 (emtansine)



LoRusso PM, et al. Clin Cancer Res 2011.

T-DM1- 2nd line MBC: EMILIA

Phase III Study: - Prior trastuzumab



- Primary endpoint: PFS
- Secondary endpoints: QoL (FACT B), DOR, PFS by investigator assessment

ClinicalTrials.gov. NCT00829166.

Blackwell ASCO 2012

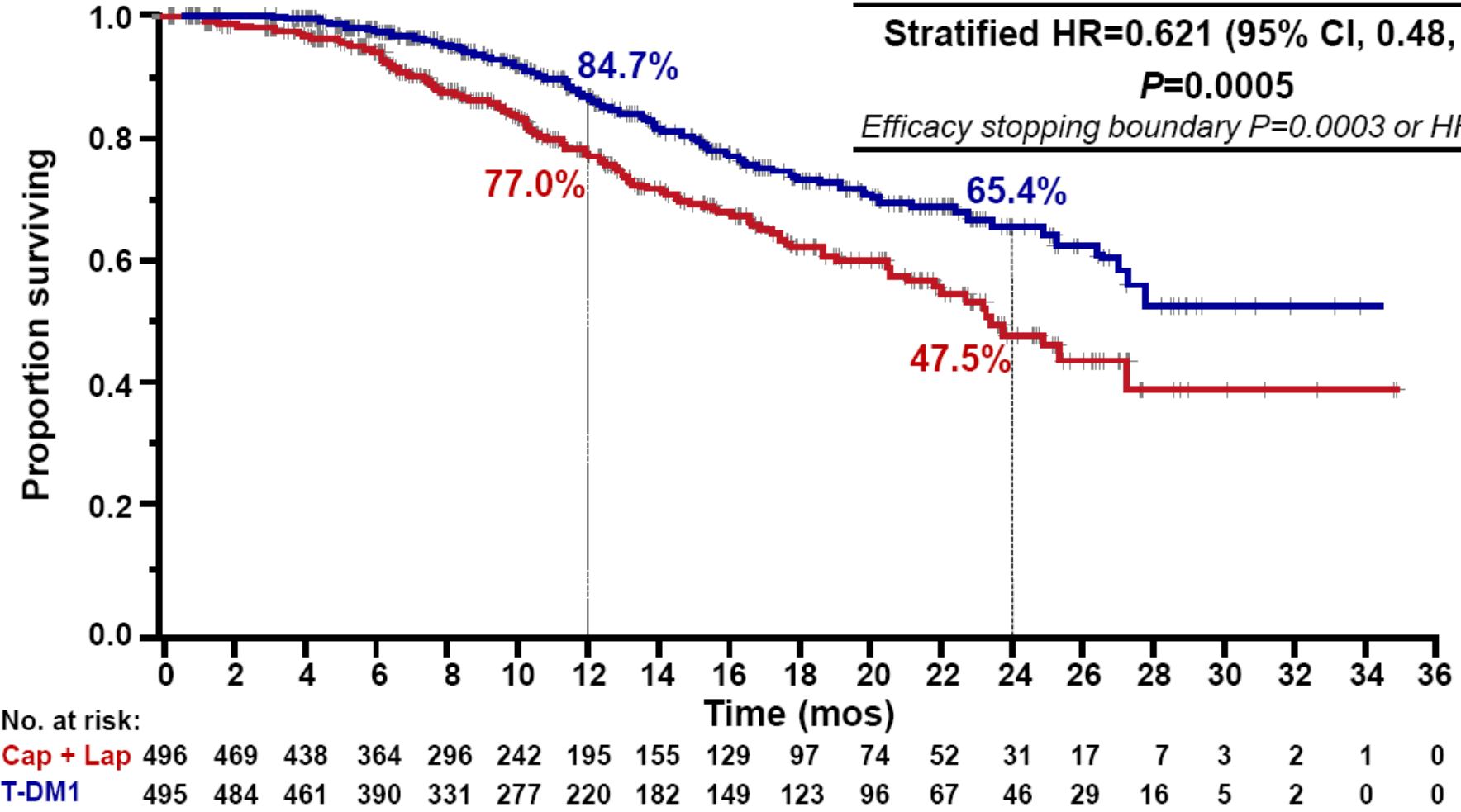
Overall Survival: Interim Analysis

	Median (mos)	No. events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.48, 0.81)

P=0.0005

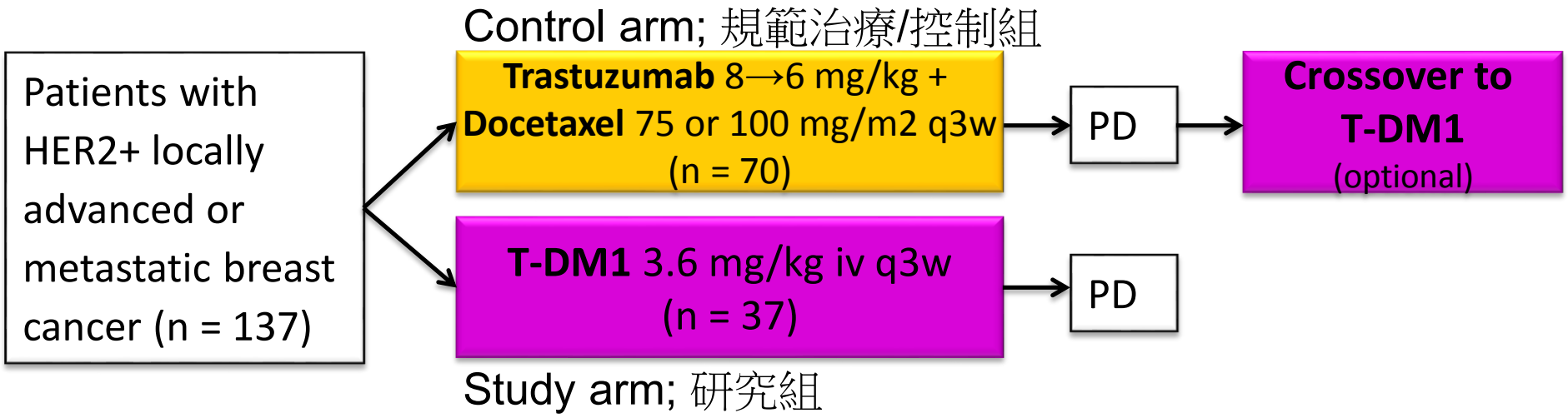
Efficacy stopping boundary P=0.0003 or HR=0.617



Geyer 2010

1st line MBC:
T-DM1 vs. Trastuzumab + Docetaxel

Study Design- Rand Phase II

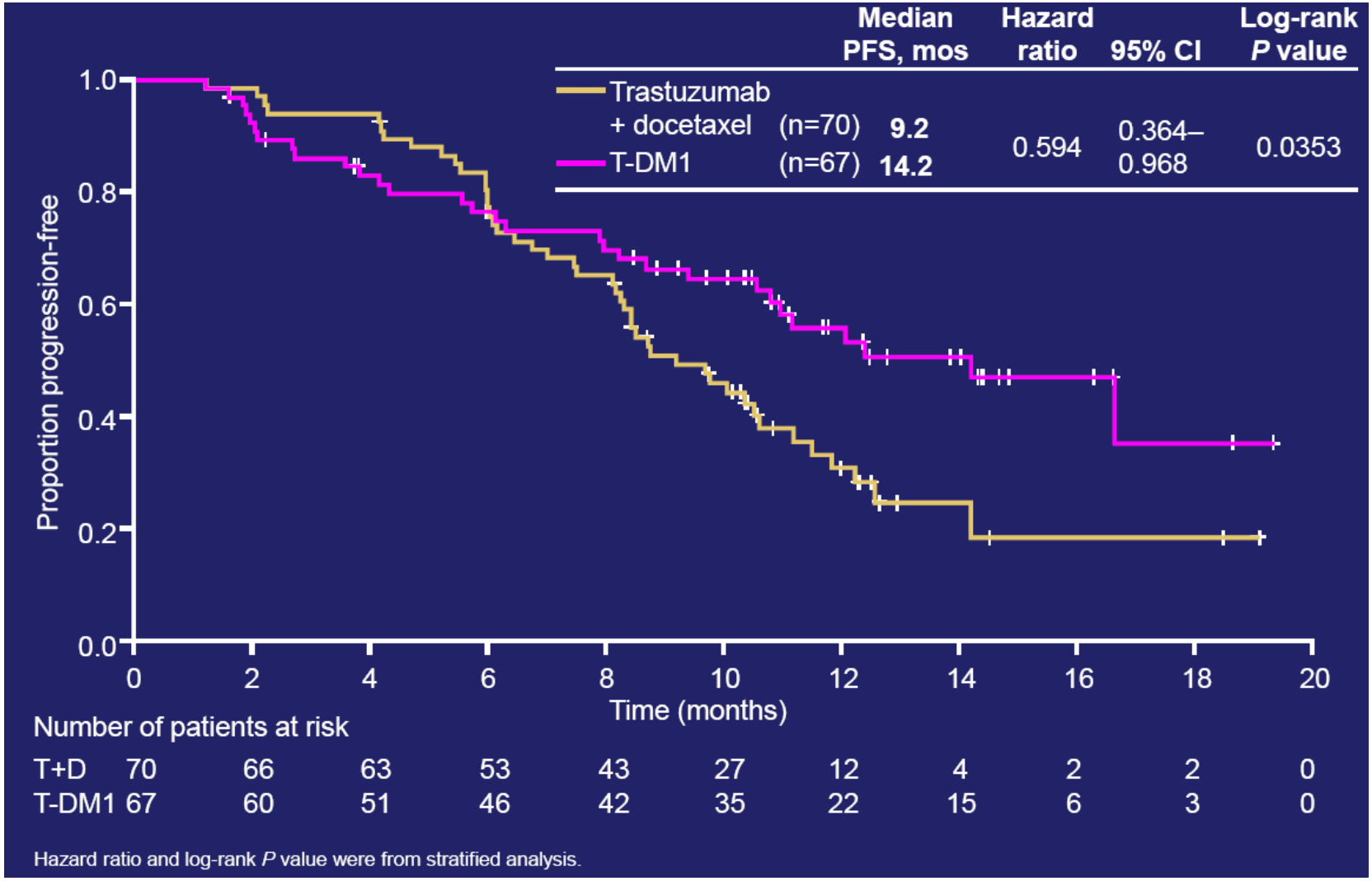


- Stratification factors: World region, prior adjuvant trastuzumab therapy, disease-free interval
- Primary end points: PFS by investigator assessment, and safety
- Data analyses were based on clinical data cut of Nov 15, 2010 prior to T-DM1 crossover
- Key secondary end points: OS, ORR, DOR, CBR, and QOL

Hurvitz, ESMO 2011

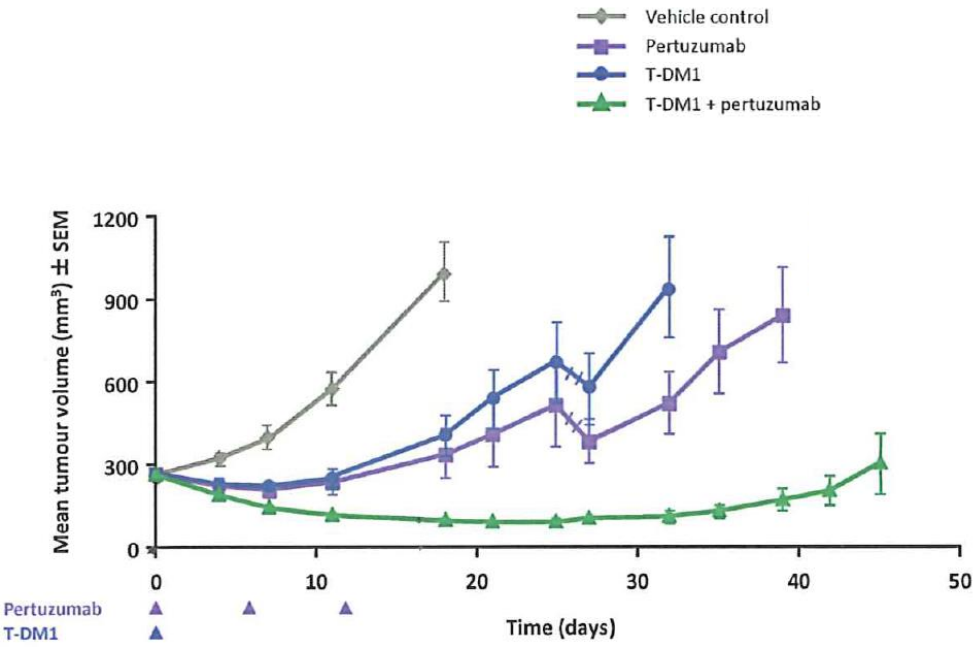
Primary endpoint: PFS

by Investigator



T-DM1 in combination with pertuzumab

KPL-4 breast cancer xenograft model



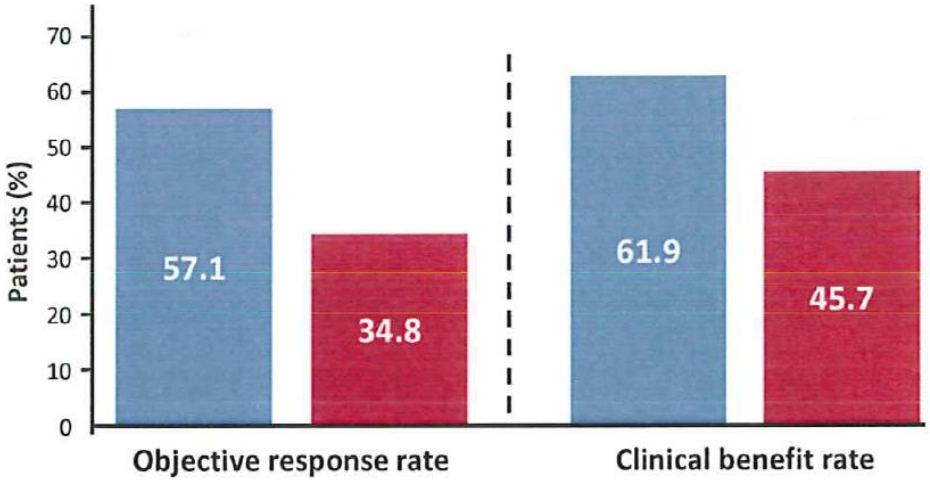
Fields et al. AACR 2010. Abstract 5607

Phase Ib/II single arm

First-line (n = 21)

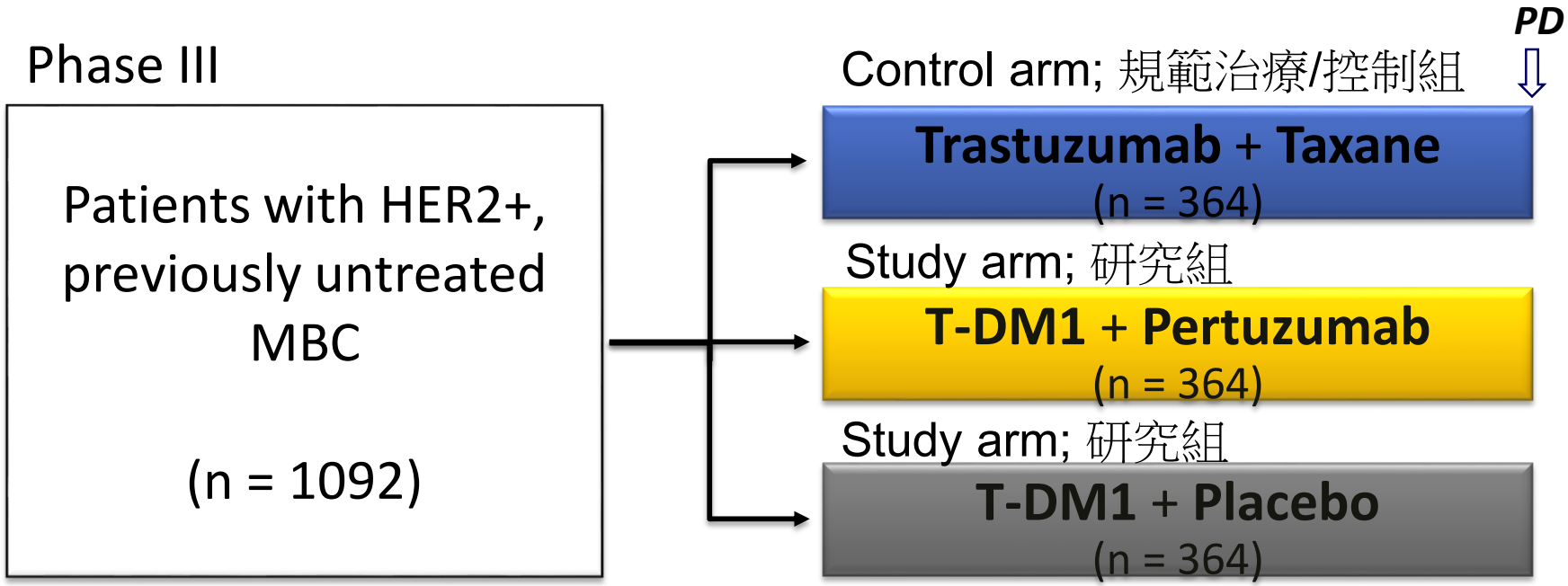
Relapsed (n = 46)

Median no. prior systemic agents in metastatic setting (range) = 6.0 (2-14); No prior T-DM1 or pertuzumab



Dieras et al. SABC 2010. P3-14-01

1st line HER2+ MBC: MARIANNE Study



- Primary endpoints: PFS as assessed by IRF, AEs
  - Superiority design with a noninferiority analyses
  - Interim futility analysis: option to drop experimental arm
- Secondary endpoints: OS, TTF by IRF, ORR, CBR, DOR

ClinicalTrials.gov. NCT01120184.

Ellis ASCO 2012
Result pending in ASCO 2015

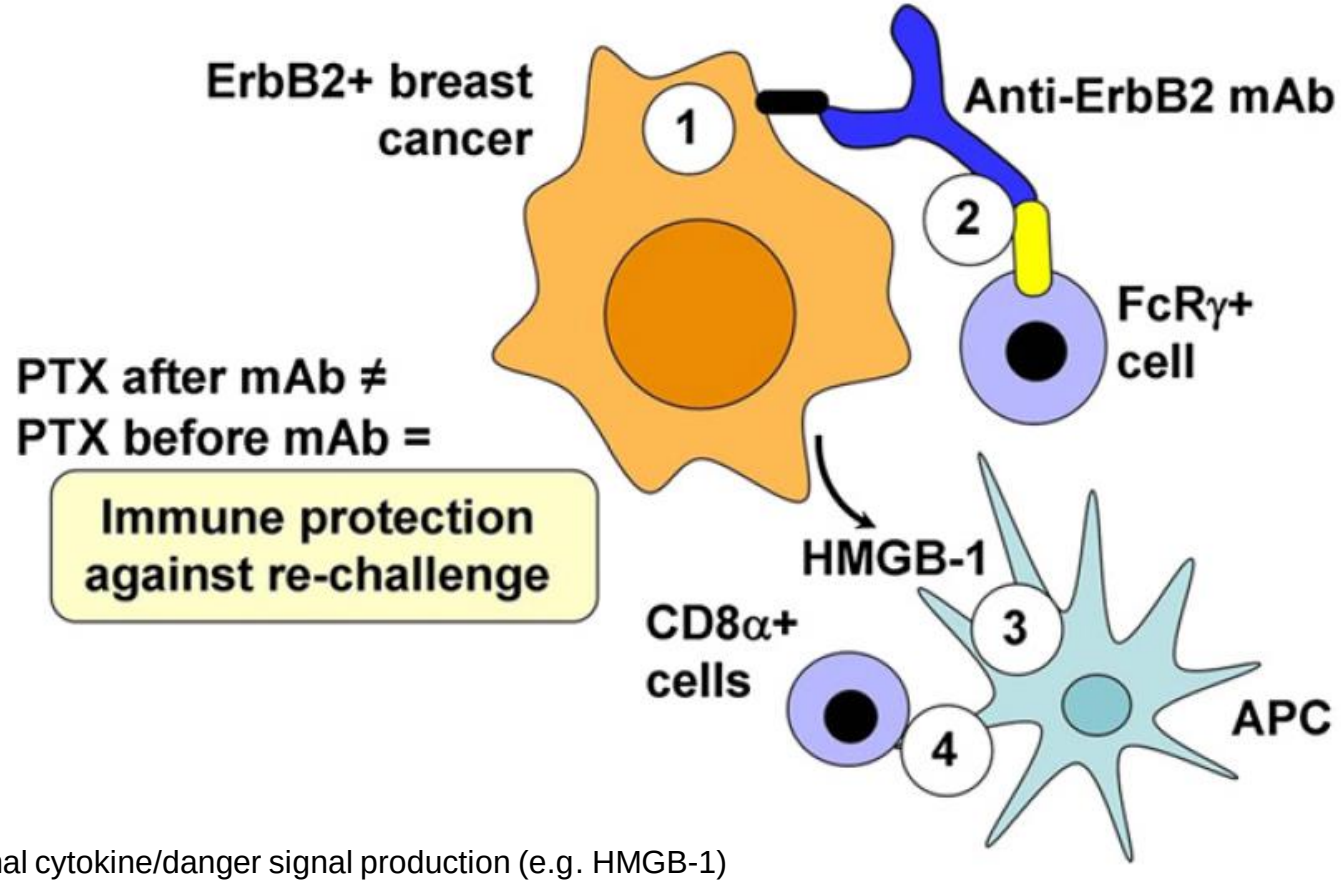
HER2 targets for anticancer therapy

5. **HER2-specific binding by antibodies**

Action for Trastuzumab-

A Revised Mechanism:

- Trastuzumab marks HER2 overexpressed tumour cells for immunological destruction (ADCC), through recruitment of cytotoxic effector cell



FcR+ cells

- ADCC
- induce additional cytokine/danger signal production (e.g. HMGB-1)
- triggers MyD88-dependent activation of antigen-presenting cells (APC)

➢ may more effectively activate the CD8α-dependent adaptive immune system for enhanced tumor control.

Smyth, Cancer Res 2010

Relationship of anti-Her2 Mab therapy and cytotoxic treatment

- **Timing** of cytotoxic agent administration :
  - anti- HER2 mAb → paclitaxel:
    - abrogated secondary immune responses to tumor
  - paclitaxel → anti- HER2 mAb:
    - preserved immune responses[1]
- **Dose** of cytotoxic agent:
  - Chemotherapy may reduced T cell responses → alter immune responses.
  - Low dose chemotherapy may significantly reduce tumour burden while boosting immune responses.

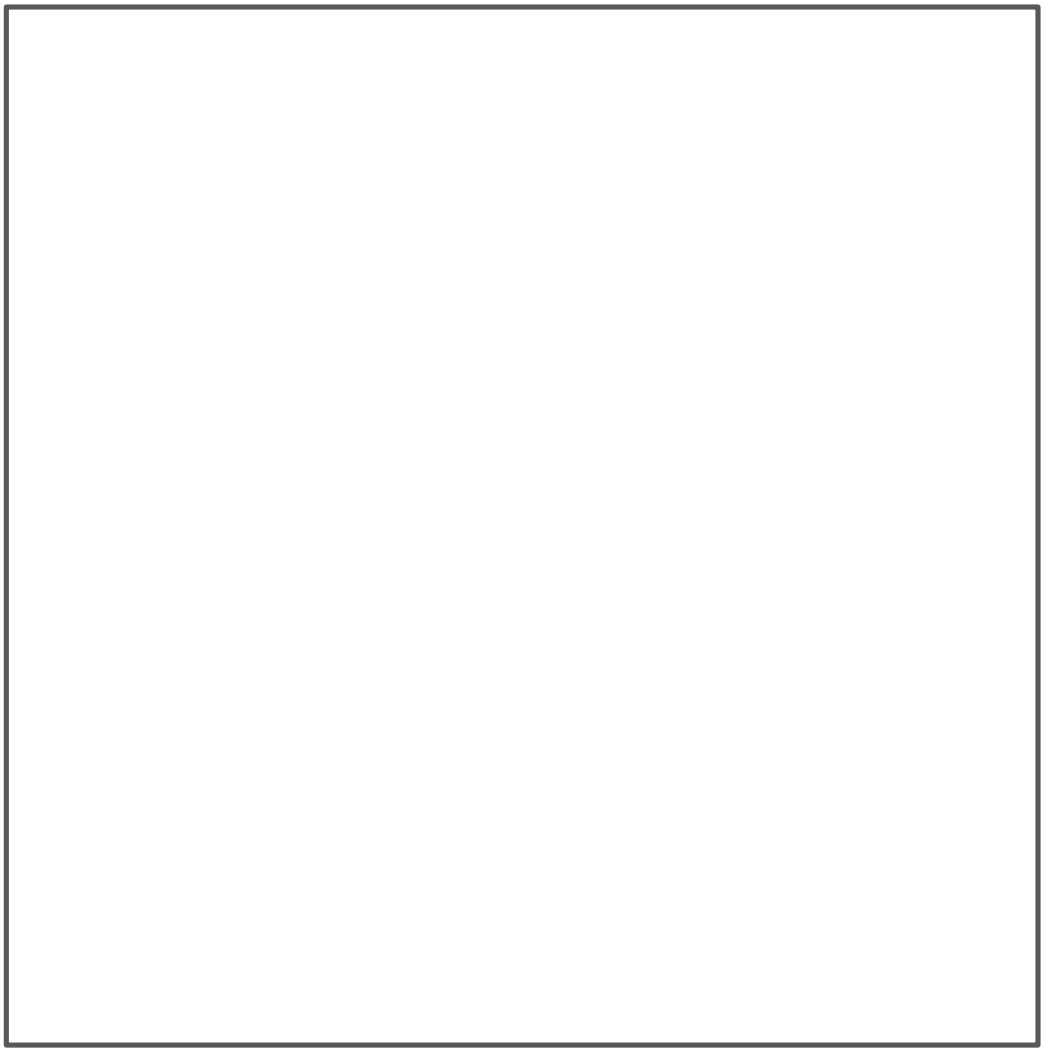
[1]*Park, Cancer Res 2010*

HER2 targets for anticancer therapy

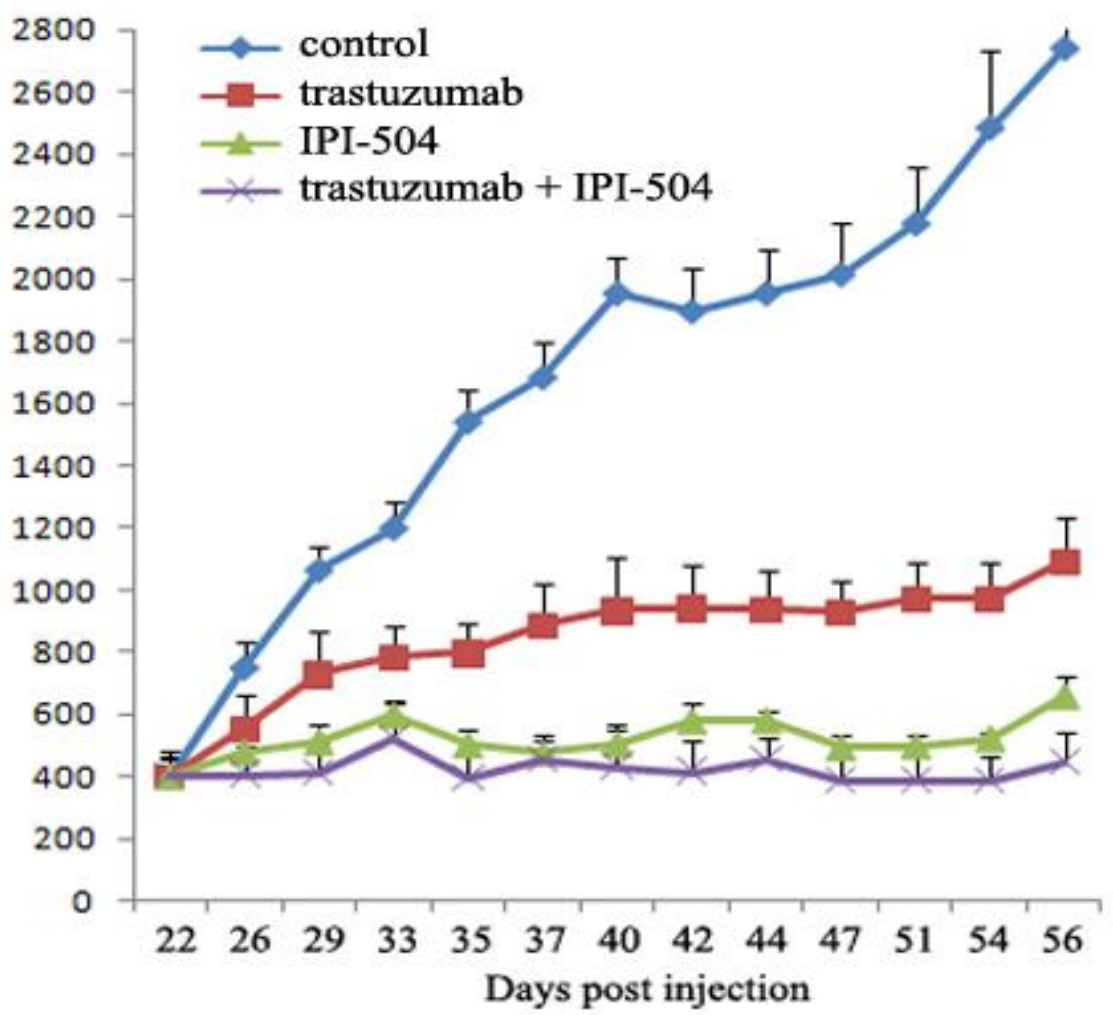
6. **Inhibition of HSP90**

HSP90 as a Therapeutic Target

- Chaperone protein
- Required for the maturation and stabilization of client proteins
- Key clients include:
  - HER2
    - mutant p53
  - ER/PR/AR
    - v-src
  - AKT
    - bcr-abl
  - MET
    - mutant B-RAF
  - Raf kinase
- HSP90 inhibition: results in ubiquitylation and proteasomal degradation of both HER2 and its downstream signalling partners

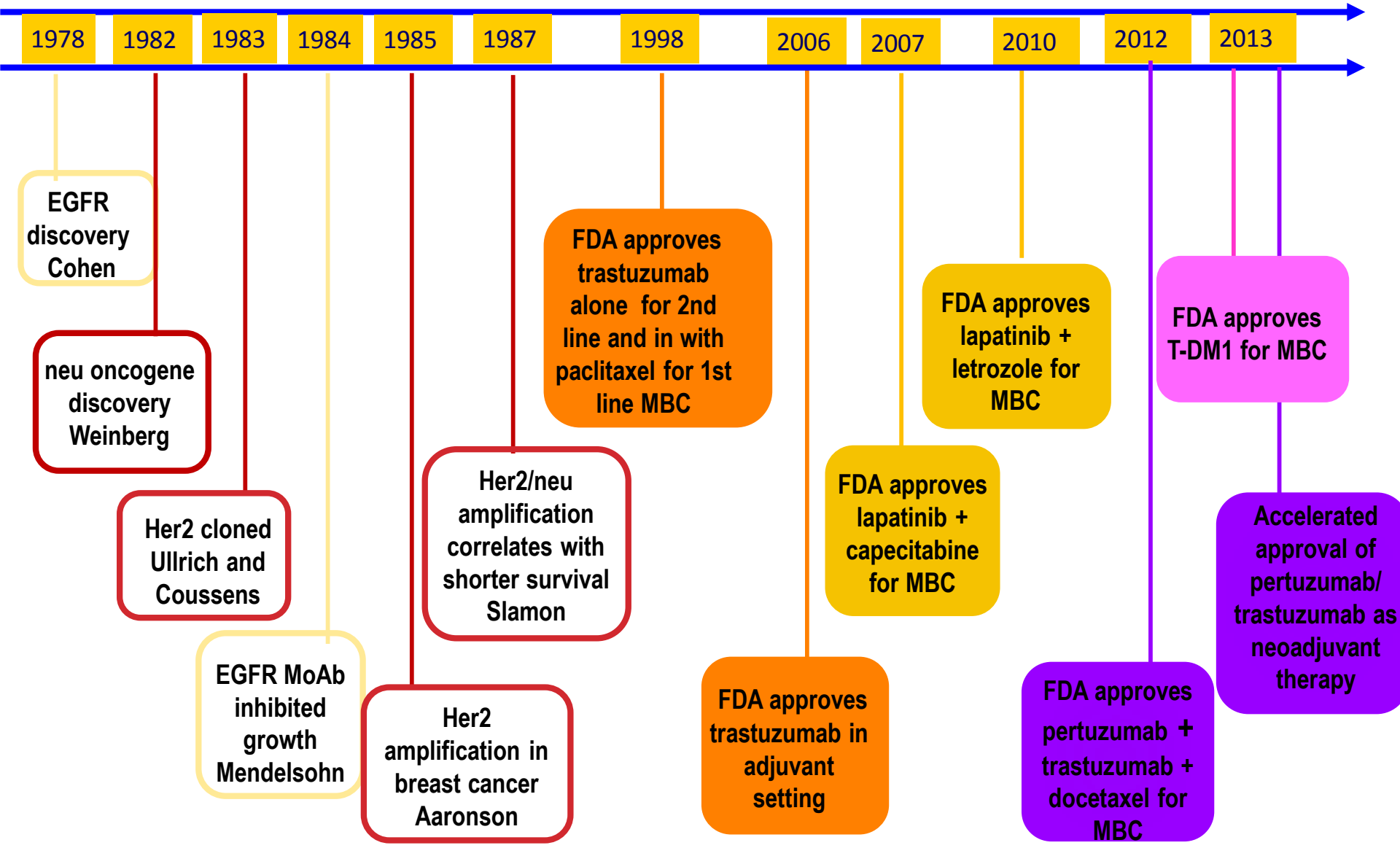


HSP-90 Inhibitors are active in trastuzumab resistant BT-474 HER2 +ve tumors



Maurizio Scaltriti

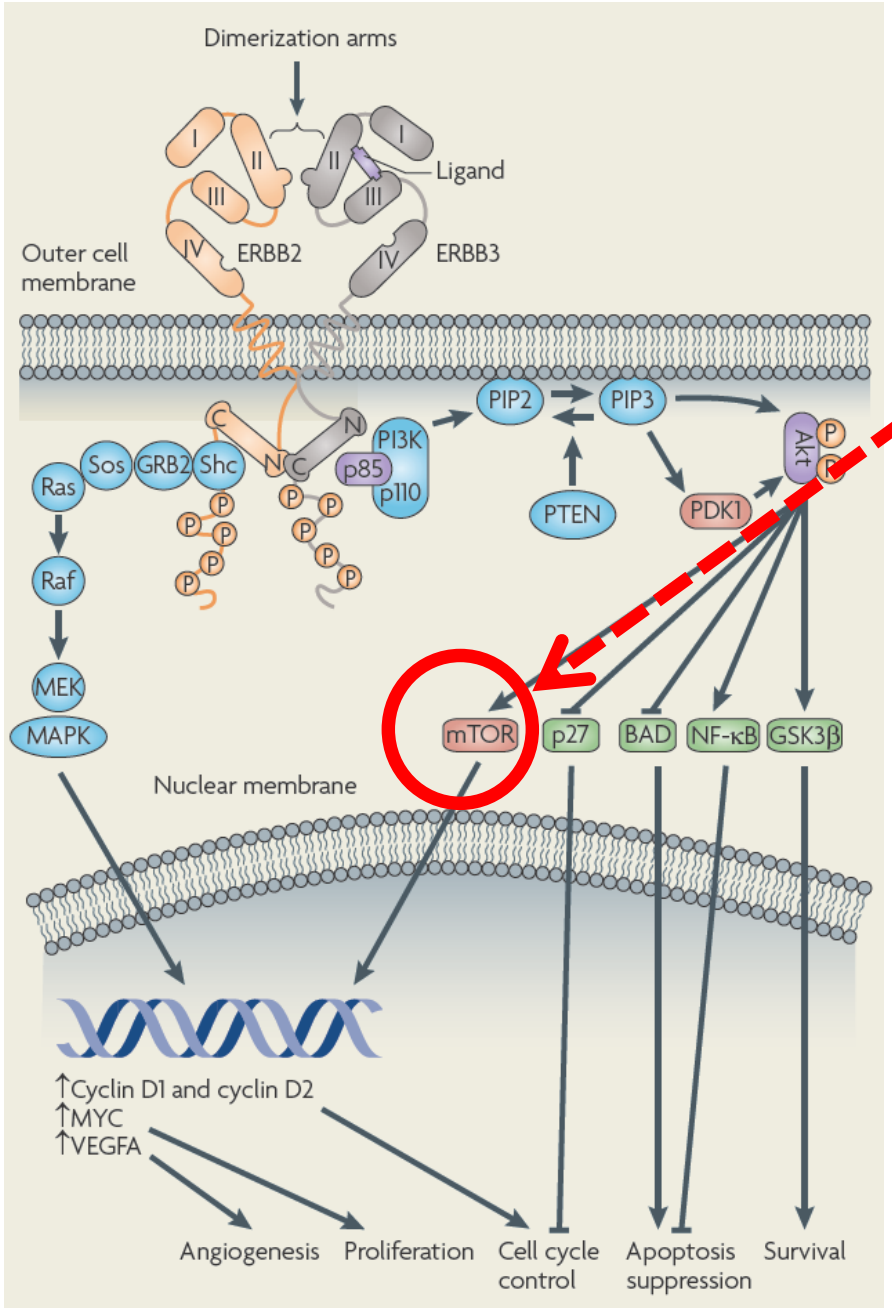
Milestones of HER2/anti-HER2 therapies in BC



MBC : metastatic breast cancer; MoAb : monoclonal antibody

Other approaches for HER2+ MBC

Signalling downstream of HER dimer formation



Two key signalling pathways :

1. MAPK pathway, which stimulates proliferation
2. PI3K–Akt pathway, which promotes tumour cell survival

Baselga, 2009

m-TOR inhibition

Everolimus in HER2+ MBC (BOLERO-3)

HER2+ MBC
Prior taxane
Trastuzumab failure
(<12 m of adjuvant Tras or
< 4/52 of PD with Tras)
N=572

Study arm; 研究組

Vinorelbine (25mg/m^2 weekly)
Trastuzumab (2mg/kg weekly)
Everolimus 5 mg po daily

Vinorelbine (25mg/m2 weekly)
Trastuzumab (2mg/kg weekly)
Placebo po daily

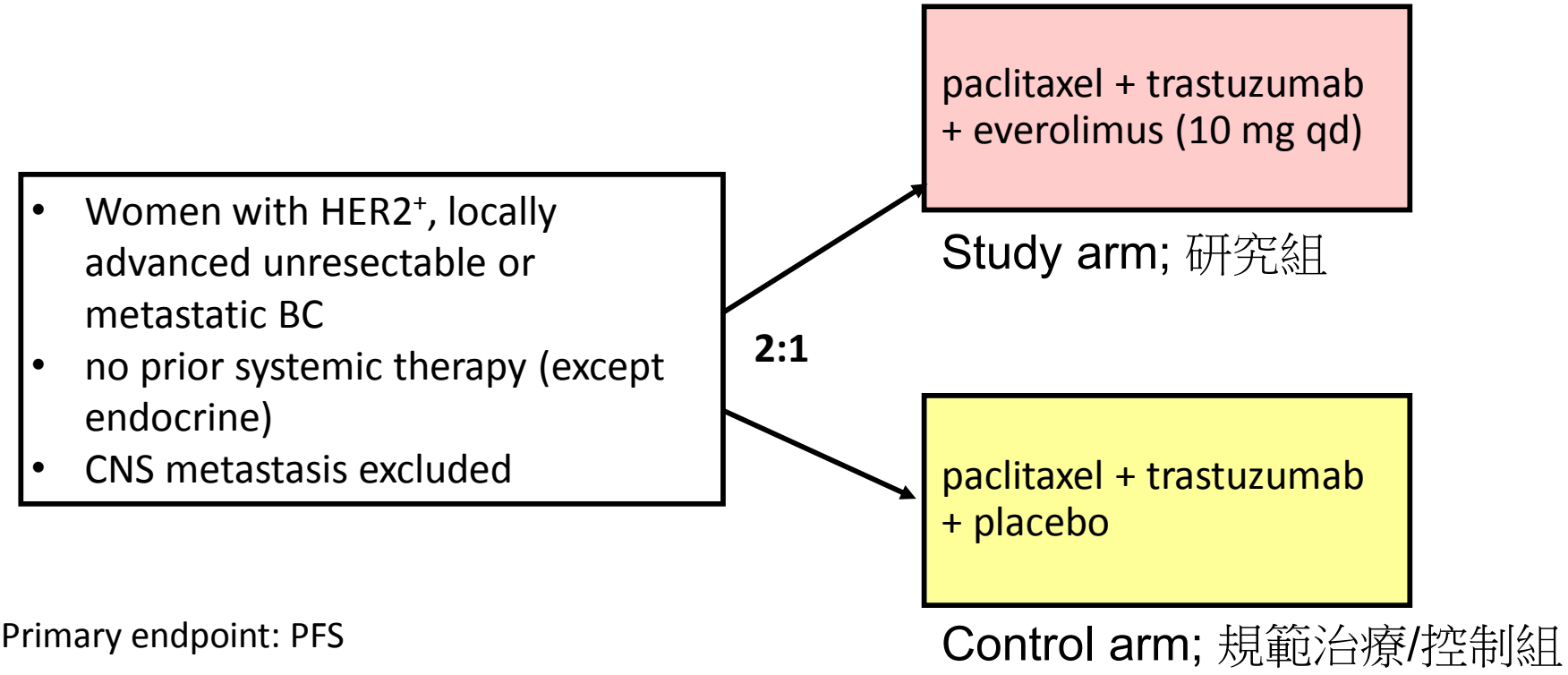
Control arm; 規範治療/控制組

	Everolimus (n= 284)	Placebo (n= 285)	p
PFS (1^0 endpoint)	7.00 m	5.78 m	0.0067; HR 0.78 (0.65-0.95)
ORR	40.8%	37.2%	0.2108
CBR	59.2%	53.3%	0.0945
OS	NR	NR	NS (Final analysis to be conducted after 384 deaths)

O'Regan, ASCO 2013

BOLERO-1: Everolimus in HER2+ locally advanced or metastatic BC

Phase III, double-blind, placebo-controlled multicenter trial



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, CBR.
- Additional endpoints: safety, performance status, biomarkers.
- This trial is sponsored by Novartis Pharmaceuticals and is registered (ClinicalTrials.gov: NCT00876395).
- Enrollment began September 2009, with a planned accrual of 717. The current accrual is 719, and the estimated primary completion date is October 2012.

Hurvitz, ASCO 2012

Novel combinations: Anti-HER2 + anti-mTOR- Neratinib + temsirolimus

Phase I/II Her2+ or TNBC:

- 15 pts HER2+ (median 2 priors)
  - 9 PR (ORR = 60%)
  - 1 SD > 6 months
  - Responses seen in pts with prior trastuzumab, lapatinib, T-DM1

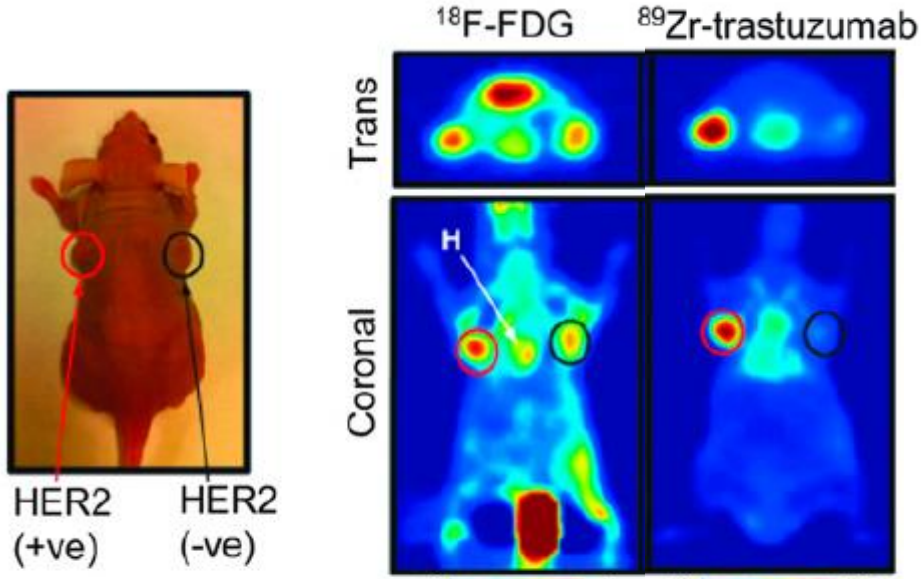
Gajria, SABC 2011

Numerous Treatments for HER2+ Breast Cancer Are in Development

Class	Agents, INSM-
HER2-directed	Liposome (MM-302), TKI (ARRY-380), Trifunctional Ab (Ertumaxomab), Vaccine (AE37)
VEGF Inhibitors	Bevacizumab: AVERAL study (Docetaxel + trastuzumab +/- Bevacizumab)- no advantage
mTOR Inhibitors	Everolimus, temsirolimus, sirolimus
HSP 90 inhibitors	Tanespimycin, alvespimycin, CNF2024, IPI-504, AUY922, SNX5422, ganetespib
IGF-IR inhibitors	CP-75187, E, IMC-AM, NVP-ADW742, INSM-18
HDAC inhibitors	Varinostat, Belinostat, depsipeptide, LBH589, NVP-LAQ824, CI_994, MS-275
PI3k Inhibitors	BEZ235, BKM120, XL765, CDC-0941, GDC-0980, GDC-0032, BYL719 Small molecule selectively binding PI3K isoforms: Inhibit P13K/Akt pathway
HSP 90 inhibitors	Tanespimycin, alvespimycin, CNF2024, IPI-504, AUY922, SNX5422, ganetespib
Akt inhibitors	Perifosine, XL418, Mk-2206

PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; HSP, heat-shock protein; VEGF, vascular endothelial growth factor

Molecular Imaging

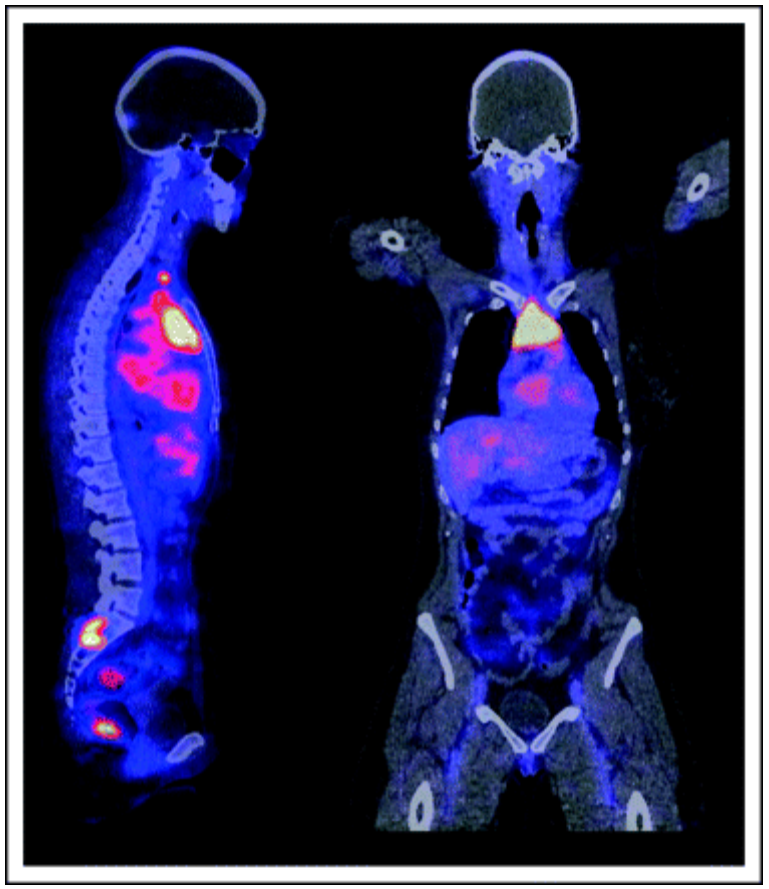


Tumor % ID/g		
HER2(+ve)	3.1 ± 0.5	18.1 ± 2.0
HER2(-ve)	3.2 ± 0.7	6.7 ± 0.8

- Specificity of Zirconium-89-trastuzumab for HER2+ tumors.
- ^{89}Zr-trastuzumab and ^{18}F-FDG PET images of athymic nude mice bearing subcutaneous HER2+ NCI-N87(left) and HER2- MKN-74 (right)
- HER2+ and HER2- tumors were ^{18}F-FDG PET-avid
- Only HER2+ tumor was ^{89}Zr-trastuzumab-FDG PET-avid

Janjigian, J Nucl Med 2013

Molecular Imaging



- ^{89}Zr-trastuzumab PET scan
  - the potential as a noninvasive assessment tool of HER2 status of MBC
    - ability to measure receptor expression for the entire disease burden
  - possibility to evaluate lesions unsuitable for a biopsy
    - avoiding the sampling error that can occur with heterogeneous receptor expression
- Potential to guide treatment options in targeted therapy in HER2+ MBC
  - ^{18}F-FDG PET positive tumours may not be ^{89}Zr-trastuzumab PET positive
  - ^{89}Zr-trastuzumab PET potentially enables evaluation of HER2 expression (with extracellular domain) for the entire disease burden:
    - Negative scan indicates tumours that may not respond to trastuzumab therapy

Gaykema, JCO 2012

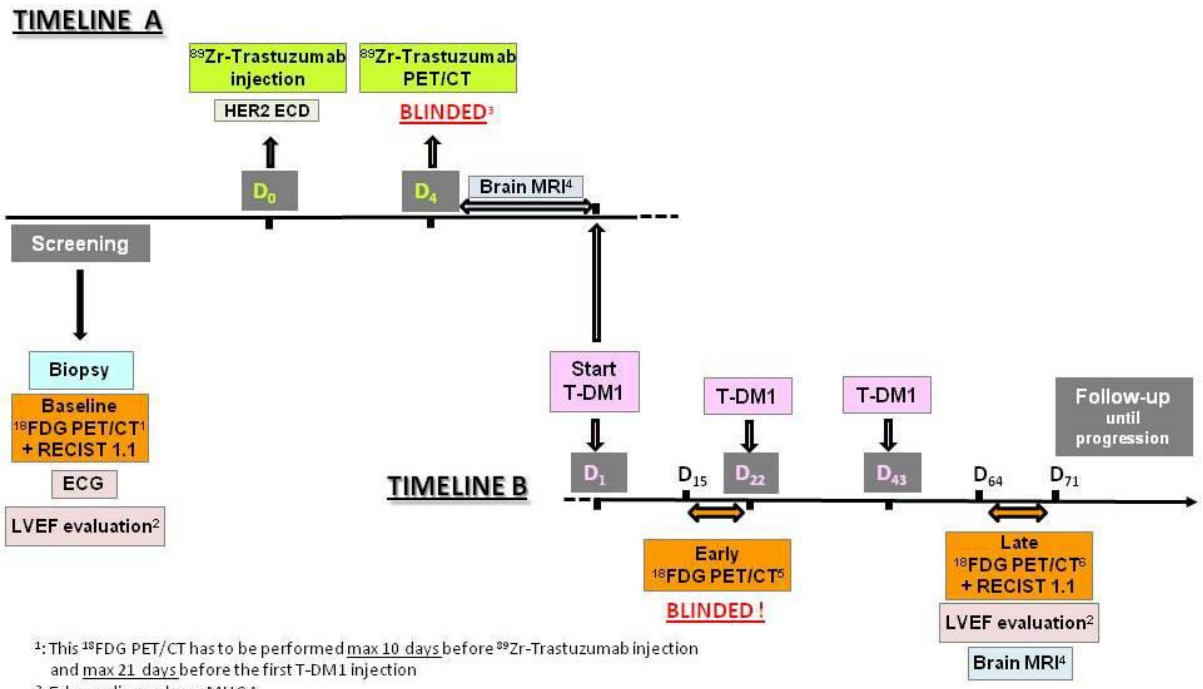
Correlative Molecular Imaging Study: ZEPHIR study

Primary objective

- To show that ^{89}Zr-trastuzumab PET /CT combined with FDG-PET/CT is able to select early lesions (patients) not benefiting from treatment with TDM1

Secondary objective

- To show that early FDG-PET/CT (after one cycle of TDM1) is able to select lesions not benefiting from treatment with TDM1



1: This ^{18}FDG PET/CT has to be performed max 10 days before ^{89}Zr-Trastuzumab injection and max 21 days before the first T-DM1 injection
2: Echocardiography or MUGA
3: ^{89}Zr-Trastuzumab will be blinded to treating Oncologist.
4: Only if unknown asymptomatic brain lesion detected on ^{89}Zr-Trastuzumab PET/CT.
5: Before the 2nd T-DM1 injection, results blinded to treating Oncologist.
6: Before the 4th T-DM1 injection.

EudratCT number: 2011-005437-39

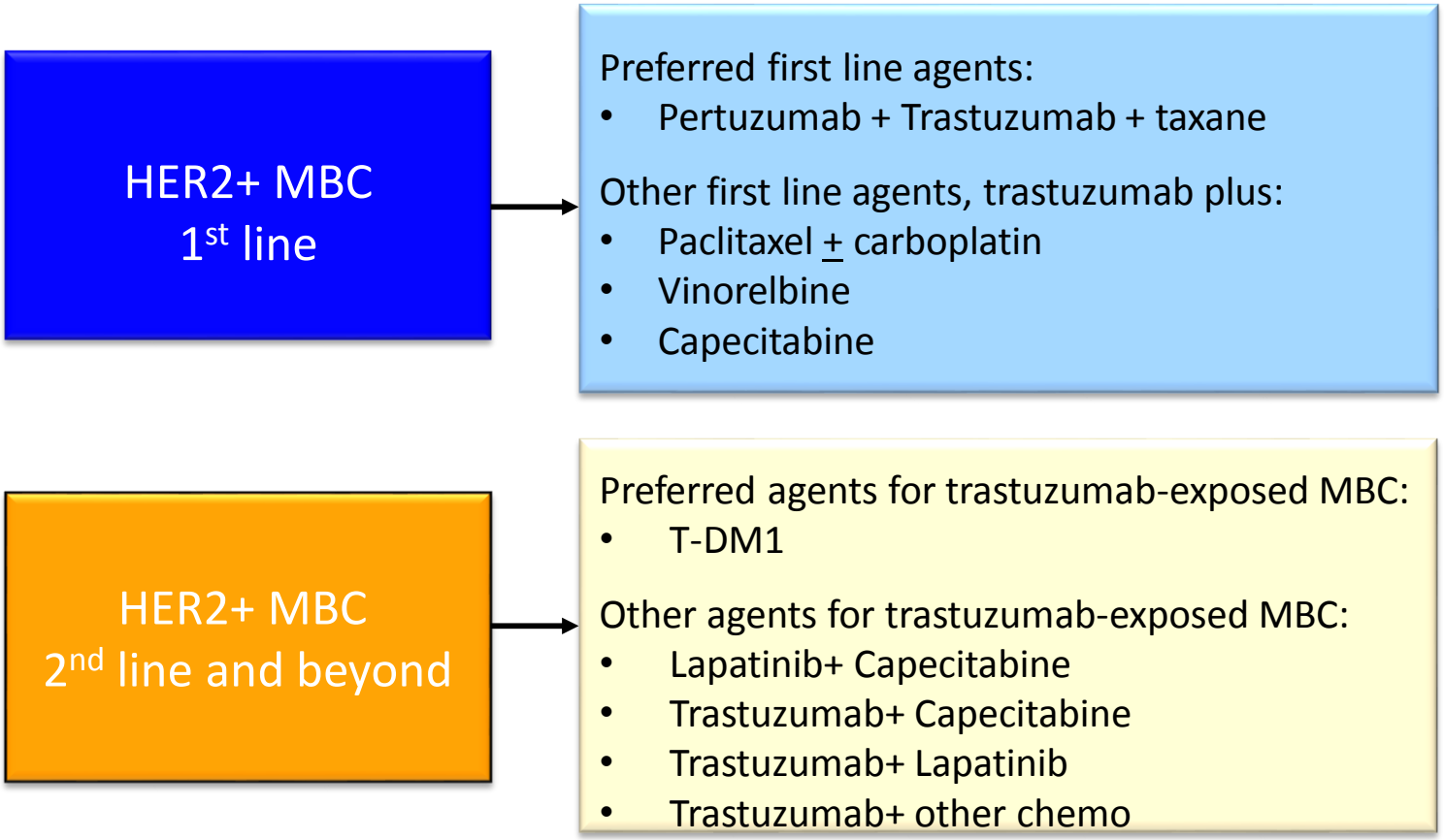
Prognosis in MBC by HER2 Status and by Therapy With Trastuzumab

N = 2091 (median f/u = 16.9 mos)	No. of pts (%)	1-yr survival (95% CI)	HR
HER2-positive	118 (5.6)	70.2% (60.3%, 78.1%)	—
HER2-negative	1782 (85.3)	75.1% (72.9%, 77.2%)	0.56 (95% CI 0.45-0.69, P = 0.0001)
HER2-positive treated with trastuzumab	191 (9.1)	86.6% (80.8%, 90.8%)	

CI = confidence interval; HR = hazard ratio; MBC = metastatic breast cancer

Dawood SS, et al. J Clin Oncol. 2010

HER2+ MBC: Treatment



HER2+ MBC treatment outcome with anti-HER2 therapies

Year	Treatment	Median survival
2001	Chemotherapy alone	20 m
2001	Chemotherapy+ trastuzumab in the 1st line	29 m
2014	Chemotherapy+ trastuzumab in the 1st line Other treatment with trastuzumab and/or lapatinib in 2nd line and beyond	41 m
2014	Chemotherapy+ trastuzumab + pertuzumab in the 1st line Other treatment with various anti-HER2 agents in 2nd line and beyond	57 m

Conclusions

- HER2+ MBC remains incurable:
  - HER2 remains a valid target after progression on trastuzumab
  - Strategies to overcome resistance
    - combinations of HER2-directed therapies
  - Becoming a chronic disease:
    - Multiple, sequential therapies available

- Does everyone needs chemo
  - Does everyone needs to have all anti-HER2 agents at the same time
    - Some may work with single anti-HER2
  - Markers to tailor personalized therapy
    - Molecular
    - Imaging

- Her2+ EBC:
  - Most patients are considered for trastuzumab-containing chemotherapy
  - We are definitively curing patients with trastuzumab in early stage breast cancer
  - On-going trials will address if further anti-HER2 agents provide additional benefit

- Financial implications associated with novel therapies

Thank you