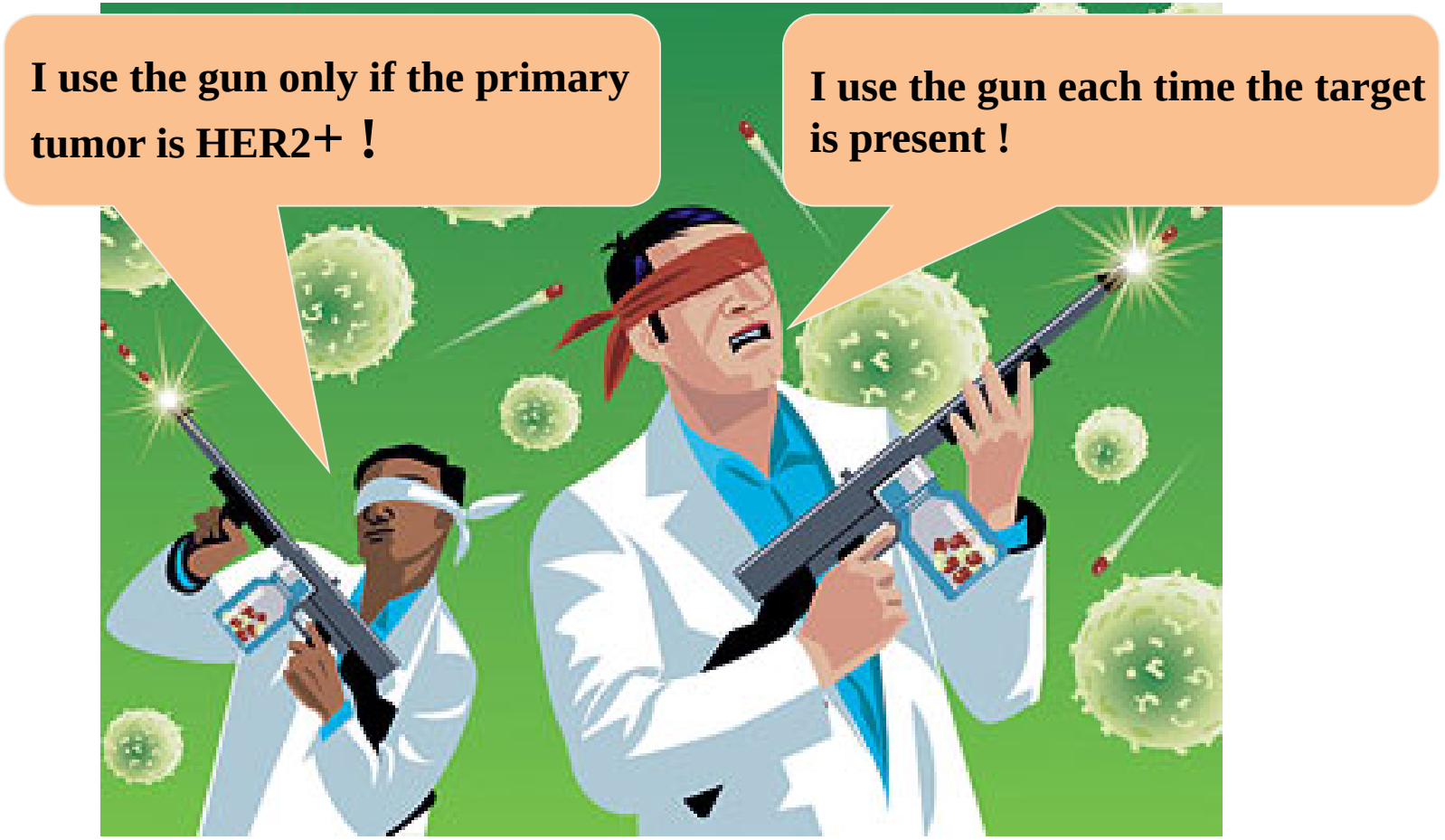
2nd International Congress of Breast Cancer Disease Centers
February 9th-10th, 2012

Future B.C. strategies

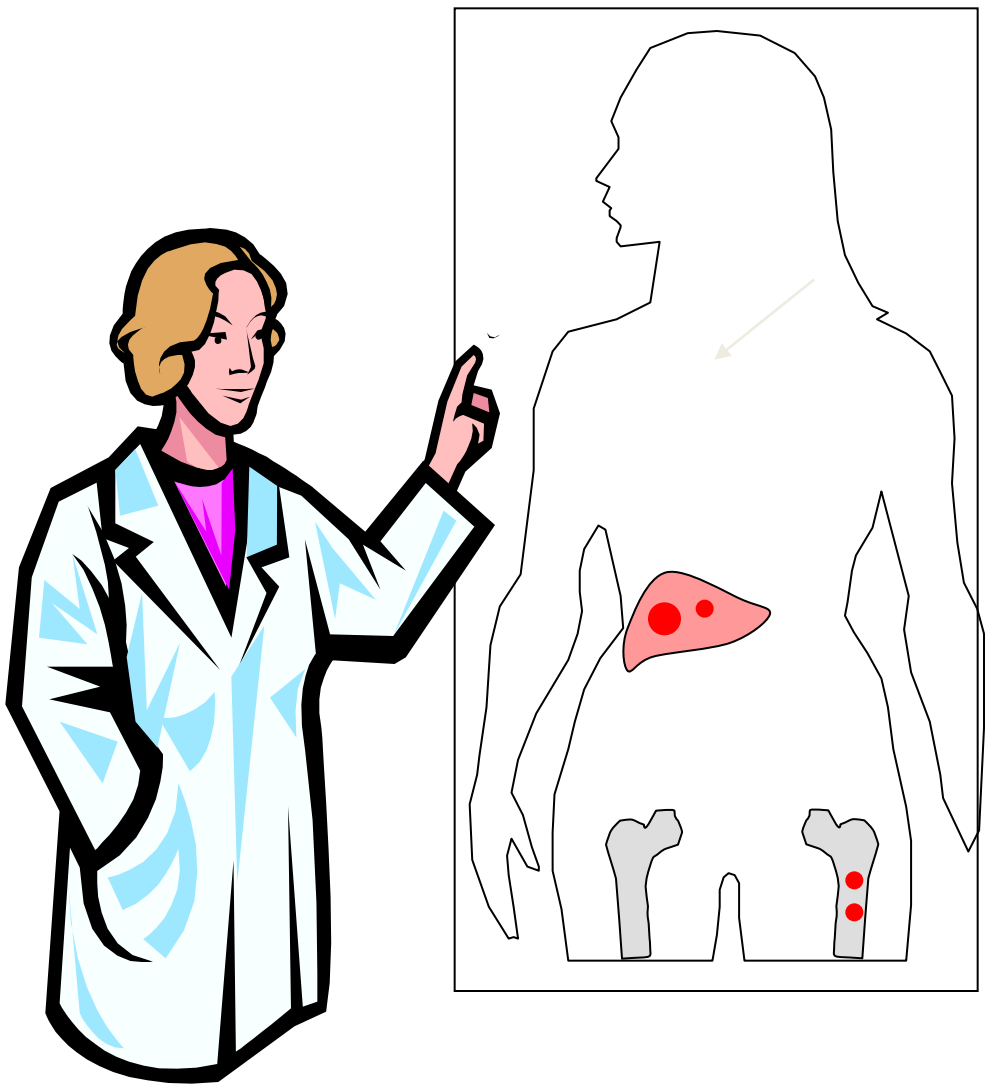
The example of HER2 positive B.C. !

Martine J. Piccart-Gebhart, MD, PhD
Jules Bordet Institute, Brussels, Belgium
Université Libre de Bruxelles
Breast International Group (BIG aisbl), Chair

TRASTUZUMAB PRESCRIPTION BY MEDICAL ONCOLOGISTS IN 2012



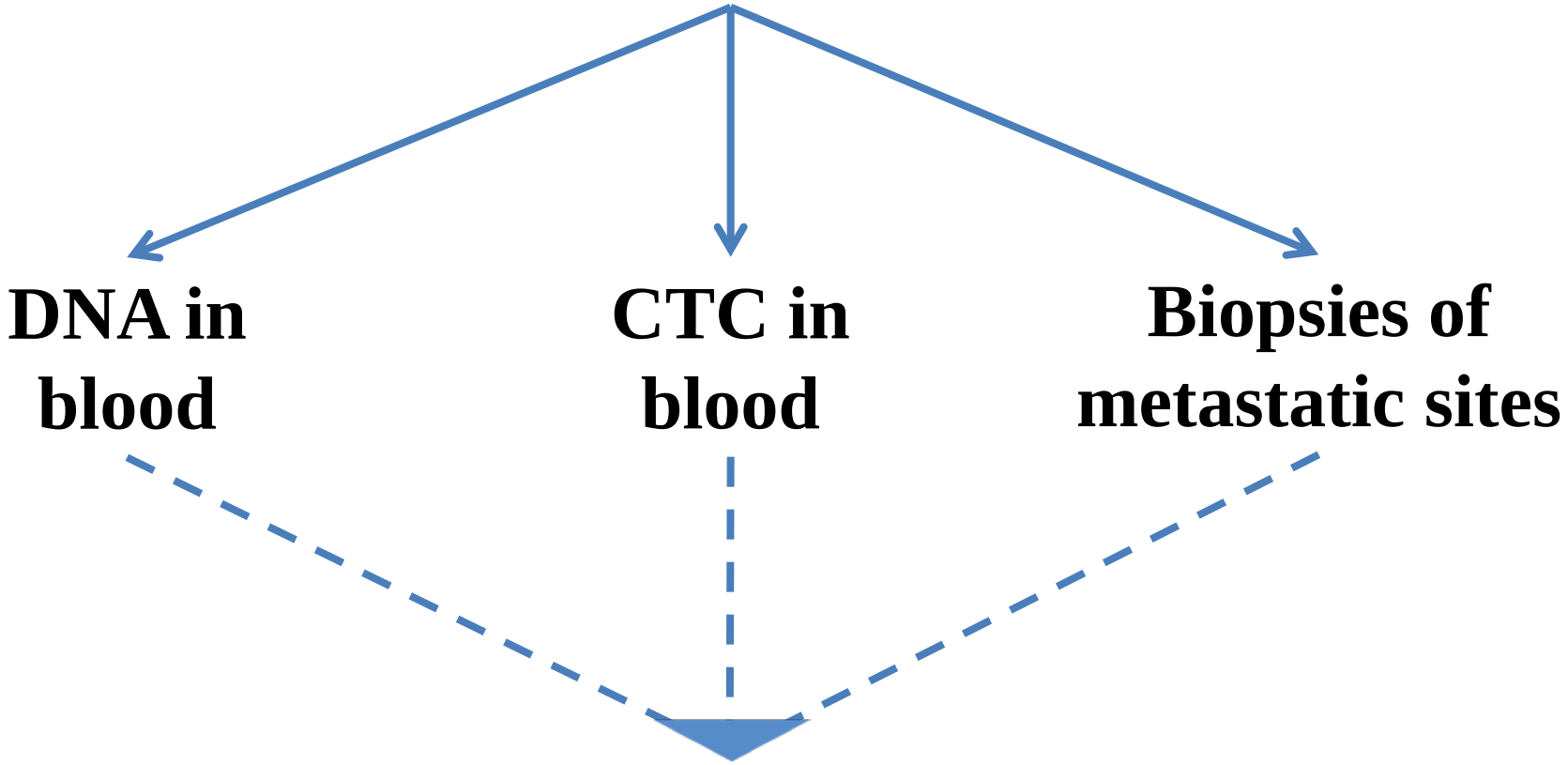
TREATING HER2 POSITIVE BC IN 2020



Better molecular diagnostic tests

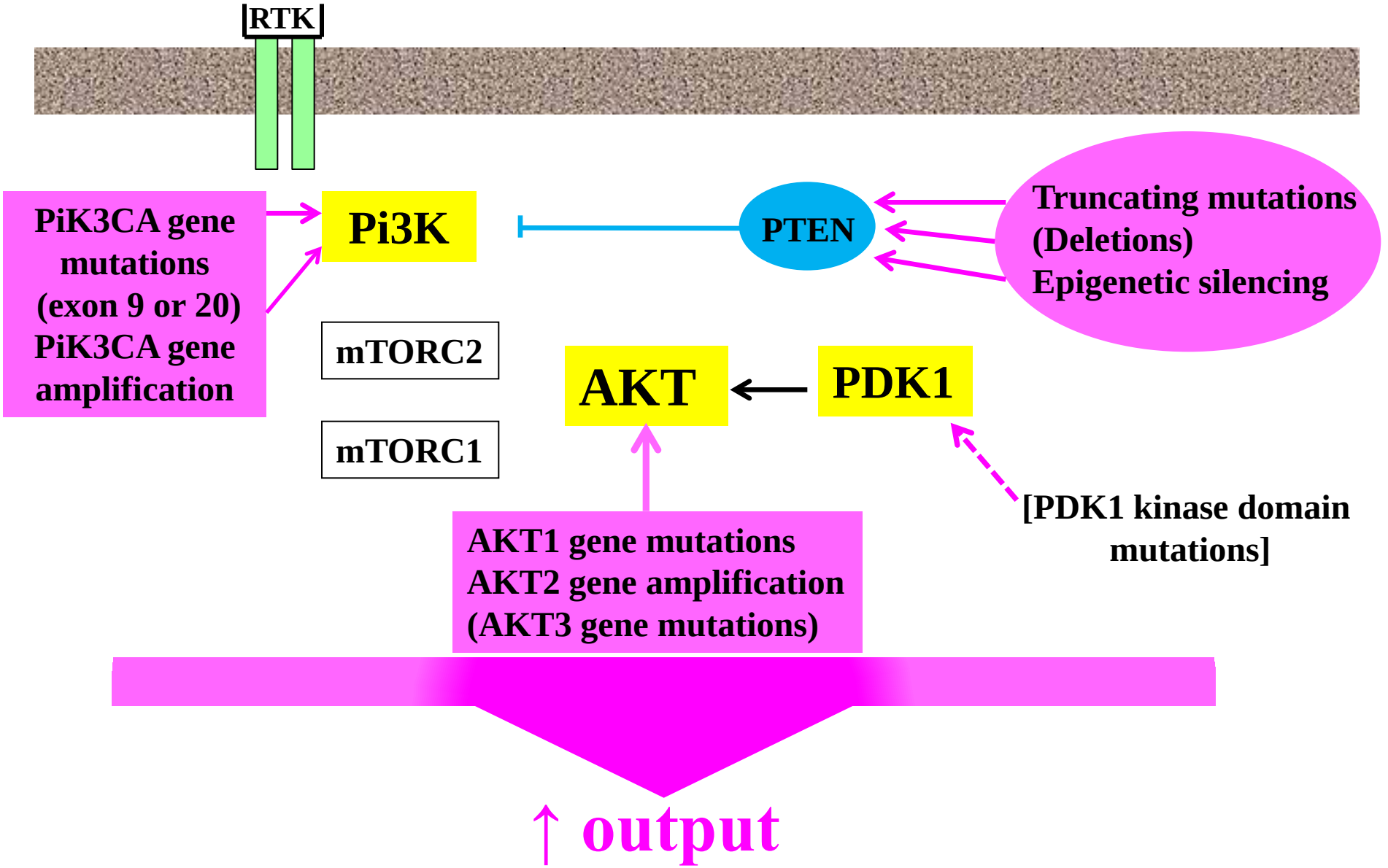
Better imaging tests

Better diagnostic tests for HER2 positive BC

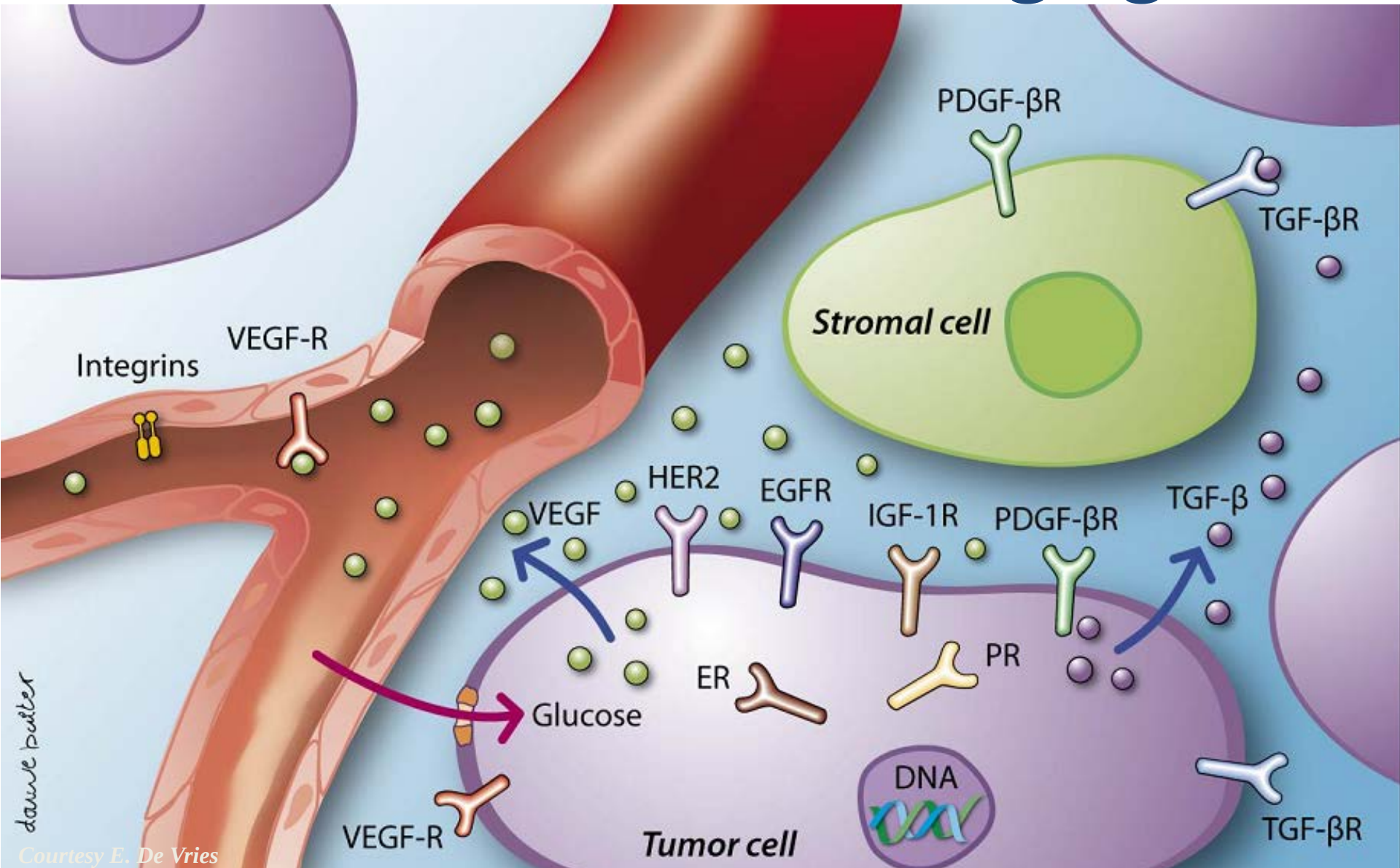


- **Dissection of alterations in the Pi3K/MEK signalling cascade**
- **Presence or not of an immmune gene signature**

Genetic aberrations of the Pi3K signaling pathway in breast cancer

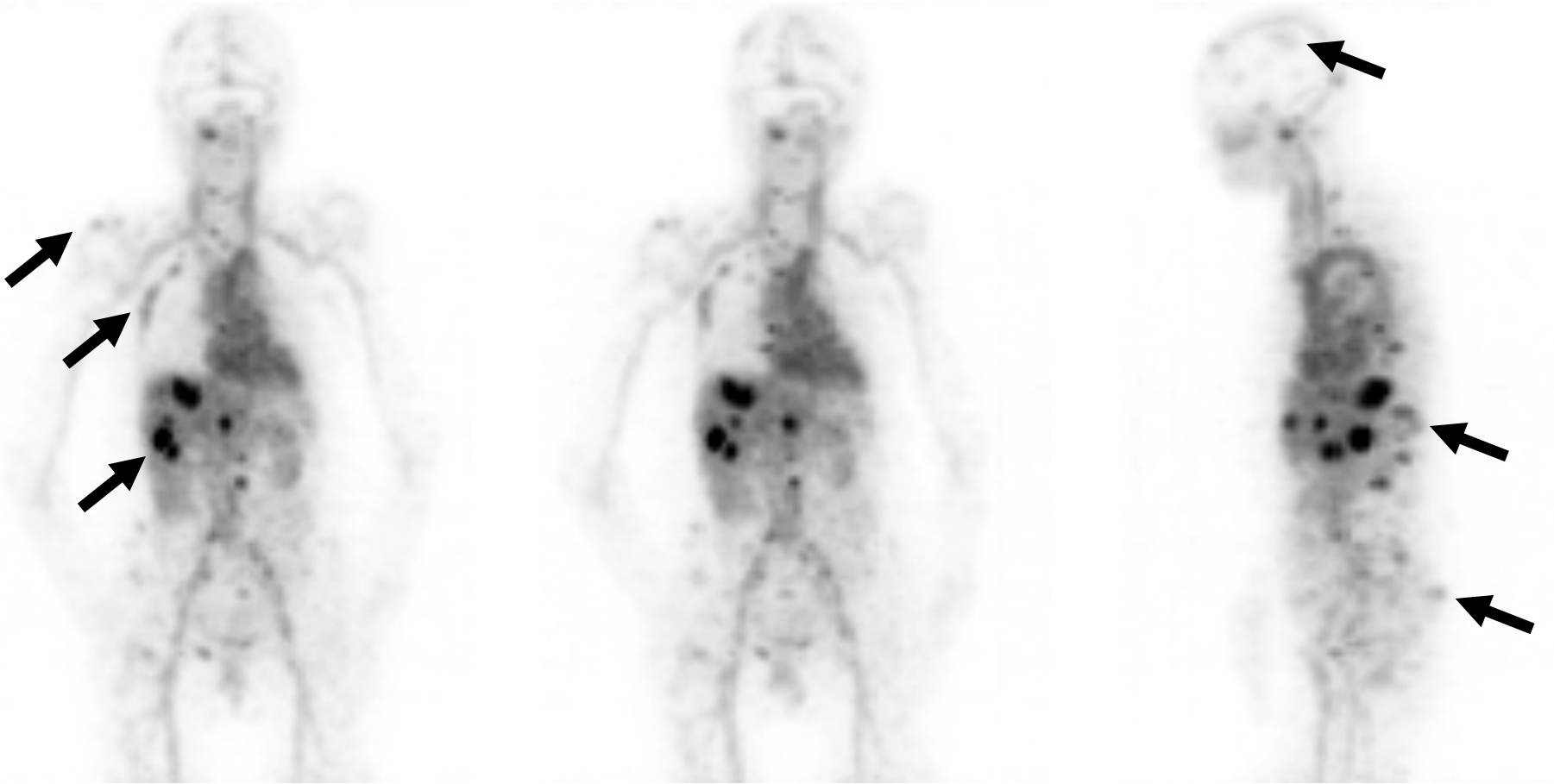


Targets for ligands: molecular tumor imaging



Courtesy E. De Vries

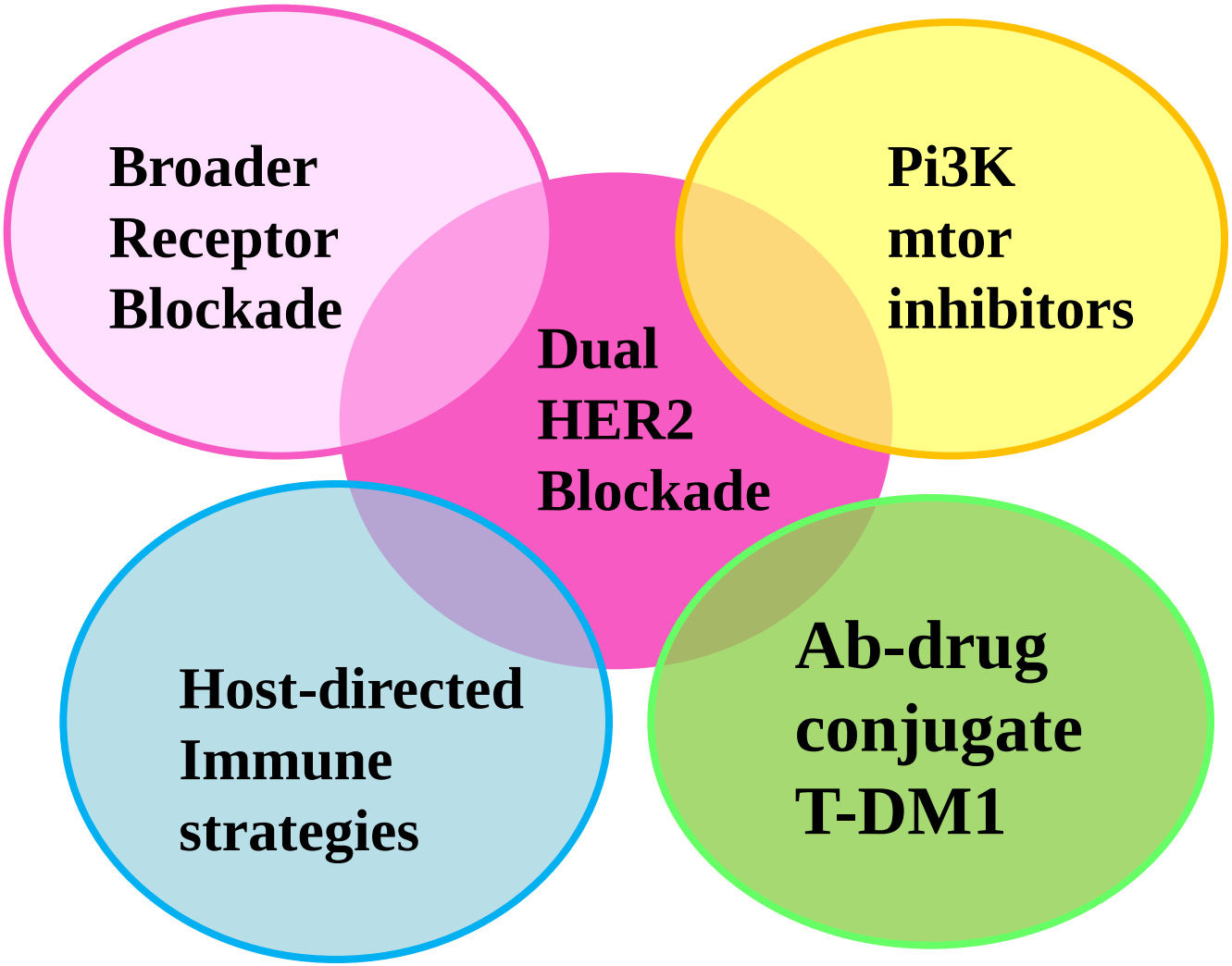
^{89}Zr-trastuzumab tumor visualization during trastuzumab treatment



Day 4

Courtesy E. De Vries

Future treatment strategies in HER2 positive BC



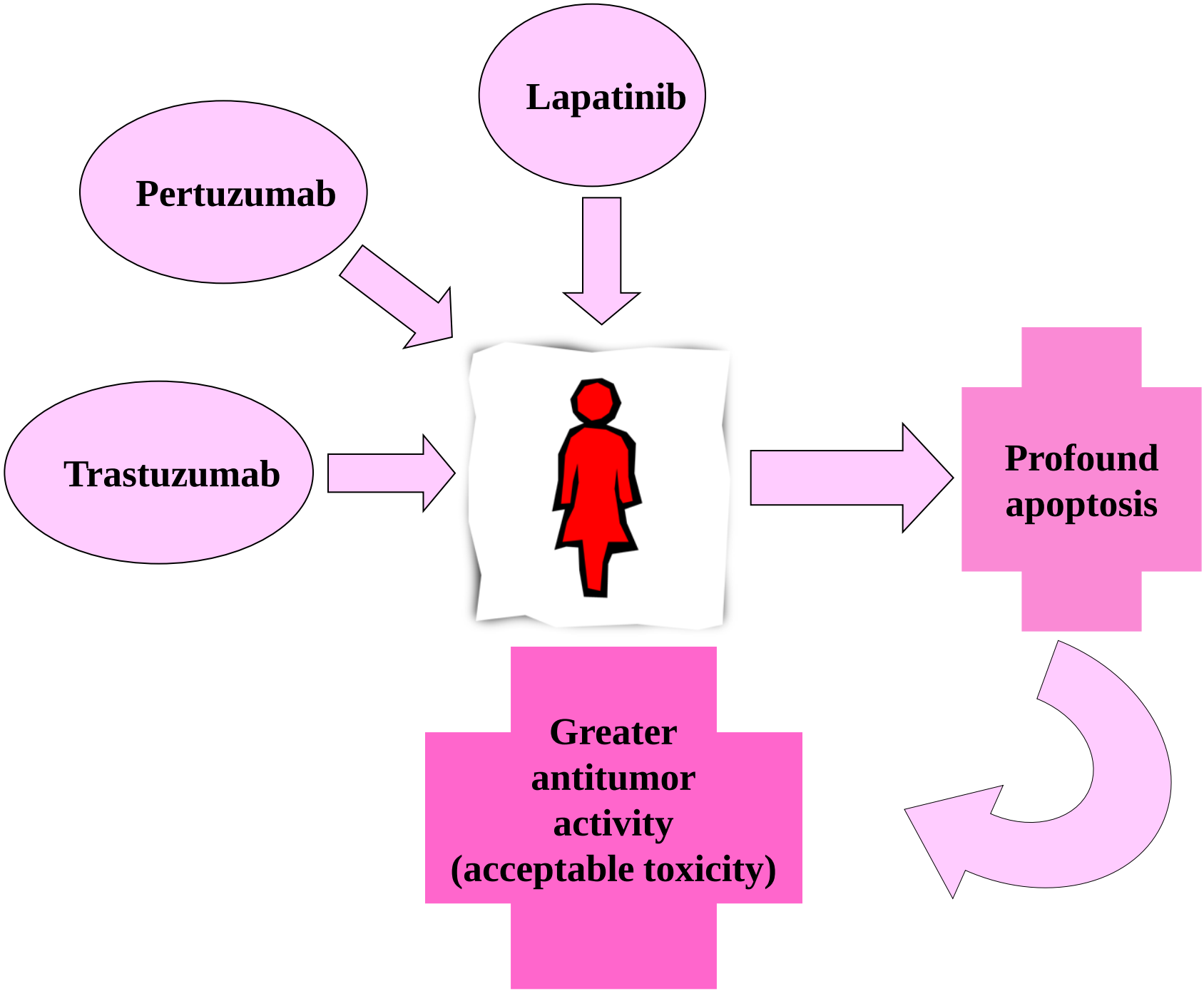
Of note, not all potential future strategies are illustrated here… !

Future treatment strategies in HER2 positive BC

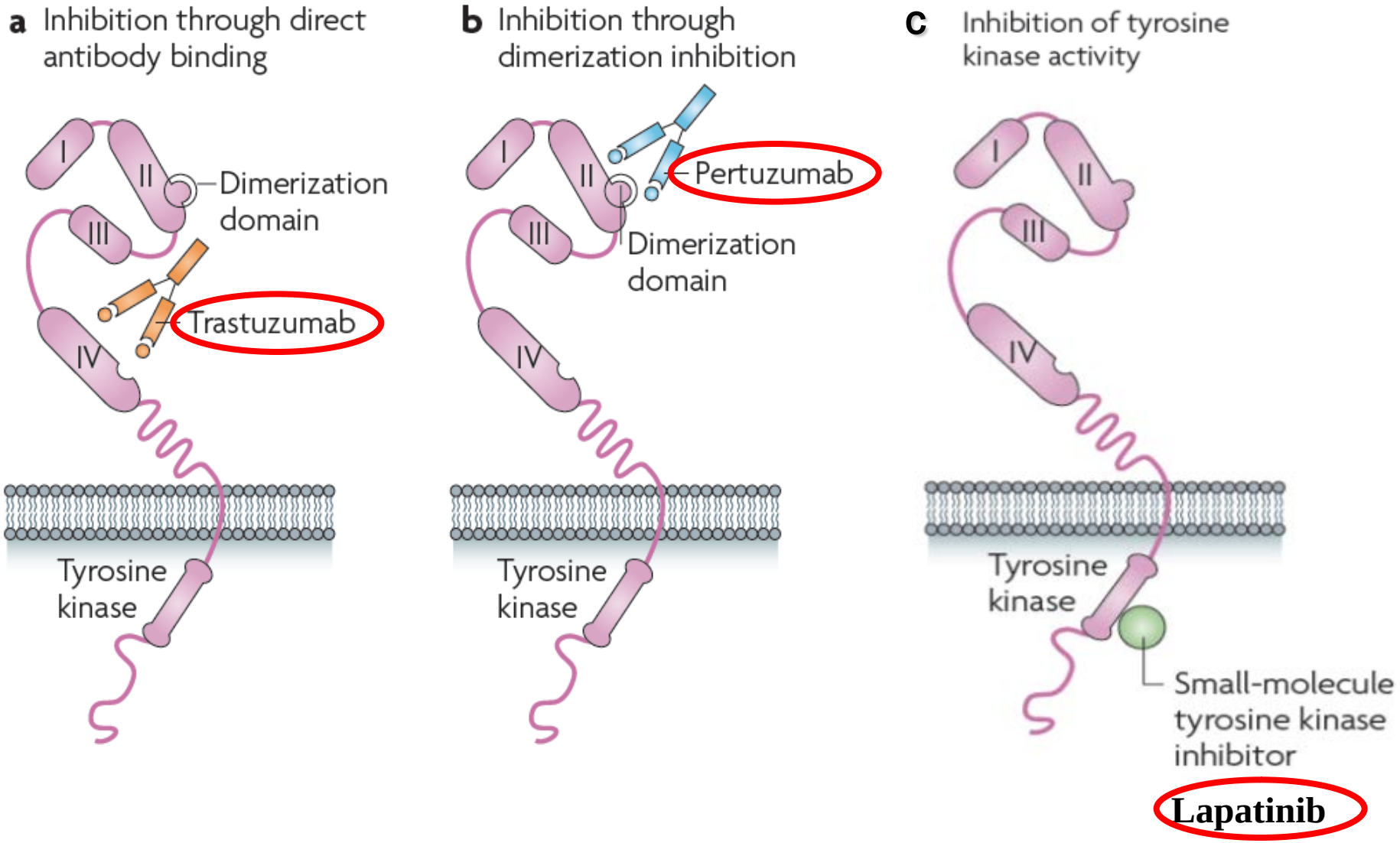
1.

Dual HER2 blockade

Courtesy M. Pegram


Lapatinib
Pertuzumab
Trastuzumab
Profound apoptosis
Greater antitumor activity (acceptable toxicity)

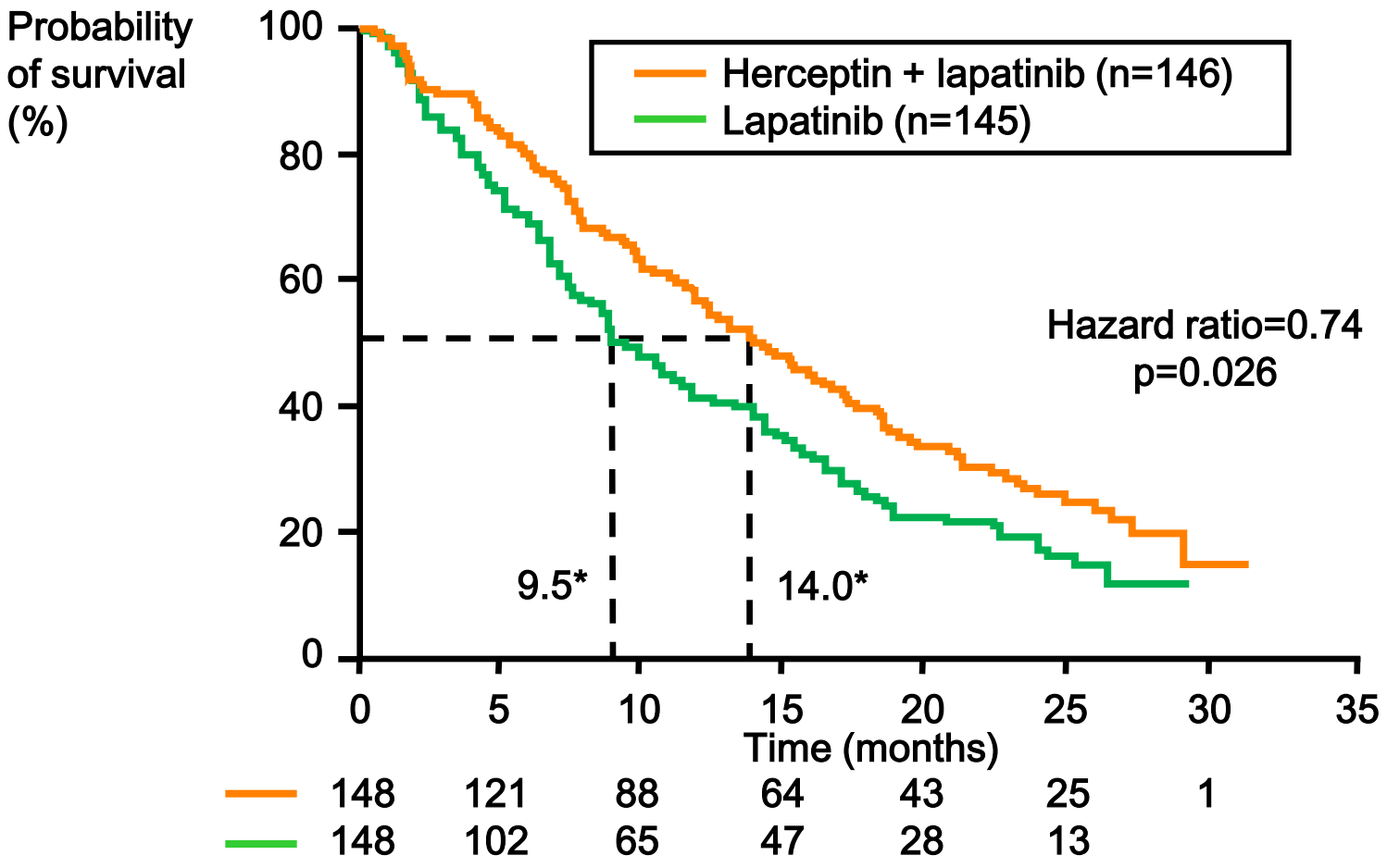
Anti HER2 therapies used in combination



J Baselga, S Swain, Nature Reviews Cancer, 2009

Dual HER2 targeting works in advanced disease !

EGF104900: significant OS benefit with Herceptin + lapatinib following disease progression



* Median OS (months)

Not within EMEA-approved indication for Herceptin

Blackwell et al 2010

CLEOPATRA TRIAL
(Baselga et al, SABCS 2011)

HER2 positive M.B.C.
- centrally confirmed
- only one line of HT for M.B.C. allowed
N = 808

1 : 1

N = 402

Pertuzumab + trastuzumab
(840 mg → 420 mg q3wks

Docetaxel
≥ 6 cycles

P.D.

H.R. PFS = 0.75
(80 % power, 381 events)

N = 406

Placebo + trastuzumab
(8 mg/kg → 6 mg/kg q3wks)

Docetaxel
≥ 6 cycles

P.D.

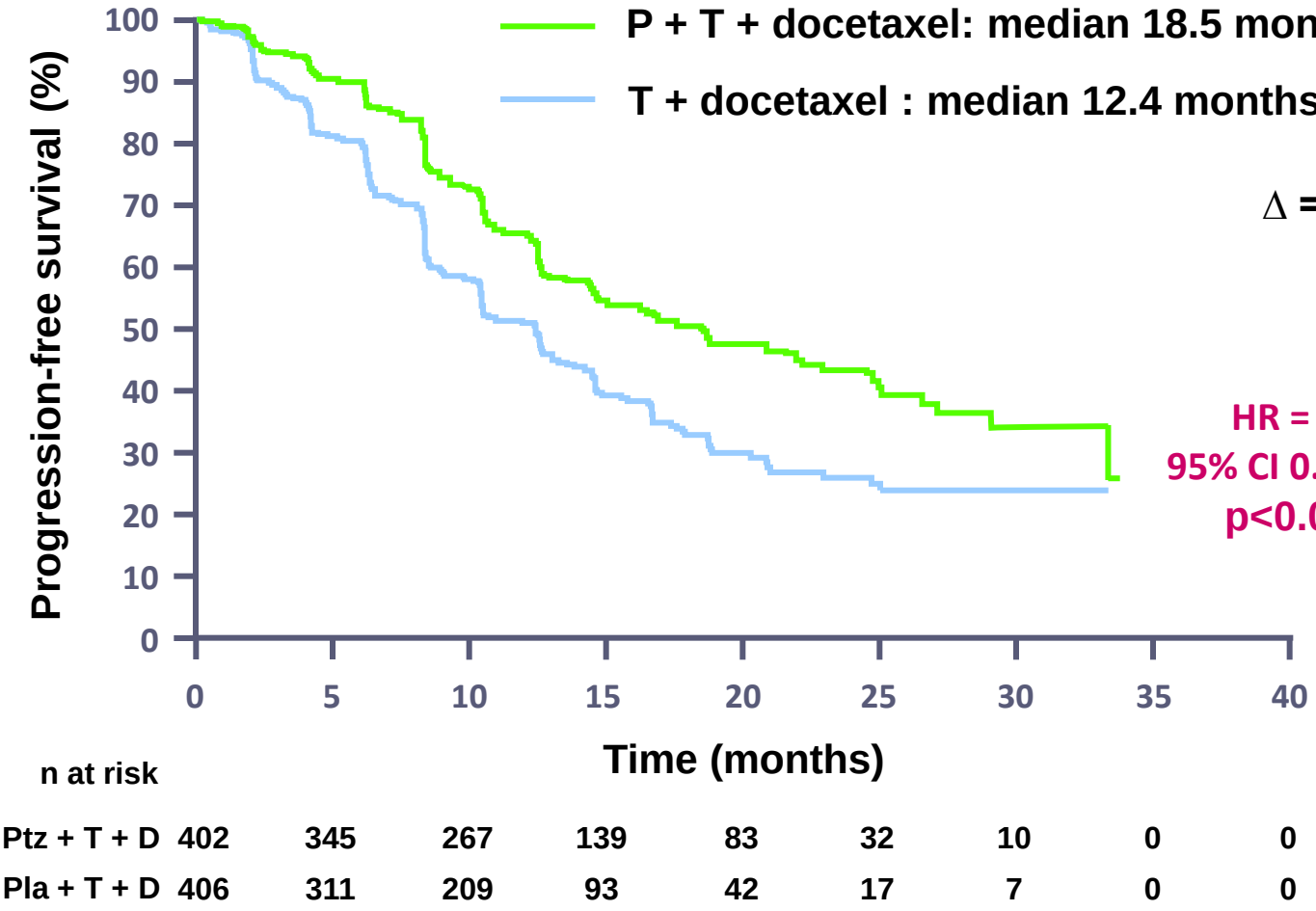
Prior (neo)adj CTX 47 %
Prior trastuzumab 10 %
Measurable disease 84 %
ER and PgR- 50 %

Median n° docetaxel # received = 8 (both arms)
Median time on any treatment: 18 m vs 12 m

CLEOPATRA PATIENT POPULATION

Cleopatra trial in advanced HER2+ BC : pertuzumab plus trastuzumab superior to trastuzumab

Primary endpoint: Independently assessed PFS
n = 433 PFS events

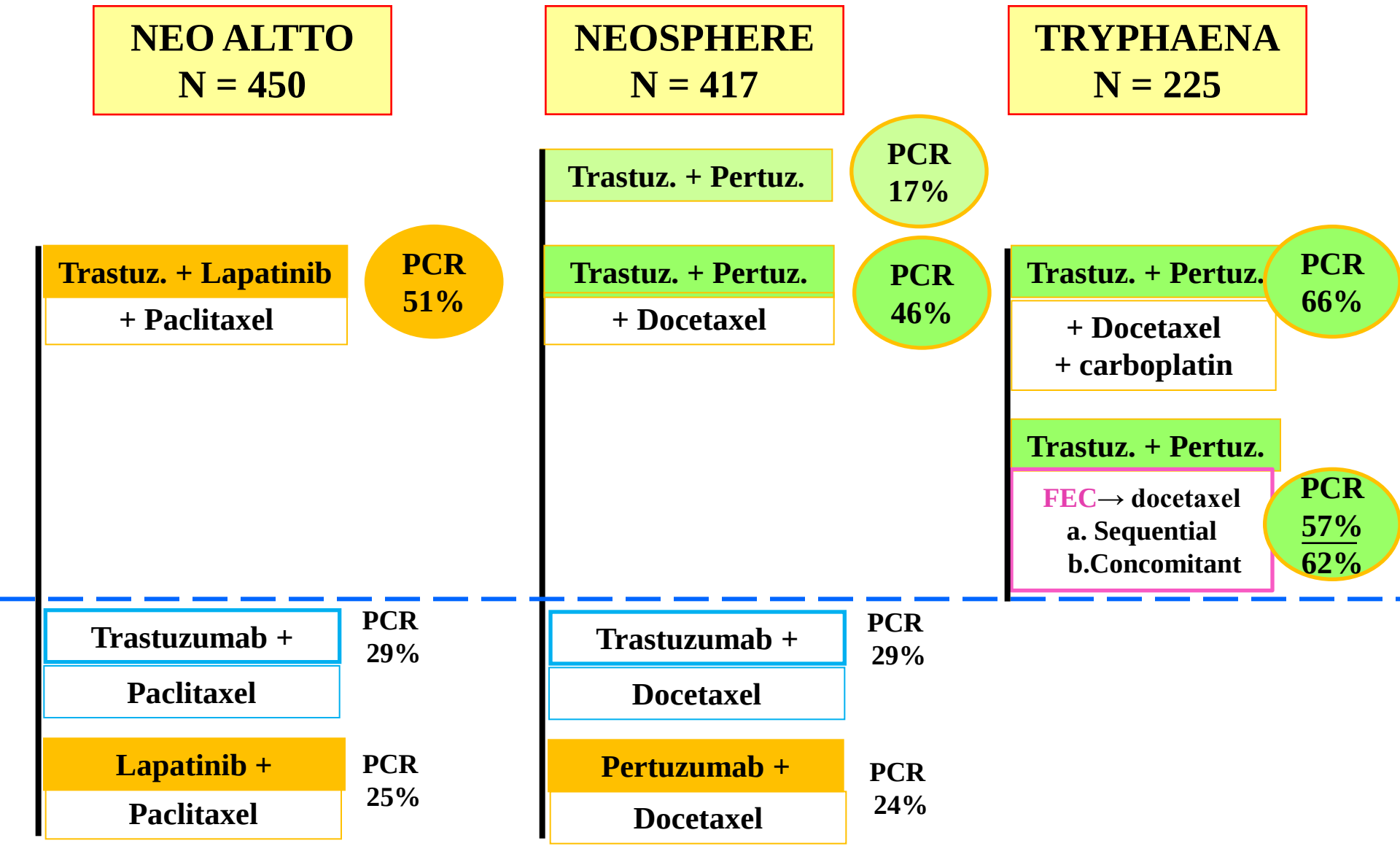


D, docetaxel; PFS, progression-free survival; Pla, placebo; P, pertuzumab; T, trastuzumab

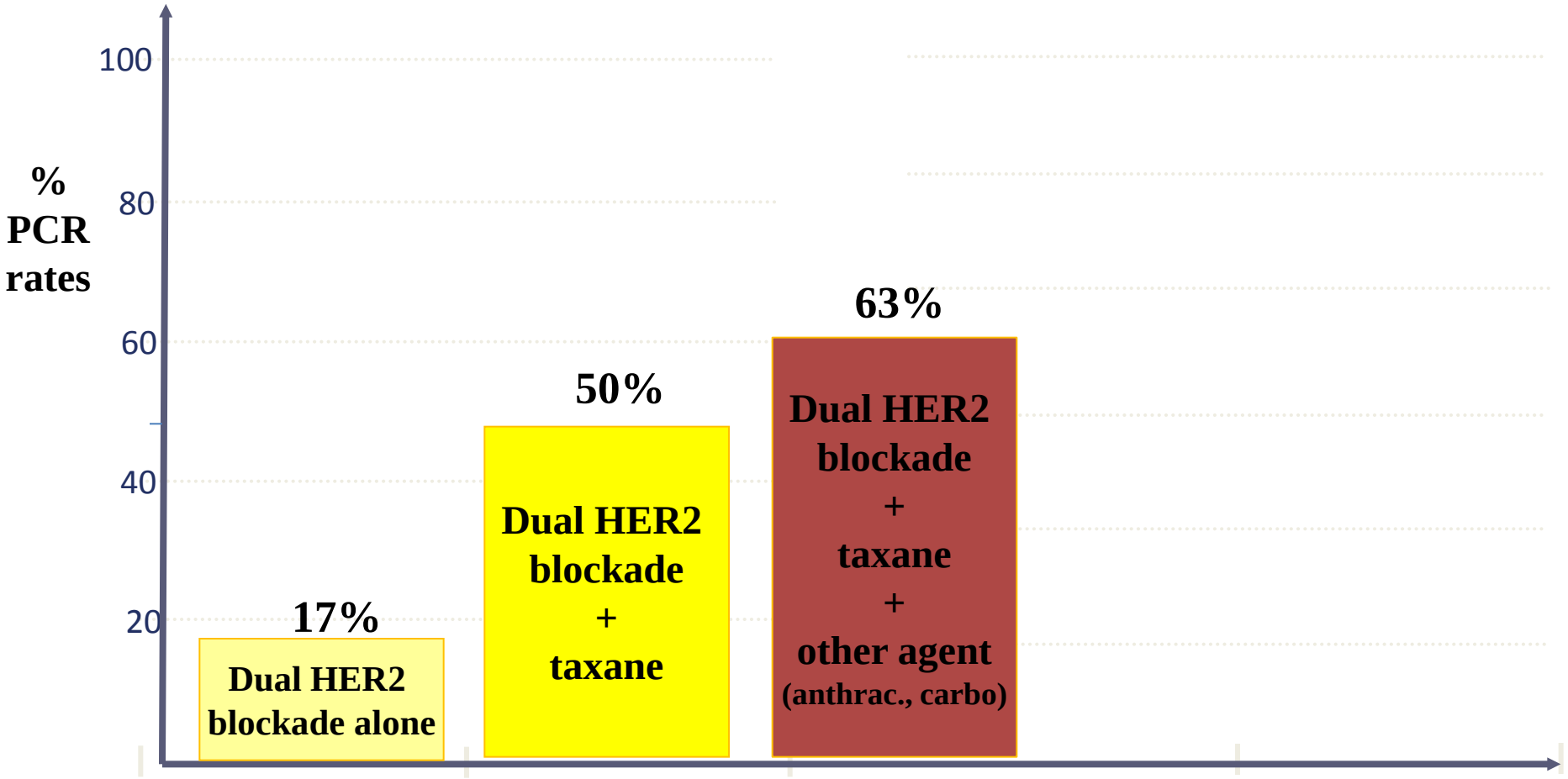
Baselga J, Kim S-B, Im S-A, et al, SABCS, 2011; Abstract S5-5

Dual HER2 targeting works in the neo-adjuvant setting !

Lessons learned from neoadjuvant trials investigating dual HER2 blockade

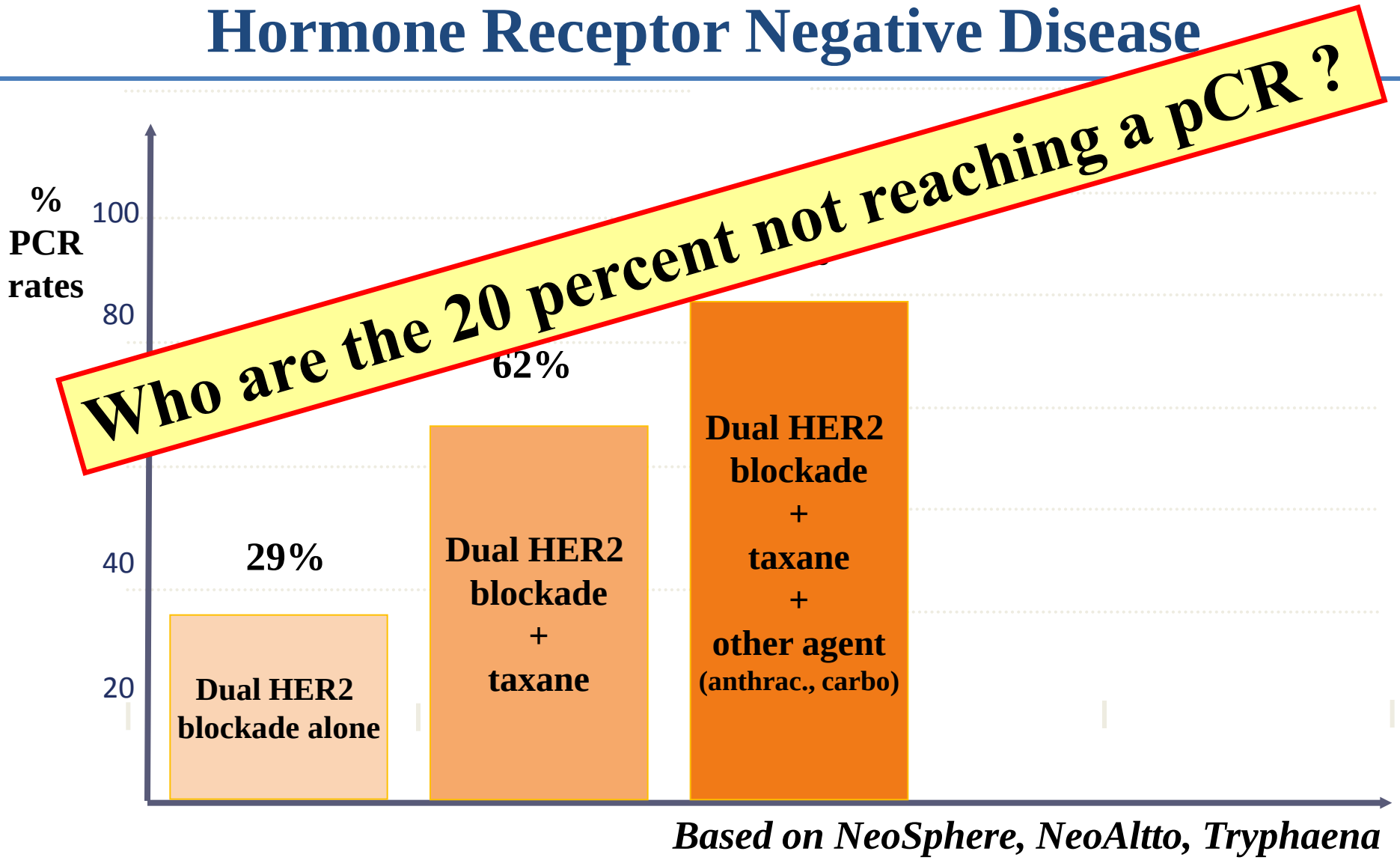


Results obtained with dual HER2 blockade alone or with chemotherapy



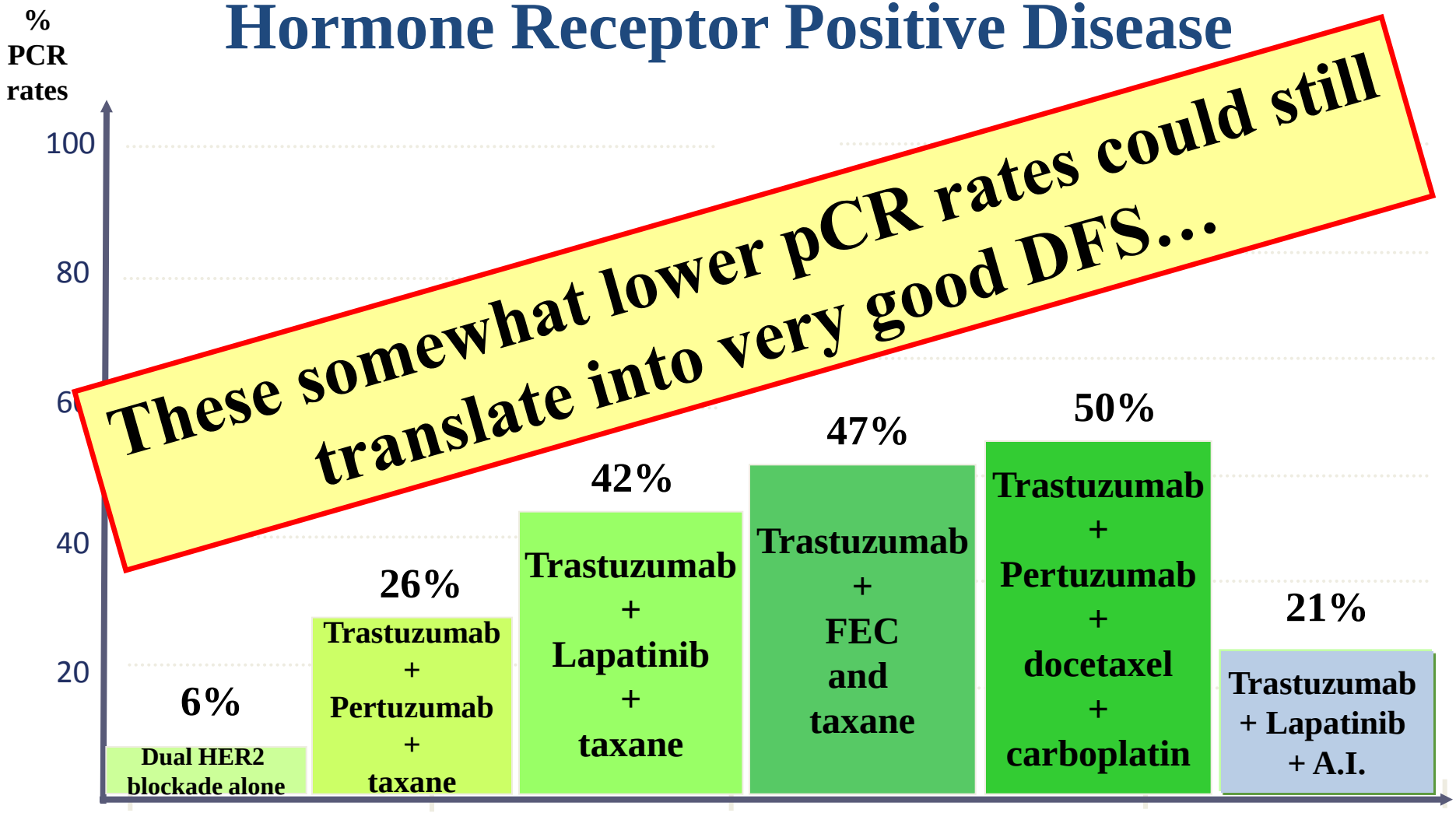
Based on NeoSphere, NeoAltto, Tryphaena

Results obtained with dual HER2 blockade alone or with chemotherapy in Hormone Receptor Negative Disease



Based on NeoSphere, NeoAltto, Tryphaena

Results obtained with dual HER2 blockade alone or with chemotherapy in Hormone Receptor Positive Disease



Based on NeoSphere, NeoAltto, Tryphaena, J. Chang Trial

Dual HER2 targeting tested in pivotal trials !

THE ALTTO TRIAL

8000 women with HER2 positive breast cancer

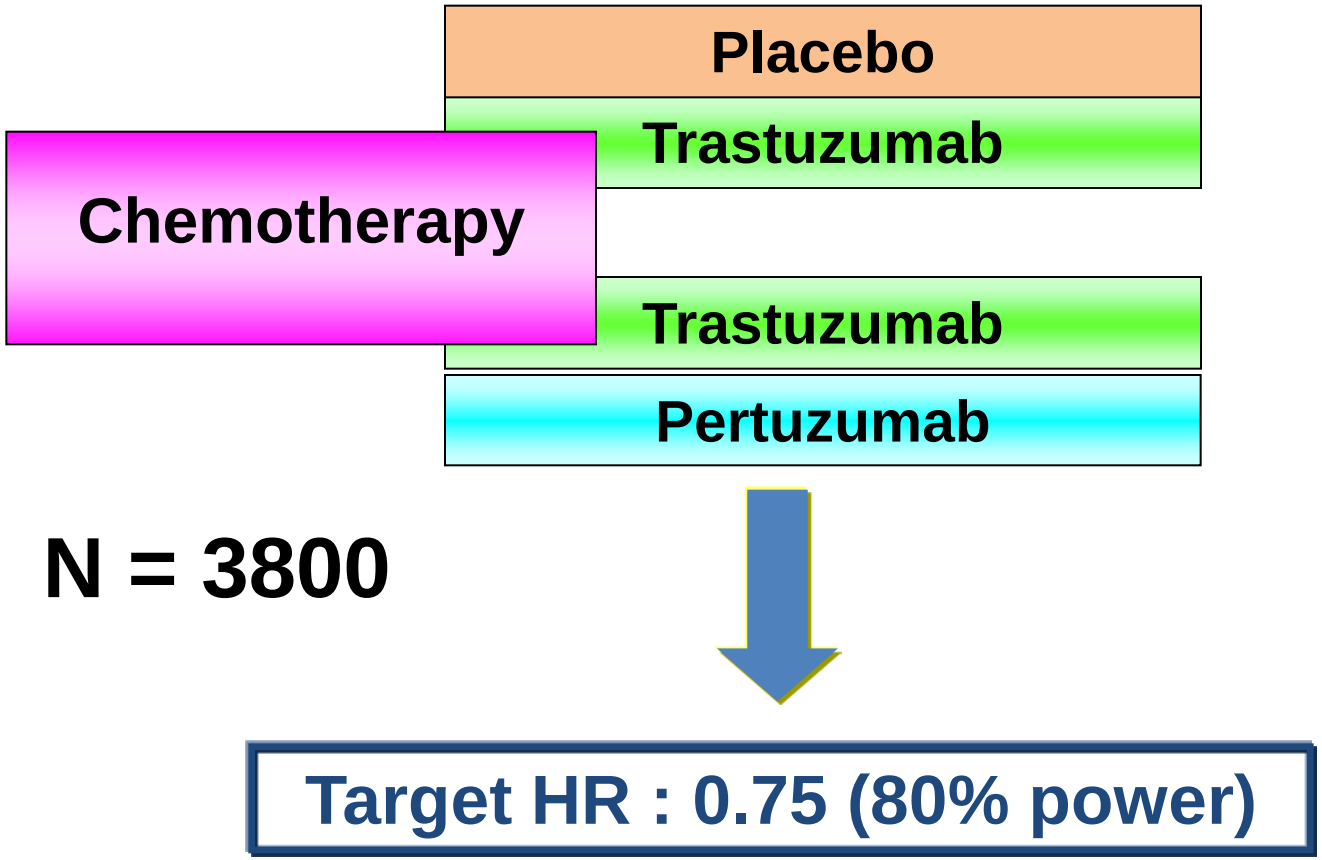
CHEMOTHERAPY

Design 1 = sequential administration

Design 2 = concomitant administration

- **Trastuzumab x 1y**
- **Lapatinib x 1y**
- **Trastuzumab ↓ then lapatinib**
- **Trastuzumab combined with lapatinib**

The new pivotal BIG trial for HER2+ breast cancer : APHINITY



Future treatment strategies in HER2 positive BC

2.

Broader receptor blockade

Broader receptor blockade is a concept being developed by several companies… !

- **« Ab cocktails » directed at :**
  - **HER2 + HER3 + HER1**
  - **HER2 + IGF1R or cMet**
  - **and so on…**

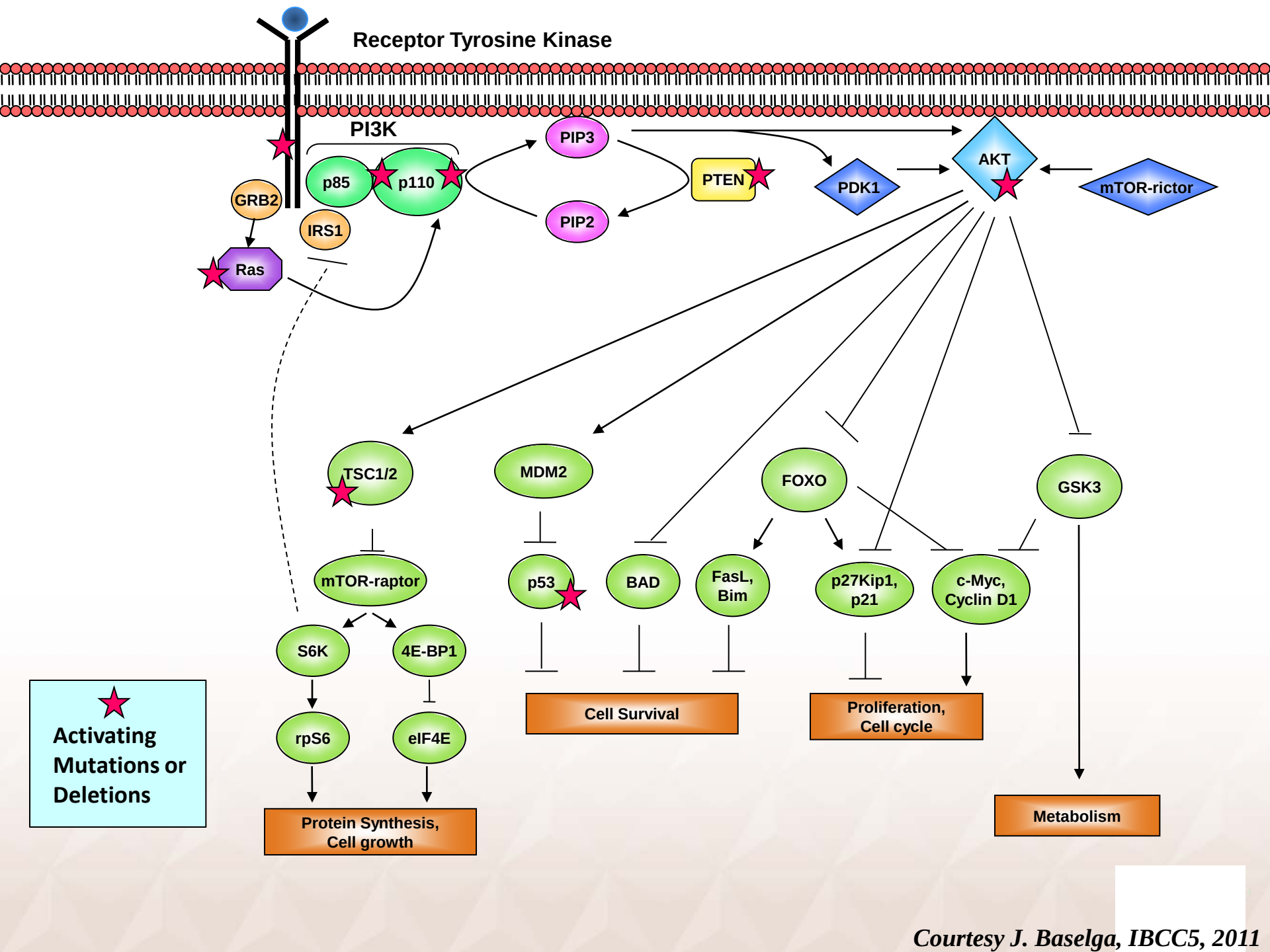
More profound and complete downregulation of receptors with less possibility of « escape » ?

- **HER1 + HER2 ± HER4 TKI :**
  - **Neratinib / Afatinib**

Future treatment strategies in HER2 positive BC

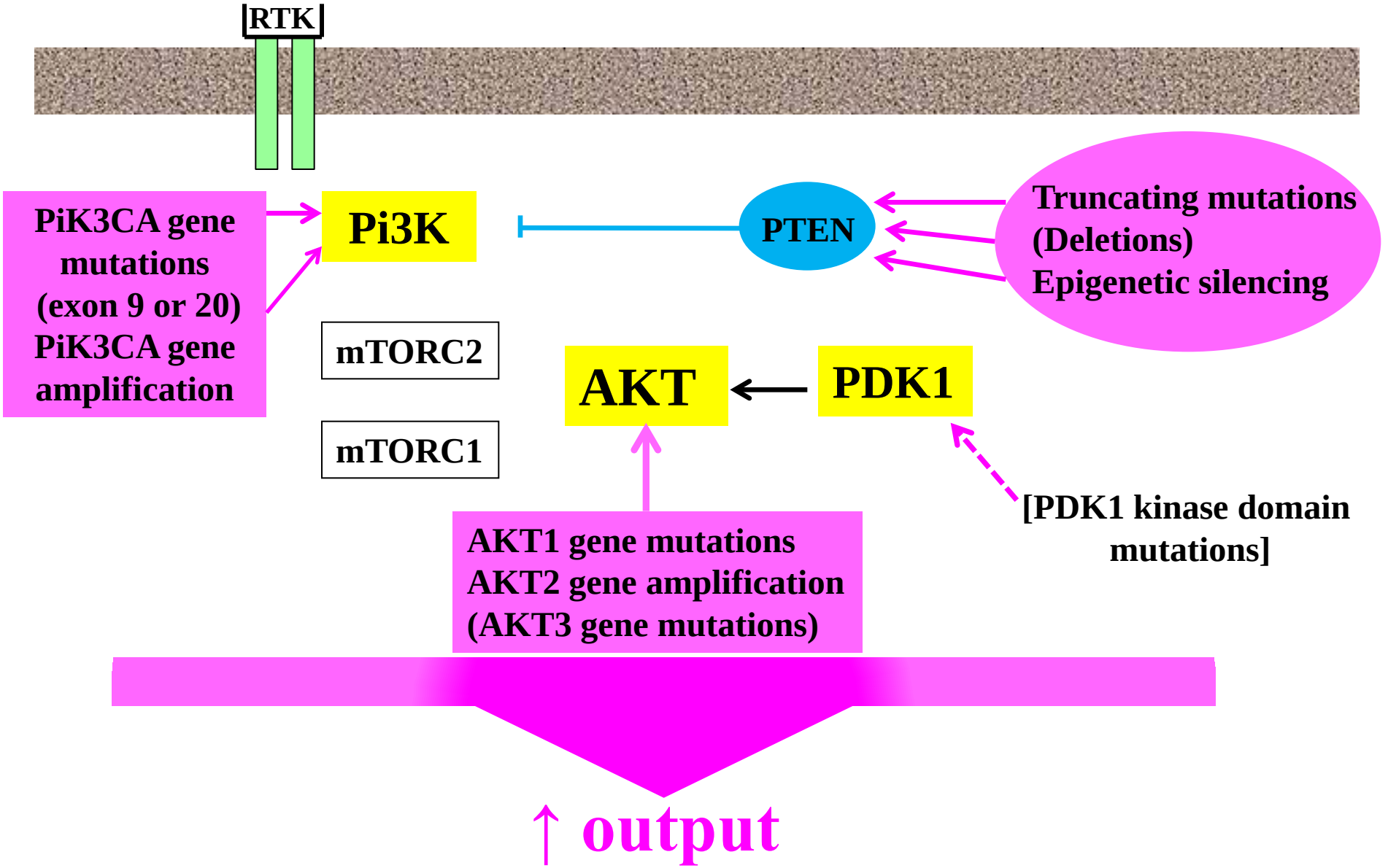
3.

Pi3K / mtor inhibitors



Courtesy J. Baselga, IBCC5, 2011

Genetic aberrations of the Pi3K signaling pathway in breast cancer

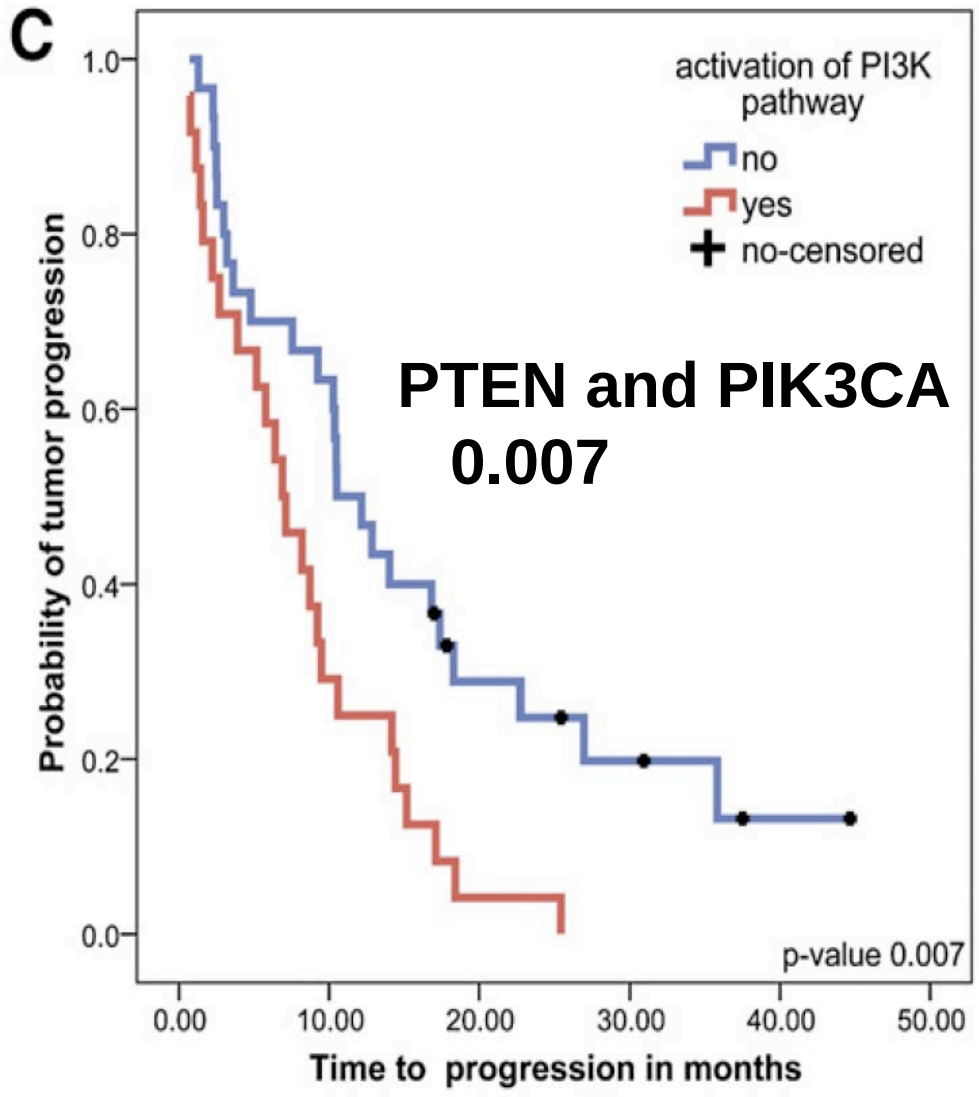


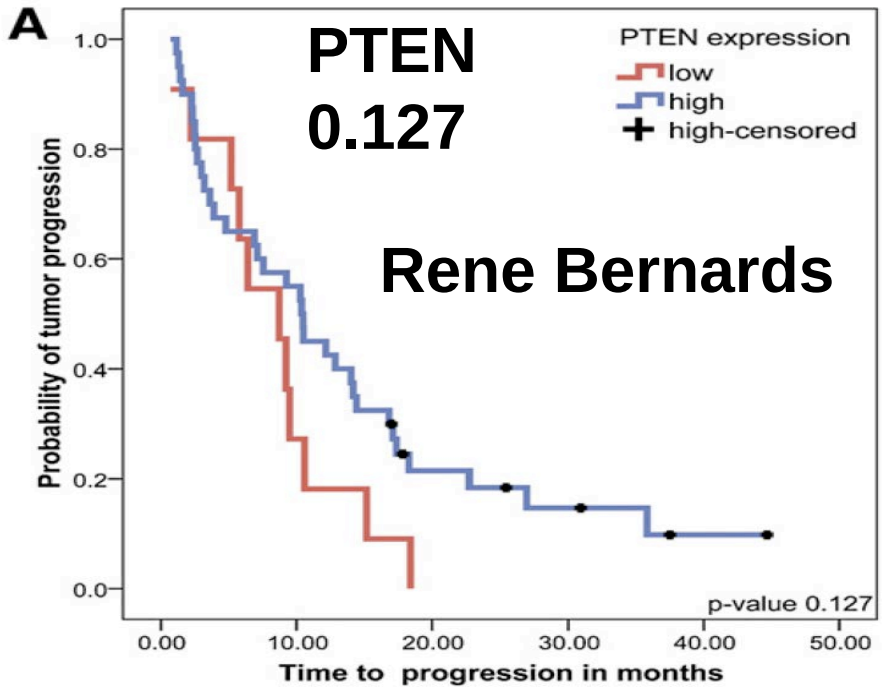
Frequency of mutations in the PIK3CA and PTEN genes in 547 human breast cancers

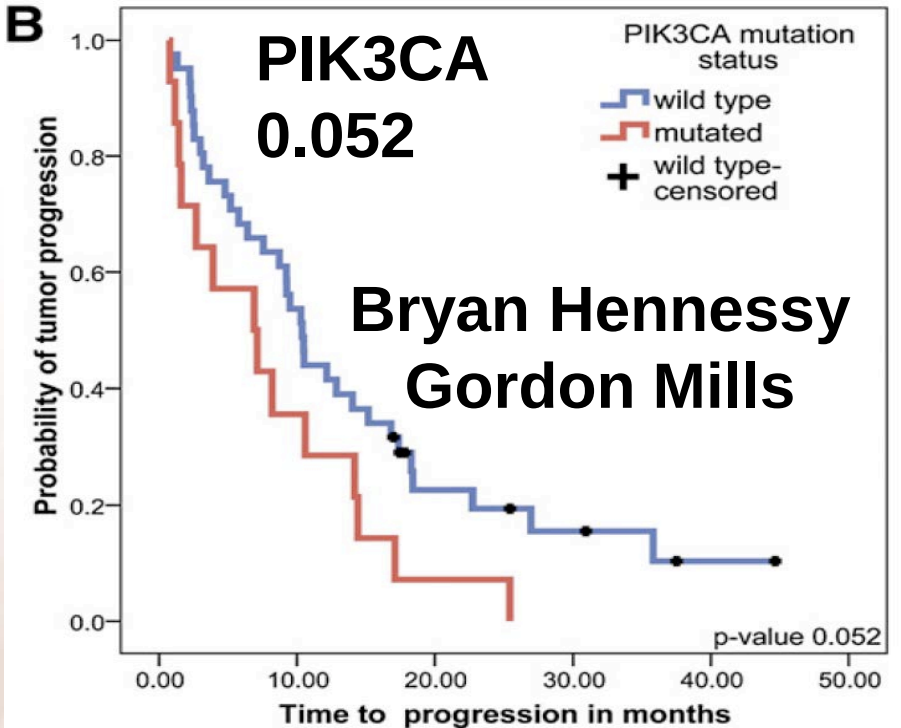
Breast Cancer Subtype	Mutation			
	PIK3CA catalytic domain*	*PIK3CA* other	*PIK3CA* total	*PTEN*
All breast tumors	73/547 (13.3%)	44/547 (8.0%)	**117/547 (21.4%)**	2/88 (2.3%)
HR+	48/232 (20.7%)	32/232 (13.8%)	**80/232 (34.5%)**	2/58 (3.4%)
ER+PR+	39/186 (21%)	22/186 (11.8%)	**61/186 (32.8%)**	1/48 (2.1%)
ER+PR–	9/41 (22%)	10/41 (24.4%)	**19/41 (46.3%)**	1/8 (12.5%)
ER–PR+	0/5 (0%)	0/5 (0%)	**0/5 (0%)**	0/2 (0%)
HER2+	13/75 (17.3%)	4/75 (5.3%)	**17/75 (22.7%)**	0/10 (0%)
Triple Negative	12/240 (5.0%)	8/240 (3.3%)	**20/240 (8.3%)**	0/20 (0%)

From Stemke-Hale, K. et al. Cancer Res 2008;68:6084-6091
Courtesy J. Baselga, IBCC5, 2011

Integrative analysis of PI3K pathway predicts response to trastuzumab







J. Baselga, IBCC5, 2011

mTORC1 inhibitors (Rapalogs)

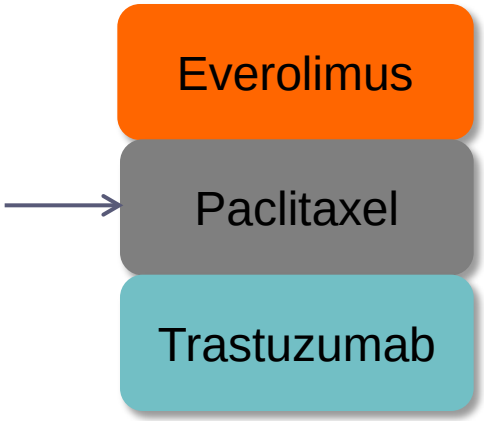
- **Temsirolimus**
- **Everolimus**

Trastuzumab and mTOR Inhibitor

Trastuzumab + Everolimus
2 trials (one with chemotherapy)
Prior trastuzumab therapy

Trial 1: Phase Ib

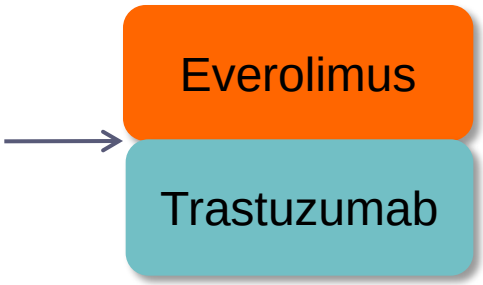
N = 33
HER2+ BC



Everolimus dose escalation: 5mg daily, 10mg daily, 30mg/wk

Trial 2: Phase I/II

N = 47
HER2+ BC

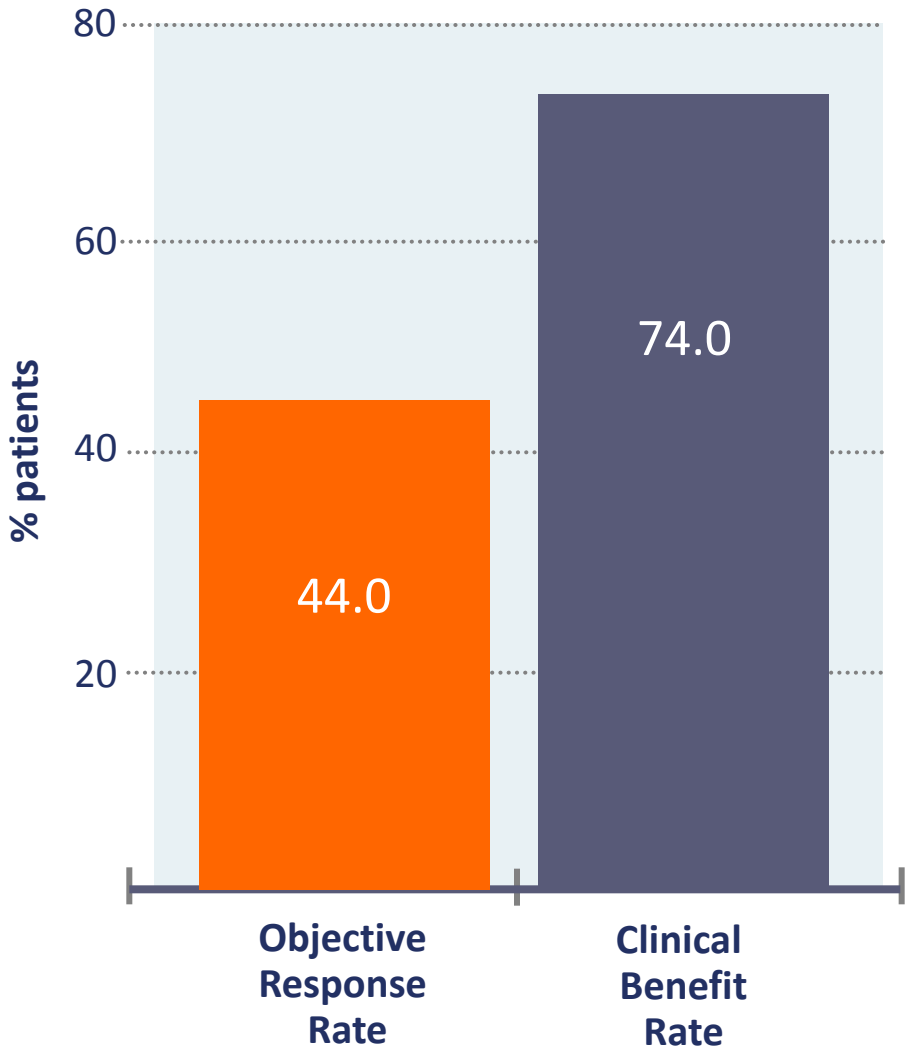


(≥ 1 trastuzumab-based therapy for MBC)

Andre F et al, J Clin Oncol 2010; 28(34):5110-5115
Morrow PK et al, J Clin Oncol 2011; 29(23):3126-3132

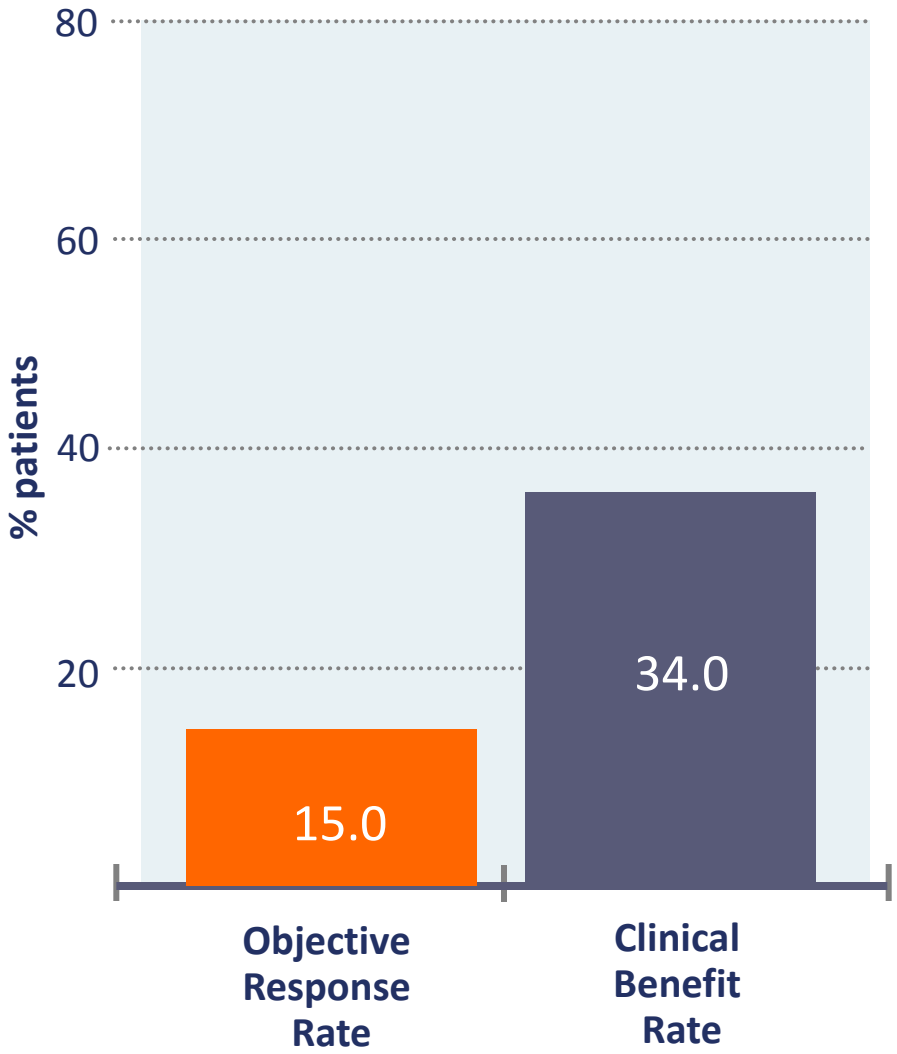
Trastuzumab and mTOR Inhibitor

Trial 1: Everolimus + Paclitaxel + Trastuzumab



Median PFS = 34 wks (95% CI 29.1 -40.7wks)

Trial 2: Everolimus + Trastuzumab



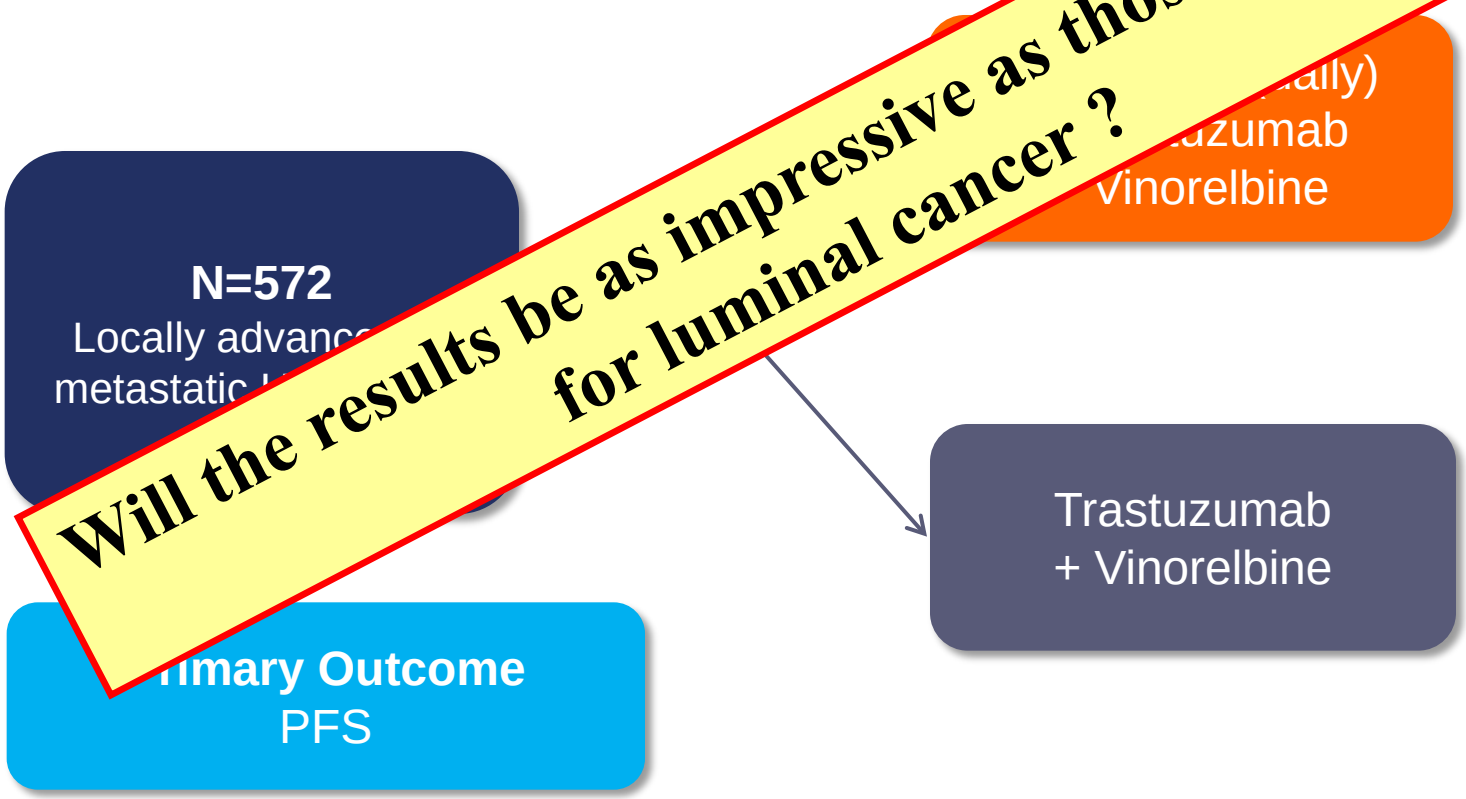
Median PFS = 4.1 months

BOLERO 3

HER2+

Phase III Randomised, double blind, placebo controlled

Resistant to trastuzumab and pre-treated with taxane



Will the results be as impressive as those of Bolero2 for luminal cancer ?

Results Expected End 2012

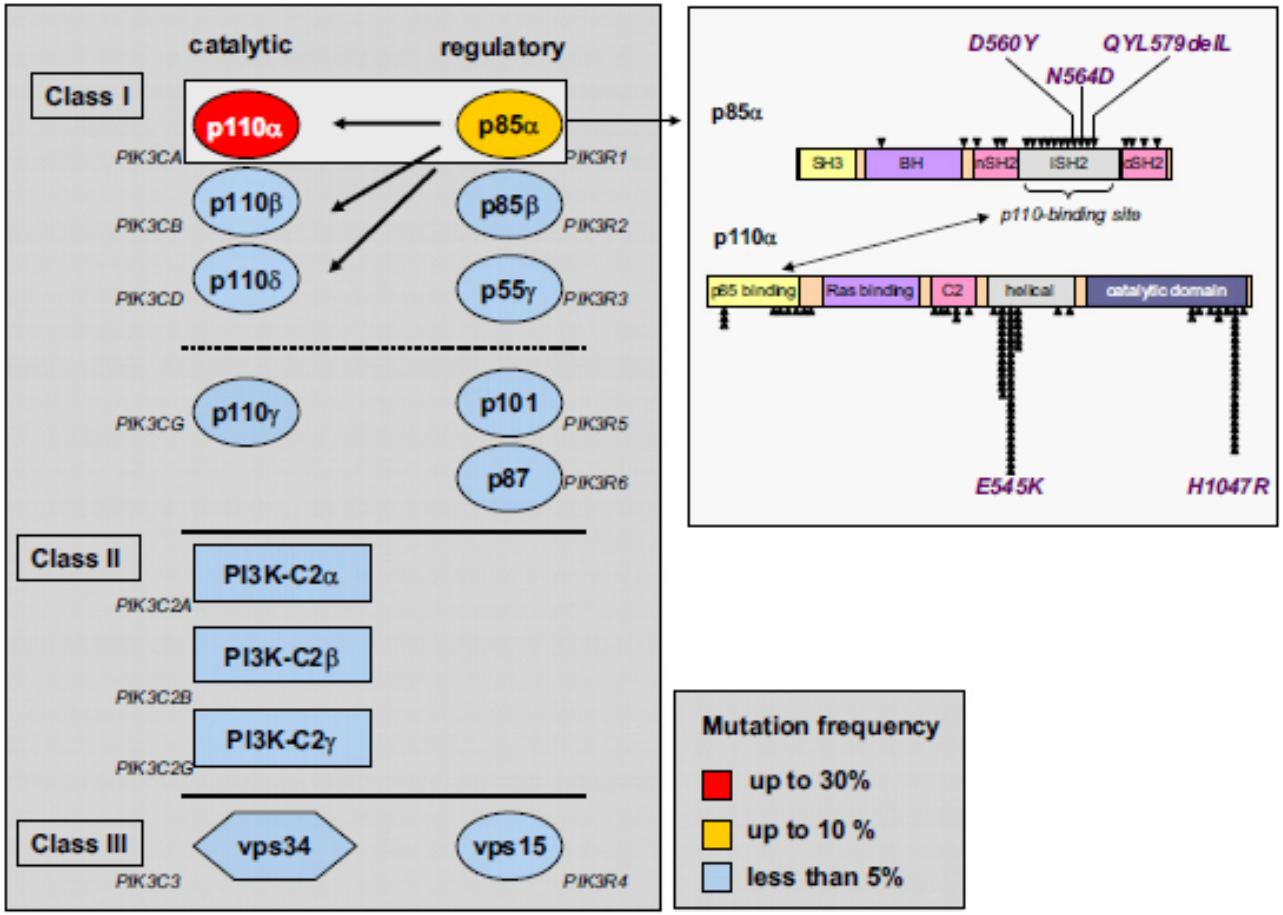
NCT01007942

Conclusions from NeoSphere biomarker analyses

- HER2 expression (H-score) associated with sensitivity to pertuzumab
- **PIK3CA mutations in exon 9 linked to lack of sensitivity to HER2-directed MAb's**
- Intrinsic differences between HER2-positive tumors based on hormone receptor status
- No predictive role for truncated forms of the HER2 receptor including $p95^{HER2}$
- **So far none of the analyses provided clinically useful assays for patient and/or regimen selection in addition or alternative to the conventional assessment of HER2 by IHC or FISH**

Courtesy L. Gianni, SABCS 2011

Cancer mutations in Pi3K family members



I. Martin-Berenjeno, B. Vanhaesebroeck, Cancer Cell 16, 2009

Pi3K pathway inhibitors

Dual Pi3K-mTor inhibitors

- BEZ 235
- BGT 226
- SF1126
- GSK 1059615
- GDC-0980
- XL765
- PF-4691502

Pi3K

Pi3K inhibitors

- **PAN-Pi3K inhib.**
  - BKM120
  - GDC-0941
  - XL147
  - PKI-587
- **Isoform specific Pi3K inhib.**

mTORC2

AKT

AKT inhibitors

- GSK 690693
- MK 2206

mTORC1

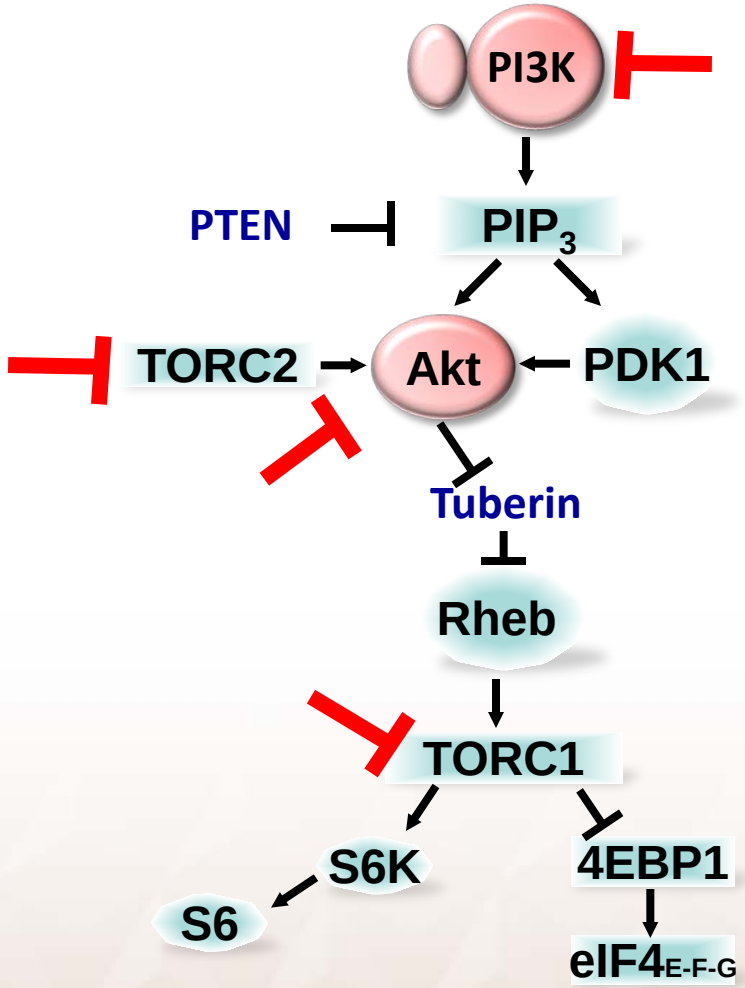
mTOR CATALYTIC SITE inhibitors

- AZD 8055
- OSI 027
- INK 128

mTORC1 inhibitors

- Everolimus

Strategies to target the PI3K pathway
Issues to address

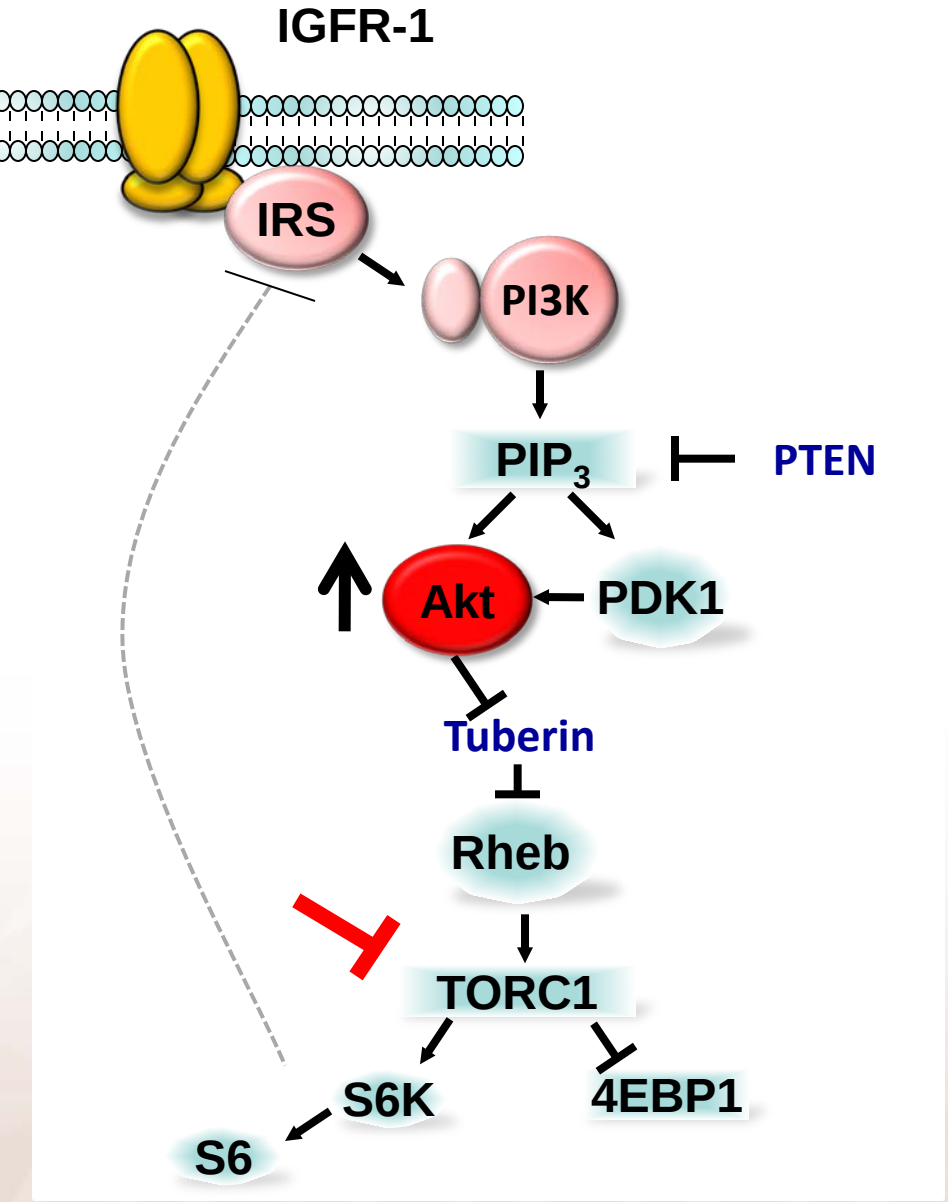


- **Best target on the pathway?**
  - Will toxicities differ?
    - Probably yes
    - It may preclude combinatorial approaches
  - Diverse clinical activity profile?
  - Will activity be dependent on specific mutations?
  - Will specific inhibitors have an improved safety profile?
- **Patient selection**
  - Mutational status to be known upfront
- **Activation of compensatory pathways**

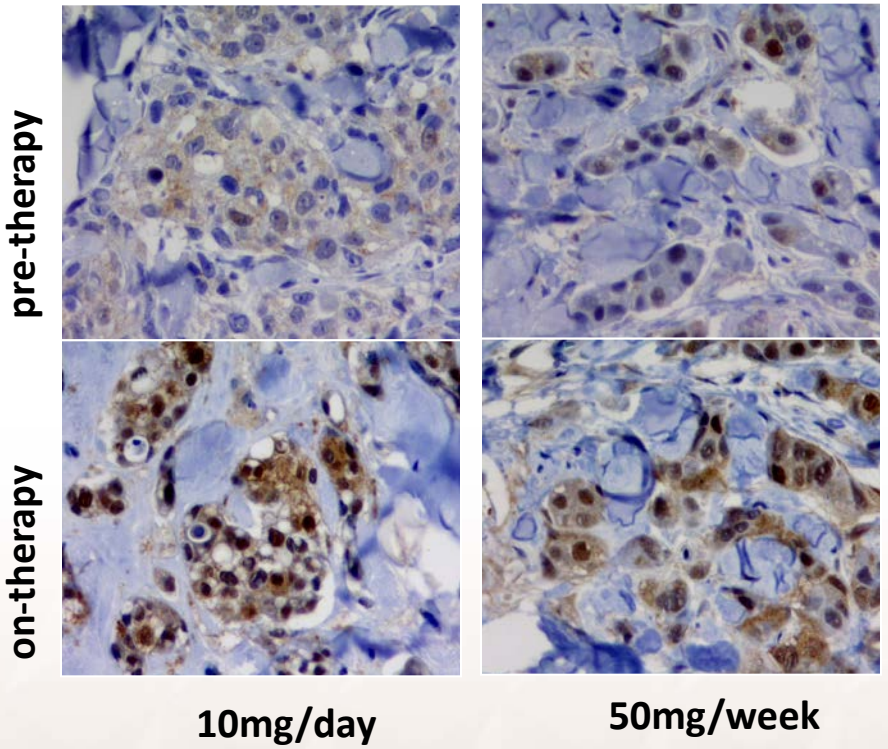
Courtesy J. Baselga, IBCC5, 2011

PI3K Compensatory Pathways

Rapalogs Activate Akt



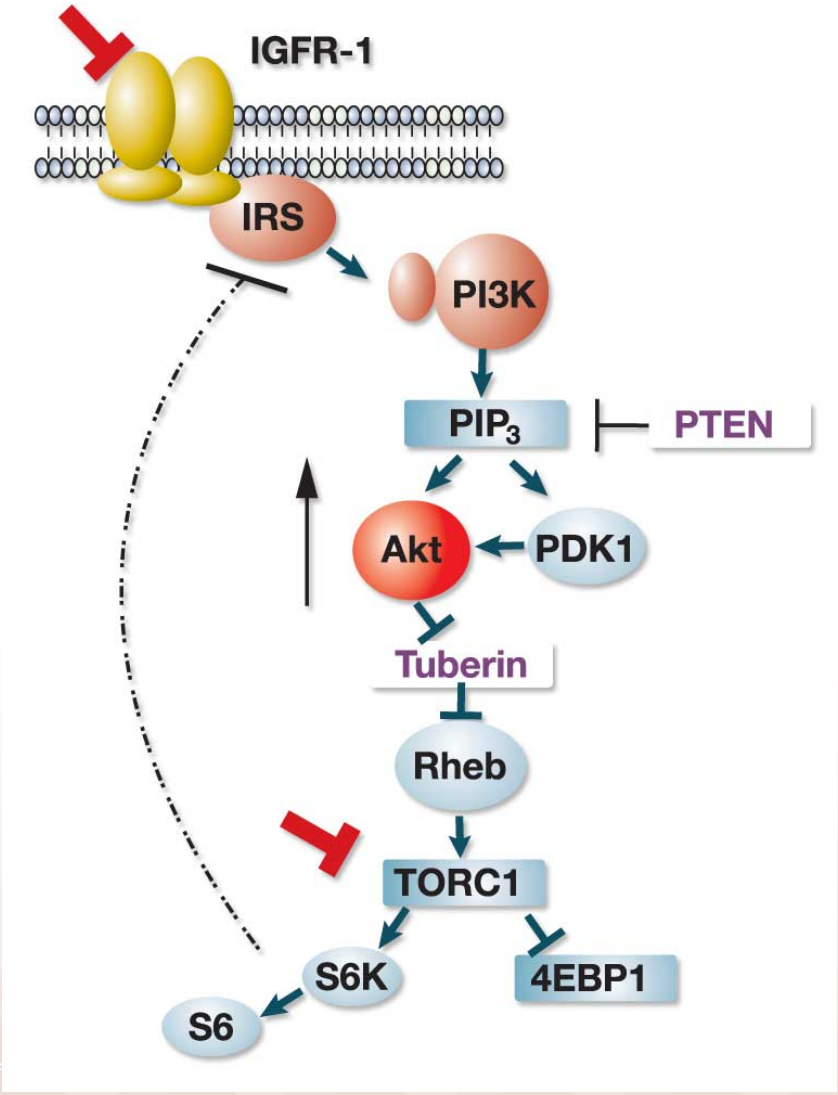
Phase I Everolimus Study
Tumor pAkt



Tabernero et al. J. Clin Oncol. 2008
Courtesy J. Baselga, IBCC5, 2011

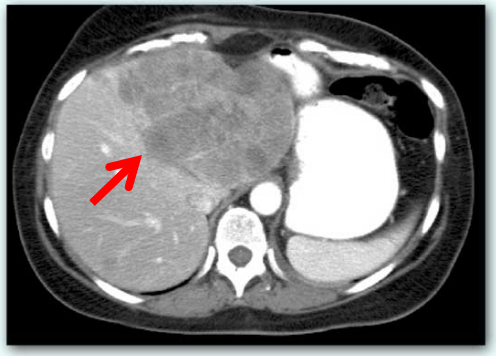
Targeting Compensatory Pathways

Suppress IGF-1R plus mTOR to prevent compensation by tumor cells

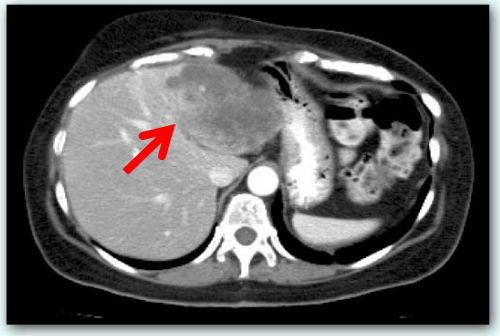


Patient had received 7 prior treatments

Before therapy



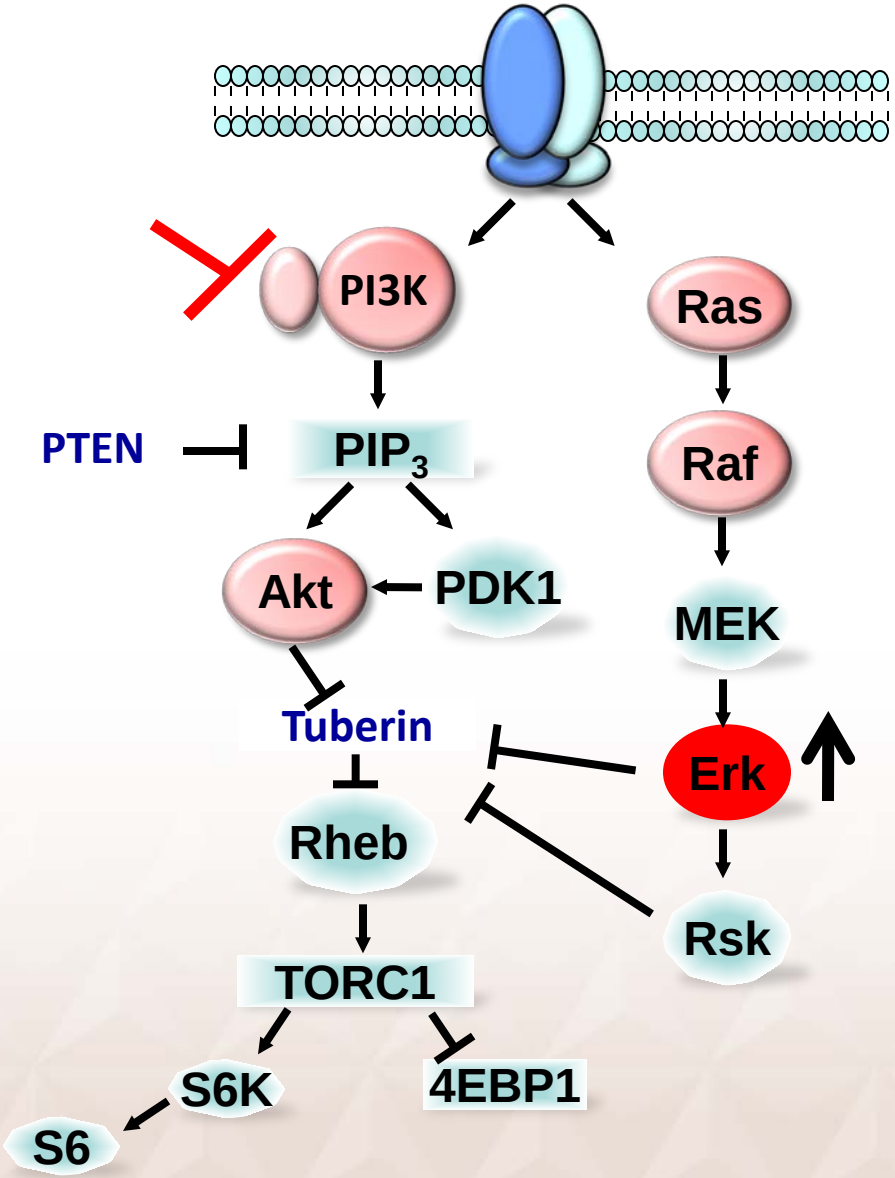
2 months later

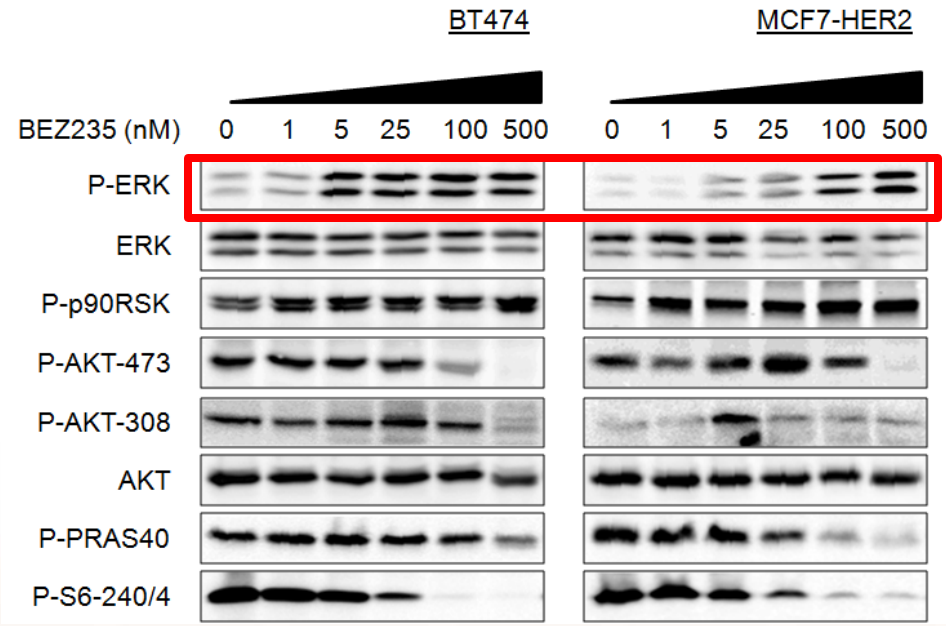


Courtesy J. Baselga, IBCC5, 2011

PI3K Compensatory Pathways

PI3k inhibitors Activate ERK pathway

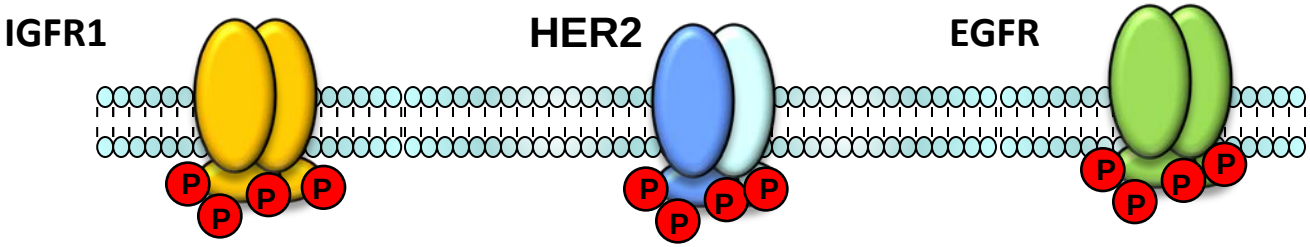


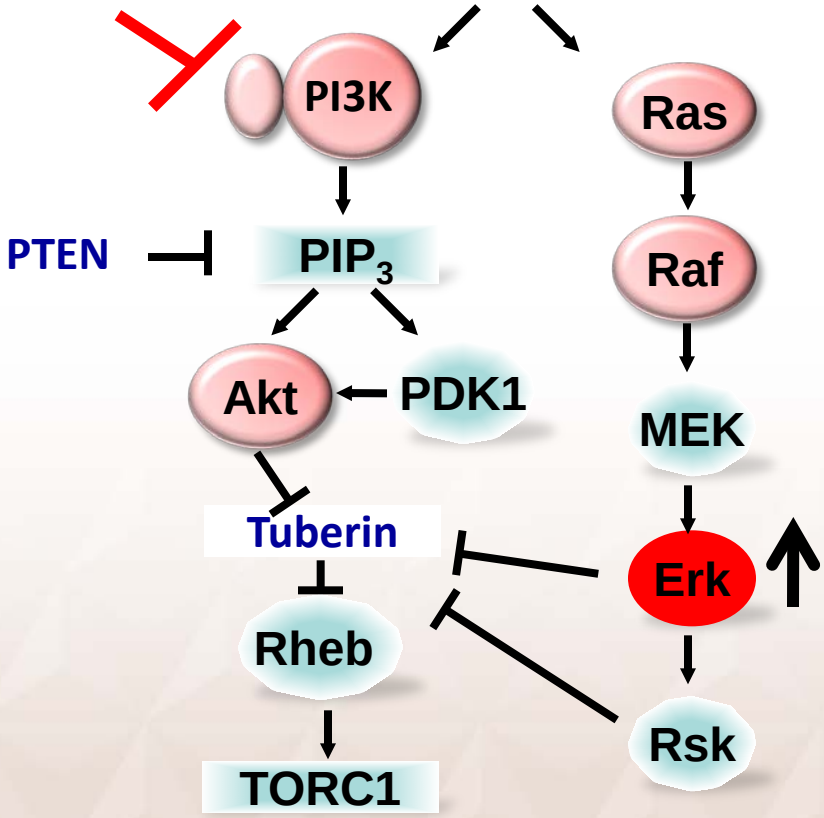


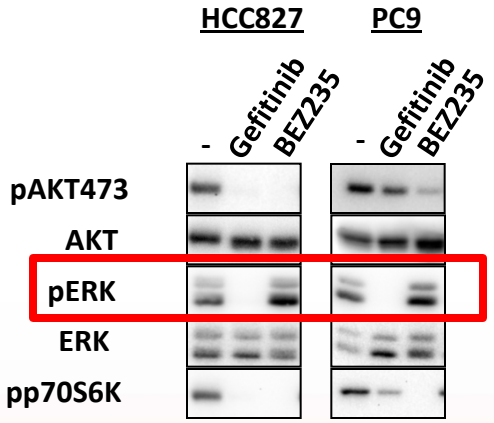
Courtesy J. Baselga, IBCC5, 2011

PI3K Compensatory Pathways

PI3K inhibitors Activate ERK pathway via enhanced RTK signaling







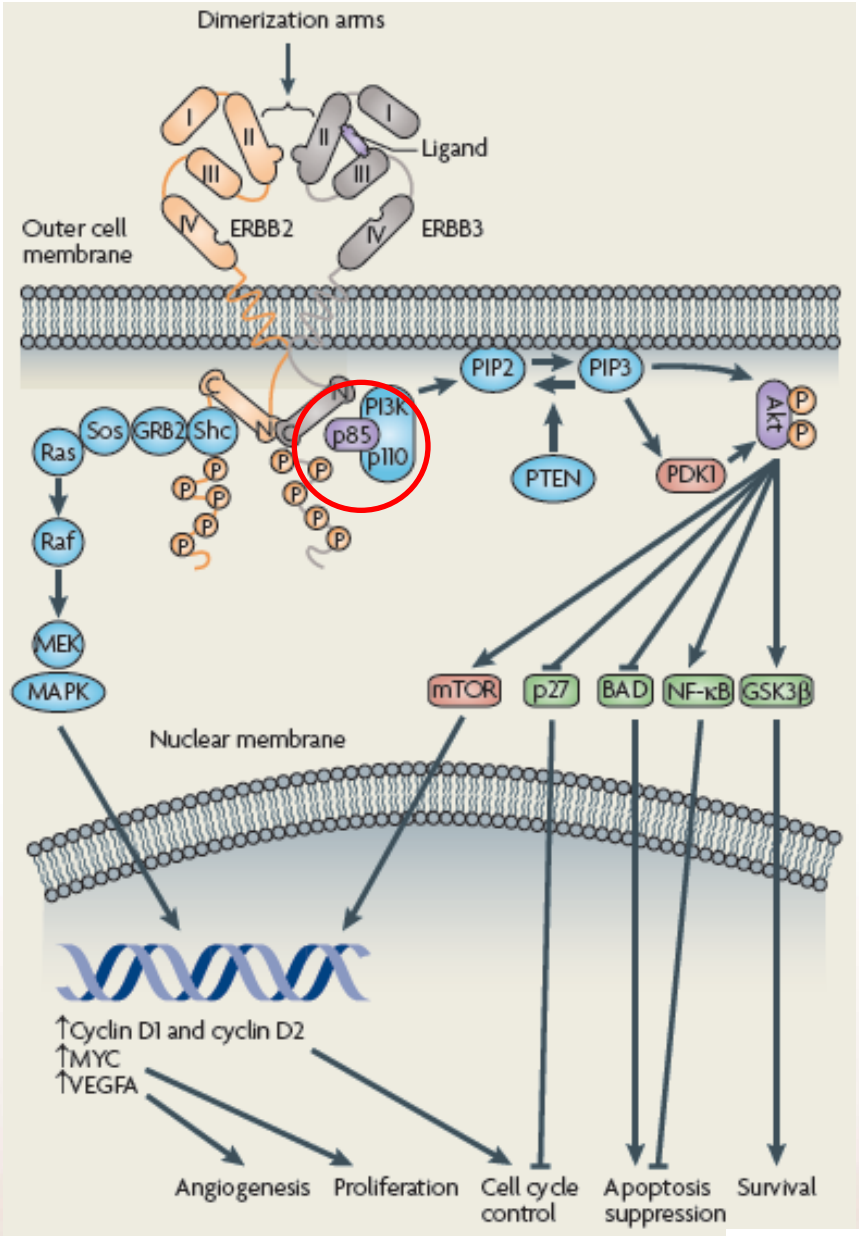
EGFR-mutated

(Faber et al, PNAS, 2009)

Courtesy J. Baselga, IBCC5, 2011

ERBB3 and PI3K activation

ERBB3 activates the PI3K-Akt pathway directly through direct binding to the p85 subunit of PI3K.



Baselga J, Swain S. Nat Rev Cancer 2009;9:463-75.

Courtesy J. Baselga, IBCC5, 2011

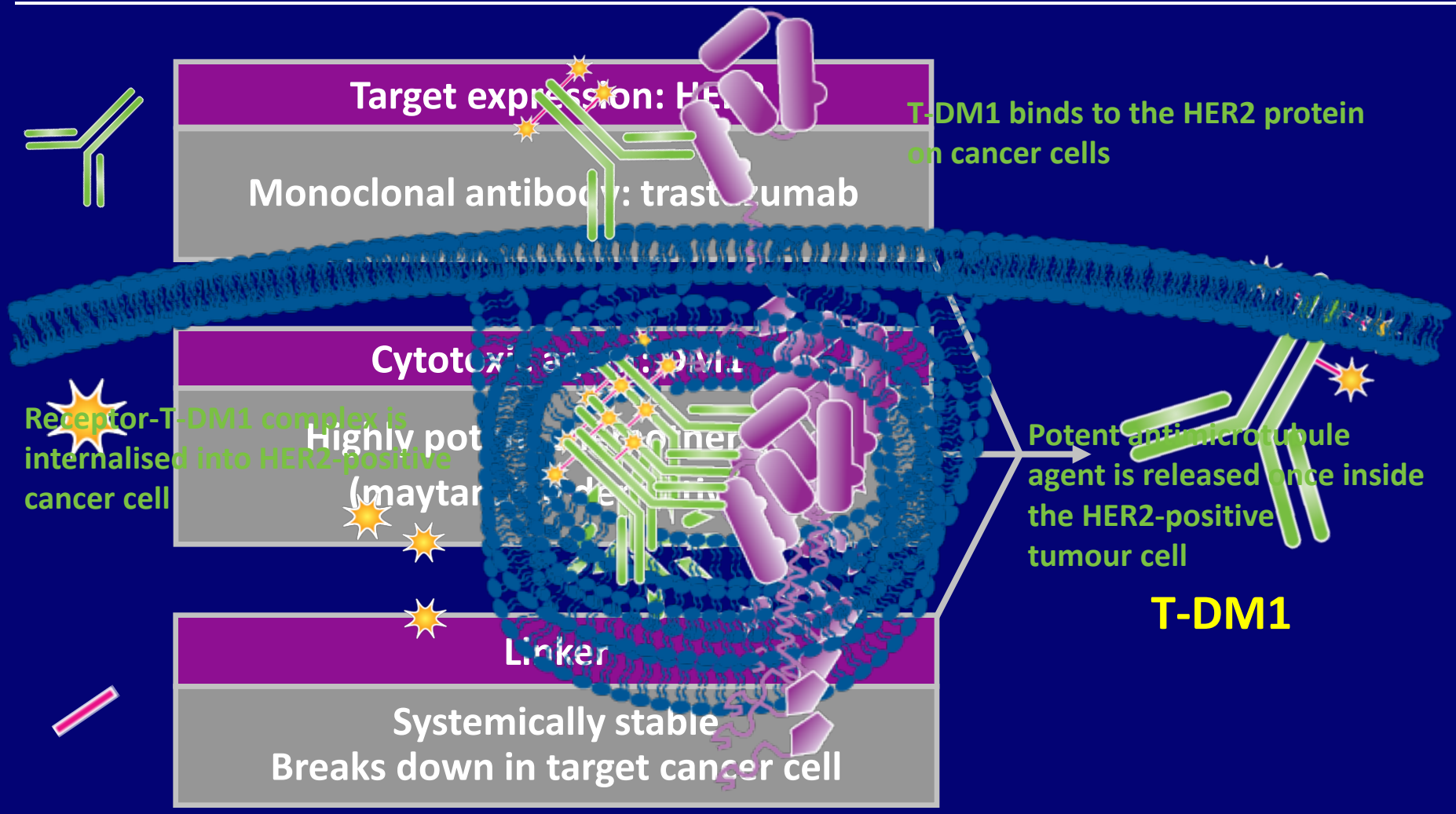
In the future we will monitor patients for the activation of compensatory pathways !

Future treatment strategies in HER2 positive BC

4.

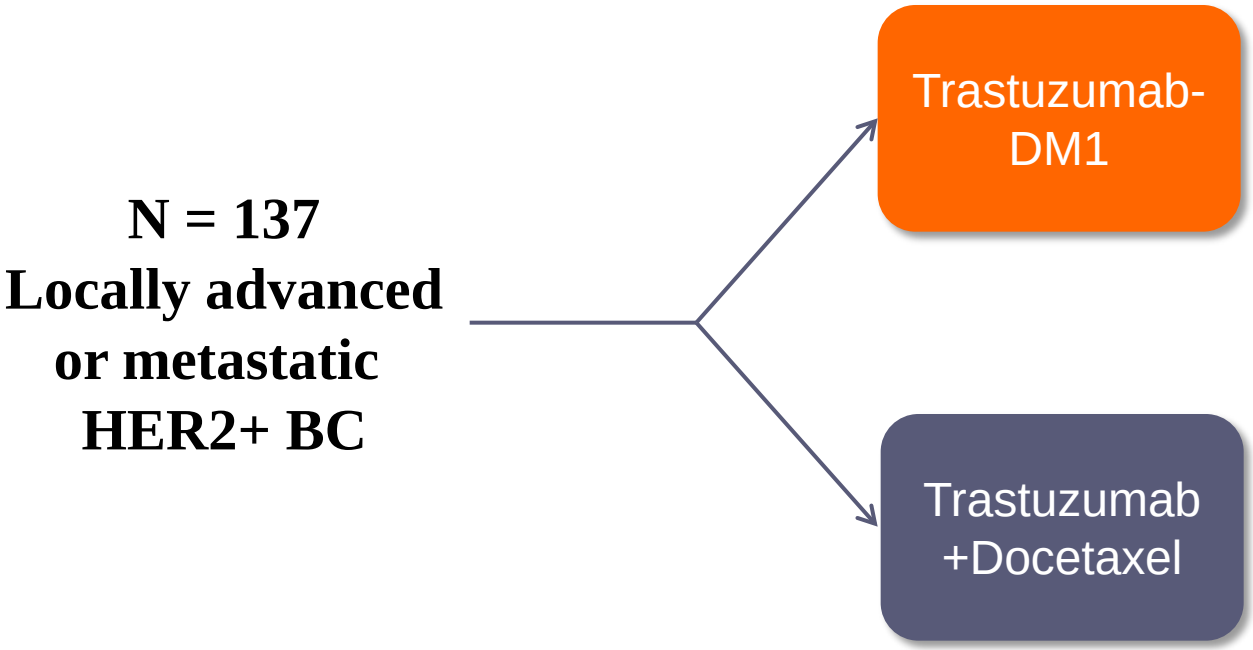
Antibody-drug conjugate: T-DM1

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



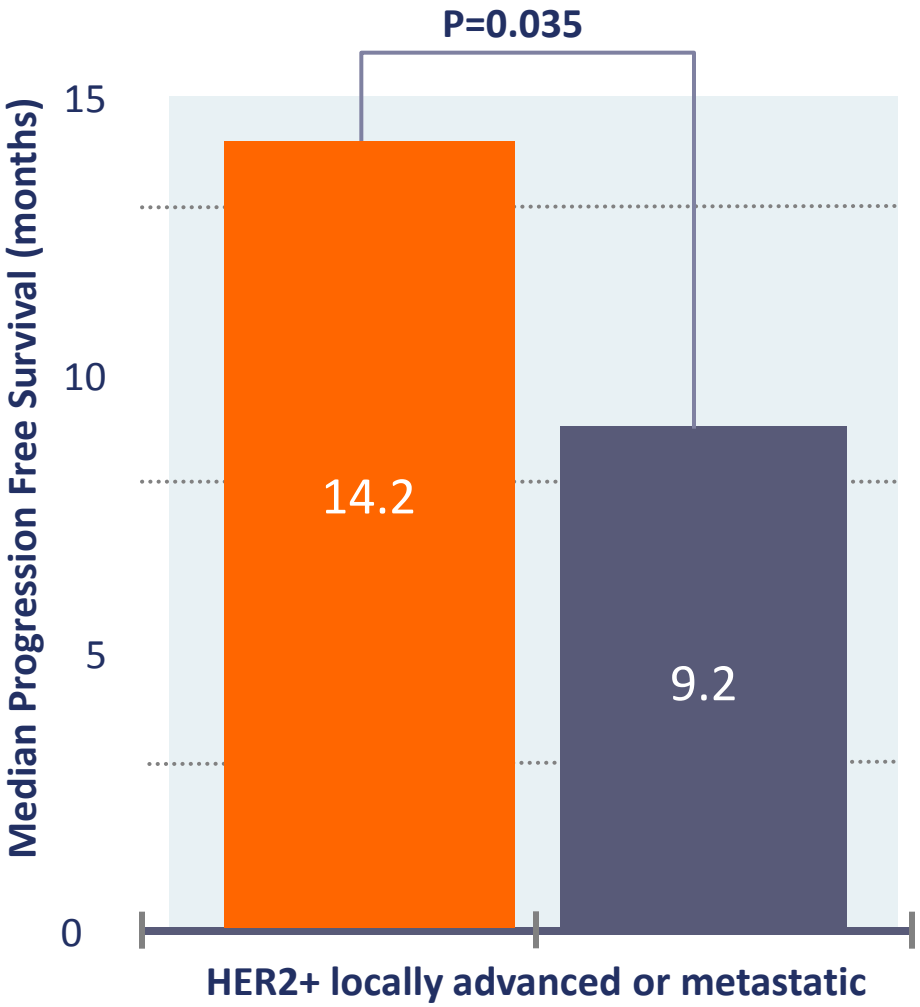
Early signal of Trastuzumab-DM1 activity

First Line Trastuzumab-DM1
Phase II open label
Anti HER2 Naive



Hurvitz S, et al, ECCO-ESMO 2011, Abstract No 5001

Early signal of Trastuzumab-DM1 activity : improved progression free survival



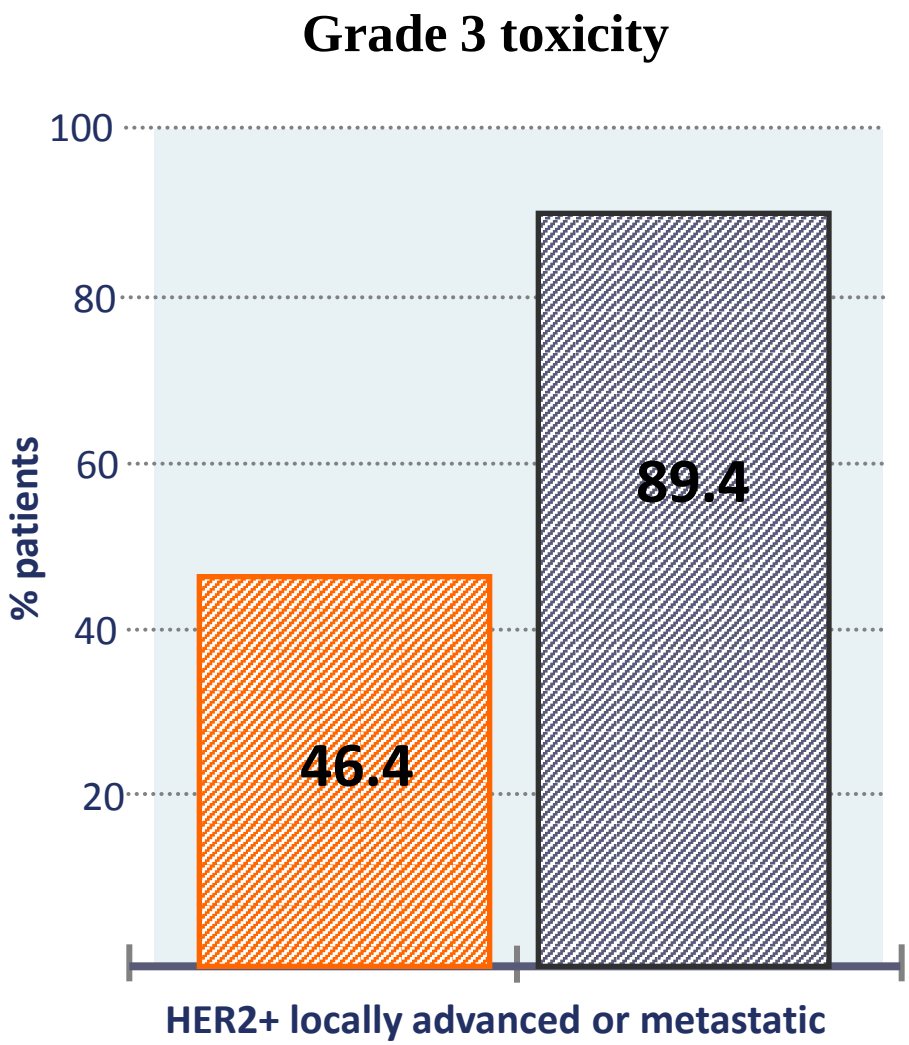
HR = 0.59, P=0.035

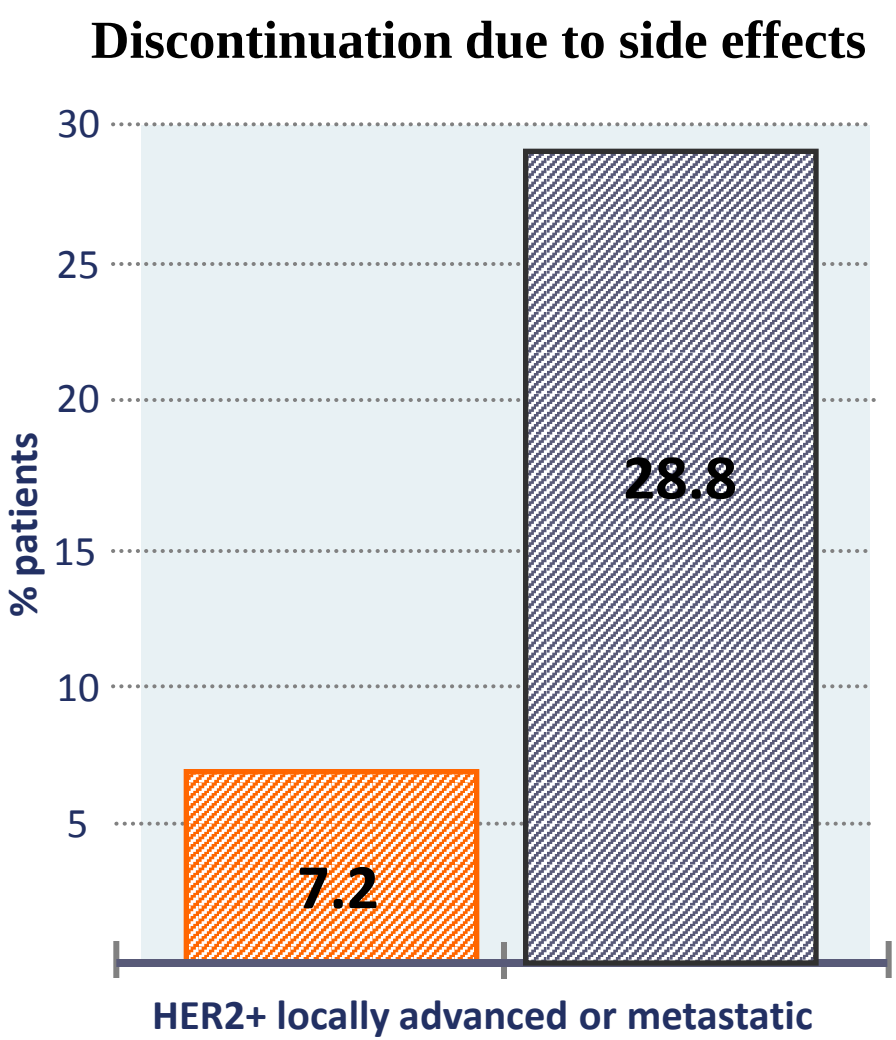
Treatment with trastuzumab-DM1 reduced the probability of disease progression or death by **41%** compared to treatment with Herceptin plus chemotherapy.

Trastuzumab-DM1 Trastuzumab + Docetaxel

Hurvitz S, et al, ECCO-ESMO 2011, Abstract No 5001

Improved toxicity-profile of Trastuzumab-DM1





Trastuzumab-DM1 Trastuzumab + Docetaxel

Hurvitz S, et al, ECCO-ESMO 2011, Abstract No 5001

HER_2 positive B.C. : advanced disease TDM_1 associated with better quality of life than docetaxel + trastuzumab

TDM_1 > docetaxel + trastuzumab

for all the following patient-reported outcomes !

- Physical well-being (FACT-B)
- « Lack of energy »
- « Bothered by side effects »
- « Feeling ill »
- « Forced to spend time in bed »
- « Trouble meeting needs of family »

abst P1-12-02, SABCS 2011

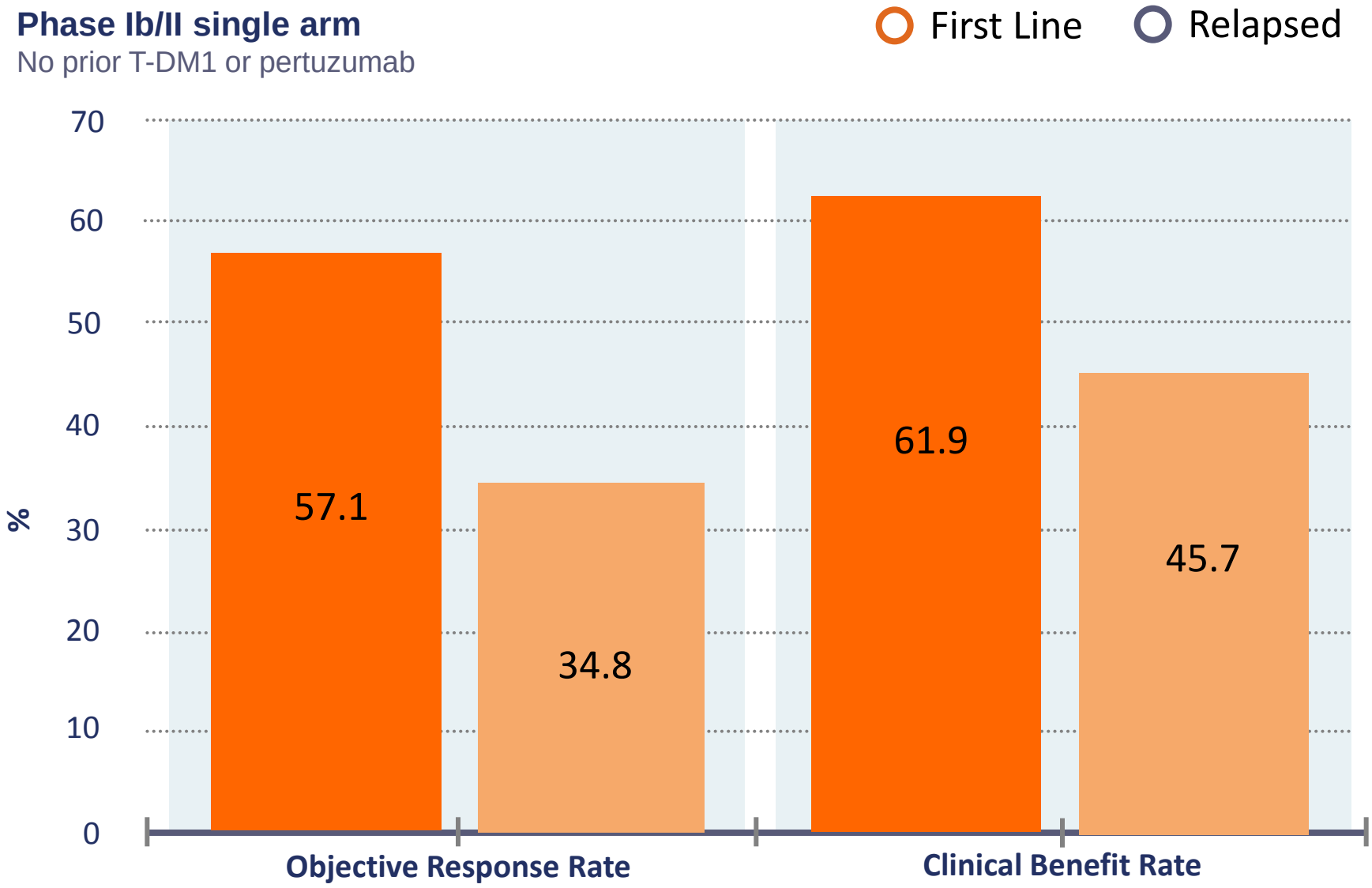
T-DM1 in the context of dual HER2 blockade …

T-DM1 in Combination with Pertuzumab

Trastuzumab-DM1 + Pertuzumab

Phase Ib/II single arm

No prior T-DM1 or pertuzumab

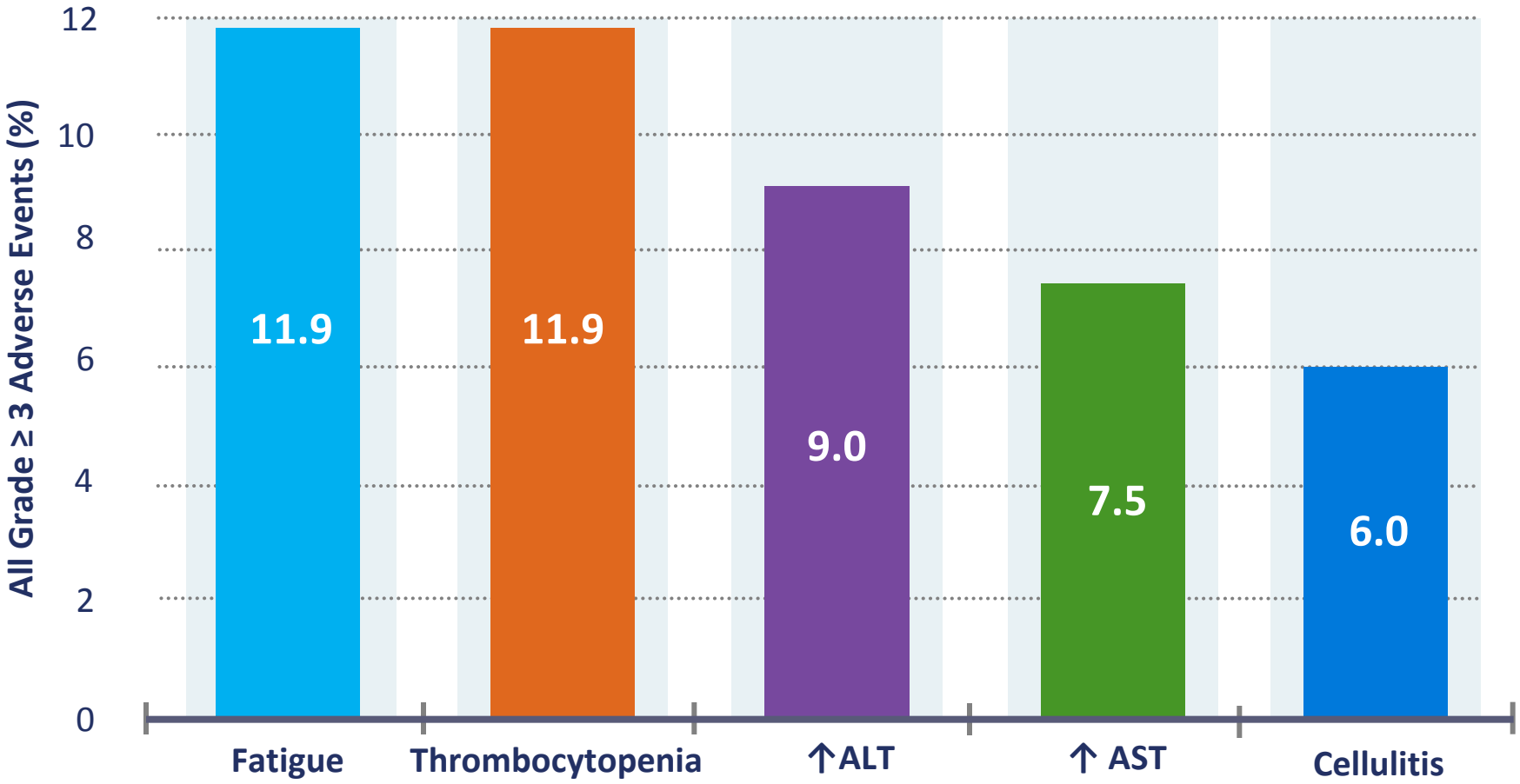


* Median number of prior systemic agents in metastatic setting (range) = 6.0 (2-14)

Dieras V et al, 33rd Annual SABC, 2010; P3-14-01

Safety of Trastuzumab-DM1 + Pertuzumab

Most Adverse events were Grade ≤ 2
Cardiac toxicity: 1 discontinuation due to LVEF dysfunction



Dieras V et al, 33rd Annual SABC, 2010; P3-14-01

Clinical development of TDM1

Advanced BC
First Line

MARIANNE
(Phase III)

T-DM1 + Pertuzumab
Vs.
Trastuzumab + taxane

Results 2014

Clinical development of TDM1

Advanced BC First Line	MARIANNE (Phase III)	T-DM1 + Pertuzumab Vs. Trastuzumab + taxane	Results 2014
Advanced BC Second Line	EMILIA (Phase III)	T-DM1 Vs. Lapatinib + Capecitabine	Results 2012

Clinical development of TDM1

Advanced BC First Line	MARIANNE (Phase III)	T-DM1 + Pertuzumab Vs. Trastuzumab + taxane	Results 2014
Advanced BC Second Line	EMILIA (Phase III)	T-DM1 Vs. Lapatinib + Capecitabine	Results 2012
Early Stage BC	Adjuvant and Neoadjuvant (Phase II)	T-DM1 post anthracycline	Results 2014

We are likely to witness the development of new members in this family… !

Future treatment strategies in HER2 positive BC

5.

Host-directed immune strategies

Biological Processes Associated with Breast Cancer Clinical Outcome Depend on the Molecular Subtypes

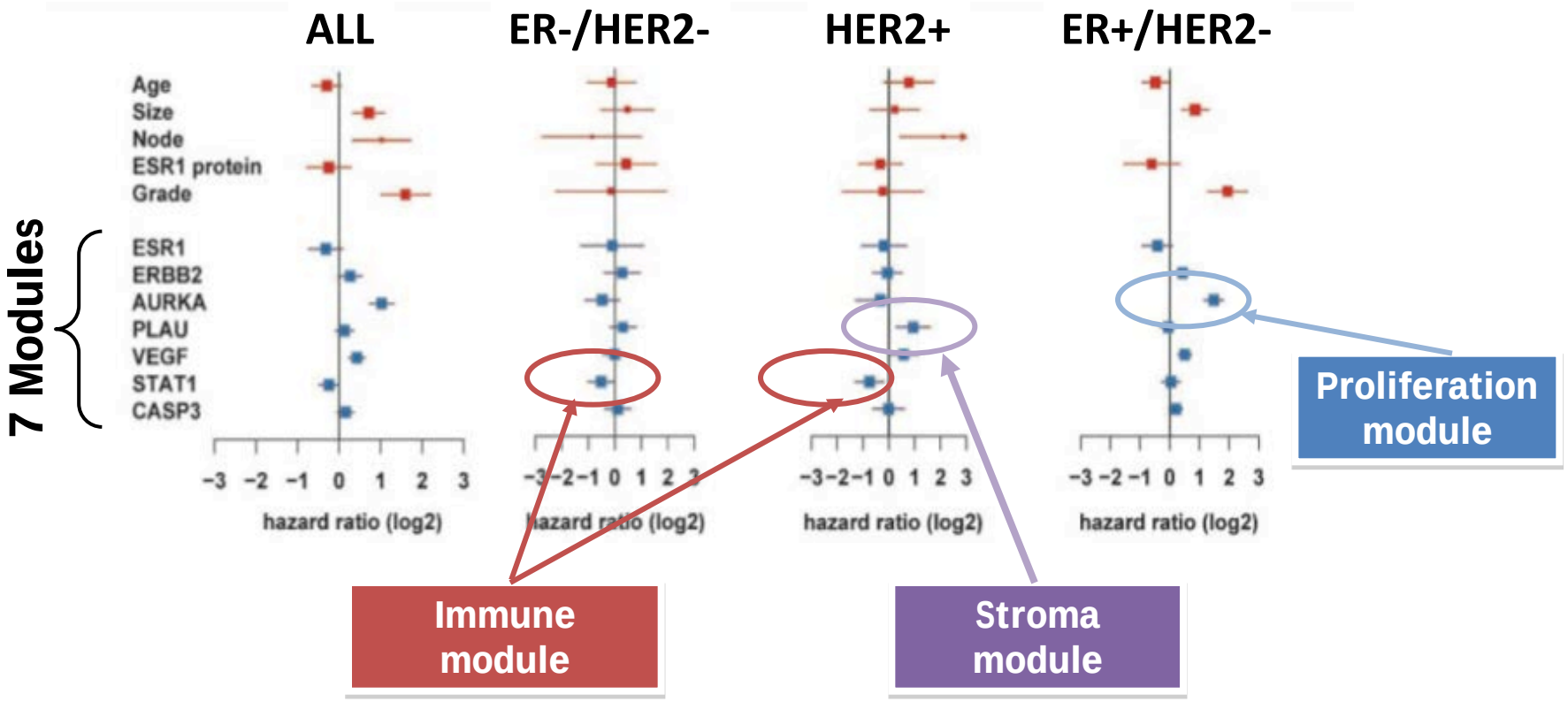
Christine Desmedt,[1] Benjamin Haibe-Kains,[1,2] Pratyaksha Wirapati,[3,4] Marc Buyse,[5] Denis Larsimont,[1] Gianluca Bontempi,[2] Mauro Delorenzi,[3,4] Martine Piccart,[1] and Christos Sotiriou[1]

Gene Modules

AURKA=proliferation

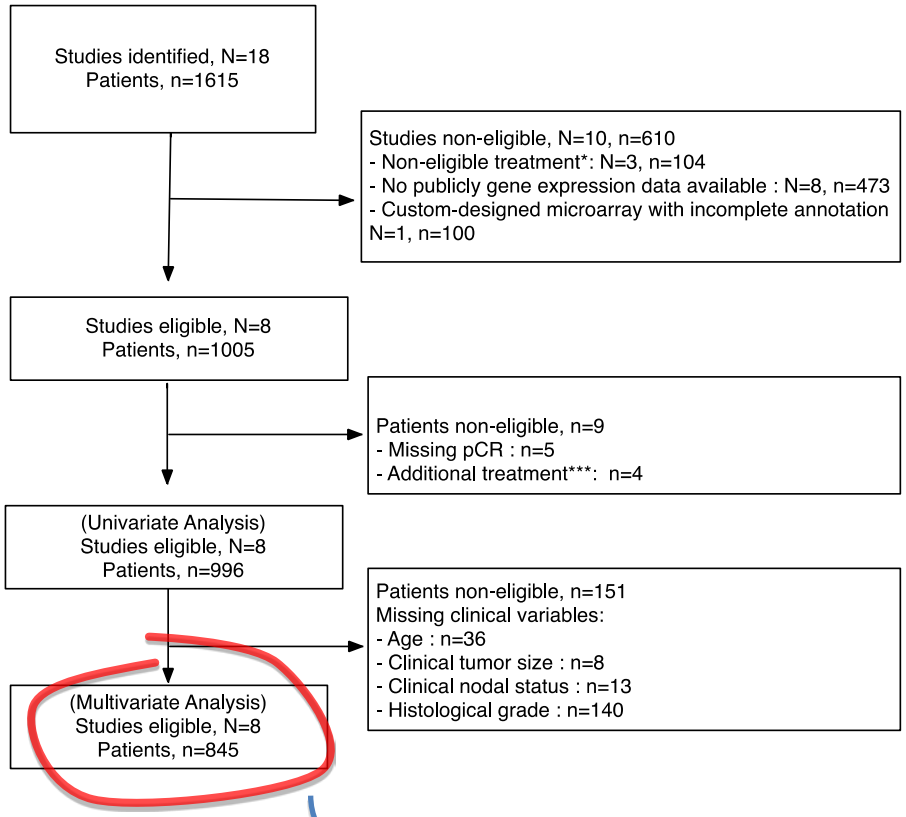
STAT1=immune

PLAU=stroma



Desmedt et al. Clin Cancer Res 2008

Pooled analysis of gene expression studies to predict neoadjuvant (taxanes and/or anthracyclines) chemotherapy response



Several molecular processes (including immune signatures) and molecular pathways

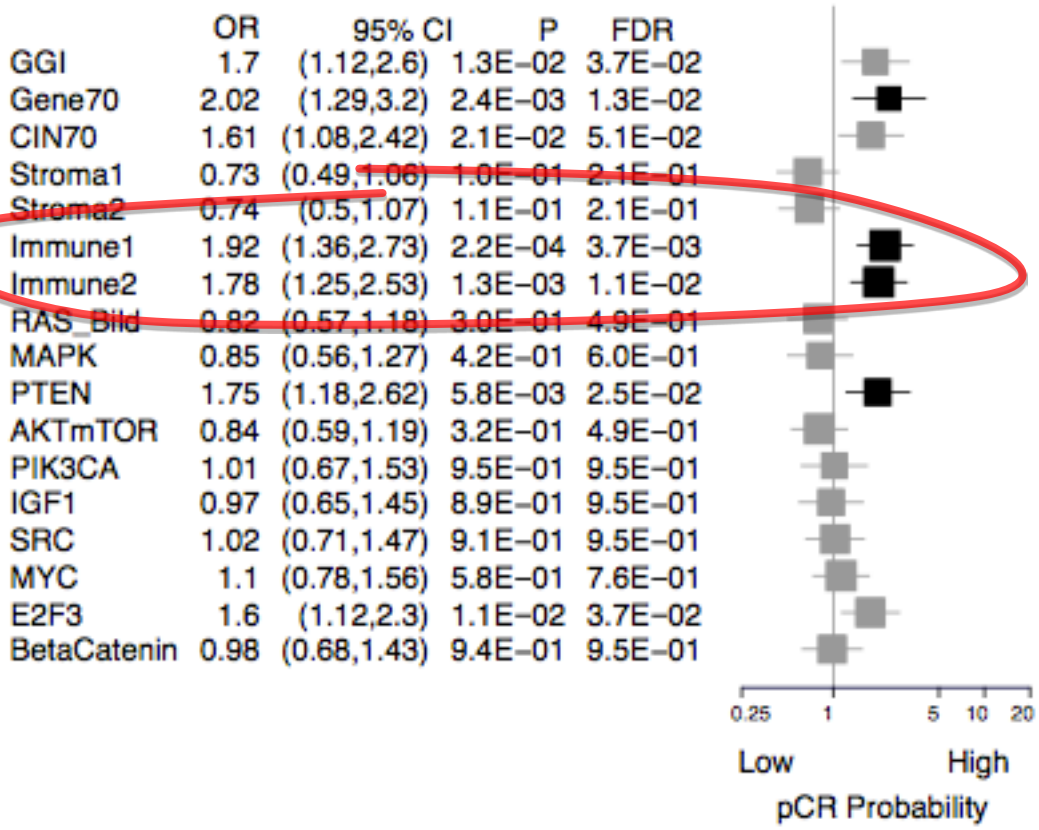
? Response to chemotherapy

M Ignatiadis submitted

Immune signatures are associated with better response to neoadjuvant chemotherapy in breast cancer beyond clinico-pathological characteristics

ALL patients

(N=845 pts; pCR=189)



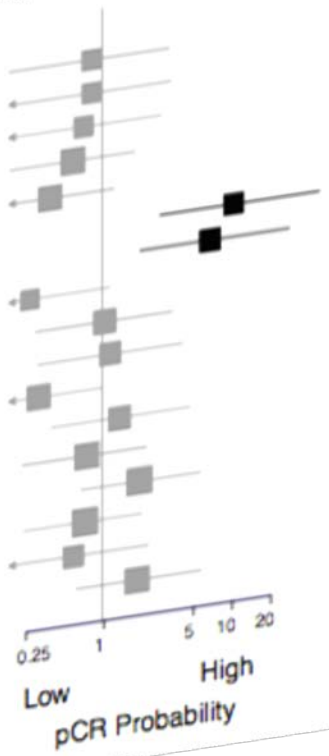
M Ignatiadis submitted

Mainly seen in HER2+ and ER-/HER2- BC

HER2+

(N=118 pts; pCR=42)

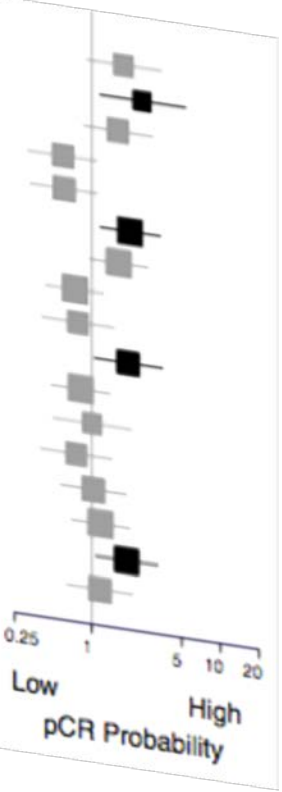
	OR	95% CI	P	FDR
GGI	0.86	(0.25,2.72)	8.0E-01	8.7E-01
Gene70	0.85	(0.24,2.8)	8.0E-01	8.7E-01
CIN70	0.76	(0.22,2.41)	6.4E-01	8.4E-01
Stroma1	0.65	(0.25,1.62)	3.5E-01	7.5E-01
Stroma2	0.46	(0.17,1.19)	1.2E-01	4.0E-01
Immune1	7.13	(2.38,25.51)	1.0E-03	1.8E-02
Immune2	5.01	(1.77,16.35)	4.1E-03	3.5E-02
RAS_Bild	0.34	(0.09,1.12)	8.7E-02	3.7E-01
MAPK	1.04	(0.37,2.84)	9.4E-01	9.4E-01
PTEN	1.13	(0.38,3.31)	8.2E-01	8.7E-01
AKTmTOR	0.39	(0.14,0.99)	5.4E-02	3.1E-01
PIK3CA	1.3	(0.47,3.69)	6.2E-01	8.4E-01
IGF1	0.79	(0.3,1.94)	6.2E-01	8.4E-01
SRC	1.74	(0.73,4.33)	2.2E-01	6.1E-01
MYC	0.77	(0.31,1.82)	5.6E-01	8.4E-01
E2F3	0.65	(0.21,1.97)	4.5E-01	8.4E-01
BetaCatenin	1.68	(0.68,4.35)	2.7E-01	6.5E-01



ER-/HER2-

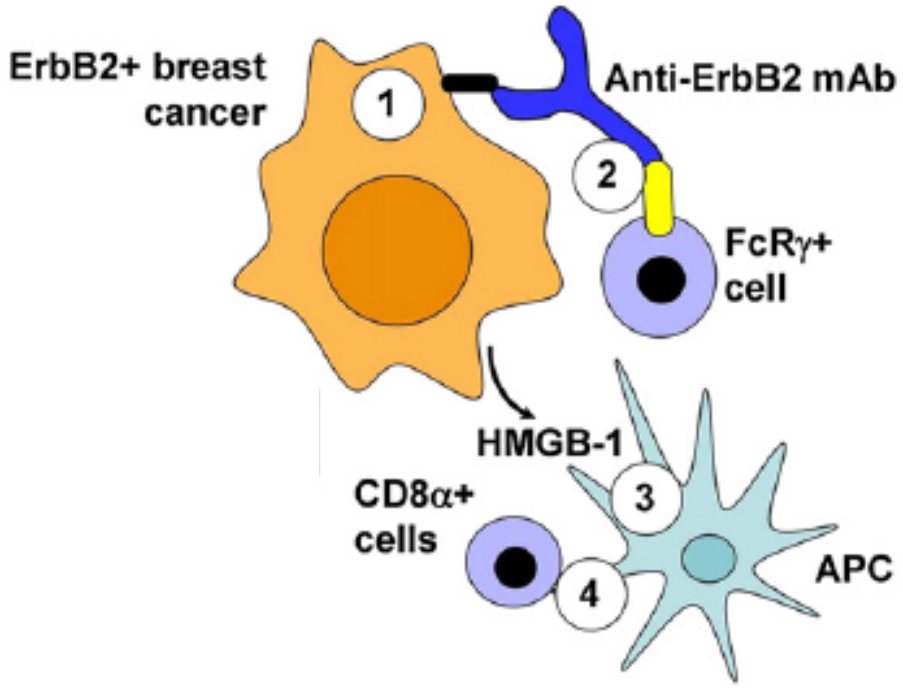
(N=394 pts; pCR=120)

	OR	95% CI	P	FDR
GGI	1.59	(0.91,2.81)	1.0E-01	2.2E-01
Gene70	2.11	(1.12,4.03)	2.2E-02	1.6E-01
CIN70	1.47	(0.88,2.47)	1.4E-01	2.7E-01
Stroma1	0.65	(0.38,1.08)	9.7E-02	2.2E-01
Stroma2	0.66	(0.4,1.08)	9.9E-02	2.2E-01
Immune1	1.76	(1.13,2.76)	1.3E-02	1.6E-01
Immune2	1.49	(0.96,2.31)	7.4E-02	2.2E-01
RAS_Bild	0.77	(0.5,1.19)	2.4E-01	4.1E-01
MAPK	0.81	(0.47,1.38)	4.3E-01	5.7E-01
PTEN	1.71	(1.04,2.85)	3.7E-02	1.6E-01
AKTmTOR	0.84	(0.54,1.3)	4.3E-01	5.7E-01
PIK3CA	1	(0.55,1.8)	9.9E-01	9.9E-01
IGF1	0.79	(0.46,1.34)	3.8E-01	5.7E-01
SRC	1.02	(0.62,1.65)	9.5E-01	9.9E-01
MYC	1.13	(0.73,1.75)	5.7E-01	6.9E-01
E2F3	1.67	(1.06,2.67)	2.9E-02	1.6E-01
BetaCatenin	1.12	(0.69,1.82)	6.4E-01	7.3E-01



M Ignatiadis submitted

A revised mechanism of action of Trastuzumab



HMGB-1 = High Mobility Group Box 1 Protein

(1+2)
Trastuzumab recruits Fc receptor expressing cells such as NK cells

(3)
ADCC (or HER2 signaling blockade) causes cell death and the release of "death signals" such as HMGB-1, which triggers the activation of Antigen presenting cells (APC)

(4) As a result CD8-dependent adaptive anti-tumor immunity is generated

M. Smyth, Cancer Cell2010

Future treatment strategies in HER2 positive BC
Host-directed immune strategies

- **Boosting « ADCC »…**

- **Boosting adaptive anti-tumor immunity…**

  - anti-CTLA4 antibody to eliminate the brake on T-cell activation ?

Winning the battle against HER2 positive BC !

The greatest challenge of tomorrow in HER2 positive B.C.

=

The tailoring of the anti-HER2 strategies !

Thank you !