Applied Molecular Biology in Metastatic Breast Cancer

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Biology of BC

Molecular Distinction between Breast Cancers:

"BC" stands for various diseases at an identical anatomic site:

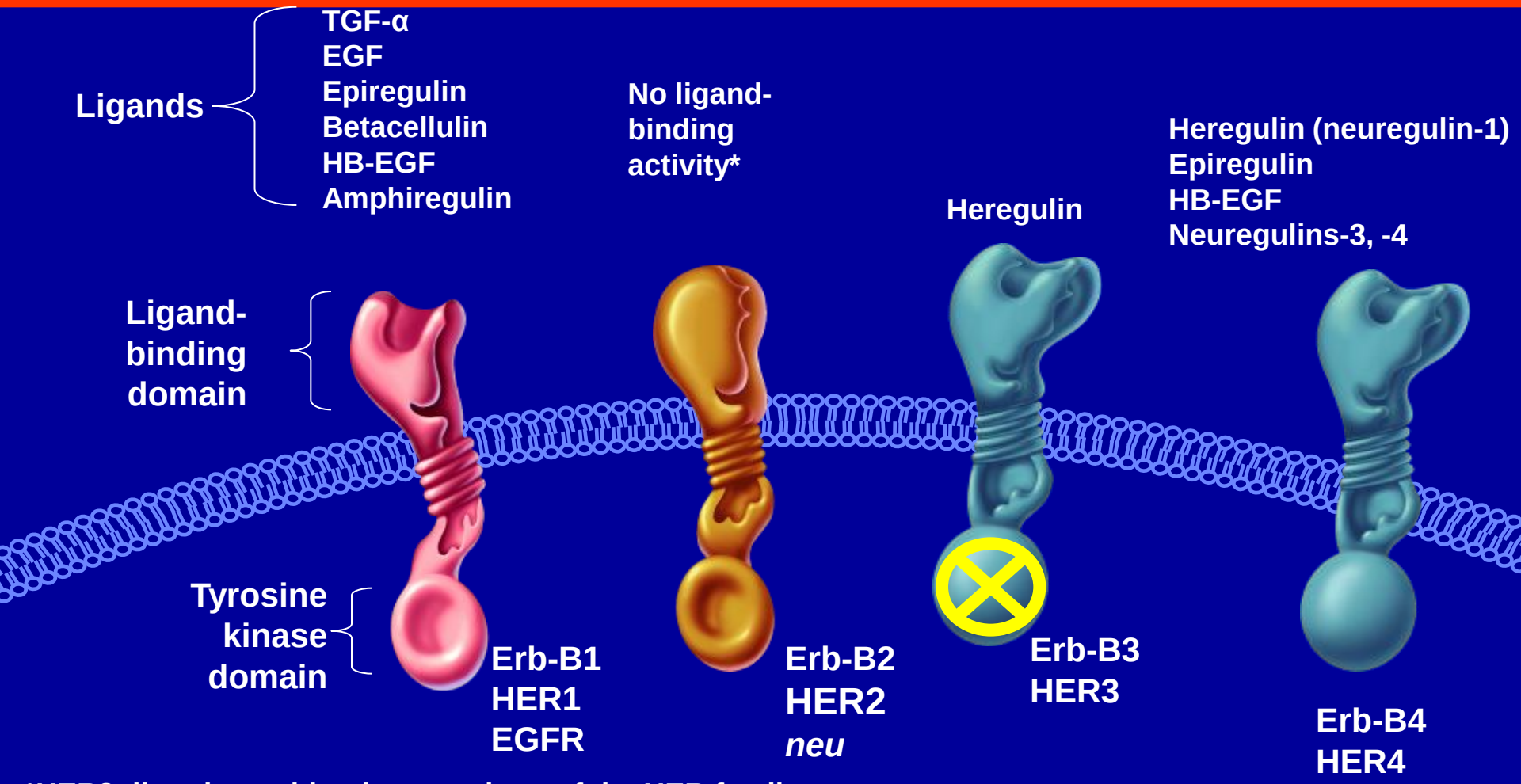
- **luminal-type and basal-like BCs are completely different diseases at molecular level[1-6]**
- **basal-type BCs show more molecular similarity with squamous lung, HN, serous ovarian or endometrial cancers**

[1] Ellis et al., Cancer Discovery 213; [2] Koboldt et al., Nature 2012; [3] Shah et al., Nature 2012; [4] Curtis et al., Nature 2012; [5] Banerji et al., Nature 2012; [6] Ellis et al., Nature 2012

Molecular Targeting in Breast Cancer

- Successes
- Promises
- Disappointments

The HER Family of Receptors



*HER2 dimerizes with other members of the HER family.

Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.
Rowinsky. *Annu Rev Med*. 2004;55:433.

Investigational pan-Her-2 – Targeting Drugs for Her-2/neu +++ MBC

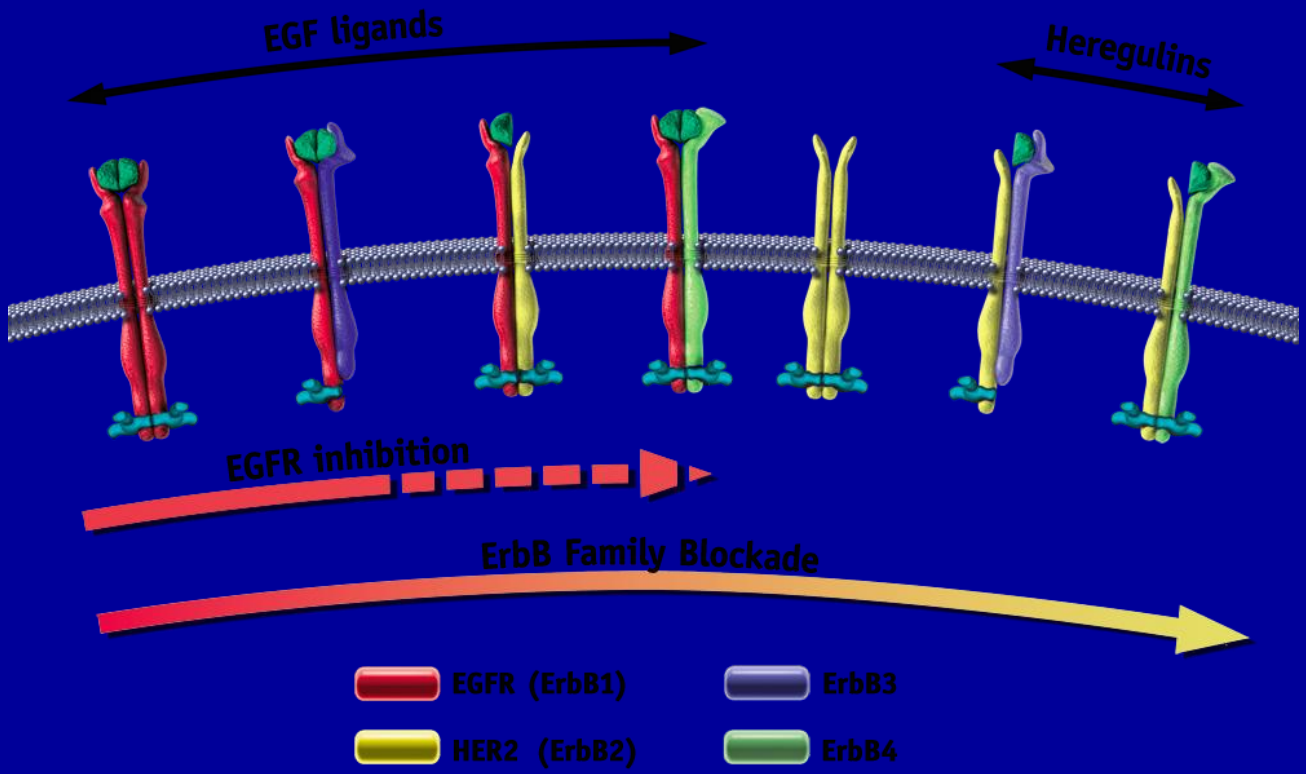
Afatinib	**Phase II, Completed***
	Phase III, Recruiting
Neratinib	**Phase II, Completed****
	Phase II Trials Ongoing

***Lin et al., Breast Cancer Res Treat 2012**

****Burstein et al., J Clin Oncol 2010**

pan Her-2 TK-Inhibition: Example Afatinib

Li D, et al. *Oncogene* 2008;27:4702–11.



Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential: Phase III Trial for Her-2/neu – Inhibitor Resistance (LUX-Breast-2 and Breast 3 Phase II Trials, recruiting)

Rationale: Inhibition of ErbB Family receptor heterodimerization

Phase II Study of Afatinib (BIBW 2992) in 41 Patients with HER2-positive MBC Progressing after Trastuzumab.

N.U. Lin et al., Breast Cancer Res Treat 133: 1057, 2012

Responses:

PR: 11% of Patients

SD: 37% of patients

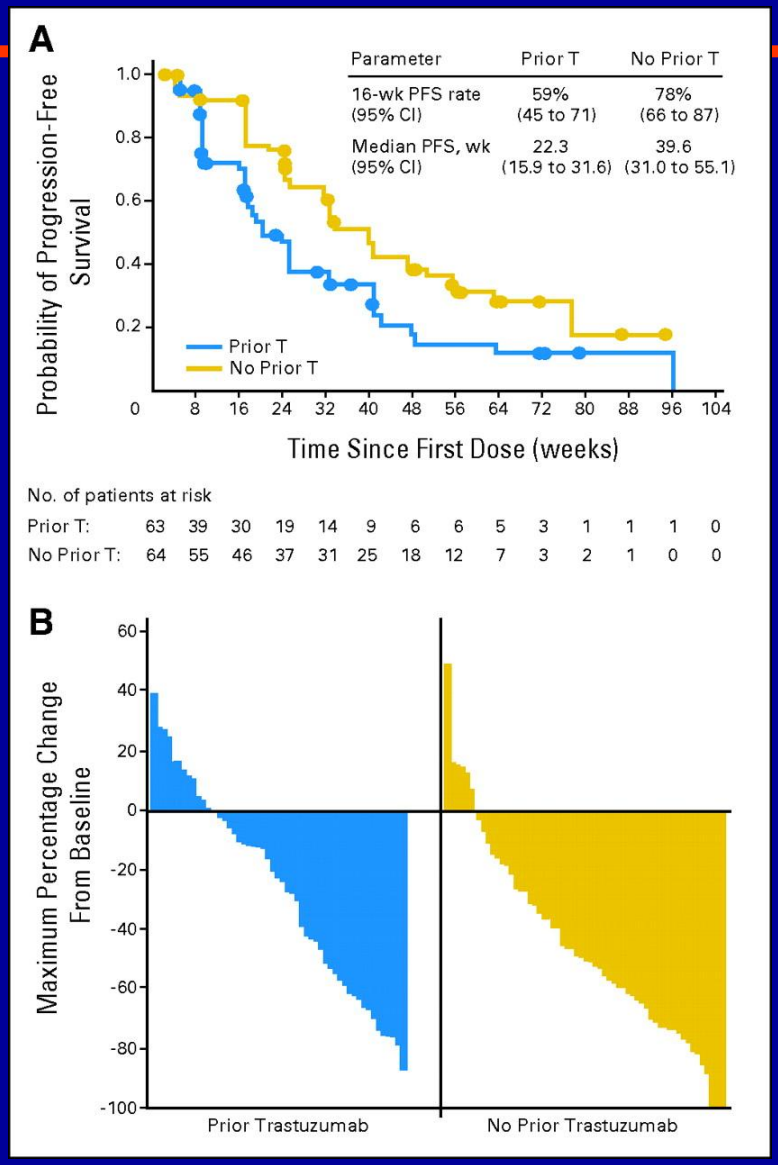
CB: 46% of patients

Time Variables:

median PFS: 15.1 weeks (95% confidence interval [CI]: 8.1-16.7)

median OS: 61.0 weeks (95% CI: 56.7-not evaluable)

PFS Under Neratinib in Her-2/neu+++ MBC with or without prior Trastuzumab.



Burstein H J et al. JCO 2010;28:1301-1307

Phase I Study of Neratinib with Temsirolimus in Her-2/neu+++ MBC.

L. Gandhi et al.: J Clin Oncol, doi: 10.1200/JCO.2012.47.2787, 2013

60 Patients

Drug Related and Dose Limiting Toxicities:

Diarrhea: 93%

Nausea: 53%

Stomatitis: 53%

Anemia: 48%

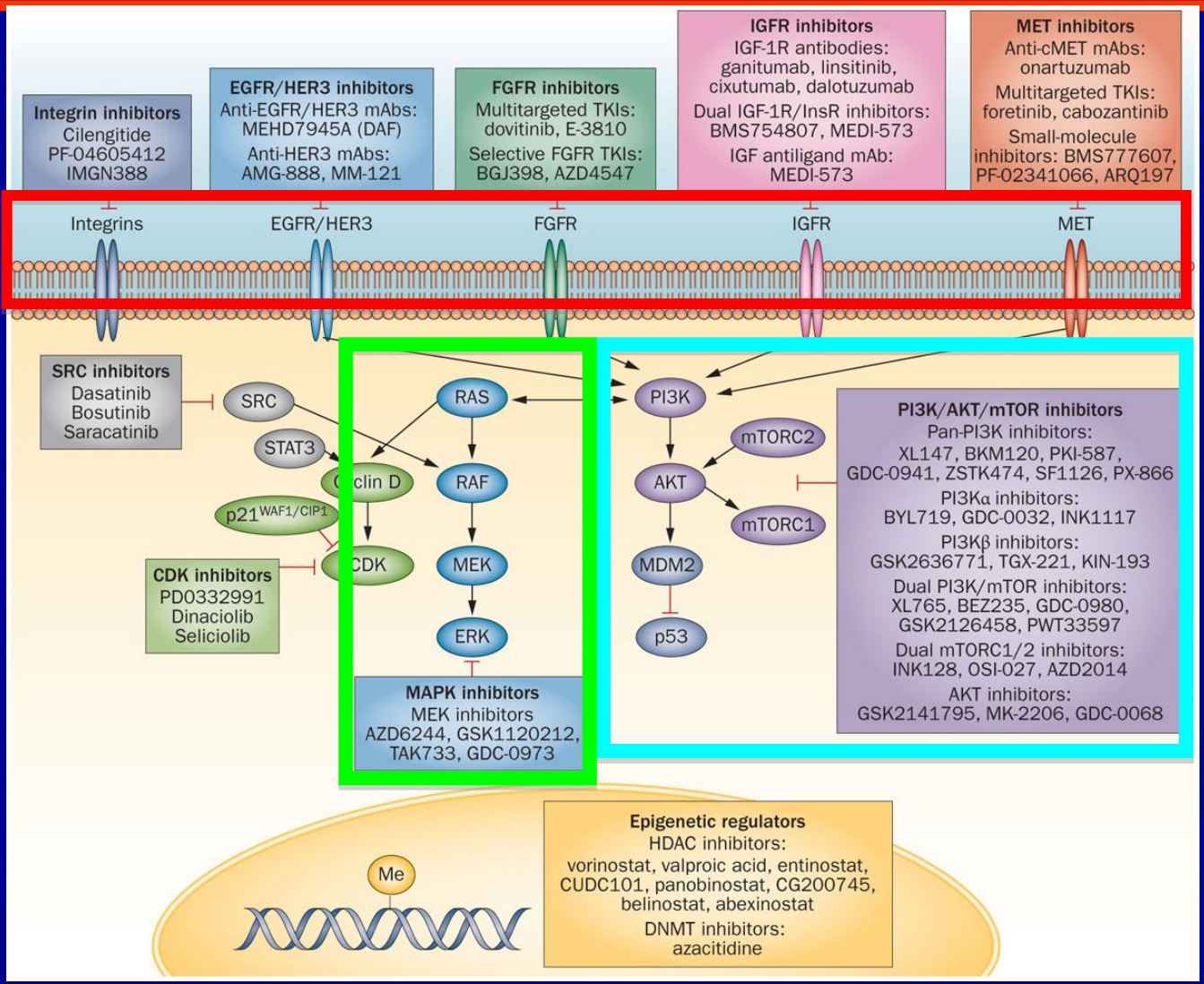
Responses:

- Her-2 – amplified breast cancers resistant to Trastuzumab,

- Her-2 – mutant lung cancer and

- tumor types without mutations in the HER-Pi3K-mTOR pathway.

Emerging Targets and Drug Development in Breast Cancer



Zardavas, D. *et al.* (2013) Emerging targeted agents in metastatic breast cancer
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.29

nature REVIEWS CLINICAL ONCOLOGY

IGF (IGF-1R, IR-alpha and IR-beta) Signalling Pathway

- Activated in >90% of breast cancer cases
- Activation associated with poor clinical outcome
- Crosstalk between ER and IGF:

  Endocrine resistance
- Crosstalk between HER2 and IGF:

  Trastuzumab-resistance: Heterotrimeric complex consisting of HER2, HER3, IGF-1R

IGF (IGF-1R, IR-alpha and IR-beta) – Targeting Drugs

- Anti-IGF Antibody: MEDI-573
- IGF-1R Inhibitors: Cixutumumab, Dalotuzumab*
- IGF-1R – Insulin Receptor Inhibitor (Dual Function): BMS-754807

* Phase I Trial Completed: 23 Patients - 2 CRs, 2 PRs, 1 SD
(S. Di Cosimo et al., J Clin Oncol 28 (Suppl. 15; A3008), 2010)

Limitations of and Disappointments in IGF-Targeting Drugs

- Lack of activity of IGF-targeting monotherapy
- Lack of activity of IGF-targeting drugs in combination with conventional therapies
- Combination of antibody Ganitumab with endocrine treatment resulting in a trend towards deterioration

Activation of PI3K / Akt / mTOR, MAPK, STAT Pathways...

...resulting in induction of cancer cell proliferation, evasion of apoptosis, facilitation of invasiveness, induction of angiogenesis.

- **FGF**

  (Drugs: AZD4547, Dovitinib, E-3810, Lucitanib, BIBF1120)

- **MET**

  (Drugs: Onartuzumab, Foretinib, Cabozantinib)

FGF Signalling Pathway

- **Amplification in >10% of breast cancers related with poor clinical outcome and endocrine resistance**

FGF – Targeting Drugs (FGFR Inhibitors)

- **Selective: AZD4547**
- **Multitargeted: Dovitinib, E-3810, Lucitanib, BIBF1120**

Completed Trials in MBC

Dovitinib[1]: 20 Patients - 0 CR, 3 PR, 9 SD

Lucitanib[2]: 12 Patients - 0 CR, 7PR, 2 SD

Ongoing, neoadjuvant

BIBF1120 (FGF, VEGF, PDGF): Paclitaxel +/- BIBF1120

[1] F. Andre et al., J Clin Oncol 29 (Suppl 27, A289), 2011

[2] R. Dienstmann et al., Ann. Oncol. 29 (Suppl. 9), 2012

MET Signalling Pathway

- **MET and MET-Ligand HGF overexpressed in >45% breast cancers.**

  Consequences: poor clinical outcome, metastatic spread, tumour cell proliferation, high grading and triple-negativity

- **Treatment resistance: Associated with resistance towards trastuzumab, lapatinib and endocrine treatment**

MET – Targeting Drugs

- Onartuzumab
- Multitargeted TKIs: Foretinib, Cabozantinib

Completed Trials in MBC

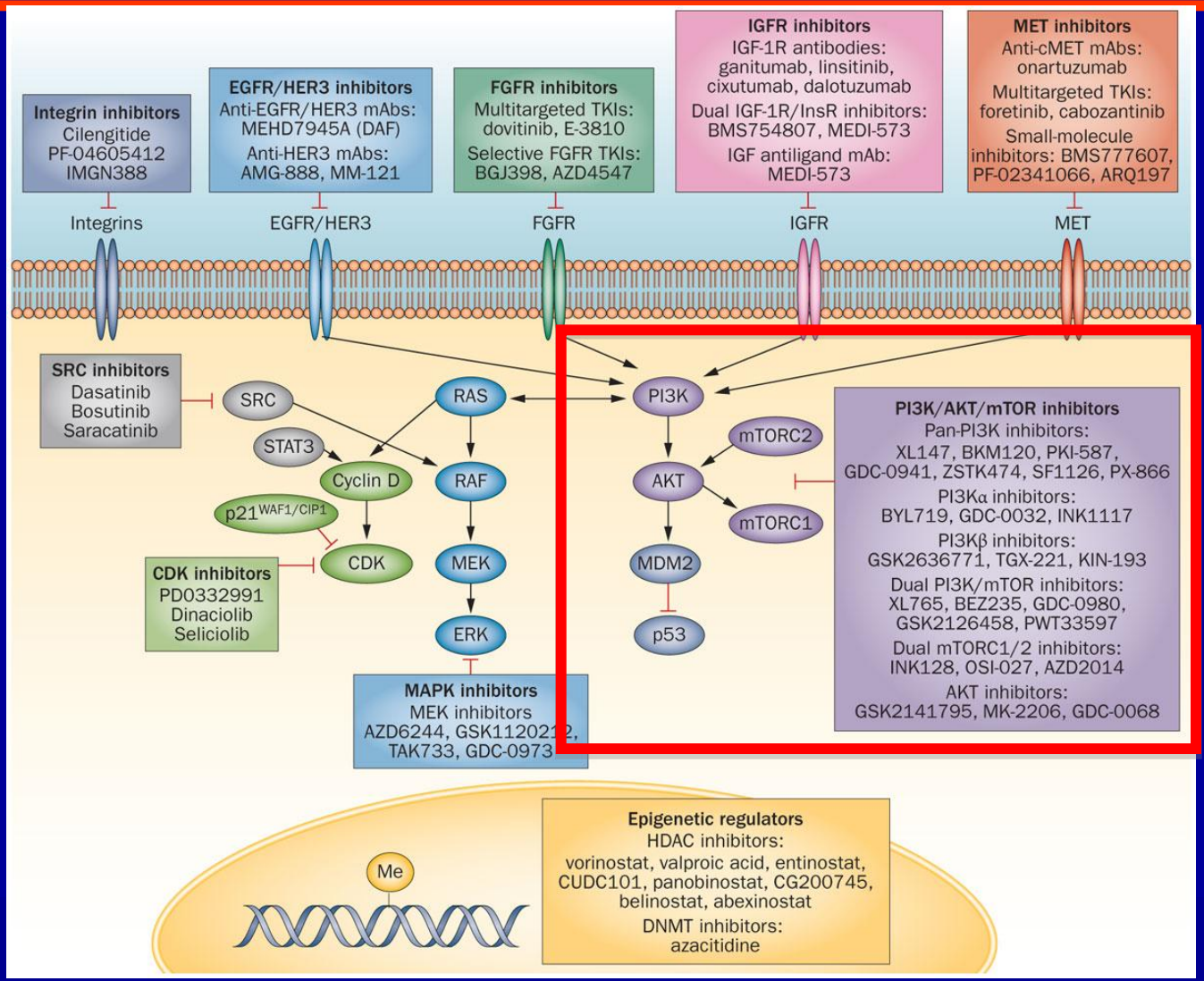
Foretinib[1]: 15 Patients with TNBC – 0 CR, 1 PR, 6 SD

Cabozantinib[2]: 44 Patients – 0 CR, 6 PR, 26 SD

[1] D. Rayson et al., J Clin Oncol 30 (Suppl., A1036), 2012

[2] E. Winer et al., J. Clin. Oncol. 30 (Suppl., A535), 2012

Emerging Targets and Drug Development in Breast Cancer



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nature REVIEWS CLINICAL ONCOLOGY

PI3K-Akt-mTOR Pathway Alterations in Cancer

Lung
- p-Akt, 23%–50%
- PTEN, 24%
- Ras, 30%
- EGFR, 32%–60%

Kidney
- TSC1/TSC2
- p-Akt, 38%
- PTEN, 31%
- TGFa/TGFb1, 60%–100%
- VHL, 30%–50%
- IGF-1/IGF-IR, 39%–69%

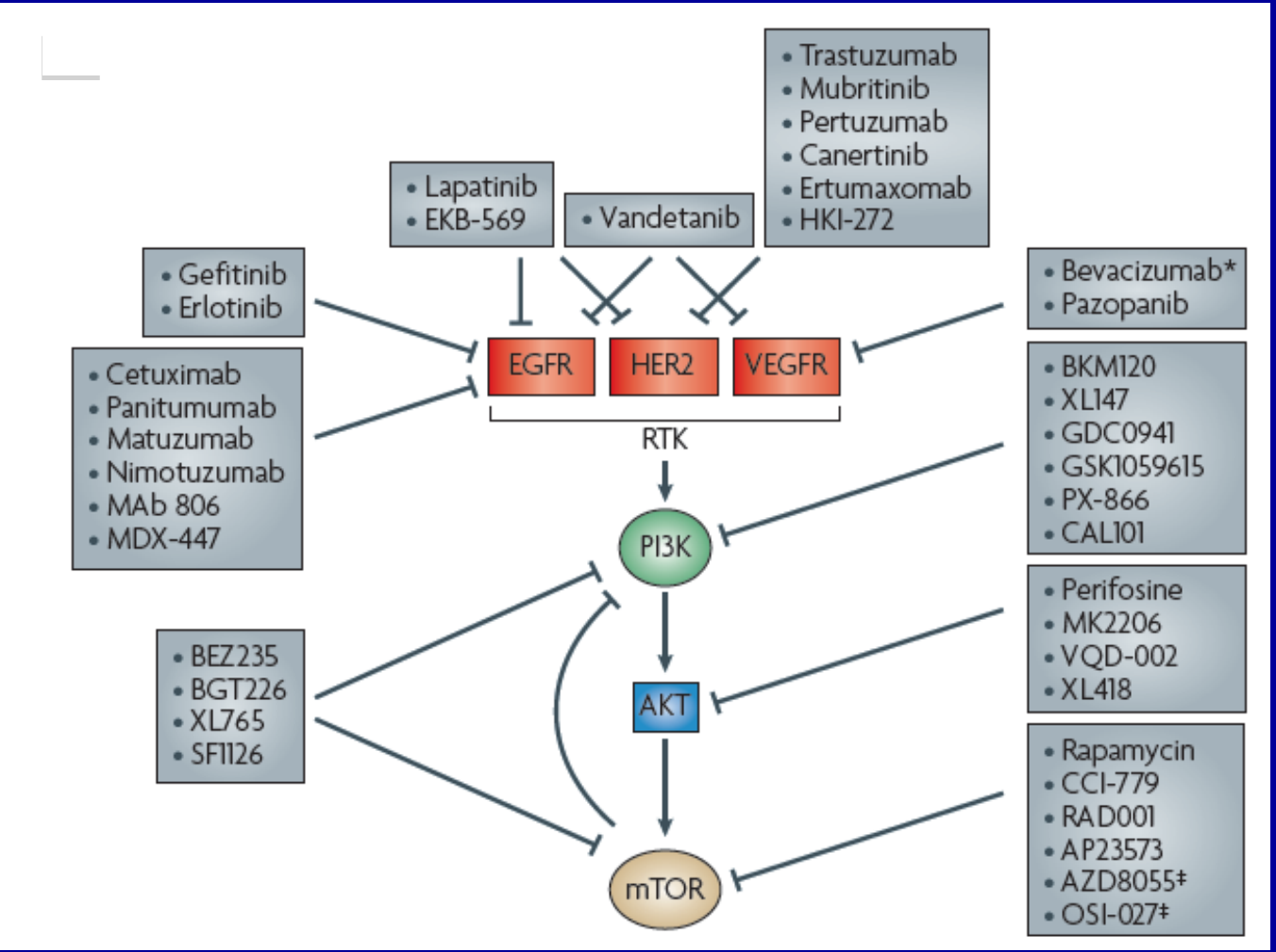
Breast
- p-Akt, 42%
- PI3K, 18%–26%
- PTEN, 15%–41%
- HER2, 30%–36%

NET
- TSC1/TSC2
- IGF-1/IGF-1R
- VHL

Colon
- p-Akt, 46%
- PI3K, 20%–32%
- PTEN, 35%
- Ras, 50%
- EGFR, 70%

% Incidence mutations

Vertical Signaling Inhibition of the PI3K / Akt / mTOR Pathway



Liu et coll. Nature Reviews Drug Discovery 2009

PI3K / Akt / mTOR Pathway

- Most frequently mutated pathway in breast cancer
- Mutation = gain of function
- Amplifications / Mutations affect almost all relevant molecular components

  Her-2, FGFR1, IGF-R1

  AKT1, AKT2

  KRAS (= PI3K Activator)

  PTEN, INPP4B (= negative PI3K regulators)

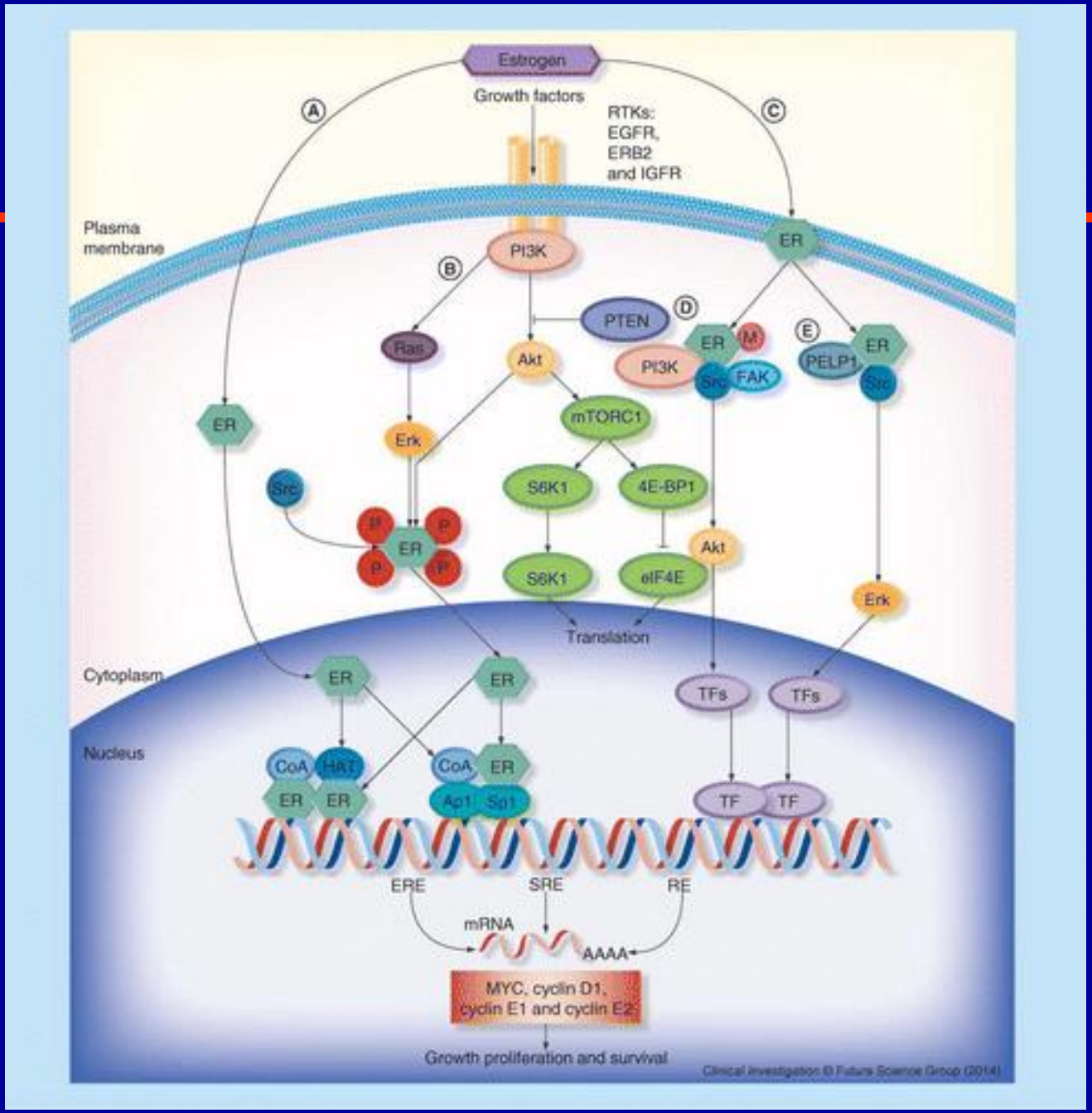
PI3K / Akt / mTOR Pathway in Breast Cancers

Biological Importance? in:

- **ER-Positivity and Endocrine Resistance**
- **Her-2/neu Overexpression and Treatment Resistance**
- **Triple Negativity**

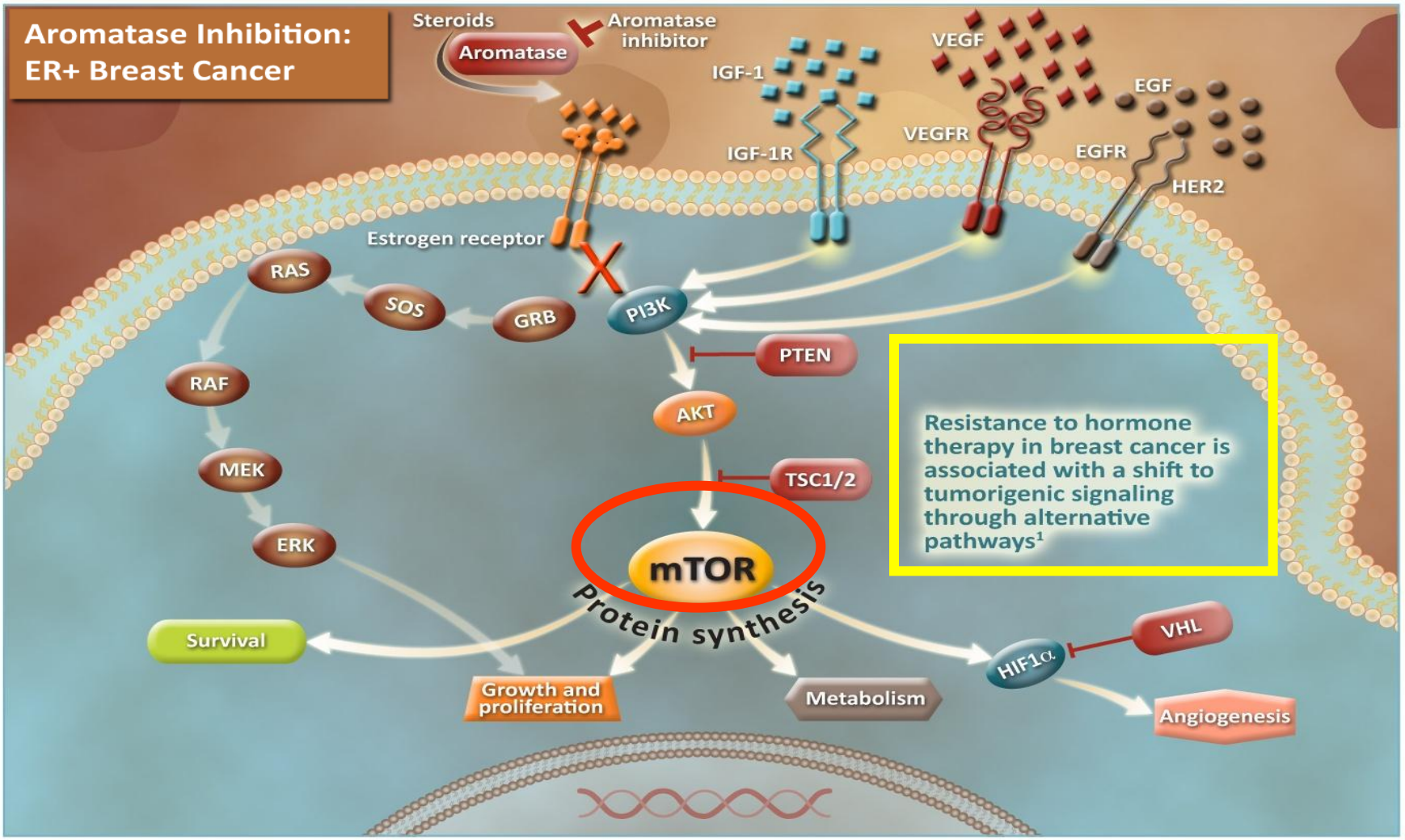
PI3K / Akt / mTOR Pathway in ER-Positivity

- PIK3CA most commonly mutated gene in luminal BC
- PI3K activation leads to endocrine resistance by crosstalk between ER and pathway-activating RTKs
- Ligand-independent activation of ER by mTORC1



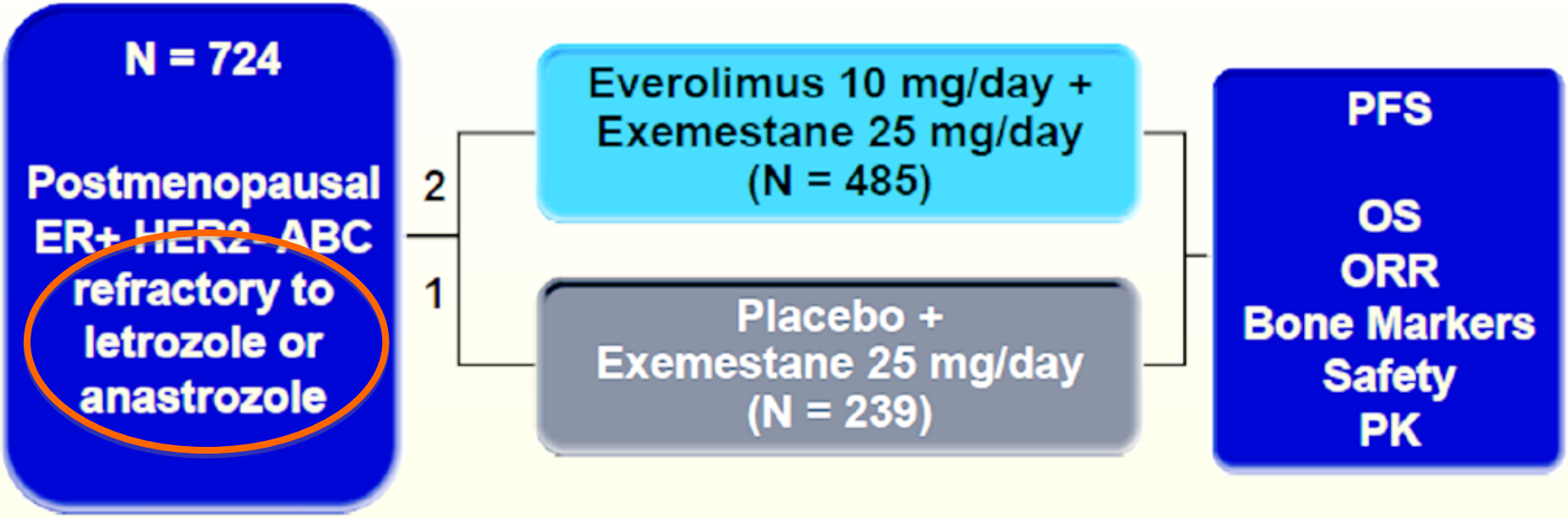
R. Chlebowski, Clinical Investigation 4: 19, 2014

Aromatase Inhibition and Treatment Resistance in ER+ Breast Cancer



Moy B, et al. Clin Cancer Res. 2006;12:4790-4793.

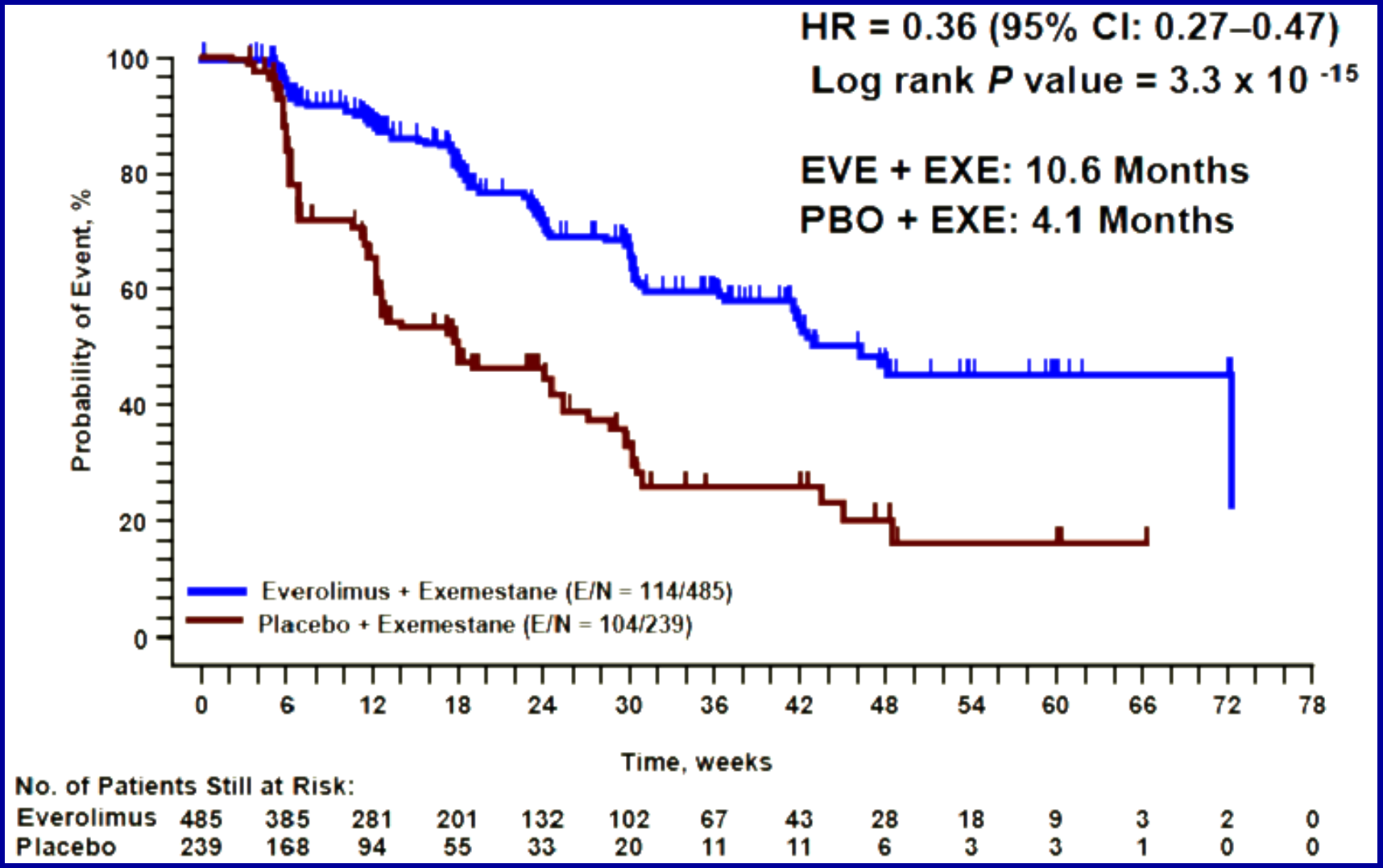
BOLERO-2: Trial Design



- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
- No crossover

J Baselga et al., N Engl J Med 2012; 366:520-529

BOLERO-2 Primary Endpoint: PFS by Central Assessment



J Baselga et al., N Engl J Med 2012; 366:520-529

PI3K / Akt / mTOR in Her-2 Overexpression

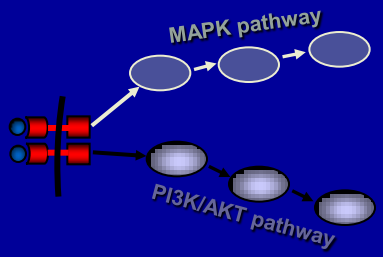
PI3K activation via mutation or PTEN loss correlated with resistance towards Her-2/neu - targeting drugs.

Resulting hypothesis: Reversibility by PI3K blockade?

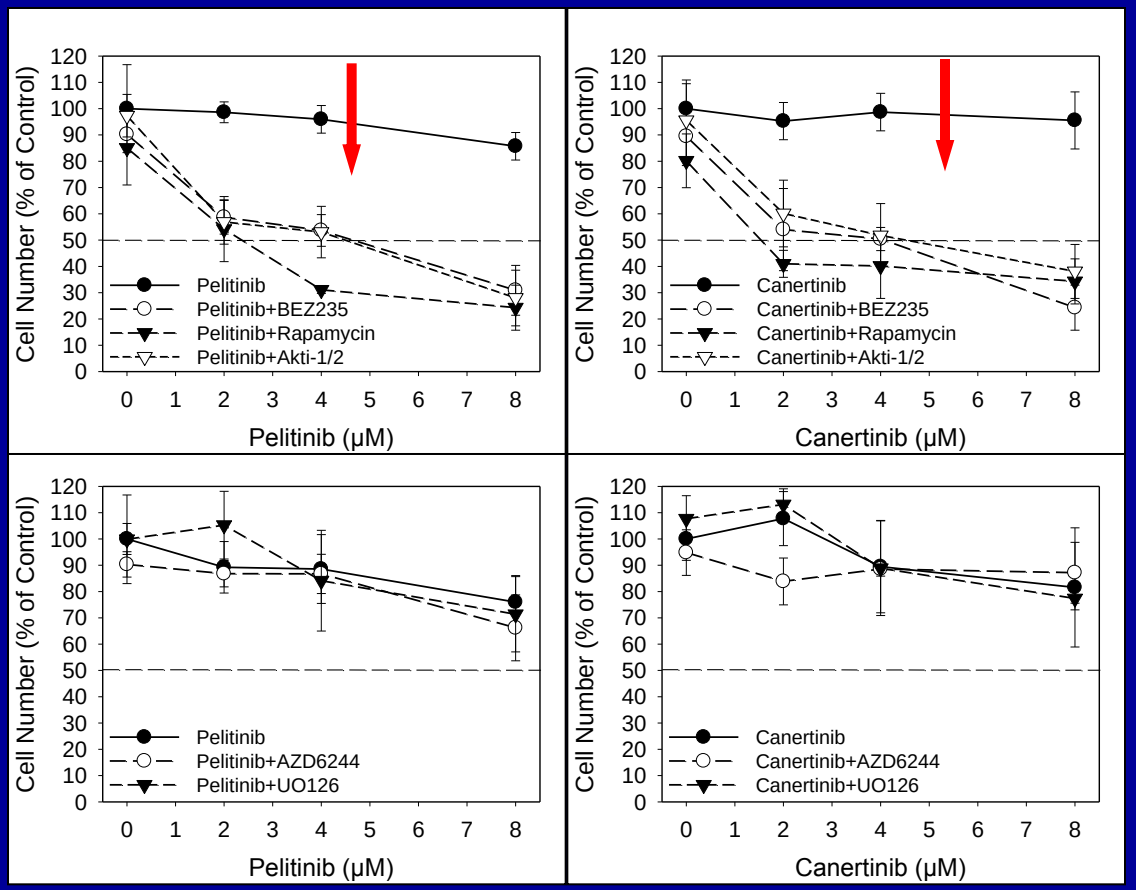
PI3K Inhibitors Overcome ErbB Drug Resistance *in vitro*

PI3K/AKT/mTOR inhibitors sensitize the cells against ErbB drugs

MAPK inhibitors do NOT sensitize the cells against ErbB drugs



ErbB drug resistant T47D breast cancer cells

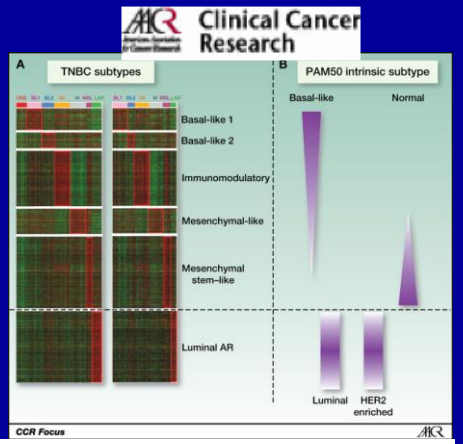


Brünner-Kubath et al., submitted

PI3K / Akt / mTOR Pathway in Triple Negativity

3 subtypes: luminal androgen receptor, mesenchymal-like, mesenchymal stem-like

- Sensitivity in vitro due to dual PI3K-mTOR blockade
- Elimination of PTEN induces PARP-inhibitor sensitization



Turner N C , and Reis-Filho J S Clin Cancer Res 2013;19:6380-6388

PI3K / Akt / mTOR Pathway Feedback Mechanisms

- **Pan PI3K Inhibitor XL-147 upregulates RTKs**
  FGFR2, FGFR3, HER3, IGF-1R, Insulin Receptor

- **AKT Inhibition upregulates RTKs**
  HER3, IGF-1R, Insulin Receptor

Completed Phase I Trials Targeting the PI3K / Akt / mTOR Pathway in MBC

Drug	n	Inclusion Criteria	Pretreatment	CR	PR	SD	ORR
BEZ235 +Trastuzumab[1]	15	Her-2/neu-Positivity	Trastuzumab	0	1	4	5
BKM120[2]	9	Any	Any	0	1	5	6
BKM120[3]	51	ER-Positivity	Aromatase Inhib.	1	1	13	15
MK-2206[4]	8	Any	Any	0	0	0	0
MK-2206 +Her-2-Inhibition[5]	32	Her-2/neu-Positivity	Her-2-Therapy	1	1	4	6

[1] Krop et al., J Clin Oncol 2012; [2] Bendell et al., J Clin Oncol 2012; [3] Mayer et al., J Clin Oncol (Suppl., A510) 2012; [4] Yap et al., J Clin Oncol 2011; [5] Han et al., J Clin Oncol 29 (Suppl., A3028), 2011.

Trials on Molecular Targets in Breast Cancer: The Neoadjuvant Setting

Target	Drugs
Her-2	Afatinib, Neratinib, T-DM1
Her-3	MM-121 (monoclonal anti Her-3 antibody)
EGFR	Cetixumab, Panitumumab[1]
c-Met	Ondartuzumab[1]
FGF	BIBF1120
PI3K	BKM120, Everolimus, GDC0032[1]
MAPK	Selumetinib[1]
PARP	Veliparib, Iniparib, Carboplatin
CDK	Palbociclib (positive for PFS in the PALOMA trial)

[1] in planning

Emerging Targeted Drugs for Breast Cancer Treatment: Conclusions

- Following the discovery of crucial molecular signalling mechanisms, targeted drugs have been developed.
- Although generally applicable as a concept, the identification of a true driver pathway, the identification of biomarkers for patient selection and, finally and most importantly, the therapeutic efficacy of targeting have to be proved for each BC subtype and each setting.
- An abundance of drugs is in development which challenge the scientific community to develop appropriate models for the clinical testing of these compounds.