Animal Models and Resistance to HER2-Targeted Therapy

C. Kent Osborne
Director
Dan L. Duncan Cancer Center
Baylor College of Medicine
Houston, Tx

Dan L. Duncan Cancer Center at Baylor College of Medicine

Lester and Sue Smith Breast Center at Baylor College of Medicine

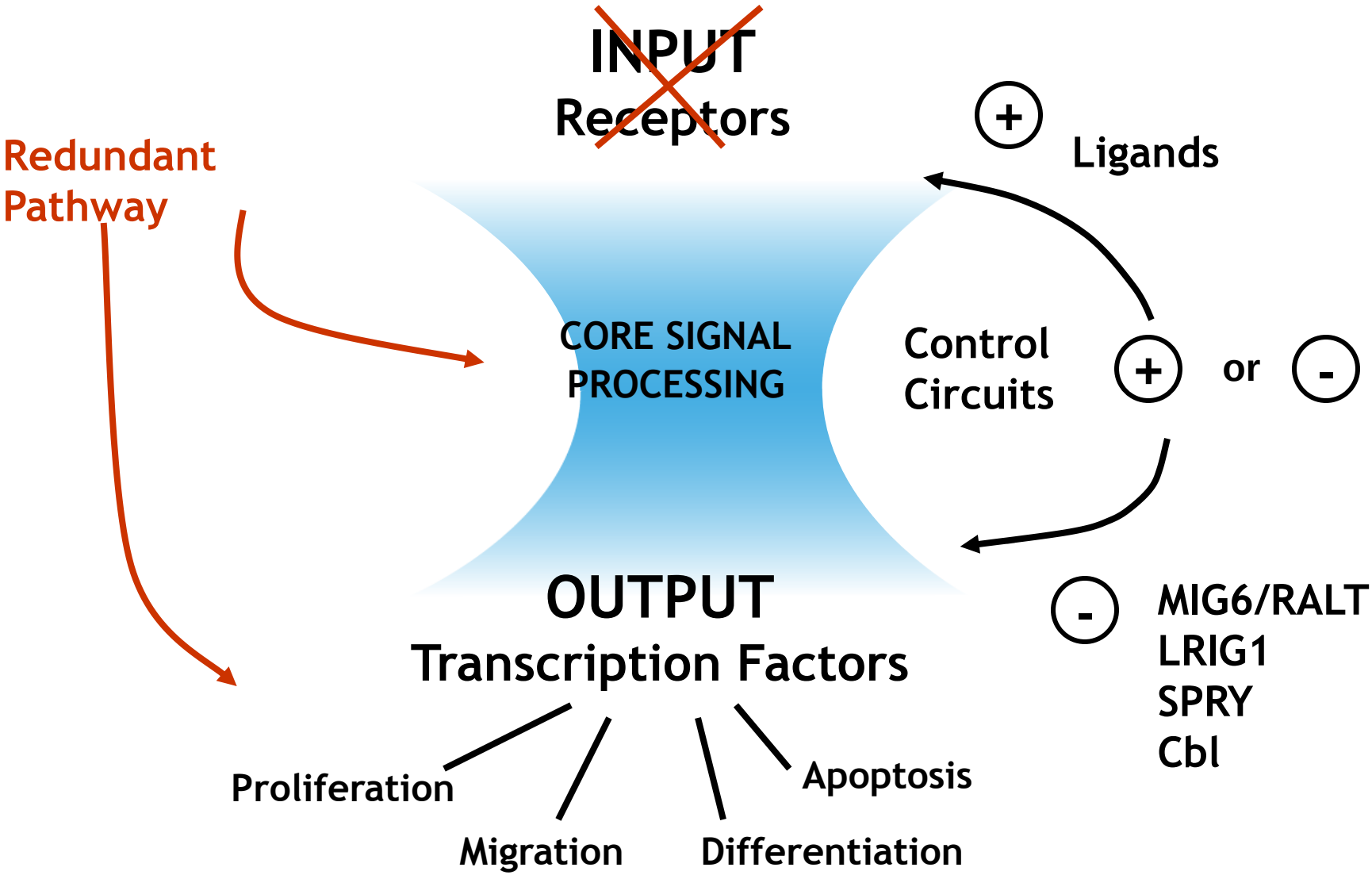
Oncogene Addiction and Treatment

- **Cell driven by a single powerful driver pathway.**
- **Other redundant survival pathways become inactive because they are not needed, but can be reactivated if the driver is blocked.**
- **Potent inhibition of the driver pathway should kill the cell.**

Optimal Targeted Therapy

1. **Identify key pathway(s), the driver.**
2. **Block this pathway completely.**
3. **Anticipate escape (resistance) mechanisms and block them.**
4. **Combination therapy.**
5. **Oncogene addiction can work in our favor.**
6. **HER2+ breast cancer is the ideal tumor to apply these principles.**

The HER Signaling Network



Citri and Yarden, Nature Reviews, 2006

Experimental Models

1. Flies, worms, bacteria, yeast
2. Cultured cells*
3. In vivo animal models
   - syngeneic
   - carcinogen induced
   - transgenic or knockout
   - xenografts of human cells into nude mice*
   - patient derived xenografts (PDXs)*
4. Patients*

Human Tumor Xenografts in Mice

1. **Good points:**

   - relatively cheap; large experiments

   - many cell lines; ER+, HER2+, triple negative

   - reproducible results

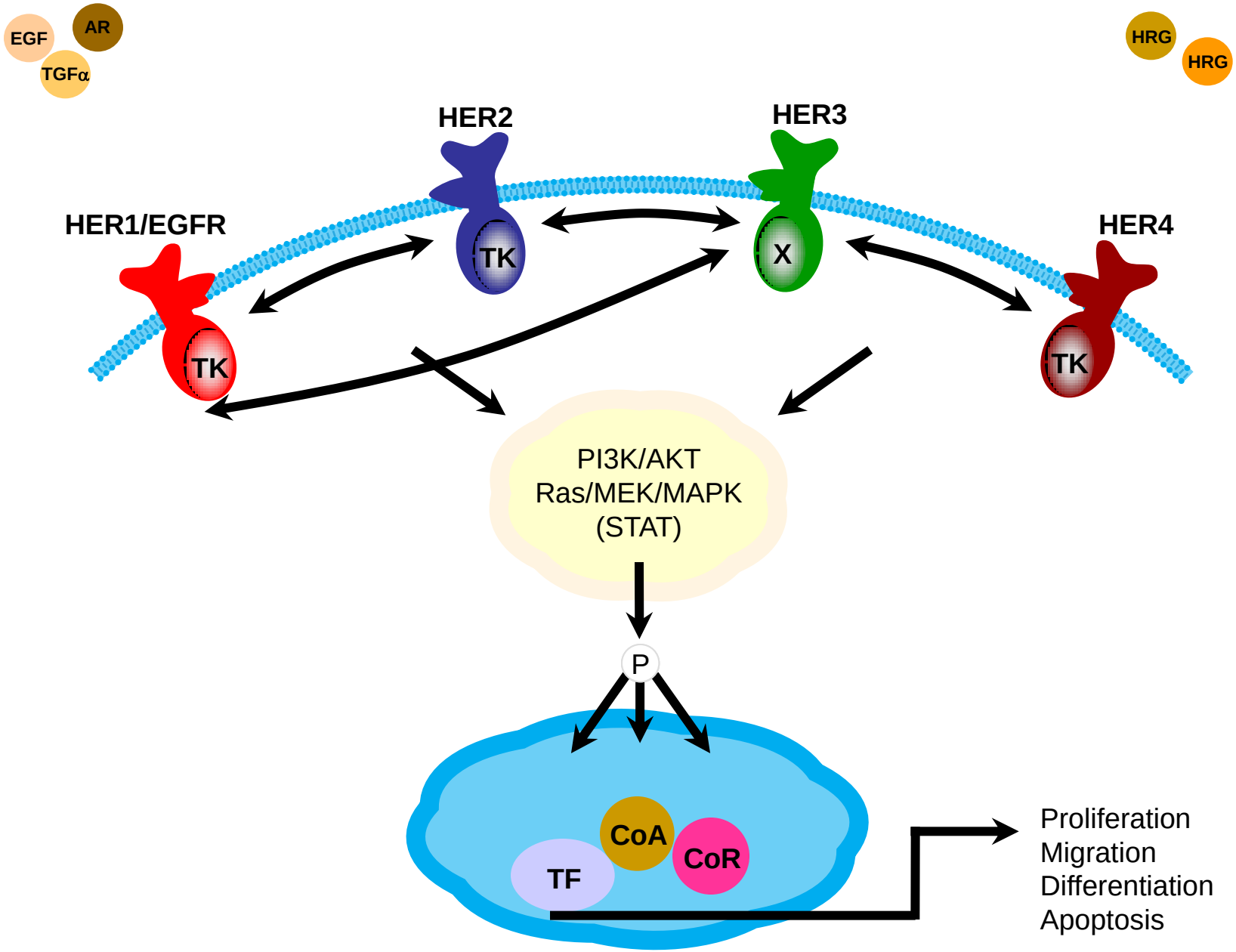
   - work well with targeted therapies (predicted fulvestrant activity in tamoxifen resistant tumors)

   - tissue for molecular studies

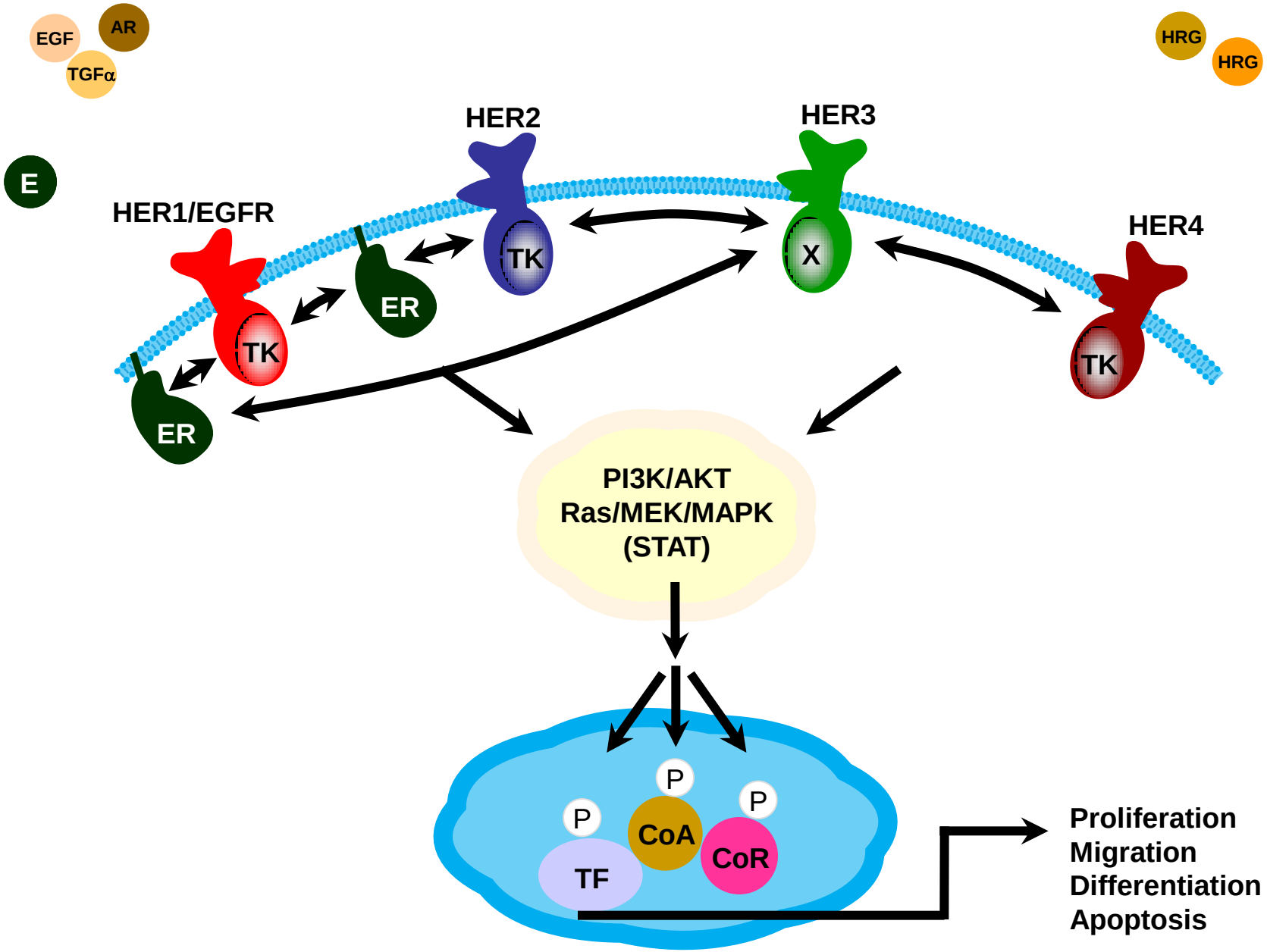
Xenografts in Mice

2. **Bad points**
   - immune deficient mice
   - mouse stroma
   - tumor growth kinetics

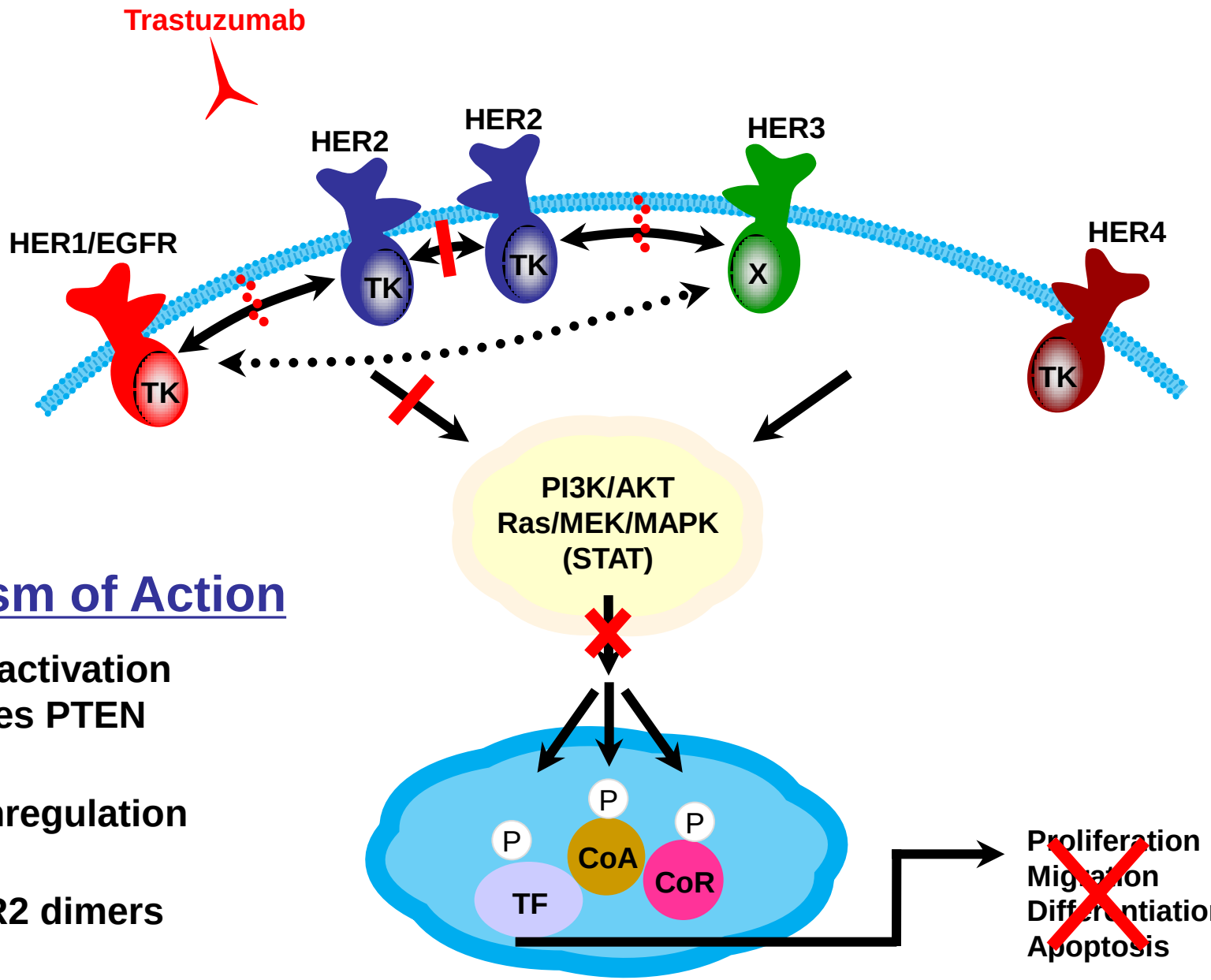
Pathway Activation – HER Ligands



Pathway Activation – ER



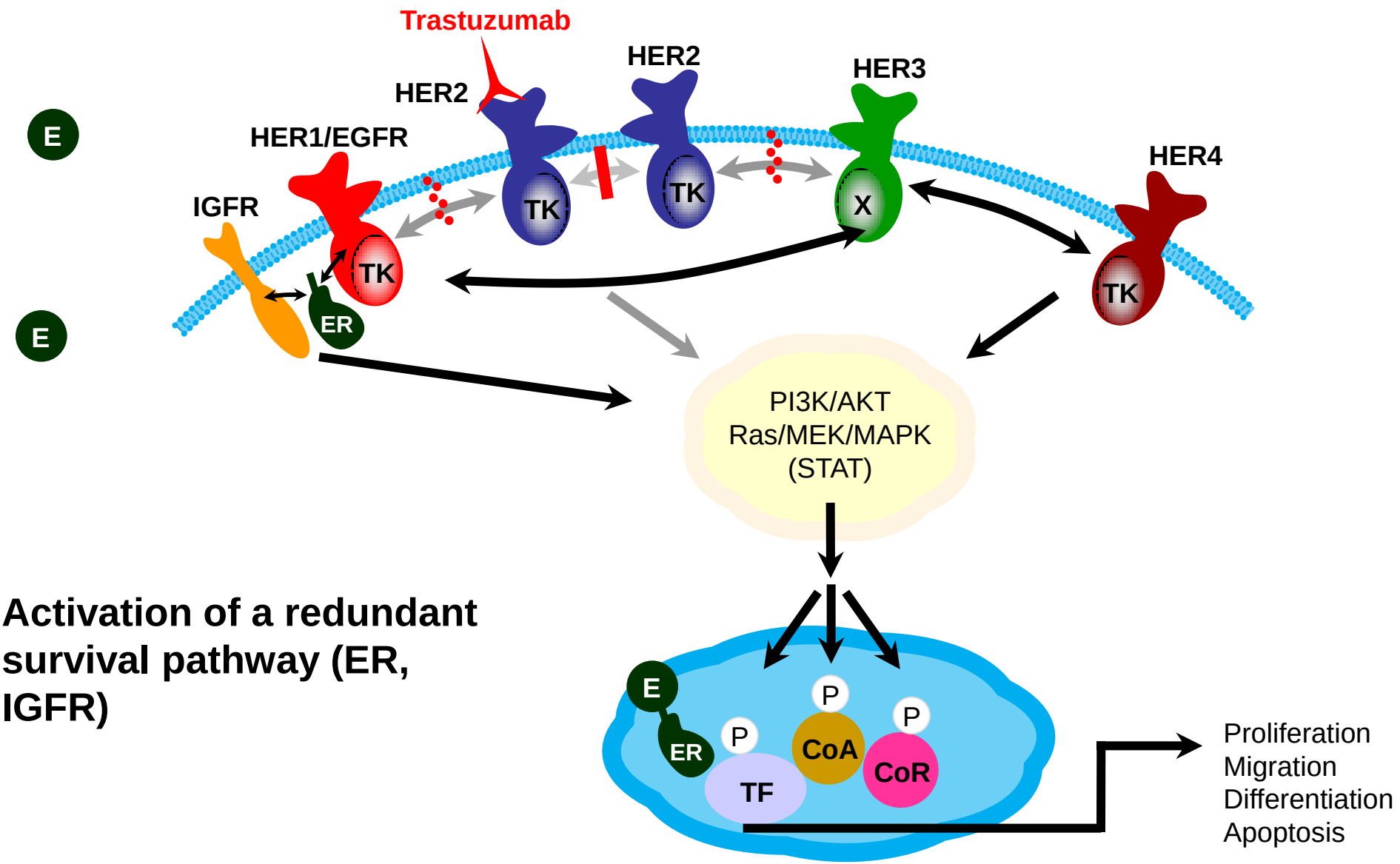
Pathway Inhibition



Mechanism of Action

- Blocks src activation
  → Increases PTEN function
- HER2 downregulation
- Apoptosis
- Blocks HER2 dimers
- ADCC

Mechanisms of Resistance to HER Targeted Therapy



Activation of a redundant survival pathway (ER, IGFR)

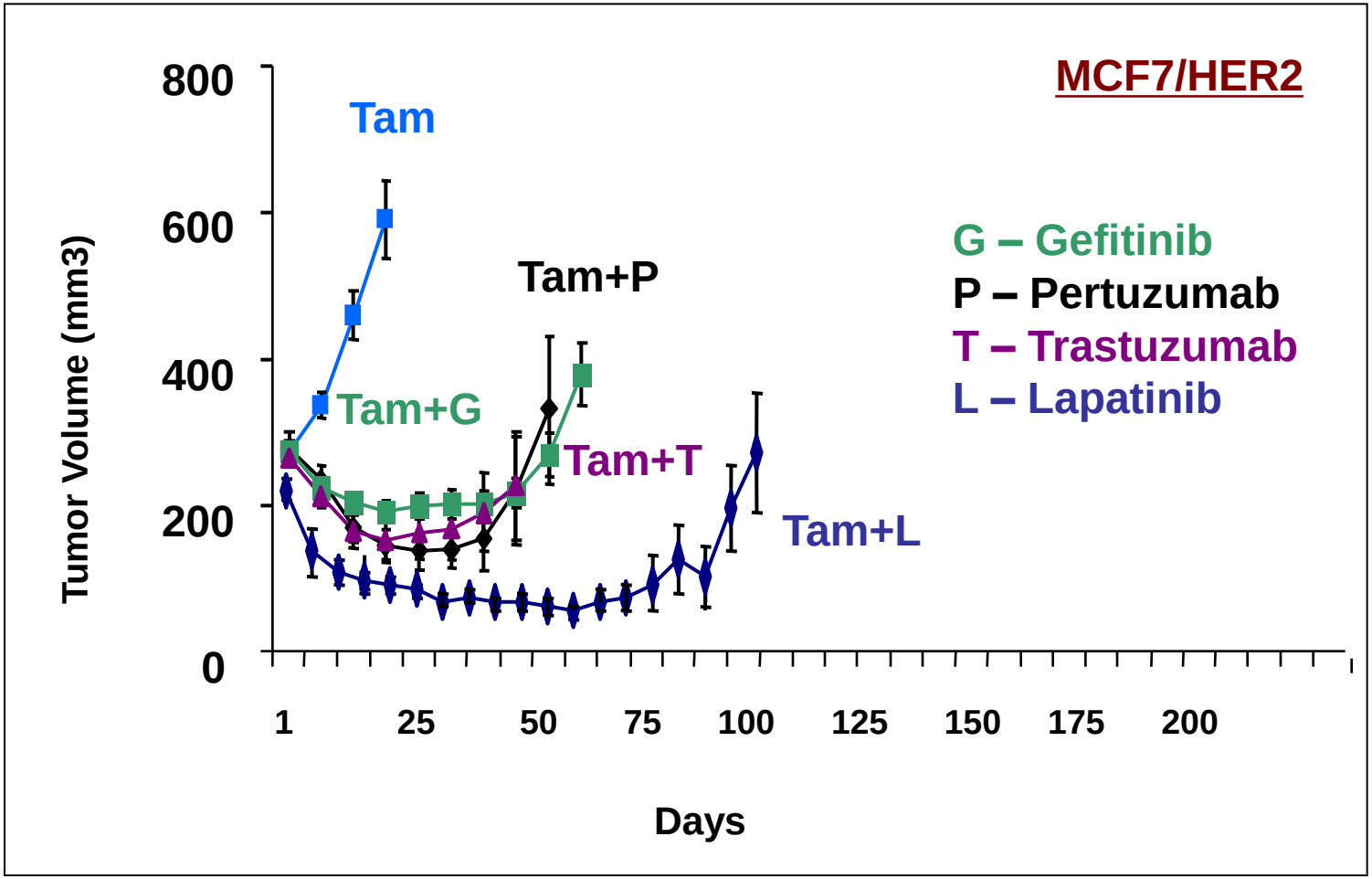
Hypotheses

1. Optimal HER2 targeted therapy requires inhibition of signaling from HER1, HER2 and HER3 dimers and heterodimers.
2. In tumors also positive for ER endocrine therapy is also important.

Inhibition of HER Family Signaling

Drug	Mechanism
Gefitinib, Erlotinib, Cetuximab	1-1, 1-2, 1-3
Trastuzumab	2-2, HER2/Src; ADCC
Pertuzumab	1-2, 2-3
Lapatinib, Neratinib, Afatinib, others	1-1, 1-2, 1-3, 2-3

Monotherapy Only Partially and Temporarily Inhibits Tumor Growth

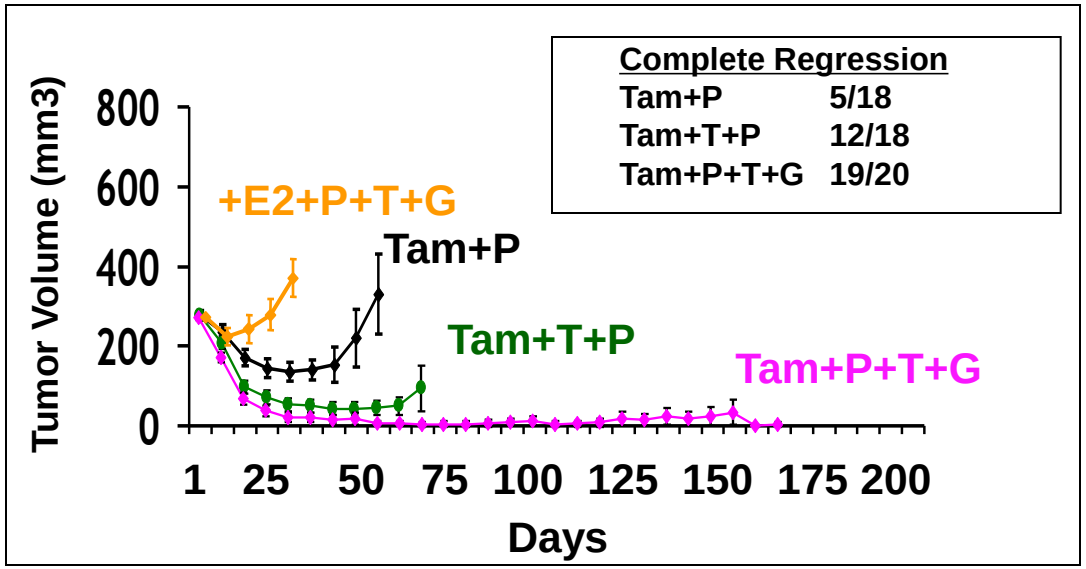


Arpino, SABCS, 2004
Arpino, JNCI, 2007

Superiority of Multidrug anti-HER Therapy in Xenograft Models

MCF7/HER2

P – Pertuzumab



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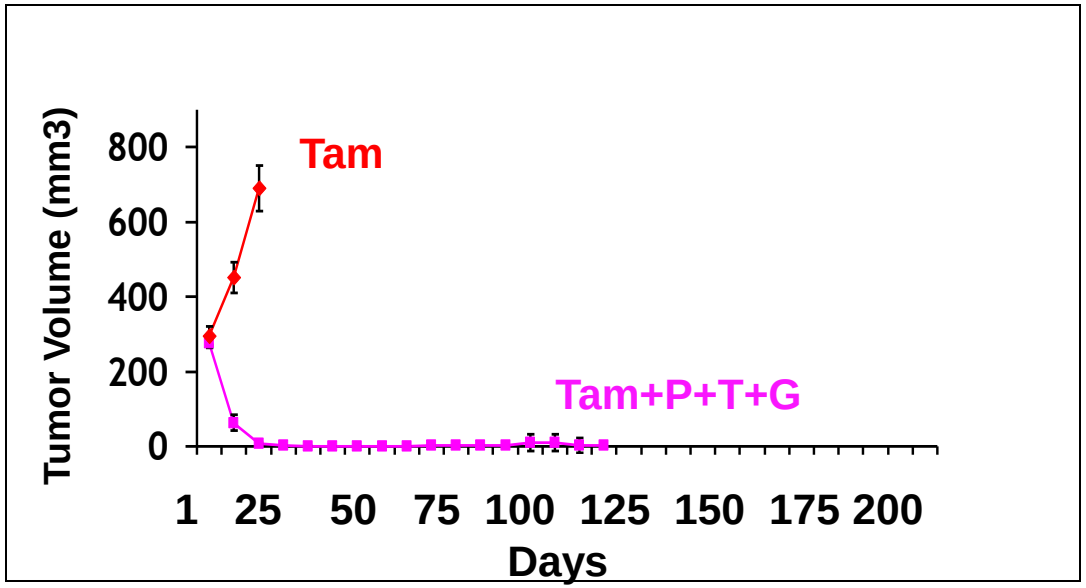

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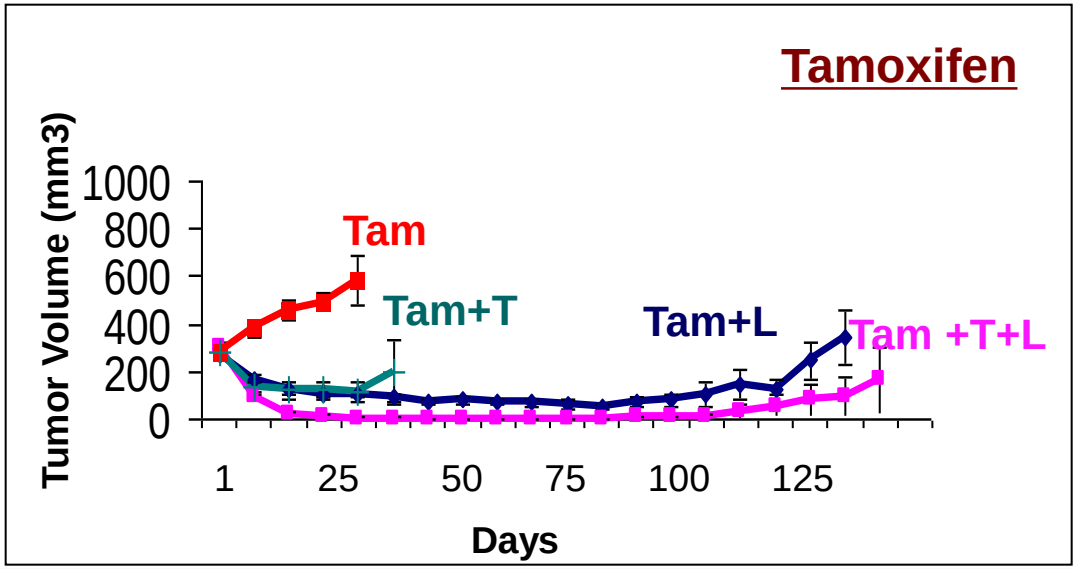
Superiority of Multidrug anti-HER therapy in Xenograft Models

MCF7/HER2

T – Trastuzumab
L – Lapatinib
L+T – Trast + Lap



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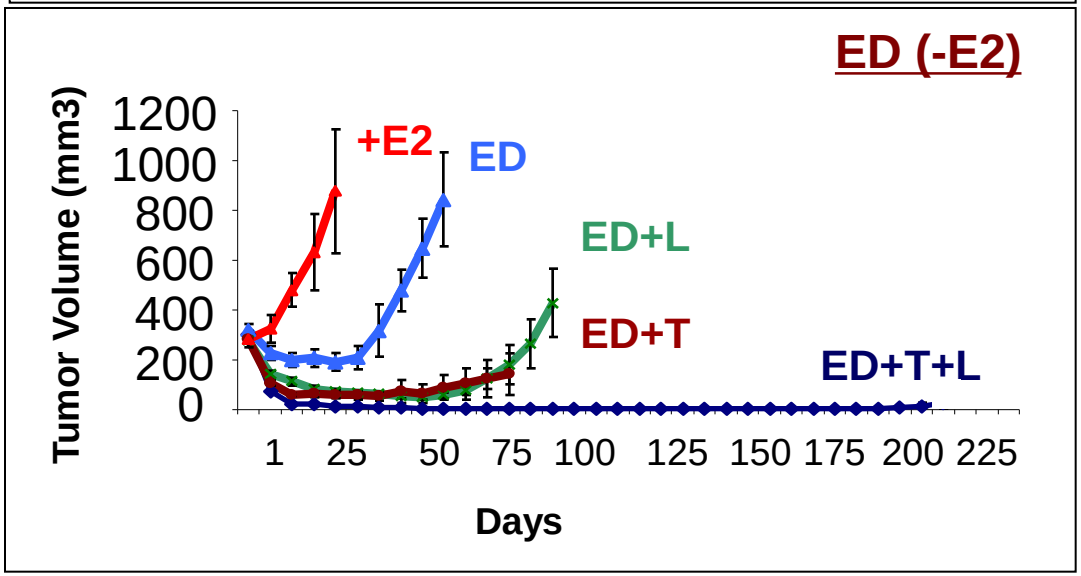
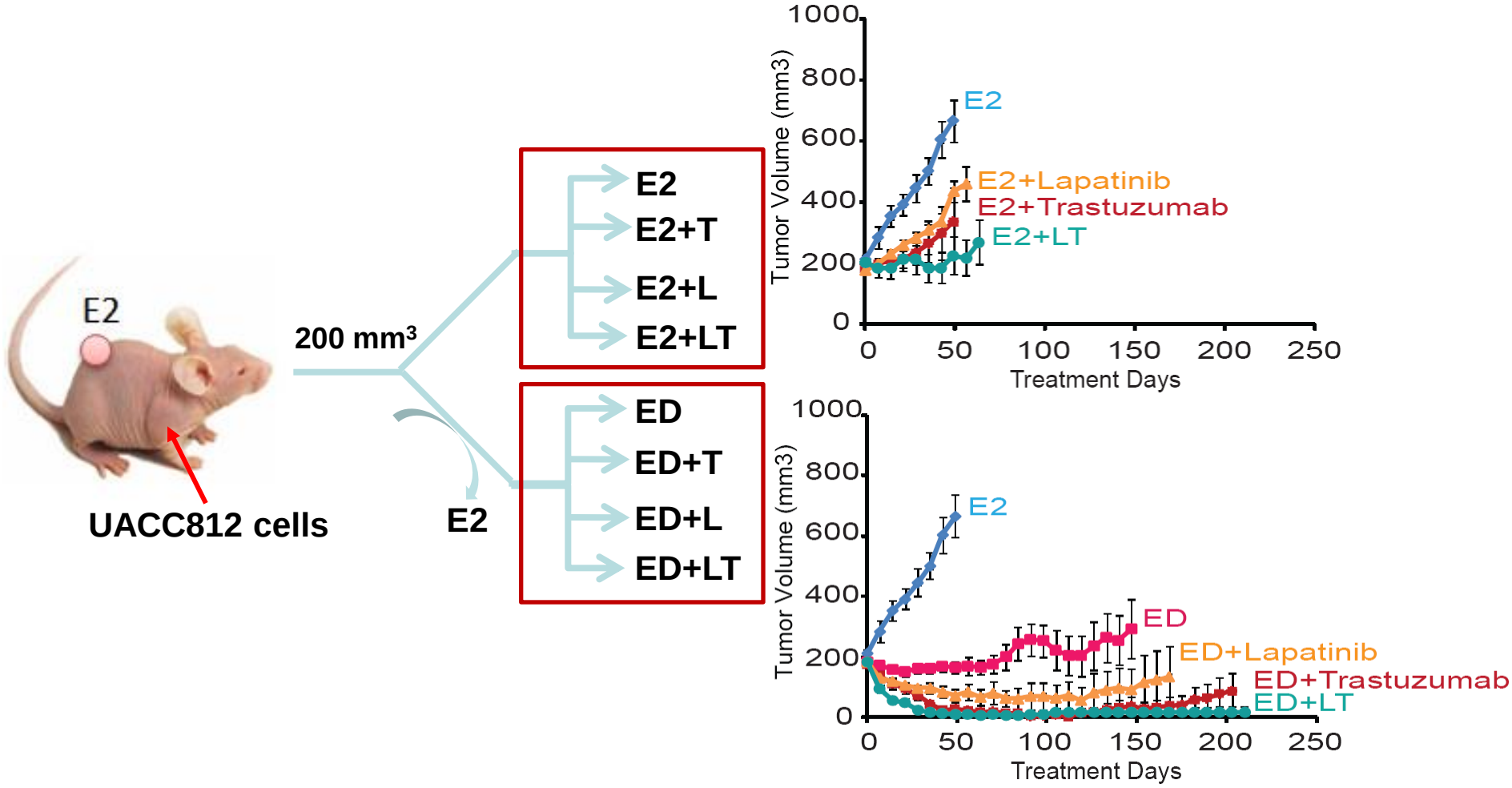


Rimawi, SABCS, 2006
Rimawi, Clin Ca Res, 2011

Growth of UACC-812 xenografts treated with various anti-HER2 treatments with or without estrogen deprivation



HER2+ PDX Models

- Do they mimic the tumor in the patient and the response to therapies?

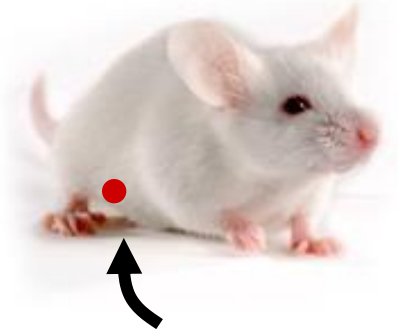
HER2^{+} PDX Lines

Line #	Specimen source	ER	PR	HER2	Treatment	Clinical response
3963	Tumor fragments collected at baseline	0	0	1	Lapatinib + Trastuzumab	Sensitive
3613	Tumor cells isolated from pleural fluid	0	0	1	AC --> Paclitaxel + Trastuzumab	Resistant to both treatments
3143	Tumor fragments collected at week 6 of treatment with lapatinib	0	0	1	Lapatinib --> Docetaxel + Trastuzumab	Resistant to both treatments
4888	Surgical fragment	1	1	1	AC --> Docetaxel + GSI	Resistant to both treatment

PDX Line 3963

Experimental Design

SCID Beige mice



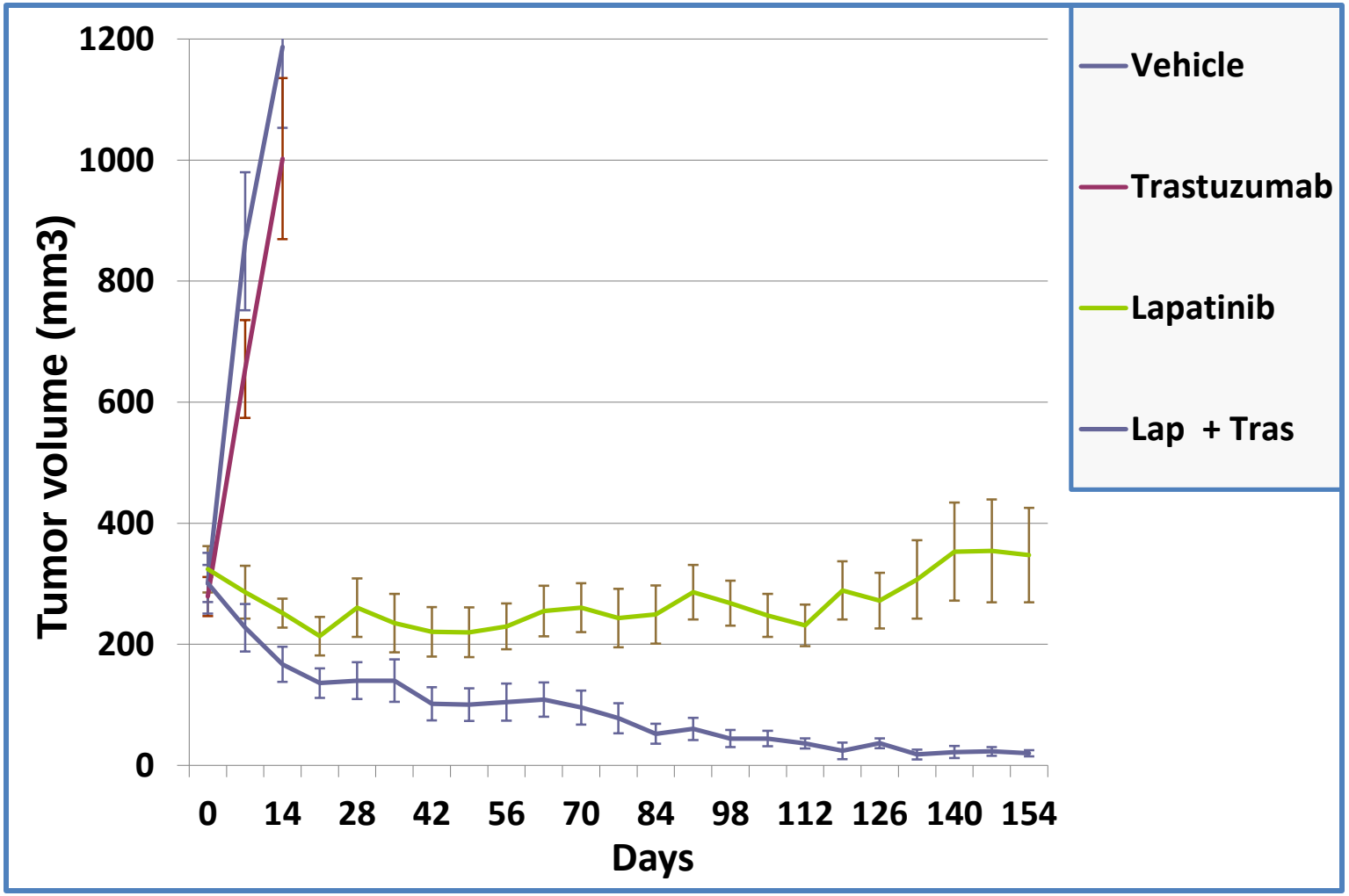
Tumor fragments transplanted in cleared mammary fat pat

250-300 mm^3 tumors

- Vehicle n= 11
- Trastuzumab n= 11
- Lapatinib n= 11
- Lapatinib + Trastuzumab n= 12

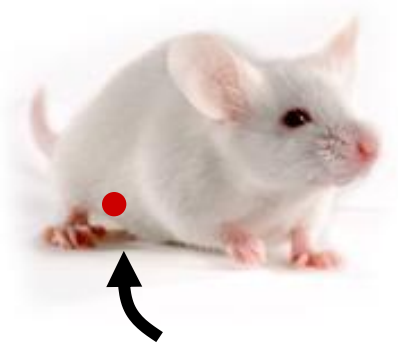
PDX Line 3963

Tumor growth Composite Curves



PDX Line 3613

Experimental design



Tumor fragments transplanted in cleared mammary fat pat

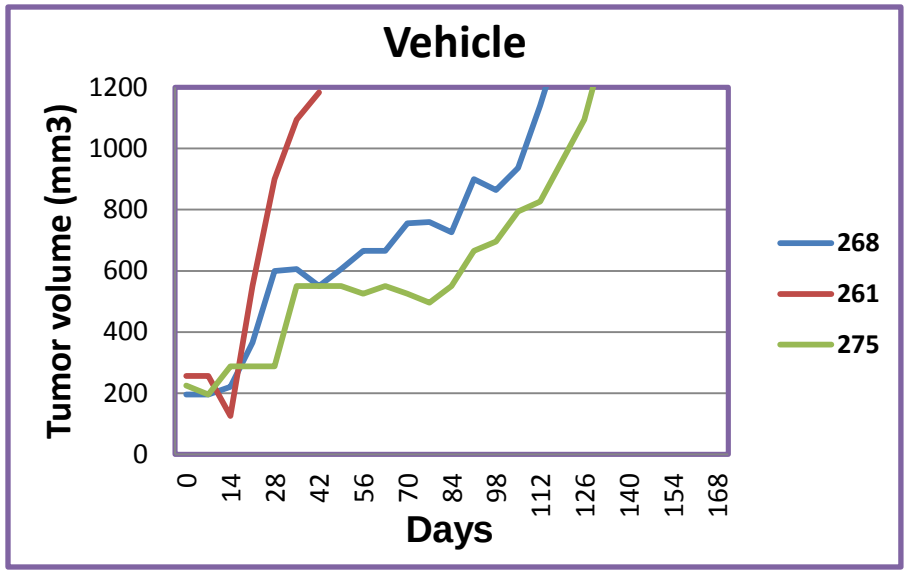
200-250 mm^3 tumors

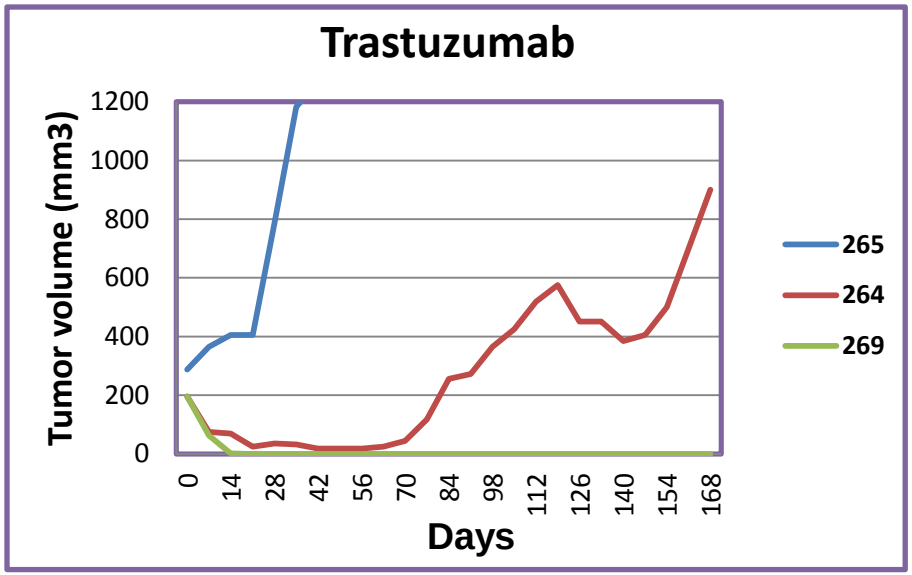
Treatment arms

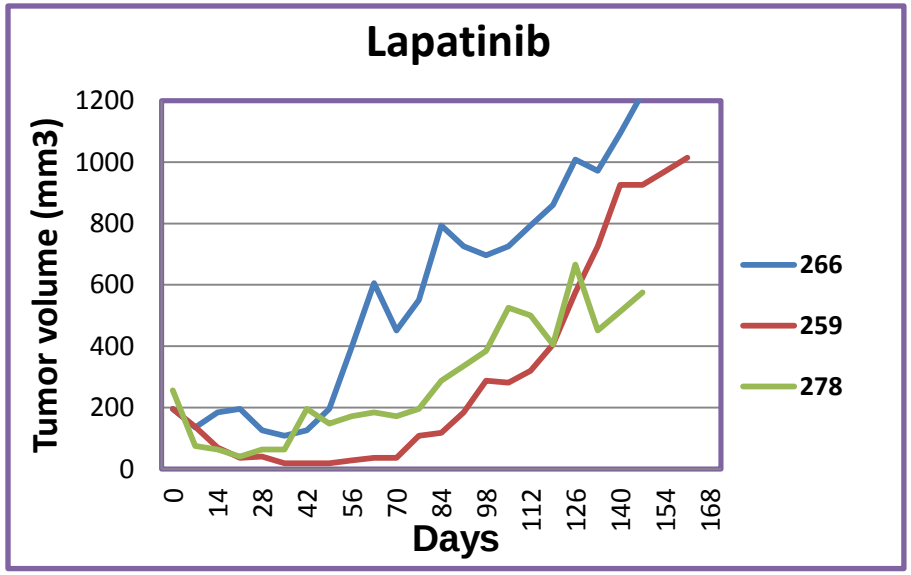
- Vehicle n=3
- Trastuzumab n=3
- Lapatinib n=3
- Lapatinib + trastuzumab n=3

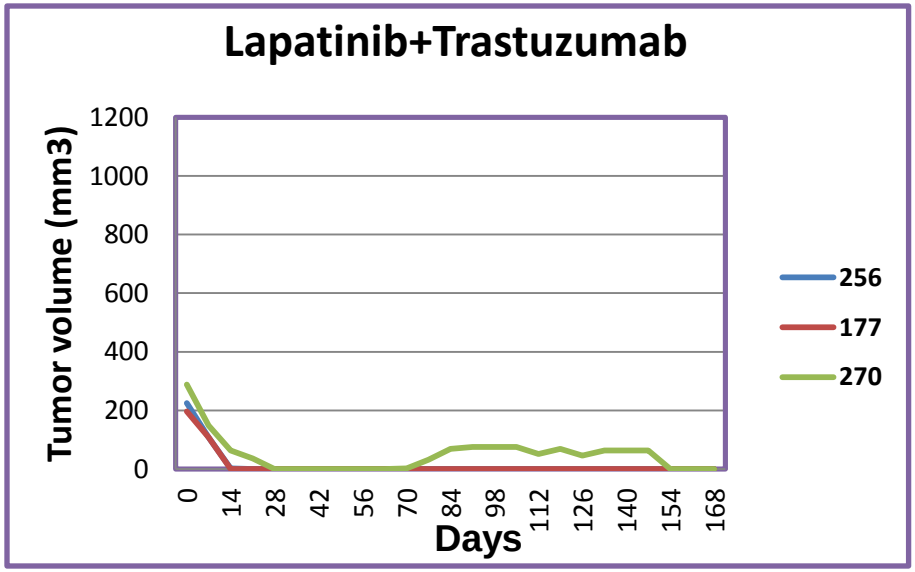
PDX Line 3613

Tumor Growth Curves









PDX Line 3143

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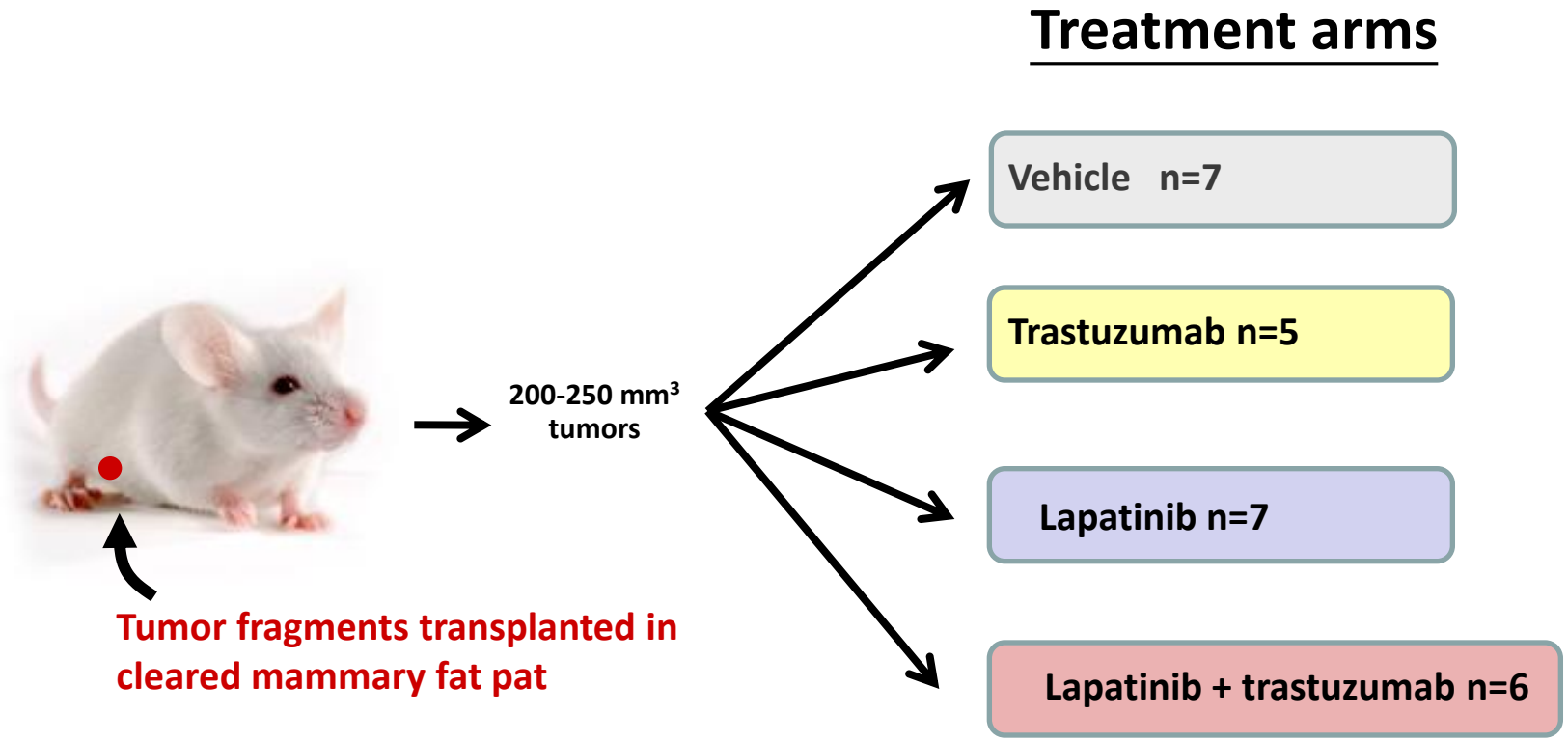

PDX Line 3143

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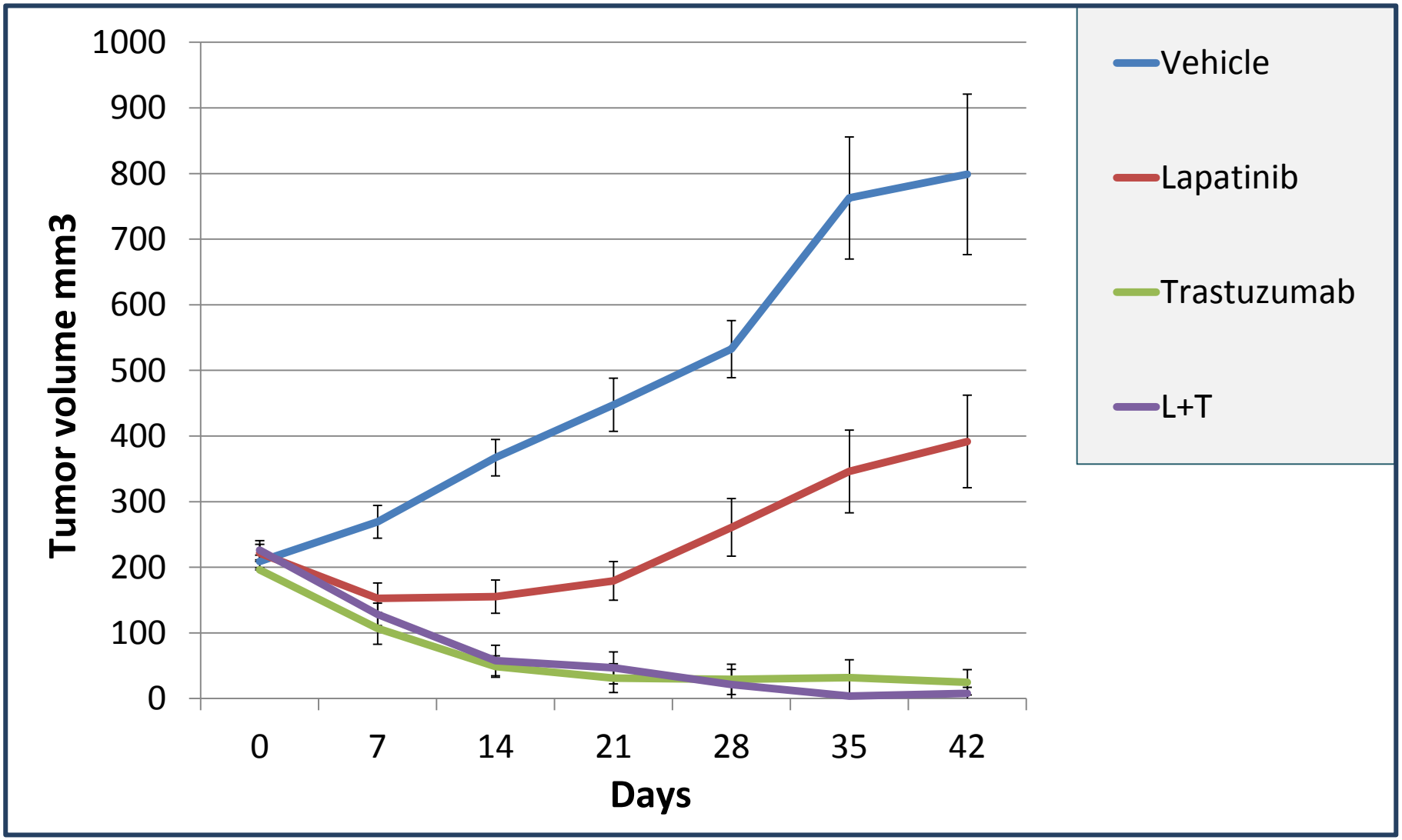
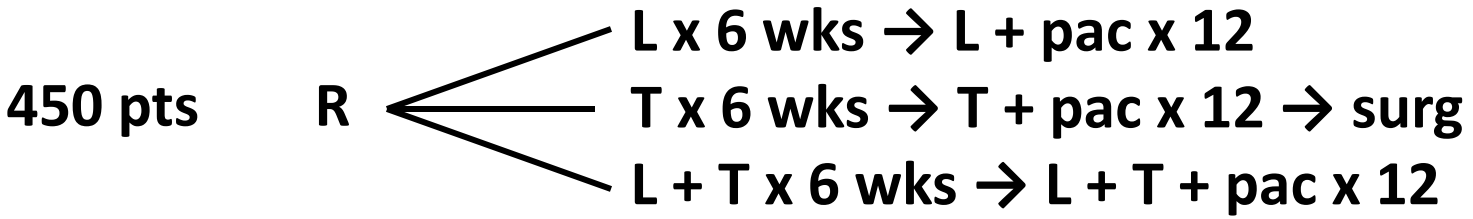


Neo-ALTTO (BIG 01-06)



ER+ = 51%

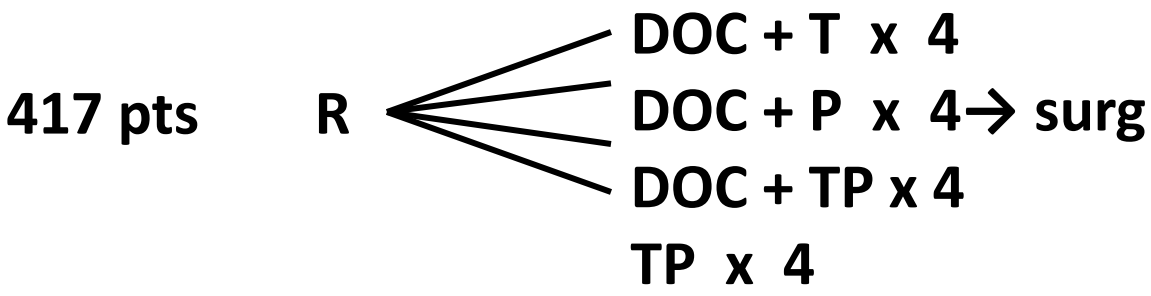
Clinical N- = 84%

TS< 5 cm = 60%

Neo-ALTTO Results

	L	T	L+T
pCR	25%	30%	51%
tpCR	20%	28%	47%
pCR ER+	16%	23%	42%
pCR ER-	34%	36%	61%

Neosphere



Locally adv = 32%

ER+ = 47%

Median Age = 50

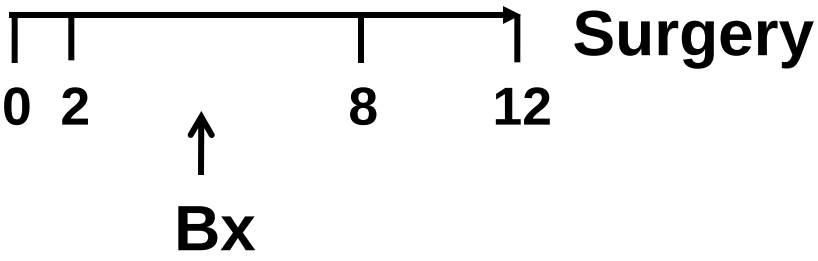
Neosphere Results

	DOC + T	DOC + P	DOC + TP	TP
pCR	29%	24%	46%	17%
tpCR	22%	18%	39%	11%
pCR ER+	20%	17%	26%	6%
pCR ER-	37%	30%	63%	29%

Neoadjuvant Lapatinib & Trastuzumab Without Chemotherapy in HER2 Positive Locally Advanced Breast Cancer

TBCRC 006

64 pts → Lap(L) + Tras (T)
+ Endo Rx if ER+



Med TS = 6 cm (61% > 5cm)

ER+ = 62%

Postmen = 52%

Lapatinib + Trastuzumab + Endo Rx

	Percent
pCR ER+	21%
npCR ER+	34%
pCR ER-	36%
npCR ER-	4%

ASCO, 2011
JCO, 2013

What About TP and TL in Absence of Chemo? Neospere and TBCRC 006

	PT	LT*
pCR	17%	28%
pCR ER+	6%	21%
pCR ER-	29%	36%

***ER targeted therapy in ER+**
HER1 is targeted in LT; larger tumors (median 6 cm).

Rimawi, JCO, 2013

Is HER1 (EGFR) Important?

- Rimm (SABCS, 2012): high HER1 is associated with less benefit to HER targeted therapies in NeoALTTO.
- Rimm(SABCS, 2013); high HER1 is associated with less benefit to trastuzumab in NCCTG N9831.

Summary of Clinical Trials

1. Combined therapy with LT or PT is superior to T alone in inducing pCR.
2. Data suggest that blocking ER and or HER1 (EGFR) might be better in some patients.
3. More study and long term follow up of adjuvant trials are needed.
4. Perhaps a third of patients might not need chemotherapy.

Alternative Schedules of L+T

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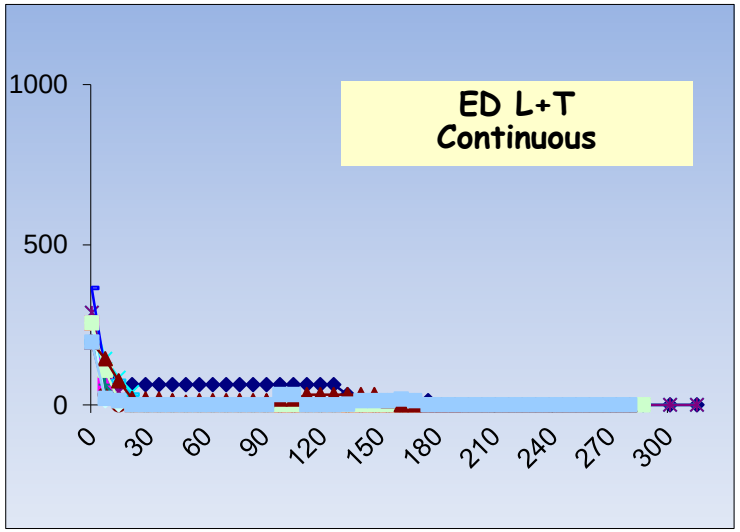
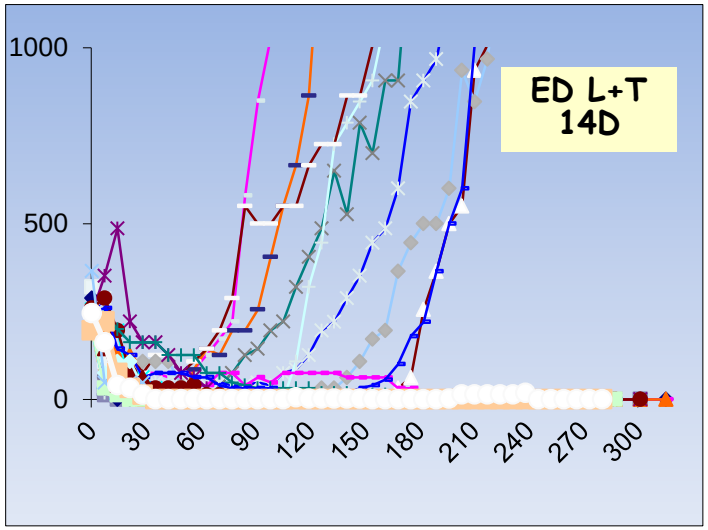
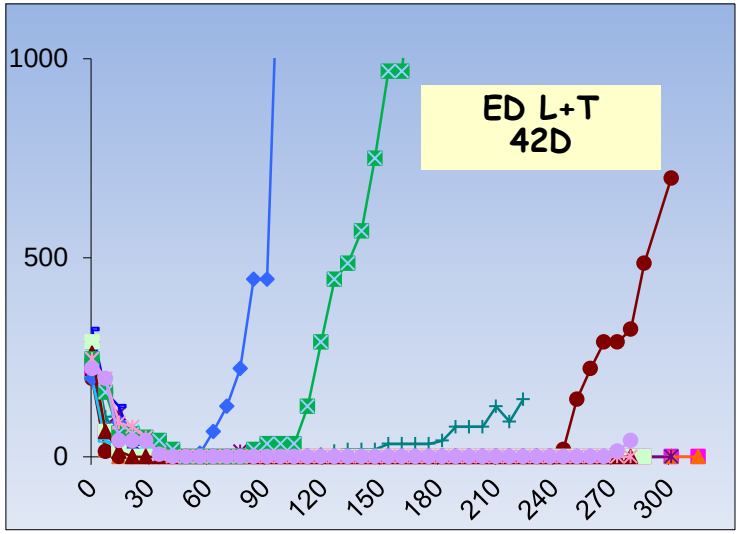
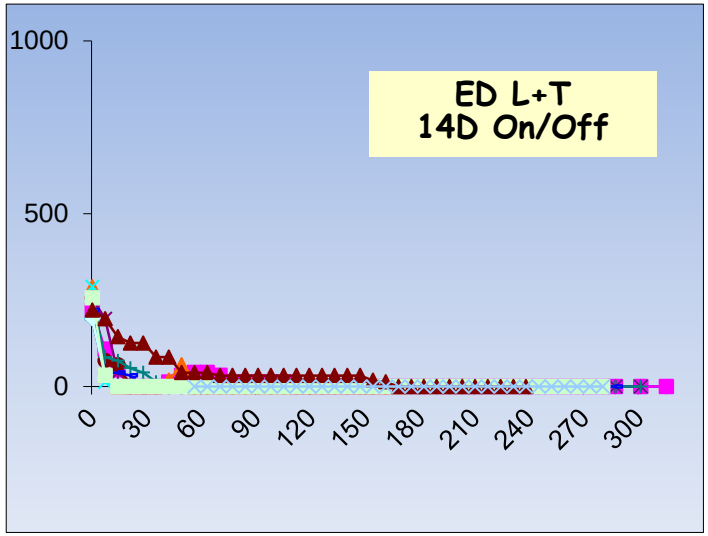






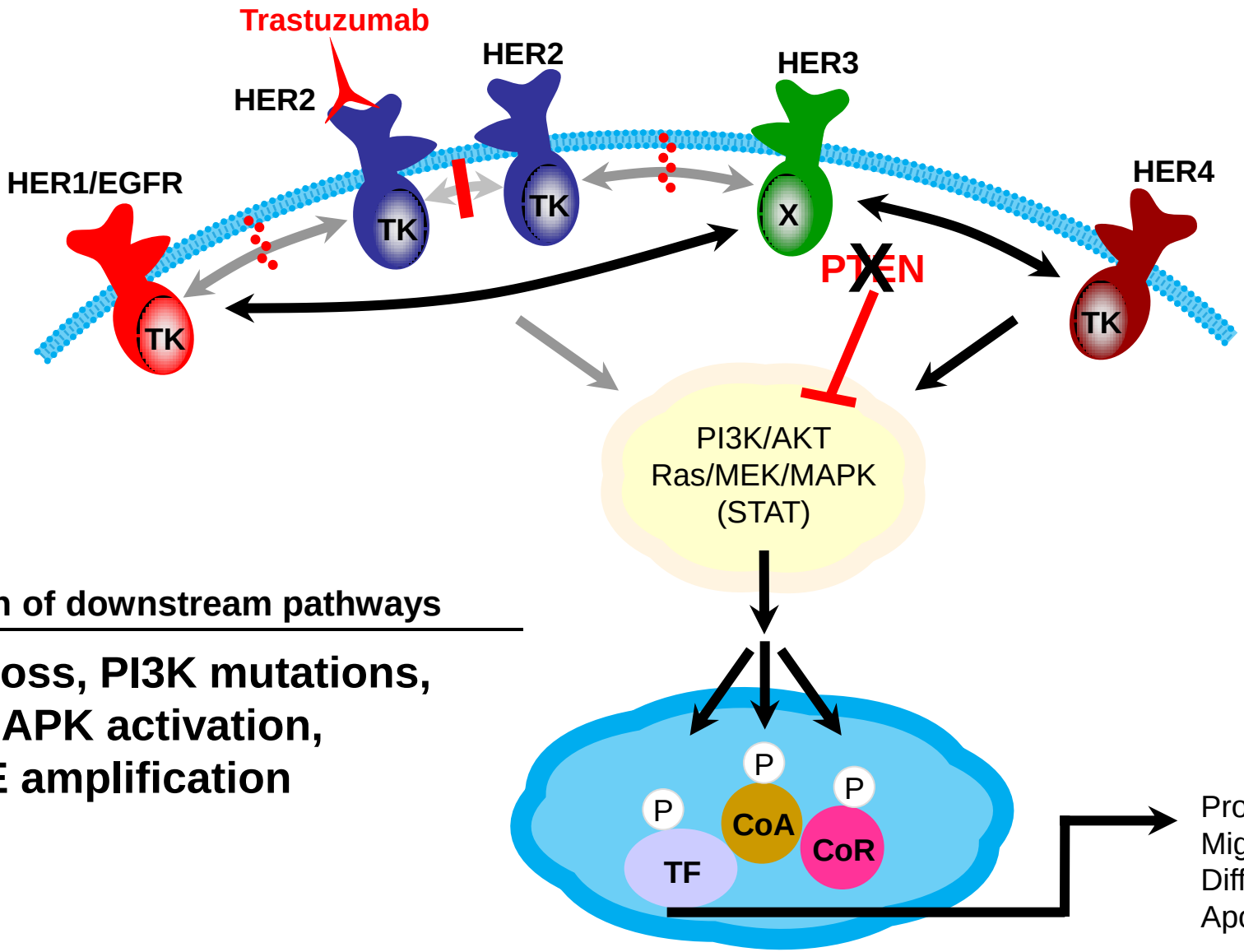


Wiechmann et al. SABCS, 2008
Rimawi et al. Clin Can Res, 2011

Conclusions

- No model is perfect but human cell lines, xenografts, and PDX's can be helpful in predicting benefit in patients with HER2+ breast cancer.
- These models can also be useful in understanding mechanisms for resistance.
- These models should be very useful in identifying the best drug combinations of the many choices to test in patients.

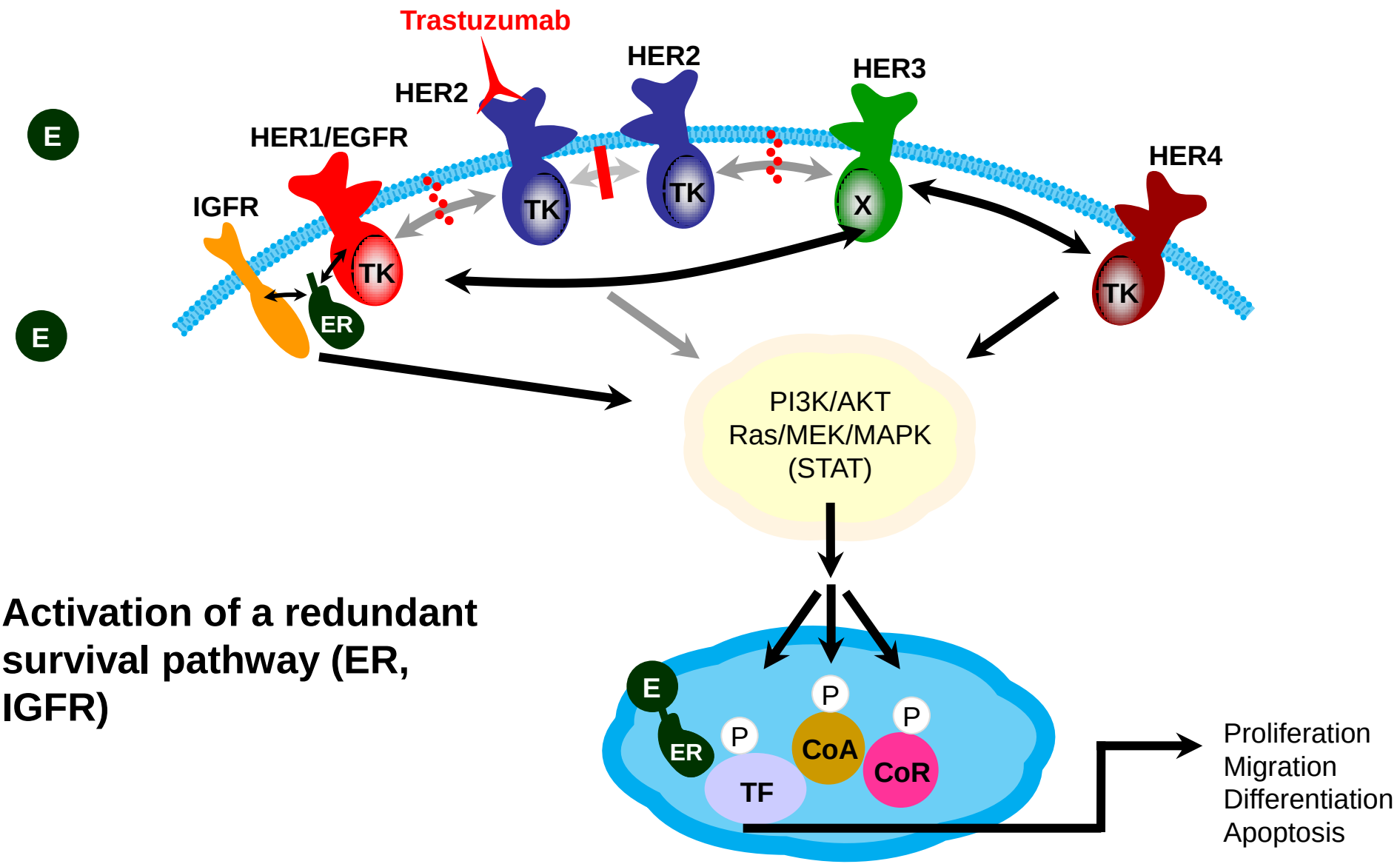
Mechanisms of Resistance to HER Targeted Therapy



Activation of downstream pathways

- **PTEN loss, PI3K mutations, MEK/ MAPK activation, cyclin E amplification**

Mechanisms of Resistance to HER Targeted Therapy



Activation of a redundant survival pathway (ER, IGFR)

PTEN and PIK3CA Mutations

PTEN Status n=59	pCR / n pts (%)	P value
Low	2/22 (9%)	0.04
High	12/37 (32%)	
PIK3CA Status n=33		
WT	6/21 (28%)	0.06
Mut	0/12 (0%)	
PTEN low/ PIK3CA mut n=31		
Yes	0/17 (0%)	0.01
No	5/14 (36%)	