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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Tumor markers and biology in gastric and esophageal cancers

Matthias Ebert

II. Medizinische Klinik

Universität Heidelberg

Presenter

Manfred P. Lutz

MARGIT

Disclosure slide

Matthias Ebert

- no conflicts of interest to declare

Manfred Lutz

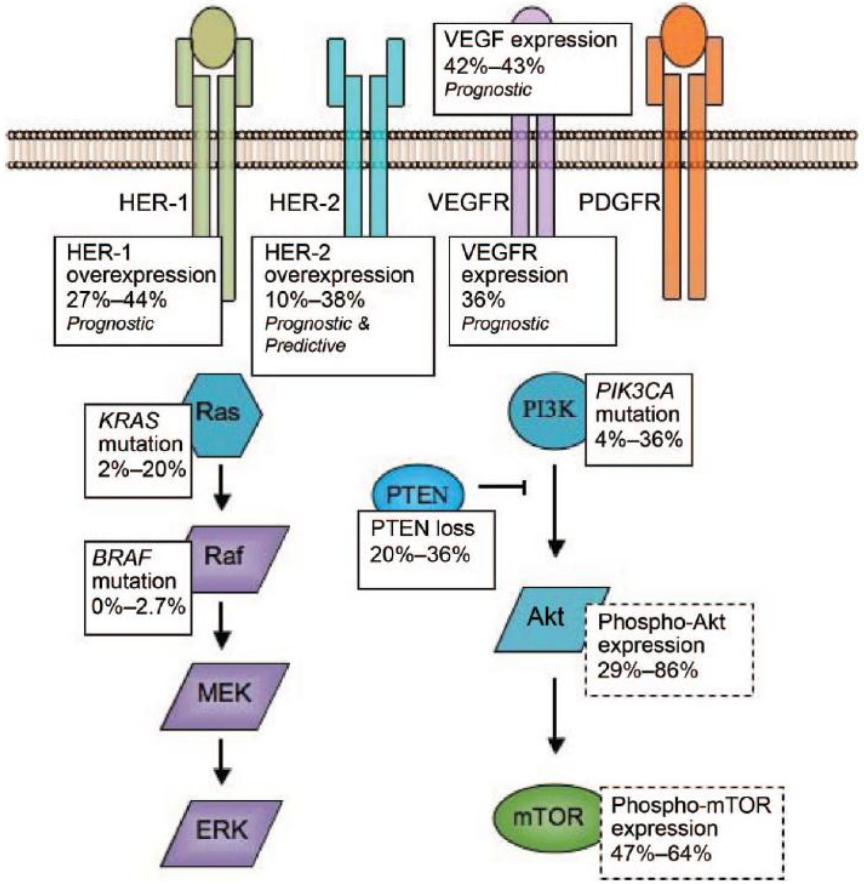
- advisory board / speaker

  Bayer
  Celgene
  Clovis
  Merck
  Sanofi-Aventis

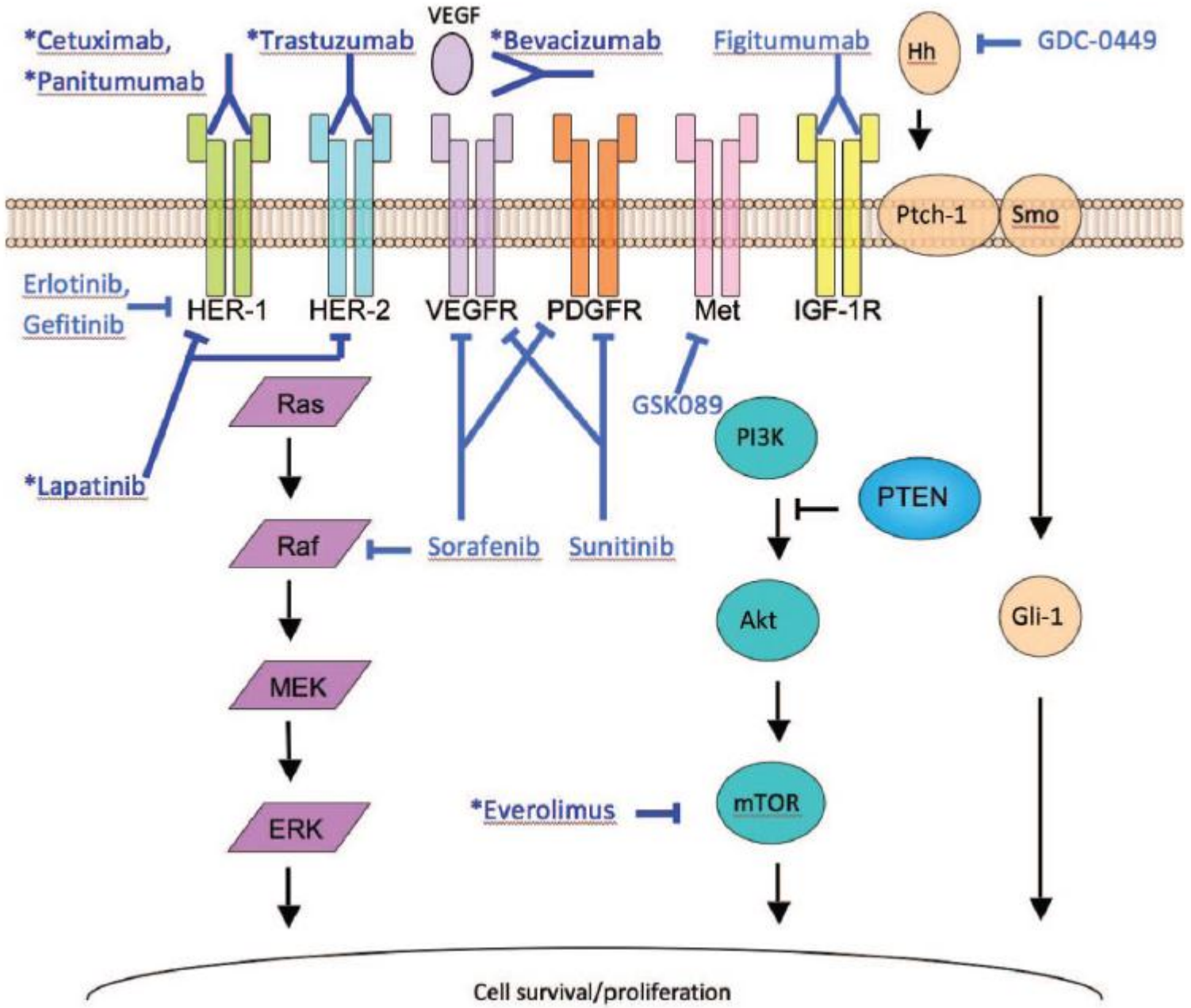
Targeted Therapy in the Management of Advanced Gastric Cancer: Are We Making Progress in the Era of Personalized Medicine?

Wong H, Yau T. Review in *The Oncologist 2012*

Alterations in critical pathways



Published evidence
- HER pathway
- Angiogenesis
- PI3K/Akt/mTor


VEGF
*Cetuximab,
*Panitumumab
*Trastuzumab
*Bevacizumab
Figitumumab
Hh
GDC-0449
Ptch-1
Smo
Erlotinib,
Gefitinib
HER-1
HER-2
VEGFR
PDGFR
Met
IGF-1R
Ras
GSK089
PI3K
PTEN
*Lapatinib
Raf
Sorafenib
Sunitinib
Akt
Gli-1
MEK
*Everolimus
mTOR
ERK
Cell survival/proliferation

Disappointing results of recent trials

Table 4. Ongoing phase III trials of targeted agents in the systemic treatment of advanced gastric cancer

Clinical trial	Targeted agent	Chemotherapy	Line of treatment	Status
ToGA, Bang et al. (2011) [109]	Trastuzumab	FP or XP	First	Completed
AVAGAST, Kang et al. (2010) [107]	Bevacizumab	XP	First	Completed
EXPAND [50] ESMO 2012	Cetuximab	XP	First	Ongoing
REAL-3 [55]	Panitumumab	EOX	First	Ongoing
LoGIC [66]	Lapatinib	OX	First	Ongoing
TYTAN, Satoh et al. (2010) [67]	Lapatinib	T	Second	Ongoing
GRANITE-1 [82]	Everolimus	–	Second or third	Ongoing
COG ESMO 2012	Gefitinib	--	second	

Success

Fail

Fail Fail

Fail

Fail

Targeted Therapy in the Management of Advanced Gastric Cancer:

Why Are We Not Making Progress in the Era of Personalized Medicine?

Wong H, Yau T. The Oncologist 2012

Tumor markers and biology

- Druggable Targets
- Overcoming resistance in targeted therapy

Phase III study of trastuzumab added to standard chemotherapy in first-line HER2-positive advanced gastric cancer

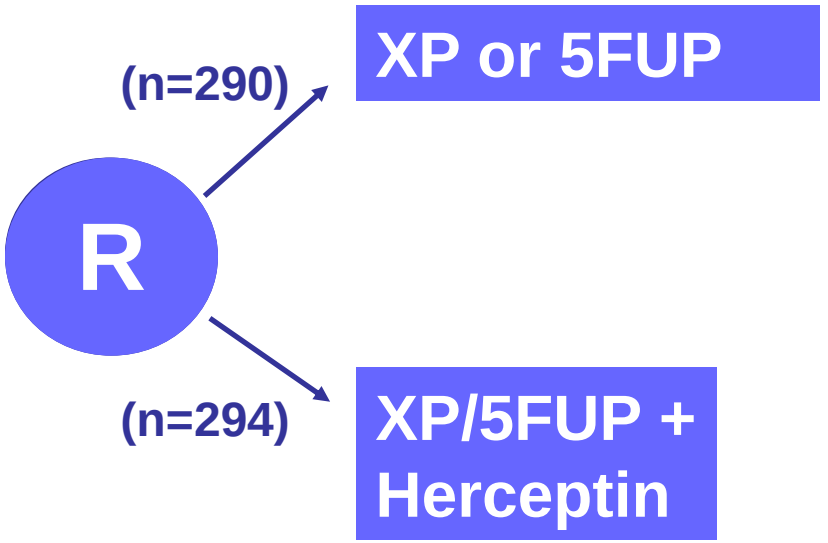
3807 Gastric Cancer

↓

810 HER2+

↓

- advanced gastric cancer
- HER2 +
- (IHC2+/FISH+ oder IHC3+)

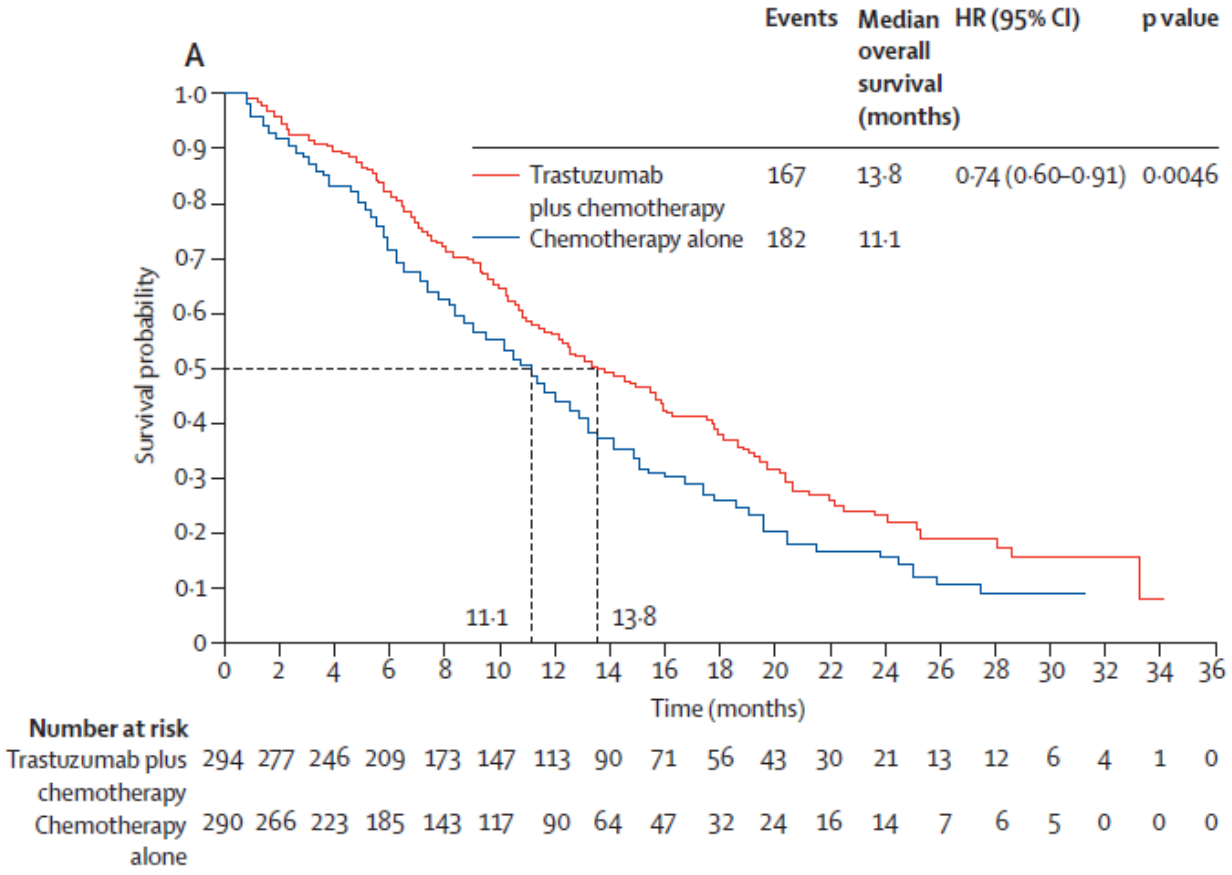


- **Capecitabine**
  1000 mg/m² bid d1-14 q3w x 6
- **5-Fluorouracil**
  800 mg/m²/day continuous iv infusion d1-5 q3w x 6
- **Cisplatin**
  80 mg/m² q3w x 6
- **Trastuzumab**
  8 mg/kg loading dose followed by 6 mg/kg q3w until PD

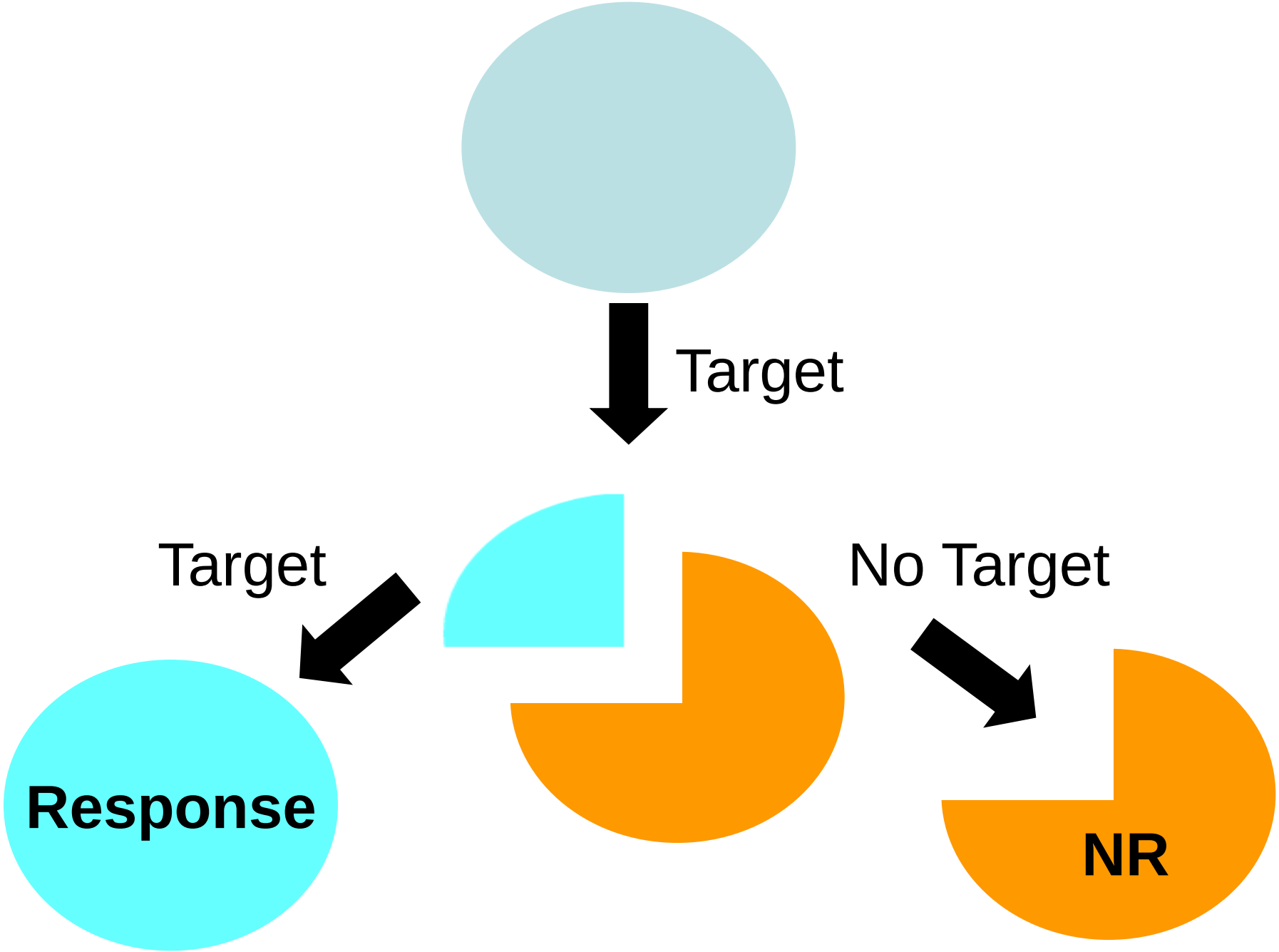
Primary EP: **OS**
Sekundary EP: **PFS, TTP, ORR, Benefit**

Bang, Lancet 2010

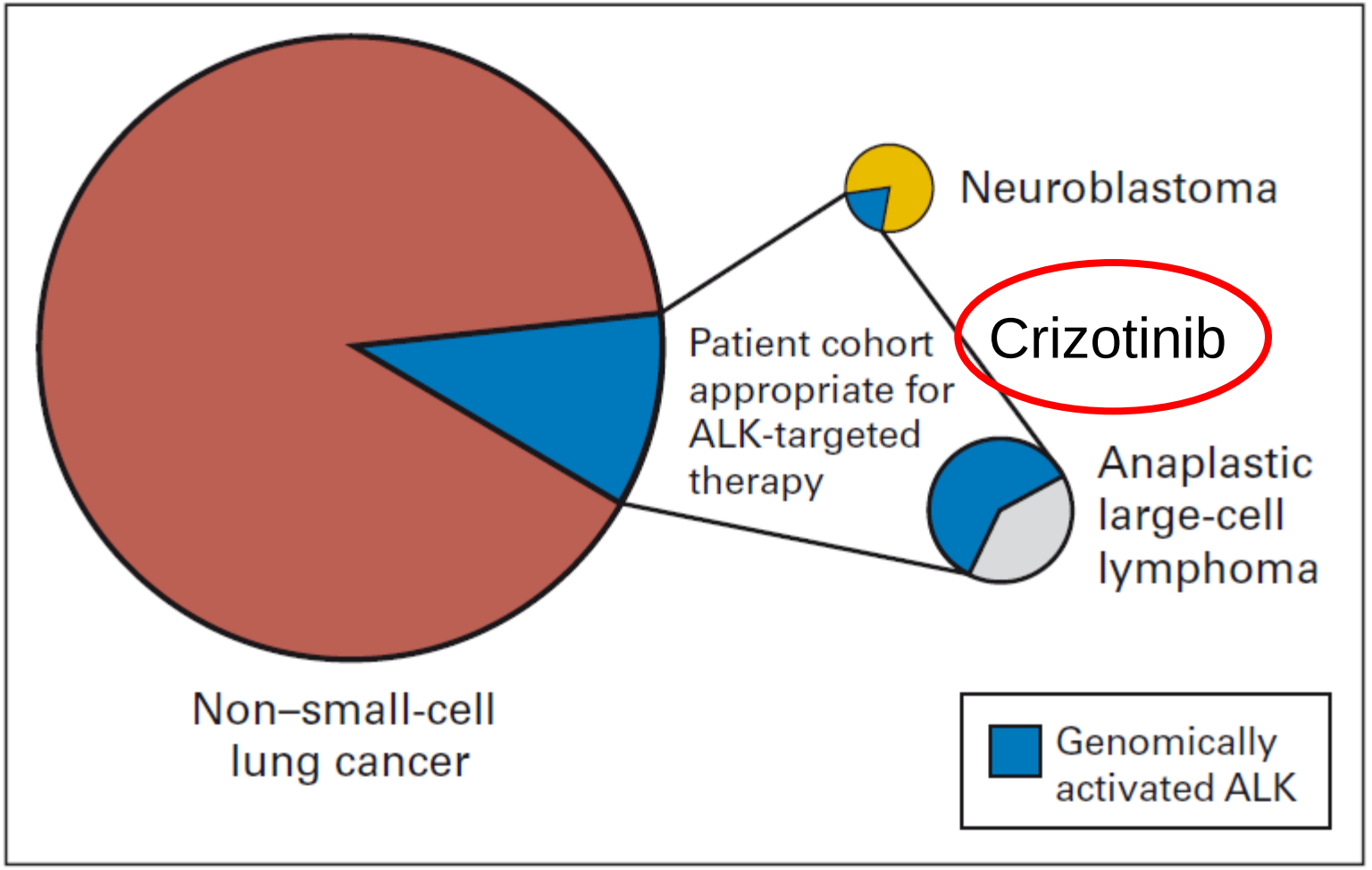
Phase III study of trastuzumab added to standard chemotherapy in first-line HER2-positive advanced gastric cancer



Bang, Lancet 2010

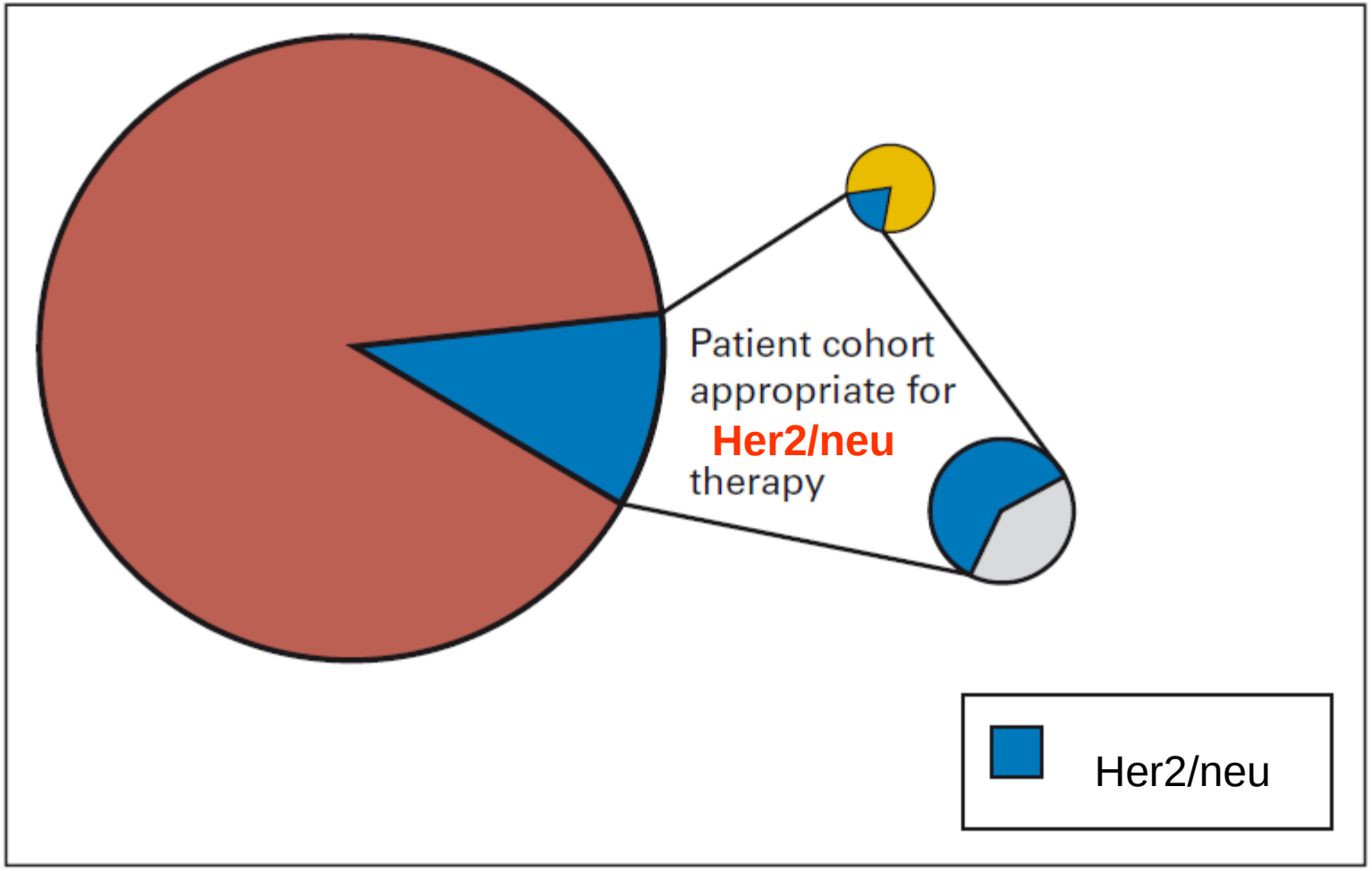

Target
Target
No Target
Response
NR

ALK, anaplastic lymphoma kinase

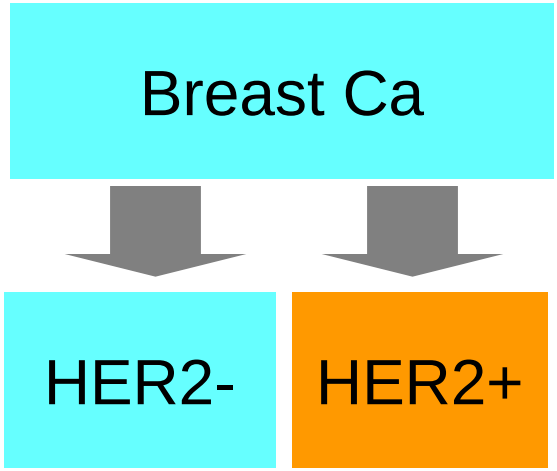


McDermott U, JCO 2009

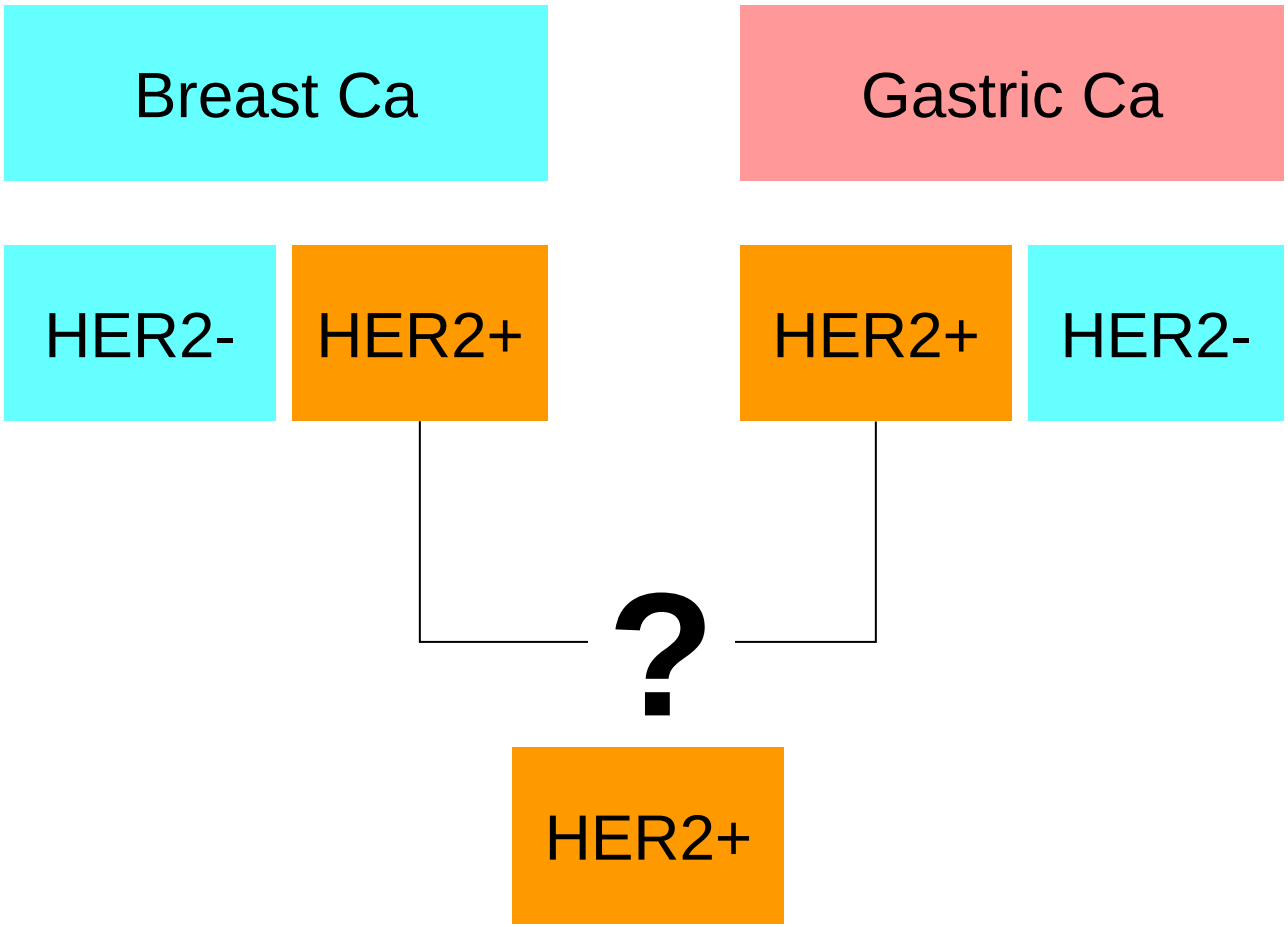
Her2/neu



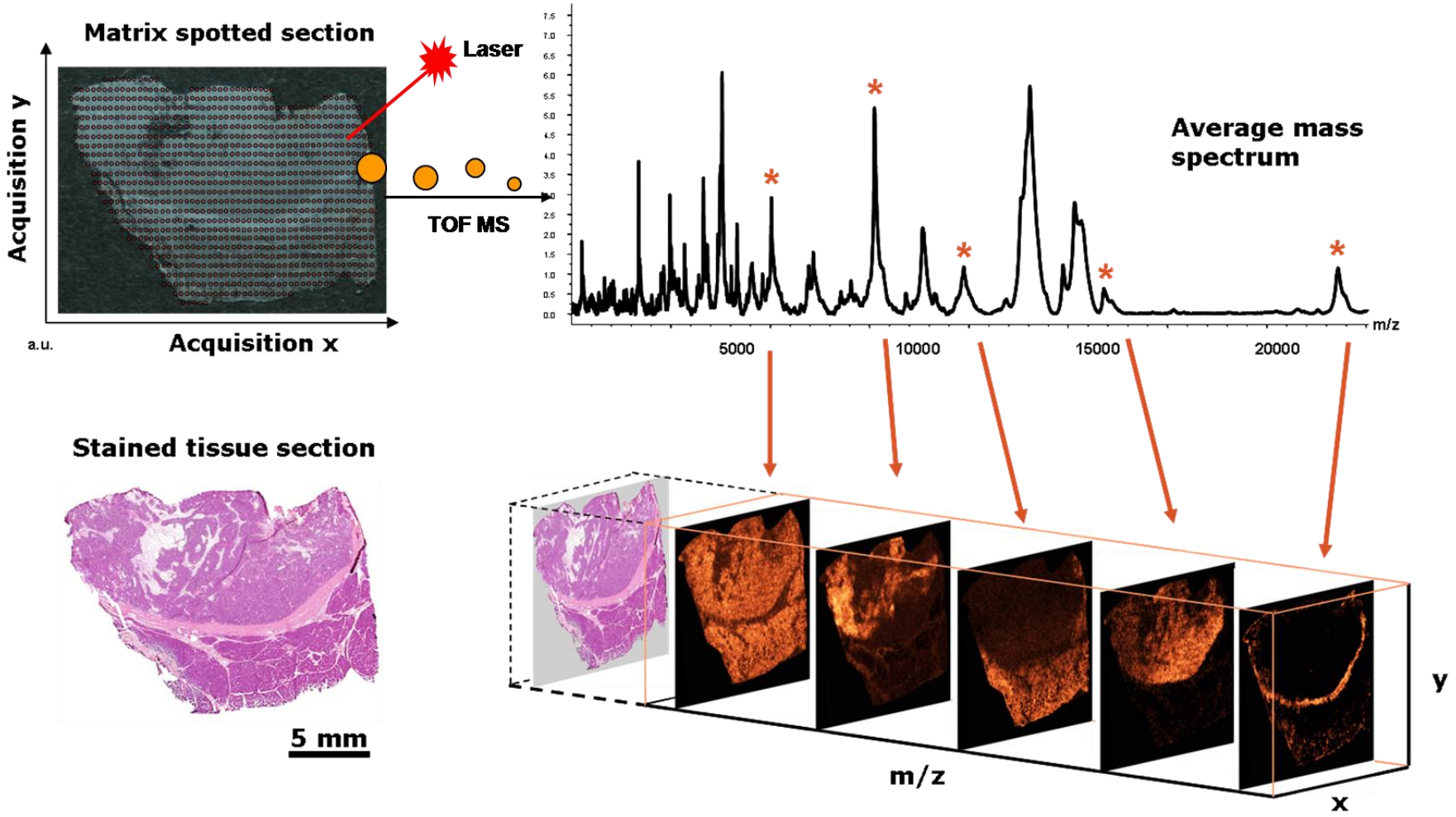
Druggable Targets



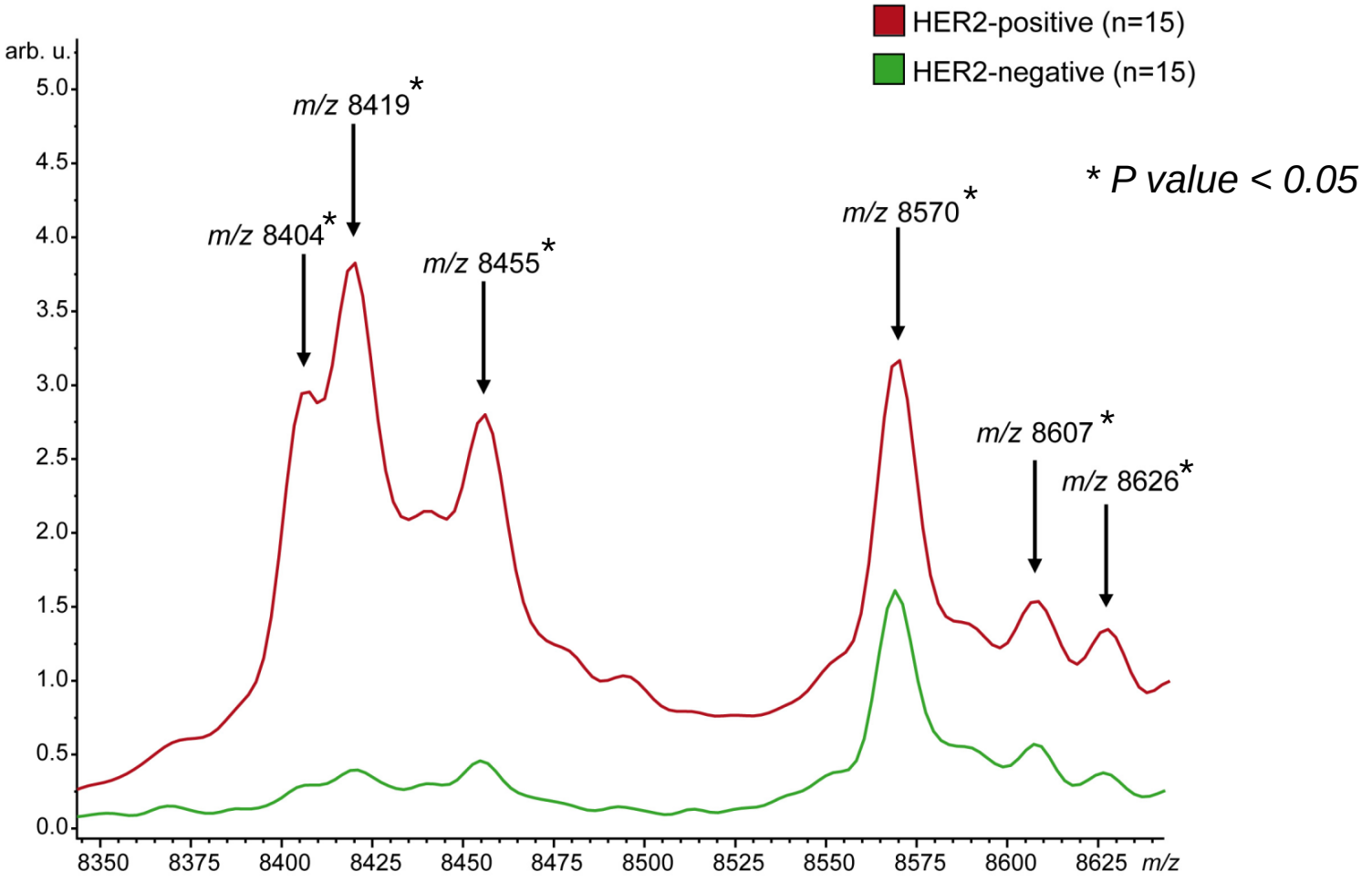
Druggable Targets



MALDI Spectroscopic Imaging



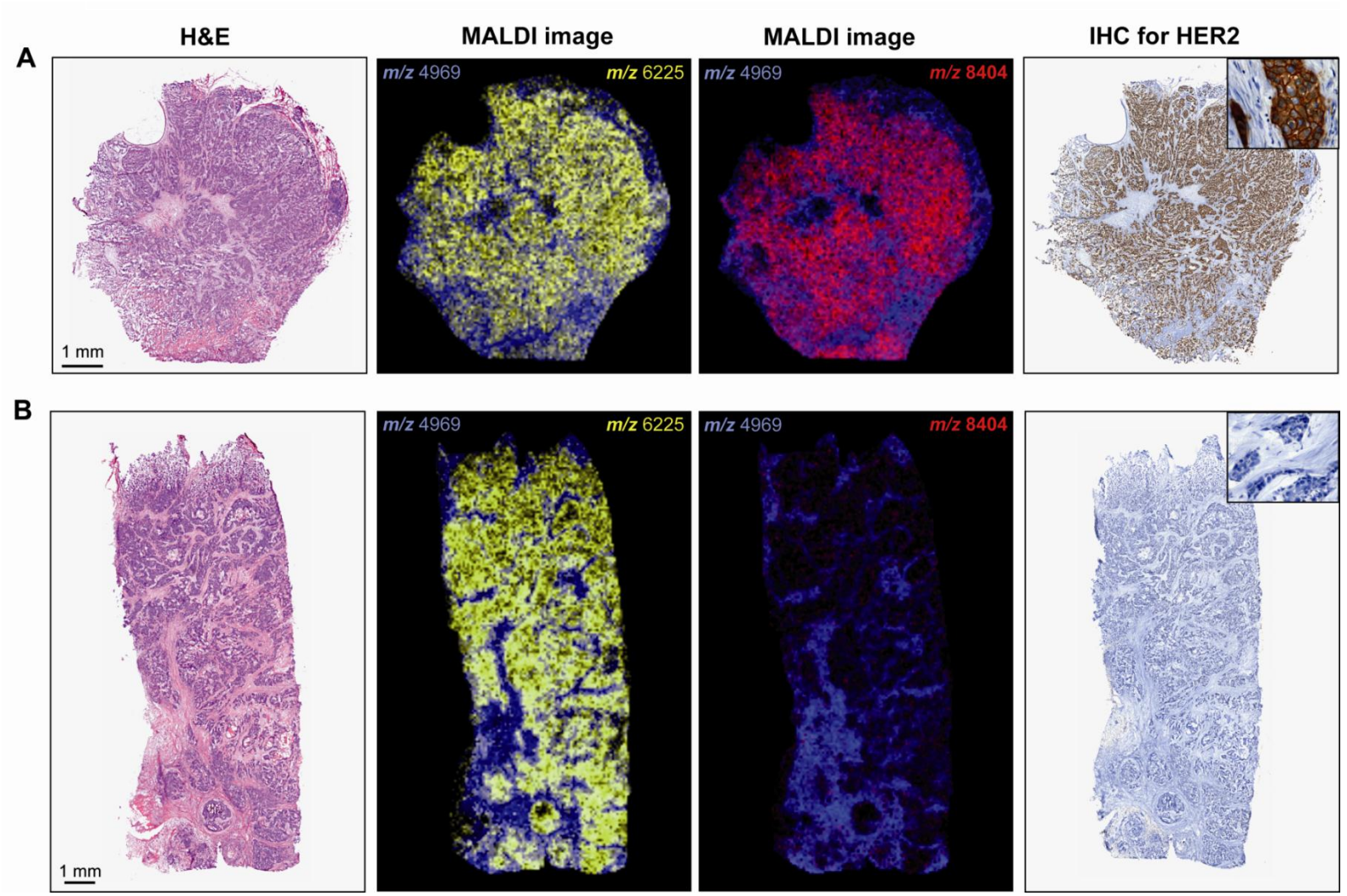
Differential Expression



* *P value < 0.05*

m/z: mass-to-charge

Visualisation Peak m/z 8404



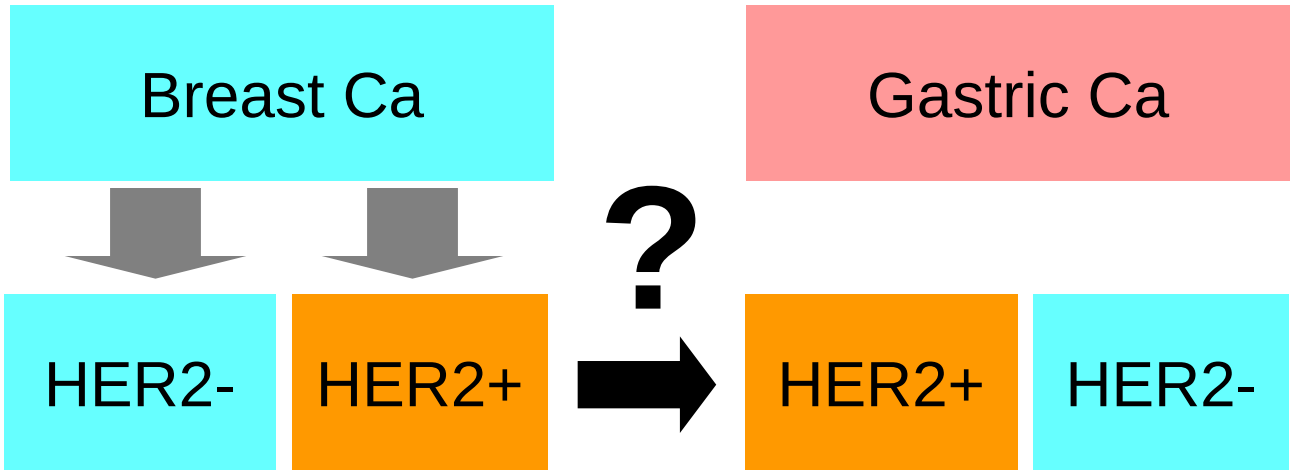
HER2 positive

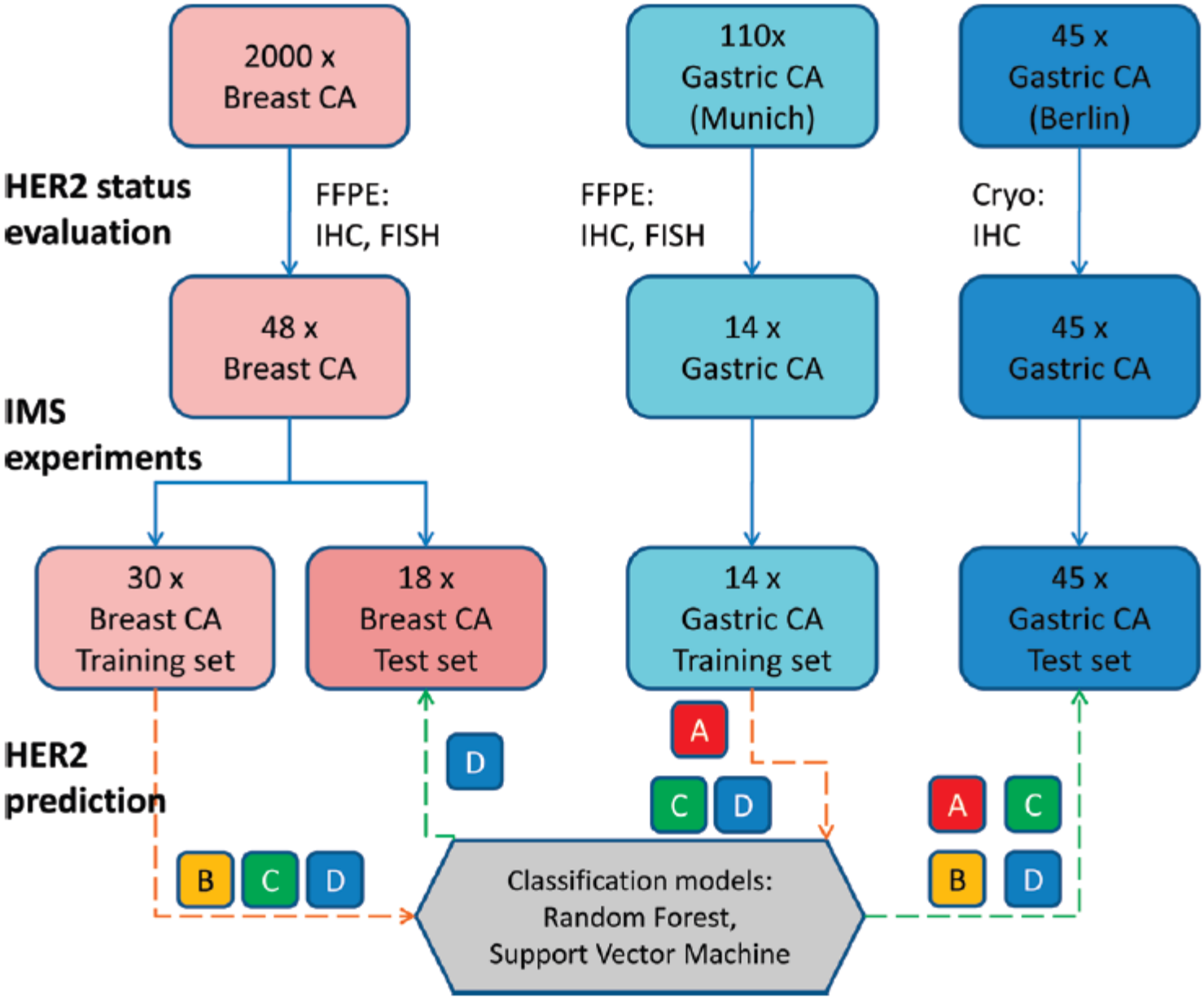
HER2 negative

m/z 4969: cancer m/z 8404: HER+

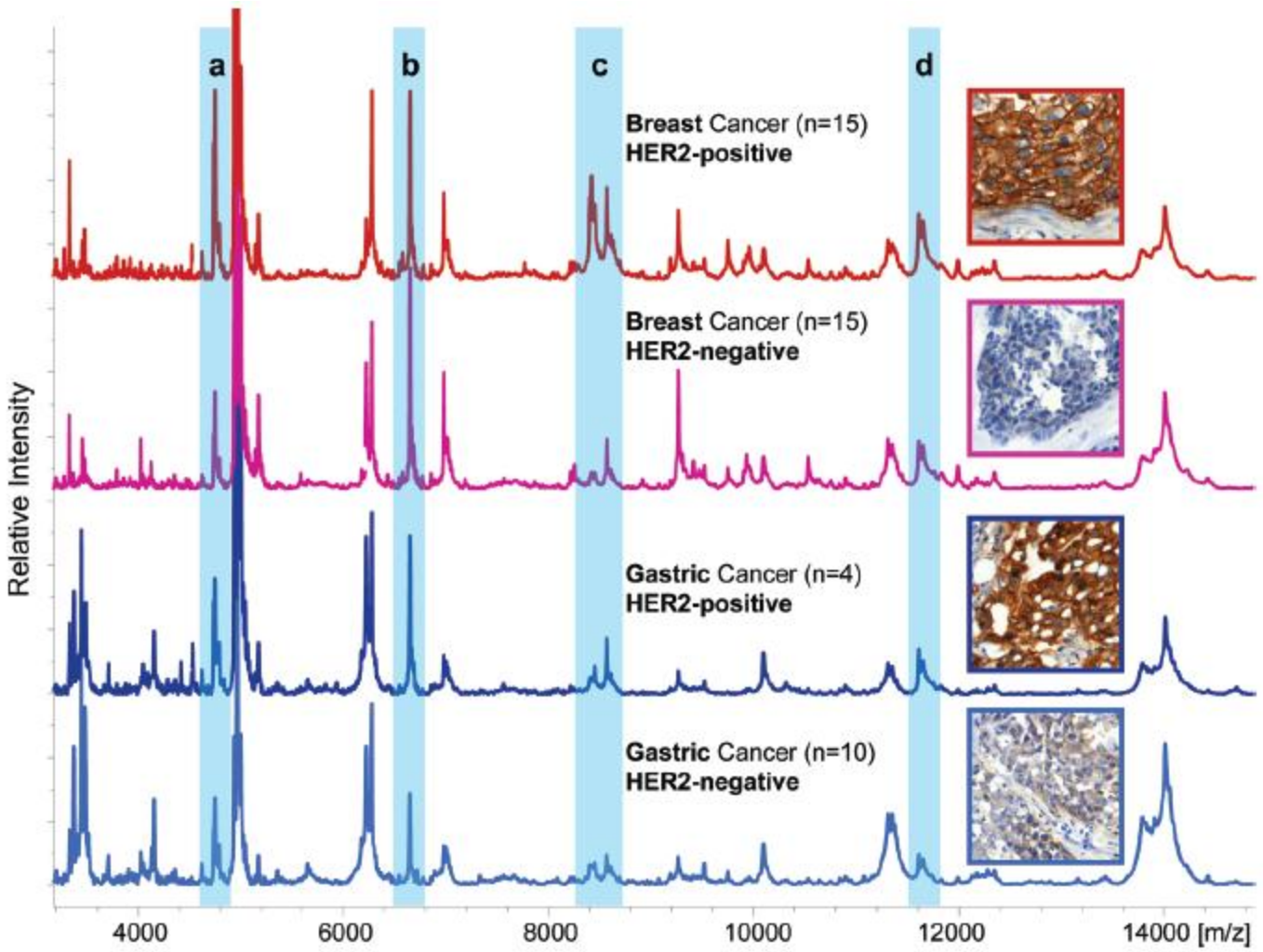
Rauser et al., J Proteome Research 2010; 9: 1854

Druggable Targets





B. Balluff, J Proteome Res 2010



B. Balluff, J Proteome Res 2010

Table 3. Classification Results for Training Set–Test Set Lineups A–D[a]

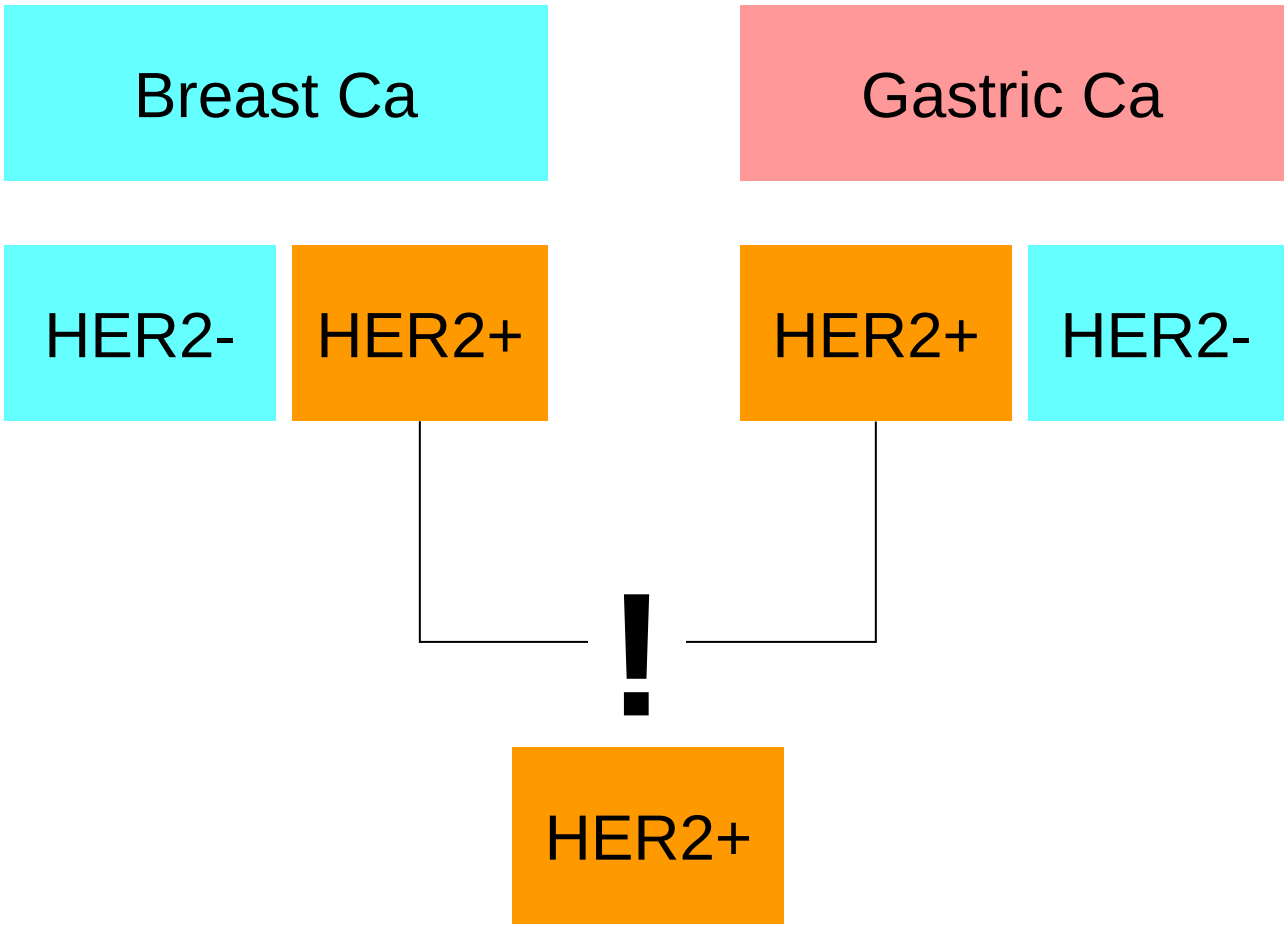
		Random Forest			Support Vector Machine		
setting		sensitivity	specificity	accuracy	sensitivity	specificity	accuracy
A	Mean	**0%**	**40%**	**37%**	**0%**	**100%**	**91%**
	CI-95%	±0%	±4%	±4%	±0%	±0%	±0%
B	Mean	**28%**	**95%**	**89%**	**65%**	**92%**	**90%**
	CI-95%	±9%	±0%	±1%	±8%	±2%	±1%
C	Mean	**50%**	**93%**	**89%**	**73%**	**91%**	**89%**
	CI-95%	±7%	±2%	±2%	±5%	±1%	±1%
D	Mean	**70%**	**87%**	**84%**	**78%**	**88%**	**87%**
	CI-95%	±3%	±2%	±2%	±3%	±1%	±1%

[a] Prediction performances of the two classification algorithms—Random Forest and Support Vector Machine—were evaluated according to their sensitivity, specificity, and accuracy within their 95% confidence intervals (CI) for each setting as described in Table 2.

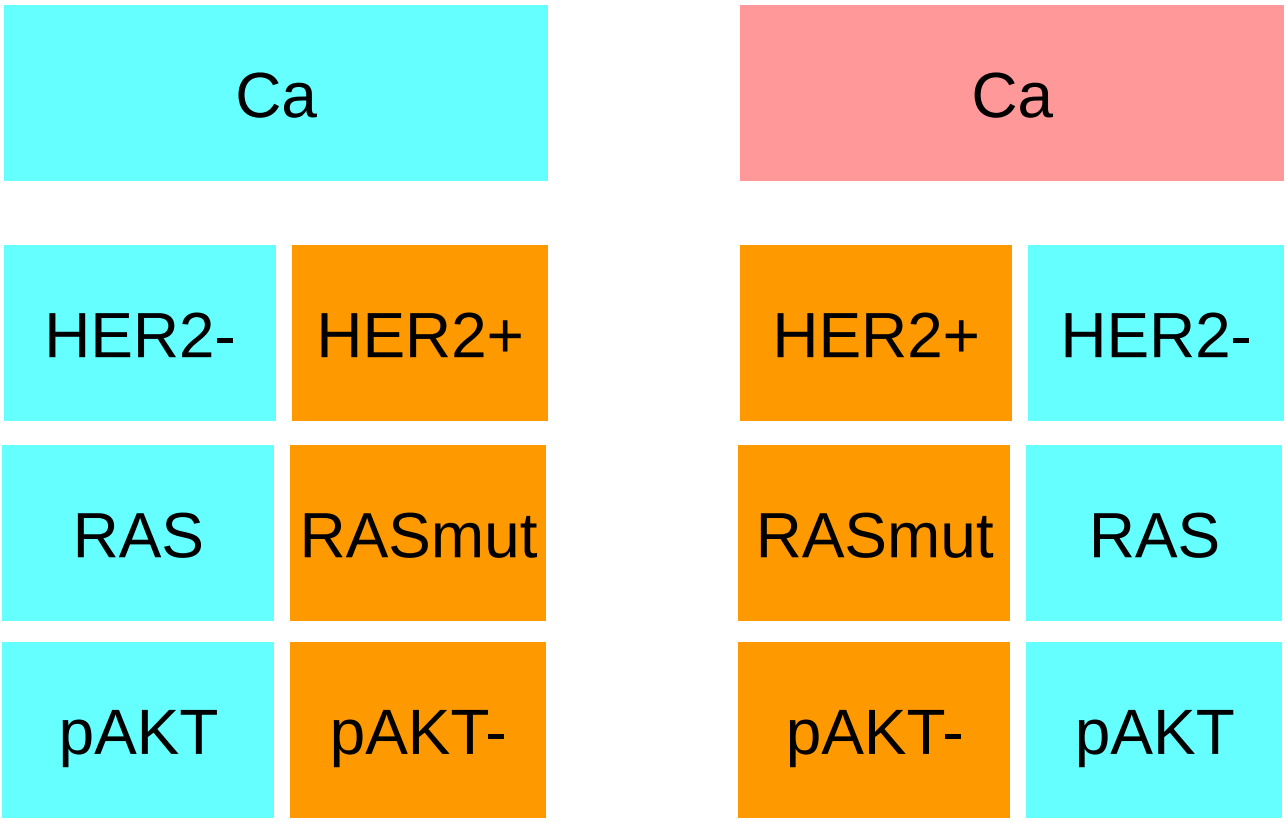
	Training set	Test set
A	Gastric	Gastric
B	Breast	Gastric
C	Gastric + Breast	Gastric
D	Gastric + Breast	Gastric + Breast

B. Balluff, J Proteome Res 2010

Druggable Targets



Druggable Targets



Tumor markers and biology

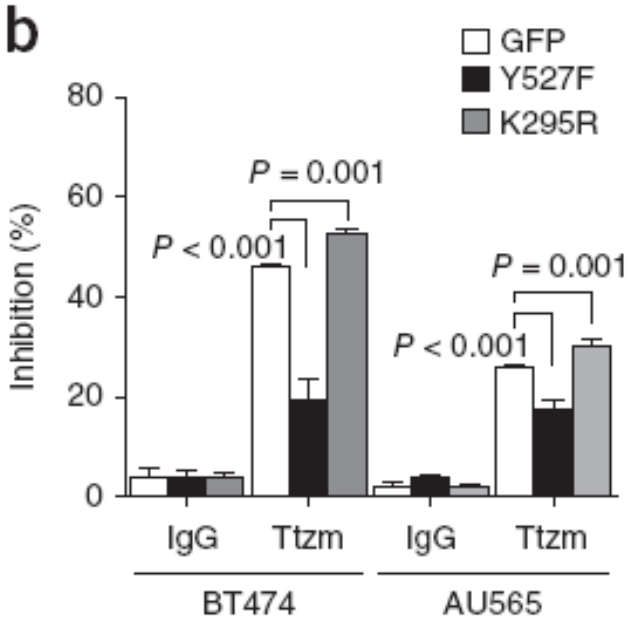
- Druggable Targets

- Overcoming resistance in targeted therapy

  - only ~ 50% of patients respond to trastuzumab in the TOGA trial

Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways

Siyuan Zhang[1], Wen-Chien Huang[1], Ping Li[1], Hua Guo[1], Say-Bee Poh[1], Samuel W Brady[1,2], Yan Xiong[1], Ling-Ming Tseng[1], Shau-Hsuan Li[1], Zhaoxi Ding[1], Aysegul A Sahin[3], Francisco J Esteva[1,2,4], Gabriel N Hortobagyi[4] & Dihua Yu[1,2]



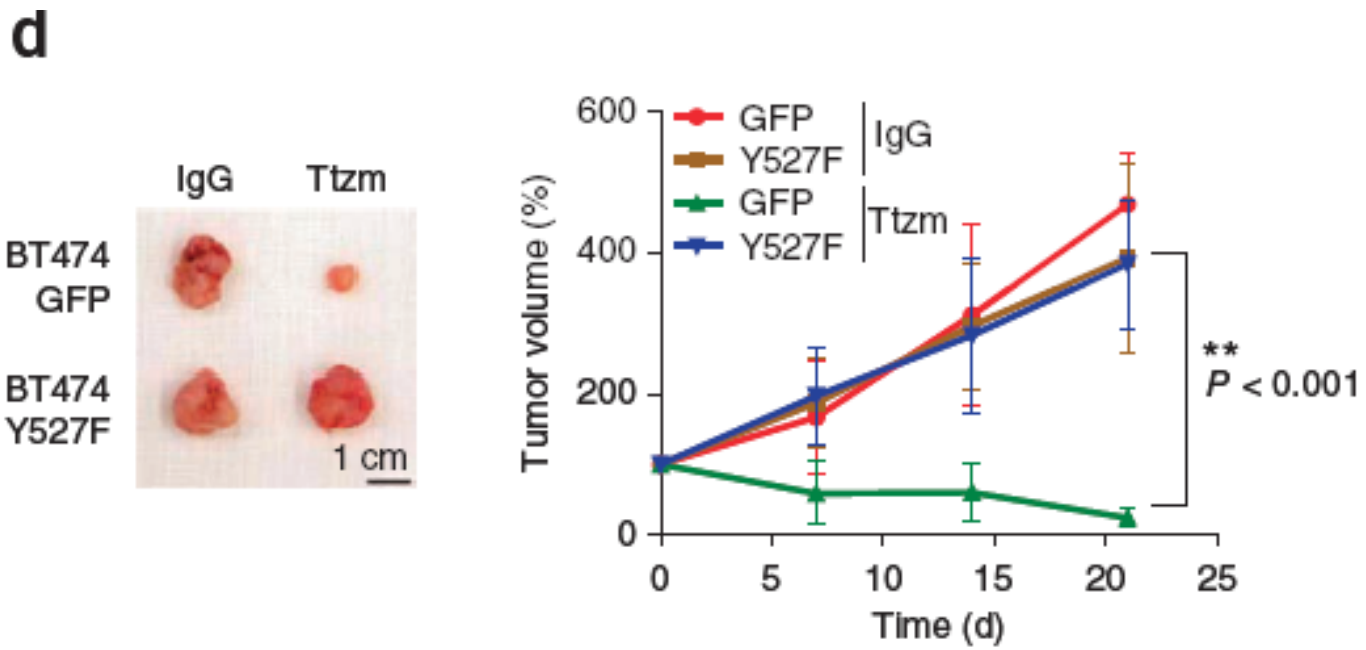
Transfection with activated SRC decreases trastuzumab activity

Y527F Src mutant active, K295R Src mutant dead

Nature Medicine 2011;4:461

Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways

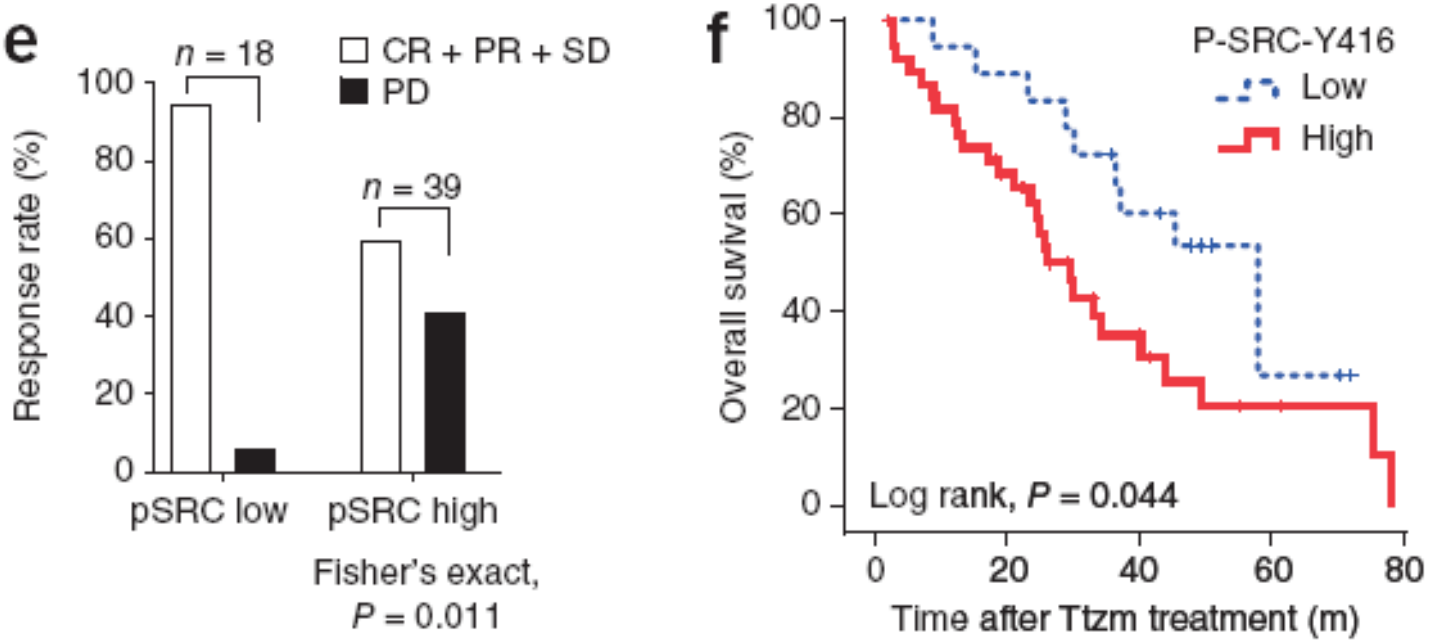
Siyuan Zhang[1], Wen-Chien Huang[1], Ping Li[1], Hua Guo[1], Say-Bee Poh[1], Samuel W Brady[1,2], Yan Xiong[1], Ling-Ming Tseng[1], Shau-Hsuan Li[1], Zhaoxi Ding[1], Aysegul A Sahin[3], Francisco J Esteva[1,2,4], Gabriel N Hortobagyi[4] & Dihua Yu[1,2]



BT474 orthotopic xenograft tumors

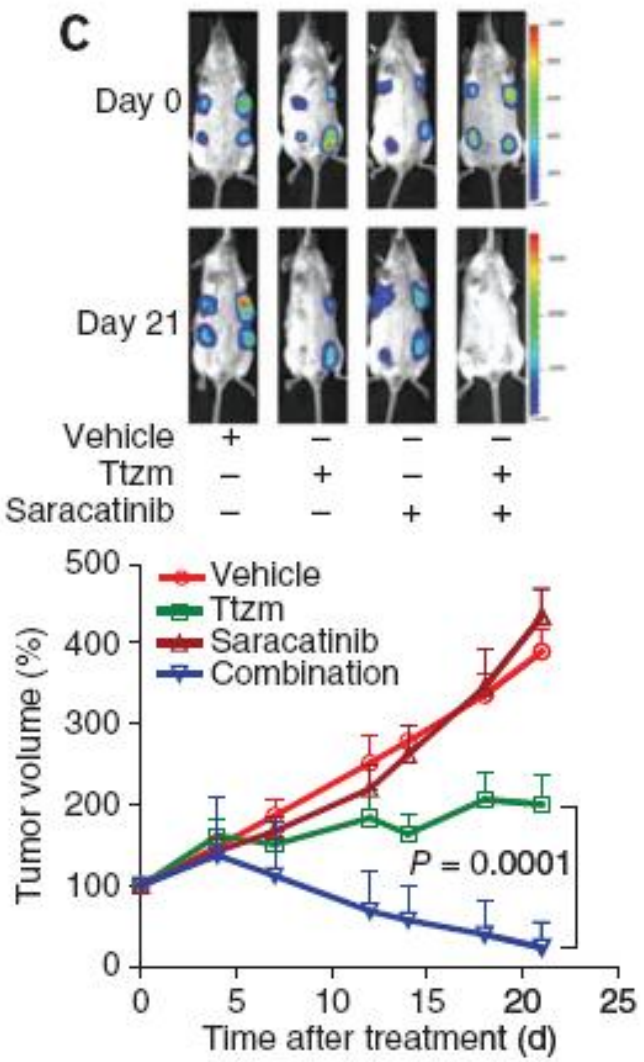
Nature Medicine 2011;4:461

Correlation of responses and survival with phospho-SRC-Y416 (pSRC) expression in breast cancer patients treated with trastuzumab 1st line

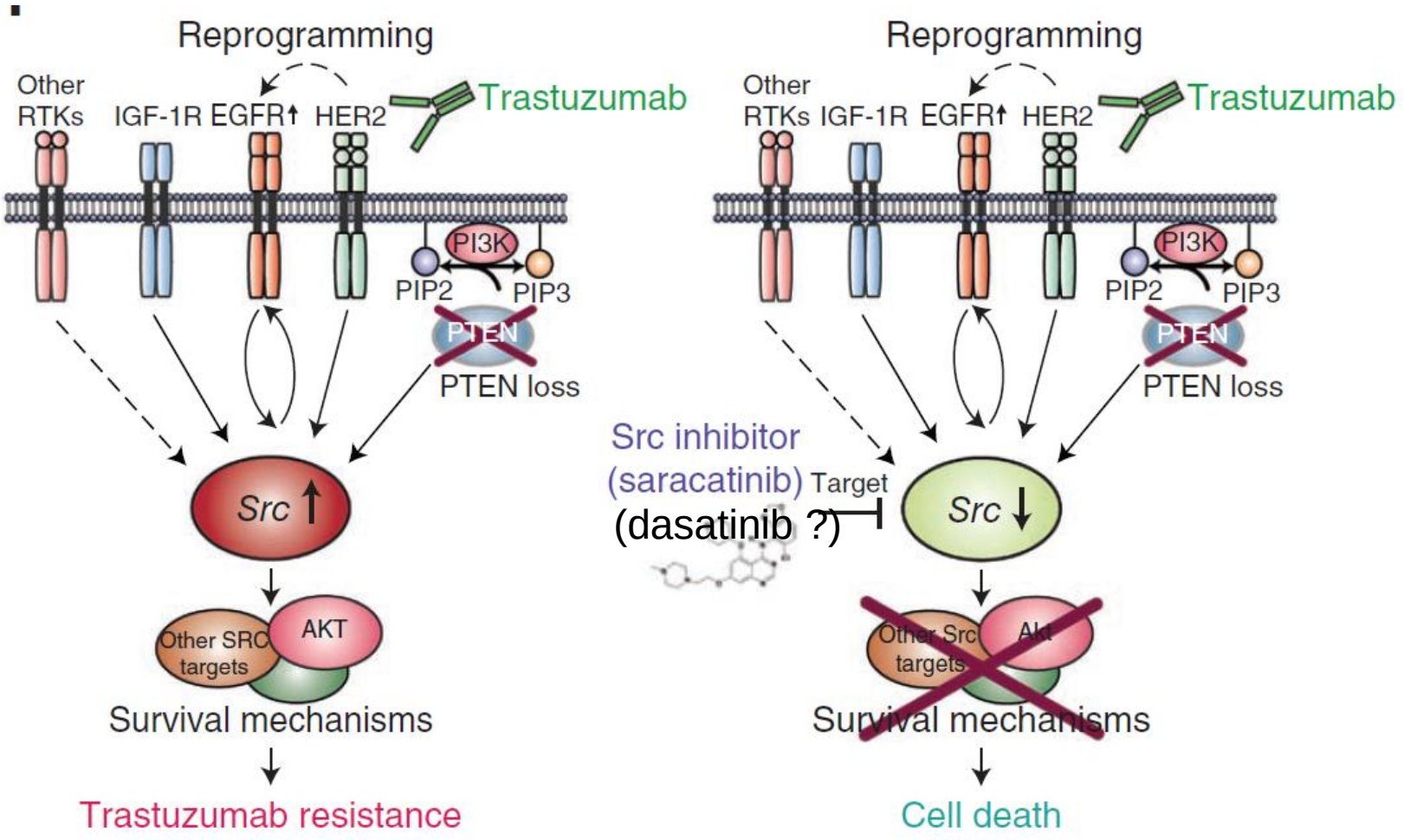


Nature Medicine 2011;4:461

Therapy: Inhibition of Src with saracatinib reverses trastuzumab-resistance



Nature Medicine 2011;4:461



1. Primary resistance
2. Trastuzumab induced resistance

→ **Src ↑**

Conclusions

- Targeted therapies and improved treatment regimens are advancing in GI cancers
- Early identification of „Druggable Targets“ will improve individualisation of therapy and treatment results
- However, novel resistance mechanisms in targeted therapies are also evolving and present a major challenge for the future