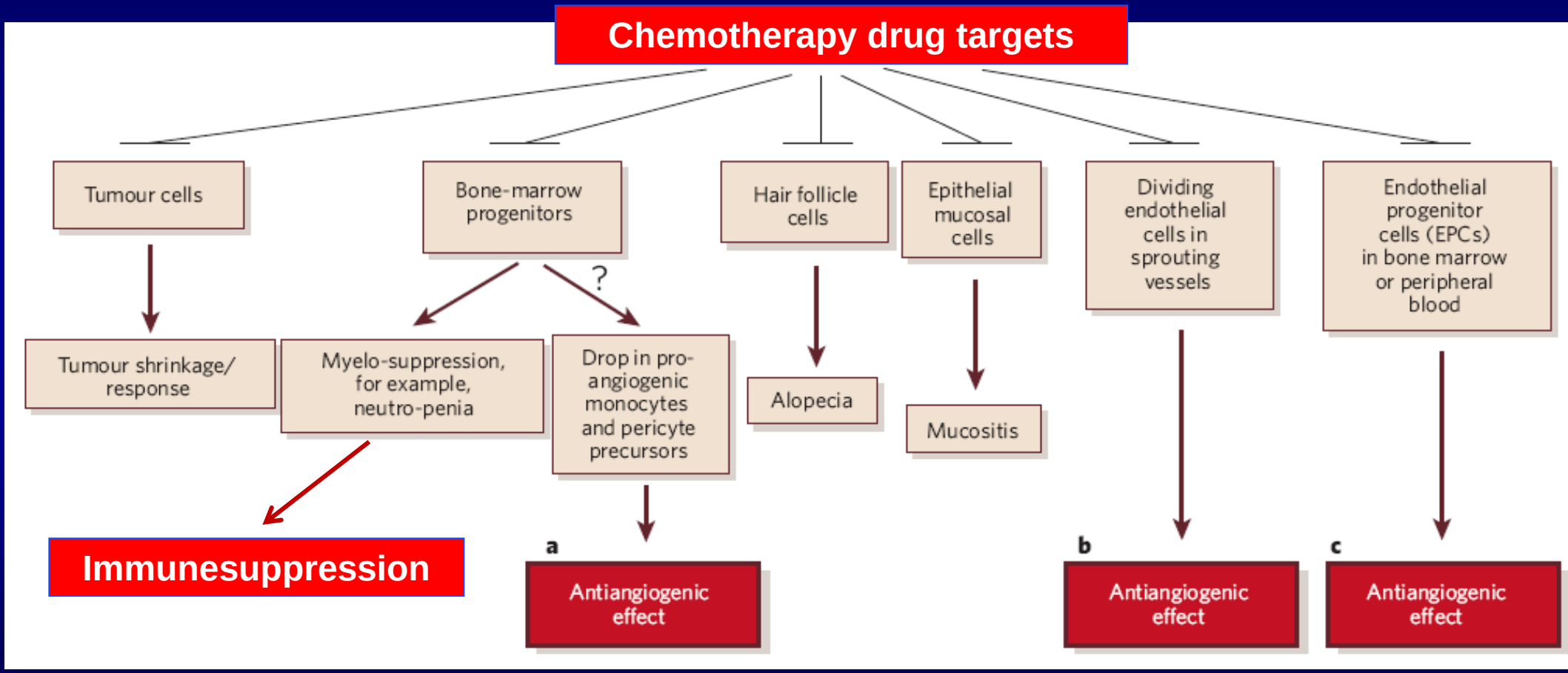
Chemotherapy may target angiogenesis



Modified from the original Ferrara & Kerbel *Nature* 438: 967–974, 2005

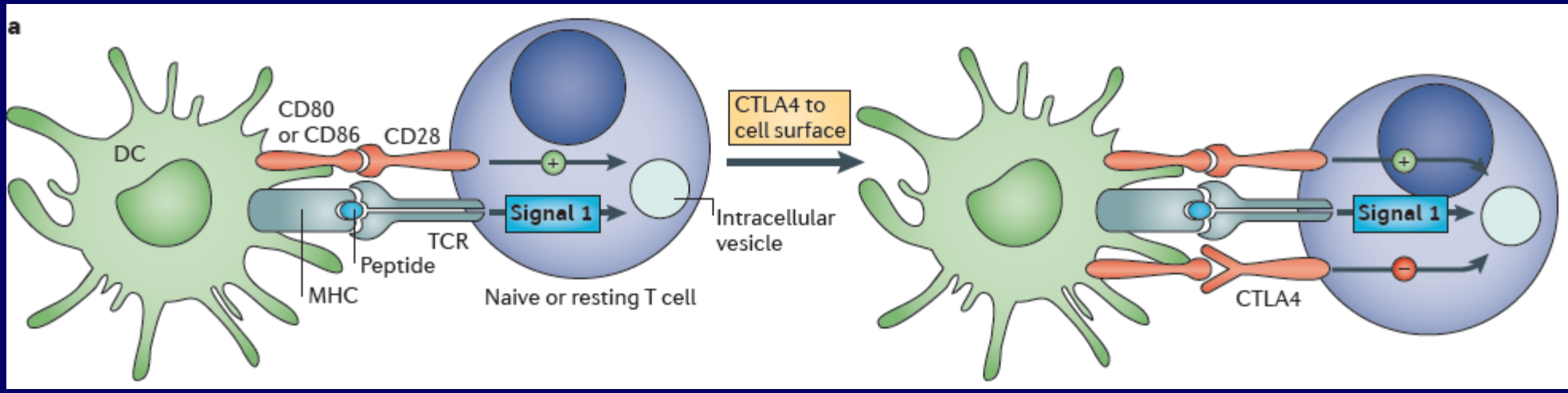
Effects of chemotherapy on ipilimumab-mediated increases in absolute lymphocyte count and activation of T cells

Scott D. Chasalow[1], Jedd D. Wolchok[2], Martin Reck[3], Sabine Maier[1], and Vafa Shahabi[1]

[1]Bristol-Myers Squibb, Research and Development, Princeton, NJ, USA;
[2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA;
[3]Hospital Grosshansdorf, Grosshansdorf, Germany

Scott.Chasalow@bms.com

Inhibition of CTLA-4



Antibodies anti-CTLA-4 block CTLA-4 and augments antitumor T-cell responses

Target	Biological function	Antibody or Ig fusion protein	State of clinical development*
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers
		Tremelimumab	Previously tested in a Phase III trial of patients with melanoma; not currently active

Pardoll D. *Nature Reviews Cancer* , volume 12, April 2012

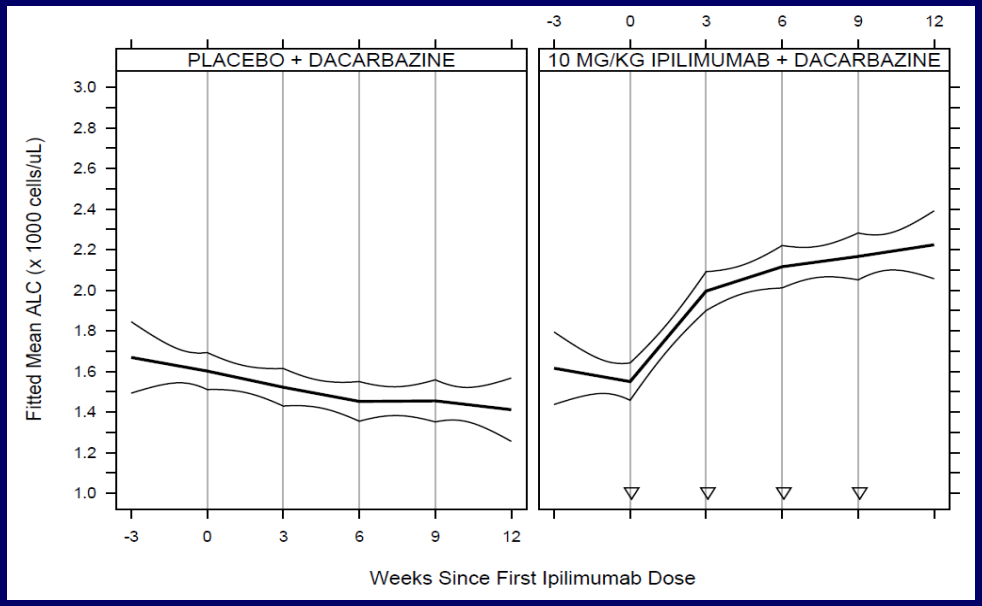
Background

- Increases in absolute lymphocyte count (ALC) and activation of peripheral-blood T cells have been observed in patients treated with IPI as monotherapy.
  - Pharmacodynamic marker of IPI activity
  - Consistent with an immune-stimulating effect
  - Associated with clinical benefit in some melanoma studies

- Goals: To assess IPI pharmacodynamic markers in the presence of chemotherapy
- Methods: Analysis of ALC and T cell activation
  - 3 IPI clinical trials (n = 887)
  - IPI combined with chemotherapy (paclitaxel/carboplatin or DTIC)
  - Patients with metastatic melanoma, advanced NSCLC, or extensive-stage SCLC

Metastatic melanoma: fitted mean ALC vs. weeks since first IPI dose (results for NSCLC and SCLC were similar)

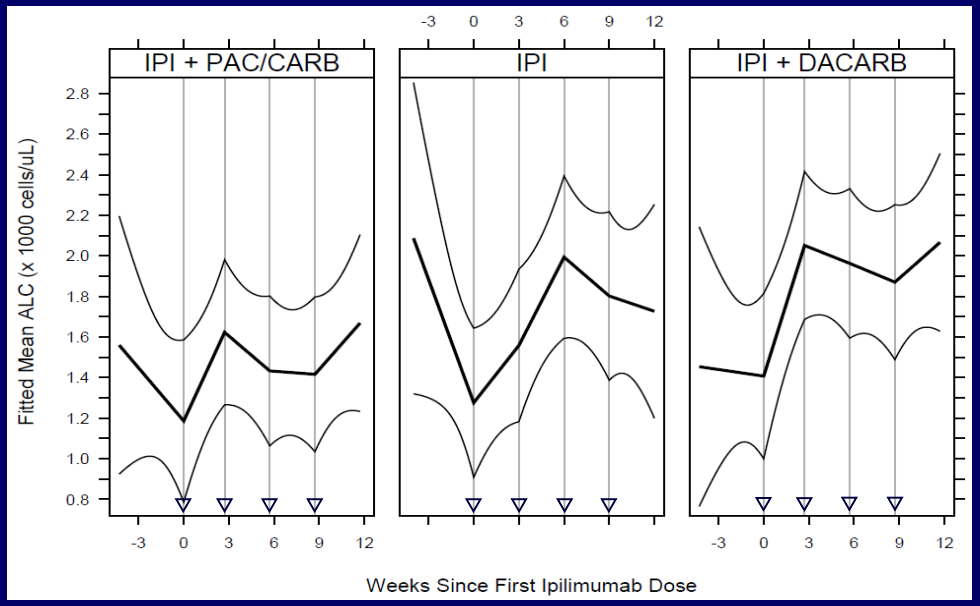
Study CA184024 (N = 497)



Hypothesis Tests

Overall time effect: P < 0.0001
Time x treatment interaction: P < 0.0001

Study CA184078 (N = 59)



Hypothesis Tests

Overall time effect: P = 0.027
Time x treatment interaction: P = 0.500

- Thick curves represent fitted means
- Thin curves represent point-wise 2-sided 95% CIs for the means
- Gray vertical lines represent nominal dosing days; triangles indicate dosing with active IPI

Conclusions

- **Addition of chemotherapy did not eliminate increases in ALC and activated T-cell frequencies.**
  - **Results were consistent between paclitaxel/carboplatin and DTIC, and across tumor types (melanoma, NSCLC, SCLC).**
  - **Mean increases in ALC and frequency of activated T cells were similar to those seen with IPI monotherapy.**
- **These findings suggest that IPI maintains biological activity when administered with chemotherapy, thus supporting continued clinical evaluation of IPI-chemotherapy combinations.**
  - **Consistent with IPI efficacy observed with IPI + chemotherapy**
- **Potential associations between efficacy measures and ALC or T cell frequency changes remain to be explored.**

Antibody-dependent cell-mediated cytotoxicity (ADCC) evolution under treatment by cetuximab and links with treatment outcome in locally advanced Head and Neck (LAHNSCC) and in metastatic colorectal cancer (mCRC) patients

Cristiana Lo Nigro1a, Martino Monteverde1a, Giuliana Strola2, Monica Maffi1a, Emanuela Miraglio1b, Laura Lattanzio1a, Daniela Vivenza1a, Francesca Messa1a, Gérard Milano3

Marco Merlano 1b

1a Laboratory of Cancer Genetics and Translational Oncology and 1b Medical Oncology, Oncology Department, S. Croce General Hospital, Cuneo, Italy
2 Laboratory Department, S. Croce General Hospital, Cuneo, Italy
3 Oncopharmacology Unit EA 3836 UNS, Centre Antoine Lacassagne, Nice, France

VOLUME 25 · NUMBER 7 · MARCH 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

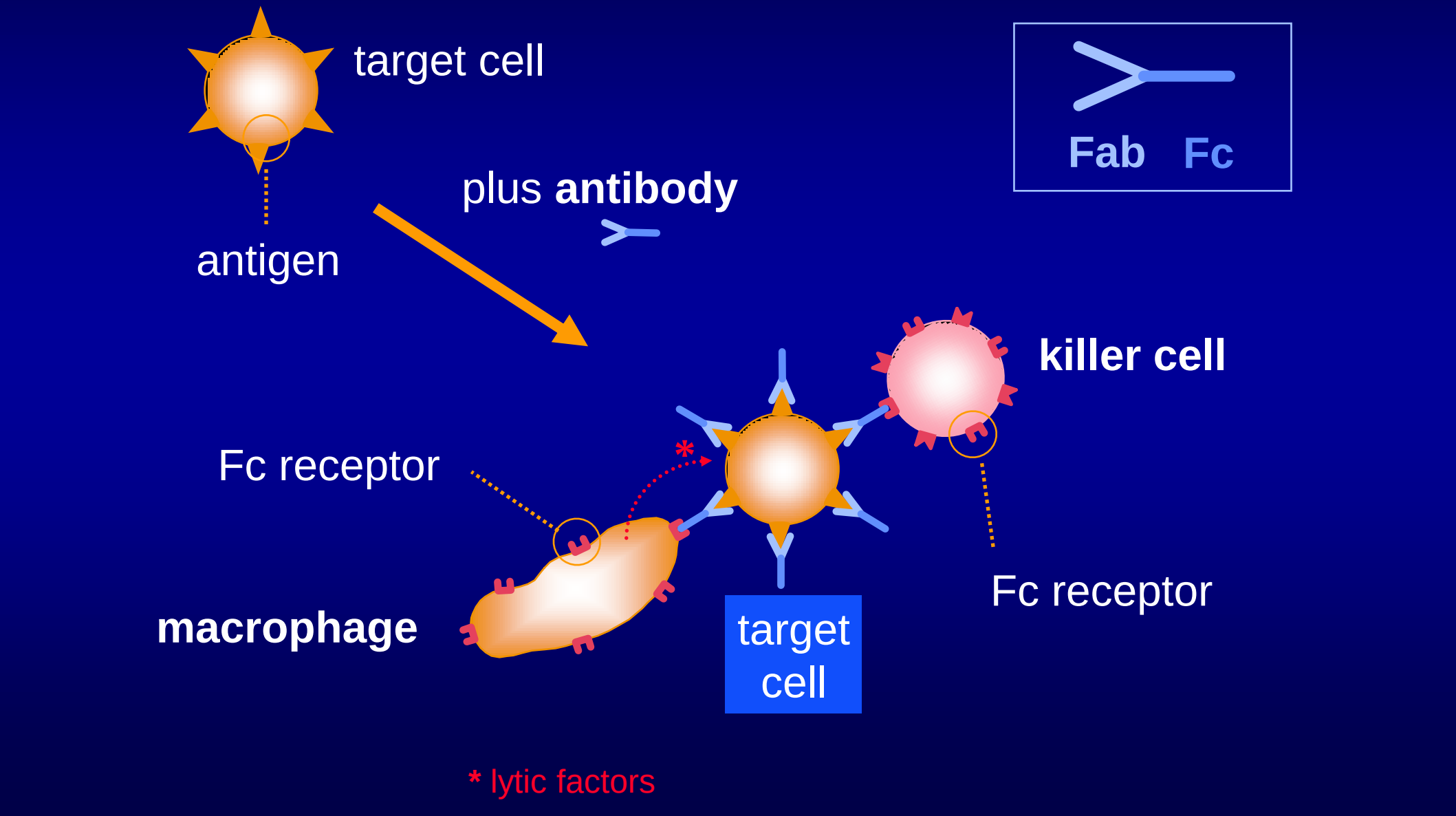
Low Levels of Circulating Invariant Natural Killer T Cells Predict Poor Clinical Outcome in Patients With Head and Neck Squamous Cell Carcinoma

Johan W. Molling, Jacqueline A.E. Langius, Johannes A. Langendijk, C. René Leemans, Hetty J. Bontkes, Hans J.J. van der Vliet, B. Mary E. von Blomberg, Rik J. Scheper, and Alfons J.M. van den Eertwegh

- Invariant CD1d-restricted natural killer T (iNKT) play a pivotal role in transactivation of immune effector cells. It has been reported that iNKT cells are reduced in peripheral blood of cancer patients compared with healthy controls.
- A prospective study, measured circulating iNKT cell numbers in 47 patients before radiotherapy. Follow-up period of 31 months.
- A small (vs. medium or high) circulating iNKT cell fraction was significantly associated with decreased 3-year overall survival rate (39% *v 75% and 92%, respectively)*, Disease-specific survival rate (43% *v 87% and 92%, respectively), and locoregional control rate* (31% *v 74% and 92%, respectively) in HNSCC patients.*
- *Cox regression revealed that the iNKT cell* level, as well as clinical T stage, was an independent prognostic parameter even after correction or the confounding effect of age.
- Screening for iNKT cell levels may be useful for determining which patients can benefit from immunotherapeutic adjuvant therapies aimed at reconstitution of the circulating iNKT cell pool.

ADCC

(*A*ntibody-*D*ependent-*C*ell mediated *C*ytotoxicity)



Impact of Fcγ RIIa-FcγRIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan.

Bibeau F, et al. J Clin Oncol. 2009 Mar 1;27(7):1122-9

ADCC is influenced by FcγRIIa-H131R and FcγRIIIa-V158F polymorphisms
Tumor and normal tissues from 69 patients were screened for KRAS mutations and genotyped for FcγRIIa and FcγRIIIa polymorphisms .
Combined FcγRIIa/FcγRIIIa polymorphisms are prognostic factors for disease progression in mCRC patients treated with cetuximab plus irinotecan. They are also clinically relevant in mutated-KRAS mCRC

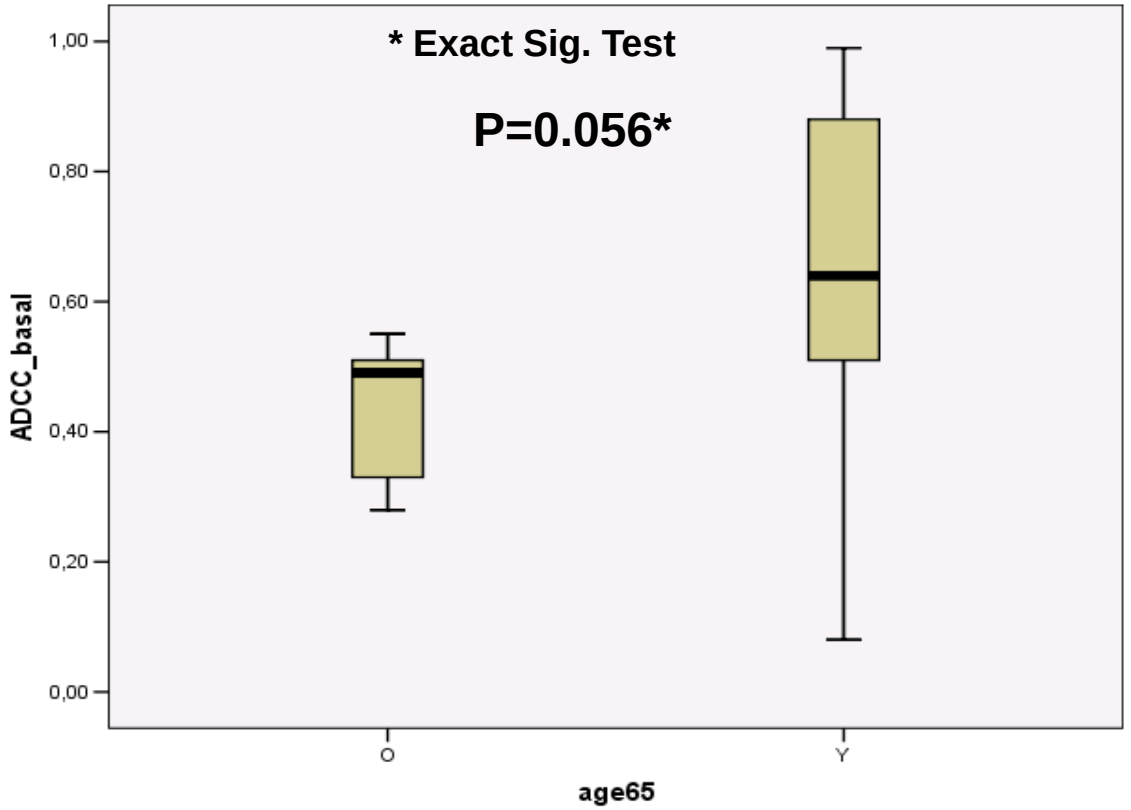
Role of polymorphic Fcγ Receptor IIIa and EGFR expression level in cetuximab mediated, NK cell dependent in vitro cytotoxicity of head and neck squamous cell carcinoma cells.

López-Albaitero A, et al. *Cancer Immunol Immunother.* 2009 Nov;58(11):1853-64.

In vitro study: The extent of lysis of SCCHN cells is influenced by the EGFR expression level, cetuximab concentration, and FcγR polymorphism. Effector cells expressing the FcγR IIIa-158 VV allele were significantly ($P < 0.0001$) more effective than those expressing FcγR IIIa VF and FF

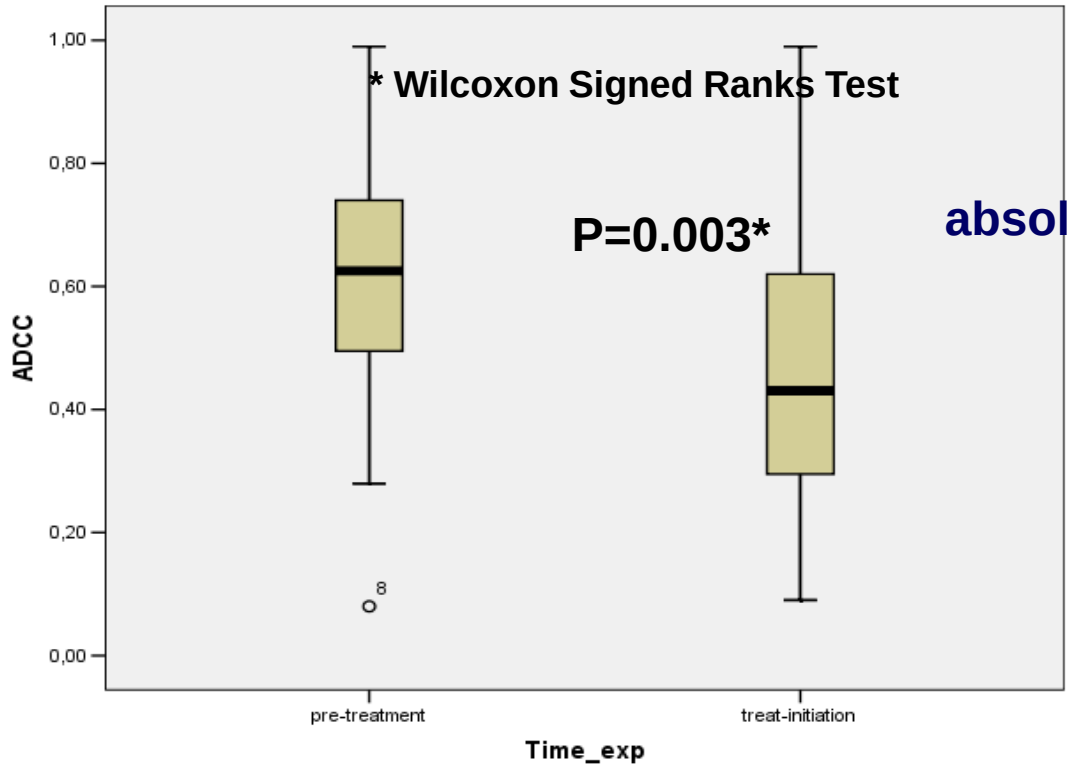
Clinical characteristics	
Number of patients: N° and (Median Age; range)	82 (64.3; 87-39)
LAHNSCC: N° and (Median Age; range)	39 (58; 38.6-87.1)
mCRC: N° and (Median Age; range)	43 (67.6; 48.4-83)
Male/Female	60 (%)/22 (%)
Rash 0 1 2 3 n.a.	 6 (21%) 8 (28%) 7 (24%) 3 (10%) 5 (17%)
EGFR grading (IHC) 0 1 2 3 Na	 11 (%) 8 (%) 22 (%) 17 (%) 24(%)
FcGr3A polymorphism V/V Other n.a.	 14 (17%) 67 (82%) 1 (1%)
Median Basal ADCC %	62.5% (-99%)
Median NKT%	6% (2%-30%)
Median basal Inv NK (cells/microl.)	0.41 (0.02-2.25)

ADCC basal comparison between younger (<65) and older (>=65) LAHNSCC patients



A trend for an increased basal ADCC was observed in younger patients: median was 66% in the 22 patients < 65 vs 56% in the 22 patients 65 years (p = 0.084),

ADCC response evolution:
Comparison between pre-treatment and after 2 months of treatment



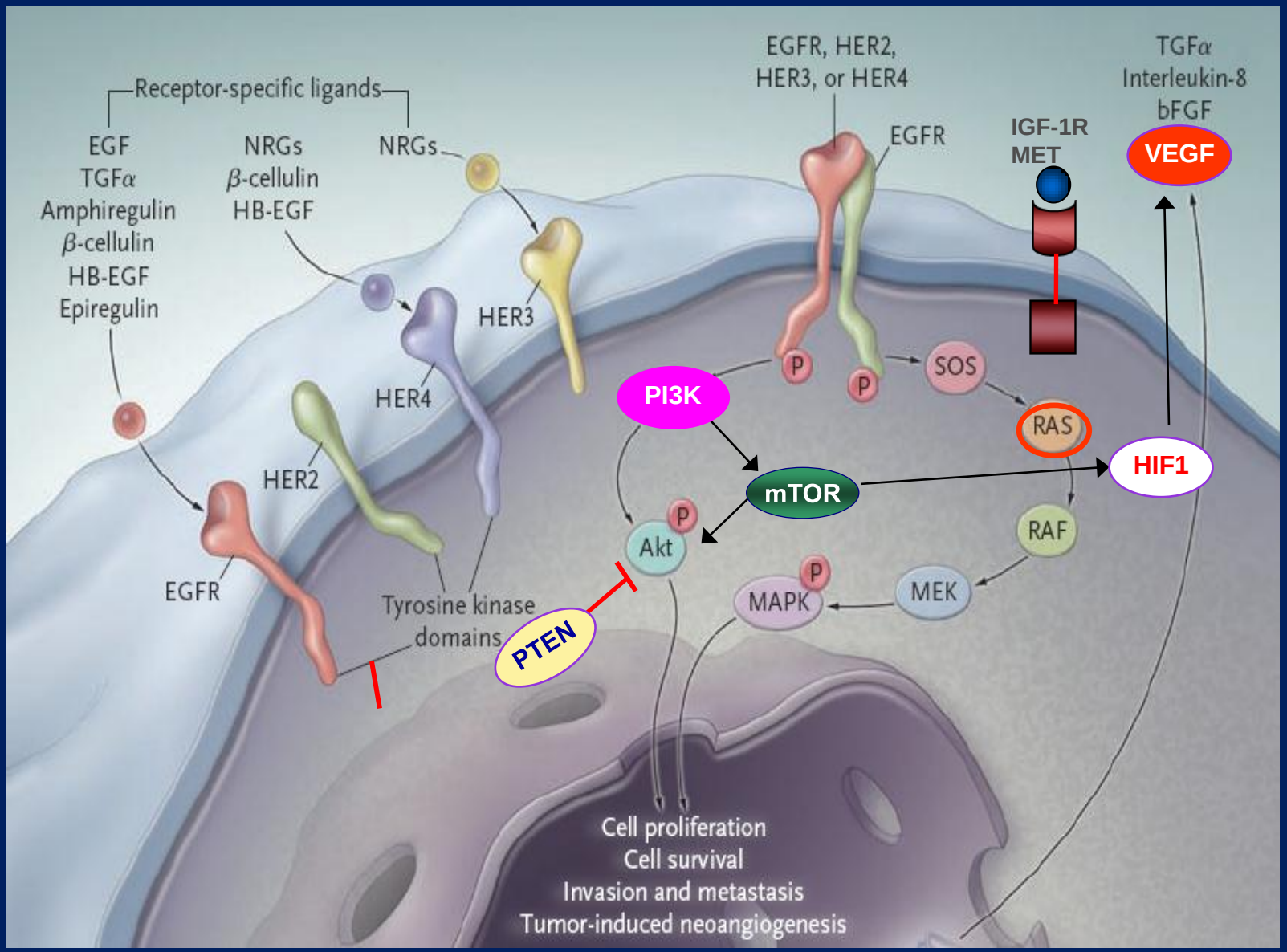
absolute median drop of 20%).

- FcgR2a and FcgR3a gene polymorphisms were not linked to basal ADCC.
- In the 82 patients assessable for survival (median follow up=10.3 month) cutaneous rash, but not basal ADCC, was related to survival (p=0.043).
- No correlation between ADCC evolution vs EGFR status nor vs cutaneous rash.

initial drop in ADCC under treatment may reflect the variable chemotherapy-induced impact on host immunity.

HER-dependent signalling pathways

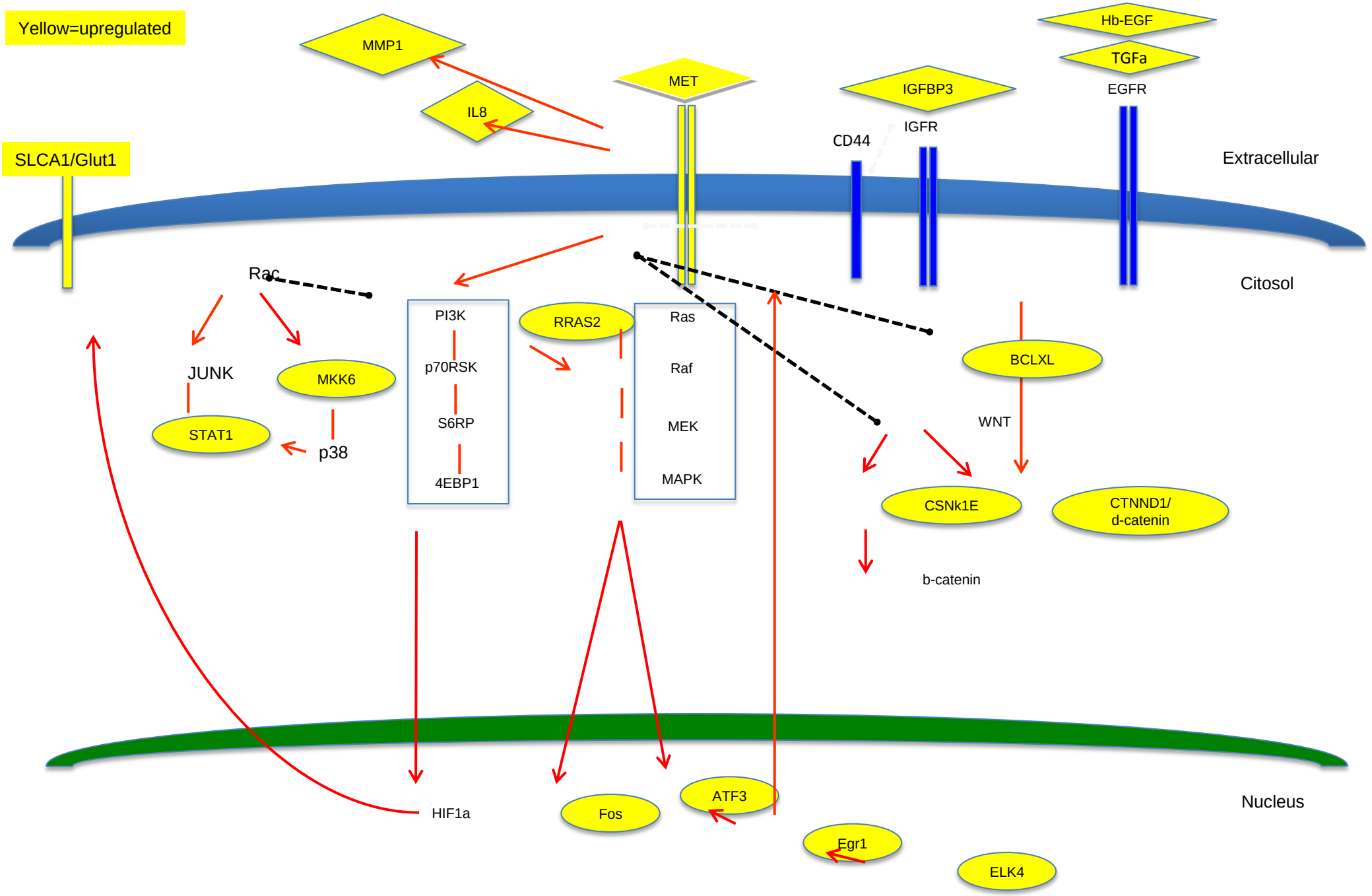
Ciardiello F & Tortora G, *New England Journal of Medicine, March 2008*



MET activation rescues colon cancer cells from sensitivity to EGFR inhibition

Abstract ID: 143PD

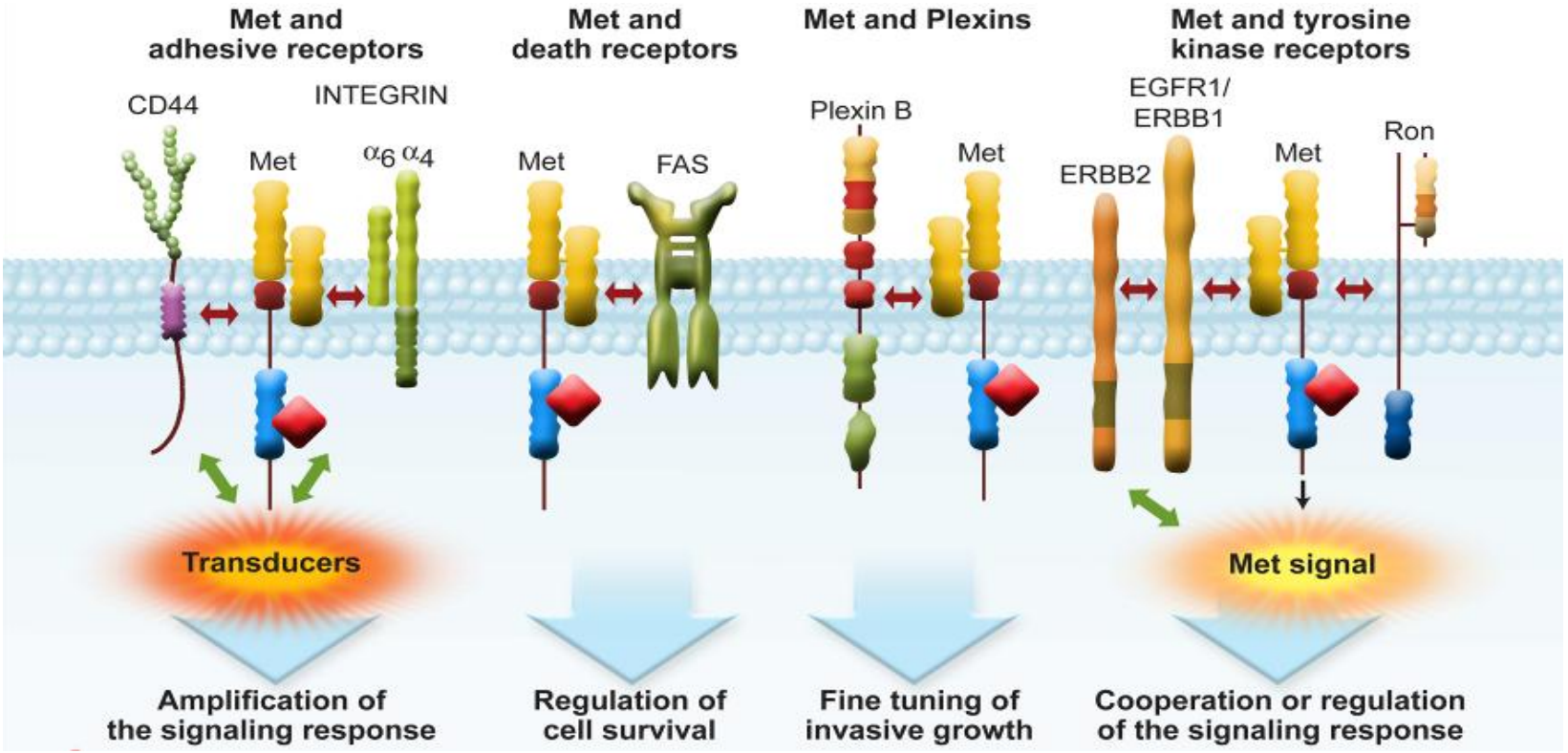
T. Troiani, D. Vitagliano, S. Napolitano, F. Morgillo, A. Capasso, V. Sforza, A. Nappi, L. Berrino, F. Ciardiello, E. Martinelli


Yellow=upregulated
MMP1
IL8
MET
Hb-EGF
TGFa
EGFR
IGFBP3
IGFR
CD44
SLCA1/Glut1
Extracellular
Citosol
Rac
JUNK
MKK6
STAT1
p38
PI3K
p70RSK
S6RP
4EBP1
RRAS2
Ras
Raf
MEK
MAPK
BCLXL
WNT
CSNk1E
CTNND1/
d-catenin
b-catenin
HIF1a
Fos
ATF3
Egr1
ELK4
Nucleus

MET

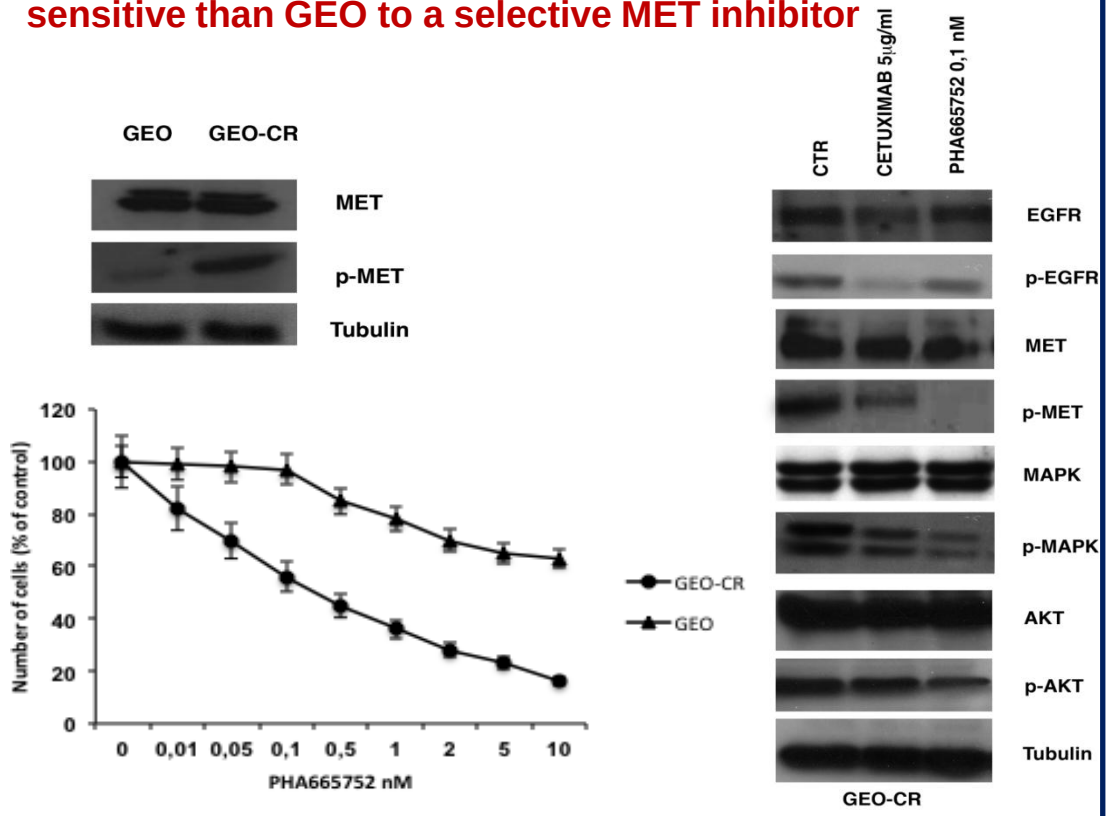
One of the most frequently genetically altered RTKs in human cancers (including colorectal, gastric, NSCLC, breast, prostate and others) with activating mutations and amplifications

- **Activating mutations**
  - Hereditary papillary RCC: 100%, sporadic papillary RCC (13%)
  - HNSCC: 10%
  - NSCLC (8%) and SCLC (13%) Activating mutations
- **Gene amplification**
  - Gastric carcinoma: 5-10%
  - Colorectal carcinoma: 4% primary tumors, 20% liver metastases
  - Esophageal adenocarcinoma: 5-10%

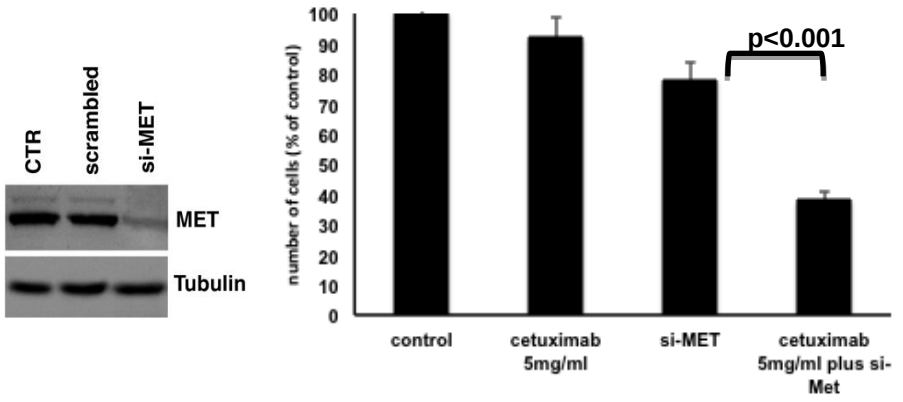


MET activation is important in cetuximab resistance

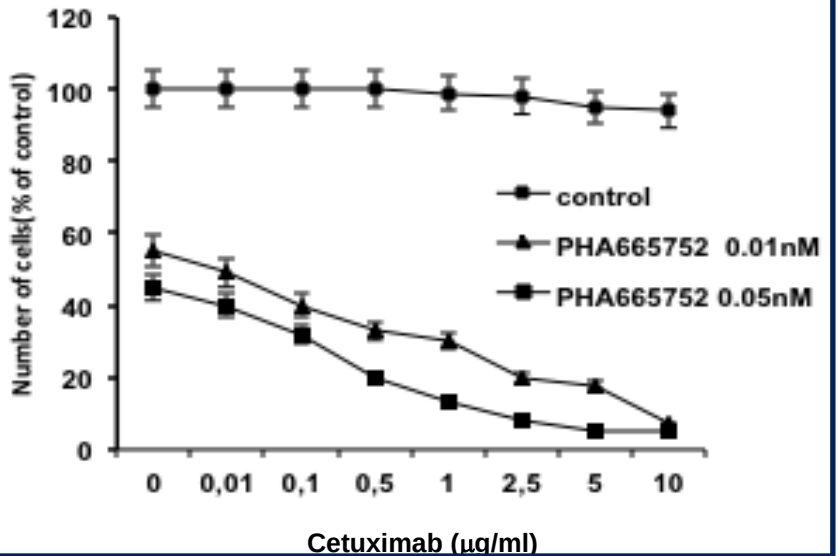
GEO CR overexpress pMET and are more sensitive than GEO to a selective MET inhibitor



Silencing of MET recovers sensitivity to cetuximab



MET inhibitor cooperates with cetuximab in GEO-CR



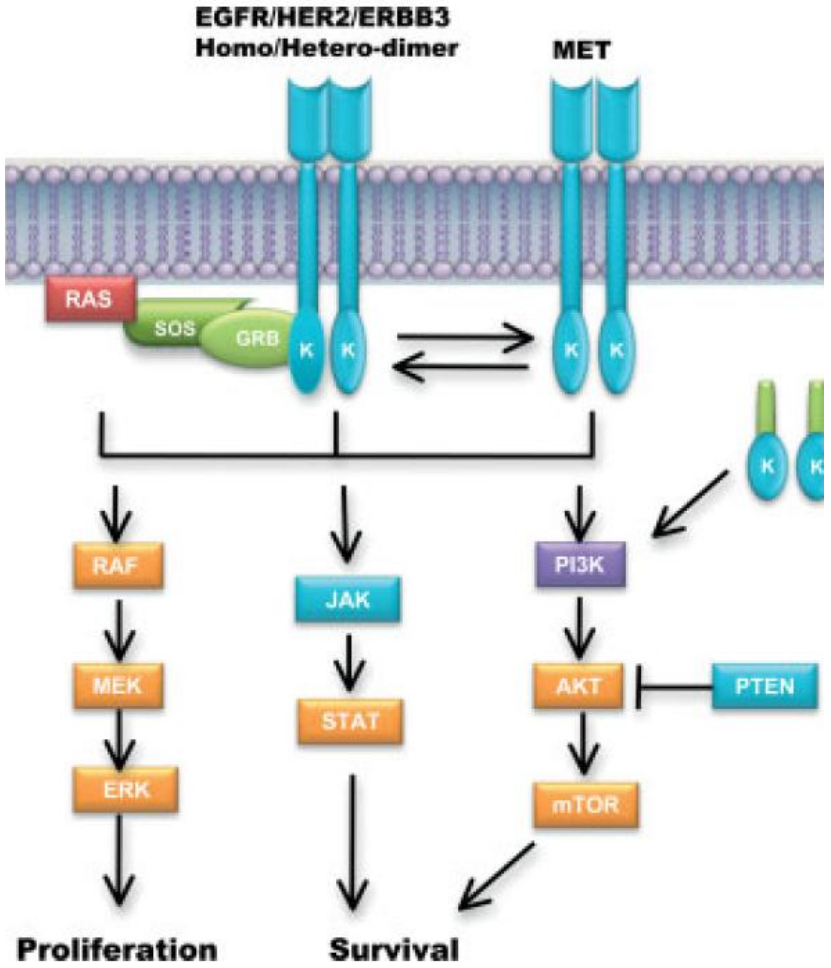
Inhibition of MET and recovery of sensitivity to cetuximab

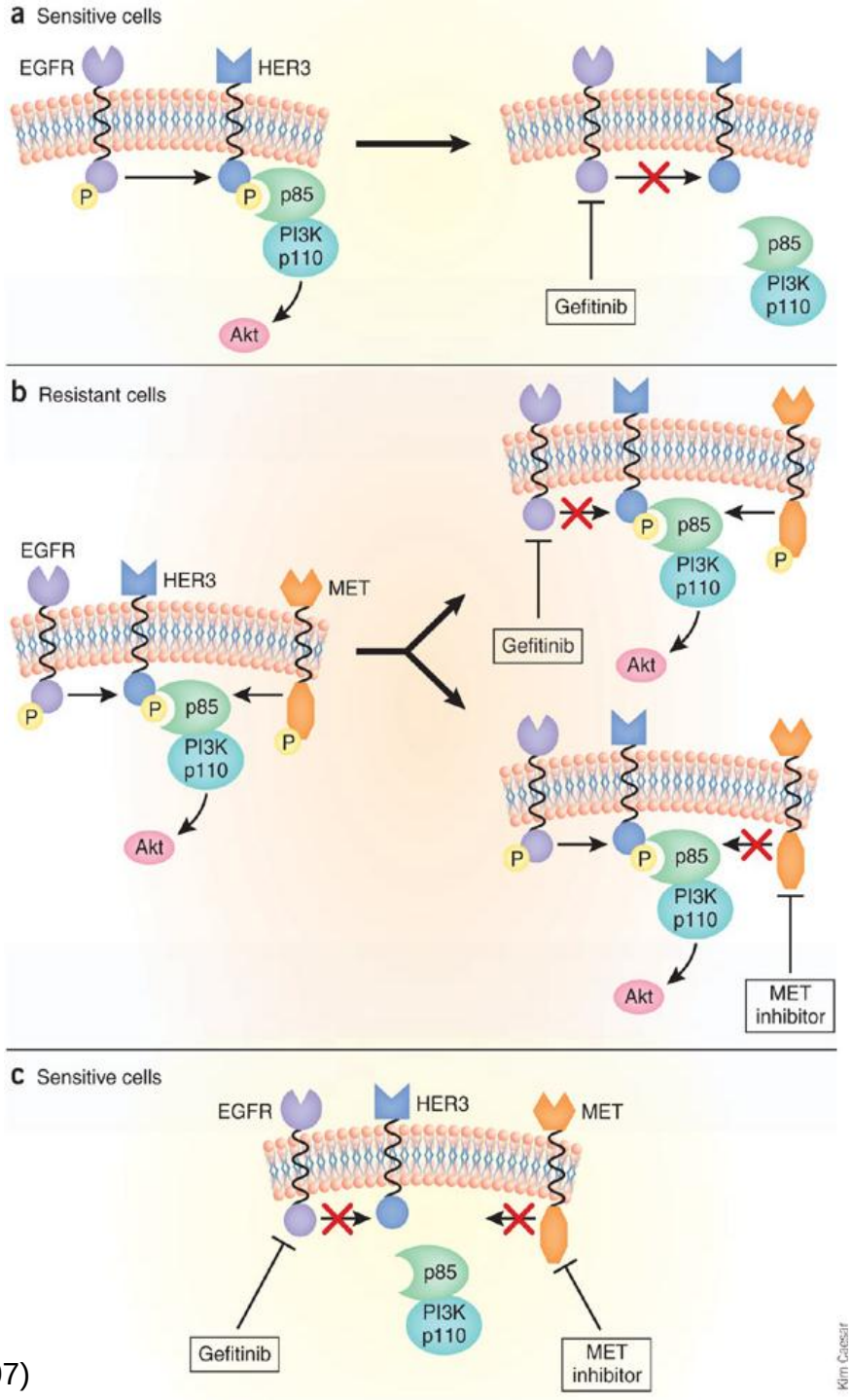
Krumbach R, Schüler J, Hofmann M, Giesemann T, Fiebig HH, Beckers T.
Primary resistance to cetuximab in a panel of patient-derived tumour xenograft models: activation of MET as one mechanism for drug resistance.
Eur J Cancer. 2011 May;47(8):1231-43.

79 human patient-derived xenografts originating from five tumour histotypes.

- In cetuximab resistant NSCL adenocarcinoma LXFA 526 and LXFA 1647 overexpression of MET was identified.
- Knock-down of MET by siRNA in the corresponding cell lines showed that anchorage-independent growth and migration are dependent on MET.
- MET knock down sensitized LXFA 526L and LXFA 1647L to EGF.
- Combined treatments of a MET inhibitor and cetuximab were additive.

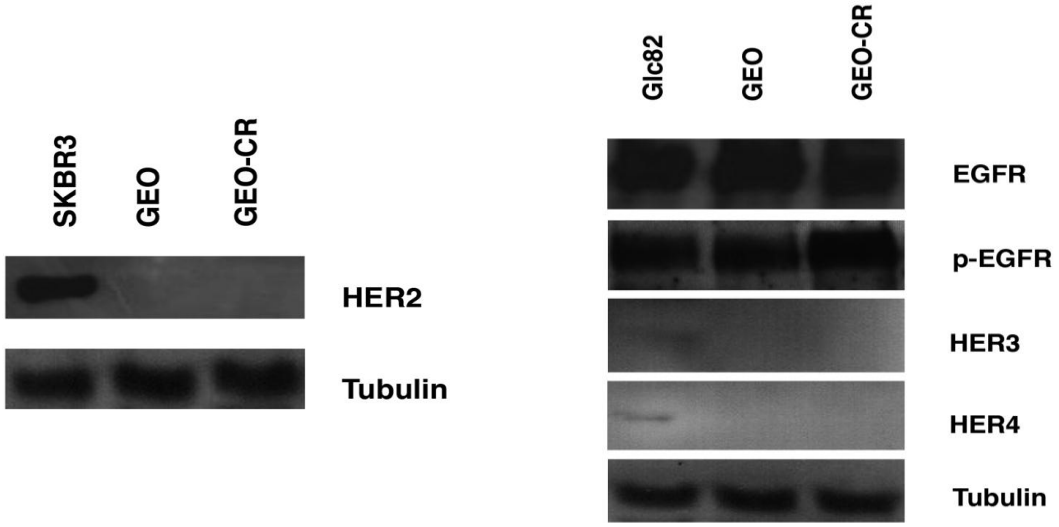
EGFR and HER meet MET



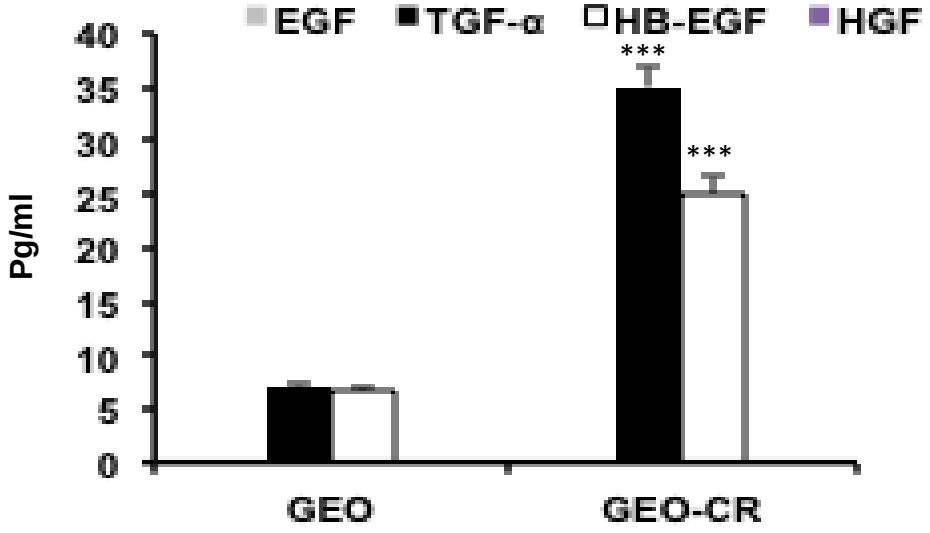


Engelman et al. *Science* 2007;
Arteaga C, *Nature Medicine* 13, 675 - 677 (2007)

Possible mechanisms of MET activation in GEO-CR cells

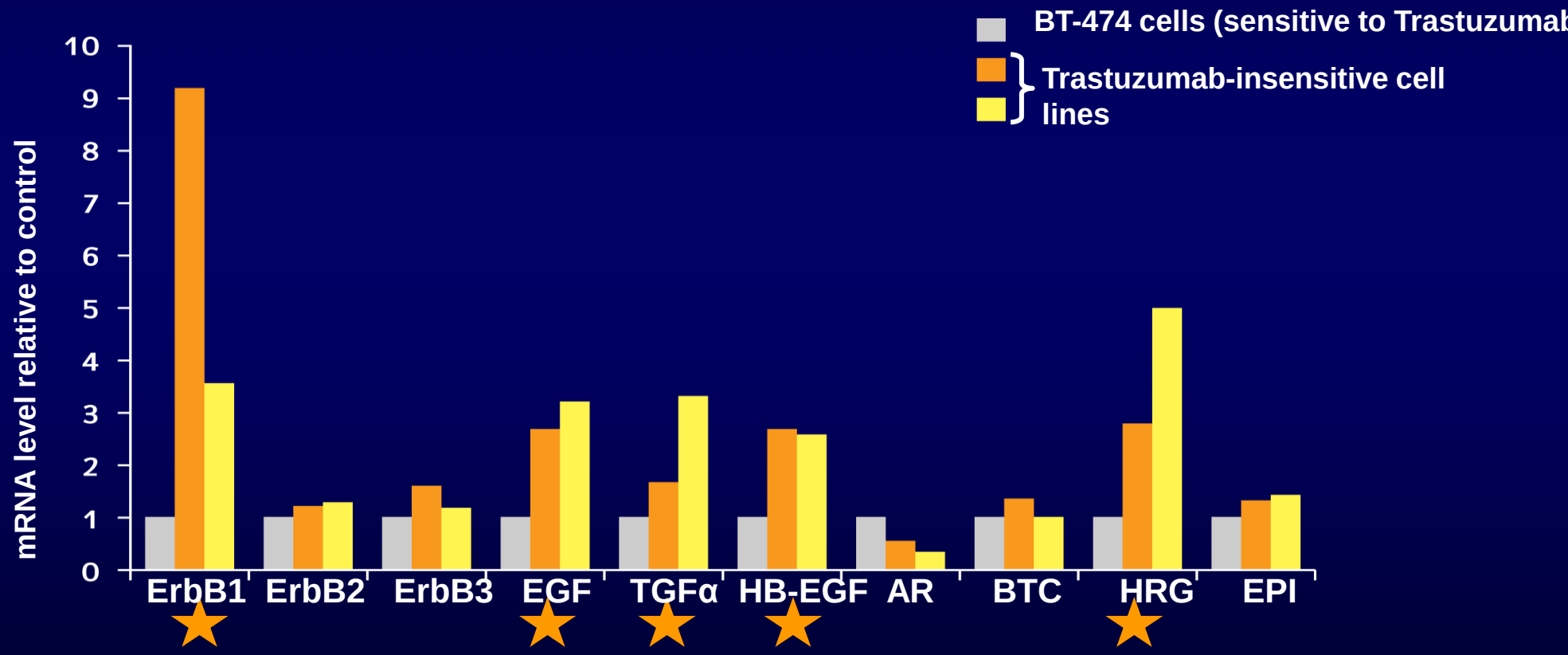


Up-regulation of EGFR ligands such as TGFα and Heparin Binding- EGF could be involved in the mechanism of MET activation in GEO-CR cells



Upregulation of other ErbB receptors can overcome trastuzumab inhibition of ErbB2

ErbB1/ErbB3 ligands are upregulated in trastuzumab-resistant cells



AR=amphiregulin; BTC=betacellulin; EPI=epiregulin; HB-EGF=Heparin-binding EGF; HRG=heregulin; TGF=transforming growth factor

1. Leitzel et al. *J Clin Oncol ASCO Annual Meeting Proceedings* 2008;**26**:Abstract 1002; 2. Ritter et al. *Clin Cancer Res* 2007;**13**:4909-19