ESMO Preceptorship Program

Gastric Cancer

Multidisciplinary management, standards of care, therapeutic targets and future perspectives-
New targets (including cMET, FGF, mTOR, …)

Salah-Eddin Al-Batran

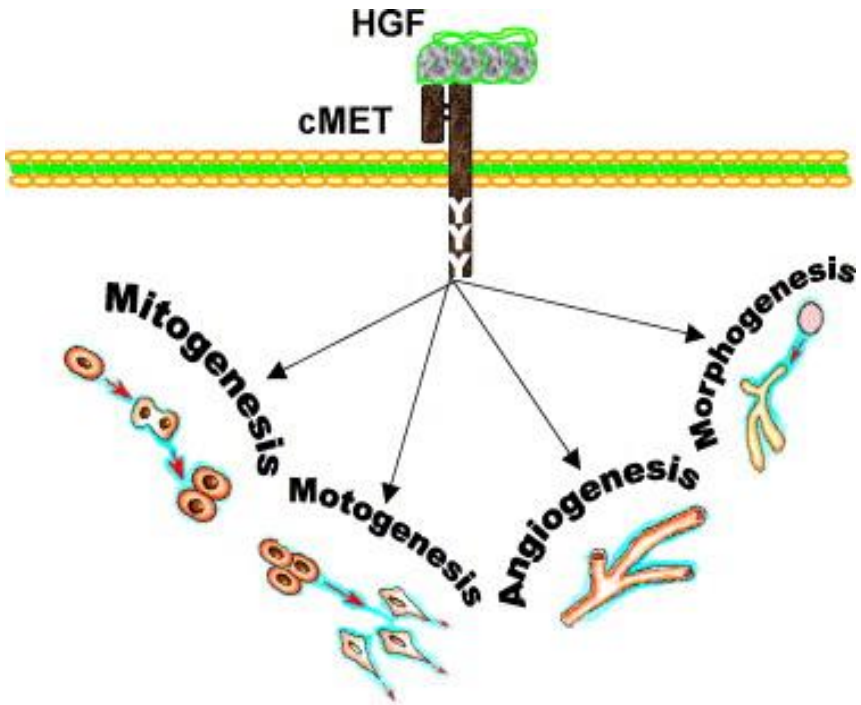
Krankenhaus Nordwest

University Cancer Center Frankfurt

Selected Biomarker for Gastric Cancer

Biomarker	Predictive	Prognostic	Drugs	Phase III Trials
C-MET/HGF	(yes)	yes	Rilotumumab, Onartuzumab, Trivantinib Foretinib AMG 337	Phase III trials on Rilotumumab and Onartuzumab have started Ongoing phase I/II with Tivatinib plus FOLFOX Foretinib failed in a phase I study AMG 337 is in a phase I/II study
PI3K/mTOR	?	?	RAD001	Granit-1: PFS improved, OS not RADPAC: ongoing
FGFR2	(yes)	(Yes)	AZD4547 Ponatinib	AZD4547: Shine phase II study ongoing Ponatinib: phase II trial in FGFR amplified patients in Asia ongoing

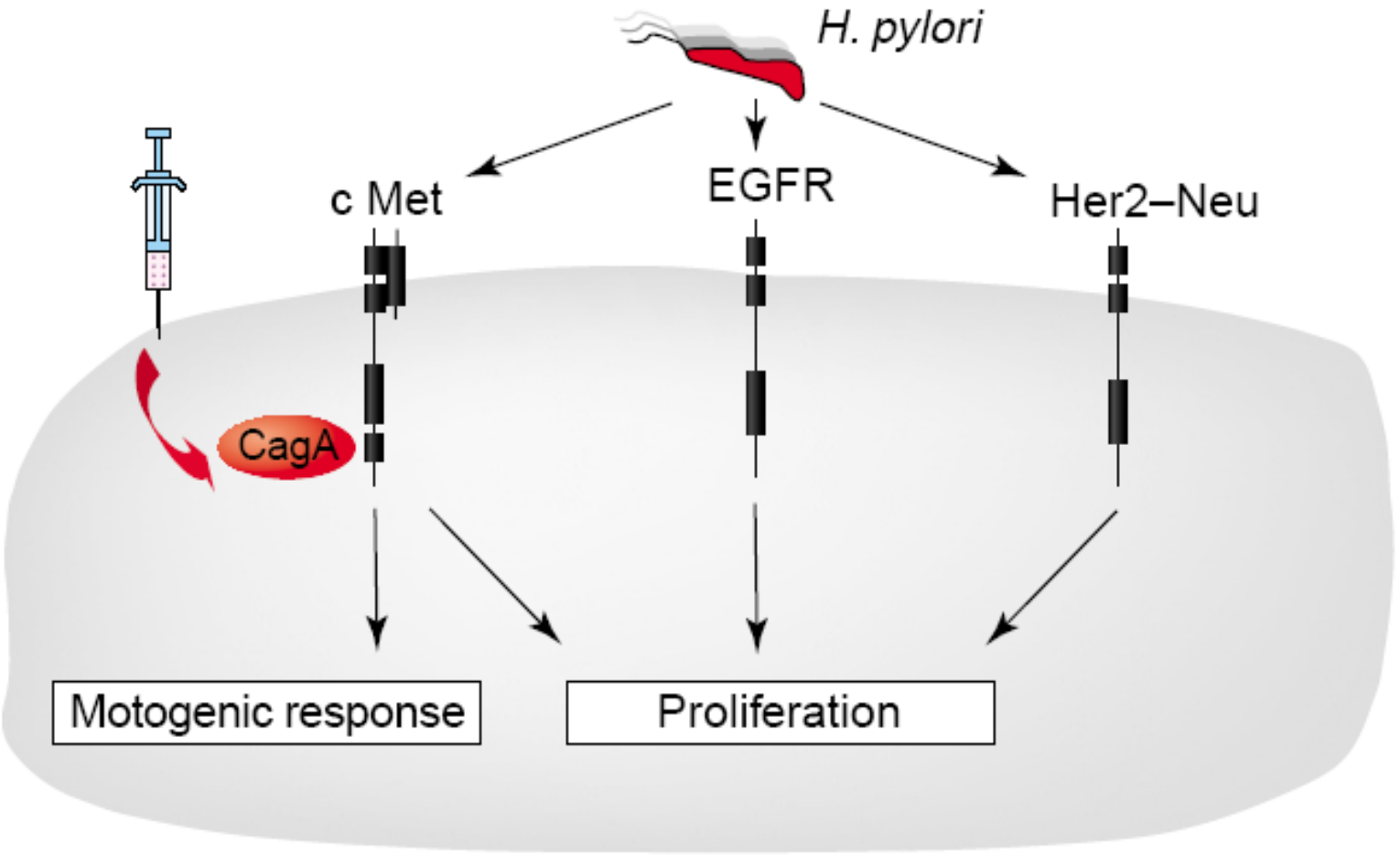
Mesenchymal Epithelial Transition Factor Receptor (c-MET)



- Activated by HGF (hepatocyte growth factor)
- Regulates multiple steps of cell survival and proliferation
- MMPs and Osteopontin upregulation

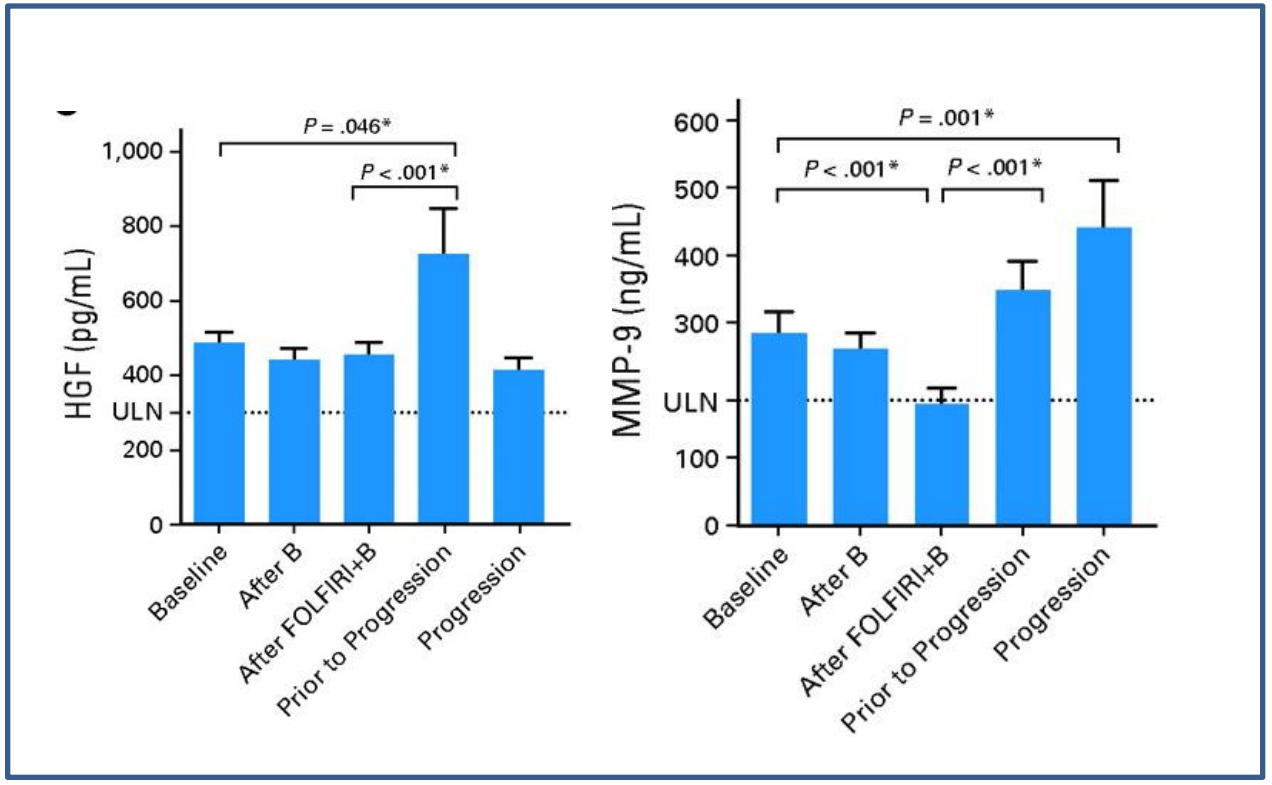
Birchmeier C 2003, Miller CT et al. 2006, WG Jiang et al. 2005

HP aktiviert c-met, EGFR und HER2/neu

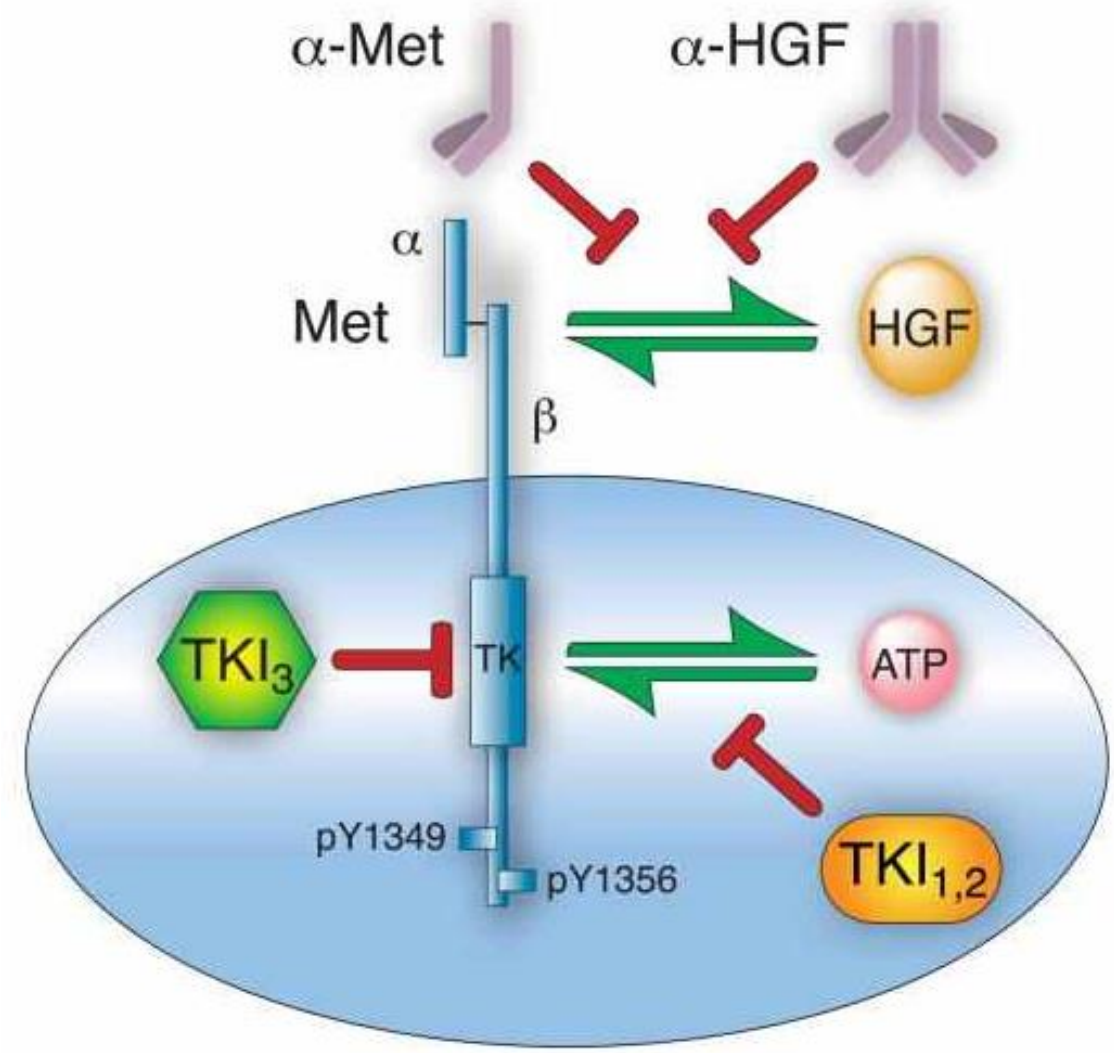


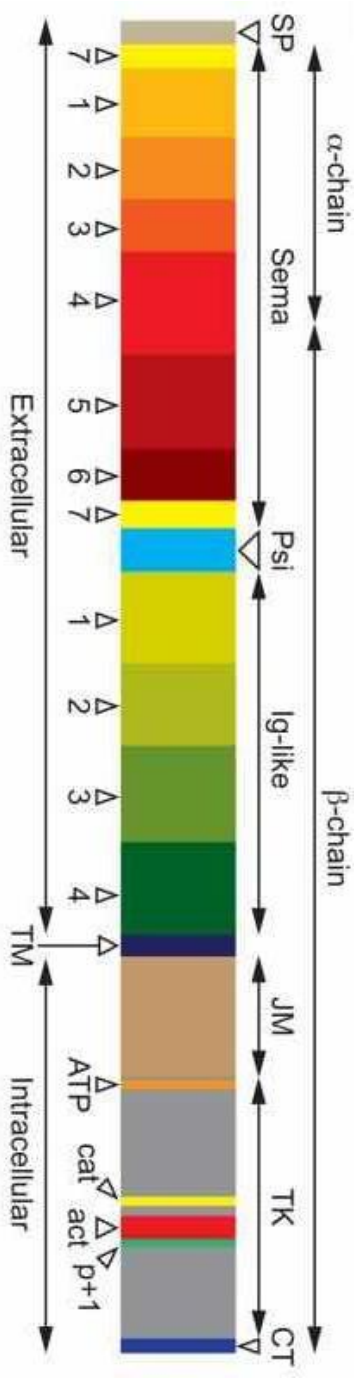
Birchmeier C 2003, Miller CT et al. 2006, WG Jiang et al. 2005

HGF/MET pathway as a mechanism of resistance against VEGF therapies



Kopetz S, et al. *J Clin Oncol*. 2010;28(3):453-459.



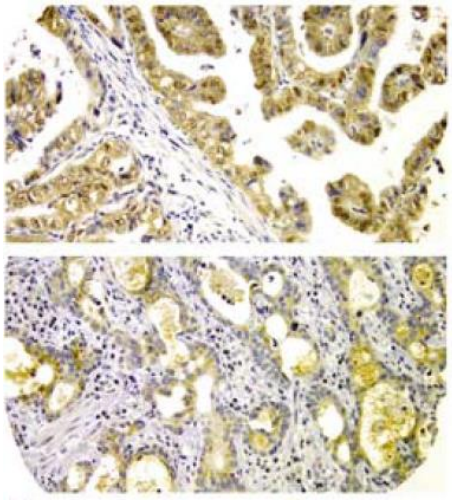


Cecchi F, Rabe DC, Bottaro DP. Expert Opin Ther Targets 2012

MET

C-MET expression (IHC)

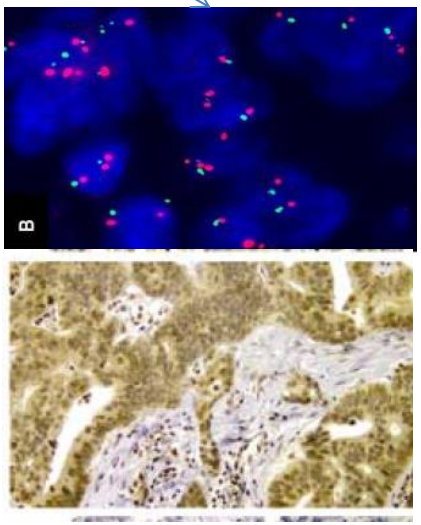
40-60% of patients



Target population for Met antibodies

C-MET gene amplification

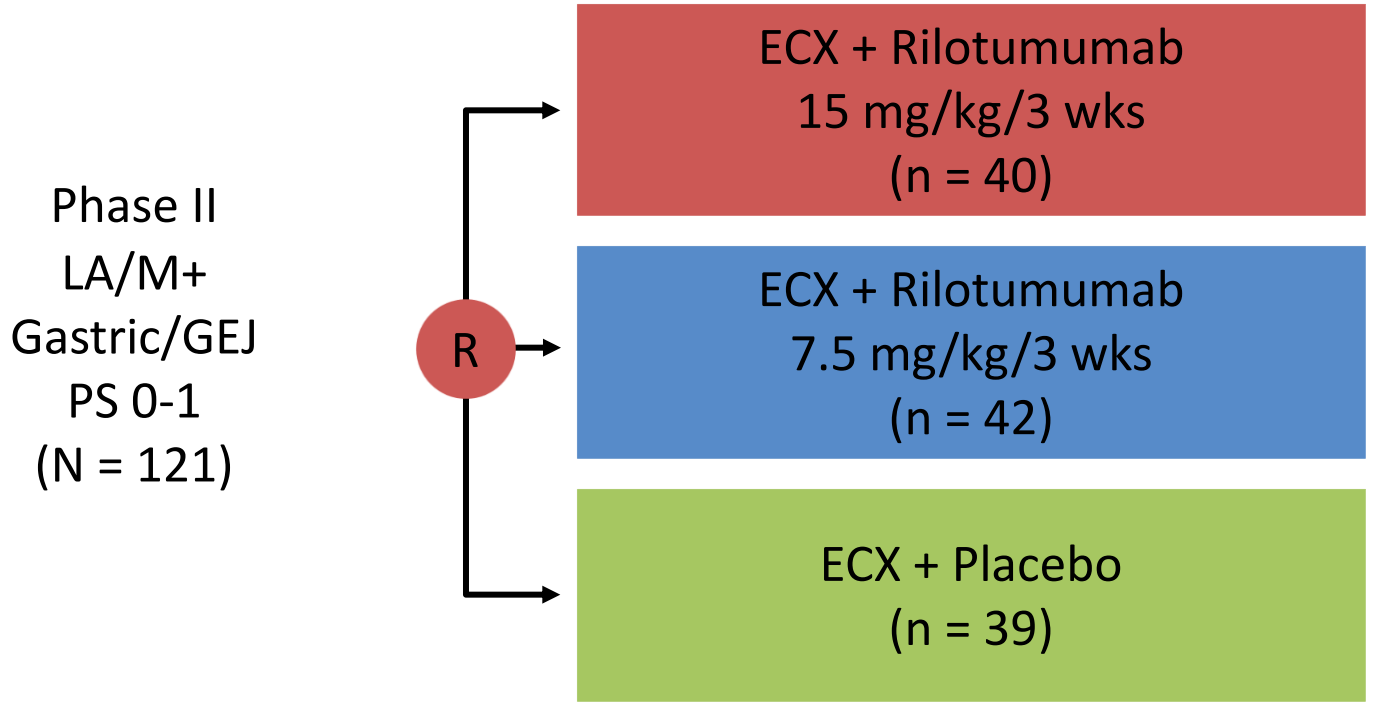
<10% of patients



Target population for Met TKIs

Miller CT et al. 2006; Janjigian et al, 2011; Lennerz et al, 2011; Drebber et al, 2008; Nakajima et al, 1999; Taniguchi et al, 1998; Wu et al, 1998; Amemiya et al, 2002

First-line CT: Rilotumumab

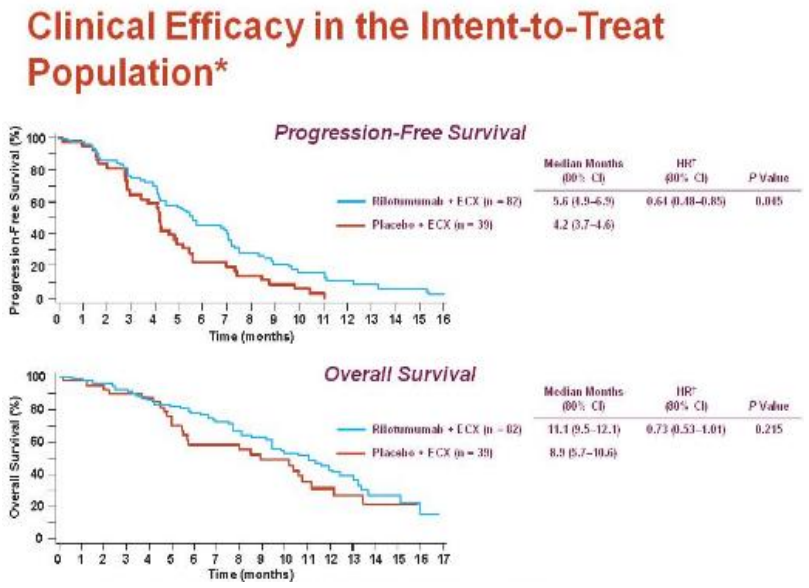


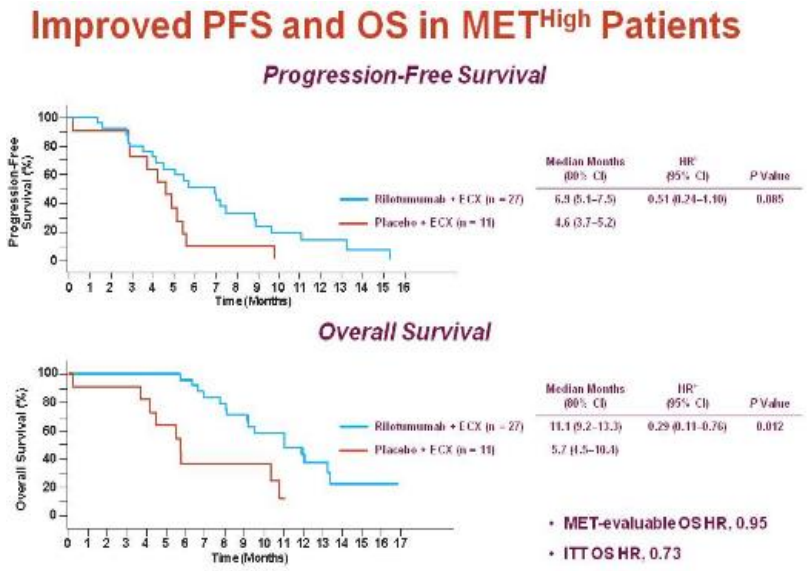
➔ primary endpoint: PFS

➔ secondary endpoints: ORR, OS, toxicity, biomarkers

Iveson T, et al. ESMO 2011. Abstract 6504.

First-line CT: Rilotumumab
PFS and OS by Met expression and in the ITT population





Iveson T, et al. ESMO 2011. Abstract 6504.

First-line CT: Rilotumumab

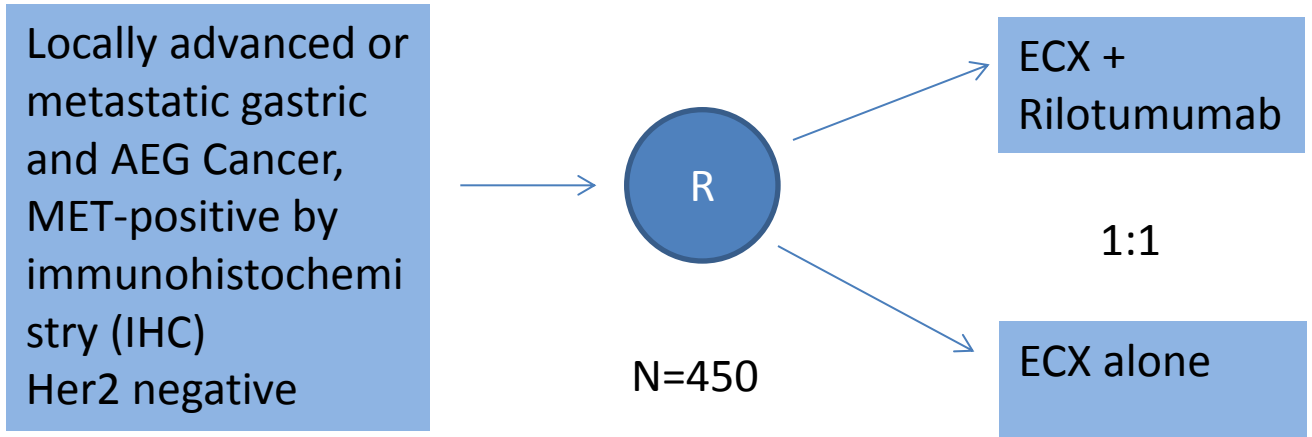
Biomarker population (n = 90)

Median OS by c-MET Status, Mos	ECX + Rilotumumab	ECX + Placebo	HR (95% CI)	P Value
IHC c-Met > 50% tumor cells (n = 38/90)	11.1	5.7	0.29 (0.11-0.76)	.012
IHC c-MET ≤ 50% tumor cells (n = 52/90)	NR	NR	1.84 (0.78-4.34)	NR

- In ECX + placebo arm, high c-Met associated with shorter OS vs low c-Met
  - HR: 3.22 (95% CI: 1.08-9.63)

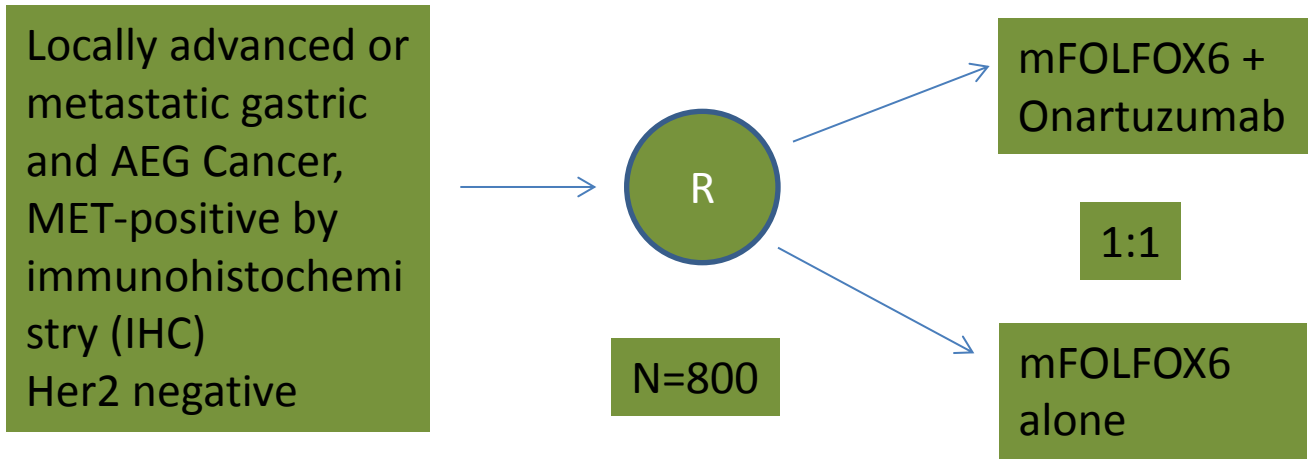
Oliner KS, et al. ASCO 2012. Abstract 4005. Note that these data were available in abstract form only at the time of drafting this slideset and are subject to change at the presentation on June 2, 2012.

RILOMET-1 ClinicalTrials.gov Identifier: NCT01697072



Primary Endpoint: OS

MetGastic ClinicalTrials.gov Identifier: NCT01662869



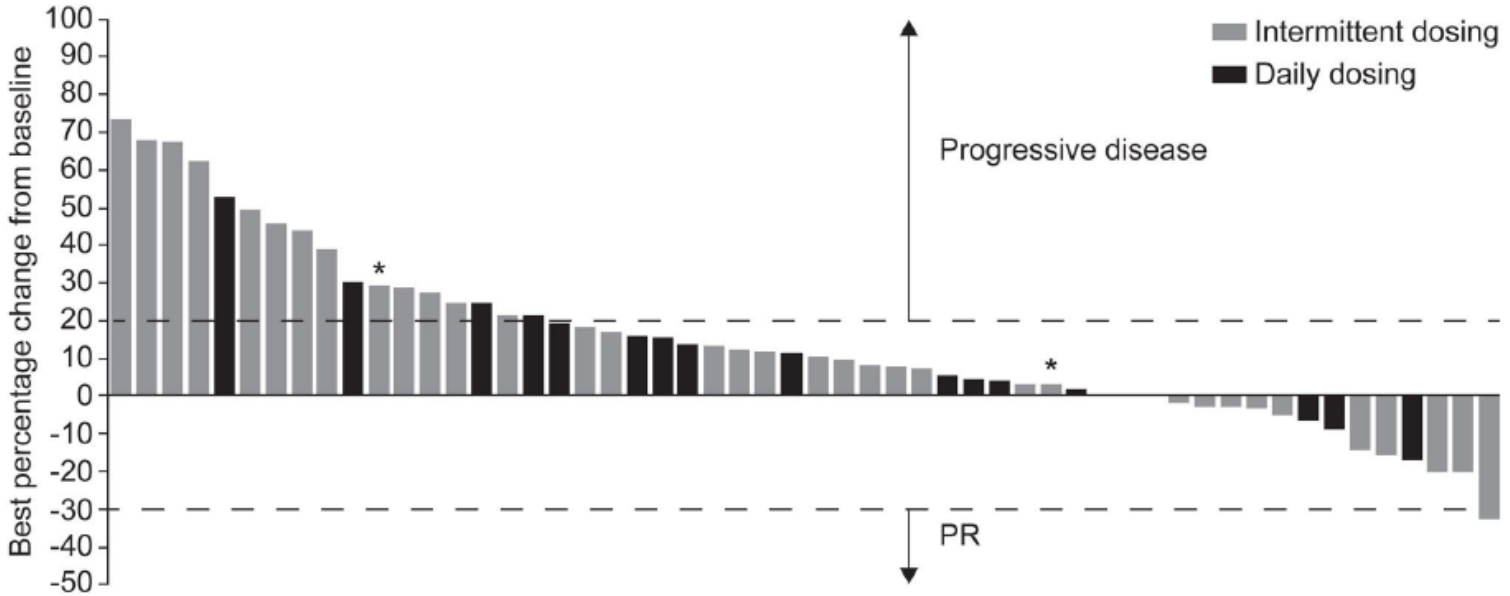
Primary Endpoint: OS in the Met IHC 2+/3+ patient subgroup

OPEN ACCESS Freely available online

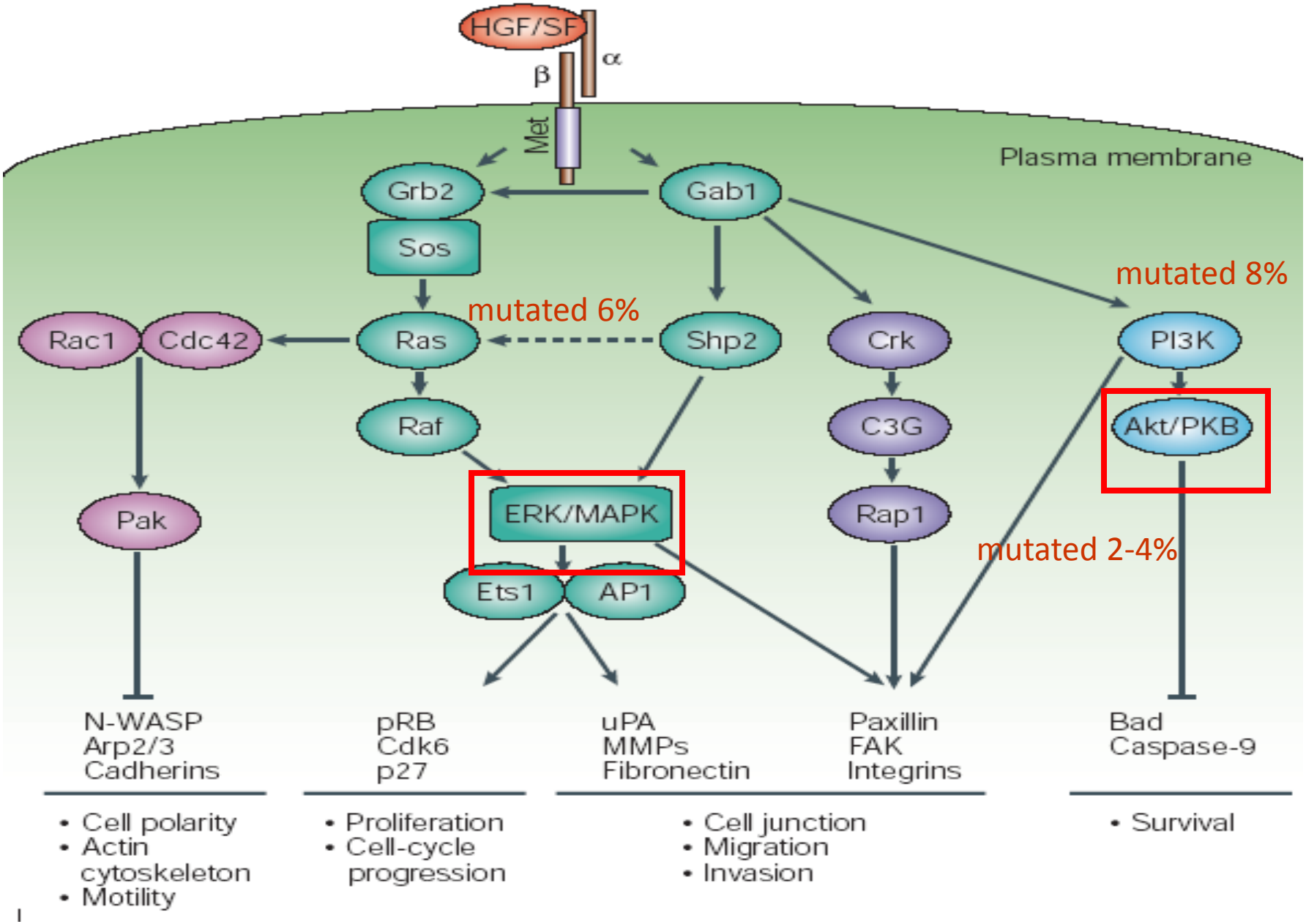
2013 PLOS ONE

Phase II Study Evaluating 2 Dosing Schedules of Oral Foretinib (GSK1363089), cMET/VEGFR2 Inhibitor, in Patients with Metastatic Gastric Cancer

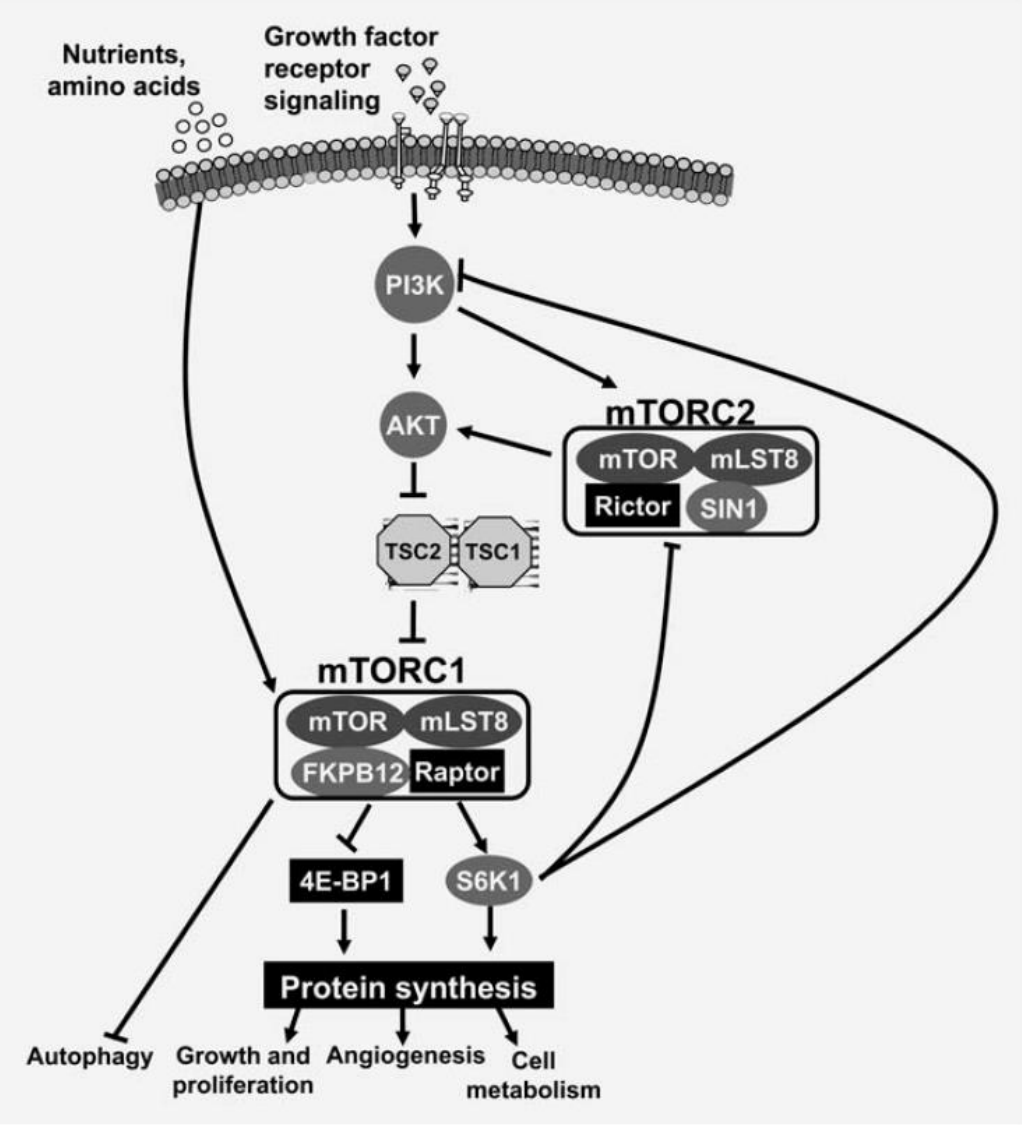
Manish A. Shah[1]*, Zev A. Wainberg[2], Daniel V. T. Catenacci[3], Howard S. Hochster[4], James Ford[5], Pamela Kunz[5], Fa-Chyi Lee[6], Howard Kallender[7], Fabiola Cecchi[8], Daniel C. Rabe[8], Harold Keer[9], Anne-Marie Martin[7], Yuan Liu[7], Robert Gagnon[7], Peter Bonate[10], Li Liu[7], Tona Gilmer[10], Donald P. Bottaro[8]



3 patients had c-MET amplification: 1, had SD (2,1 months); 1 PD, and 1 NE



Birchmeier,C. Nature Reviews. 2003

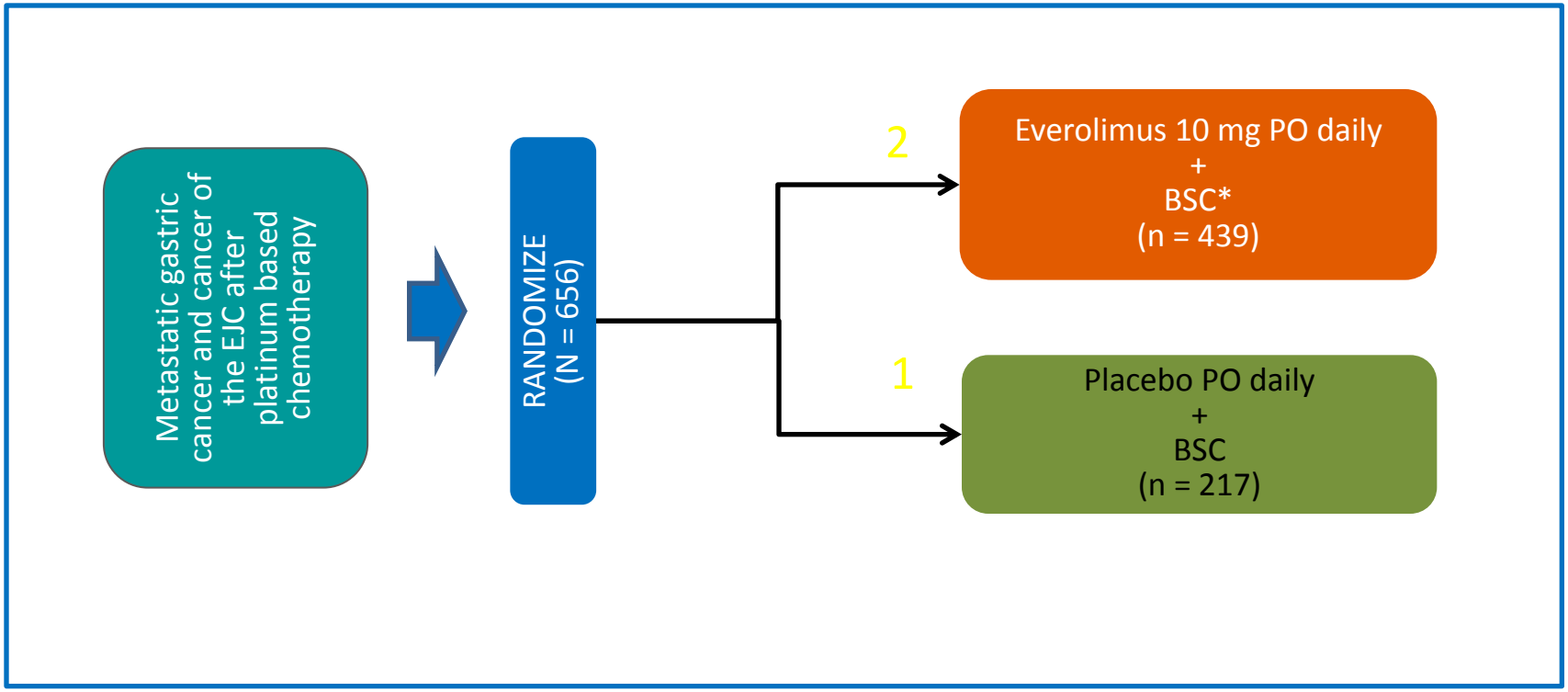


mTOR: aktivation of mTOR or upstream molecules is frequent in gastric cancer

Phase II trials: favourable disease control rates

Al-Batran SE, Ducreux M, Ohtsu. Int J Cancer 2012

Phase 3 GRANITE-1 Study Design



BSC, best supportive care

ClinicalTrials.gov identifier: NCT00879333.

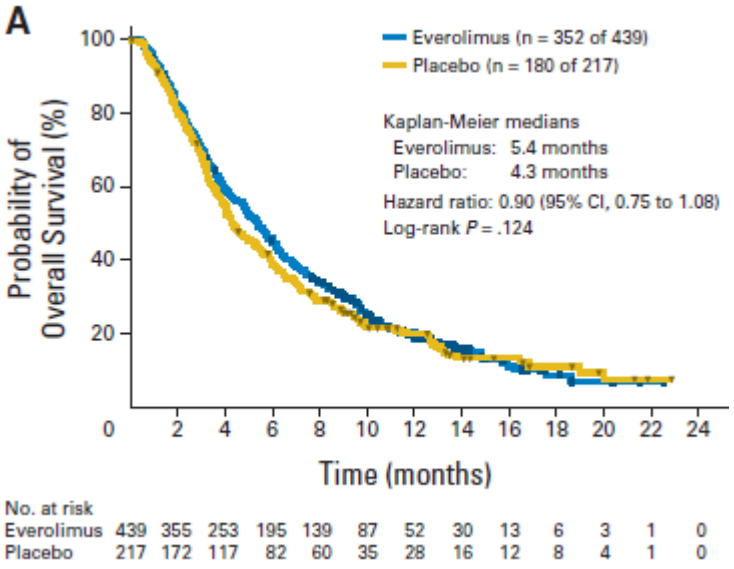
Graph: Van Cutsem et al. ASCO GI 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study

Atsushi Ohtsu, Jaffer A. Ajani, Yu-Xian Bai, Yung-Jue Bang, Hyun-Cheol Chung, Hong-Ming Pan, Tarek Sahmoud, Lin Shen, Kun-Huei Yeh, Keisho Chin, Kei Muro, Yeul Hong Kim, David Ferry, Niall C. Tebbutt, Salah-Eddin Al-Batran, Heind Smith, Chiara Costantini, Syed Rizvi, David Lebwohl, and Eric Van Cutsem



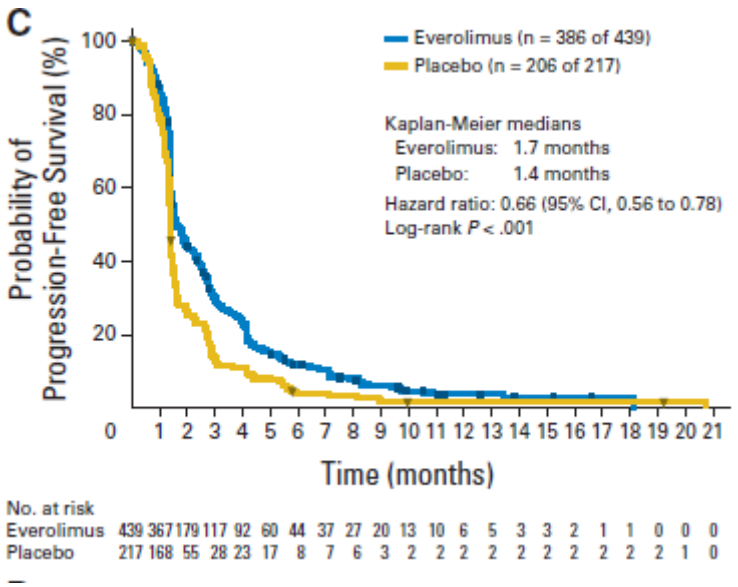


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Table 3. Best Overall Tumor Response According to RECIST for Patients With Measurable Disease

	Everolimus Plus BSC (n = 379)		Placebo Plus BSC (n = 191)	
Response	No. of Patients	%	No. of Patients	%
Best overall response				
CR	1	< 1	0	0
PR	16	4	4	2
SD	147	39	38	20
PD	157	41	119	62
Unknown*	58	15	30	16
ORR (CR and PR)	17	4	4	2
DCR (CR, PR, and SD)	164	43	42	22

Abbreviations: BSC, best supportive care; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Tumor response data not available.

Cancer Medicine

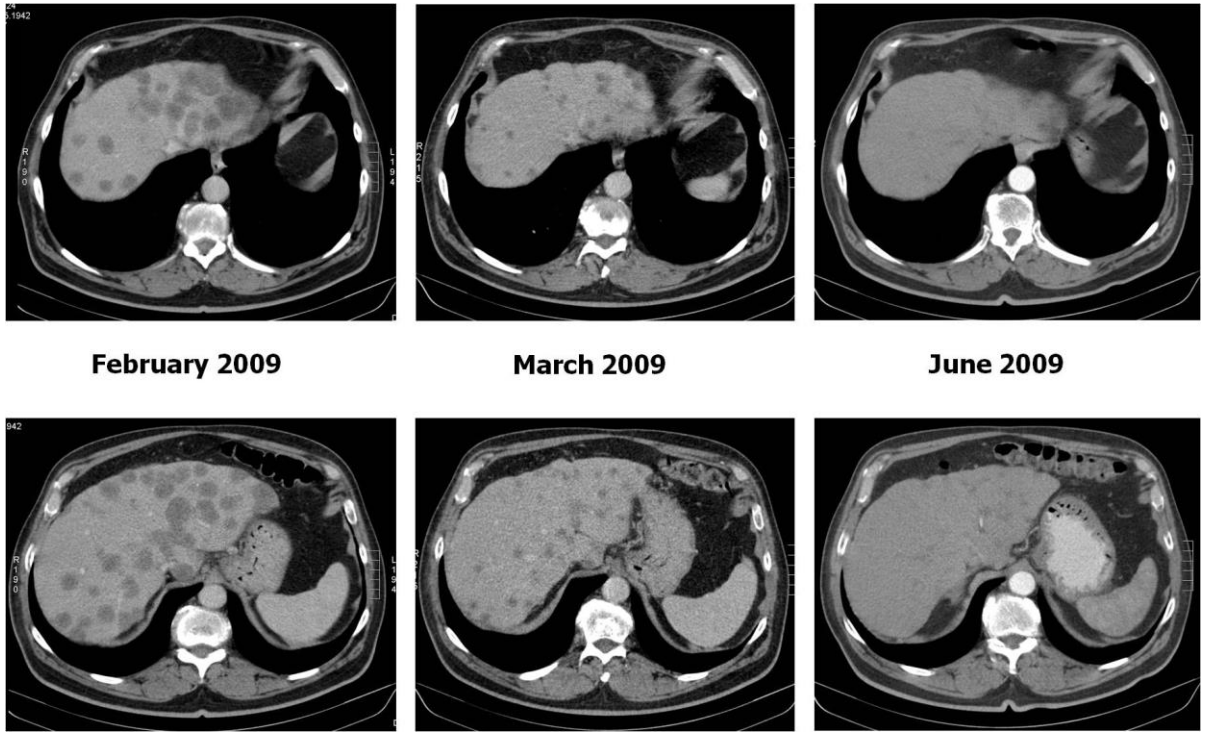
Open Access

ORIGINAL RESEARCH

Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma

Dominique Werner[1]*, Akin Atmaca[1]*, Claudia Pauligk[1], Anette Pustowka[2], Elke Jäger[1] & Salah-Eddin Al-Batran[1]

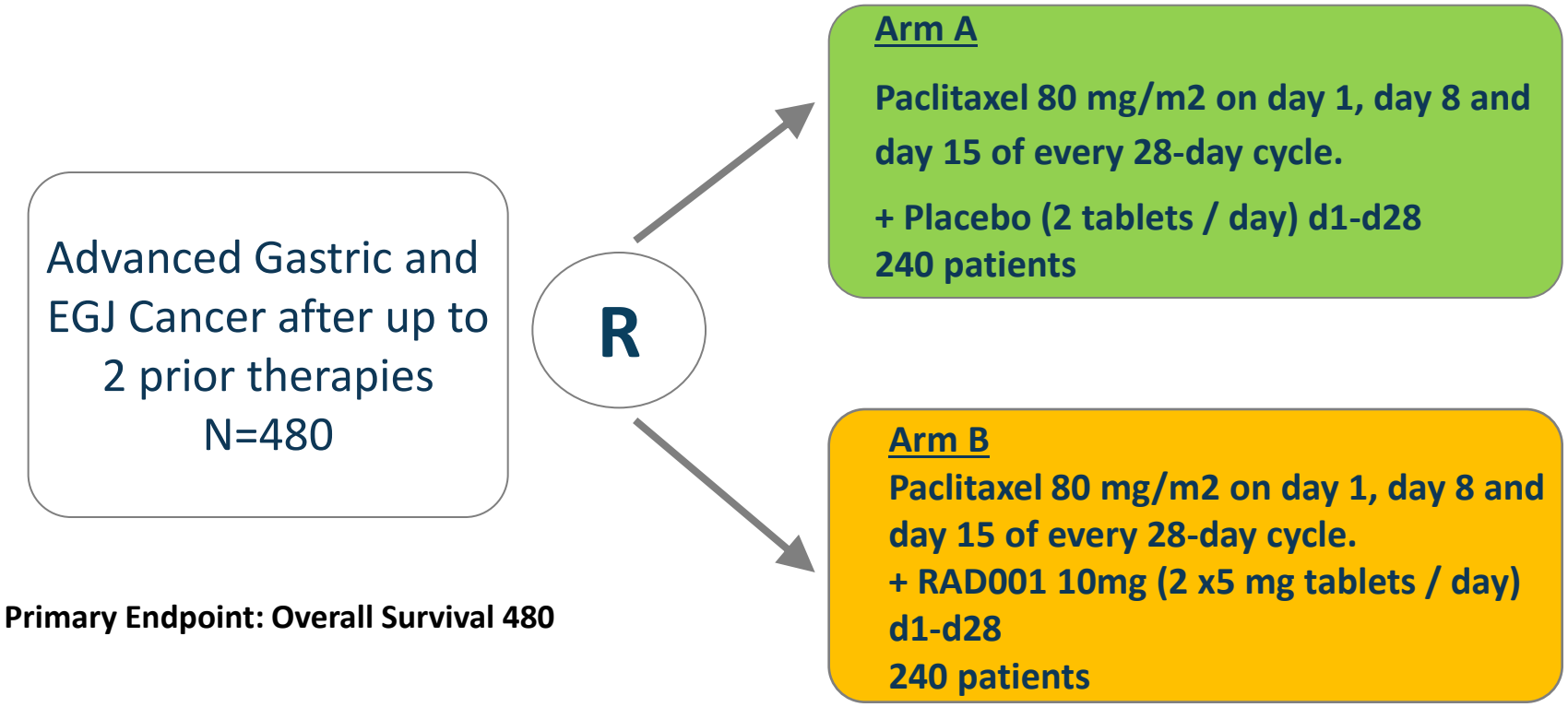
[1]Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt am Main, Germany
[2]Novartis Pharma GmbH, Nürnberg, Germany



February 2009 March 2009 June 2009

Al-Batran et al. Cancer Med. 2013

mTOR: The RADPac Trial (AIO-STO-0111)



Primary Endpoint: Overall Survival 480

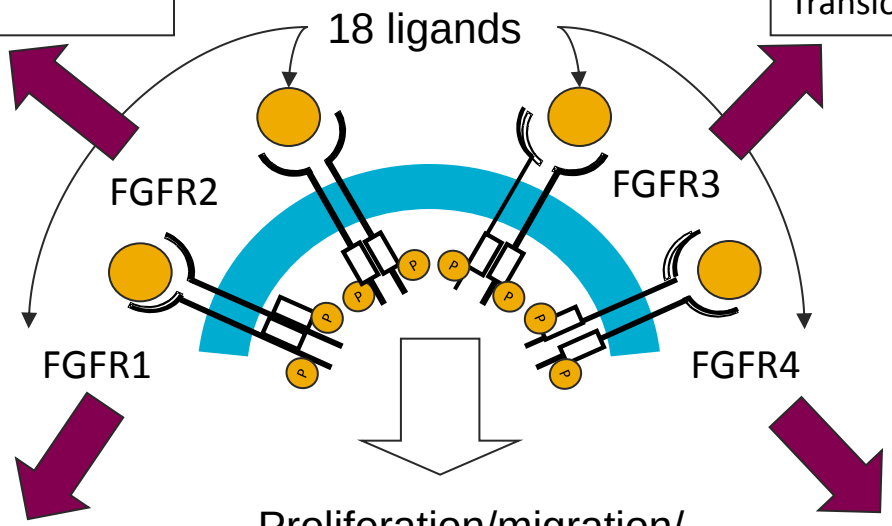
Stratification:
ECOG performance status 0-1 versus 2
prior taxan use yes vs. no
treatment line 2. versus 3. line

Biomarker: Next Generation Sequencing

FGFR

Gastric cancer
Amplification ~5% tumors
Endometrial cancer
Mutations ~15%

Non-invasive bladder cancer
Mutations ~70% tumors
Multiple myeloma
Translocation ~20% tumors



Proliferation/migration/
anti-apoptosis/angiogenesis

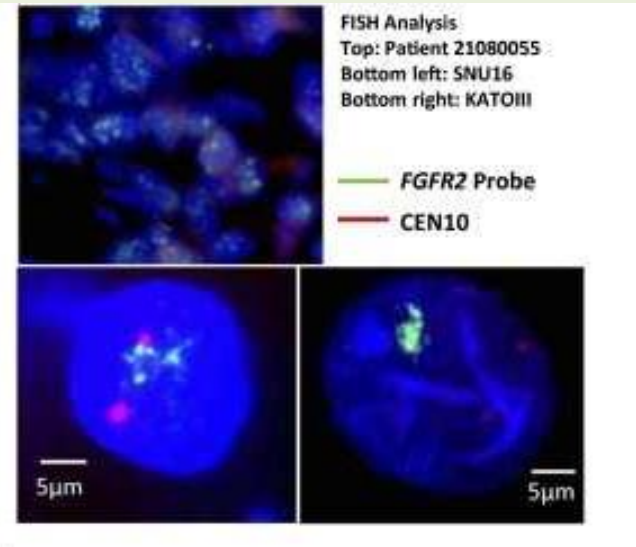
Breast cancer
Amplification ~10% ER +ve
Squamous NSCLC
Amplification ~15 %

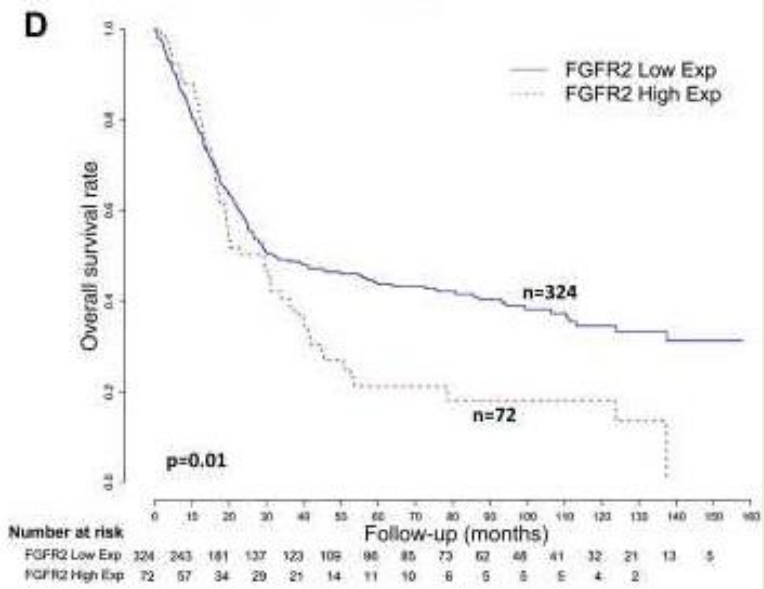
Prostate (FGFR1 and 4)
Up-regulated FGFR4 and FGF ligands

Colorectal and Hepatocellular cancer
Up-regulated FGF19

Brooks .AACR 2011 (Abs DDT01-01)

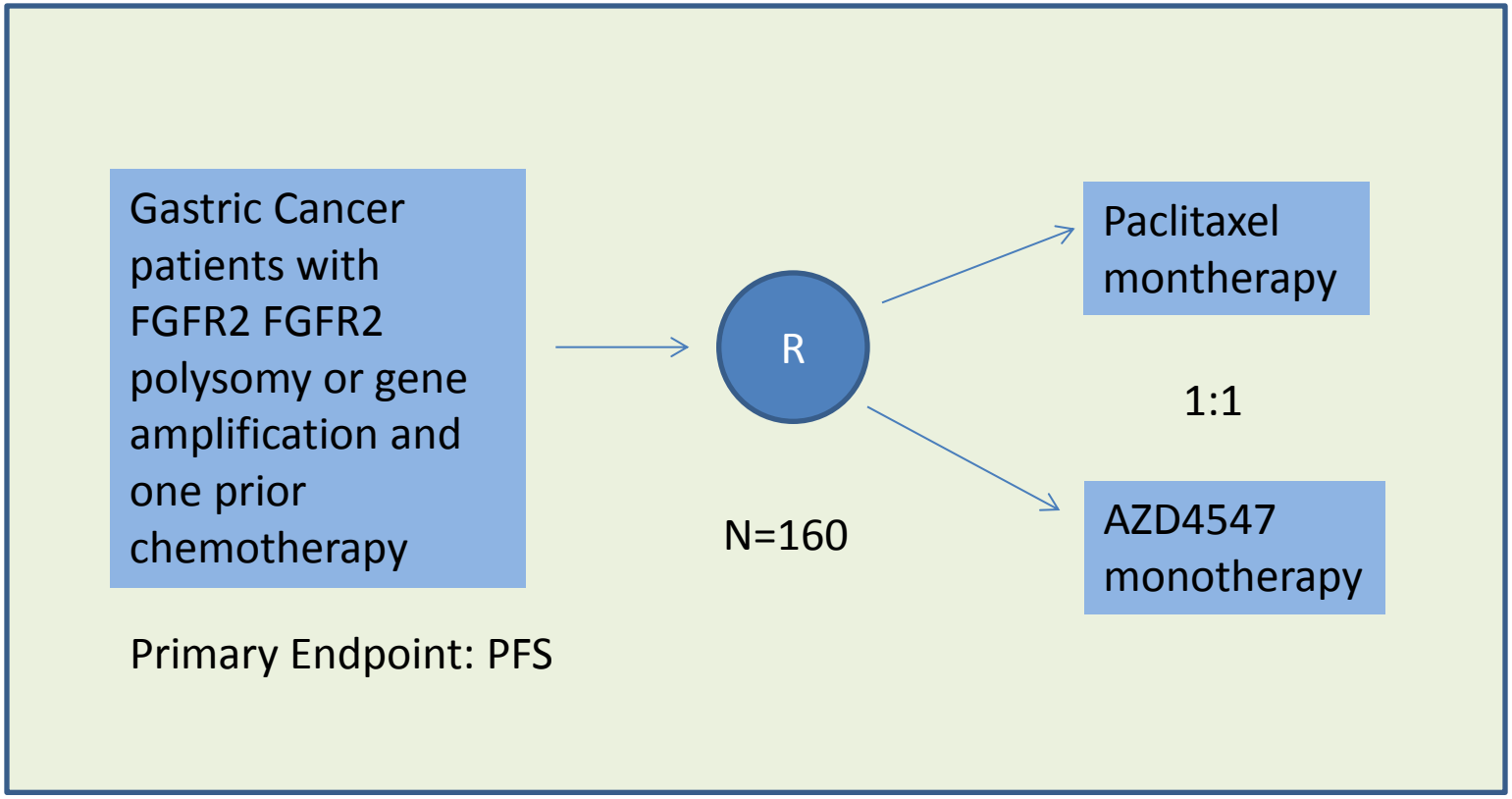
FGFR2 gene amplification in gastric cancer





Deng N et al. Gut. 2012 May; 61(5): 673–684

Safety and Efficacy of AZD4547 Versus Paclitaxel in Advanced Gastric or Gastro-oesophageal Junction Cancer Patients (SHINE)



ClinicalTrials.gov identifier: NCT01457846

Phase I - Emerging Safety and Tolerability Profile of AZD4547

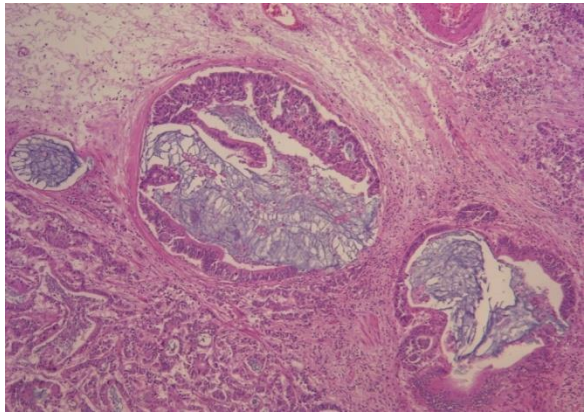
Side effects include:

- Ophthalmological
  Pre-clinical data: Corneal epithelial degeneration and keratitis
  Clinical data:
  - Dry eyes , keratitis but no corneal ulceration
  - Retinal Pigmented Epithelium Detachment (RPED)

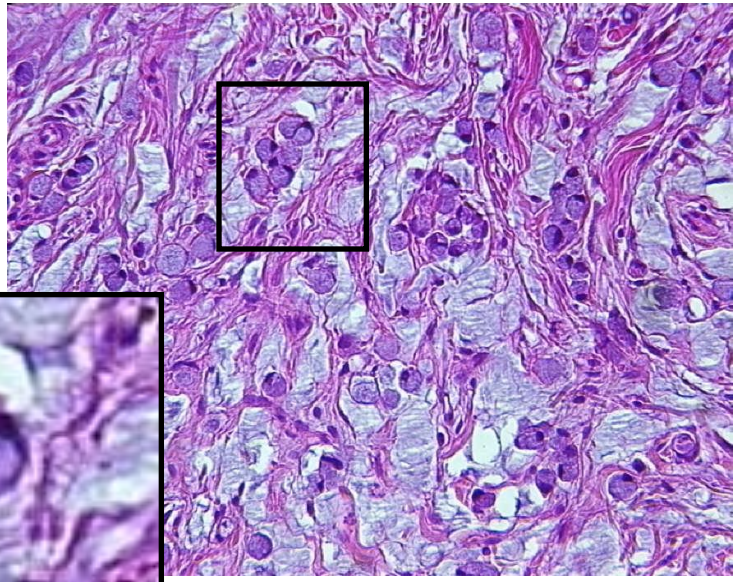
- Keratin-related
  - nail bed changes - brittle nails – onycholysis – nail bed detachment
  - increased hair (at low dose) alopecia (at higher doses)
  - Trichomegaly

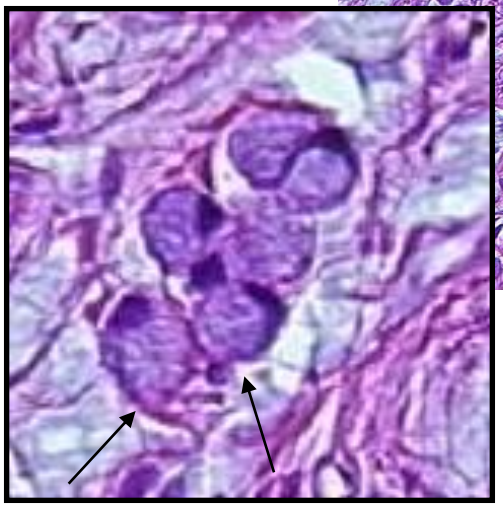
AstraZeneca data on file

The heterogeneity of Gastric Cancer Histology

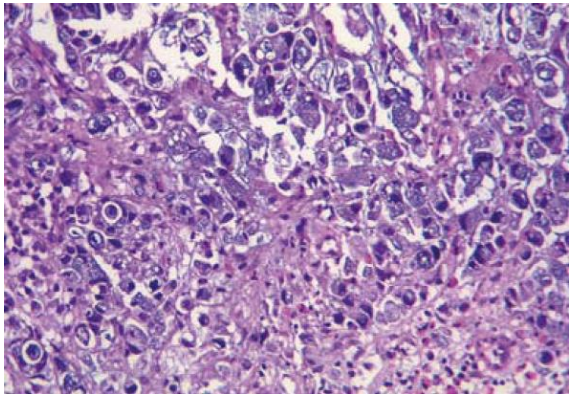


Intestinal Type





Signet Cell Type



Diffuse Type

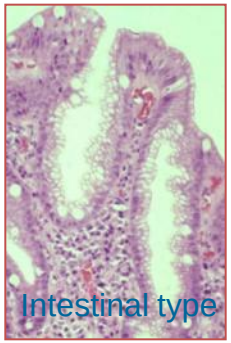
GEJ Adenocarcinoma = Barrett´s Ca

Reflux (GERD) → Barrett´s Metaplasia → Dysplasia → Adenocarcinoma

Accumulation of chromosomal Aberrations

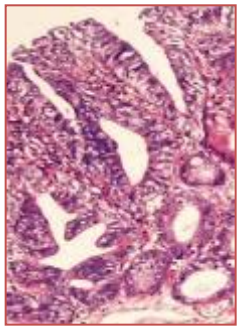
Normal Mucosa

LOH 18q
Telomerase rT ↑



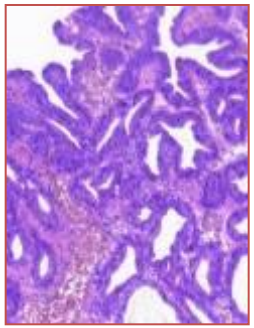
Barrett´s Mucosa

p16 Hypermeth.
DNA Aneuploidy
Polysomy 17
LOH p53



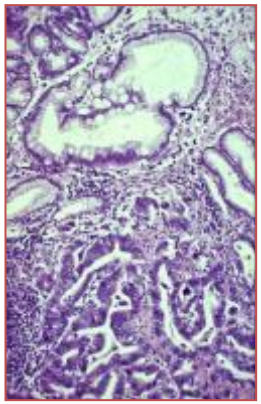
Low-grade IEN

Mutation p53
Cox2 ↑
C-myc ↑
Her2-neu/EGFR/
C-MET ↑



High-grade IEN

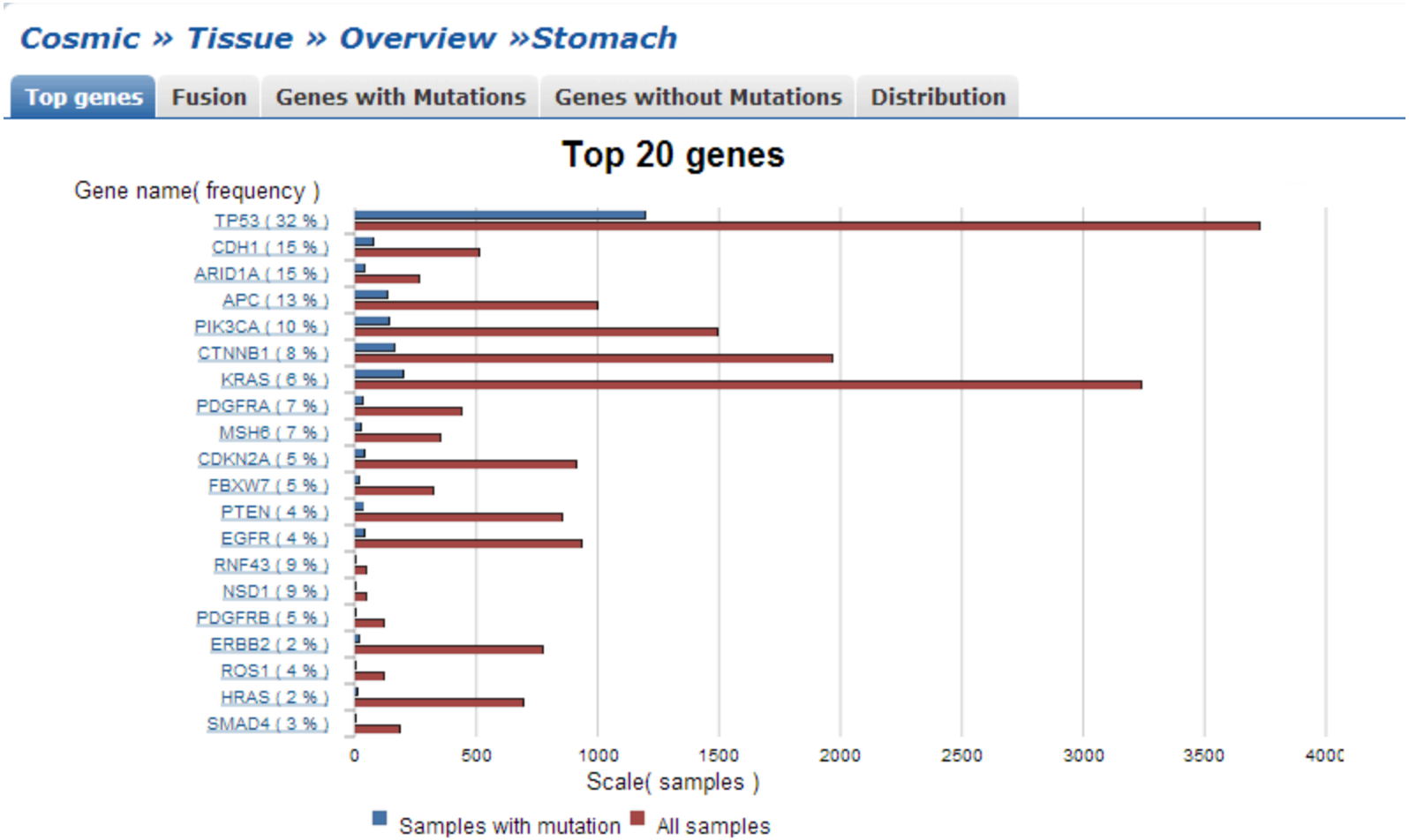
Loss of E-cad



Adeno-carcinoma

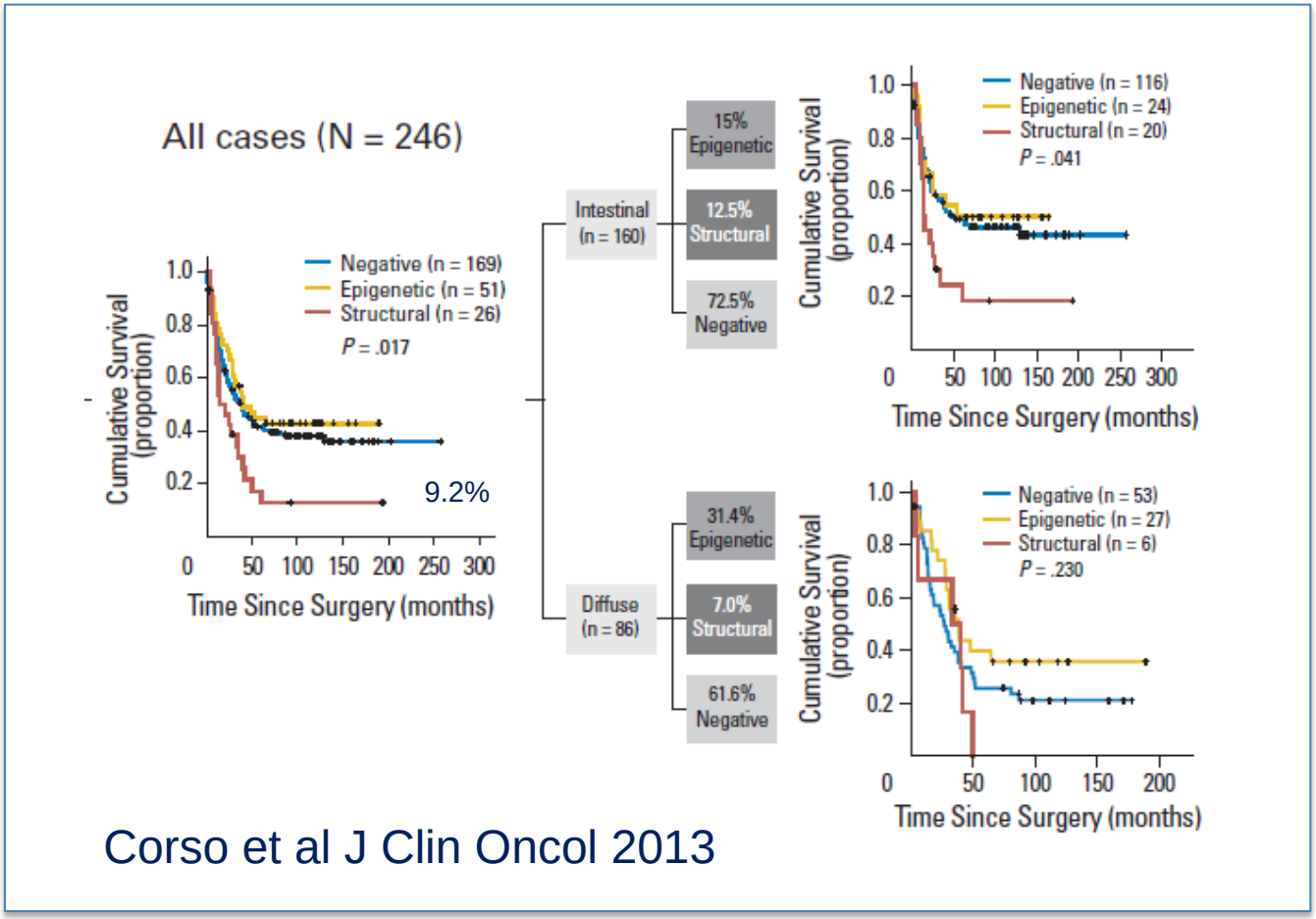
(Courtesy: Prof. Baretton, Dresden)
(Barretton u. Aust, Pathologe 2012)

Gene alternations in Gastric Cancer



Cosmic data base 2013

Somatic CDH1 mutations are prognostic for gastric cancer



Corso et al J Clin Oncol 2013

Thank you very much!