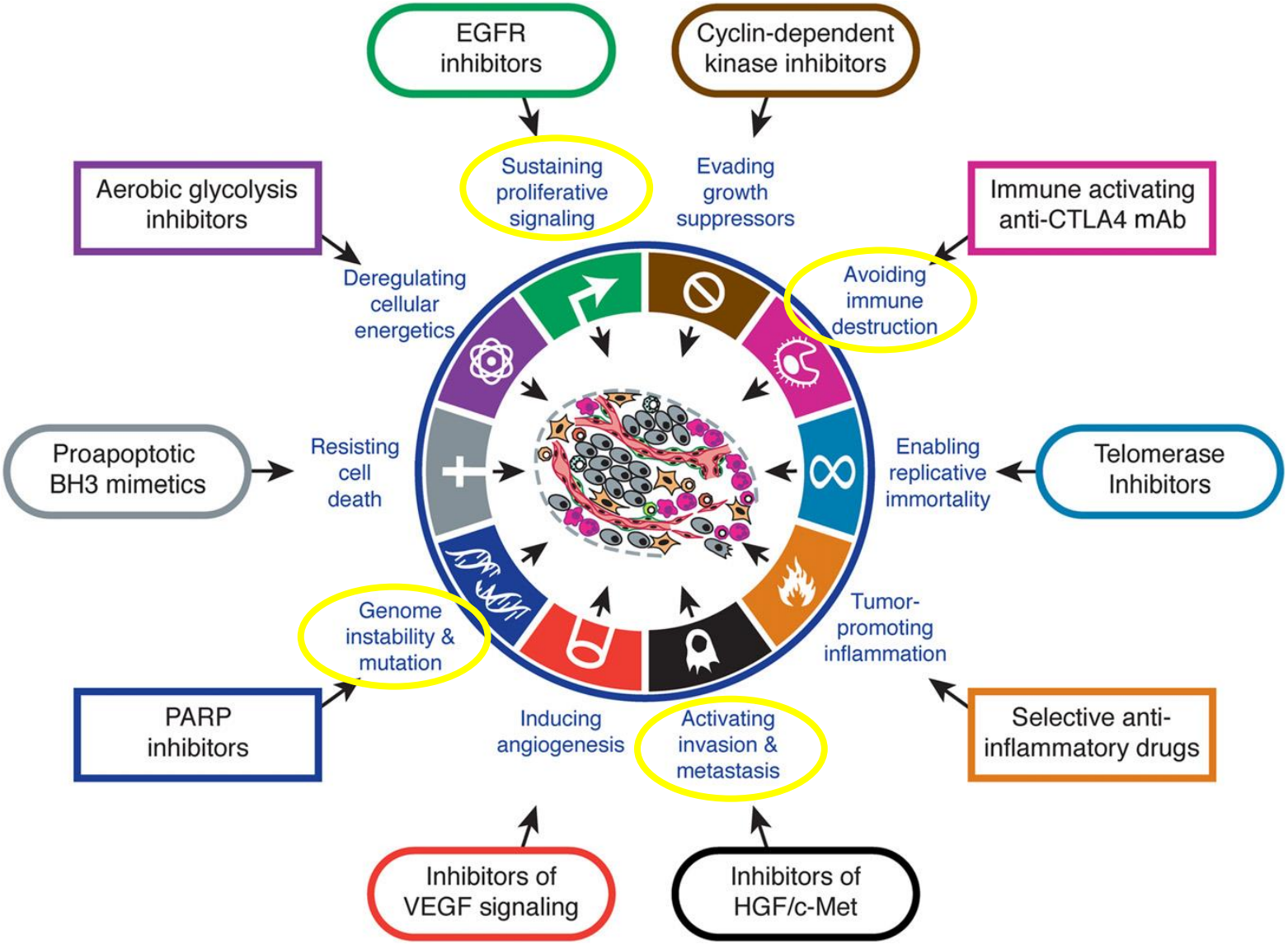
Signal transduction inhibitors and pipeline drugs

Josep Tabernero MD PhD
Vall d'Hebron University Hospital
Barcelona, Spain

Advances in precision medicine of metastatic colorectal cancer
ESMO 2014, Madrid, September 28th, 2014

Acquired capacities of cancer: phenotype



Hanahan & Weinberg, Cell 144, 2011

Beyond EGFR inhibition

- More efficient anti-EGFR MoAbs
- MoAbs directed to other members of the EGFR/HER family
- MoAbs directed to other receptors
- Combination with downstream effector inhibitors

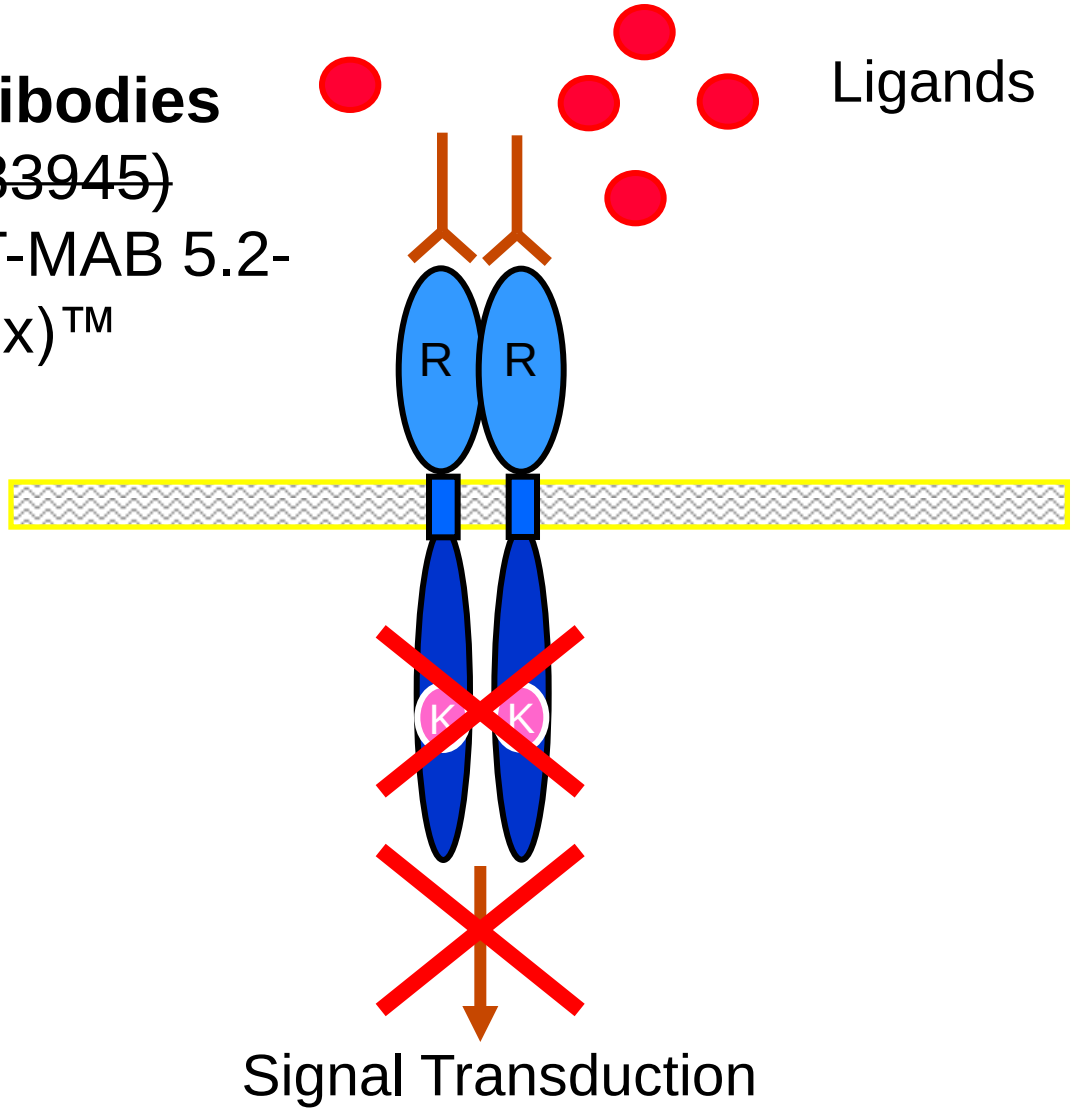
New EGFR Inhibitors

Monoclonal Antibodies

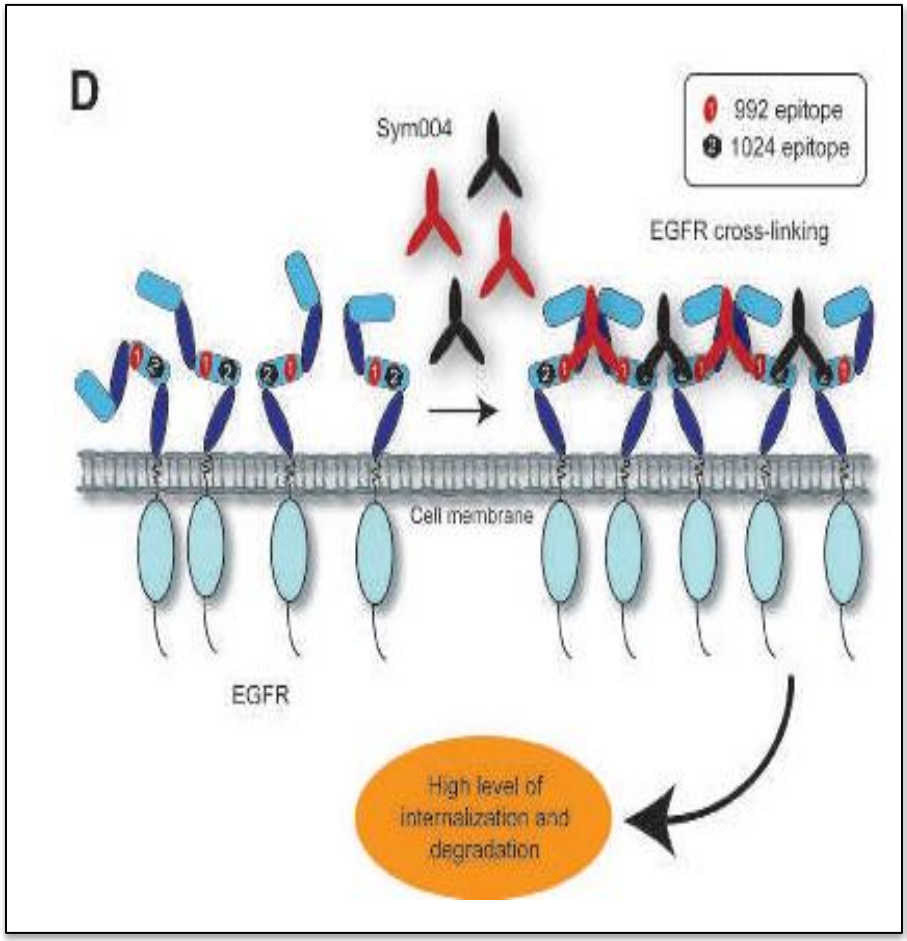
~~GA201 (RO5083945)~~

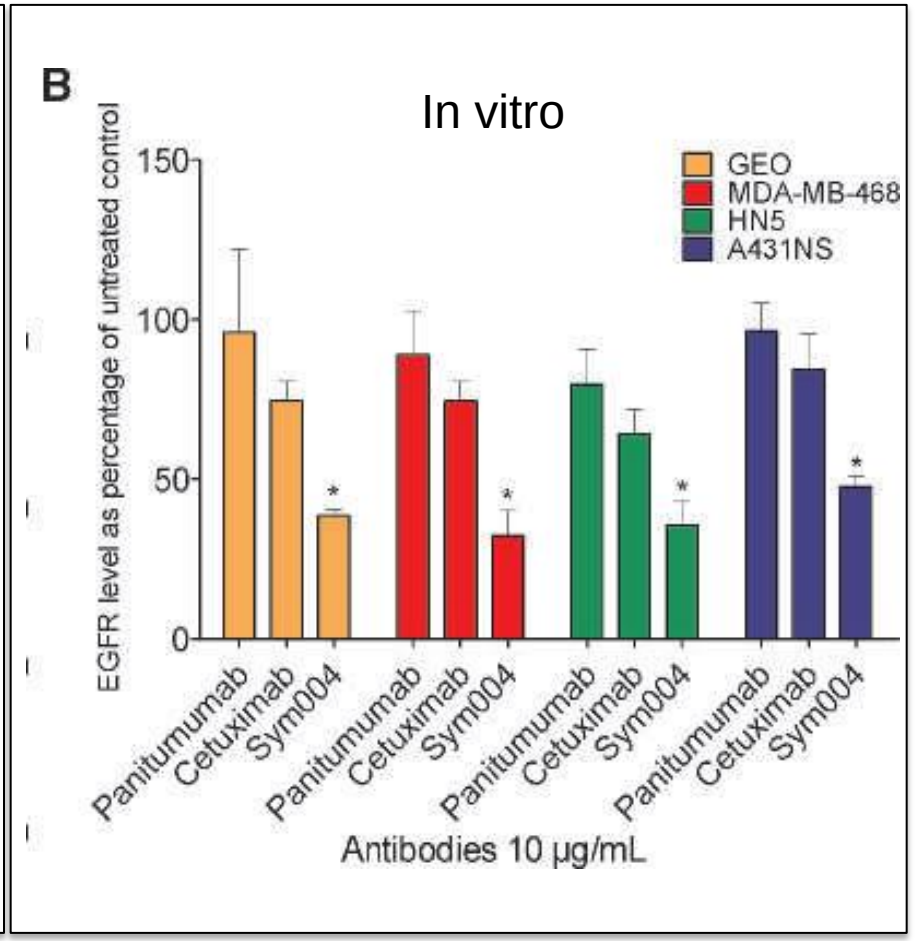
GlycoOptimized GT-MAB 5.2-GEX (Cetugex)™

Sym004



Sym004: A novel synergistic anti-EGFR Ab mixture





Pedersen MW et al, Cancer Res 2010;70:588-97
Skartved NJ et al, Clin Cancer Res 2011;17:5962-72

Sym004: A novel synergistic anti-EGFR Ab mixture

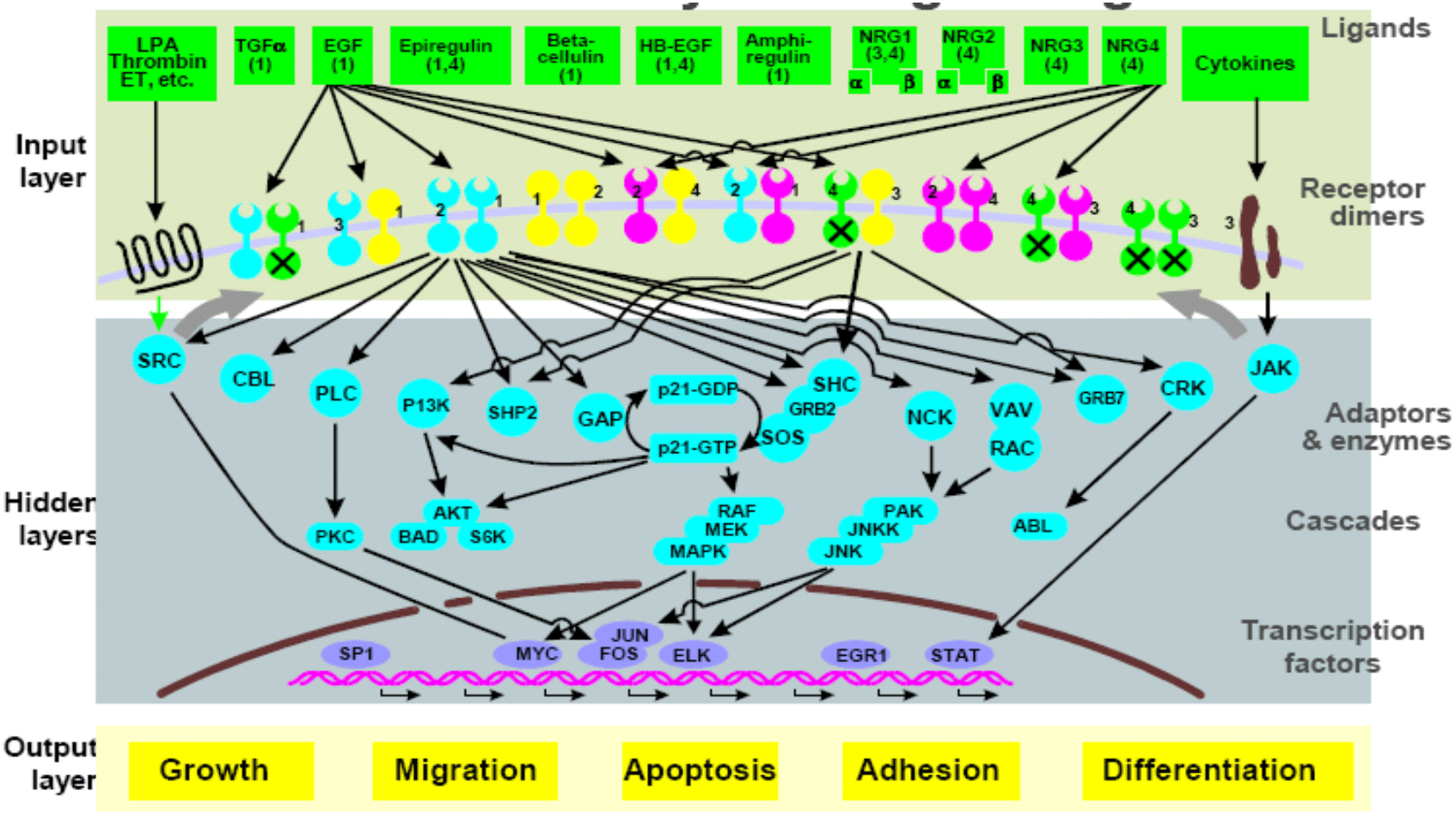
- Phase I study in advanced solid tumors (NCT01117428): ongoing
  - Enrichment with patients with colorectal cancer
  - Cohort of patients refractory to anti-EGFR MoAbs
- Randomized phase II study in refractory KRAS wt colorectal cancer launched (NCT02083653)

Dienstmann R et al. Proc ASCO 2011

Beyond EGFR inhibition

- More efficient anti-EGFR MoAbs
- MoAbs directed to other members of the EGFR/HER family
- MoAbs directed to other receptors
- Combination with downstream effector inhibitors

EGFR & HER-3
EGFR & HER-2



Yarden & Sliwkowski. Nature Rev Mol Cell Biol 2001

HER-3 and colon cancer

- HER3 has been associated with tumor resistance to therapeutic agents targeting EGFR or HER2 in NSCLC and breast cancer[1]
- HER3 is occasionally mutated in CCR, but increased HER3 mRNA or protein is commonly detected[2,3]
- ERBB3 has been identified as a potential therapeutic target in breast cancer and NSCLC, and currently its potential role as a potential mechanism of resistance of EGFR inhibitors is being evaluated[1,4]

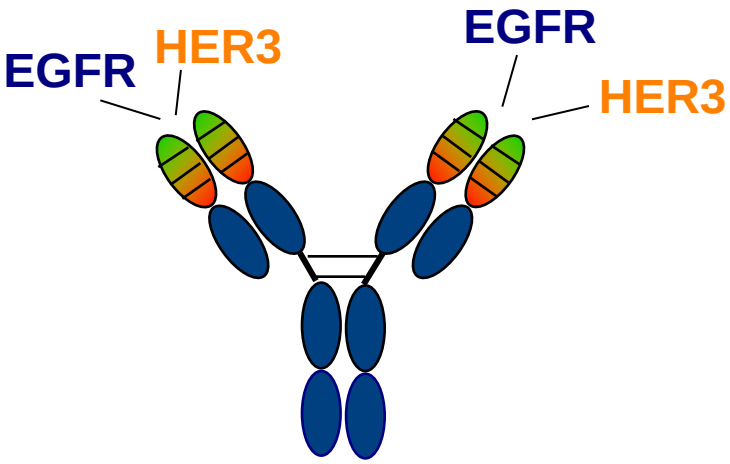
[1]Baselga & Swain, Nature Rev Cancer 2009
[2]Hu et al, J Biol Chem 2005
[3]Kountourakis Pet al, BMC Cancer 2006
[4]Kruser et al, ExpCell Res 2010

MoAbs targeting HER-3

- U3-1287 - AMG888 (phase I NCT00730470)
- MM-121 (phase I NCT00734305)
- LJM716 (phase I NCT01598077)
- MEHD7945A, dual EGFR & HER3 MoAb (phase I NCT01207323, RP2 NCT01652482)

MEHD7945A (dual EGFR & HER-3 MoAb)

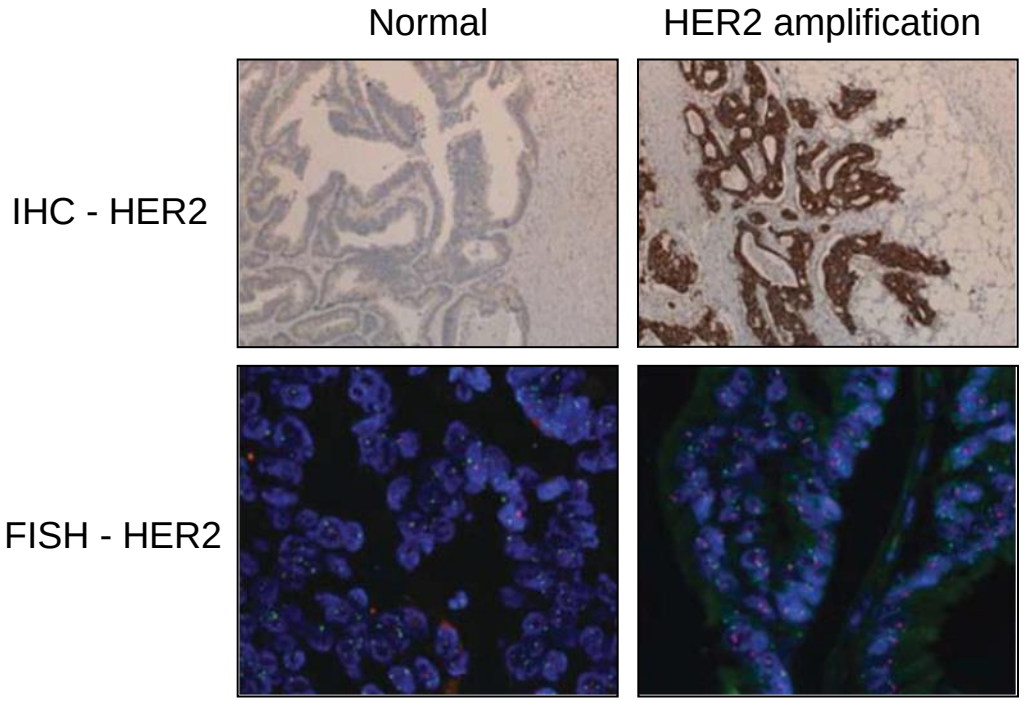
- IgG1 MoAb
- Blocks ligand binding to HER3 and EGFR and downstream signaling
  - Kd (hu HER3) = 0.39 nM
  - Kd (hu EGFR) = 1.9 nM
- Shows broader activity *in vitro* and *in vivo* compared to monospecific antibodies
- Shows significant activity in colon, lung, pancreatic, HNSCC, breast and ovarian xenograft models
- Clinical data reported at ASCO 2012
- 2nd-line mCRC: FOLFIRI + MEHD7945A vs FOLFIRI + Cetuximab (NCT01652482)



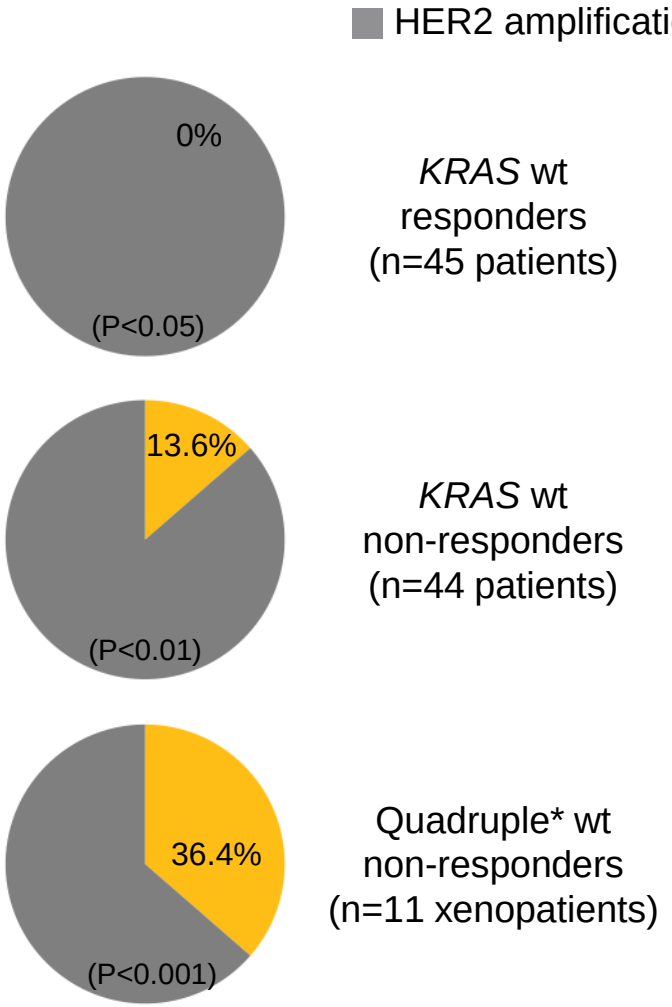
MEHD7945A

Kamath AV et al, Cancer Chemother Pharmacol 2012
Schaefer G et al. Cancer Cell 2011
Cervantes A et al; Hidalgo M et al. Proc ASCO 2012

Correlation between HER2 amplification and therapeutic resistance to cetuximab in xenopatients



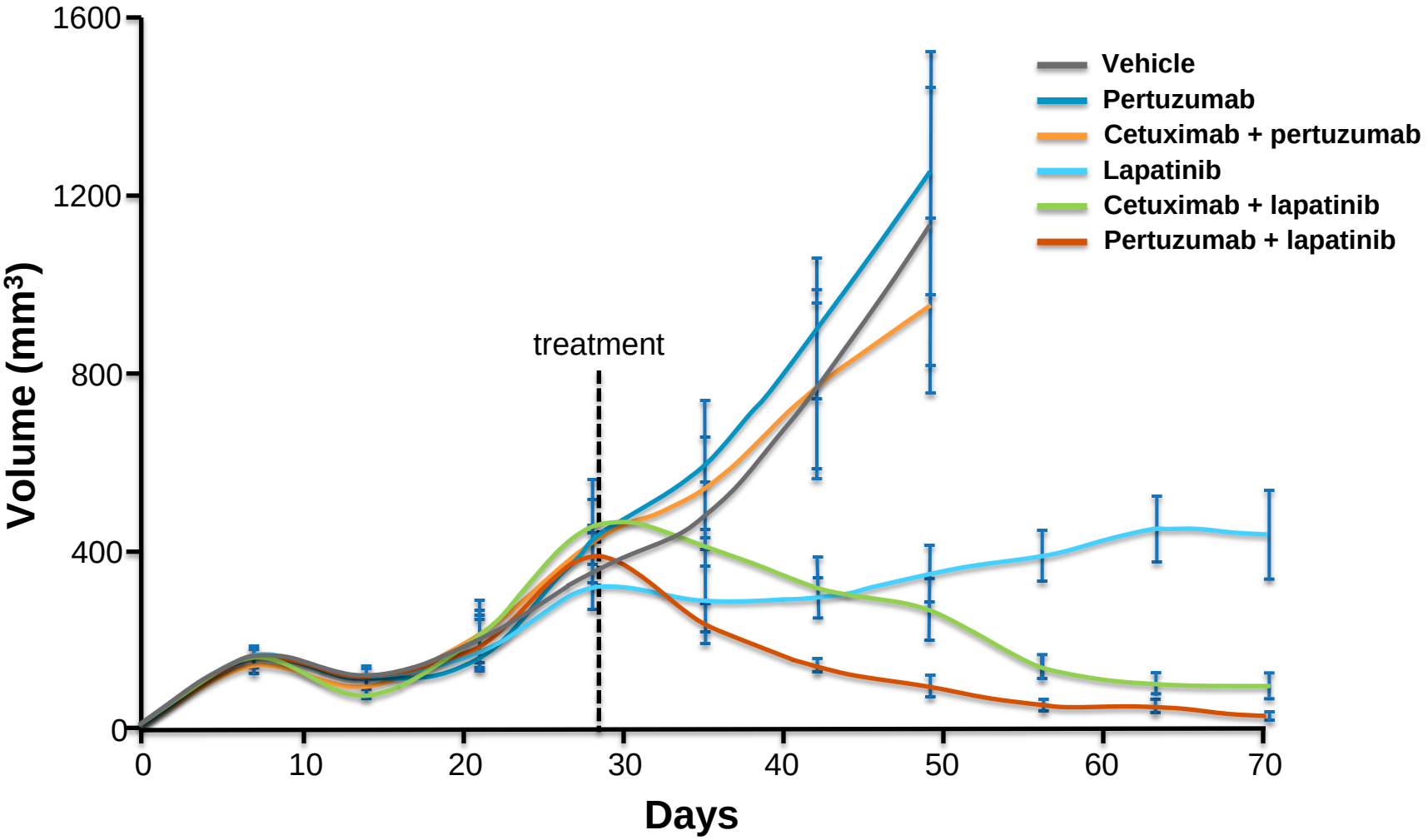
In mCRC patients there is a progressive enrichment of HER2 amplification along with refinement of genetic selection



* *KRAS/NRAS/BRAF/PIK3CA

Bertotti A et al. Cancer Discov 2011;1:508-23

Anti-EGFR and anti-HER2 therapies in cetuximab-resistant HER2-amplified xenopatients with mCRC



Bertotti et al. Cancer Discovery 2011

Clinical anti-HER-2 strategies in mCRC

- Limited patient population: HER2 amplification (5%) was associated with resistance to cetuximab (Yonesaka et al, Sci Transl Med 2011)

HERACLES study

Single arm, Phase II, multi-center, sequential trial designed to assess the ORR in an HER2 amplification-enriched population of mCRC patients receiving, in two separate and consecutive cohorts:

- Cohort 1 trastuzumab + lapatinib
- Cohort 2 trastuzumab + pertuzumab

PI: S. Siena, Italy

MCLA-128

MCLA-128 is a human bispecific IgG1 antibody that simultaneously targets HER2 and HER3 receptors

- In phase I with expansion cohorts in mCRC Her-2 +

Beyond EGFR inhibition

- More efficient anti-EGFR MoAbs
- MoAbs directed to other members of the EGFR/HER family
- MoAbs directed to other receptors
- Combination with downstream effector inhibitors

c-Met and HGF

- Oncogene implicated in:
  - Tumor invasiveness, metastasis and proliferation
  - Angiogenesis
  - Resistance to treatment
  - c-Met is a high affinity tyrosine kinase receptor for the HGF/SF
- Activation occurs through both autocrine and paracrine signaling (HGF)
- c-Met overexpression or mutation/amplification found in many tumors

	Primary Tumor		
Tumor Type	MET Expression (% patients)	MET Mutation (% patients)	MET Amplification (% patients)
Brain	54-88	0-9	9-20
Head & Neck	52-68	11-27	n/a
Mesothelioma	74-100	0	n/a
Lung	41-72	8-13	0
Thyroid	40-91	6-10	n/a
Breast	25-60	0	n/a
Renal Cell	54-87	13-100	(Trisomy 7)
Hepatoma	68-69	0-30	n/a
Colon	55-78	0	4-89
Cervical	30-72	0	n/a
Ovarian	64	0-4	0
Sarcoma	20-87	0-3	n/a
Melanoma	17-39	0	n/a
Multiple Myeloma	48-80	n/a	n/a
Gastric	75-90	n/a	10-20

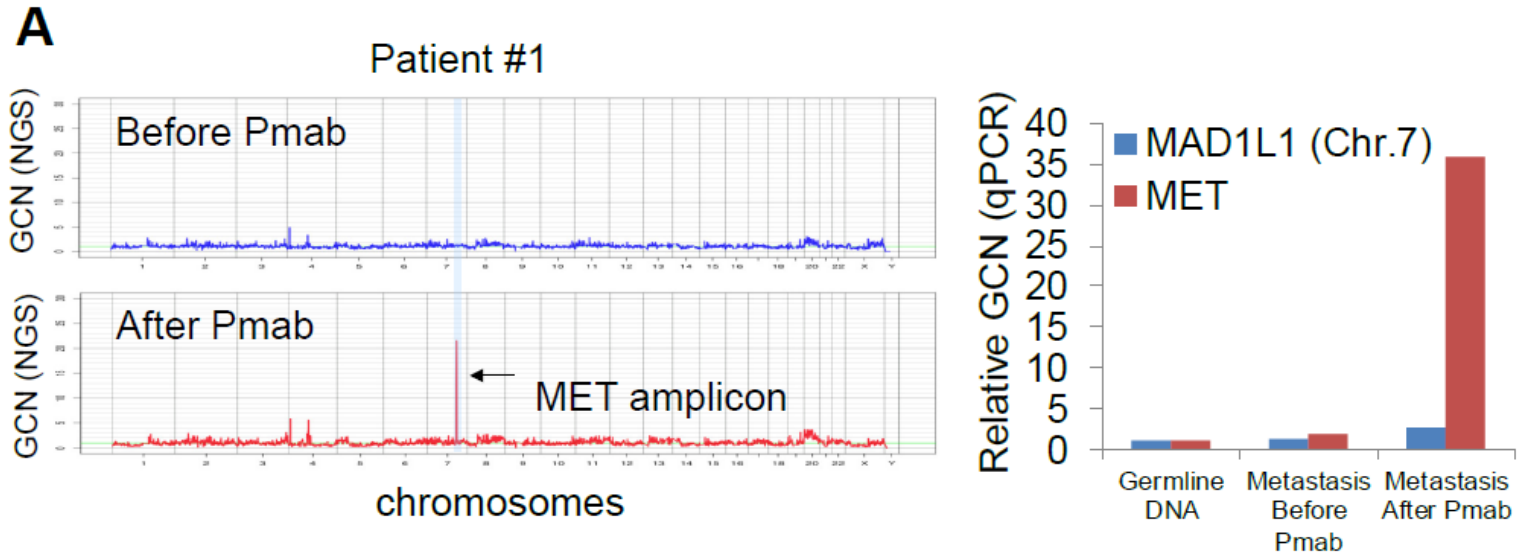
Salgia R. Semin Oncol 2009

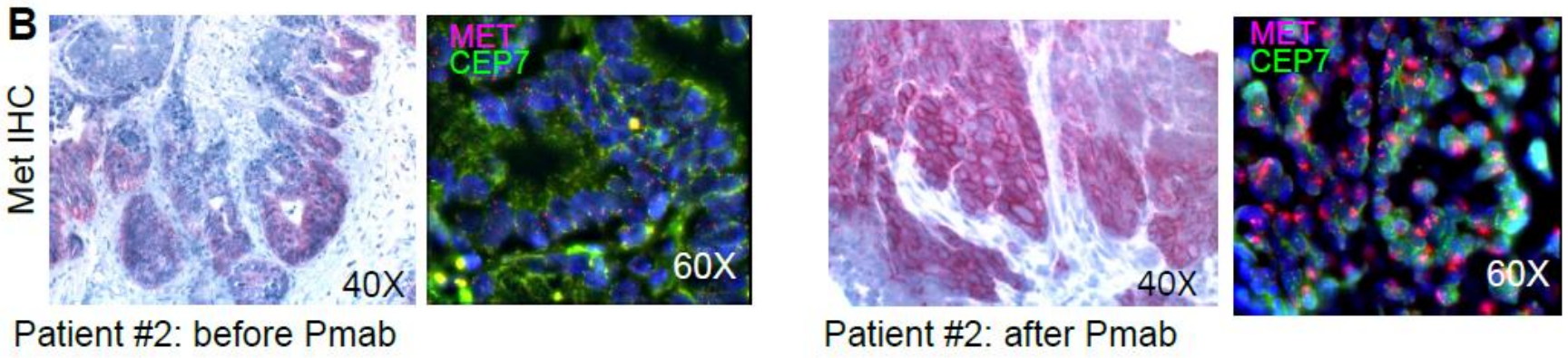
c-Met and colon cancer

- c-Met activation by HGF plays an important role in metastatic growth of colon tumor cells in the liver and cooperates with *KRAS* mutation to enhance tumorigenicity of CRC cells[1]
- The expression of the c-Met receptor and the ligand HGF has been correlated with advanced stage and poor survival in colon cancer[2]
- Amplification of c-Met receptor has been clinically demonstrated as one of the mechanisms of secondary resistance to EGFR inhibitors[3]
- Unselected population: inactive strategy
- Demonstration of dependency is cumbersome: amplification vs mutation vs (over)expression

[1]Seiden-Long et al. Oncogene 2006
[2]Kammula et al. Cancer Lett 2007
[3]Bardelli et al. Cancer Discov 2013

c-Met amplification and secondary resistance to Anti-EGFR treatments





Bardelli. *et al.* Cancer Discov 2013

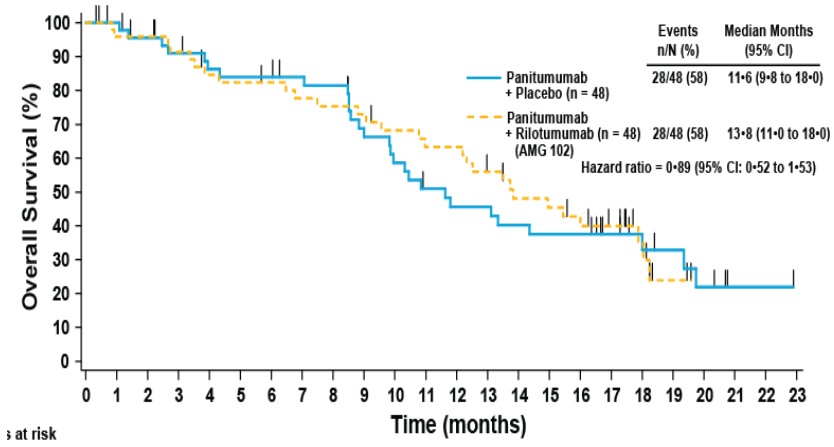
c-Met and colon cancer

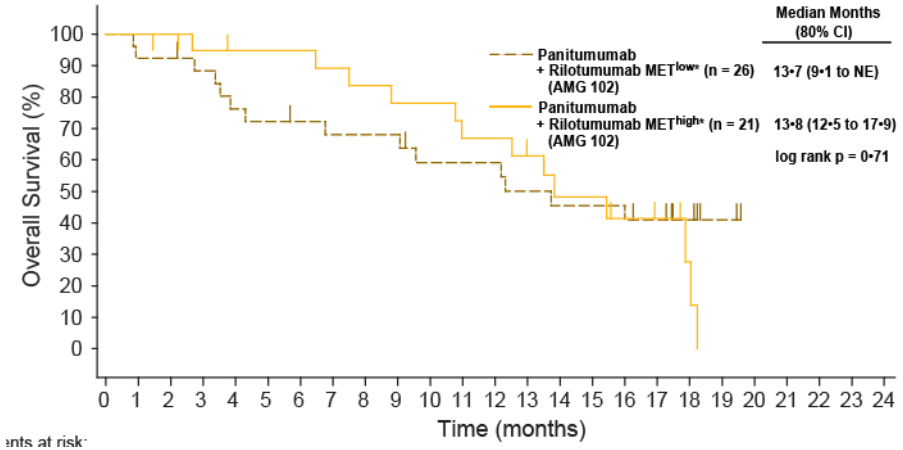
- c-Met activation by HGF plays an important role in metastatic growth of colon tumor cells in the liver and cooperates with *KRAS* mutation to enhance tumorigenicity of CRC cells[1]
- The expression of the c-Met receptor and the ligand HGF has been correlated with advanced stage and poor survival in colon cancer[2]
- Amplification of c-Met receptor has been clinically demonstrated as one of the mechanisms of secondary resistance to EGFR inhibitors[3]
- Unselected population: inactive strategy
- Demonstration of dependency is cumbersome: amplification vs mutation vs (over)expression

[1]Seiden-Long et al. Oncogene 2006
[2]Kammula et al. Cancer Lett 2007
[3]Bardelli et al. Cancer Discov 2013

Panitumumab + Rilotumumab

- NCT00788957
- Phase Ib/randomized II study of Ganitumab or Rilotumumab in combination with panitumumab versus panitumumab alone in subjects with mCRC whose tumors are <u>wt *KRAS*</u>
- 142 patients refractory to Iri- and/or Oxl-based chemotherapy





Van Cutsem et al, Clin Cancer Res 2014

Studies in EGFR RAS wild-type (naïve) mCRC

Genomic profile	Strategy	Trial
KRAS wt anti-EGFR naïve	• **novel anti-EGFR/HER3 mAbs**	Phase 2
	MEHD7945A + FOLFIRI vs. Cetuximab FOLFIRI	NCT01652482
	• **anti-EGFR mAbs + irreversible ERBB TKIs**	Phase 2
	Cetuximab + Afatinib vs. Cetuximab	NCT01919879
	• **PI3K pathway inhibitors**	Phase 2
	Cetuximab + Irinotecan vs. PF-05212384 + Irinotecan	NCT01925274

Dienstmann R et al. ASCO Educ Book 2014

Studies in EGFR RAS wild-type (anti-EGFR pretreated) mCRC

Genomic profile	Strategy	Trial
KRAS wt progressing to anti-EGFR mAbs	• **novel anti-EGFR mAbs with potent ADCC**	Phase 1/2
	SYM004	NCT01117428
		RP2
		NCT02083653
	• **anti-EGFR mAbs + MEK inhibitors**	Phase 2
	Panitumumab + MEK162	NCT01927341
KRAS wt *HER2* amp progressing to anti-EGFR mAbs	• **dual anti-HER2 therapy**	Phase 2
	Trastuzumab + Pertuzumab or Lapatinib	Heracles trial
KRAS wt MET high progressing to anti-EGFR mAbs	• **anti-EGFR mAbs + MET inhibitors**	Phase 2
	Cetuximab + ARQ197	NCT01892527
Quadruple negative (*KRAS, NRAS, BRAF, PIK3CA*) progressing to anti-EGFR mAbs	• **anti-EGFR mAbs + irreversible ERBB TKIs**	Phase 2
	Cetuximab + Neratinib	NCT01960023

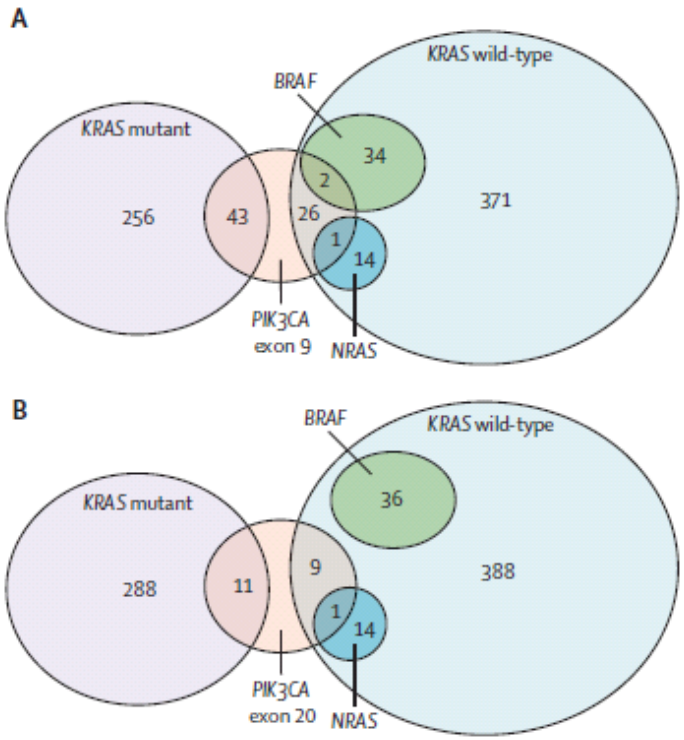
Dienstmann R et al. ASCO Educ Book 2014

Beyond EGFR inhibition

- More efficient anti-EGFR MoAbs
- MoAbs directed to other members of the EGFR/HER family
- MoAbs directed to other receptors
- Combination with downstream effector inhibitors

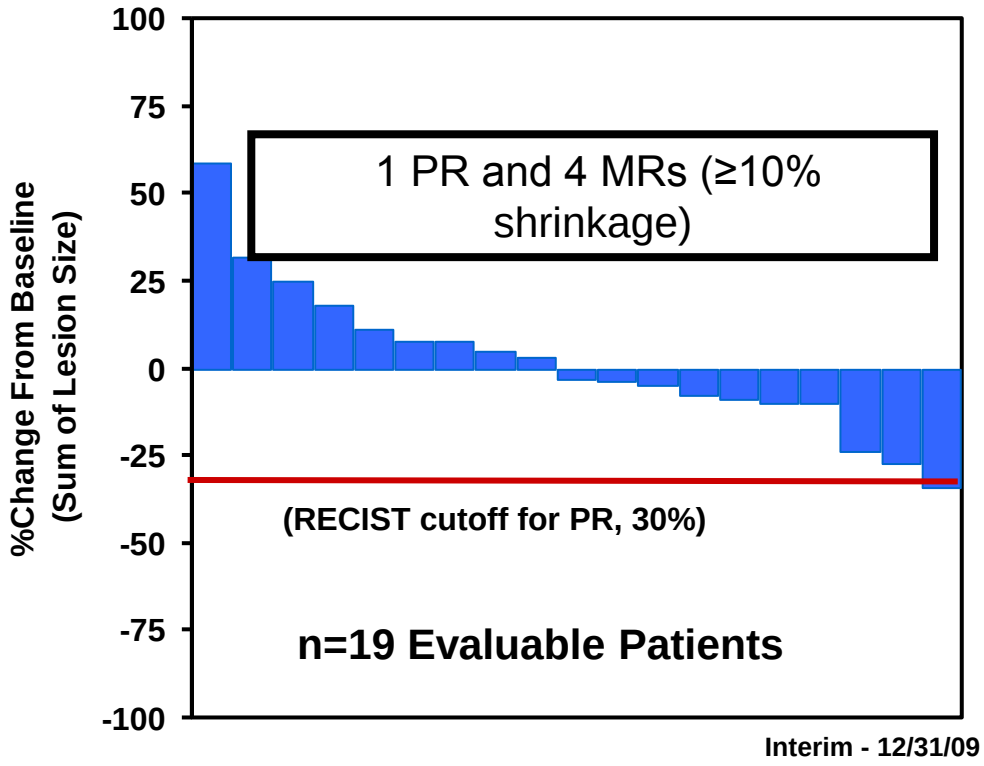
BRAF (V600E) mutated CRC

- Small population:
  - 8-10% early stage
  - 4-5% late stage
- BRAF V600E mutations as a biomarker?
  - very poor prognosis in late stage (mCRC)
  - no clear prognostic effect in early stage
  - predictive: negative predictive effect for anti-EGFR MoAbs in some studies:
    - Cetuximab: refractory (European cons.)[1,2] & first-line setting (CRYSTAL study)[3]
    - Panitumumab: 2nd line setting (PICCOLO study)[4]
    - No change in the label by any regulatory authority predicted



[1] Di Nicolantonio F, J Clin Oncol 2018; [2] De Roock et al, Lancet Oncol 2010; [3]Van Cutsem et al, J Clin Oncol 2011; [4]Seymour MT et al, Lancet Oncol 2013

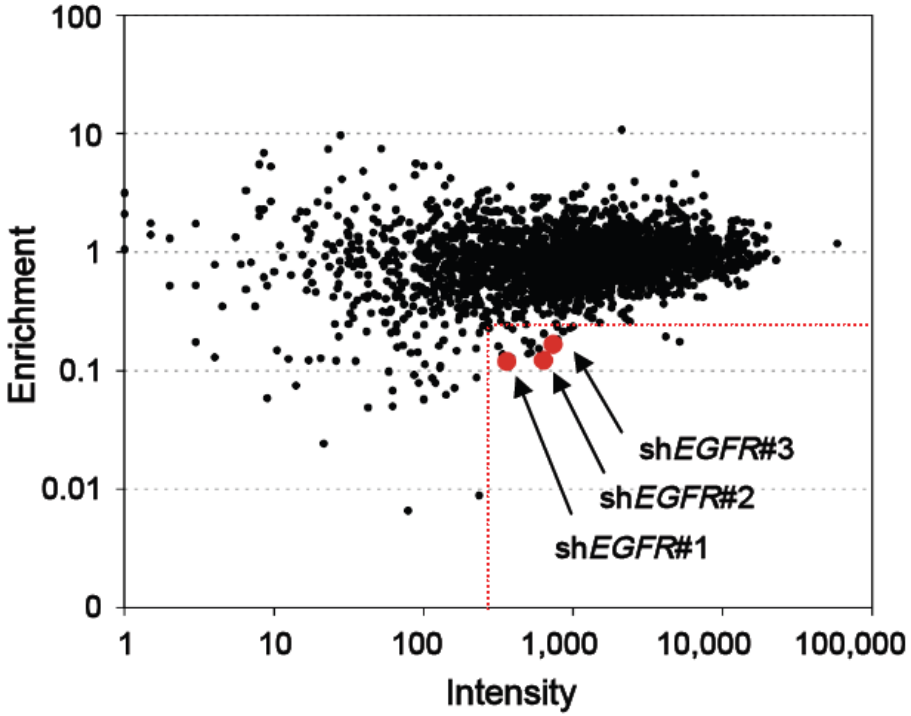
Vemurafenib in BRAF (V600E) mutant mCRC

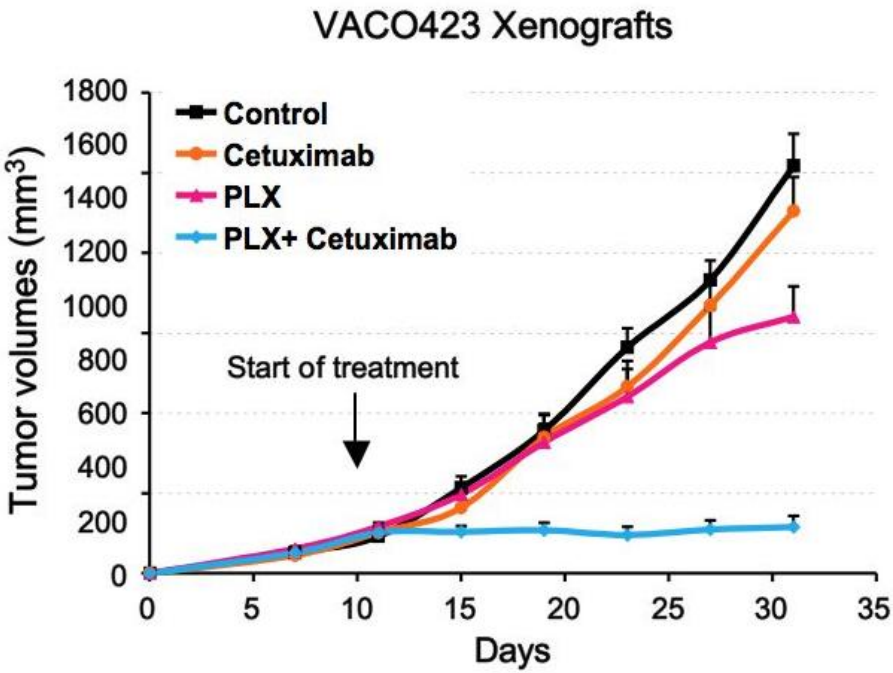


- Outstanding activity of vemurafenib in metastatic melanoma with BRAF V600E mutations
- Preclinical activity shown in limited CRC BRAF V600 mutated cells[1]
- Marginal activity in metastatic CRC with BRAF V600E mutations[2]

[1]Yang H et al. Clin Cancer Res 2011; [2]Kopetz S et al, Proc ASCO 2010

BRAF inhibitors + EGFR inhibitors have *in vivo* activity in BRAF^{V600E} mutated CRC xenografts





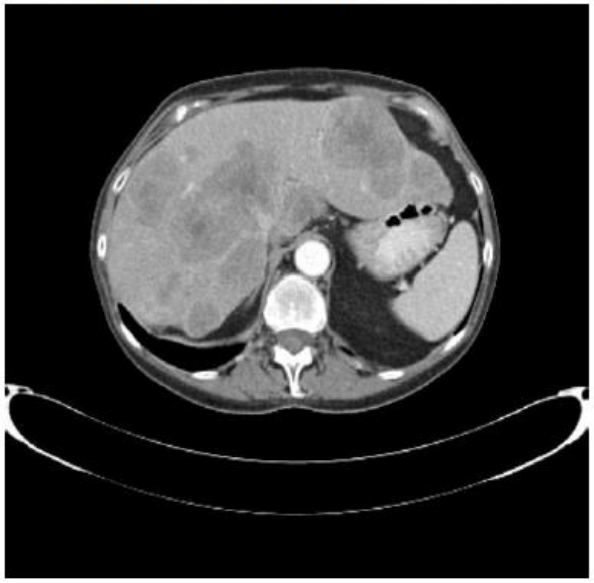
Corcoran RB et al, Cancer Discov 2012;2:227-35
Prahallad A et al, Nature 2012;483:100-3

New studies in the $BRAF^{V600E}$ mutant CRC population

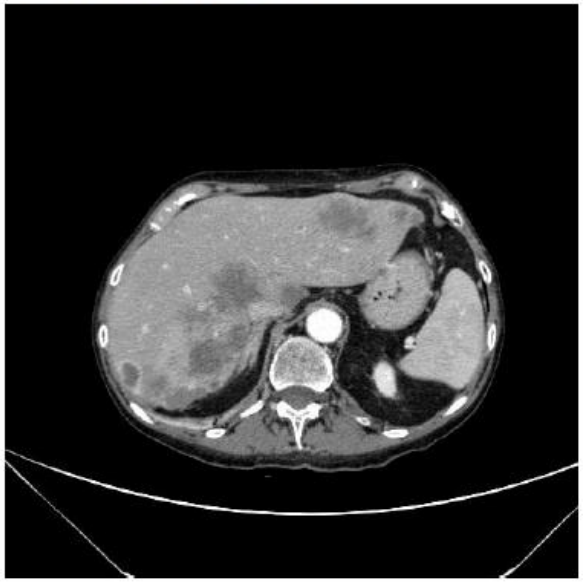
- As examples of clinical trials evaluating the combination of BRAFV600E inhibitors plus anti-EGFR inhibitors in the BRAF mutant population in CRC:
  - NCT01524978: Vemurafenib + Cetuximab (BASKET) – Roche: Phase Ib
  - NCT01750918: BRAF/MEK Inhibitors (dabrafenib + trametinib) + Panitumumab – GSK: Phase Ib ➔RP2
  - NCT01719380: LGX818 and Cetuximab or LGX818, BYL719, and Cetuximab – Novartis: Phase Ib➔RP2
  - NCT01787500 (MDACC): Vemurafenib + Cetuximab + Irinotecan

Dienstmann R et al. ASCO Educ Book 2014

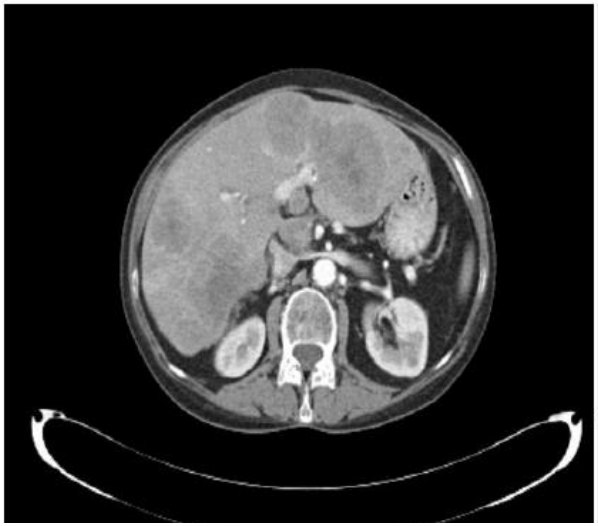
Baseline CT scan (11.07.2013)



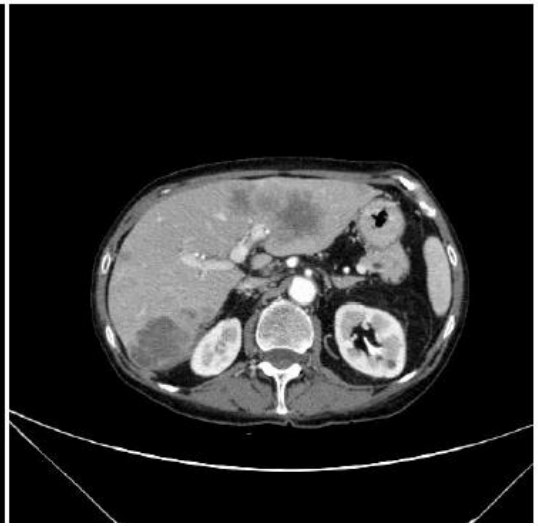
CT scan 09.08.2013



Baseline CT scan (11.07.2013)



09.08.2013



Early efficacy comparison of BRAFi/EGFRi combos

Regimen	N	PR/CR (%)	SD (%)	DCR (%)
Dabrafenib + Trabetinib	43	12	51	63
Dabrafenib + Panitumumab	15	13	73	87
Vemurafenib + Cetuximab*	11	-	36	36
Encorafenib + Cetuximab	24	29	50	79
Dabrafenib + Trabetinib + Panitumumab	15	40	40	80
Vemurafenib + Cetuximab + Irinotecan	8	50	50	100
Encorafenib + Cetuximab + BYL719	20	30	60	90

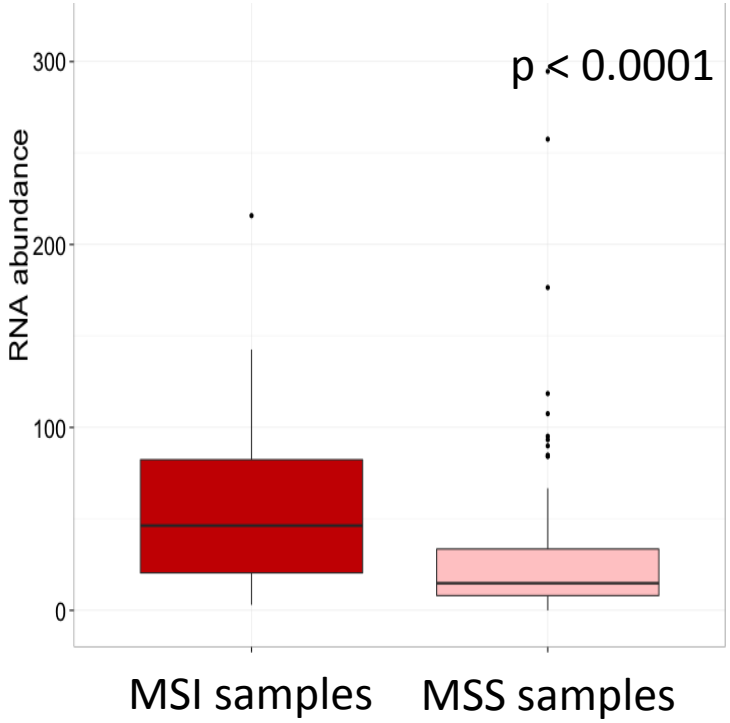
*No confirmation response assessment

Dienstmann R et al. ASCO Educ Book 2014

Immune activating agents

Anti-PD1/PDL1 in mCRC

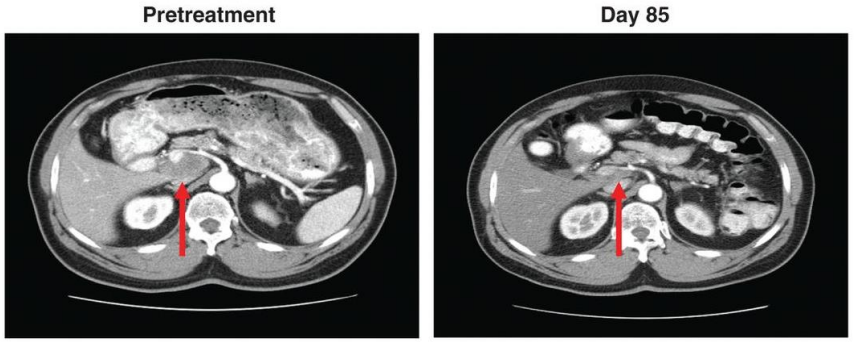
TCGA CRC - RNA seq (n=328)
CD274 (PDL1) gene expression



Dienstmann, Unpublished

Case report of durable complete response

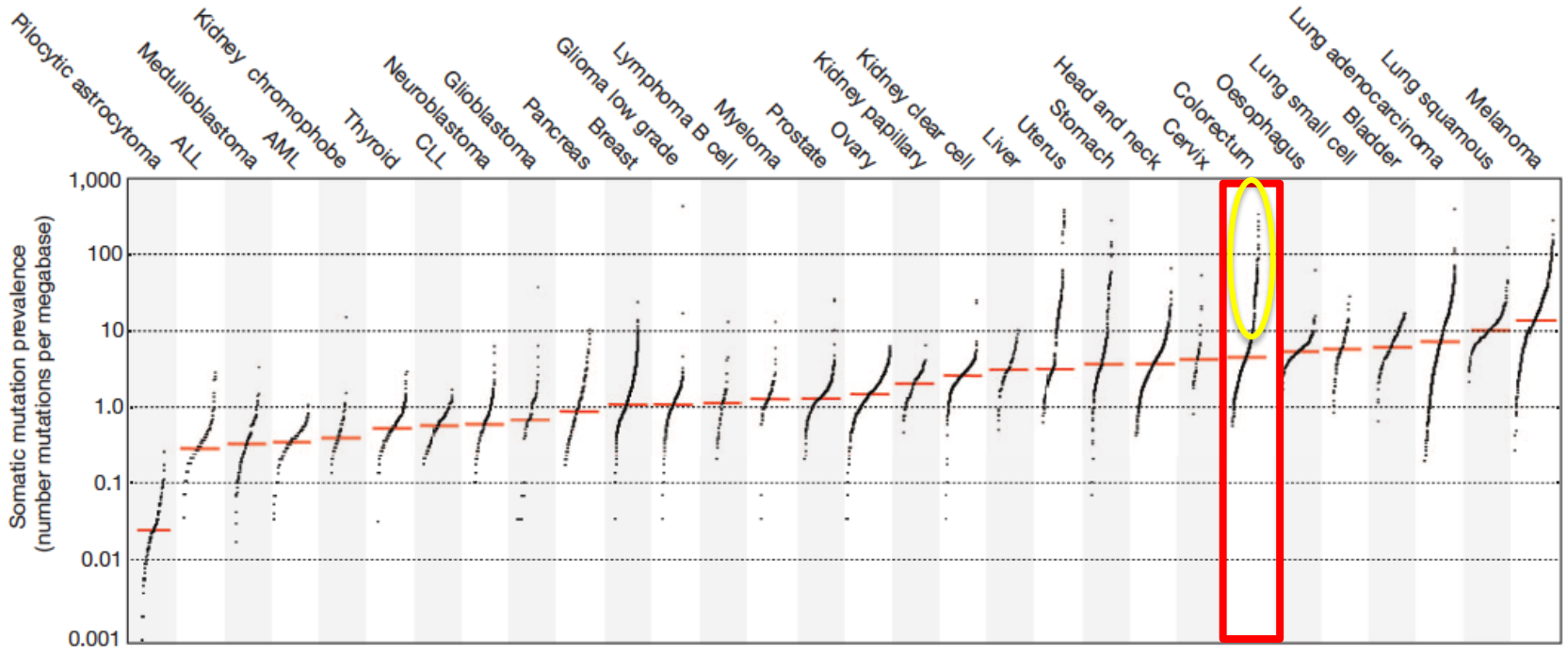
MSI CRC patient on anti-PD1 mAb



Lipson, Clin Cancer Res 2013

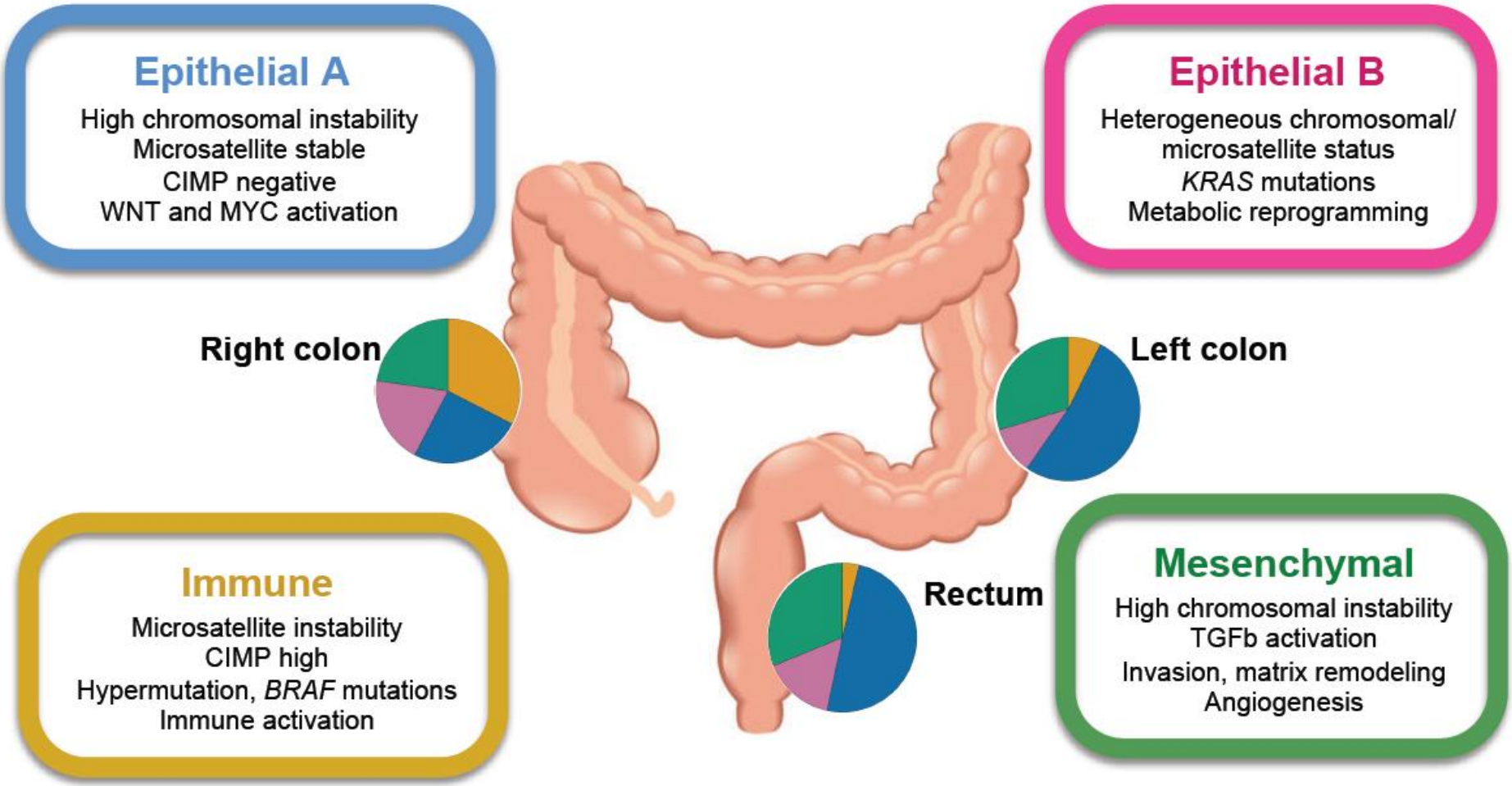
Molecular understanding of CRC

TCGA



Pan-Cancer TCGA, Nature 2013

CRCSC – clinical and molecular correlates



Dienstmann R. J Clin Oncol 2004

Summary

- Target discovery has resulted in numerous novel drugs in clinical development but with very limited survival gain in mCRC
- Signal transduction inhibition does not guarantee tumor response:
  - Target presence and dependence
  - Redundancy, Cross-talk
- Need for molecular profile, characterization in multiple subtypes and selection
- Need for strong science-sound rationale for the combinations, these addressing mechanistic interactions: *BRAF* mutant
- Need to sequentially evaluate tumor cells (tumor tissue, CTCs, circulating DNA, …) to have evolutive/dynamic information