Dynamics of EGFR inhibition: Implications for treatment

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Outline

Anti-EGFR therapy in mCRC
Challenges

Background

1. Acquired resistance

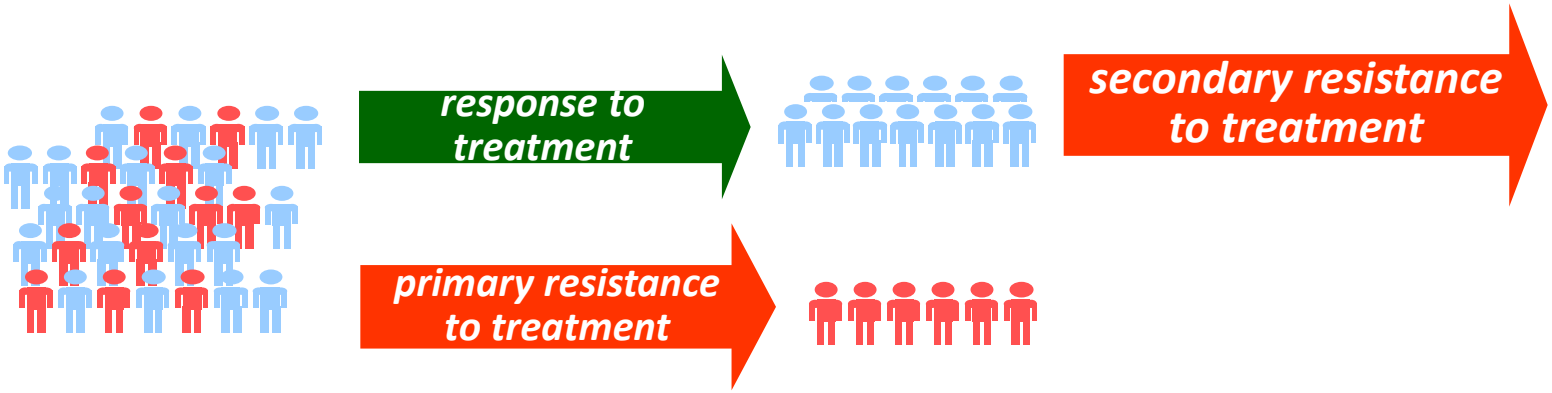
2. Hetereogeneity and clonal evolution

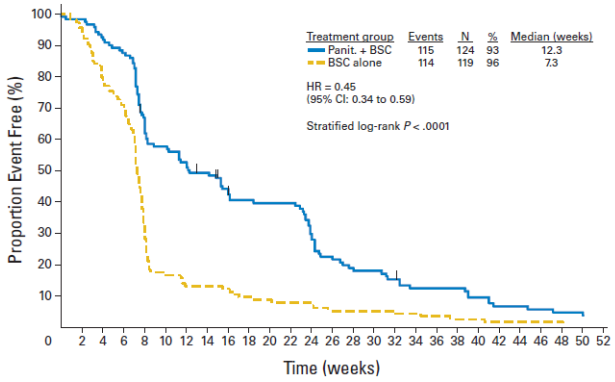
Clinical implications

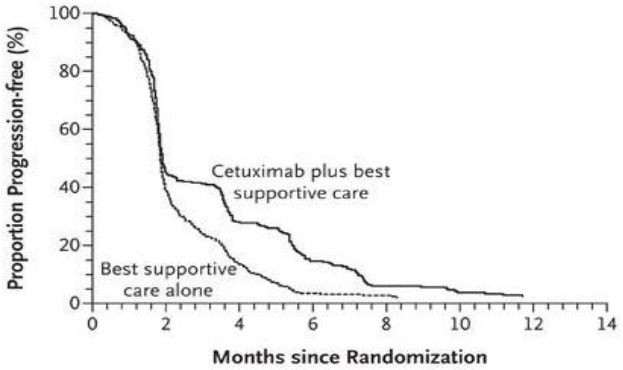
3. Monitoring clonal dynamics (liquid biopsy)

4. Treating resistance to anti-EGFR therapy

Acquired resistance to anti-EGFR therapy in CRC



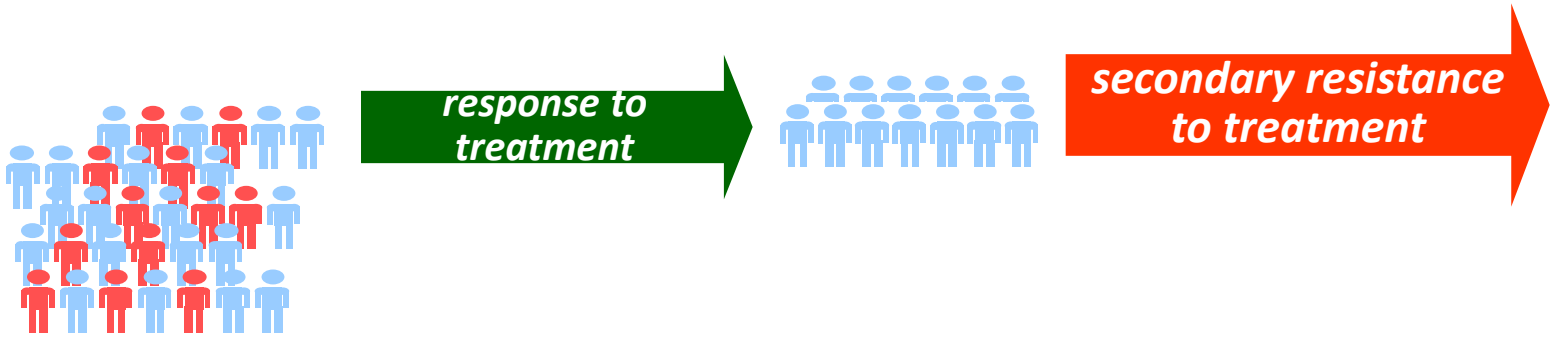




All KRAS wt patients treated with cetuximab / panitumumab present tumor progression after 1 year

Jonker. N Engl J Med 2007; Amado. J Clin Oncol 2008

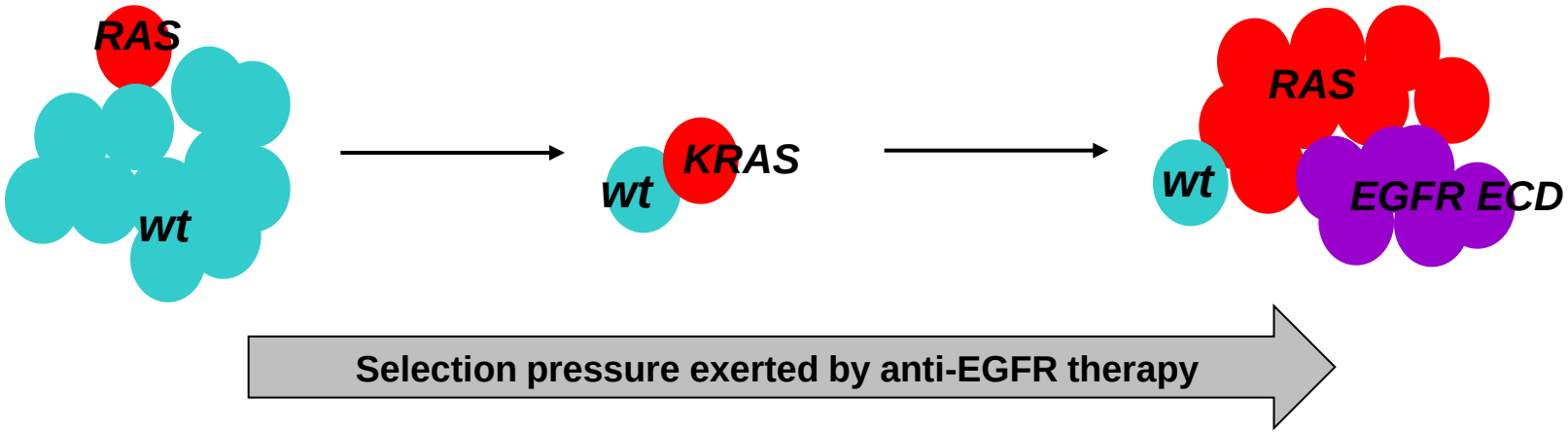
Acquired resistance, intratumoral heterogeneity and clonal selection



Basal tumor

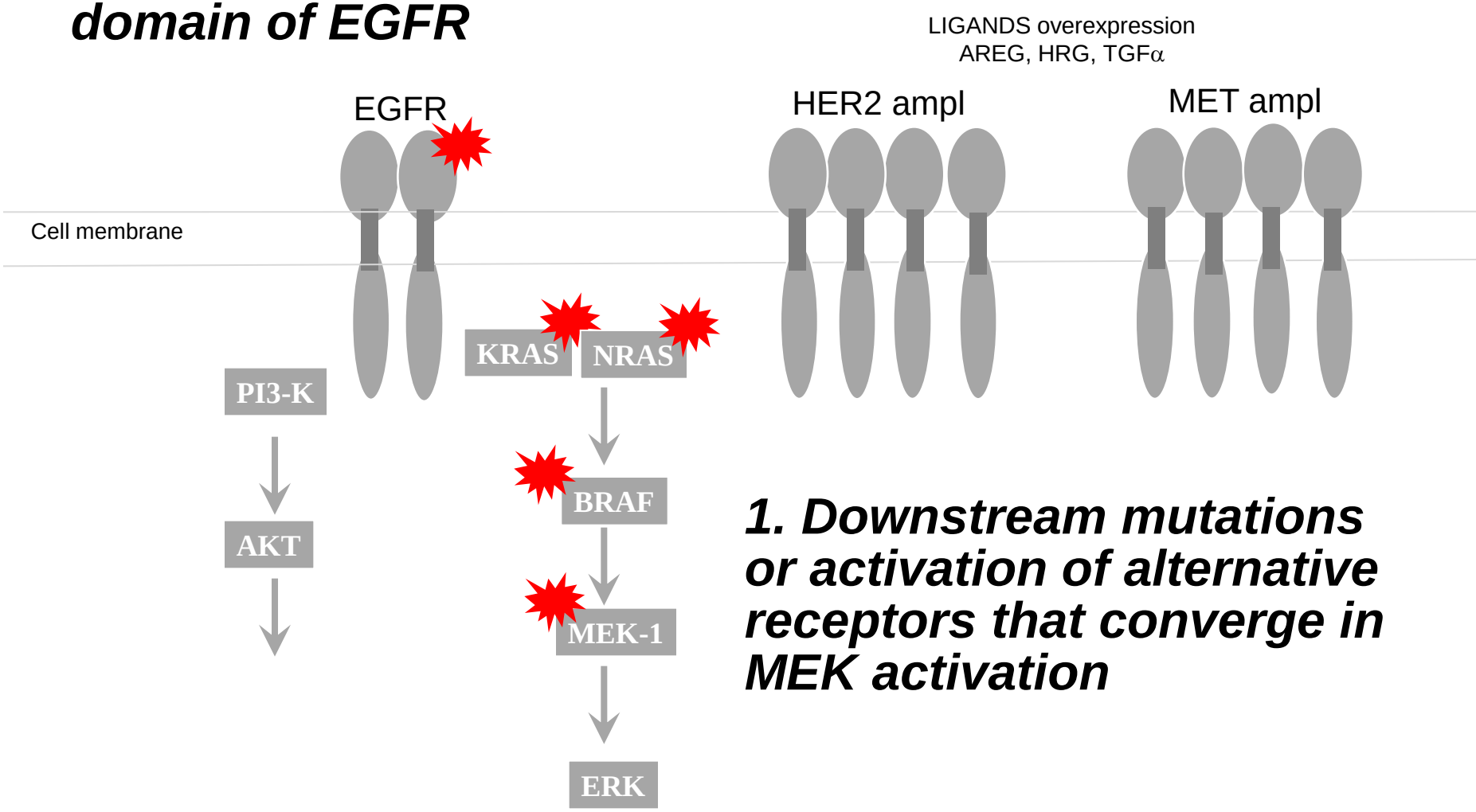
Targeting sensitive clones

Expansion of resistant clones



Acquired resistance to anti-EGFR treatment in CRC

2. Mutations in extracellular domain of EGFR

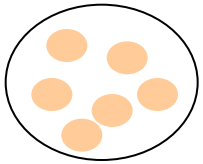


1. Downstream mutations or activation of alternative receptors that converge in MEK activation

Yonesaka, STM 2011; Montagut, Nat Med 2012; Misale, Nature 2012; Diaz, Nature 2012; Bardelli, Cancer Discov 2013; Troiani, CCR 2013; Misale, STM 2014; Hobor, CCR 2014; Arena, CCR 2015; Siravegna, Nat Med 2015; Russo, Cancer Discov 2016

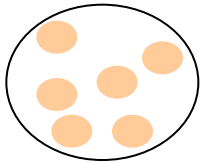
EGFR Extracellular domain mutations

Cell culture

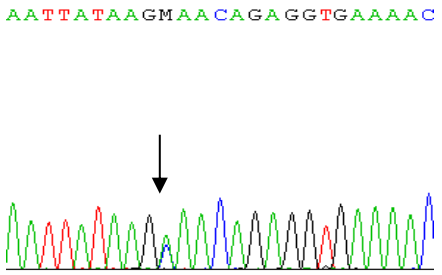


DiFI SENSITIVE cells

Continuous exposure to cetuximab



RESISTANT cells



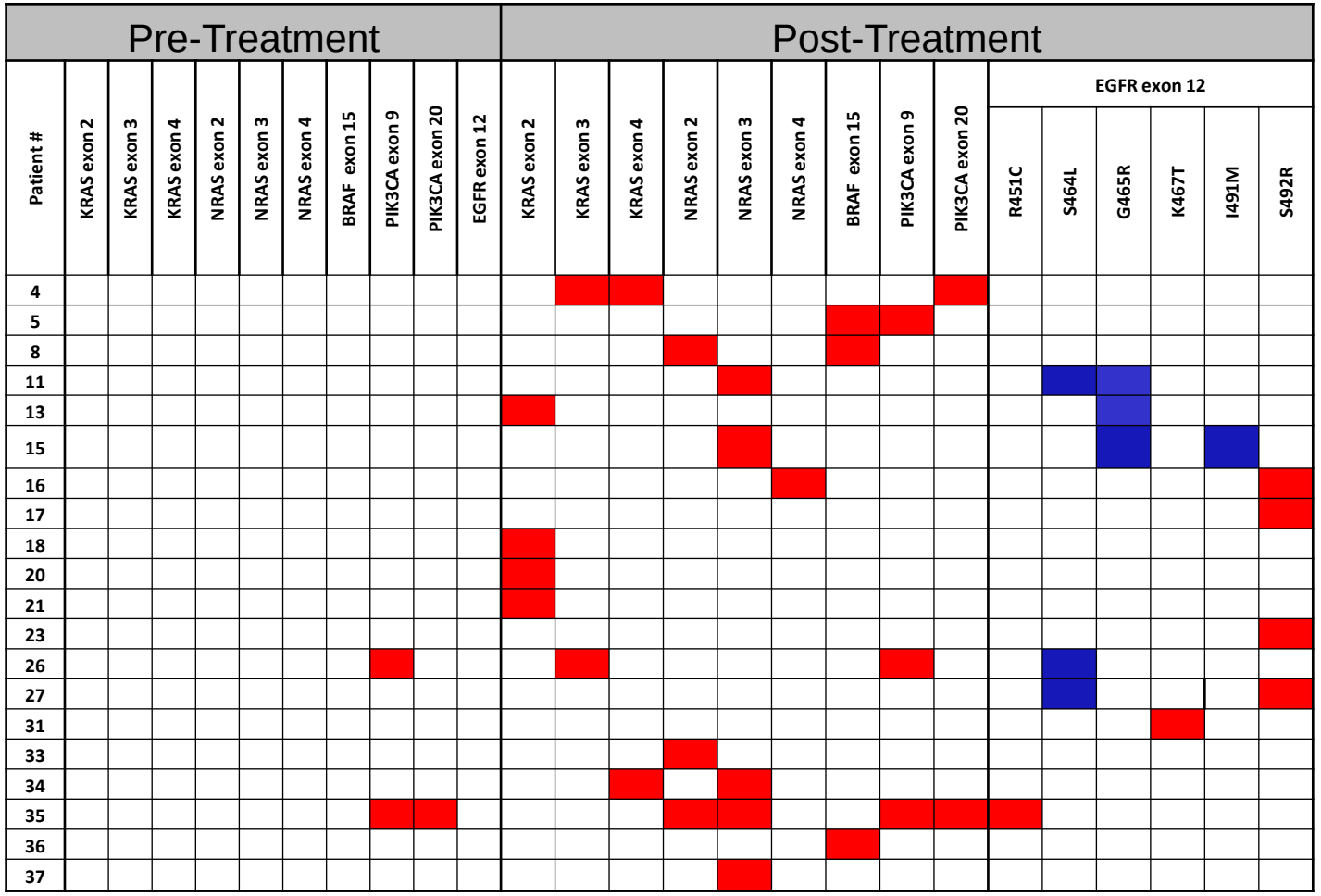
C1476T, S492R mutation

Patient No.	Sex	Age	Pre-cetuximab mutation status				Post-cetuximab mutation status			
			KRAS	*BRAF*	*PIK3CA*	*EGFR*	*KRAS*	*PIK3CA*	*BRAF*	*EGFR*
1	M	55	wt	wt	wt	wt	***G12V***	wt	wt	wt
2	F	42	wt	wt	wt	wt	wt	wt	wt	wt
→ 3	M	64	wt	wt	wt	wt	wt	wt	wt	***S492R***
4	F	54	wt	wt	wt	wt	wt	wt	wt	wt
5	M	59	wt	wt	wt	wt	wt	wt	wt	wt
6	M	54	wt	wt	wt	wt	wt	wt	wt	wt
7	M	62	wt	wt	wt	wt	wt	wt	***V600E***	wt
8	M	79	wt	wt	wt	wt	wt	wt	wt	wt
→ 9	M	52	wt	V600E	wt	wt	wt	wt	***V600E***	***S492R***
10	M	61	wt	wt	wt	wt	wt	wt	wt	wt

Montagut et al. Nature Med 2012

Emergence of mutations of resistance during cetuximab treatment in CRC

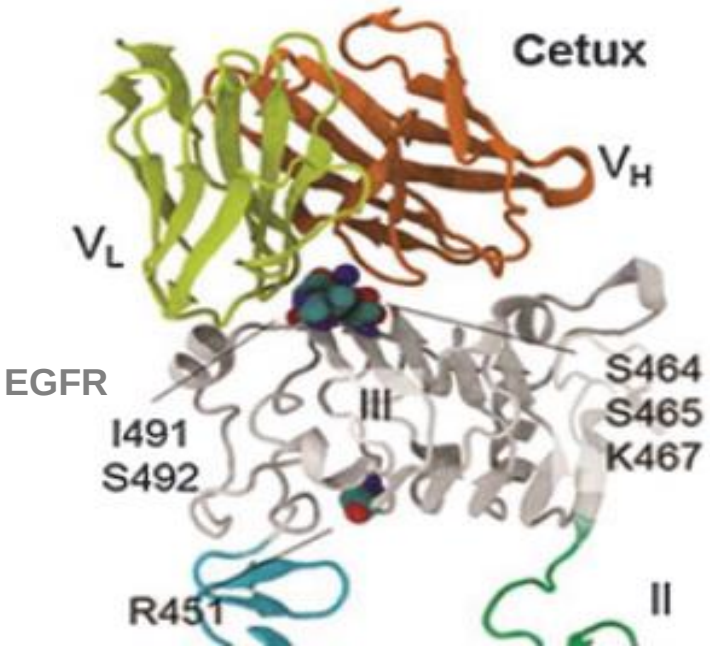
EGFR Extracellular domain mutations

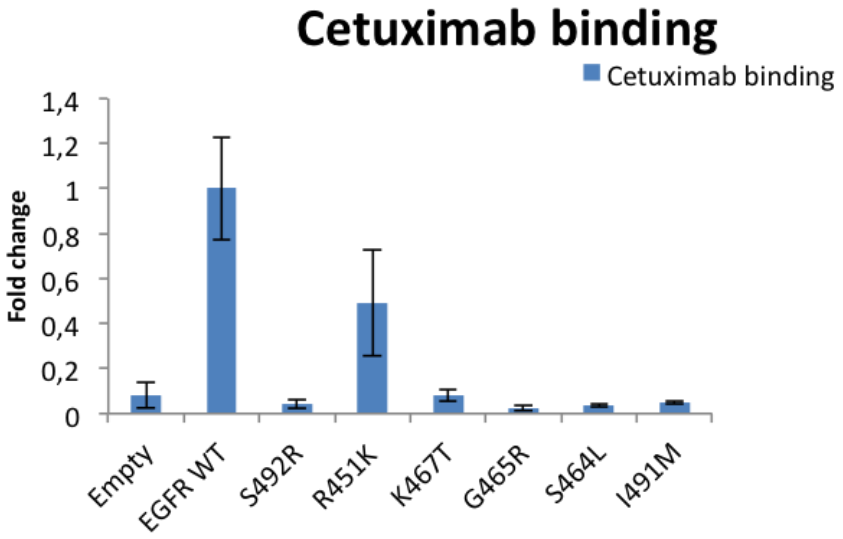


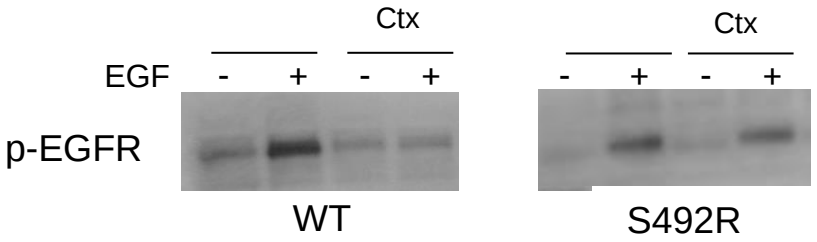
Only detected in plasma

Adapted from Arena&Bellosillo et al. Clin Cancer Res 2015

EGFR ECD mutations prevent cetuximab binding to EGFR

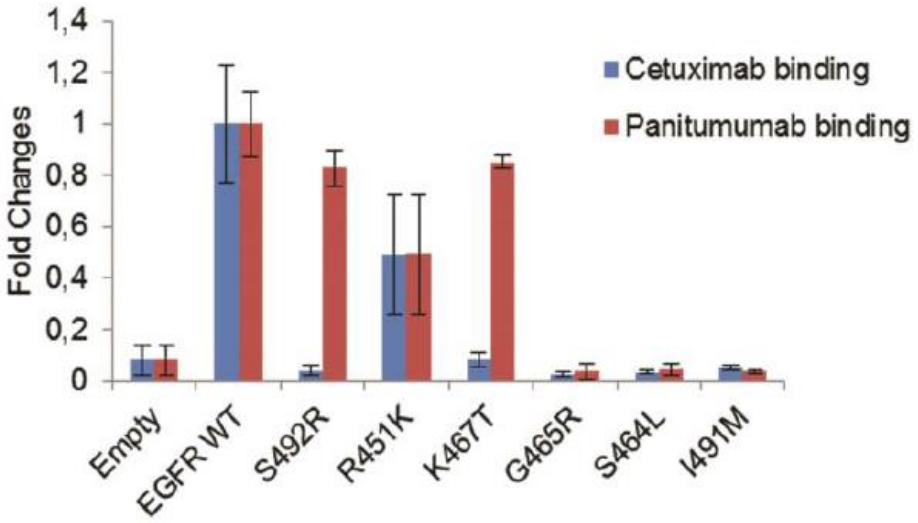




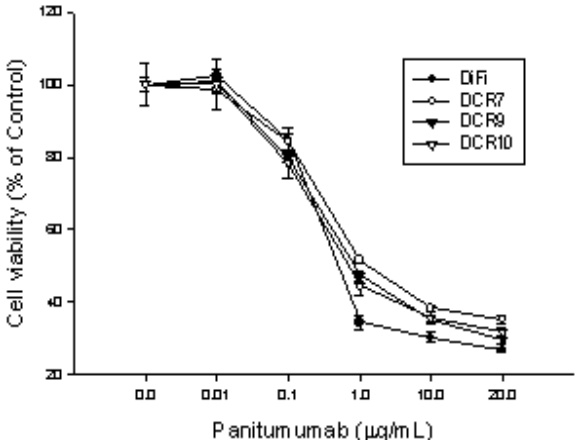


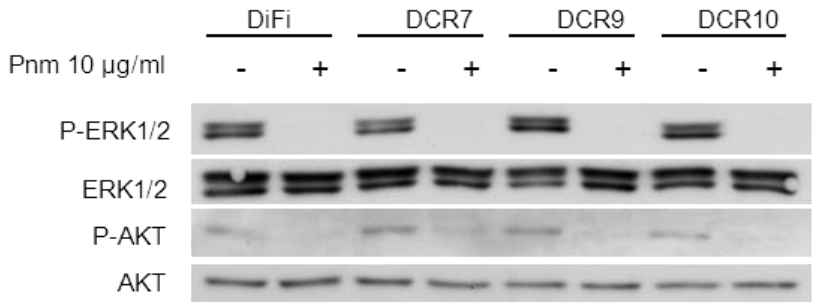
Montagut et al. Nat Med 2012
Arena&Bellosillo et al. Clin Cancer Res 2015

A subset of EGFR ECD mutations of resistance to cetuximab are sensitive to panitumumab



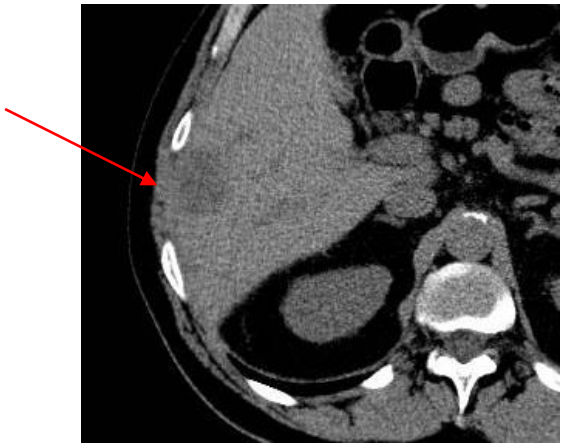
S492R mutant cells



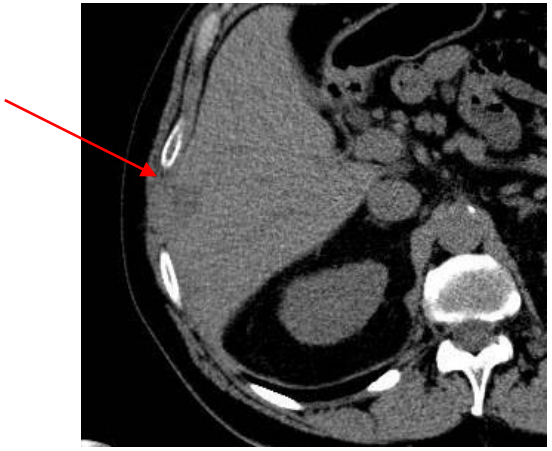


Montagut et al. Nat Med 2012
Arena&Bellosillo et al. Clin Cancer Res 2015

As a proof-of-concept, one patient with EGFR S492R mutation after cetuximab therapy, responded to panitumumab



Pre- panitumumab



After 2 cycles of panitumumab

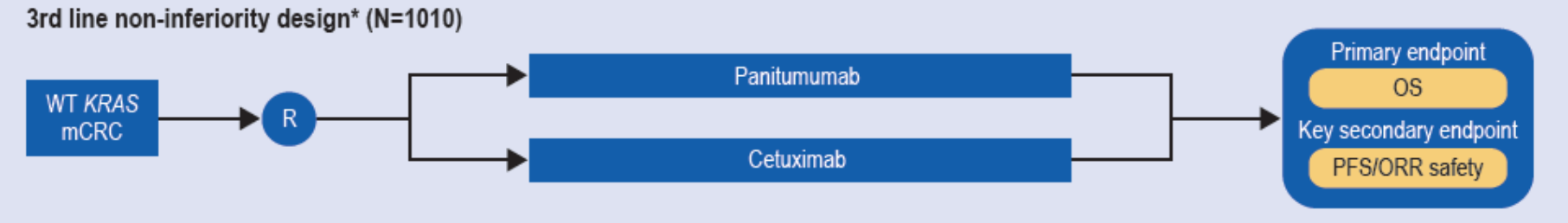
Montagut et al. Nat Med 2012

Clinical implications of EGFR ECD mutations
Prevalence in patients

EGFR ECD mut	Clinical work	Frequency	%	median
G465R / G465E	Arena. STM 2016	3/11	3%	4%
	Bertotti. Nature 2015	2/22	1%	
	Sanchez. CCR 2016	1/13	8%	
	Non-published data	3/20	3%	
S464L	Arena. STM 2016	1/11	9%	5%
	Non-published data	3/20	2%	
K467T	Arena. CCR 2015	1/37	3%	3%
I491M	Non-published data	1/20	<1%	1%
R451C	Arena. CCR 2015	1/37	3%	3%
	Heracles study	1/?		
S492R	Montagut. Nat Med 2012	2/10	20%	11%
	Morelli. Ann Oncol 2015	5/62	8%	
	Dienstmann. Can Discov 2015	1/26	1%	
	Newhall, WCGIC 2014	46/258	16%	

Total frequency (median) 27%

EGFR S492R clinical implications
ASPECCT study



Treatment	Wild-type, n	Mutant, n	Frequency of S492R mutation, %	95% CI	p-value
Cetuximab	239	46	16.1	12.1-20.9	p<0.0001
Panitumumab	258	3	1.1	0.2-3.3	

EGFR ECD mutations detected in plasma by ddPCR

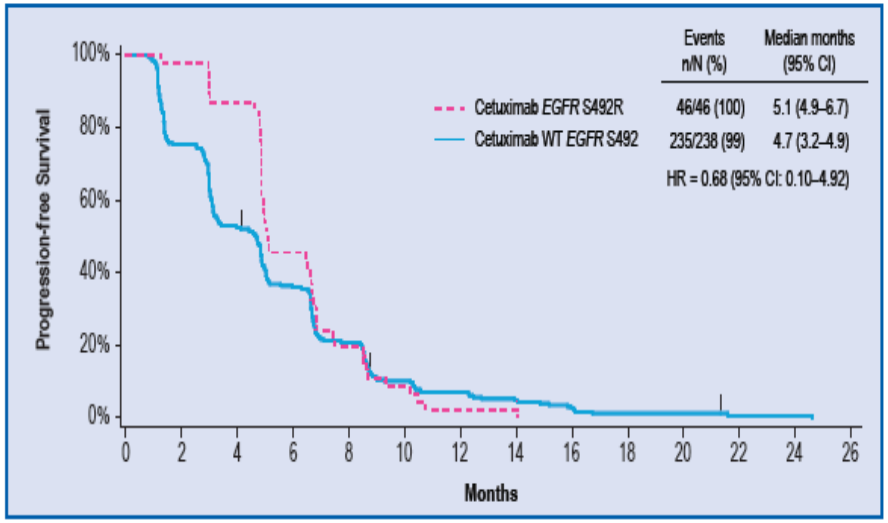
No EGFR mutations were detected pre-treatment samples

Newhall, WCGIC 2014

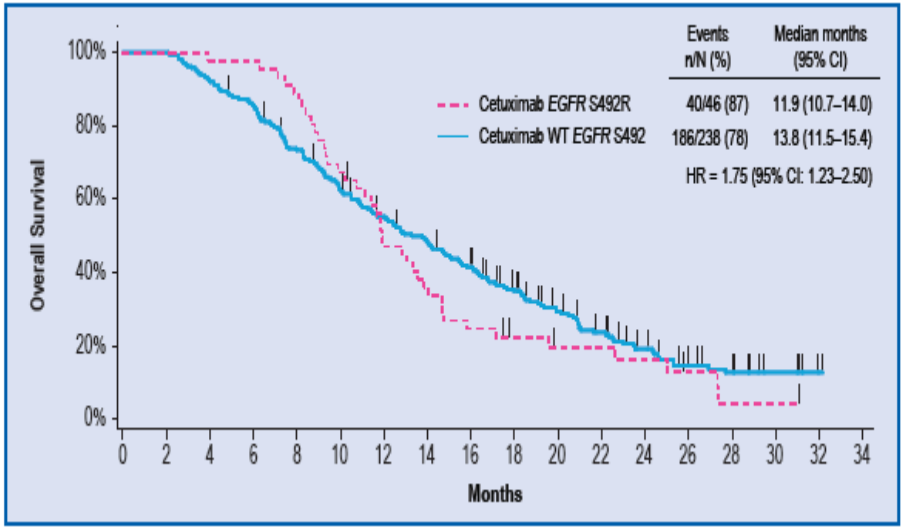
EGFR S492R clinical implications
ASPECCT trial

	Cetuximab EGFR S492R (N=46)	Cetuximab WT EGFR (N= 238)
Treatment duration – weeks (range)	**22 (6-61)**	**15 (1-94)**

PFS by EGFR S492 Status in Patients Treated With Cetuximab



OS by EGFR S492 Status in Patients Treated With Cetuximab



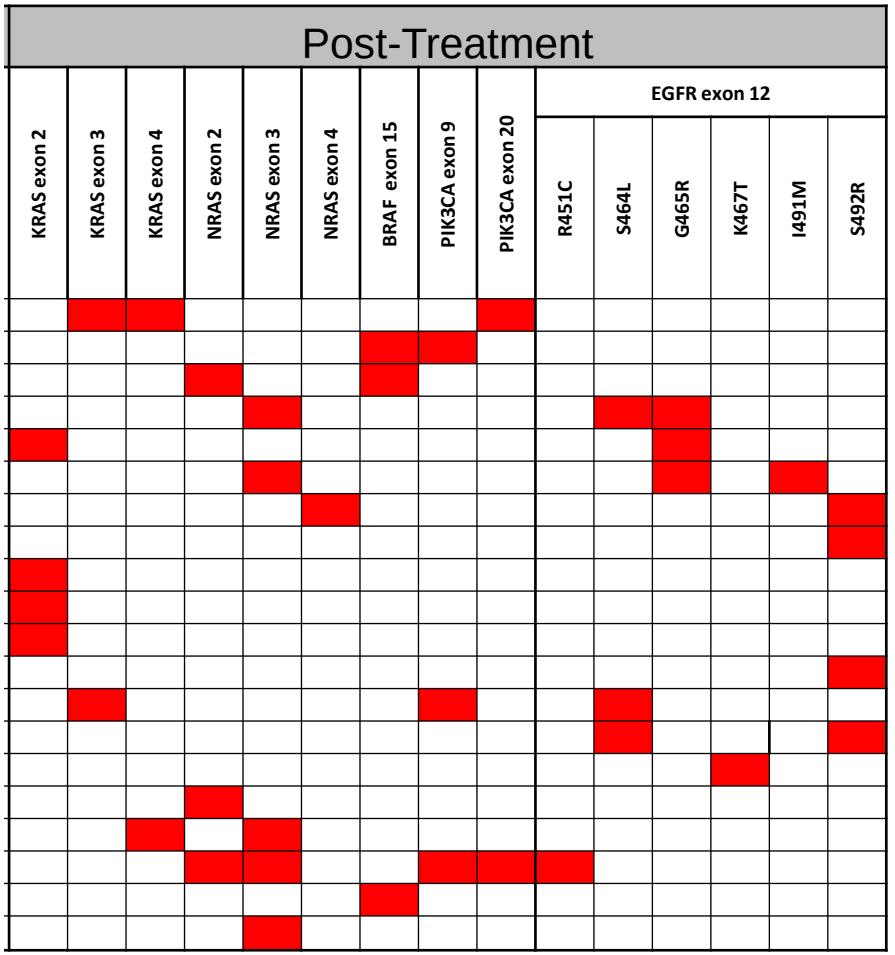
Patients treated with cetuximab that acquire an EGFR S492R mutation, have a longer duration of treatment before progression but have worse Overall Survival

Adapted from Newhall, WCGIC 2014

Mutations of resistance. Clinical implications

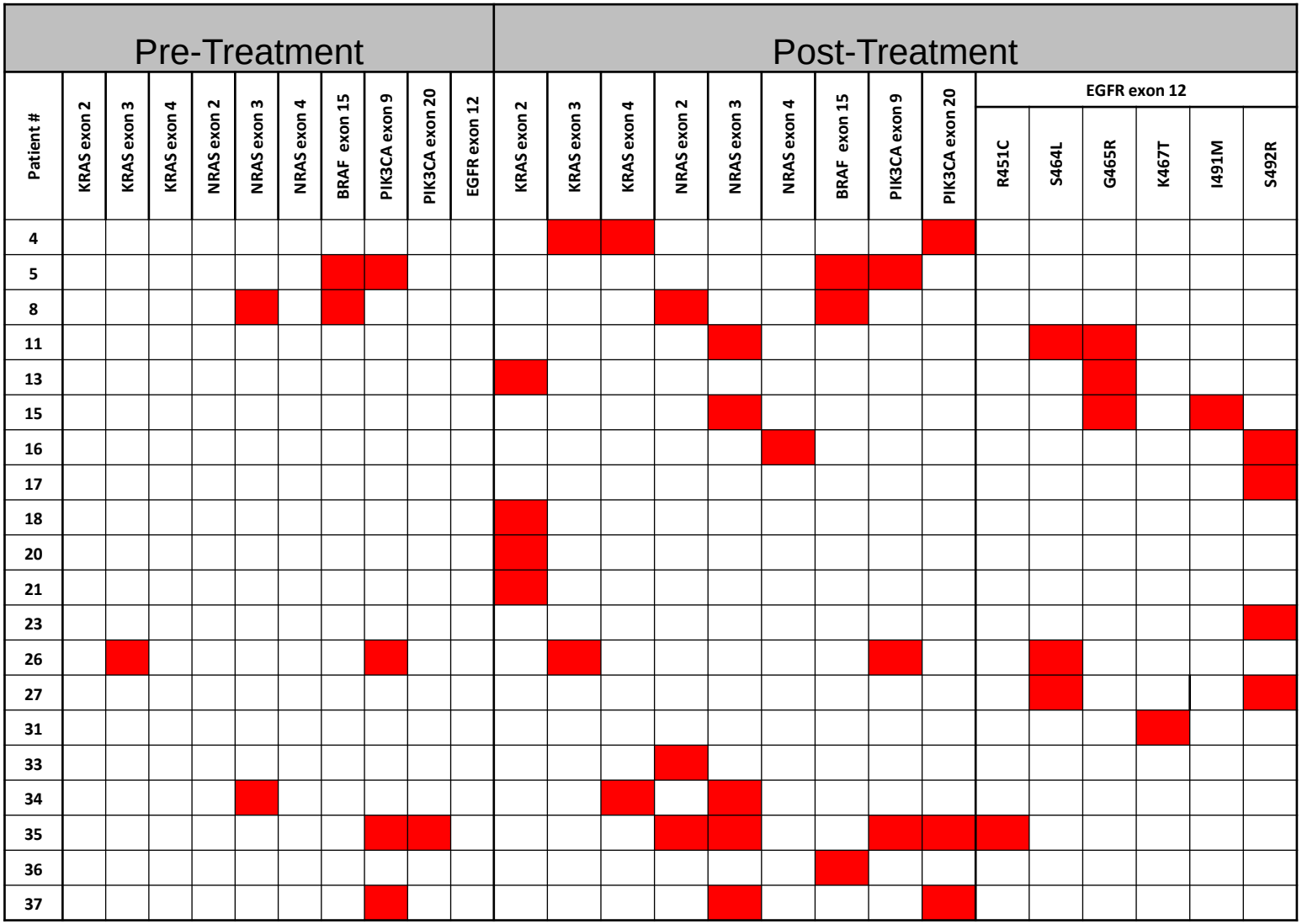
Mutations of resistance. Clinical implications

Mutations of acquired resistance **co-exist**



Adapted from Arena&Bellosillo et al. Clin Cancer Res 2015

RAS mutations pre-exist / EGFR mutations evolve?



Adapted from Arena, CCR 2015; Esposito, Cancer Biol Ther 2013; Newhall, WCGIC 2014; Misale, Nature 2012; Diaz, Nature 2012

RAS mutations pre-exist / EGFR mutations evolve?

	Pre-Treatment										Post-Treatment															
																				EGFR exon 12						
Patient #	KRAS exon 2	KRAS exon 3	KRAS exon 4	NRAS exon 2	NRAS exon 3	NRAS exon 4	BRAF exon 15	PIK3CA exon 9	PIK3CA exon 20	EGFR exon 12	KRAS exon 2	KRAS exon 3	KRAS exon 4	NRAS exon 2	NRAS exon 3	NRAS exon 4	BRAF exon 15	PIK3CA exon 9	PIK3CA exon 20	R451C	S464L	G465R	K467T	I491M	S492R
4												■	■						■						
5							■	■									■	■							
8					■		■							■			■								
11															■						■	■			
13											■											■			
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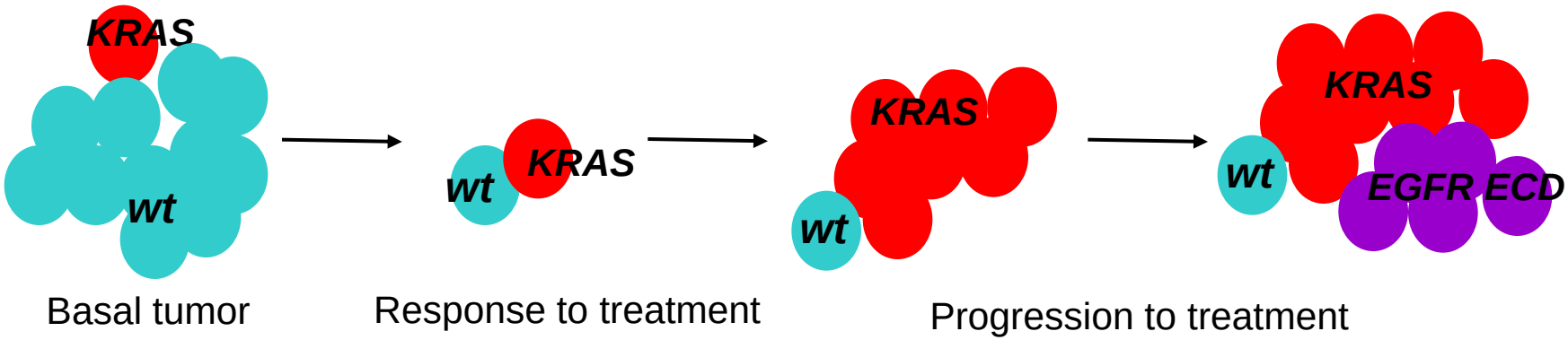
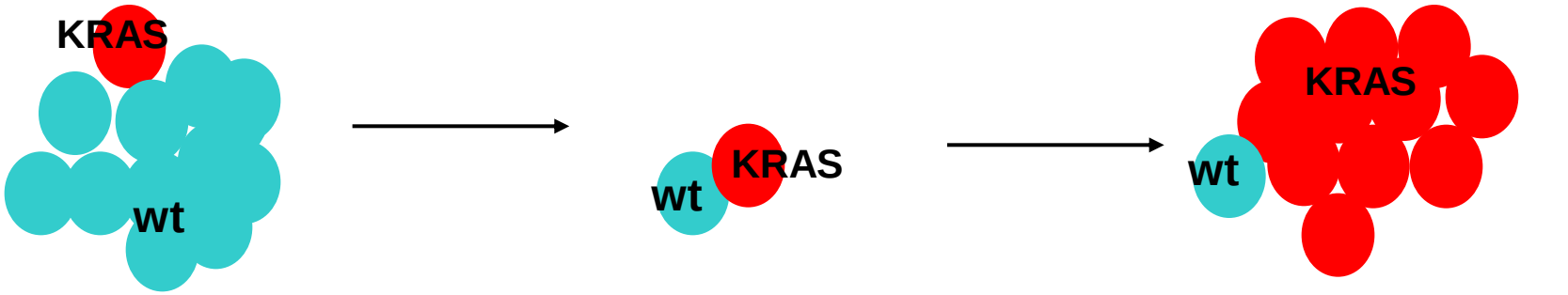
35								■	■					■	■			■	■	■					
36																	■								
37								■							■				■						



Adapted from Arena, CCR 2015; Esposito, Cancer Biol Ther 2013; Newhall, WCGIC 2014; Misale, Nature 2012; Diaz, Nature 2012

Mutations of resistance to anti-EGFR
Clinical implications

Mutations in KRAS emerge during anti-EGFR treatment



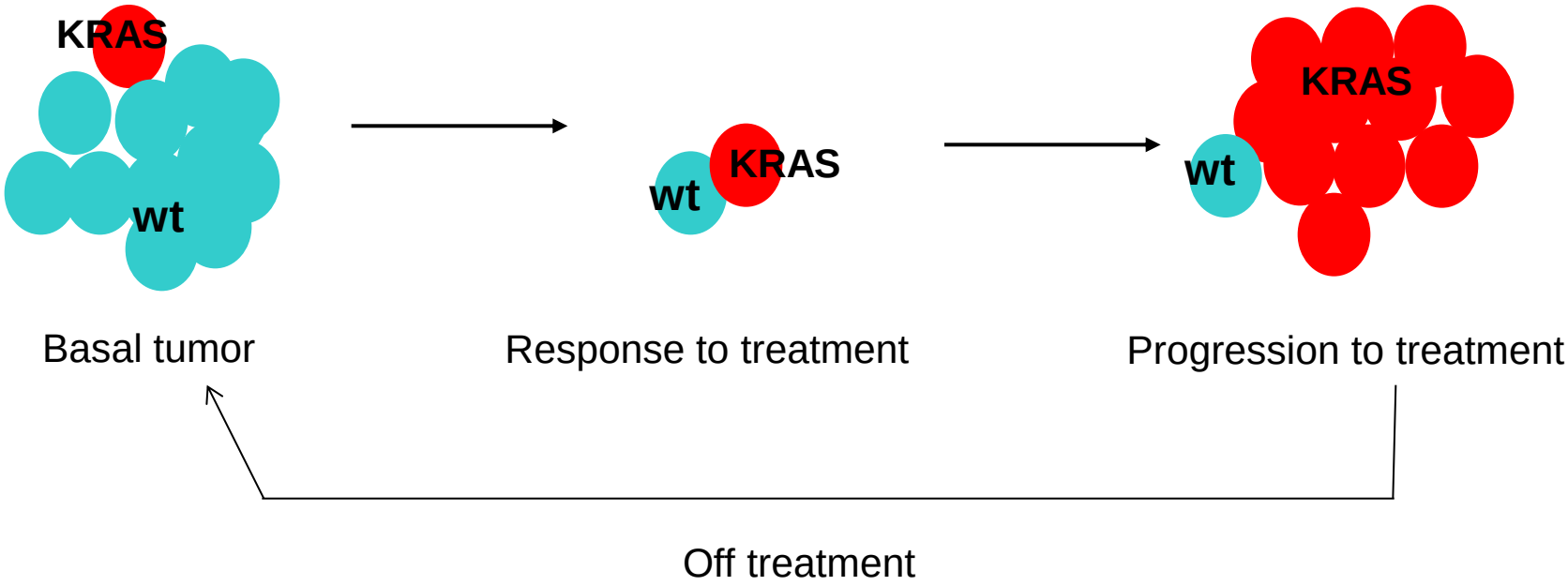
Basal tumor

Response to treatment

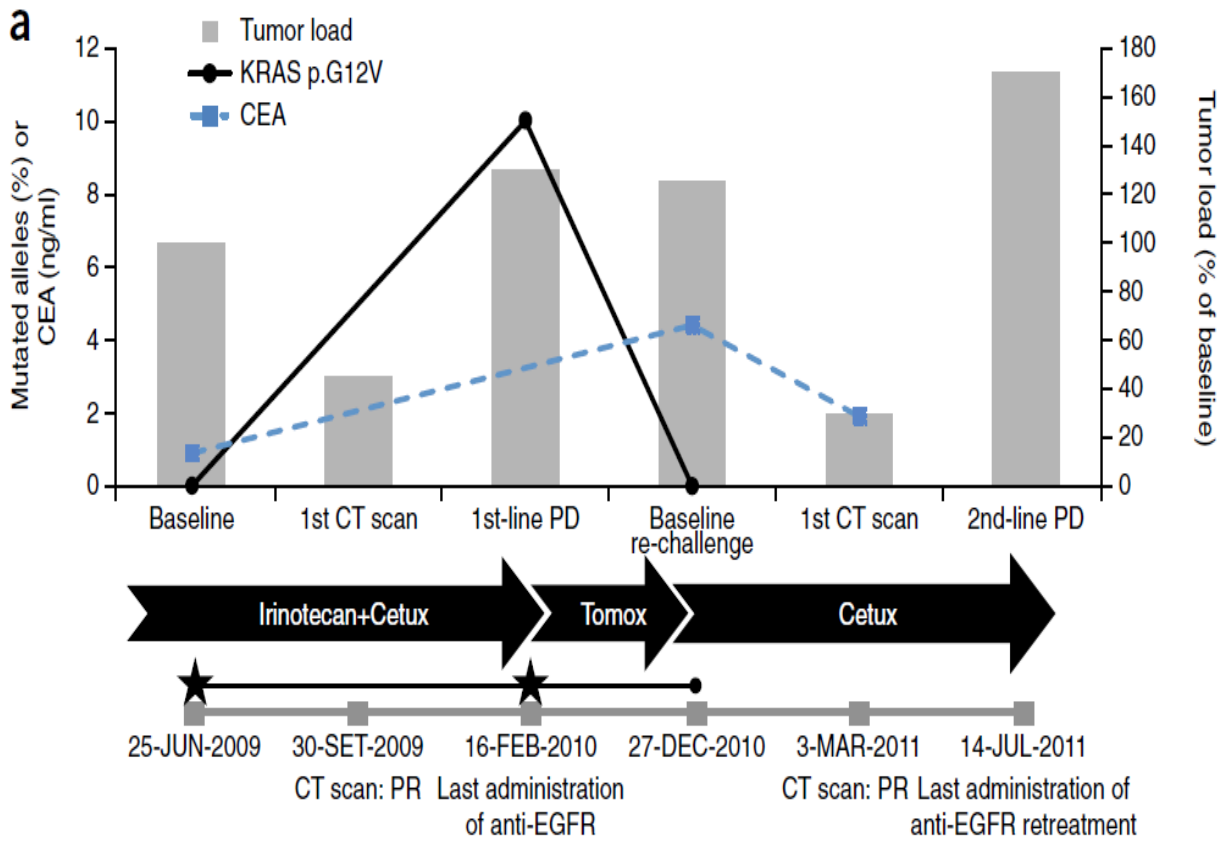
Progression to treatment

Mutations of resistance to anti-EGFR
Clinical implications

Mutations in KRAS emerge during anti-EGFR treatment and **decline** when treatment is suspendend



Liquid biopsy for longitudinal monitoring of RAS mutations in blood of patients
Rechallenge with cetuximab



Siravegna et al. Nat Med 2015

Anti-EGFR therapy in mCRC
Clonal dynamics

Background

1. Acquired resistance

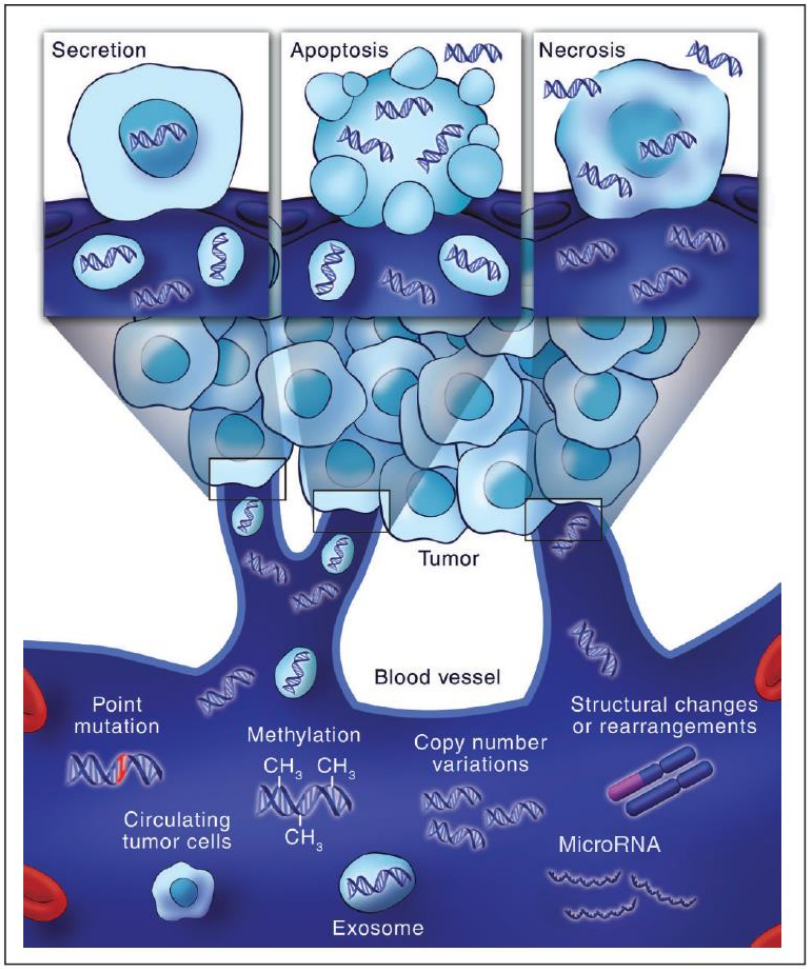
2. Hetereogeneity and clonal evolution

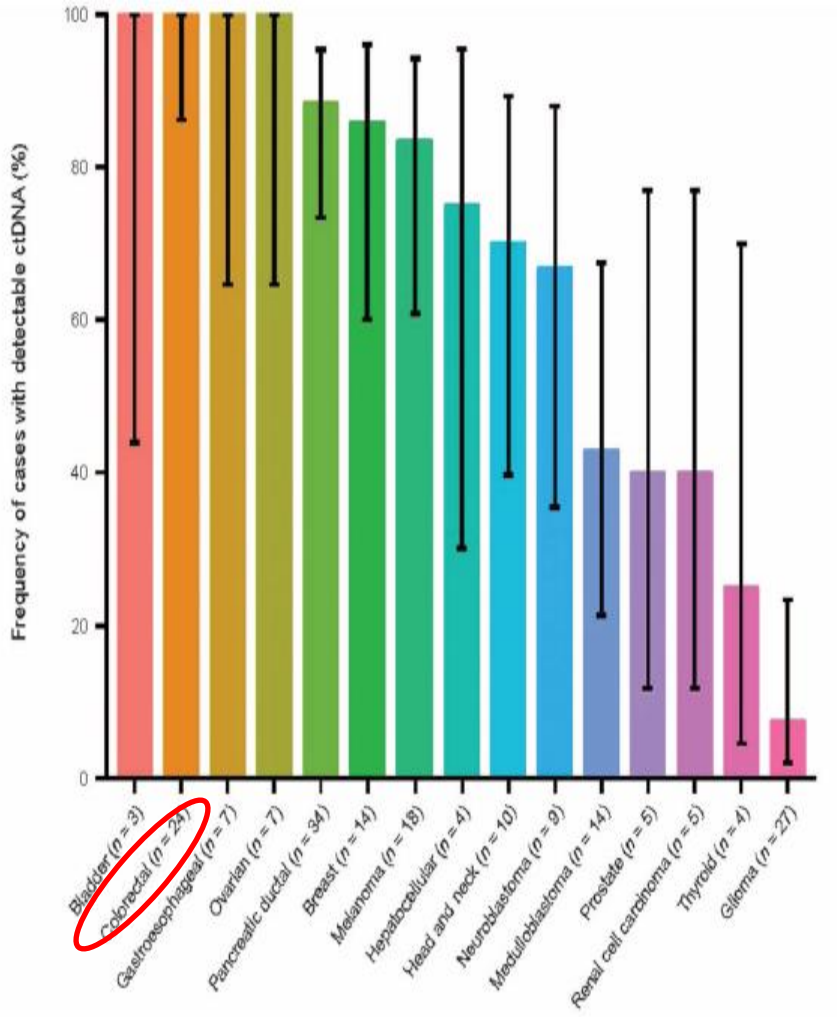
Clinical applicatons

3. Monitoring clonal dynamics (liquid biopsy)

4. Treating resistance to anti-EGFR therapy

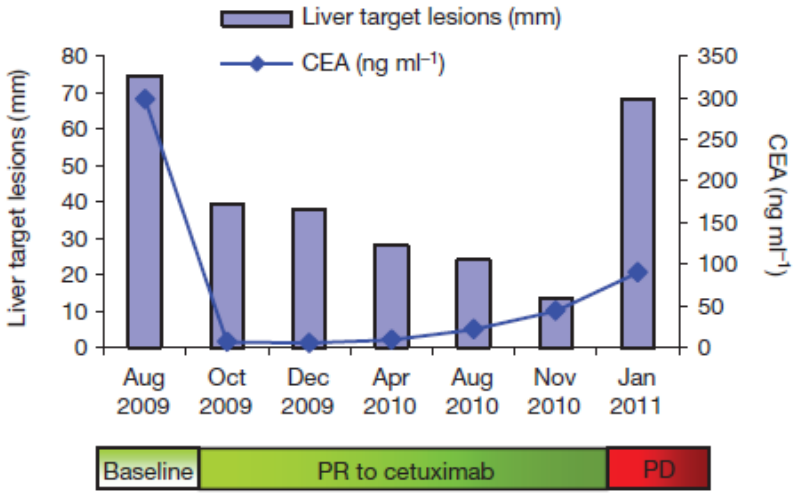
Challenge 3. Monitoring clonal dynamics
Genotyping ctDNA

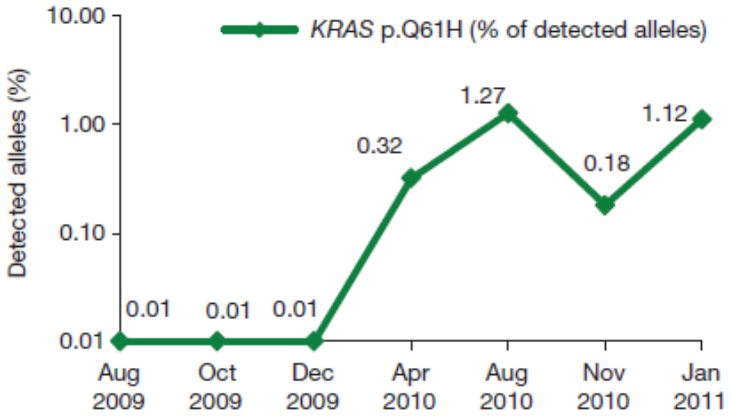




Diaz&Bardelli, J Clin Oncol 2014
Bettegowda et al. C Sci Transl Med. 2014

Monitoring mutations of resistance in the blood of patients



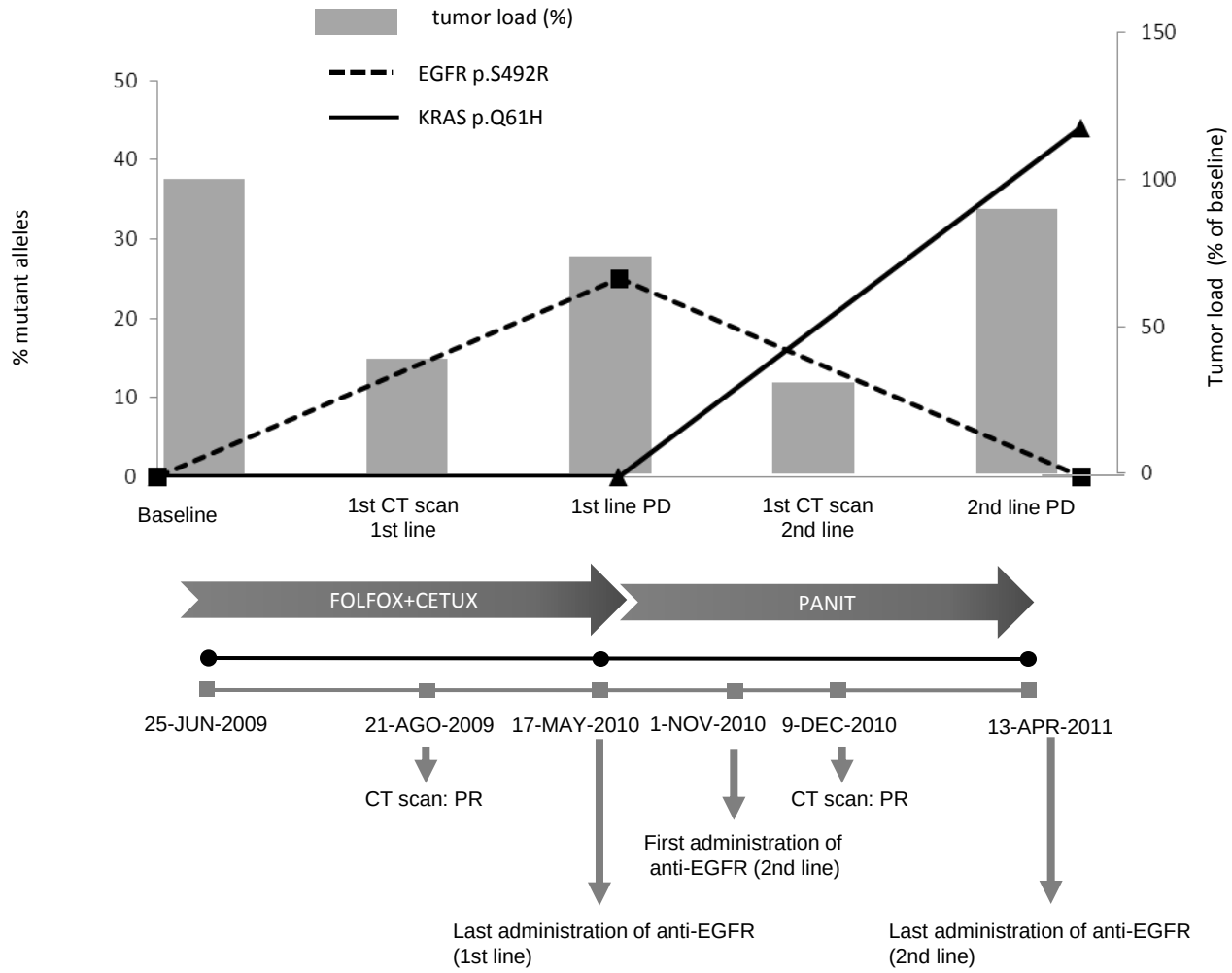


	Pretreatment										Posttreatment						
Sample ID	KRAS 12	KRAS 13	KRAS 61	NRAS 12	NRAS 61	BRAF 600	PIK3CA 538 – 549	PIK3CA 1039 – 1050	EGFR 714	EGFR 794	KRAS 12	KRAS 61	NRAS 12	NRAS 61	BRAF 600	EGFR 714	EGFR 794
Patient #5											■						
Patient #16												■					■
Patient #17																	
Patient #18											■		■				
Patient #19														■			
Patient #21											■			■			
Patient #22											■					■	
Patient #24											■			■			
Patient #26											■						
Patient #27											■						
Patient #1											■	■		■			
Patient #2											■						
Patient #4											■	■					
Patient #7											■			■			
Patient #9											■			■			
Patient #10											■	■					
Patient #12											■	■					
BARD 101											■	■		■			
BARD 102											■	■					
BARD 103											■						
CRC 188											■						
CRC 189												■					
CRC 190											■	■		■	■		
CRC 191											■	■					
Total # of cases	0	0	0	0	0	0	0	0	0	0	34	16	1	15	1	1	1

■ Single mutation
■ Multiple mutations

Misale, Nature 2012; Diaz, Nature 2012; Bettegowda, STM 2014 ; Morelli, Ann Oncol 2015

Clonal dynamics in a CRC patient treated with anti-EGFR therapy

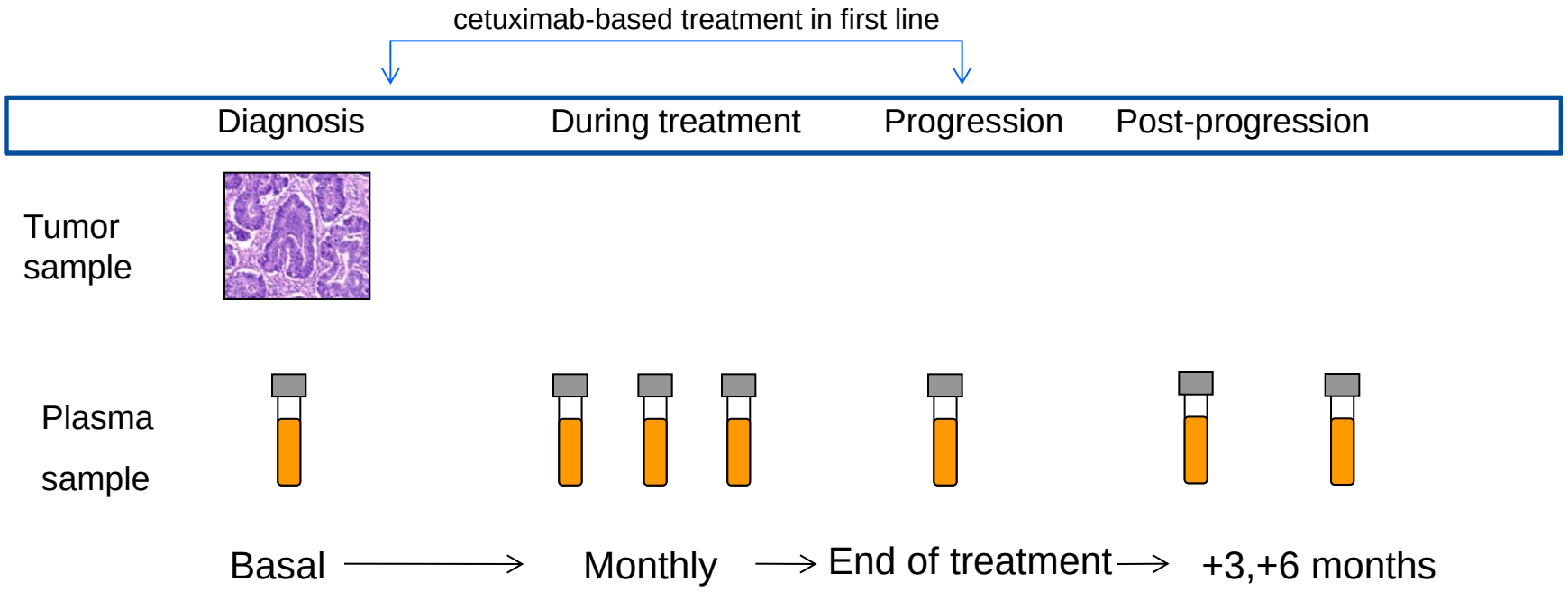


Joana Vidal.Unpublished data

Spanish Cooperative Group for the Treatment of Digestive Tumors

PLATFORM-B

Aim: Assessing the clinical relevance of monitoring mutations in serial plasma samples from 160 RAS wt mCRC patients treated with cetuximab based-therapy in first-line



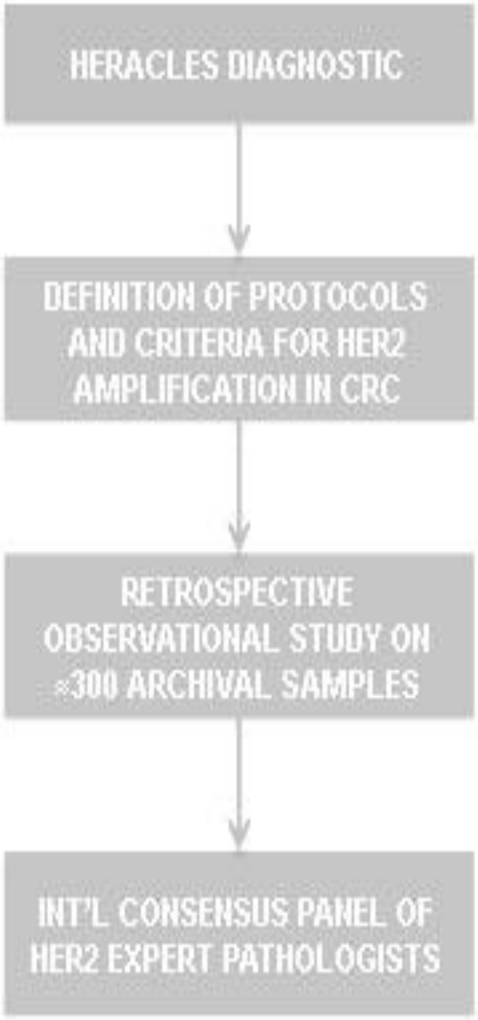
* Plasma analysis performed by BEAMing (Sysmex-Ionostics) and Idylla (Biocartis)

Challenge 4. Treating resistance to anti-EGFR

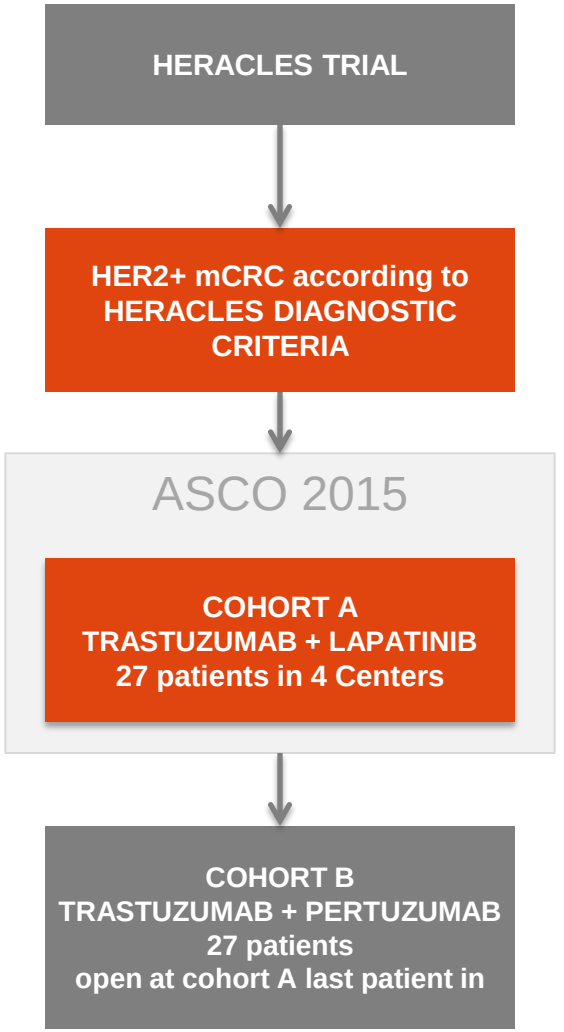
Ongoing clinical trials

mechanism of resistance	strategy	example	selected trials
***HER2* amplification**	dual anti-EGFR/HER2 therapy	Trastuzumab + pertuzumab or lapatinib	Heracles trial (Phase II)
***MET* amplification**	anti-EGFR mAbs + MET inhibitors	Cetuximab + ARQ197 (tivantinib)	NCT01892527 (Phase II)
		Cetuximab + INC280	NCT02205398 (Phase I)
***EGFR downstream* mutations (RAS/RAF/MEK)**	anti-EGFR mAbs + MEK inhibitors	Panitumumab + MEK162	NCT01927341 (Phase II)
	rechallenge		FIRE-4
***EGFR S492R* mutation**	panitumumab	NA	NA
***EGFR* ECD mutations**	Novel anti-EGFR	Sym004	NCT02083653 (Phase II)
		MM-151	NCT01520389 (Phase I)

HERACLES clinical project



Valtorta E. et al, Modern Pathol, 2015



S. Siena et al, ASCO 2015

Response

Best Response RECIST 1.1 by centralized revision	N	%
Responses (PR+CR)	8	34.7
Complete Response	1	4.3
Partial Response	7	30.4
Stable Disease ≥4 mos	7	30.4
Stable Disease <4 mos	3	13.0
Progressive Disease	5	21.7
Total	23	100

78% disease control

O – 008

Phase II study of tivantinib (ARQ 197) in combination with Cetuximab in EGFR Inhibitor-resistant, MET-High, KRAS Wild-Type (KRASwt) Metastatic Colorectal Cancer (mCRC)

L. Rimassa[1], S. Bozzarelli[1], S. Cordio[2], L. Toppo[3], S. Lonardi[4], A. Zaniboni[5], R. Bordonaro[2], W. Liguigli[3], V. Zagonel[4], M.C. Tronconi[1], L. Di Tommaso[6], L. Giordano[1], A. Santoro[1]

Best Response

RECIST 1.1 by centralized revision

	N	%
Responses	2	11
Stable Disease	8	42
Progressive Disease	9	47
Total	19	100

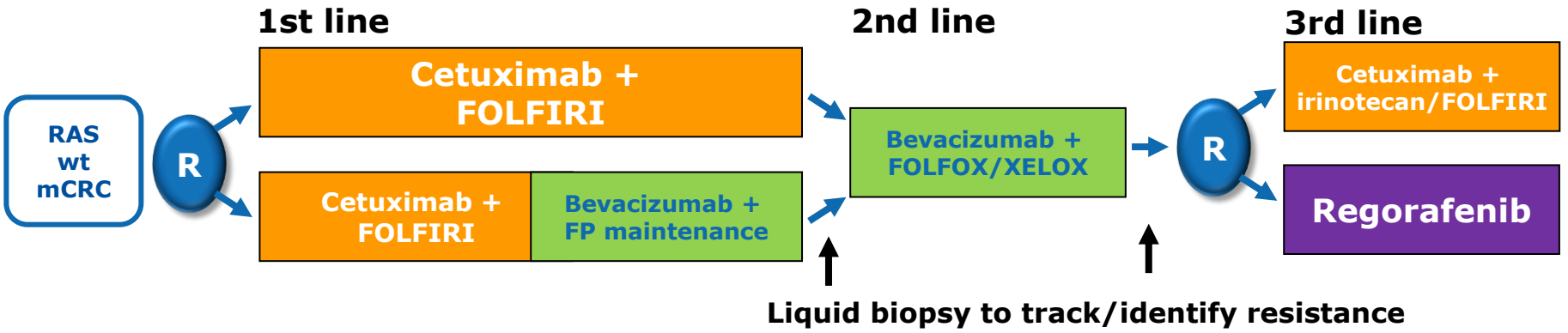
51% disease control

Most frequent adverse events (any grade):

Fatigue 30%; Neutropenia 38%, rash 33%

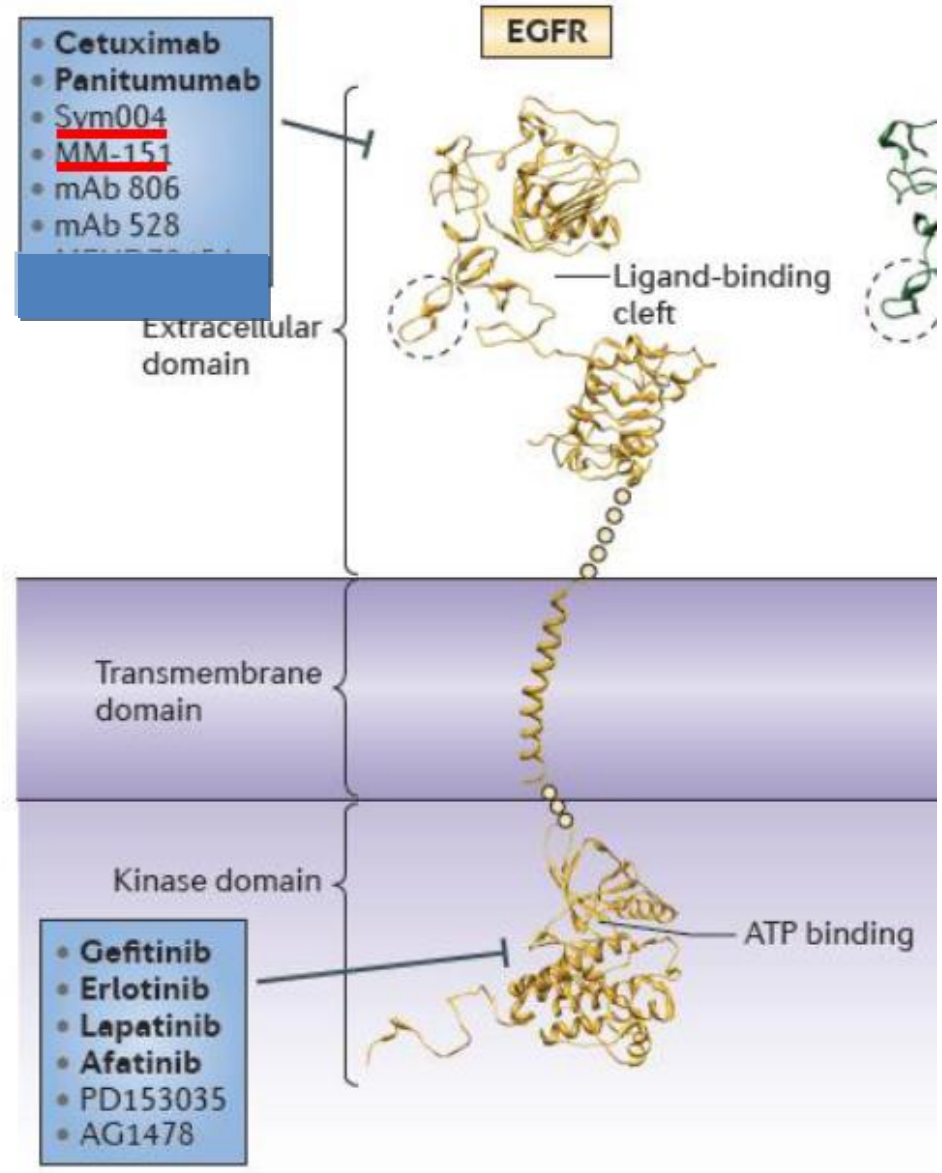
Rechallenge with anti-EGFR therapy

FIRE-4 (Phase III, n=550)



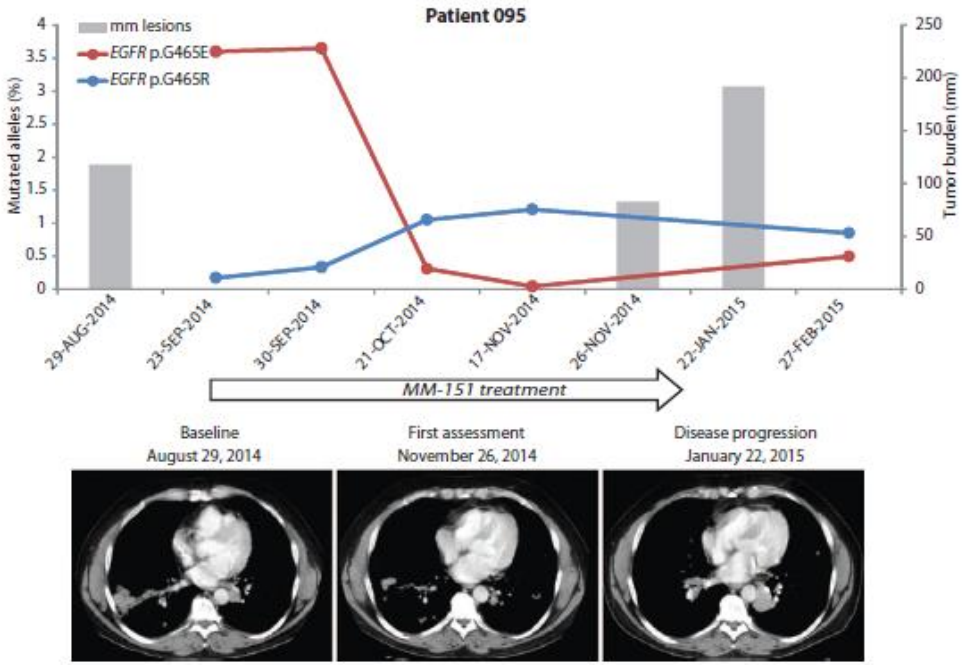
- Primary endpoint: OS after randomization 2
- Results expected: January 2022

New generation anti-EGFR moAb



MM-151 overcomes acquired resistance to cetuximab and panitumumab in CRC harbouring EGFR ECD mutations

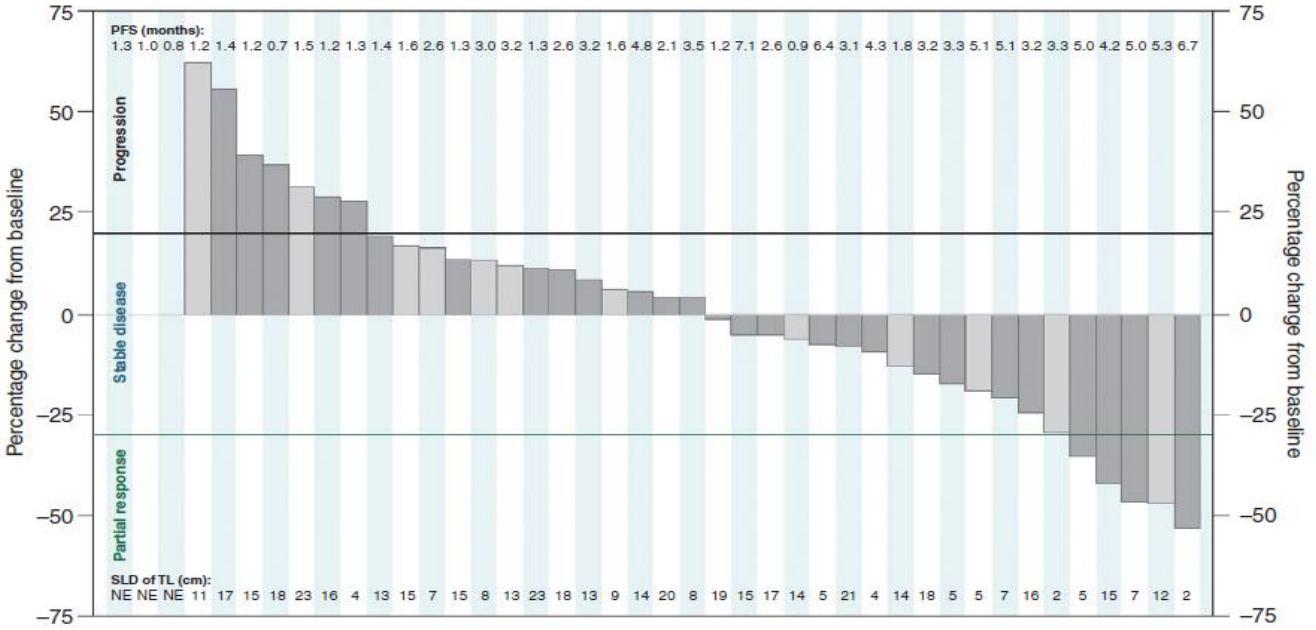
Subject ID	Study treatment	*EGFR* ECD mutations	Best RECIST v.1.1 response on MM-151
005-30-008	MM-151 monotherapy	ND	PD
010-30-007	MM-151 monotherapy	ND	PD
010-42-020	MM-151 monotherapy	ND	SD
054-62-051	MM-151 monotherapy	*EGFR* p.S464L *EGFR* p.G465R	SD
065-72-065	MM-151 monotherapy	ND	PD
054-92-095	MM-151 monotherapy	*EGFR* p.G465E *EGFR* p.G465R	SD (29.7% reduction)
065-92-103	MM-151 monotherapy	ND	PD
005-02-109	MM-151 monotherapy	ND	PD
065-02-093	MM-151 monotherapy	ND	PD
054-03-106	MM-151 + irinotecan	ND	PD
010-03-086	MM-151 + irinotecan	ND	SD



Arena et al, STM 2015

Safety and Activity of **Sym004** in patients progressing to cetuximab

- Hipomagnesemia and skin toxiciy G3 as limiting toxicities



17/39 (44%) tumor shrinkage

1 patient harbouring **EGFR G465R** mutation

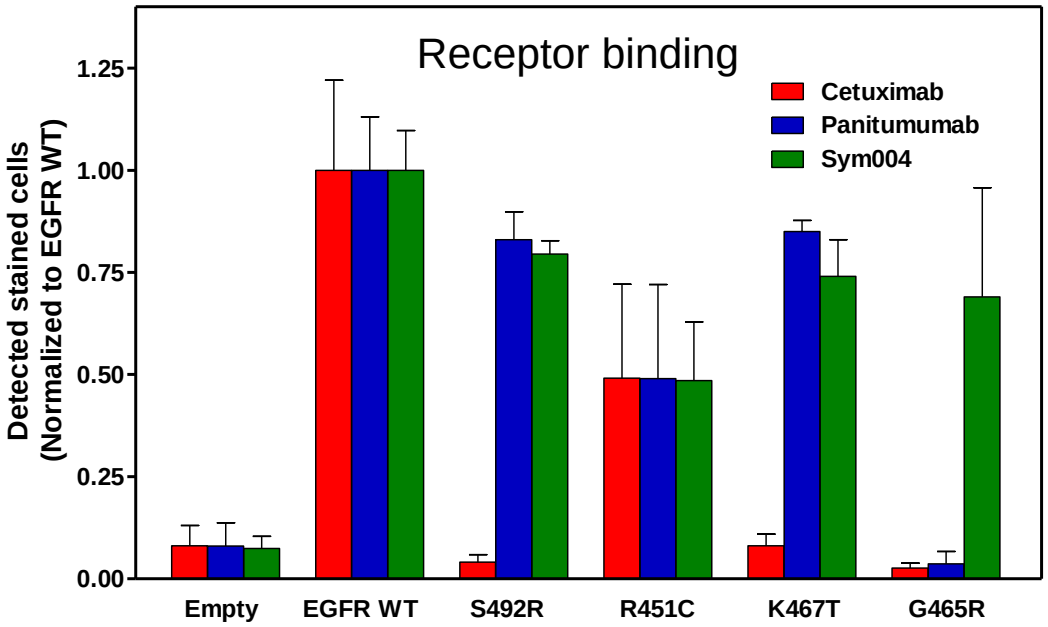
4/39 (13%) partial response:

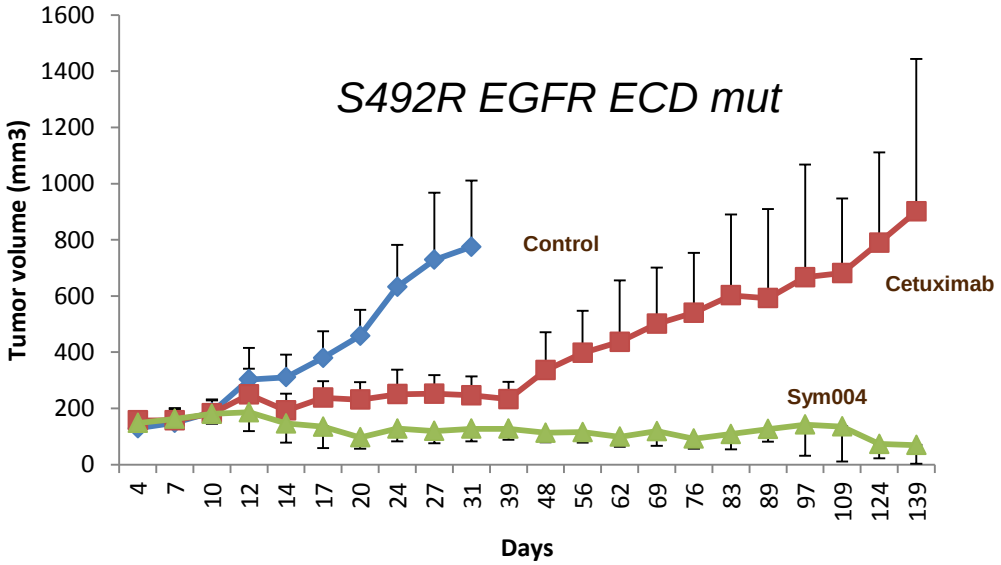
1 patient harbouring **EGFR S492R** mutation

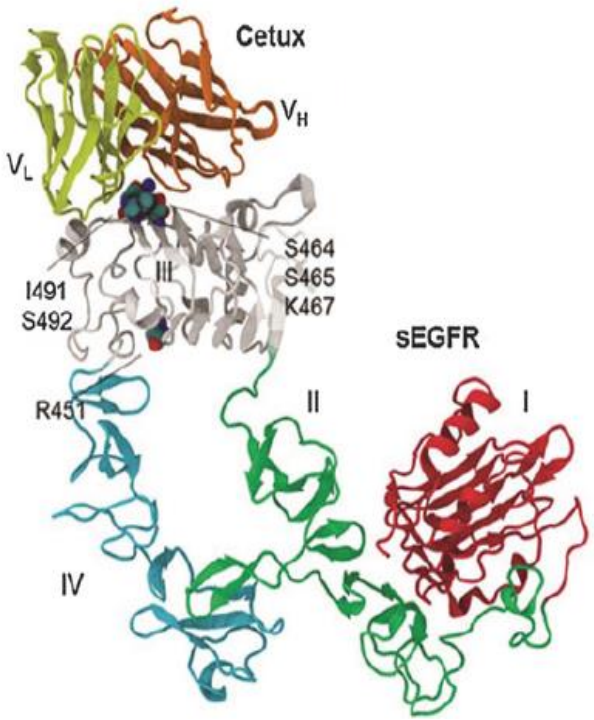
3 patients quadruple negative tumors

Dientsmann. Cancer Discov 2015; Sánchez-Martin, CCR 2016

Contrary to cetuximab and panitumumba, Sym004 is effective in colorectal cancer harbouring EGFR ECD mutations







Sánchez-Martín *et al*. CCR 2016

Clinical Trial Protocol

Title	Open-label, Multicenter Phase II Trial Investigating Sym004 Dose in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies and Documented Mutation of Extra Cellular Domain of EGFR (ECD)
Trial Phase	II
Coordinating Investigator	Josep Tabernero, MD PhD

mCRC patients with acquired resistance to cetuximab/ panitumumab

EGFR ECD mut

Sym004

Liquid biopsy
EGFR ECD
RAS/RAF

Primary endpoint: Response Rate

Take-home message

- CRC cells evade EGFR inhibition mainly by: (1) downstream mutations or activation of alternative receptors that converge in MEK activation (2) EGFR ECD mutations

- Clonal evolution drives acquired resistance to anti-EGFR drugs

- Clonal evolution may be tracked by serial liquid biopsies longitudinally performed during anti-EGFR treatment

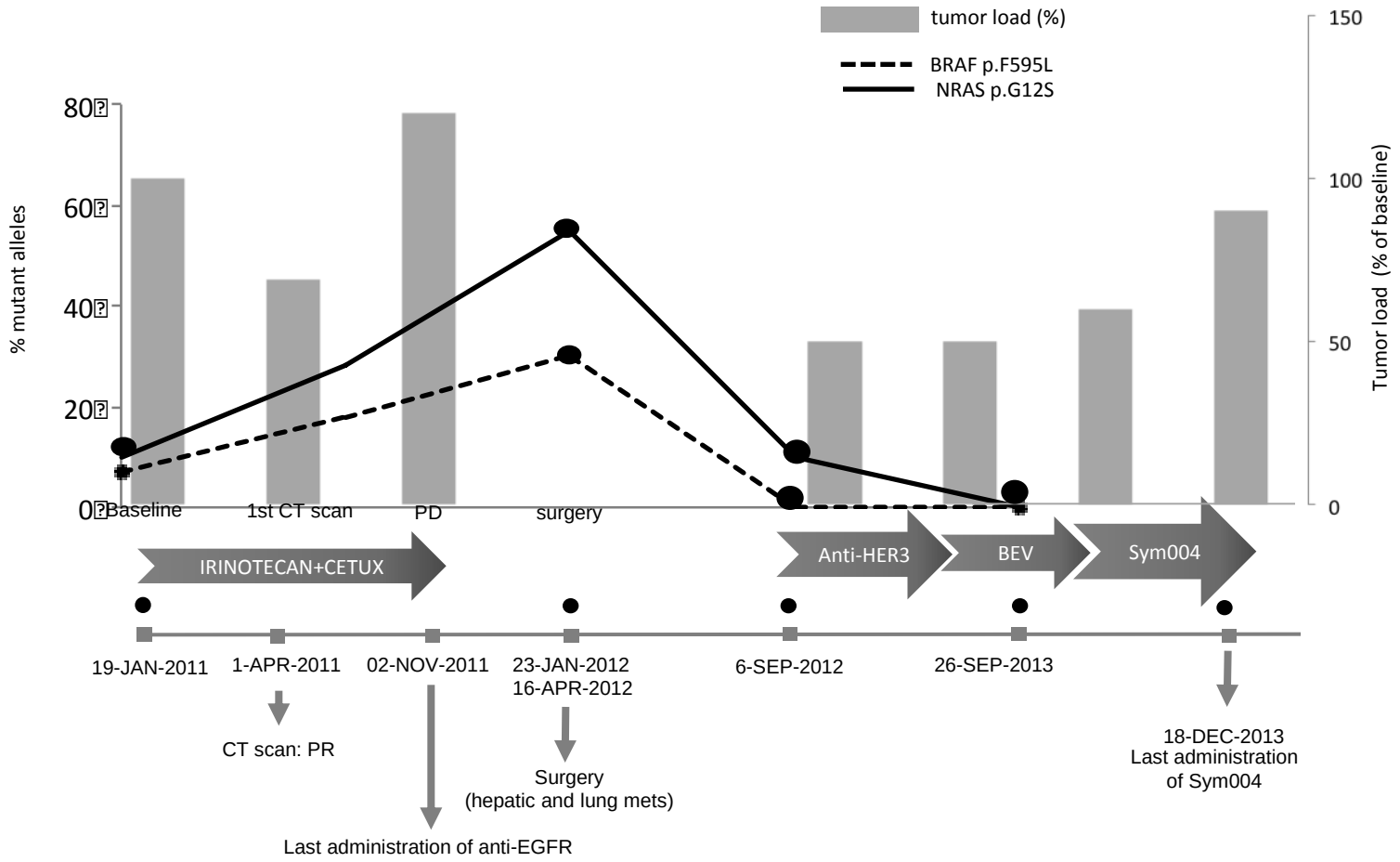
- Clonal monitoring is mandatory to personalize further treatment decisions

- Therapeutic strategies to overcome acquired resistance are being investigated in clinical trials with promising results

Thanks

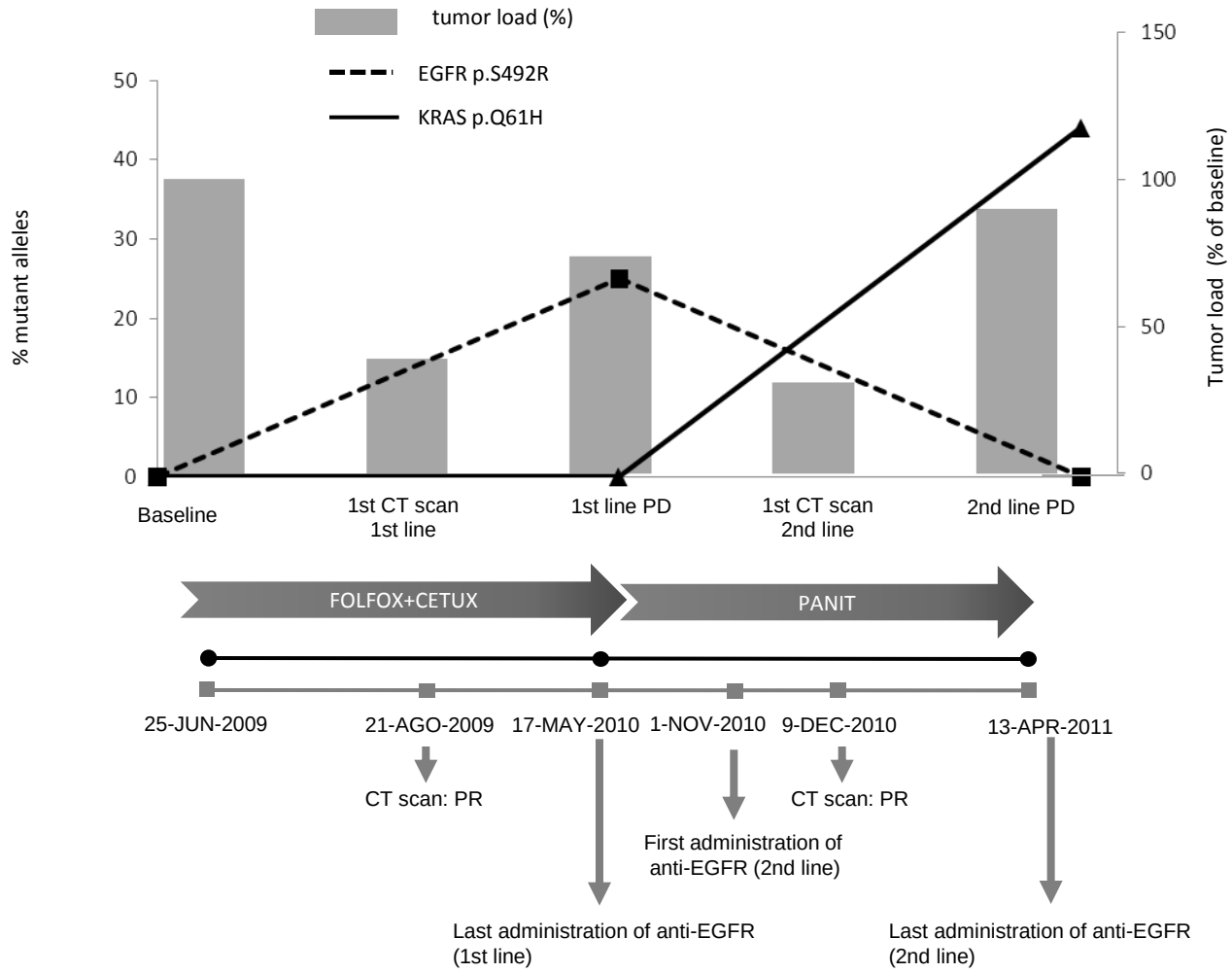
cmontagut@hospitaldelmar.cat

Clonal dynamics in a CRC patient



Joana Vidal.Unpublished data

Clonal dynamics in a CRC patient treated with anti-EGFR therapy



Joana Vidal.Unpublished data

Main eligibility criteria

- Histological diagnosis of colorectal cancer
- Metastatic disease not amenable to R0 surgery
- KRAS exon 2 wild type
- HER2+ according to HERACLES Diagnostic Criteria
- Failure of previous fluoropyrimidines, irinotecan, oxaliplatin, cetuximab or panitumumab; prior bevacizumab, aflibercept or regorafenib allowed but not mandatory
- ECOG Performance Status 0-1
- No symptomatic CNS metastases
- Normal blood, liver, renal, and cardiovascular function

S. Siena et al, ASCO 2015