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IS IT TIME TO RE-CHALLENGE ANTI-EGFR IN MCRC?

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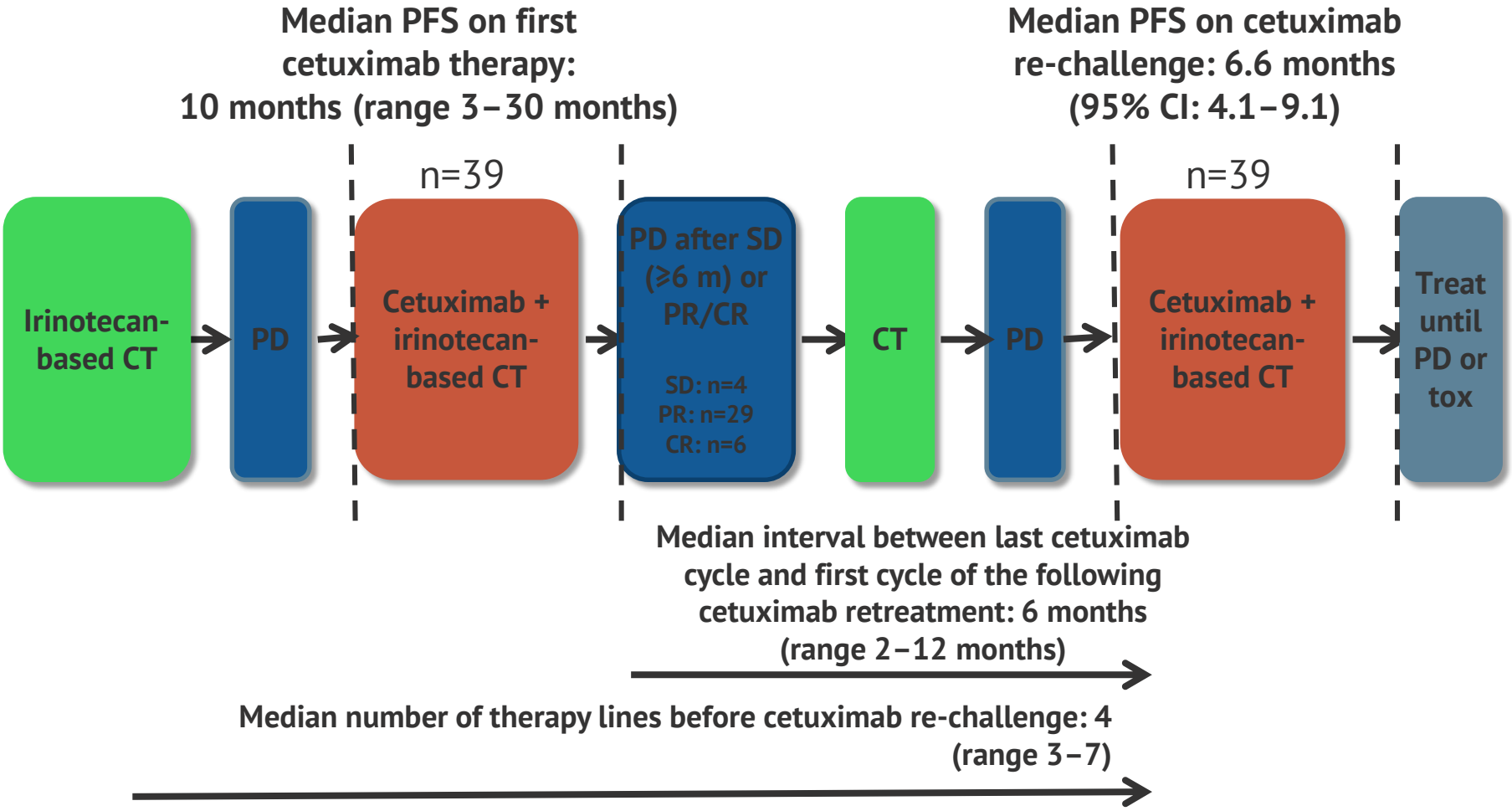
CURRENT EVIDENCE: PFS AFTER CETUXIMAB TREATMENT AND RE-CHALLENGE



Santini D, et al. Ann Oncol 2012; 23:2313–2318

TUMOR RESPONSE AFTER CETUXIMAB TREATMENT AND RE-CHALLENGE IN IRINOTECAN-REFRACTORY MCRC

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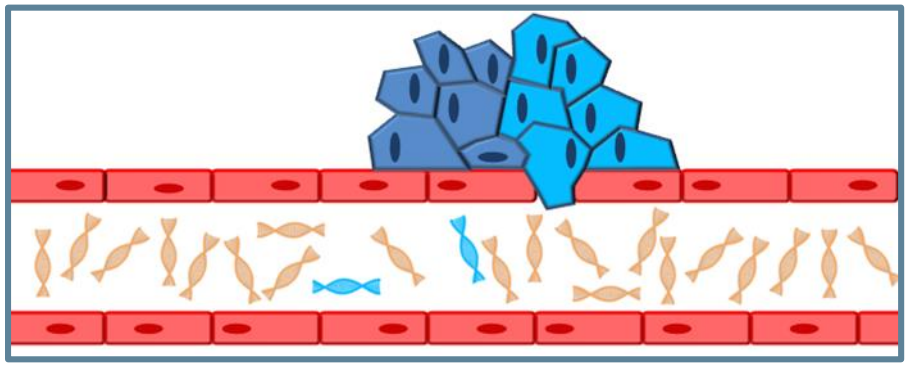
Approximately half the patients showed a partial or complete tumor response to cetuximab re-challenge

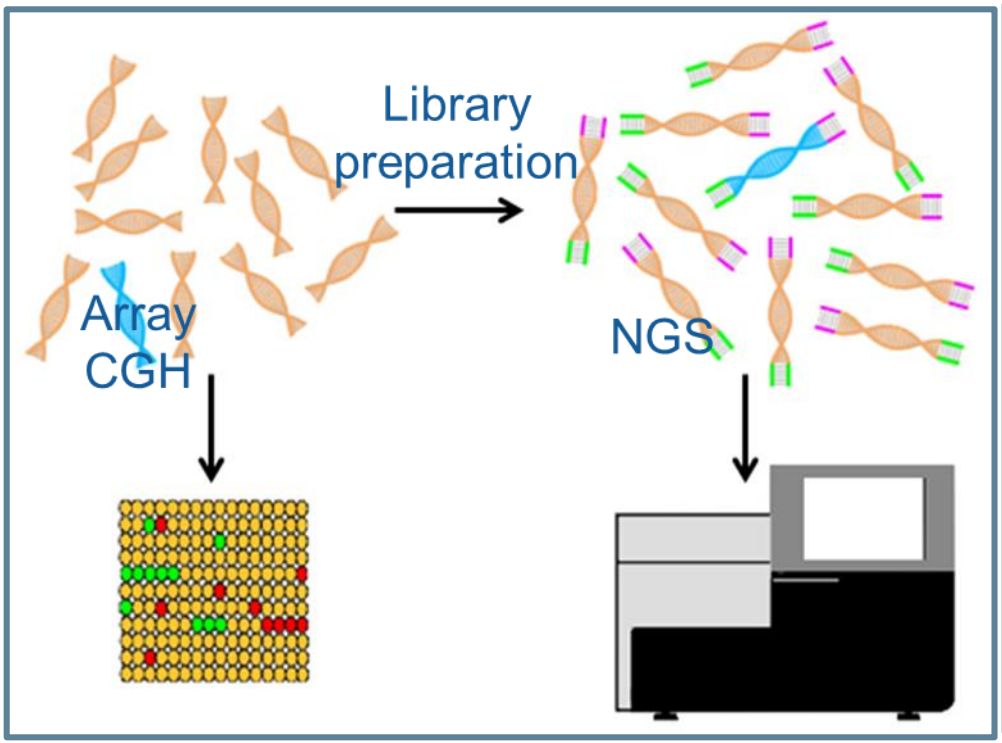
Response to cetuximab re-challenge after previous benefit from cetuximab (n=39)	
	% patients (95% CI)
ORR	53.8 (39.1–63.7)
PR	48.7
CR	5.1
SD	35.9 (24.7–51.6)
DCR	89.8
PD	10.2

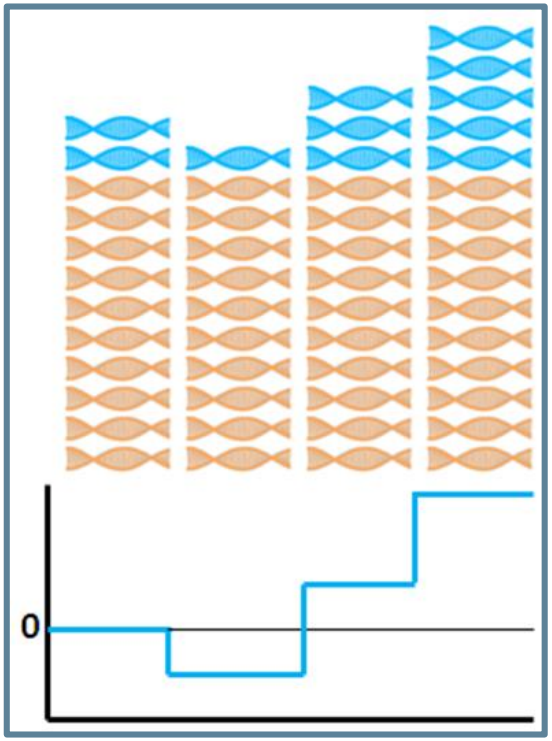
- **Primary endpoint:** ORR
- Tumor response (both during cetuximab treatment and re-challenge, prior or further treatments) was evaluated every 8 weeks by consistent imaging techniques (CT or MRI)
- RECIST evaluations performed centrally by two radiologists, confirmed by investigators

Santini D et al. Ann Oncol 2012; 23:2313–2318

LIQUID BIOPSIES: PLASMA DNA-ANALYSIS

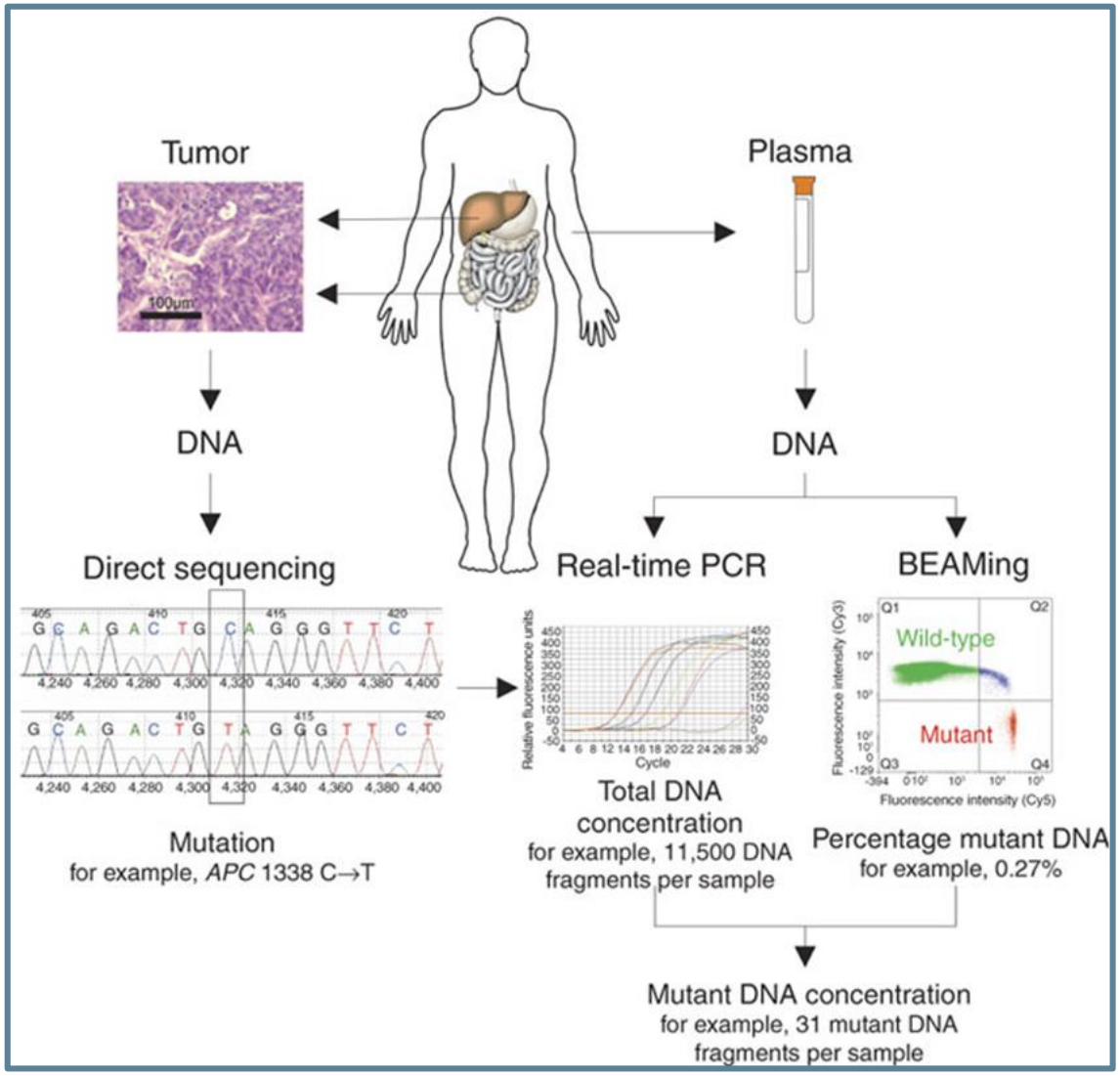






Heitzer et al. Genome Med 2013: 5;73

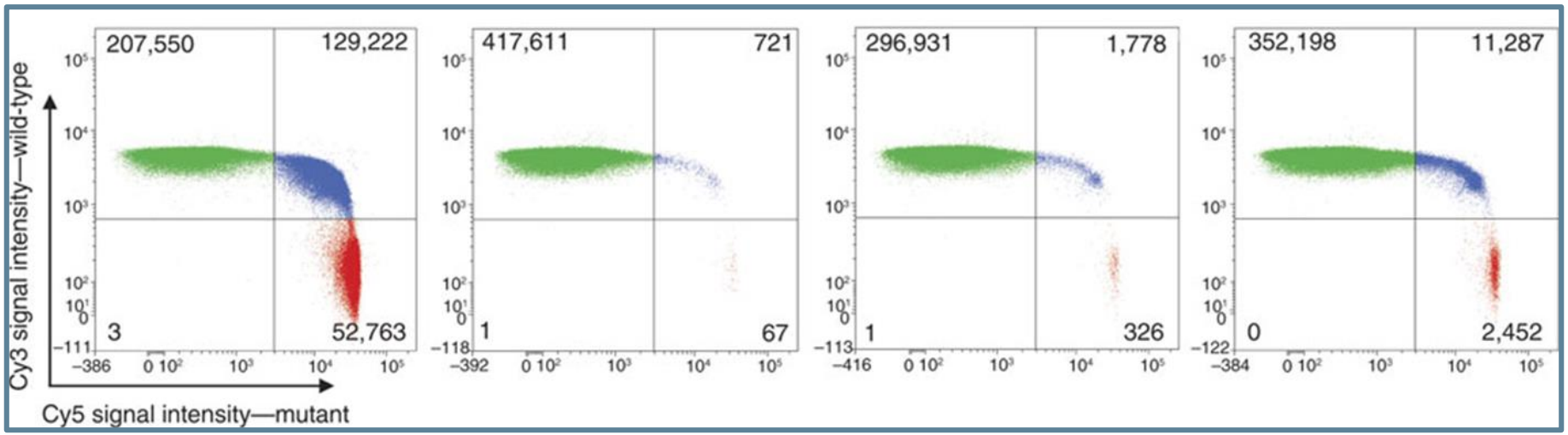
BEAMing* TECHNOLOGY



*beads, emulsion, amplification, magnetics

Diehl-F et al. Nat Med 2008;14(9):985-990

EXAMPLE: KINETICS OF ctDNA PREDICTS RELAPSE



before surgery (13.4%)	Day 3 (0.015%)	Day 48 (0.11%)	Day 244 (0.66%)

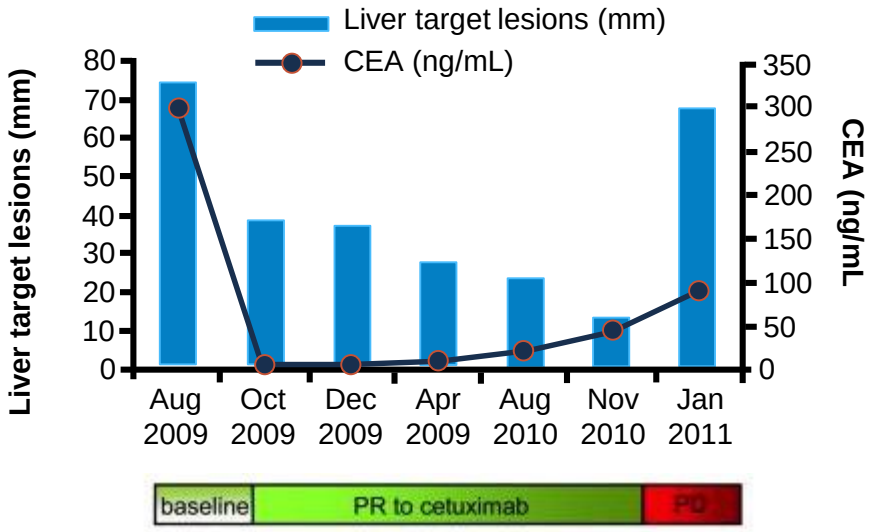
half-life time of ctDNA

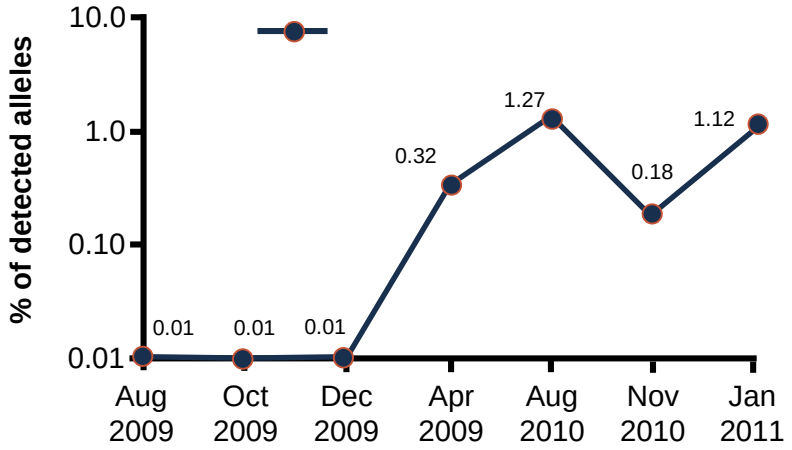
→

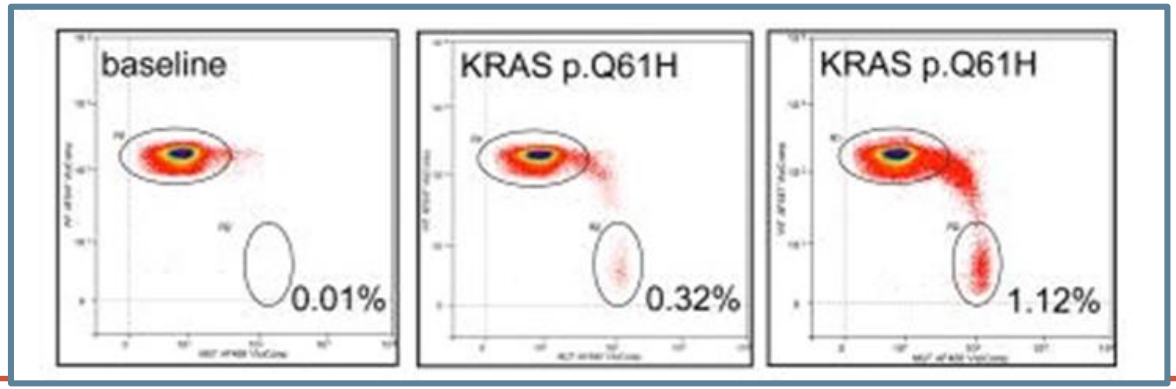
114 min

Diehl-F et al. Nat Med 2008; 14(9):985-990

EARLY DETECTION OF ANTI-EGFR RESISTANCE







Misale S et al. Nature 2012; 486(7404):532–536

RESEARCH ARTICLE

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RESEARCH ARTICLE

CANCER

Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies

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CONCORDANCE BETWEEN TUMOR TISSUE ASSESSMENT AND ctDNA-ANALYSIS (n=95)

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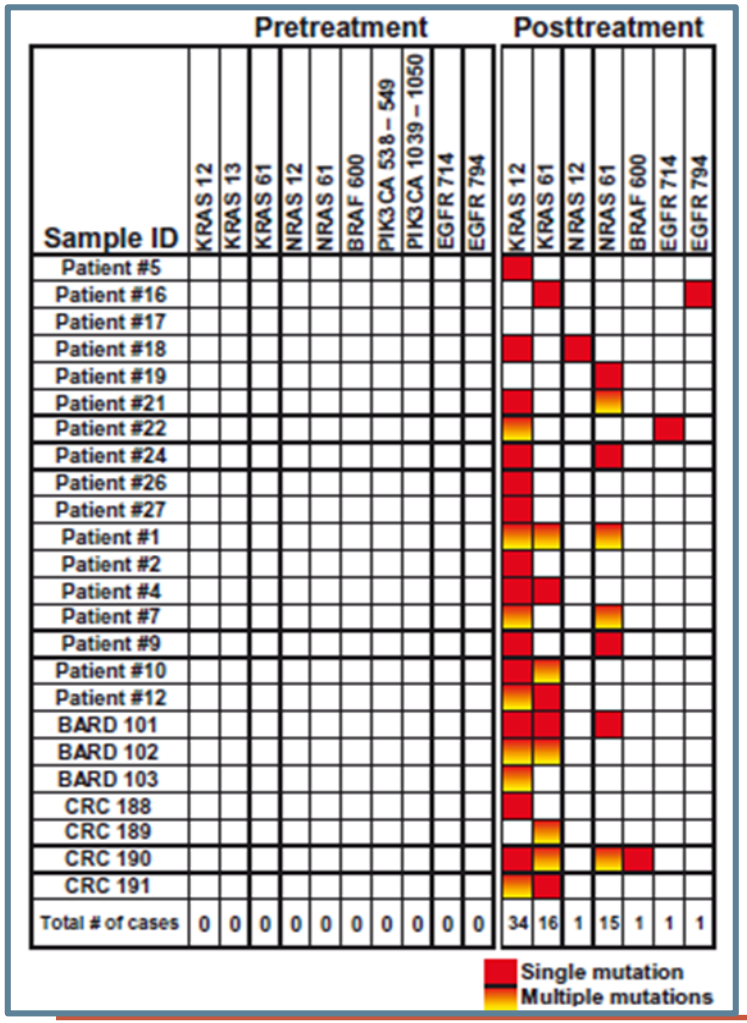
		Tumorgewebs-Analyse				
Accuracy	KRAS	Mutante	WT	Sensitivity	Specificity	Accuracy
cfDNA -Analyse	Mutante	36	1	92%	98%	96%
	WT	3	55			
	Total	39	56			

	BRAF	Mutante	WT	Sensitivity	Specificity	Accuracy
cfDNA -Analyse	Mutante	5	0	100%	100%	100%
	WT	0	90			
	total	5	90			

	All Mutationen	Mutante	WT	Sensitivity	Specificity	Accuracy
cfDNA -Analyse	Mutante	41	1	93%	98%	96%
	WT	3	50			
	total	44	51			

Thierry et al. Nat Med 2014; Apr;20(4): 430-5

RE-CHALLENGE OF ANTI-EGFR IS FEASIBLE IF REAL-TIME MOLECULAR ANALYSIS IS PERFORMED



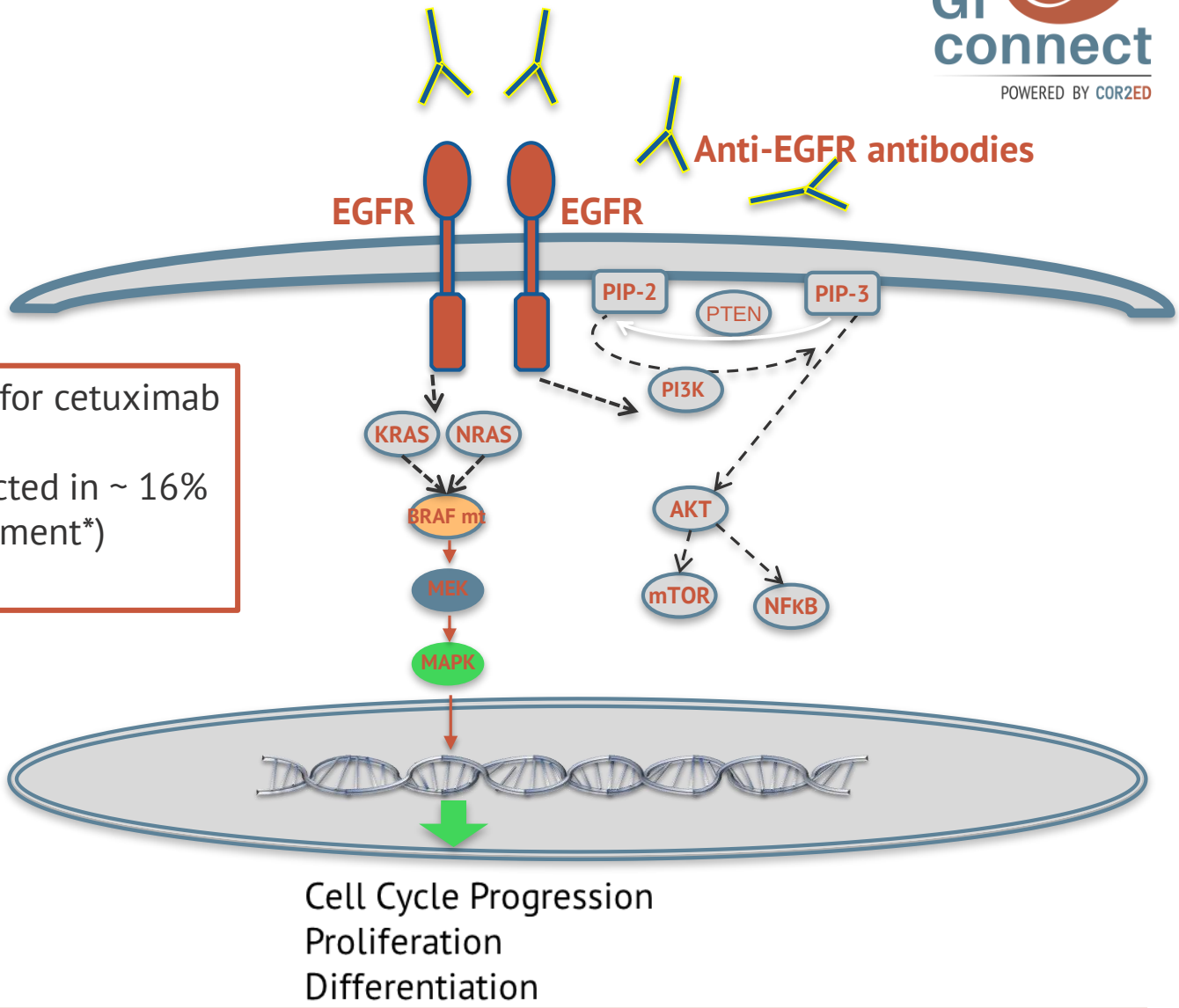
"the most surprising observation was the fact that during anti-EGFR-blockage a high number of tumors developed mutations in codon 61 of either KRAS or NRAS

- *15 out of 24 patients (62,5%) developed a Codon 61- mutation*
- *31 mutationen in 15 patients accounted for 45% of all observed 69 detected mutations*
- *48% of Codon 61-mutations were found in NRAS, the other in KRAS"*

Bettegowda et al. Sci Transl Med 2014; 6:224ra24

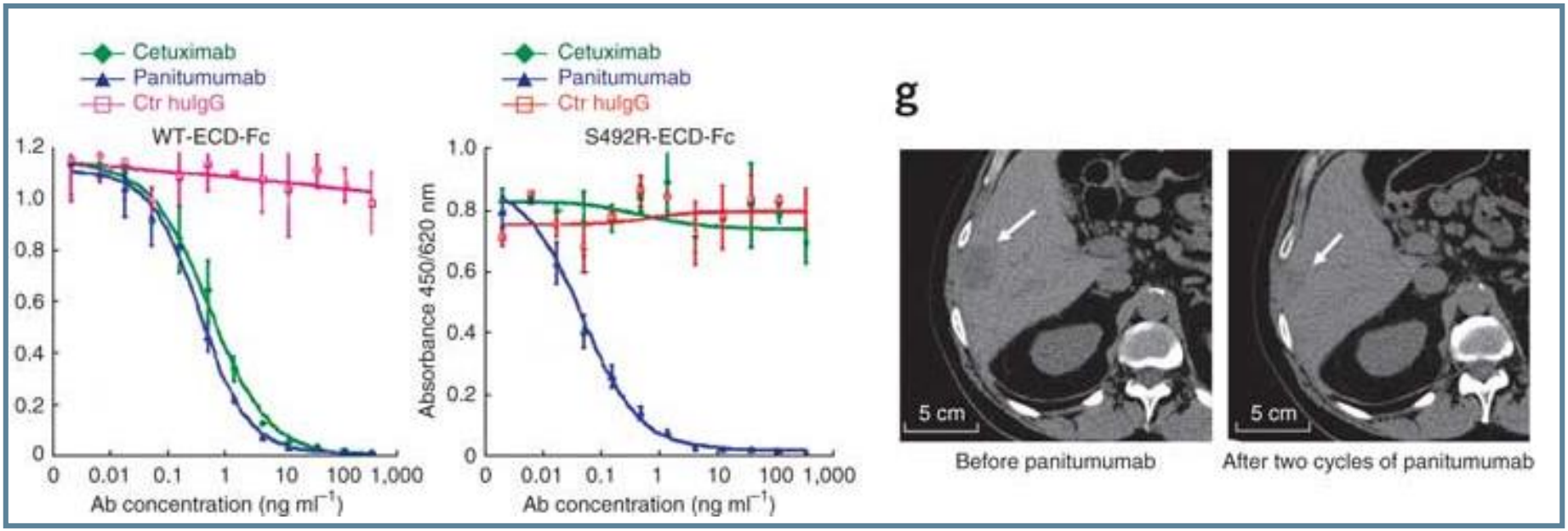
S492R EGFR MUTATION

- in the binding epitop for cetuximab
- blocks AB Binding
- klonal Selectio (detected in ~ 16% after cetuximab treatment*)
- might be predictive



EGFR EPITOPE MUTATION:

In 16% of cetuximab and in 1% of panitumumab treated patients a S492R mutation is detected



Nature Medicine 2012; 18:221–223

S492R MUTATION LEADS TO RESISTANCE TOWARDS CETUXIMAB

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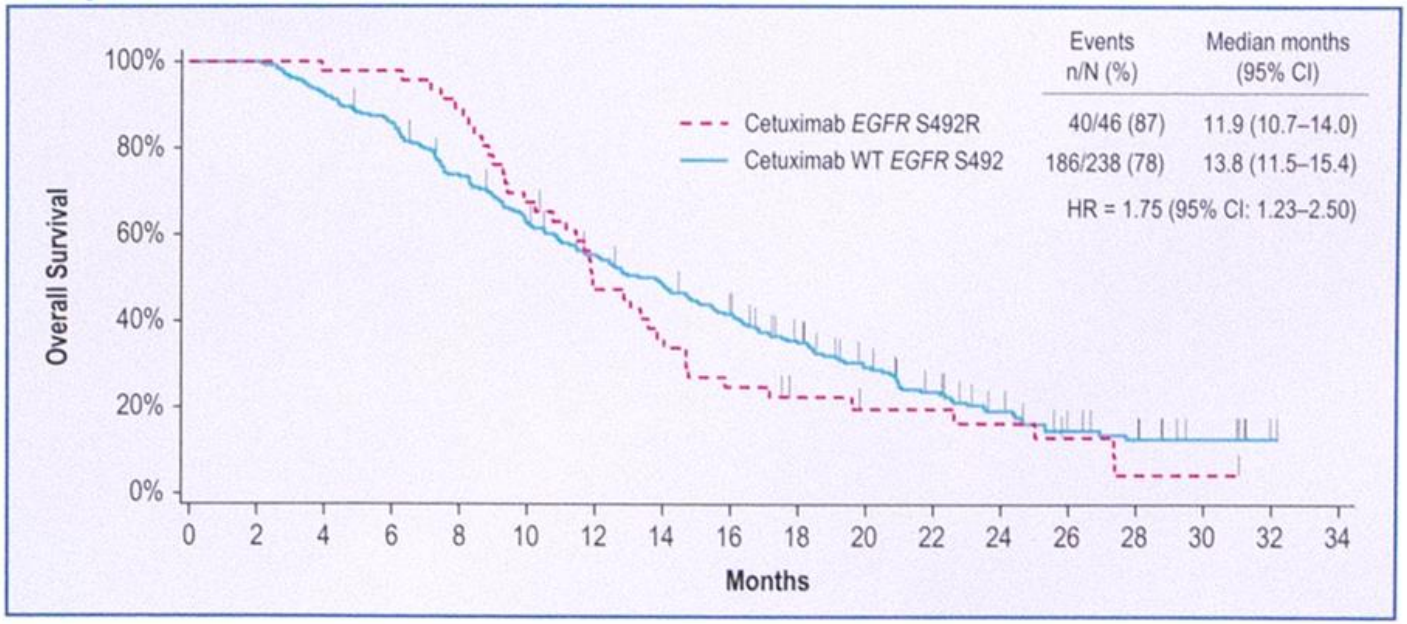
OS by EGFR S492 Status in Patients Treated With Cetuximab

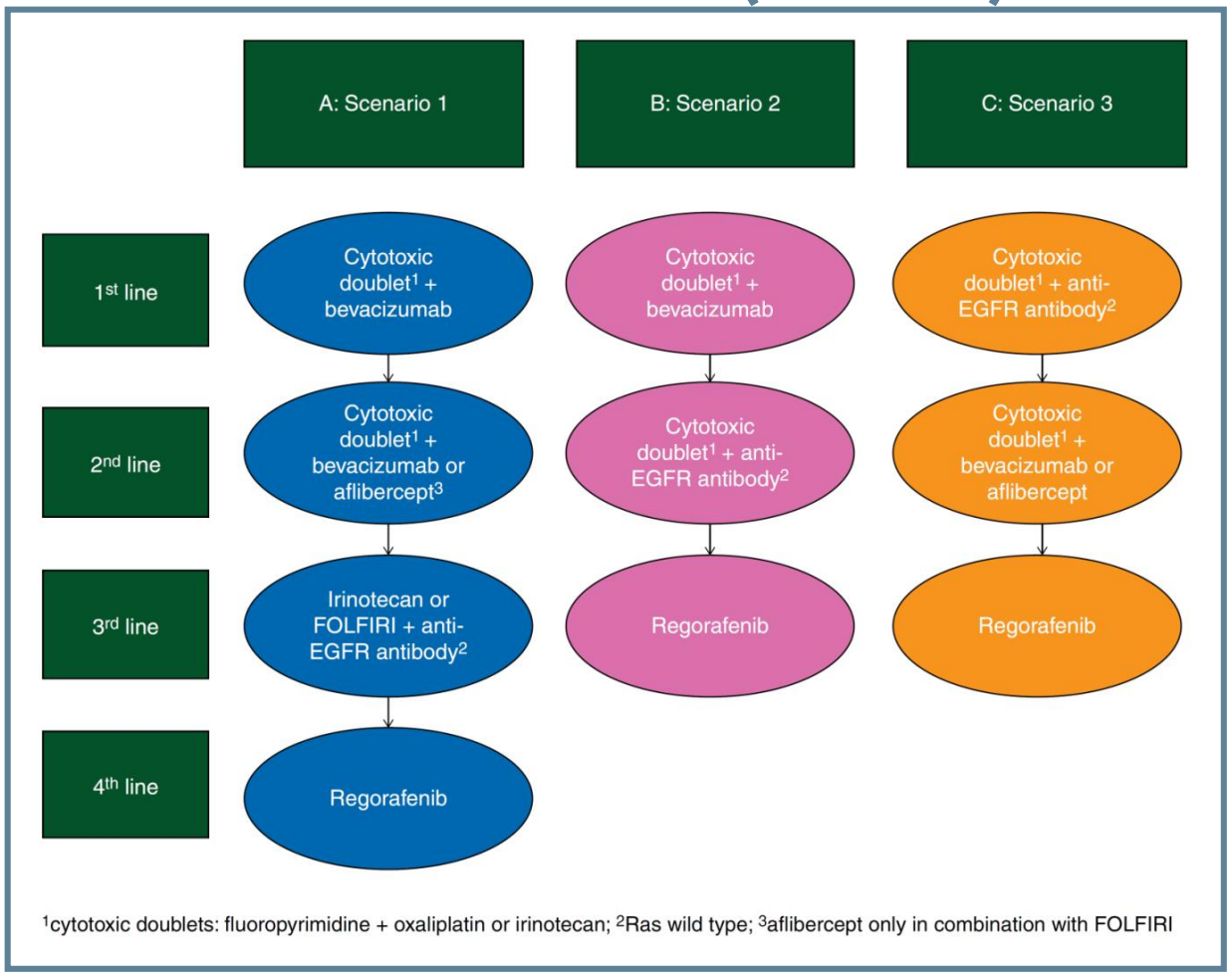


Summary of Efficacy Results

	Panitumumab (n = 262)*	Cetuximab (n = 284)*	Cetuximab EGFR S492R (n = 46)	Cetuximab WT EGFR S492 (n = 238)
Median OS - mos (95% CI)	12.5 (11.2–14.3)	12.8 (11.7–14.7)	11.9 (10.7–14.0)	13.8 (11.5–15.4)
HR (95% CI)	1.03 (0.85–1.25)		1.75 (1.23–2.50)	

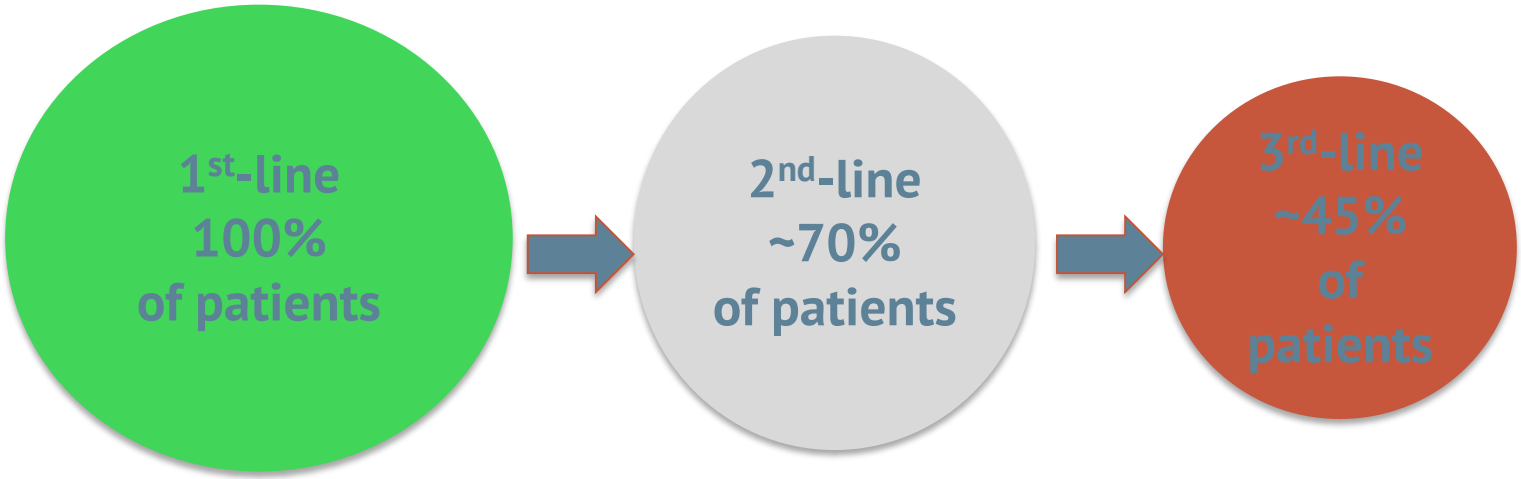
J Clin Oncol 2015; 33:(suppl 3; abstr 740)

mCRC- ESMO CLIN. PRAC. GL (RAS wt)



With Regorafenib (taken off market in Germany) and TAS102, two options with limited activity beyond combination therapy available

PATIENTS EXPOSED IN TREATMENT LINES



Approximately every second patient with metastatic colorectal cancer receives third/last-line therapy. Therefore a high need for clinical meaningful treatment options can be presumed

Registry colorectal carcinoma TKK; iOMEDICO AG; Modest DP et al J Clin Oncol 2015; Cremolini et al. Lancet Oncol 2015

TREATMENT EFFICACY IN THE CONTINUUM OF CARE

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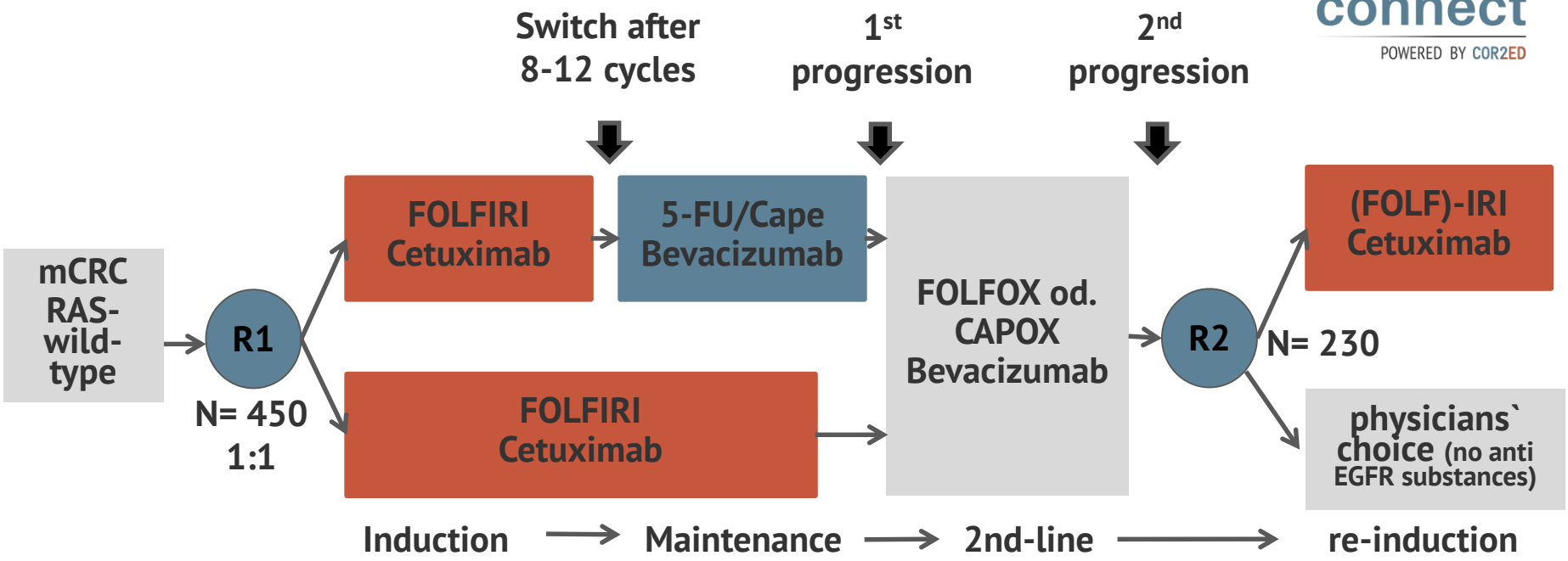
Parameter*	1st line	2nd line	Later lines
Response rate	38–64%[1,2]	10–35%[5,6]	1–13%[8,9,11]
Progression-free survival	8–11 months[3,4]	4–7 months[5,7]	2–3 months[8,11]

*Range of results for targeted treatment arms of key Phase II and III trials (KRAS wt exon 2 for EGFR inhibitor trials)

Conclusion: for later-line therapies, tumor shrinkage cannot be expected

1. Maughan TS, et al. Lancet 2011;377:2103–2114 2. Saltz LB, et al. J Clin Oncol 2008;26:2013–2019 3. Bokemeyer C, et al. Ann Oncol 2011;22:1535–1546 4. Hurwitz H, et al. New Engl J Med 2004;350:2335–2342 5. Langer C, et al. ESMO 2008 (Abstract No. 385P) 6. Peeters M, et al. J Clin Oncol 2010;28:4706–4713 7. Giantonio BJ, et al. J Clin Oncol 2007;25:1539–1544 8. Grothey A, et al. Lancet 2013;38:303–312 9. Karapetis CS, et al. N Engl J Med 2008;359:1757–1765 10. Amado RG, et al. J Clin Oncol 2008;26:1626–1634 11. Mayer RJ, et al. N Engl J Med. 2015 May 14;372(20):1909-19

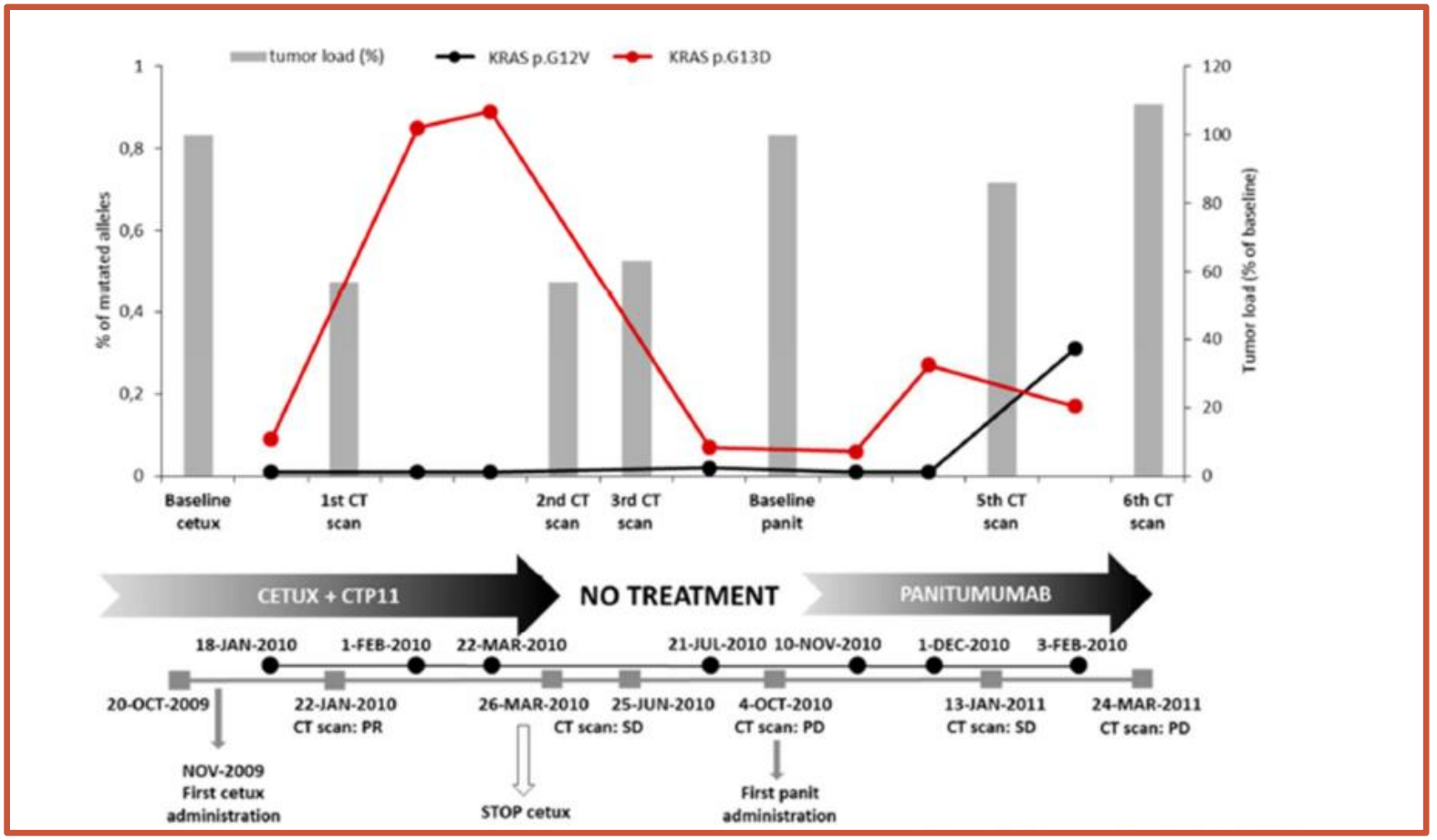
FIRE-4 (AIO KRK-0114)



primary tumor tissue liquid biopsy	liquid biopsy	liquid biopsy	tumor biopsy liquid biopsy	liquid biopsy

Primary Endpoint: OS3 after randomisation 2 (R2)
Co-primary Endpoint: PFS in 1st-line

WHEN *KRAS* CLONES DECLINE IN BLOOD, RE-CHALLENGE WITH ANTI-EGFR ANTIBODIES CAN BE CLINICALLY EFFECTIVE



Siravegna S et al. Nature Medicine 2015

ONGOING STUDIES OF RECHALLENGE WITH ANTI-EGFR IN MCRC

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Study (Study ID)	Anti-EGFR agent or combination	Main selection criteria
CRICKET (NCT02296203)	Cetuximab	*RAS* and *BRAF* wild-type; First-line irinotecan-based (FOLFIRI or FOLFOXIRI) cetuximab-containing therapy producing at least a partial response
REGAIN (NCT02316496)	Cetuximab + irinotecan	*RAS* and *BRAF* WT; First line chemotherapy regimen with a fluoropyrimidine and Irinotecan (FOLFIRI) + cetuximab with initial PR/CR and PD with PD >6 weeks after the last administration of cetuximab
FIRE-4 (EudraCT 2014-003787-21)	Cetuximab	*RAS* WT First-line FOLFIRI + cetuximab therapy producing at least a partial response
A PHASE II TRIAL OF RECHALLENGE WITH PANITUMUMAB DRIVEN BY RAS CLONAL-MEDIATED DYNAMIC OF RESISTANCE: *CHRONOS* (EudraCT 2016-002597-12)	Panitumumab	*RAS* and *BRAF* WT; First-line anti-EGFR-containing therapy producing at least a partial response; Predefined criteria of *RAS* mutational load measured on plasma ctDNA at progression of first-line and before rechallenge

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