

# Liquid biopsy to predict benefit from rechallenge with cetuximab + irinotecan in *RAS/BRAF* wild-type metastatic colorectal cancer patients with acquired resistance to 1st-line cetuximab + irinotecan:

## Final results and translational analyses of the CRICKET study by GONO

Rossini D., Cremolini C., Conca E., Del Re M., Busico A., Pietrantonio F., Bergamo F., Danesi R., Casagrande M., Tamburini E., Dell'Aquila E., Strippoli A., Masi G., Tonini G., Negri F., C. Corsi D.C., Ermacora P., Intini I., Falcone A. and Santini D.  
On behalf of the GONO (Gruppo Oncologico del Nord Ovest, Italy) investigators



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### Background

- ✓ CRICKET (NCT02296203) trial was designed to investigate the activity of the rechallenge strategy with cetuximab and irinotecan as 3<sup>rd</sup>-line treatment in and *BRAF* wild-type metastatic colorectal cancer (mCRC) patients with acquired resistance to 1<sup>st</sup>-line cetuximab and irinotecan based therapy.
- ✓ Recent data highlighted the clonal evolution and heterogeneity of acquired resistance to anti-EGFR treatments, and suggested the role of liquid biopsy as a reliable tool to track molecular events in circulating tumor DNA (ctDNA) and to properly inform treatment choices.

Siravegna G. et al., *Nat Med* 2015

### Methods

CRICKET was a multicenter phase II single-arm study investigating the activity of 3<sup>rd</sup>-line cetuximab plus irinotecan in mCRC patients, who became resistant to 1<sup>st</sup>-line cetuximab + irinotecan.

Main Eligibility Criteria were:

- ✓ *RAS* and *BRAF* wild-type status of primary colorectal cancer and/or related metastases;
- ✓ ECOG Performance Status ≤ 2;
- ✓ Measurable, unresectable mCRC;
- ✓ 1<sup>st</sup>-line irinotecan based (FOLFIRI or FOLFOXIRI) and cetuximab containing therapy producing at least partial response, with 1<sup>st</sup>-line PFS ≥ 6 months;
- ✓ Documentation of progression to 1<sup>st</sup>-line cetuximab within 4 weeks after the last cetuximab administration;
- ✓ 2<sup>nd</sup>-line oxaliplatin-based (FOLFOXIRI, FOLFOX or XELOX) and bevacizumab containing therapy;
- ✓ Time between the end of 1<sup>st</sup>-line therapy and the start of 3<sup>rd</sup>-line treatment with cetuximab plus irinotecan ≥ 4 months;

### Molecular Analyses

Liquid biopsies were collected at the rechallenge baseline. Circulating tumor DNA was analyzed with ddPCR for specific *RAS* and *BRAF* mutations, and then by means of ultra-deep next-generation sequencing (NGS) with Ion Torrent S5 XL (Thermo Fisher Scientific, Waltham, MA, USA).

### Statistics

Primary endpoint: response rate (RR) according to RECIST v1.1.

- H0: RR: 5%
- H1: RR: 20%
- Alpha error: 0.05, Beta error: 0.20
- Design: Fleming single-stage
- 27 patients to be enrolled

Rechallenge with cetuximab plus irinotecan could be considered promising if a RECIST response is observed in ≥ 4 patients.

Secondary endpoints:

- Progression free survival
- Overall survival
- Toxicity rates
- Overall toxicity rate
- Translational analyses with special regard to *RAS* and *BRAF* mutations in circulating tumor DNA from liquid biopsies

### Study population

Between January 2015 and June 2017, 28 patients were enrolled in 9 centers

#### Demographics and disease characteristics

Characteristic	Study population (n= 28)	Characteristic	Study population (n= 28)
Age in years (range)	69 (45-79)	Primary Tumor Site	
Sex		Right	9 (32%)
Male	19 (68%)	Left	13 (47%)
Female	9 (32%)	Rectum	6 (21%)
ECOG PS		Resected Primary Tumor	
0	18 (64%)	Yes	25 (89%)
1-2	10 (36%)	No	3 (11%)
Synchronous Metastases		Number of Metastatic Sites	
Yes	20 (71%)	1	7 (25%)
No	8 (29%)	>1	21 (75%)
		Time from diagnosis of mCRC	
		<18 months	5 (18%)
		≥18 months	23 (82%)

### Results

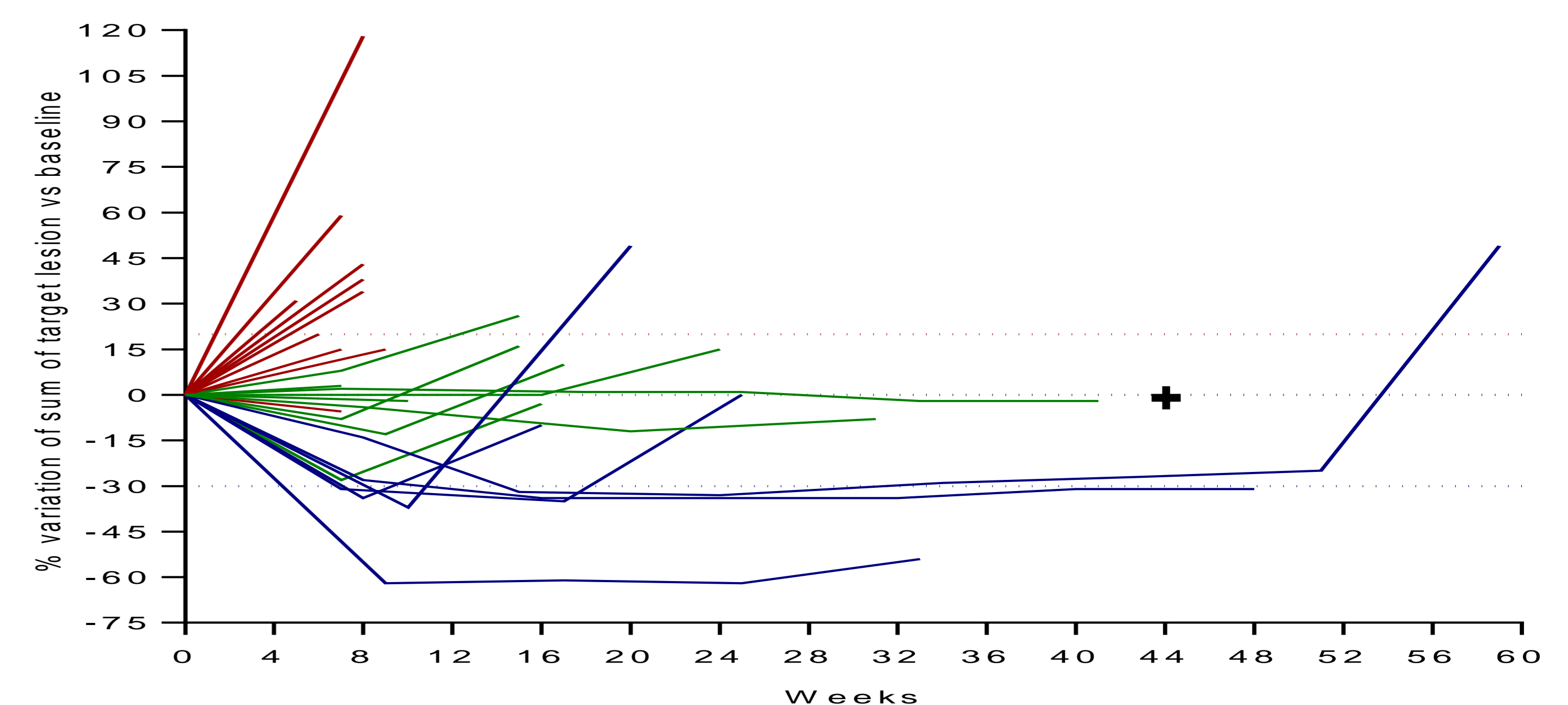
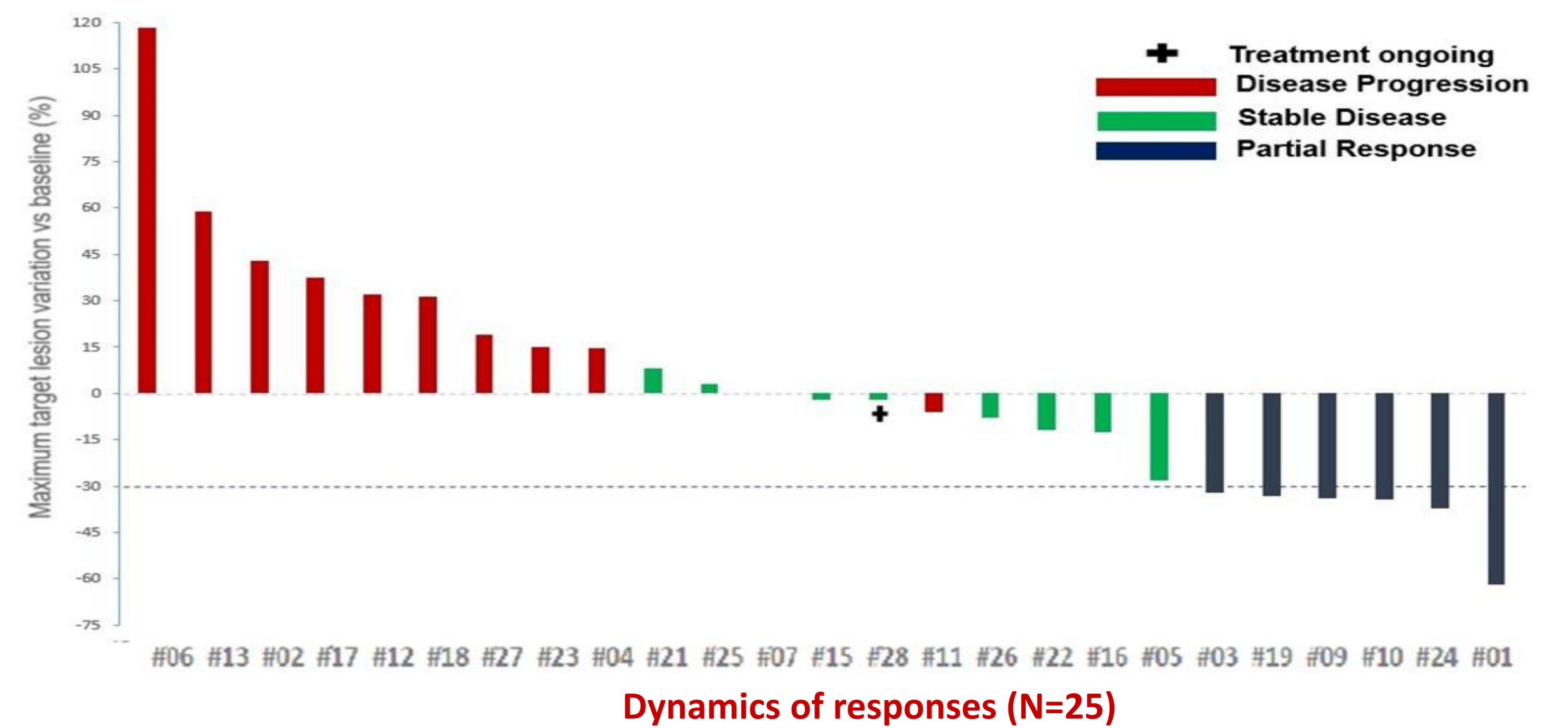
Between January 2015 and June 2017, 28 patients were enrolled in 9 centers. The primary endpoint was met.

Six patients had partial response (Response Rate: 21.5%) that was not confirmed in two consecutive evaluations in two cases, and 9 achieved disease stabilization (Disease Control Rate: 53.6%). Three patients were not evaluable for RECIST response (Table 1).

danielrossini87@gmail.com

Best Response, N (%)	Overall population N=28
Partial Response	6 (21.5%)
Confirmed Response	4 (14.3%)
Unconfirmed Response	2 (7.1%)
Stable Disease	9 (32.1%)
Disease Progression	13 (46.4%)
Radiological PD	10 (35.7%)
Clinical PD	3 (10.7%)
RECIST RR	6 (21.5%)
Disease Control Rate	15 (53.6%)

Best radiologic response of evaluable patients (N=25)



### Translational Results

*RAS* mutations were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable patients.

No *BRAF* or *PI3KCA* mutations were found.

As shown in table 1, no *RAS* mutations were detected in samples from patients who achieved a confirmed partial response.

Patients	<i>RAS</i> status on ctDNA	Objective Response
#1	Wild-type	Confirmed PR
#2	KRAS G12D	PD
#3	Wild-type	Confirmed PR
#4	Wild-type	PD
#5	Wild-type	SD
#6	KRAS G12D	PD
#7	Wild-type	SD
#9	Wild-type	Confirmed PR
#10	Wild-type	Unconfirmed PR
#11	Wild-type	PD
#12	KRAS G12D	PD
#13	KRAS G12V	PD
#15	NRAS Q61L	SD
#16	Wild-type	SD
#17	KRAS G12V/ Q61H	PD
#18	KRAS G12V	PD
#19	Wild-type	Confirmed PR
#21	KRAS G12D	SD
#22	KRAS G12V	SD
#23	KRAS G12V	PD
#24	KRAS G12D	Unconfirmed PR
#25	KRAS G12D	SD
#26	Wild-type	SD
#27	Wild-type	PD
#28	Wild-type	SD

Table 1 *RAS* Status on ctDNA and Objective Response

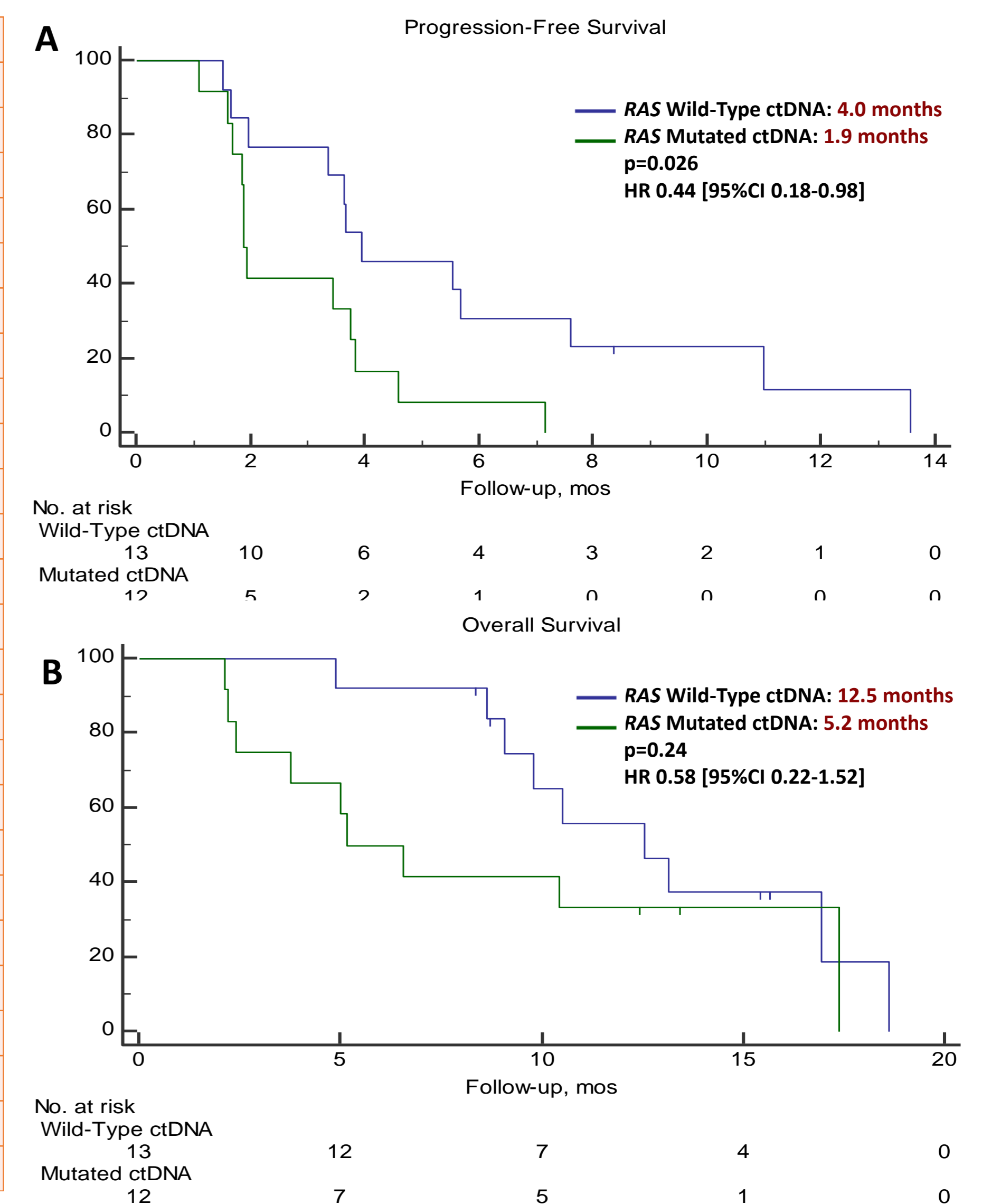


Figure 2. Progression-Free survival (A) and Overall Survival (B)

### Conclusions

Rechallenge with cetuximab + irinotecan was active in some *RAS* and *BRAF* wild-type mCRC patients with acquired resistance to 1<sup>st</sup>-line irinotecan and cetuximab based therapy.

Candidate patients' selection may be improved by treating only those who do not bear any *RAS* mutations or other less frequent resistance mechanisms in ctDNA at the rechallenge baseline.

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