

# Rechallenge for Patients With *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan

## A Phase 2 Single-Arm Clinical Trial

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**IMPORTANCE** Based on a small retrospective study, rechallenge with cetuximab-based therapy for patients with *KRAS* wild-type metastatic colorectal cancer (mCRC) who were previously treated with the same anti-epidermal growth factor receptor-based regimen might be efficacious. Recent data suggest the role of liquid biopsy as a tool to track molecular events in circulating tumor DNA (ctDNA).

**OBJECTIVE** To prospectively assess the activity of cetuximab plus irinotecan as third-line treatment for patients with *RAS* and *BRAF* wild-type mCRC who were initially sensitive to and then resistant to first-line irinotecan- and cetuximab-based therapy.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter phase 2 single-arm trial conducted from January 7, 2015, to June 19, 2017. Liquid biopsies for analysis of ctDNA were collected at baseline. Main eligibility criteria included *RAS* and *BRAF* wild-type status on tissue samples; prior first-line irinotecan- and cetuximab-based regimen with at least partial response, progression-free survival of at least 6 months with first-line therapy, and progression within 4 weeks after last dose of cetuximab; and prior second-line oxaliplatin- and bevacizumab-based treatment.

**INTERVENTIONS** Biweekly cetuximab, 500 mg/m<sup>2</sup>, plus irinotecan, 180 mg/m<sup>2</sup>.

**MAIN OUTCOMES AND MEASURES** Overall response rate according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary end points included progression-free survival and overall survival and, as an exploratory analysis, *RAS* mutations in ctDNA.

**RESULTS** Twenty-eight patients (9 women and 19 men; median age, 69 years [range, 45-79 years]) were enrolled. Six partial responses (4 confirmed) and 9 disease stabilizations were reported (response rate, 21%; 95% CI, 10%-40%; disease control rate, 54%; 95% CI, 36%-70%). Primary end point was met because lower limit of 95% CI of response rate was higher than 5%. *RAS* mutations were found in ctDNA collected at rechallenge baseline in 12 of 25 evaluable patients (48%). No *RAS* mutations were detected in samples from patients who achieved confirmed partial response. Patients with *RAS* wild-type ctDNA had significantly longer progression-free survival than those with *RAS* mutated ctDNA (median progression-free survival, 4.0 vs 1.9 months; hazard ratio, 0.44; 95% CI, 0.18-0.98; *P* = .03).

**CONCLUSIONS AND RELEVANCE** This is the first prospective demonstration that a rechallenge strategy with cetuximab and irinotecan may be active in patients with *RAS* and *BRAF* wild-type mCRC with acquired resistance to first-line irinotecan- and cetuximab-based therapy. The evaluation of *RAS* mutational status on ctDNA might be helpful in selecting candidate patients.

**TRIAL REGISTRATION** ClinicalTrials.gov identifier: [NCT02296203](https://clinicaltrials.gov/ct2/show/study/NCT02296203)

*JAMA Oncol.* 2019;5(3):343-350. doi:10.1001/jamaoncol.2018.5080  
Published online November 21, 2018.

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The combination of an anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (cetuximab or panitumumab) with a chemotherapy doublet is a first-line treatment option for patients with *RAS* (*KRAS*: OMIM, 190070; and *NRAS*: OMIM, 164790) and *BRAF* (OMIM, 164757) wild-type metastatic colorectal cancer (mCRC).<sup>1-3</sup> A retrospective study highlighted the potential efficacy of reintroducing cetuximab for patients with acquired resistance to a previous treatment with chemotherapy plus cetuximab, followed by at least 1 intervening line of therapy.<sup>4</sup> Although the study was limited by its retrospective nature, the finding is currently supported by an intriguing biological rationale. The emergence of *RAS* mutations in tumors that were initially *RAS* wild-type is a well-recognized mechanism of acquired resistance to anti-EGFR monoclonal antibodies.<sup>5-8</sup> It is currently unclear whether this event might be due to the late acquisition of these mutations by cellular subclones or to the progressive selection of initially undetectable mutated subclones. According to the latter hypothesis, an anti-EGFR-based therapy would be able to substantially decrease the bulk of sensitive (wild-type) cells, thus making the resistant (mutant) clones progressively predominant until the clinical evidence of disease progression. During a subsequent treatment that was not anti-EGFR based, sensitive clones would be at least partially restored, thus laying the foundation for the potential and reported activity of anti-EGFR rechallenge.<sup>5</sup>

More recently, a growing amount of molecular evidence highlighted the intratumoral heterogeneity of colorectal cancer and the dynamism of clonal evolution under the pressure exerted by treatments. In particular, preliminary proof of concept results pointed out the biological relevance of circulating tumor DNA (ctDNA) as an extremely sensitive tool to document the complexity of the tumor and to potentially drive strategies of therapy adaptation.<sup>5,9-12</sup> The emergence of *RAS* mutations at the time of disease progression to first-line chemotherapy plus anti-EGFR monoclonal antibodies may be followed by a dwindling of the fractional abundance of acquired *RAS* mutations—even to undetectable levels—after withdrawal of EGFR blockade.<sup>5</sup>

The CRICKET (Cetuximab Rechallenge in Irinotecan-Pretreated mCRC, *KRAS*, *NRAS* and *BRAF* Wild-Type Treated in 1st line With Anti-EGFR Therapy) trial was designed to prospectively evaluate the activity of a rechallenge strategy with irinotecan and cetuximab as third-line treatment for patients experiencing an initial response and then progression with a first-line irinotecan- and cetuximab-containing therapy, and receiving second-line chemotherapy plus bevacizumab. The prospective collection of liquid biopsy samples from enrolled patients was planned to investigate whether the analysis of potential mechanisms of acquired resistance to anti-EGFR monoclonal antibodies in ctDNA could help determine the benefit of this strategy.

## Methods

### Patient Population

The CRICKET trial (trial protocol in Supplement 1) was a prospective, open-label, multicenter, single-arm phase 2 trial that

## Key Points

**Question** Is third-line cetuximab plus irinotecan an active option for patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer who have acquired resistance to first-line irinotecan- and cetuximab-based therapy?

**Findings** In this phase 2 single-arm clinical trial, rechallenge with cetuximab plus irinotecan was active in 21% of patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer. Preplanned circulating tumor DNA profiling revealed that only patients with *RAS* and *BRAF* wild-type circulating tumor DNA at the time of rechallenge could derive benefit.

**Meaning** These findings lay the foundation for further evaluating the efficacy of anti-epidermal growth factor receptor rechallenge in larger studies including only patients with no mechanisms of acquired resistance detectable in circulating tumor DNA.

recruited patients with mCRC from 9 Italian oncology units from January 7, 2015, to June 19, 2017. The main inclusion criteria were histologically confirmed colorectal adenocarcinoma; *RAS* and *BRAF* wild-type status of primary colorectal cancer and/or related metastasis; older than 18 years of age; an Eastern Cooperative Oncology Group performance status of 0 to 2; measurable metastatic disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1<sup>13</sup>; first-line irinotecan-based cetuximab-containing therapy (FOLFIRI [fluorouracil and leucovorin combined with irinotecan] or FOLFOXIRI [fluorouracil, leucovorin, oxaliplatin, and irinotecan] plus cetuximab) producing at least a partial response; first-line progression-free survival (PFS) of 6 months or more; documentation of progression to first-line therapy within 4 weeks after the last administration of cetuximab; time between the end of first-line therapy and the start of third-line therapy of 4 months or more; and progression to a second-line oxaliplatin-based bevacizumab-containing therapy (FOLFOXIRI, FOLFOX [leucovorin, fluorouracil, and oxaliplatin], or XELOX [capecitabine and oxaliplatin] plus bevacizumab). The trial was conducted in accordance with the Declaration of Helsinki<sup>14</sup> and adhered to the international Good Clinical Practice guidelines. The protocol was approved by local ethics committees of participating sites (Centre of Pisa and Pontedera: Comitato Etico Area Vasta Nord Ovest and Sezione Autonoma Del Comitato Etico Regionale Per La Sperimentazione Clinica, Centre of Roma Campus Biomedico: Comitato Etico dell'Università Campus Biomedico di Roma, Centre of Parma: Comitato Etico per Parma, Centre of Padova: Comitato Etico per la Sperimentazione Clinica dell'Istituto Oncologico Veneto, Centre of Roma-Isola Tiberina: Comitato Etico Lazio 1 c/o Farmacia dell'Ospedale San Camillo, Centre of Udine: Comitato Etico Regionale Unico, Centre of Roma-Gemelli: Comitato Etico Università Cattolica del Sacro Cuore, and Centre of Rimini: Comitato Etico di Area Vasta Romagna). All patients provided written informed consent to study procedures.

### Study Treatment and Procedures

Patients were treated with intravenous cetuximab, 500 mg/m<sup>2</sup>, and intravenous irinotecan 180, mg/m<sup>2</sup>, repeated

biweekly until disease progression, patient's refusal, unacceptable toxic effects, or withdrawal of consent. The response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1. A computed tomographic scan was recommended every 8 weeks.<sup>13</sup> Investigator-reported measurements were subsequently centrally reviewed. Adverse events were recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events guidelines, version 4.0.<sup>15</sup> Patients' registration and data collection were centralized by the Gruppo Oncologico del Nord Ovest.

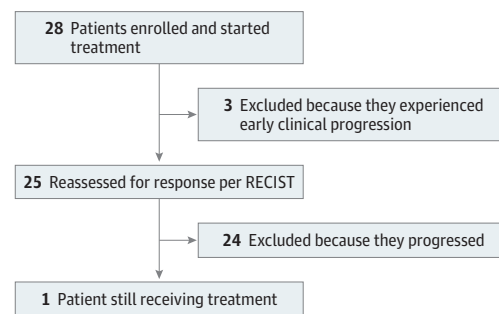
### Molecular Analyses

Liquid biopsies were collected at the rechallenge baseline. Circulating tumor DNA was analyzed with droplet digital polymerase chain reaction for specific RAS and BRAF mutations and then by means of ultra-deep next-generation sequencing with Ion Torrent S5 XL (Thermo Fisher Scientific).

Six milliliters of blood were collected in EDTA tubes and centrifuged at 4°C for 10 minutes at 3000 rpm within 2 hours after blood collection. Plasma samples were stored at -80°C until analysis. Circulating tumor DNA was extracted using a QIAmp Circulating nucleic acid Kit (Qiagen) from 2 to 3 mL of plasma following the manufacturer's protocol, and the ctDNA was eluted in 50 µL of elution buffer. The analysis was performed with a droplet digital polymerase chain reaction KRAS and NRAS Screening Multiplex Kit, and the results were confirmed using single mutation assays (BioRad). BRAF analysis for the V600E mutation was conducted using the droplet digital polymerase chain reaction BRAF V600E Mutation Assay (BioRad). The droplet reader (BioRad) was used for the fluorescence signal quantification, the QuantaSoft (BioRad) software was used to measure the number of positive vs negative droplets for both fluorophores (5(6)-carboxyfluorescein and 6-carboxy-2',4,4',5',7,7'-hexachlorofluorescein [FAM/HEX]), and their ratio was fitted to a Poisson distribution to determine the copy number per milliliter of the target molecule in the input reaction. A fluorescence intensity threshold of 3000 was set as a cutoff point, and all droplets above this threshold were scored as positive for RAS and BRAF mutations.

The next-generation sequencing was performed using the Ion AmpliSeq Cancer Hotspot Panel (Thermo Fisher); this panel is designed to amplify 207 amplicons covering approximately 2800 COSMIC (Catalogue Of Somatic Mutations In Cancer) mutations from 50 oncogenes and tumor suppressor genes commonly mutated in human cancers, including RAS and BRAF mutations (eTable 1 in Supplement 2). The libraries were prepared by IonAmpliSeq Library kit 2.0 (Thermo Fisher).<sup>16</sup> Emulsion polymerase chain reaction and chip loading were performed on the IonChef System (Thermo Fisher), according to the manufacturer's instructions. Sequencing was performed on the ION S5 XL System (Thermo Fisher) using Ion 540 Chips and Ion 540 Kit-Chef according to the manufacturer's instructions (MAN0010846). Data were processed by using Torrent Suite (Thermo Fisher); the variant calling from sequencing data was generated by using the Variant Caller plugin. The resulting variants were annotated using the Ensemble Variant Effect Predictor pipeline, Ion Reporter analysis software, the

Figure 1. Study CONSORT Diagram



RECIST indicates Response Evaluation Criteria in Solid Tumors.

COSMIC database,<sup>17</sup> the dbSNP database,<sup>18</sup> and the ClinVar database of the National Center for Biotechnology Information.<sup>19</sup> The filtered variants were examined using the Integrative Genomic Viewer IGV tool (Broad Institute) to check their quality level and confirm the variant's presence on both the positive and the negative strand.<sup>20</sup> For all plasma ctDNA samples, the coverage depth of most amplicons was over 5000×.

### Statistical Analysis

The primary end point of the study was the overall response rate, defined as the proportion of patients achieving complete response or partial response. Patients whose disease was not reassessed and those who were unavailable for follow-up or who were dead before disease reassessment were considered not to be responders for the purpose of the primary end-point analysis. According to the Fleming single-stage design, selecting  $P = .05$  (overall response rate in the null hypothesis) based on results with second-line irinotecan-based therapies<sup>21,22</sup> and selecting  $P = .20$  (overall response rate in the alternative hypothesis) as a potential target of interest for future studies, with  $\alpha$  (1-sided) errors of .05 and  $\beta$  errors of .20, we found that a total of 27 patients were required. The null hypothesis would have been rejected if at least 4 patients had achieved a response.<sup>23,24</sup> Secondary end points included PFS, overall survival (OS) calculated from the start of treatment, the toxicity profile, and the results of translational analyses. Progression-free survival and OS were summarized using the Kaplan-Meier method; hazard ratios and corresponding 95% CIs were estimated with the Cox proportional hazards regression model. Patients not experiencing disease progression or death were censored at the date of the last follow-up visit. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan-Meier method. Statistical analyses were performed by using MedCalc Statistical Software, version 14.8.1 (MedCalc Software) and GraphPad Prism, version 6.00 for Windows (GraphPad Software).

## Results

From January 7, 2015, to June 19, 2017, 28 patients were enrolled in 9 Italian oncology units (Figure 1). The patients' main

**Table. Data on Responses of Patients**

Type of Response	No. (%) (N = 28)
Complete response	0
Partial response	6 (21)
Confirmed	4 (14)
Unconfirmed	2 (7)
Stable disease	9 (32)
Progressive disease	10 (36)
Not evaluable	3 (11)
Objective response rate <sup>a</sup> (95% CI)	6 (21) (10-40)
Disease control rate <sup>b</sup> (95% CI)	15 (54) (36-70)

<sup>a</sup> Complete response or partial response.

<sup>b</sup> Complete response, partial response, or stable disease.

characteristics are reported in eTable 2 in Supplement 2: the median age was 69 years (range, 45-79 years), 18 patients (64%) had an Eastern Cooperative Oncology Group performance status of 0, metastases' presentation was synchronous in 20 cases (71%), 25 patients (89%) had undergone resection of the primary tumor, and 21 patients (75%) had multiple sites of metastases, while metastases were still limited to the liver in 5 patients (18%). The median time from the diagnosis of metastatic disease to study entry was 24.4 months (95% CI, 20.2-31.7 months).

At the time of data cutoff on March 1, 2018, the median follow-up was 15.4 months (interquartile range, 4.35-13.25 months). Six patients (21%) achieved a partial response that was confirmed in 4 patients at the subsequent computed tomographic scan assessment (Table). The overall response rate was 21% (95% CI, 10%-40%). Nine patients (32%) reported stable disease, for a disease control rate of 54% (95% CI, 36%-70%). Thirteen of 25 patients (52%) assessed for a radiologic response had tumor shrinkage (Figure 2A). Three patients (11%) had clinically detectable disease progression before undergoing the first computed tomographic scan reassessment. The median duration of disease control was 9.9 weeks (95% CI, 8.1-23.1 weeks) (Figure 2B). The median PFS was 3.4 months (95% CI, 1.9-3.8 months), and the median OS was 9.8 months (95% CI, 5.2-13.10 months) (eFigure in Supplement 2).

eTable 3 in Supplement 2 shows treatment-related grade 3 or higher adverse events. The most common adverse events were diarrhea (5 [18%]), acneiform skin rash (4 [14%]), neutropenia (4 [14%]), and hand-foot syndrome (2 [7%]). No grade 5 adverse events occurred. No patient interrupted treatment because of adverse events, and treatment withdrawal was not requested by any patient.

A total of 202 cycles (median, 4.5 cycles per patient) were administered. Treatment was delayed for any reason in 29 cycles (14.4%) or because of an adverse event in 11 cycles (5.4%) and was administered with reduced dosage in 35 cycles (17.3%). The mean (SD) relative dose intensities were 87.3% (20.8%) for irinotecan and 94.8% (13.4%) for cetuximab.

As described in eTable 4 in Supplement 2, RAS mutations were found in liquid biopsy samples collected at the rechallenge baseline in 12 (48%) of 25 patients reassessed by computed tomographic scan (6 KRAS G12D, 5 KRAS G12V with 1 also

harboring a Q61H mutation, and 1 NRAS Q61L). No BRAF or PIK3CA (OMIM 171834) mutations were found.

No RAS mutations were detected in ctDNA from patients who achieved a confirmed partial response compared with 12 (57%) of 21 patients who did not achieve a partial response ( $P = .10$  determined by the Fisher exact test). Patients with RAS wild-type ctDNA ( $n = 13$ ) had significantly longer PFS than did those with RAS mutated ctDNA ( $n = 12$ ), with a median PFS of 4.0 vs 1.9 months (hazard ratio, 0.44; 95% CI, 0.18-0.98;  $P = .03$ ) (Figure 3A), while no significant differences were reported in terms of OS (median OS, 12.5 vs 5.2 months; hazard ratio, 0.58; 95% CI, 0.22-1.52;  $P = .24$ ) (Figure 3B). The percentage variation of the sum of target lesions at different time points according to ctDNA RAS status at rechallenge baseline is shown in Figure 2C.

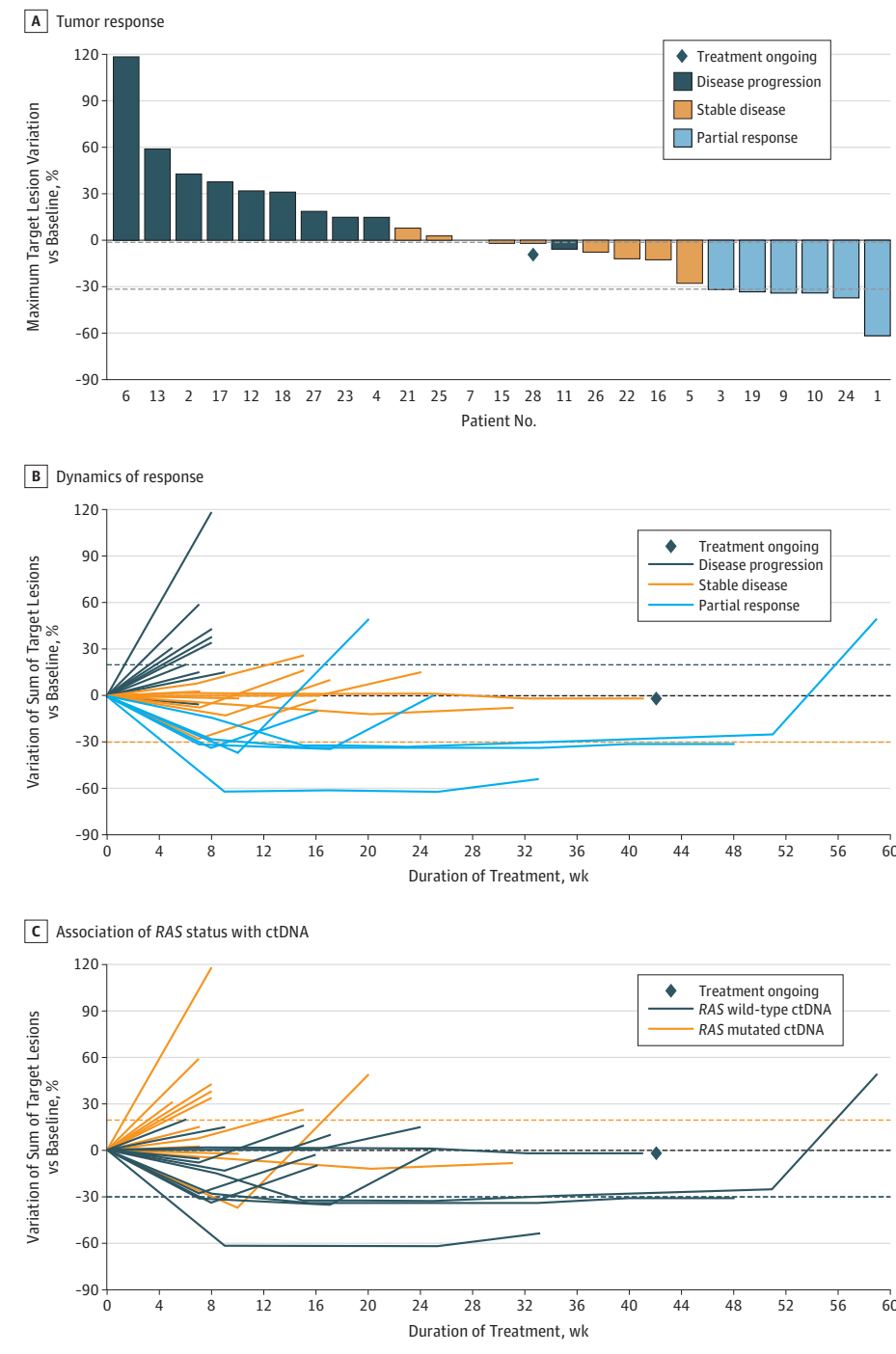
## Discussion

The therapeutic landscape of later lines of treatment of mCRC has recently become more complex owing to the availability of 2 drugs with demonstrated efficacy in prolonging survival of chemorefractory patients when compared with placebo: the multitarget tyrosine kinase inhibitor regorafenib<sup>25,26</sup> and the novel fluoropyrimidine trifluridine-tipiracil, also known as TAS-102.<sup>27,28</sup> The magnitude of OS benefit provided by both these agents is limited because half of treated patients are unable to derive any advantage in terms of PFS. Moreover, no molecular or clinical factors associated with benefit from these drugs have been identified so far, making their cost-benefit ratio quite narrow. Alternatively, data from uncontrolled studies support other therapeutic strategies for small molecular subgroups, such as dual-targeted ERBB2/HER2 (OMIM 164870) therapy for HER2-positive tumors,<sup>29</sup> immune checkpoints for microsatellite instable tumors,<sup>30,31</sup> and tyrosine kinase inhibition for gene fusion-positive tumors.<sup>32,33</sup>

Here we provide the first prospective demonstration, to our knowledge, of the potential usefulness of another treatment option for a molecularly and clinically defined subgroup of patients with mCRC: rechallenge with cetuximab and irinotecan for patients with RAS and BRAF wild-type mCRC who experienced an initial benefit and then became resistant to a first-line cetuximab-containing regimen and received second-line oxaliplatin-based chemotherapy plus bevacizumab. Although acknowledging the intrinsic limitations of a single-arm phase 2 study, our results provide a clear signal of activity for the anti-EGFR rechallenge in the third-line setting, in patients with strict clinical and molecular criteria for defining acquired resistance to first-line treatment based on anti-EGFR monoclonal antibodies. Given the increasing amount of evidence of the role of anti-EGFR-based maintenance after first-line induction regimens, the clinical scenario of anti-EGFR rechallenge might be frequently faced in future clinical practice.

The analysis of ctDNA revealed that approximately 50% of these patients still had detectable RAS mutations at the time of rechallenge, and it highlights the actual reliability of liquid biopsy as a tool to inform therapeutic decisions. None of the

Figure 2. Radiographic Response



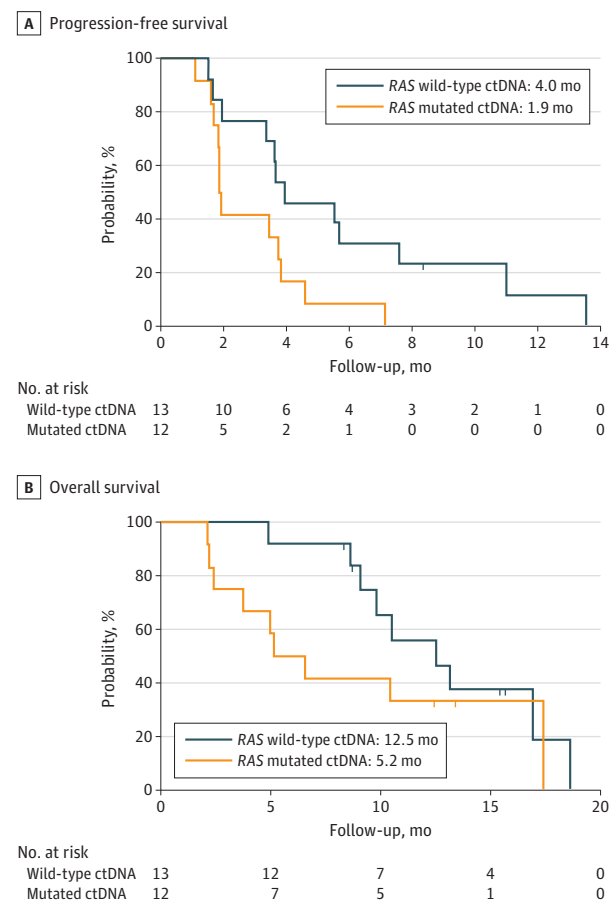
A, Tumor response in 25 evaluable patients. The bars show the best percentage change in the target lesions from baseline. Three patients progressed before the first disease assessment. The dashed horizontal line at -30 indicates the threshold value to define partial response. B, Dynamics of response according to best response in 25 evaluable patients. The individual lines represent the percentage variation of the sum of target lesions at different time points. C, Association of RAS status with circulating tumor DNA (ctDNA) in 25 evaluable patients. The longitudinal assessment of the sum of target lesions is shown according to RAS mutational status of ctDNA at rechallenge baseline.

patients with RAS mutations in ctDNA at the start of rechallenge achieved response, thus making the choice of rechallenge inappropriate for them. Only 1 patient with a small fractional abundance of RAS mutation in ctDNA experienced a transient response to rechallenge. A potential explanation is that, even if RAS mutation was still detectable at the time of study entry, a significant drop in its frequency from the time of disease progression at first-line treatment had occurred, thus suggesting a dwindling of the mutant clones and a contem-

porary increasing prevalence of wild-type cells at the tumor level during second-line therapy. Unfortunately, the lack of longitudinal paired samples during previous lines of therapy does not allow drawing any conclusion about this hypothesis.

Lack of RAS mutations in ctDNA is associated in our small series with a probability of 31% of achieving response (13 patients had no RAS mutations in ctDNA; 4 of these patients had a response [eTable 4 in Supplement 2]). Although we did not identify any BRAF or PIK3CA mutation in analyzed samples,

**Figure 3. Kaplan-Meier Estimates of Progression-Free Survival and Overall Survival According to RAS and BRAF Circulating Tumor DNA (ctDNA) Status**



A, Hazard ratio, 0.44 (95% CI, 0.18-0.98;  $P = .03$ ). B, Hazard ratio, 0.58 (95% CI, 0.22-1.52;  $P = .24$ ).

other mechanisms of acquired resistance to anti-EGFR monoclonal antibodies may occur or co-occur with RAS mutations and have been identified in liquid biopsy samples from patients with disease progression.<sup>5,6,9,11,34-36</sup>

However, despite intriguing preliminary proof-of-concept evidence about the potential role of liquid biopsy in

driving therapeutic choices, the translation of these findings from the bench to the bedside will definitely need robust confirmation from biomarker-driven clinical trials. A further step forward on this route will be marked by the currently ongoing CHRONOS (Phase II Trial of Rechallenge With Panitumumab Driven by RAS Clonal-Mediated Dynamic of Resistance) study (NCT03227926), in which patients eligible for anti-EGFR rechallenge are eligible only if a decrease of at least 50% in the fractional abundance of RAS mutations in ctDNA is evident at the time of rechallenge when compared with the time of progression to the first-line anti-EGFR-containing therapy.

### Limitations

This study has some limitations. Owing to its phase 2 single-arm design, the CRICKET trial is a proof-of-concept study, able to provide signals of activity and to generate preliminary evidence, supported by a sound translational background, to be further confirmed in a larger clinical trial. The registration of patients at the time of rechallenge (ie, after the second evidence of disease progression) prevents us from deriving any conclusion about how many patients with RAS and BRAF wild-type tumors who are receiving chemotherapy plus anti-EGFR monoclonal antibodies as initial treatment may be candidates for this third-line approach.

### Conclusions

Based on results of the CRICKET trial, whereas trifluridine-tipiracil or regorafenib do still represent third-line options with the highest levels of evidence for patients with chemorefractory mCRC, anti-EGFR rechallenge could be a tailored strategy for selected patients. Although markers of EGFR dependency are still lacking, patients with RAS and BRAF wild-type left-sided tumors, possibly not showing other molecular mechanisms of intrinsic resistance to EGFR inhibition,<sup>37</sup> who derived clinically meaningful benefit from first-line anti-EGFR-containing therapy, and with undetectable markers of acquired resistance to anti-EGFR monoclonal antibodies in tissue and/or liquid biopsy samples at the time of retreatment, might be the optimal candidates for rechallenge.

### ARTICLE INFORMATION

**Accepted for Publication:** August 29, 2018.

**Published Online:** November 21, 2018.  
doi:10.1001/jamaoncol.2018.5080

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**Author Contributions:** Dr Falcone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Cremolini and Rossini contributed equally to this work.

**Concept and design:** Cremolini, Rossini, Dell'Aquila, Masi, Falcone, Santini.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Cremolini, Rossini, Dell'Aquila, Del Re, Danesi, Rofi.

**Critical revision of the manuscript for important intellectual content:** Cremolini, Rossini, Lonardi,

Conca, Busico, Pietrantonio, Danesi, Aprile, Tamburini, Barone, Masi, Pantano, Pucci, Corsi, Pella, Bergamo, Barbara, Falcone, Santini. *Statistical analysis:* Cremolini, Rossini, Pantano, Santini. *Obtained funding:* Rossini, Danesi, Falcone, Santini. *Administrative, technical, or material support:* Rossini, Dell'Aquila, Conca, Busico, Pietrantonio, Danesi. *Supervision:* Rossini, Lonardi, Conca, Tamburini, Barone, Masi, Falcone, Santini.

**Conflict of Interest Disclosures:** Dr Cremolini reported receiving personal fees from F. Hoffman-La Roche, Bayer, Sirtex, and Amgen. Dr Del Re reported receiving honoraria from Celgene, Sanofi Aventis, Ipsen, and Novartis. Dr Danesi reported receiving research funding from F. Hoffman-La Roche, Amgen, Merck Serono, Celgene, Bayer, Sanofi Aventis, Pfizer, Novartis, and Lilly. Dr Barone reported receiving research funding from Novartis and Merck-Serono; honoraria for serving in an advisory role from Eisai, Servier, Bayer, MSD, Merck-Serono, Amgen, Celgene, and Lilly; and reported serving on speakers' bureaus for Novartis, Roche, MSD, Celgene, and Merck. Dr Falcone reported receiving grants and personal fees from F. Hoffman-La Roche, Amgen, and Merck Serono and personal fees from Celgene, Bayer, and Sanofi Aventis. No other disclosures were reported.

**Funding/Support:** The CRICKET (Cetuximab Rechallenge in Irinotecan-Pretreated mCRC, KRAS, NRAS and BRAF Wild-Type Treated in 1st line With Anti-EGFR therapy) trial was funded in part by the Gruppo Oncologico Nord Ovest, the ARCO Foundation, and Merck Serono SpA in Italy (an affiliate of Merck KGaA, Darmstadt, Germany). Merck Serono SpA provided the study drug cetuximab.

**Role of the Funder/Sponsor:** Gruppo Oncologico del Nord Ovest investigators were responsible for the study design, data collection, data analysis, and data interpretation. Gruppo Oncologico del Nord Ovest was also in charge of writing the manuscript and approving its submission for publication. The ARCO Foundation supported molecular analyses but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr Falcone had final responsibility for the decision to submit for publication. Merck Serono SpA had no role in the study's conduction, in data collection and analysis, or in data interpretation. Merck KGaA reviewed the manuscript for medical accuracy only before submission.

**Disclaimer:** The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors

**Additional Contributions:** We are grateful to all participating patients, their families, and their caregivers, as well as to the Gruppo Oncologico del Nord Ovest investigators from all participating oncology units in Italy.

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#### POETRY AND ONCOLOGY

### The Best Medicine

Gregory A. Abel, MD, MPH

Laughing with a patient  
is like opening the dishwasher

after it has started  
to add another plate inside:

whether it works out  
depends a lot on your timing,

and how hot and loaded  
the damn thing is.

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**Published Online:** January 31, 2019. doi:10.1001/jamaoncol.2018.6689

**Conflict of Interest Disclosures:** None reported.