clinical trial updates

# Acquired Genomic Alterations on First-Line Chemotherapy With Cetuximab in Advanced Colorectal Cancer: Circulating Tumor DNA Analysis of the CALGB/SWOG-80405 Trial (Alliance)

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abstract

*Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.*

Acquired genomic alterations (Acq-GAs), specifically *RAS*, *BRAF*, and *EGFR*-ectodomain mutations and *ERBB2* and *MET* amplifications, are recognized as major mechanisms of resistance to later-line anti–EGFR-antibody therapy in metastatic colorectal cancer (mCRC). However, data regarding emergence of these Acq-GAs under the selective pressure of first-line anti–EGFR-chemotherapy are lacking. We performed next-generation sequencing (Guardant360) on circulating tumor DNA obtained from paired plasma samples (pretreatment and postprogression) from the CALGB/SWOG-80405 trial, which randomly assigned patients with mCRC between first-line chemotherapy with cetuximab (anti–EGFR-chemotherapy) or bevacizumab (anti–VEGF-chemotherapy). The primary objective was to determine the prevalence of Acq-GAs on anti–EGFR-chemotherapy and compare this to the prevalence with anti–VEGF-chemotherapy on trial and pooled estimates (N = 292) seen with later-line anti–EGFR-antibody therapy as reported in the literature. Among the 61 patients on anti–EGFR-chemotherapy, only four (6.6%) developed ≥ 1 Acq-GAs of interest compared with 10.1% (7) on anti–VEGF-chemotherapy (odds ratio, 0.62; 95% CI, 0.20 to 2.11) and 62.0% on anti–EGFR-antibody therapy in later lines (odds ratio, 0.09; 95% CI, 0.03 to 0.23). Acq-GAs, classically associated with anti–EGFR-antibody resistance in later lines (*RAS*, *BRAF*, and *EGFR*-ectodomain mutations; *ERBB2* and *MET* amplifications), were rare with upfront use of anti–EGFR-chemotherapy indicating divergent resistance mechanisms. These findings have critical translational relevance to timing and value of circulating tumor DNA–guided anti-EGFR rechallenge in patients with mCRC, especially those treated with anti-EGFR therapy upfront.

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**ASSOCIATED CONTENT**

**See accompanying editorial on page 436**

**Data Supplement**

**Protocol**

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Antiepidermal growth factor receptor antibodies (anti–EGFR-Abs), panitumumab and cetuximab, are highly effective against *RAS/BRAF* wild-type (WT) metastatic colorectal cancer (mCRC).[1,2] Barring patients who have intrinsic or primary resistance to EGFR inhibition, a substantial proportion will derive initial benefit, but eventually progress.[1-4] This acquired or secondary resistance remains a major limitation in treating mCRC. Acquisition of genomic alterations under selective pressure exerted by EGFR inhibition, specifically *RAS*, *BRAF*, or *EGFR*-ectodomain mutations and *ERBB2* (*HER2*) or *MET* amplifications, have been commonly (30%-50%) implicated as key resistance mechanisms to anti–EGFR-Ab therapy in later lines in mCRC (Data Supplement, online only).[4-9] Although traditionally anti-EGFR agents have been used in later lines, the current evidence supports use in frontline therapy combined with cytotoxic chemotherapy (FOLFOX or FOLFIRI), especially for left-sided *RAS/BRAF*-WT mCRC.[10,11] However, data regarding emergence of these acquired alterations associated with anti–EGFR-Ab resistance under the treatment stress of anti–EGFR-Abs in first line combined with cytotoxic chemotherapy, which is now considered the standard of care, are lacking.

To understand the dynamics of tumor evolution and resistance mechanisms to frontline therapy in mCRC, we performed this prospective-retrospective circulating

tumor DNA (ctDNA) analyses on serial blood specimens collected from the randomized Cancer and Leukemia B and Southwest Oncology Group (CALGB/SWOG) 80405 trial (cetuximab-chemotherapy *v* bevacizumab-chemotherapy; ClinicalTrials.gov identifier: NCT00265850).[1]

## METHODS

The CALGB/SWOG-80405 (September 2005-March 2012) was a randomized phase III trial designed to evaluate efficacy of chemotherapy with either cetuximab or bevacizumab (or both) as first-line treatment for (*KRAS*-WT) mCRC.[1] Trial eligibility, design, treatment, and primary analyses have been reported previously.[1] The primary end point was overall survival. Among eligible patients, the study found no significant difference in overall survival (median: 30.0 *v* 29.0 months) between treatment arms.[1]

This biomarker substudy was a post hoc analysis and included patients treated with either cetuximab or bevacizumab on CALGB/SWOG-80405, who progressed on study treatment at discontinuation and had paired plasma samples (pretreatment and postprogression) available for ctDNA testing.[1] Figure 1 depicts study schema, patient selection, and flow for the current study cohort. Sequencing of ctDNA was performed by next-generation sequencing (Guardant360) assay optimized for detecting alterations (mutations and amplifications) in 73 genes (Data Supplement).[12] Patient *RAS/BRAF* status (WT or mutant) was defined by clonal mutations (relative maximum-allele frequency ≥ 25%) in ctDNA. A predefined cutoff of 0.1% for mutant allele frequency was used to determine the presence of mutations. Patients with baseline clonal *RAS/BRAF* mutations by ctDNA were excluded. Samples without any detectable alterations were also excluded to minimize false negatives (Fig 1).

The primary objective was to determine the prevalence of key acquired genomic alterations (Acq-GAs) of interest, prespecified as those implicated in anti–EGFR-Ab resistance (Data Supplement), on cetuximab-chemotherapy in the first-line setting. The secondary objective was to compare this prevalence to the prevalence seen with bevacizumab-chemotherapy on current trial and to the pooled prevalence estimates derived from all relevant published studies of anti–EGFR-Ab in later lines of therapy in mCRC (Data Supplement). Descriptive statistics and Fisher's exact test were used. For proportions, 95% CI were calculated using the modified Wald method. All *P* values are for exploratory purposes and not powered for statistical hypothesis testing. Participating site's institutional review board approval and written informed consent for all patients were obtained for

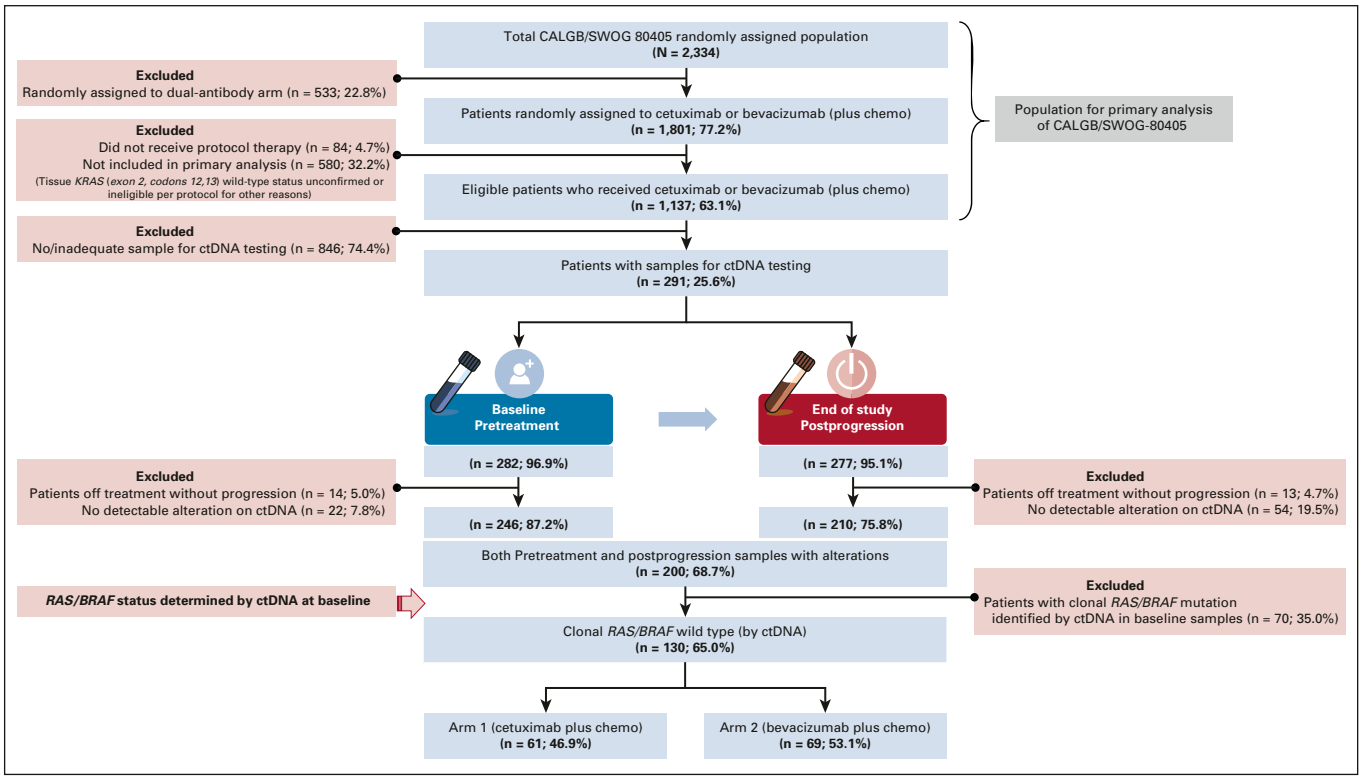



**FIG 1.** Schematic flow of patients and samples for ctDNA analysis of the CALGB/SWOG-80405 trial. Eligible patients for the current biomarker study included those who were randomly assigned, treated, and subsequently progressed on cetuximab or bevacizumab; had plasma samples (both baseline and postprogression end-of-protocol treatment) available for ctDNA testing; and had at least one detectable genomic alteration. *RAS/BRAF* status (mutant or wild type) was determined by the presence of clonal mutations (relative mutant allele frequency of ≥ 25% in the sample) in ctDNA, and only *RAS/BRAF* wild-type patients identified by ctDNA were included in current study. chemo, chemotherapy; ctDNA, circulating tumor DNA.

CALGB/SWOG-80405.[1] Detailed methodology is provided as Supplementary Methods (Data Supplement).

## RESULTS

Baseline characteristics of patients who underwent ctDNA testing were similar to the entire CALGB/SWOG-80405 population (Data Supplement). Furthermore, the clinical outcomes with respect to *RAS/BRAF* status detected by ctDNA at baseline, type of targeted therapy, and tumor sidedness in this cohort were consistent with those observed in the primary 80405 analysis (Data Supplement). Of them, 130 patients met eligibility criteria for current biomarker substudy and were equally distributed between cetuximab (n = 61) and bevacizumab (n = 69) arms. Baseline characteristics of these evaluable patients were comparable between treatment arms (Table 1). Among those treated with cetuximab-chemotherapy, only four (6.6%) of 61 patients developed at least one Acq-GA of interest at progression. This prevalence was similar to that

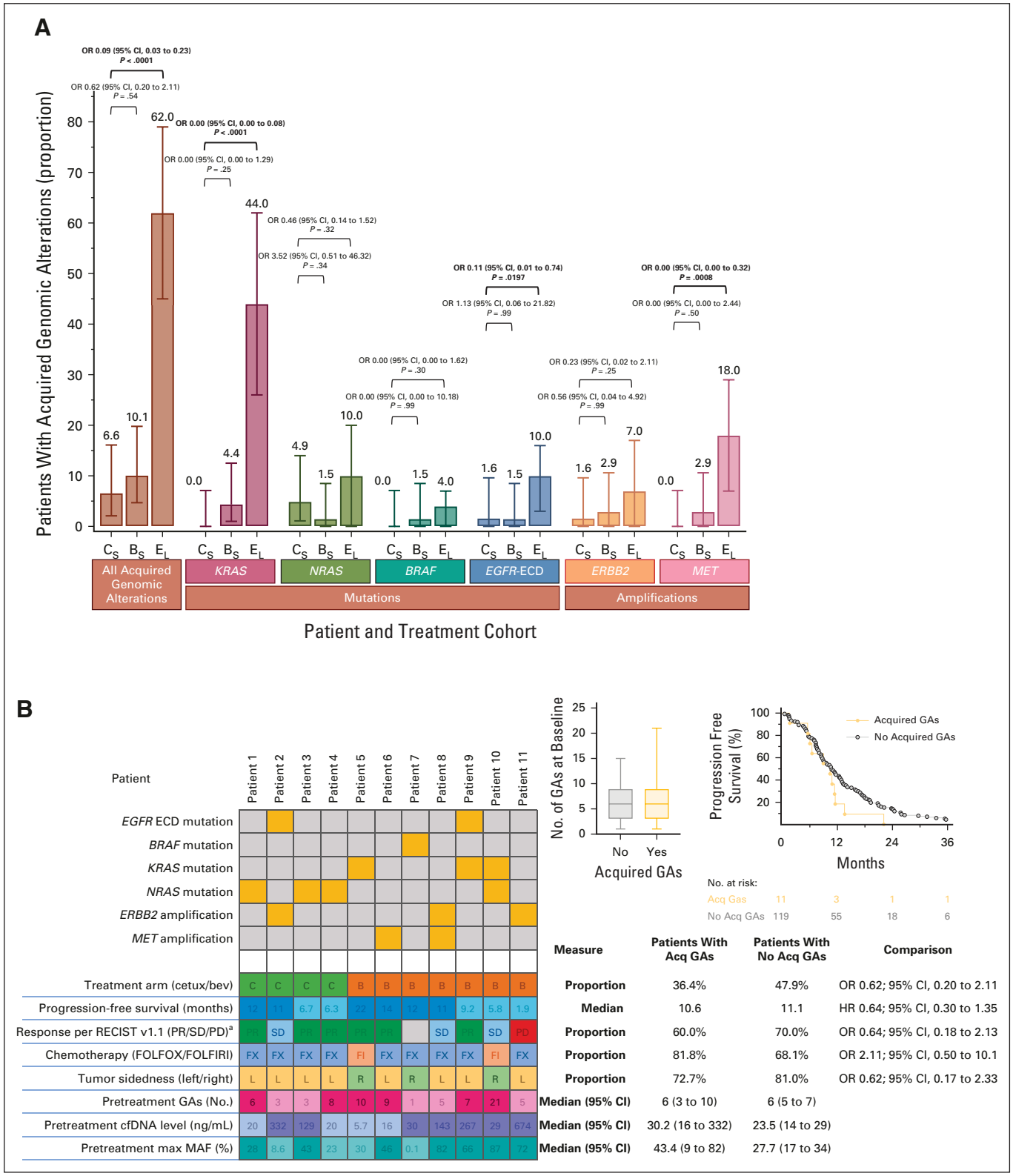
**TABLE 1.** Baseline Characteristics

| Characteristic[a] | Cetuximab Arm (n = 61) | Bevacizumab Arm (n = 69) | *P* |
|---|---|---|---|
| Age, years | | | |
| Median (95% CI) | 60.8 (57.9 to 62.9) | 60.0 (54.6 to 62.4) | .27 |
| Range | 29.6-79.1 | 21.8-81.9 | |
| Sex, No. (%) | | | |
| Male | 39 (63.9) | 41 (59.4) | .71 |
| Female | 22 (36.1) | 28 (40.6) | |
| ECOG performance status, No. (%) | | | |
| 0 | 36 (59.0) | 37 (53.6) | .59 |
| 1 | 25 (51.0) | 32 (46.4) | |
| Tumor sidedness, No. (%) | | | |
| Left | 47 (77.1) | 55 (83.3) | .39 |
| Right | 14 (22.9) | 11 (16.7) | |
| No. of metastatic sites, No. (%) | | | |
| < 3 | 52 (85.2) | 56 (81.2) | .64 |
| ≥ 3 | 9 (14.8) | 13 (18.8) | |
| Metastatic disease, No. (%) | | | |
| Synchronous | 42 (68.8) | 54 (78.3) | .24 |
| Metachronous | 19 (31.2) | 15 (21.7) | |
| Chemotherapy arm, No. (%) | | | |
| FOLFOX | 43 (70.5) | 47 (68.1) | .85 |
| FOLFIRI | 18 (29.5) | 22 (31.9) | |
| Response (per RECIST), No. (%) | | | |
| Responder (CR plus PR) | 41 (73.2) | 42 (65.6) | .43 |
| Nonresponder | 15 (26.8) | 22 (34.4) | |
| Overall survival[b] | | | |
| Median, months | 34.6 | 31.1 | .06 |
| HR (95% CI) | | 0.71 (0.49 to 1.03) | |
| Progression-free survival[b] | | | |
| Median, months | 11.1 | 11.1 | .85 |
| HR (95% CI) | | 0.99 (0.70 to 1.39) | |
| ctDNA level per sample | | | |
| Mean, ng/mL (95% CI) | 70.1 (18.3 to 121.9) | 113.4 (55.6 to 171.2) | .27 |

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PR, partial response.

[a]Missing data. Proportions are calculated from patients with available data. *P* values are exploratory.

[b]HR are calculated treating cetuximab arm as the referent arm.




| Measure | Patients With Acq GAs | Patients With No Acq GAs | Comparison |
|---|---|---|---|
| Proportion | 36.4% | 47.9% | OR 0.62; 95% CI, 0.20 to 2.11 |
| Median | 10.6 | 11.1 | HR 0.64; 95% CI, 0.30 to 1.35 |
| Proportion | 60.0% | 70.0% | OR 0.64; 95% CI, 0.18 to 2.13 |
| Proportion | 81.8% | 68.1% | OR 2.11; 95% CI, 0.50 to 10.1 |
| Proportion | 72.7% | 81.0% | OR 0.62; 95% CI, 0.17 to 2.33 |
| Median (95% CI) | 6 (3 to 10) | 6 (5 to 7) | |
| Median (95% CI) | 30.2 (16 to 332) | 23.5 (14 to 29) | |
| Median (95% CI) | 43.4 (9 to 82) | 27.7 (17 to 34) | |

**FIG 2.** Acquired genomic alterations (mutations and amplifications) in patients with mCRC on systemic therapy. (A) Comparison of acquired genomic alterations between cetuximab-chemotherapy ($C_S$) and bevacizumab-chemotherapy ($B_S$) treatment arms on CALGB/SWOG-80405 study and acquired genomic alterations on anti–EGFR-Ab–based therapy in later lines in mCRC as reported in the literature ($E_L$). The error bars on each represent 95% CIs of the proportion. (B) Key clinical characteristics of patients who acquired genomic alterations and comparisons of these characteristics with those patients who did not develop acquired genomic alterations. All *P* values reported are for exploratory purposes only and not powered for statistical hypothesis testing. (continued on following page)

**FIG 2.** (Continued). [a]Response per RECIST v1.1 (PR/SD/PD). Acq, acquired; anti–EGFR-Abs, antiepidermal growth factor receptor antibodies; bev, bevacizumab; cetux, cetuximab; chemo, chemotherapy; CR, complete response; GAs, genomic alterations; HR, hazard ratio; max MAF, maximum mutant allele frequency; mCRC, metastatic colorectal cancer; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease.

seen with bevacizumab-chemotherapy (7 of 69 [10.1%]; odds ratio [OR] 0.62 [95% CI, 0.20 to 2.11]). No meaningful difference was seen in prevalence of key alterations between treatment arms (cetuximab *v* bevacizumab): mutations (all: 6.6% *v* 10.1%) in *RAS* (4.9% *v* 5.8%), *KRAS* (0% *v* 4.4%), *NRAS* (4.9% *v* 1.5%), *BRAF* (0% *v* 1.5%), and *EGFR*-ectodomain (1.6% *v* 1.5%) and amplifications (all: 1.6% *v* 4.3%) in *ERBB2* (1.6% *v* 2.9%) and *MET* (0% *v* 2.9%; Fig 2A). No differences in key clinical characteristics were seen between patients who had Acq-GAs and those who did not (Fig 2B). The observed prevalence of all Acq-GAs on first-line cetuximab-chemotherapy was also considerably lower than the pooled prevalence (N = 292) on prior studies with anti–EGFR-Ab–based regimen in later lines of therapy (6.6% *v* 62.0%, OR 0.09 [95% CI, 0.03 to 0.23]), including key alterations such as acquired *KRAS* mutations (0% *v* 44%, OR 0.00 [95% CI, 0.00 to 0.08]; Fig 2A and Data Supplement).

## DISCUSSION

Enhanced understanding of evolving clonal architecture under treatment is crucial to optimizing care and developing effective therapies. This report is the first broad characterization of Acq-GAs to anti–EGFR-Abs in a randomized prospective first-line setting with doublet chemotherapy and demonstrates a distinctly different profile of acquired ctDNA compared with that seen with anti–EGFR-Ab therapy in later lines. Acq-GAs, classically associated with EGFR resistance in later lines, were rare with up-front use of anti–EGFR-Ab combined with highly active chemotherapy and comparable with non–anti-EGFR regimen, suggesting divergent mechanisms of acquired resistance subject to line of therapy and concomitant cytotoxic exposure. This study is exploratory in nature and hypothesis generating, subject to limitations inherent to post hoc analysis and limited sample size, but the results reported represent a randomized cohort. Validation is necessary in future prospective efforts.

Alternate mechanisms of resistance to anti–EGFR-Abs beyond acquisition of resistance conferring genomic modifications (adaptive mutability) exist that can explain this phenomenon. Epigenetic or transcriptional reprogramming and ensuing therapy-induced senescence or EMT (epithelial-to-mesenchymal transition) may enable mCRC to survive the brunt of combined targeted chemotherapy.[13,14] EMT gene expression signatures have been associated with both a generic resistance to cytotoxic chemotherapy and EGFR inhibition.[15-17] An activated EMT program enables chemotherapy-induced cancer cell plasticity and may confer cross-resistance to cytotoxic and targeted components of frontline therapy in mCRC.[18,19] Early evidence shows that acquisition of resistance mechanisms in mCRC can vary with line of therapy and with use of non–anti-EGFR biologics.[6,20]

Although traditionally used in later lines, there has been a recent trend toward use of anti–EGFR-Abs as frontline therapy, especially for left-sided *RAS/BRAF*-WT mCRC.[1,11] Despite this shift in treatment landscape of mCRC and limited understanding of resistance in this setting, large research efforts and resources are being invested to target previously identified mechanisms, which may not play a sizable role in real world. Furthermore, ctDNA is being increasingly used as a tool to rechallenge patients with anti-EGFR therapy because of clinical benefit seen with application of ctDNA in small prospective investigations.[21,22] However, it is unclear whether patients who acquire resistance to first-line cetuximab-chemotherapy without acquisition of any genomic alterations are distinct from those that acquire and loose these genomic alterations with later lines of therapy or the duration for which the phenotypic plasticity induced will confer resistance to subsequent anti-EGFR inhibition. Consequently, urgent efforts are needed to delineate characteristics of this therapeutic resistance in mCRC in the first-line setting and advancing therapeutics directed against these mechanisms. Our findings have critical translational relevance to the timing and value of ctDNA-guided anti-EGFR rechallenge in these patients with mCRC.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## PRIOR PRESENTATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## DATA SHARING STATEMENT

Data collected for the study, including deidentified individual patient data and a data dictionary, will be made available to others. Please contact Alliance for Clinical Trials in Oncology via email: concepts@alliancenctn.org. Data will be made available as required for specific, approved analyses, and all requests will be reviewed prior to approval. Data will be provided from locked, cleaned, and deidentified study database starting with the date of publication.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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