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ORIGINAL ARTICLE

Cetuximab rechallenge in molecularly selected metastatic colorectal cancer: the randomized CAVE-2 GOIM trial

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Background: Anti-epidermal growth factor receptor (EGFR) drug rechallenge could be of therapeutic value in a subgroup of refractory metastatic colorectal cancer (mCRC).

Patients and methods: The randomized phase II CAVE-2 GOIM trial compared two rechallenge regimens in *RAS/BRAF* wild-type mCRC (cetuximab monotherapy or in combination with avelumab). Patients were selected according to baseline plasma circulating tumor DNA (ctDNA) comprehensive genomic profiling (CGP) by FoundationOne Liquid CDx. Primary endpoint was overall survival (OS).

Results: From August 2022 to December 2024, 156 out of 328 screened patients were randomly assigned in a 2 : 1 ratio to cetuximab plus avelumab (arm A, 104 patients) or cetuximab (arm B, 52 patients). Median progression-free survival (mPFS) was 5.3 months [95% confidence interval (CI) 4.3-6 months] in arm A versus 4.3 months (95% CI 3.5-5.5 months) in arm B [hazard ratio (HR) 0.78, 95% CI 0.55-1.10, $P = 0.158$]. Median OS (mOS) was 14.8 months (95% CI 12.1-18.3 months) in arm A versus 12.9 months (95% CI 11 months-not evaluable) in arm B (HR 1.00, 95% CI 0.65-1.52, $P = 0.983$). A pre-planned exploratory analysis evaluated the impact of genomic pathogenic variants on therapeutic efficacy in the EGFR pathway. In the whole study population, 124/156 patients had tumors without any genomic alteration in *KRAS, NRAS, BRAF, EGFR* extracellular domain, *PIK3CA* exon 20, *MAP2K1, AKT1, MET, PTEN*, and *ERBB2* ('negative hyperselection'). These patients had significantly improved mPFS [5.35 months (95% CI 4.4-5.9 months) versus 3.65 months (95% CI 2.8-4.8 months); HR 0.62, 95% CI 0.42-0.92, $P = 0.017$] and mOS [15.0 months (95% CI 12.6-19.9 months) versus 11.1 months (95% CI 8.6-15.6 months); HR 0.61, 95% CI 0.39-0.97, $P = 0.037$] compared with patients having at least one pathogenic variant ('positive hyperselection'). Similarly, improved objective response rate, mPFS, and OS were observed for each treatment arm in patients with 'negative hyperselection'.

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Conclusion: Addition of avelumab does not increase efficacy of cetuximab rechallenge. Liquid biopsy CGP identifies patients who benefit from anti-EGFR rechallenge supporting its implementation in the continuum of care of mCRC.
Key words: metastatic colorectal cancer, anti-EGFR drug rechallenge, plasma ctDNA, comprehensive genomic profiling, immunotherapy

INTRODUCTION

Management of metastatic colorectal cancer (mCRC) is still a therapeutic challenge due to its molecular heterogeneity and the development of cancer resistance. Recent advances in systemic therapies, including molecular targeted agents, improved surgical techniques, and local ablative treatments, have revolutionized treatment approaches, which are mainly based on continuum of care across subsequent lines of therapy.[1,2] However, despite these improvements, the prognosis for most patients with refractory mCRC remains poor with a median overall survival (mOS) of 7-10 months. Moreover, available treatment options exhibit a mainly cytostatic effect with near half of the patients experiencing progressive disease as best response.[1]

In recent years, immunotherapy has dramatically changed the treatment landscape in several cancers.[3] However, its application in mCRC has been limited, primarily since only a small subset of patients with hypermutated tumors, which are due to high microsatellite instability or *POLE/POLD-1* mutations, are responsive to immune checkpoint inhibitors.[4,5] The vast majority of mCRC patients (∼95%) have microsatellite stable (MSS) and *POLE/POLD-1* wild-type (WT) tumors, which are intrinsically resistant to immunotherapy.[6] Therefore, a major clinical challenge is to develop therapeutic approaches that can switch MSS mCRC to immune responsiveness.

Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, such as cetuximab and panitumumab, in combination with doublet chemotherapy are the cornerstone for first-line treatment in *RAS/BRAF* WT mCRC.[7] Recently, 'rechallenge' with anti-EGFR drugs has been proposed as a potential strategy in later lines of therapy for patients who previously responded to anti-EGFR treatments but subsequently experienced disease progression and received at least a subsequent anti-EGFR-free therapy and retained a *RAS/BRAF* WT status by liquid biopsy analysis.[8] In this context, anti-EGFR drug rechallenge could be an additional line of therapy in the continuum of care with an objective response rate (ORR) ranging from 10% to 30%, a progression-free survival (PFS) of 4-5 months, and an mOS that exceeded 1 year.[8,9] However, several key questions for implementing this therapeutic strategy remain unsolved, including the identification of the most appropriate molecular criteria to select patients who are likely to benefit from anti-EGFR drug rechallenge, the optimal therapeutic combinations to enhance efficacy, and the best setting (third line or subsequent lines of treatment) in which this approach could be applied.

Preclinical and clinical evidence suggests that combining anti-EGFR therapy with immune checkpoint inhibitors could have potential therapeutic activity.[10,11] Of note, both cetuximab and the anti-programmed death-ligand 1 (PD-L1) monoclonal antibody avelumab can activate natural killer cells through antibody-dependent cellular cytotoxicity, thus providing a biological rationale for their combination.[11,12] We have previously conducted a multicenter, single-arm phase II trial (CAVE GOIM) to evaluate the antitumor activity of cetuximab rechallenge plus avelumab in refractory mCRC patients with MSS *RAS/BRAF* WT tumors.[13] The trial demonstrated promising clinical activity in patients with circulating tumor DNA (ctDNA) *RAS/BRAF* WT at baseline liquid biopsy. In patients without resistance alterations, the overall survival (OS) exceeded 17 months. Of note, 40% of the patients exhibited a PFS longer than 6 months. The treatment was feasible and well tolerated with a manageable safety profile. Nevertheless, this single-arm phase II study required further validation. Therefore, to assess the role of anti-EGFR drug rechallenge and the potential value of adding immunotherapy to cetuximab, we have conducted the randomized phase II CAVE-2 GOIM trial, in which refractory MSS mCRC patients with baseline *RAS/BRAF* WT plasma ctDNA were treated with cetuximab monotherapy or in combination with avelumab. We have explored the role of potential biomarkers in response to cetuximab plus avelumab combination. Finally, the role of a deeper molecular stratification in predicting response to anti-EGFR therapies has been investigated.

PATIENTS AND METHODS

Trial design and study population

The CAVE-2 GOIM study (NCT05291156) was an academic, multicenter, phase II, open-label, randomized trial, evaluating the combination of avelumab plus cetuximab compared with cetuximab single agent as anti-EGFR rechallenge strategy in refractory patients with *RAS/BRAF* WT, MSS mCRC.[14]

Eligible patients should have received an anti-EGFR drug-based first-line treatment and should have obtained complete response (CR) or partial response (PR), should have progressed, and, thereafter, have received at least one subsequent anti-EGFR drug-free line of therapy, with an anti-EGFR drug-free interval of at least 4 months. At baseline during the screening phase, a blood sample was obtained using FoundationOne Liquid (F1L) CDx collection tubes. Plasma ctDNA was measured by the F1L CDx assay (Boston, MA; https://www.foundationmedicine.com/test/foundationone-liquid-cdx) to identify patients without resistance mutations for *RAS/BRAF*^{V600E} to be enrolled in the trial.[15] Patients were randomly assigned (2 : 1) as

follows: arm A (cetuximab plus avelumab), in which cetuximab was administered intravenously at 400 mg/m^2 as loading dose, followed by 250 mg/m^2 weekly, and avelumab was given intravenously at a flat dose of 800 mg, once every 2 weeks; arm B (cetuximab), in which cetuximab was administered intravenously at 400 mg/m^2 as a loading dose and subsequently at 250 mg/m^2 weekly.

Treatment was discontinued at disease progression, or it could be interrupted for significant toxicity or for patient choice. Tumor measurements by computed tomography scan or magnetic resonance imaging were carried out every 8 weeks for 40 weeks and every 12 weeks thereafter to assess response to treatment. Response was evaluated using RECIST 1.1. Safety was scored by using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v 5.0).

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice Guidelines and has been approved by the Ethics Committee of Università degli Studi della Campania Luigi Vanvitelli/Azienda Ospedaliera Universitaria Luigi Vanvitelli/AORN Ospedale dei Colli and by the ethics committees of the other centers involved in the study. All patients have provided written informed consent to participate in the trial.

Statistical analysis

The primary endpoint of the study was OS, defined as the interval from enrollment to death from any cause. The trial aimed to demonstrate an increase of OS of 10 months for cetuximab to 15 months for cetuximab plus avelumab, which corresponds to an improvement of 33% in mOS [hazard ratio (HR) 0.67]. To obtain a power of 90%, with a one-sided alpha of 0.20 and a randomization ratio of 2 : 1, considering a potential dropout of 20%, a study population of 173 patients (115 cetuximab + avelumab and 58 cetuximab single agent) was estimated.

Secondary endpoints included the following: (i) ORR according to RECIST 1.1 criteria, defined as the proportion of patients with PR plus CR; (ii) PFS according to RECIST 1.1 criteria, defined as the time from random assignment in the clinical trial to disease progression or death from any cause; (iii) safety with evaluation of adverse events (AEs), assessed by using the NCI-CTCAE v 5.0.

Pre-planned exploratory analyses were done to evaluate the impact of additional anti-EGFR drug resistance pathogenic variants (PVs) (molecular hyperselection) as well tumor mutational burden (TMB) on clinical outcome. Molecular hyperselection was based on plasma ctDNA analysis of the following genes, which are involved in anti-EGFR drug resistance: *KRAS, NRAS, BRAF, EGFR* extracellular domain, *PIK3CA* exon 20, *MAP2K1, AKT1, MET, PTEN* mutations, and *ERBB2* amplification. Patients with baseline positive plasma ctDNA sample for any of these PVs were defined as 'positive hyperselected' cases, while in the absence of any gene alteration they were defined as 'negative hyperselected' cases. Tumors were classified TMB high in case of $\geq$10 mutations/megabase (mut/Mb) or TMB low in case of $<$10 mut/Mb.

Continuous variables were reported as medians and interquartile range (IQR), while categorical variables were summarized as frequency counts and proportions. Categorical and continuous variables were compared using Fisher's exact test and the Wilcox—Mann—Whitney test, respectively. Median PFS (mPFS) and mOS were estimated using the Kaplan—Meier method. Comparison between groups was carried out using the log-rank statistics. HR was calculated using the Cox proportional model. Median follow-up was calculated from the start of the therapy to last follow-up. Inferential statistical tests were carried out using a two-tailed alpha value of 0.05. Statistical analyses were conducted using Jamovi software version 2.7.7 (Sidney, Australia; https://www.jamovi.org/about.html).

RESULTS

Patients

From July 2022 to December 2024, 328 patients were screened. While 172 patients were not eligible (4: blood sample not available; 118: clonal *RAS/BRAF*^{V600E} mutations; 48: clinical deterioration; 2: withdrawal of consent), 156 patients were included in the trial, and randomly assigned (2 : 1) and treated with cetuximab plus avelumab (104 patients, arm A) or with cetuximab (52 patients, arm B) (Figure 1). Baseline clinical-pathological characteristics are summarized in Table 1. No significant difference was observed between the two treatment arms. Of note, in the CAVE-2 GOIM study, 27% of the patients in the two groups received three or more lines of therapy for metastatic disease indicating the inclusion of a heavily pre-treated population.

Efficacy

At a median follow-up of 20.4 months (IQR1, IQR3 15.1-27.3 months) (cut-off date, 30 September 2025), 96/104 (92%) patients in arm A and 50/52 (96%) patients in arm B had disease progression. Eight (8%) and two (4%) patients were still on treatment with cetuximab plus avelumab or with cetuximab, respectively. Overall, 63 (60.5%) and 32 (61.5%) deaths were observed in arms A and B, respectively. Therapy with cetuximab plus avelumab led to a numerical but not significant improvement in clinical outcomes. The ORR for patients treated with cetuximab plus avelumab compared with cetuximab was 12% versus 8% [odds ratio (OR) 1.57, 95% confidence interval (CI) 0.479-5.12, $P = 0.581$] (Figure 2A). The mPFS of patients treated in arm A versus arm B was 5.3 months (95% CI 4.3-6 months) versus 4.3 months (95% CI 3.5-5.5 months) (HR 0.78, 95% CI 0.55-1.10, $P = 0.158$; Figure 2B). The mOS was 14.8 months (95% CI 12.1-18.3 months) compared with 12.9 months [95% CI 11 months-not evaluable (NE)] (HR 1.00, 95% CI 0.65-1.52, $P = 0.983$) for patients who received cetuximab plus avelumab or cetuximab, respectively (Figure 2C).

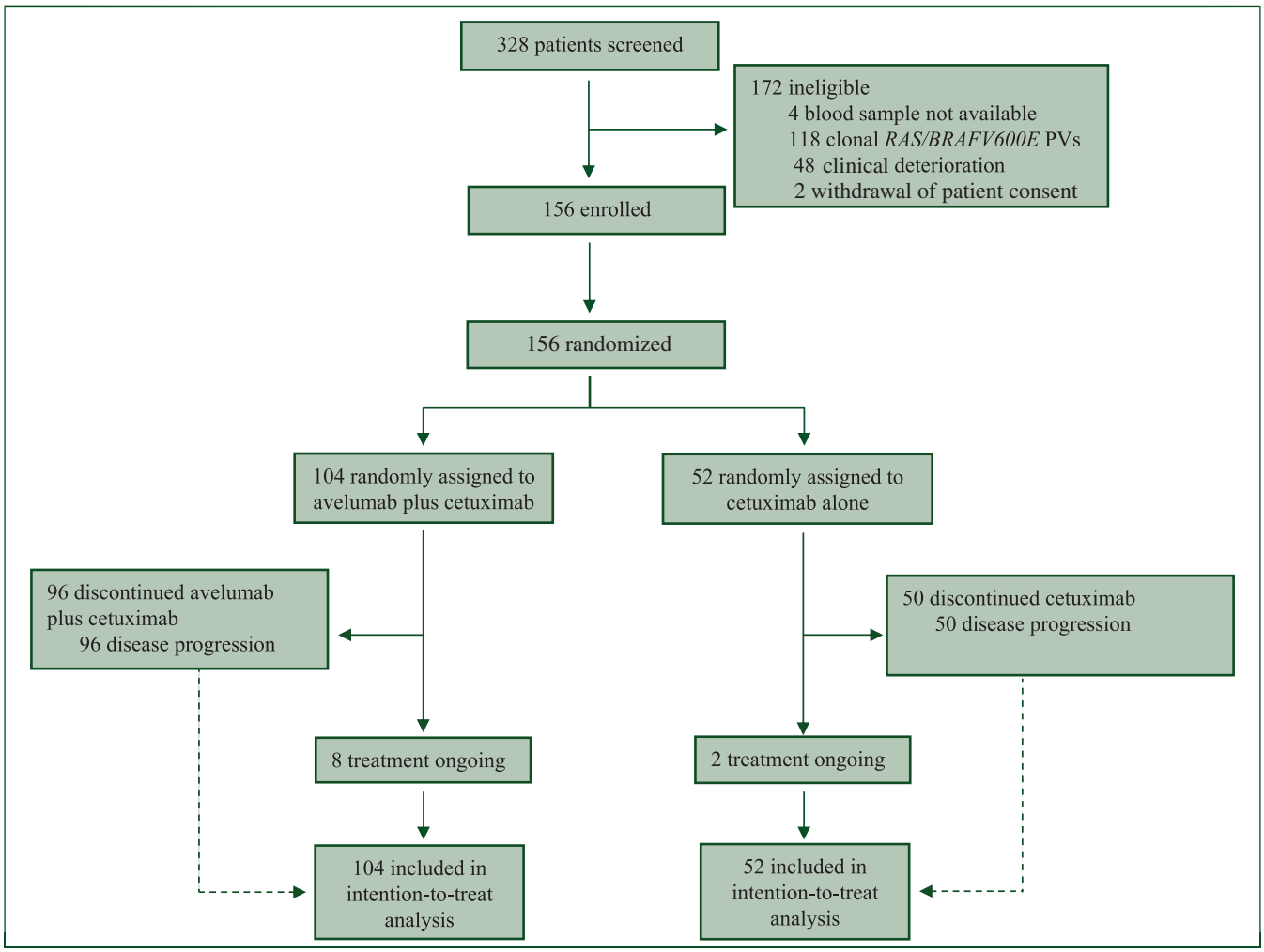

Figure 1. Study diagram.
PV, pathogenic variant.

Since the presence of high TMB and the absence of liver metastatic involvement are considered putative biomarkers that might predict antitumor activity of immunotherapy in MSS mCRC, we explored the impact of these factors on antitumor efficacy.[16-18] Presence of high TMB was a negative prognostic factor and was associated with limited responses and poor outcomes in both arms (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.12.014). In fact, mOS was 8.6 months (95% CI 7.2-15.6 months) versus 8.8 months (95% CI 3.1 months-NE) (HR 0.95, 95% CI 0.37-2.41, $P = 0.908$) for arm A and arm B, respectively. In patients with low TMB tumors, both treatment arms exerted better antitumor activity (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.12.014). In the subgroup of patients without liver involvement, the combination of cetuximab plus avelumab had signals of improved clinical activity compared with cetuximab monotherapy (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.12.014). In this subgroup, 5/44 (11%) patients who received cetuximab plus avelumab had PR, whereas no patients (0/16, 0%) in the cetuximab monotherapy arm obtained a PR (OR 0.22, 95% CI 0.01-4.16, $P = 0.31$) (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2025.12.014). The mPFS and mOS of patients treated with cetuximab plus avelumab compared with cetuximab monotherapy were 6.0 months (95% CI 4.4-7.8 months) versus 4.3 months (95% CI 2.7-7.6 months) (HR 0.65, 95% CI 0.35-1.21, $P = 0.174$) (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2025.12.014) and 15.6 months (95% CI 12.1 months-NE) versus 13.5 months (95% CI 8.7 months-NE) (HR 0.87, 95% CI 0.40-1.89, $P = 0.722$), respectively. No difference in clinical outcomes between the two treatment arms was observed in patients with liver metastases (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.12.014).

Efficacy of anti-EGFR drug rechallenge in patients with extended molecular selection

Emerging data suggest that extended molecular stratification, which takes into account not only *RAS/BRAF* mutations but also PVs in other EGFR pathway genes, could better identify patients who benefit from anti-EGFR therapies both as first-line and as rechallenge therapies. Improved therapeutic efficacy has been reported for both

Table 1. Baseline characteristics of the study population

Characteristic	Cetuximab + avelumab	Cetuximab	*P* value
	n = 104	*n* = 52	
Age at enrollment, years (IQR)	64 (57-72)	65 (59-72)	0.70
Sex, *n* (%)			0.860
Female	37 (36)	20 (38)	
Male	67 (64)	32 (62)	
ECOG PS, *n* (%)			0.711
0	73 (70)	38 (73)	
1	31 (30)	13 (27)	
Sidedness, *n* (%)			0.123
Left	96 (92)	43 (83)	
Right	8 (7.7)	9 (17)	
Number of metastatic sites, *n* (%)			0.511
<3	71 (68)	32 (62)	
≥3	33 (32)	20 (38)	
Liver metastasis, *n* (%)	60 (58)	36 (69)	0.222
Lung metastasis, *n* (%)	68 (65)	30 (58)	0.446
Peritoneal metastasis, *n* (%)	24 (23)	6 (12)	0.132
Lymph node metastasis, *n* (%)	40 (38)	21 (40)	0.954
Number of previous lines of therapy, *n* (%)			1.00
2	76 (73)	38 (73)	
≥3	28 (27)	14 (27)	
Anti-EGFR-free interval, months, mean (range)	14 (5-64)	16.5 (5-46)	0.25
Molecular hyperselection, *n* (%)			0.76
Positive hyperselected	20 (19)	12 (23)	
Negative hyperselected	84 (81)	40 (77)	
TMB, *n* (%)			0.22
High	22 (21)	7 (13)	
Low	81 (79)	45 (87)	

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor; IQR, interquartile range; PS, performance status; TMB, tumor mutational burden.

cetuximab and panitumumab in mCRC patients whose tumors are WT ('negative hyperselection') for genes in the EGFR pathway, as compared with patients with tumors having PVs in at least one of these genes ('positive hyperselection').[19-24]

Therefore, we pre-planned an exploratory analysis to evaluate the impact of these genomic alterations on anti-EGFR drug rechallenge efficacy for the whole study population and for the two arms of treatment (Figures 3 and 4). Collectively, 124/156 patients had tumors without any genomic alteration in *KRAS, NRAS, BRAF, EGFR* extracellular domain, *PIK3CA* exon 20, *MAP2K1, AKT1, MET, PTEN,* and *ERBB2* ('negative hyperselection'). The ORR was 12% versus 3% (OR 4.7, 95% CI 0.542-33.6, $P = 0.980$) in patients with 'negative' versus 'positive hyperselected' tumors (Figure 3A). Of note, significant improvement in both PFS and OS was observed in patients whose tumors lacked anti-EGFR drug resistance-related PVs (Figure 3). The mPFS and mOS of patients with 'negative' compared with 'positive hyperselected' tumors were 5.35 months (95% CI 4.4-5.9 months) versus 3.65 months (95% CI 2.8-4.8 months) (HR 0.62, 95% CI 0.42-0.92, $P = 0.017$) (Figure 3B) and 15.0 months (95% CI 12.6-19.9 months) versus 11.1 months (95% CI 8.6-15.6 months) (HR 0.61, 95% CI 0.39-0.97, $P = 0.037$) (Figure 3C), respectively. In the group of patients who received cetuximab monotherapy, 4/40 (10%) PRs were reported in the 'negative hyperselected' cases, whereas no response (0/12, 0%) was found in patients with 'positive hyperselected' tumors (OR 3.08, 95% CI 0.155-61.4, $P = 0.562$) (Figure 4A). Further, mPFS and mOS for patients treated with cetuximab monotherapy were 5.1 months (95% CI 3.9-6.1 months) versus 2.8 months (95% CI 2.2 months-NE) (HR 0.30, 95% CI 0.14-0.62, $P = 0.001$) (Figure 4B) and 14.8 months (95% CI 11.30 months-NE) versus 9.95 months (95% CI 6.1 months-NE) (HR 0.52, 95% CI 0.24-1.11, $P = 0.089$) (Figure 4C) in 'negative' versus 'positive hyperselected' cases, respectively. Similar differential ORR, mPFS, and mOS were observed for patients treated with cetuximab plus avelumab according to 'negative' versus 'positive hyperselection' (Figure 4D-F).

Safety

There were no unexpected safety signals, with no treatment-related grade >3 AEs (Table 2). No treatment discontinuation related to AEs was reported. As expected, most frequent grade 3 AEs were skin rash (8% and 4%, for patients receiving either cetuximab plus avelumab or cetuximab, respectively).

DISCUSSION

Rechallenge with EGFR inhibitors is emerging as a valid later-line therapeutic option in refractory *RAS/BRAF* WT mCRC patients.[9,22-28] However, it is still not clear whether anti-EGFR monotherapy is sufficient for optimal therapeutic efficacy or combined treatments with chemotherapy or with biologic drugs, including immune checkpoint inhibitors, are required. The CAVE-2 GOIM trial has evaluated two different rechallenge strategies, including the assessment of the potential efficacy of adding immunotherapy (avelumab) to cetuximab.

The results of the CAVE-2 GOIM trial demonstrate that the combination of cetuximab and avelumab does not result in statistically significant improvement in ORR, PFS, or OS compared with cetuximab monotherapy. Nevertheless, some considerations should be done. Firstly, the outcome of patients treated in the cetuximab monotherapy arm was more favorable than expected in a refractory mCRC setting. This was possibly due to the clinical impact of molecular selection by plasma ctDNA comprehensive genomic profiling (CGP) for the identification of PVs of cancer cell resistance. When the CAVE-2 GOIM trial was designed, we expected ∼10 months of mOS for patients treated with cetuximab monotherapy. Of note, the results of the CAVE-2 GOIM study have shown mOS of ∼13 months in these patients. Moreover, mCRC patients with 'negative hyperselected' tumors (i.e. without any potential genomic mechanism of anti-EGFR drug resistance) had an even higher clinical benefit with mOS approaching 15 months following cetuximab monotherapy. Therefore, despite the signal for numerically better clinical outcomes in patients receiving cetuximab plus avelumab as compared with those treated with cetuximab monotherapy, this randomized phase II study was most likely underpowered to

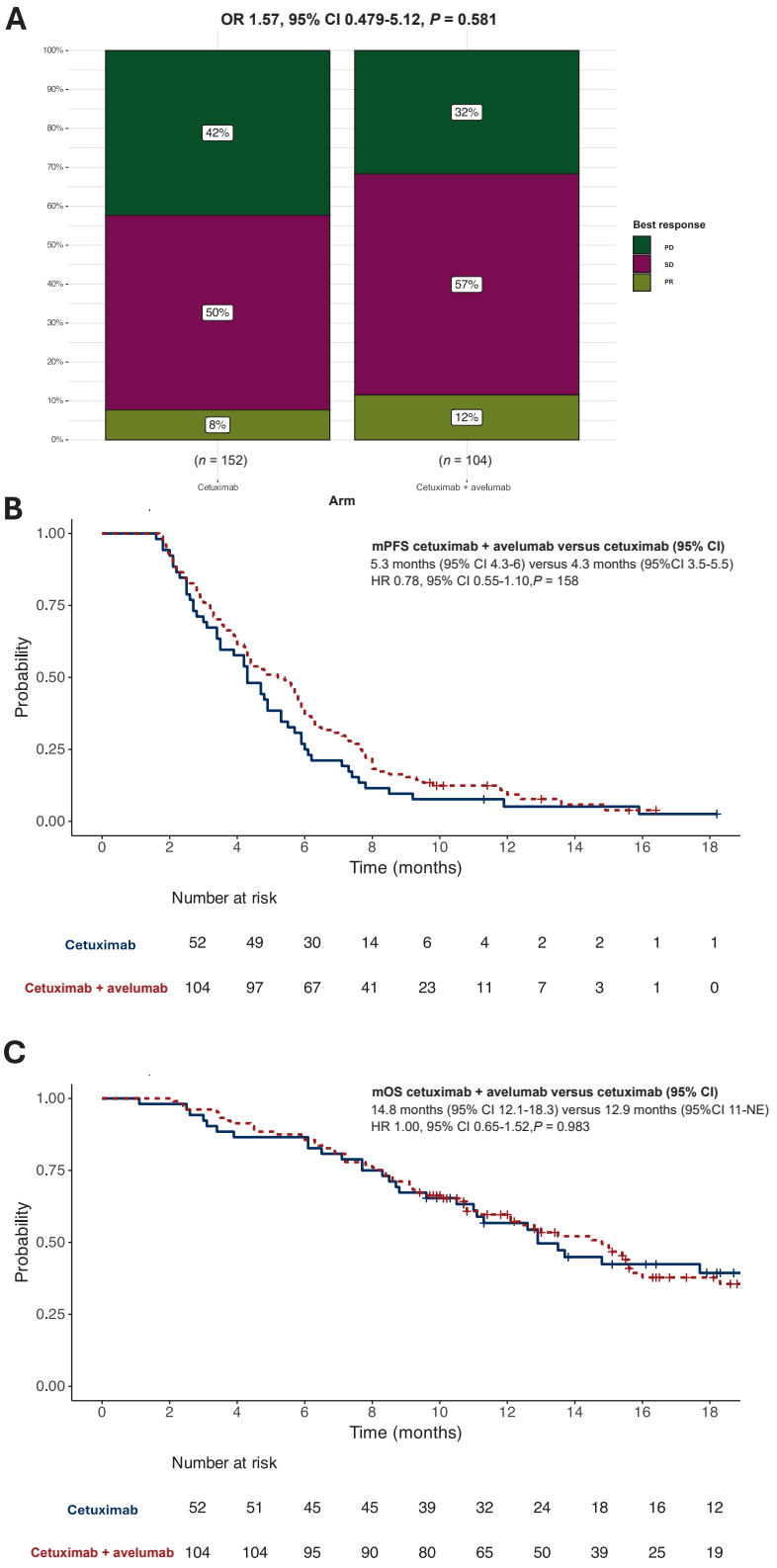

Figure 2. Clinical activity of cetuximab plus avelumab compared with cetuximab. (A) Objective response rate, (B) progression-free survival, and (C) overall survival of arm A versus arm B.
CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease.

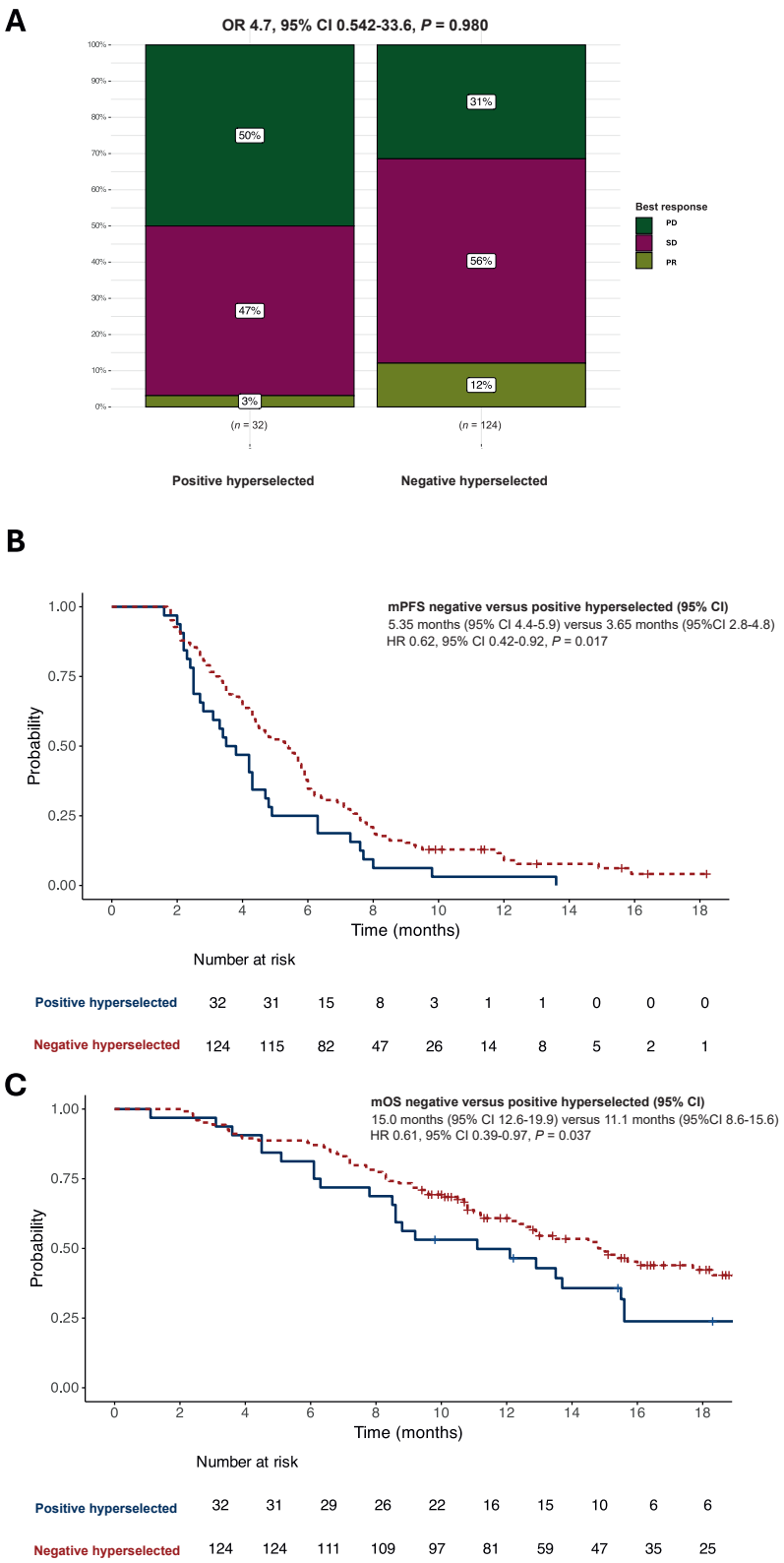

Figure 3. Clinical activity in the whole study population according to molecular hyperselection. (A) Objective response rate, (B) progression-free survival, and (C) overall survival of positive hyperselected versus negative hyperselected cases.
CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease.

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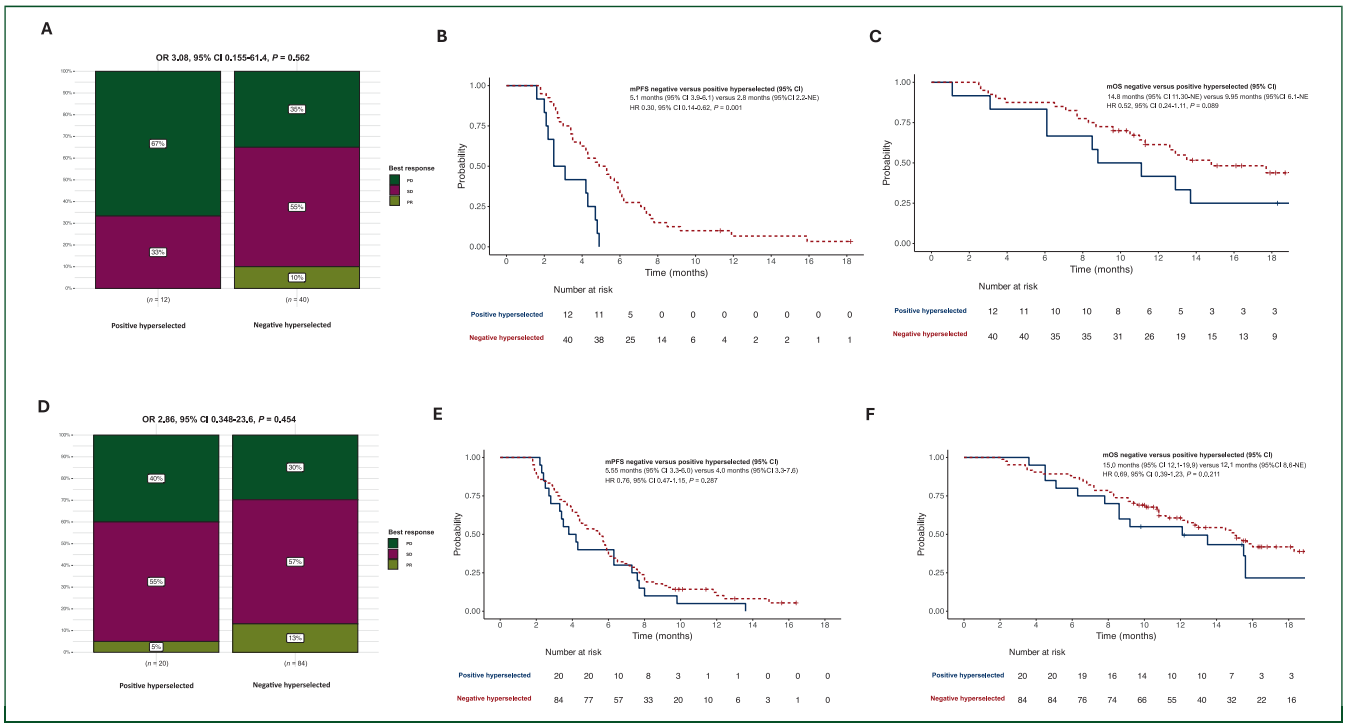

Figure 4. Clinical activity of cetuximab and cetuximab plus avelumab according to molecular hyperselection. (A) Objective response rate, (B) progression-free survival, and (C) overall survival of patients treated with cetuximab according to molecular hyperselection. (D) Objective response rate, (E) progression-free survival, and (F) overall survival of patients treated with cetuximab plus avelumab according to molecular hyperselection.
CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease.

detect smaller differences in OS between the two treatment arms.

The large majority of mCRC are MSS tumors, which are characterized by low immunogenicity and lack of responsiveness to immune checkpoint inhibitors.[6,29] In this context, there was a biological rationale for combining cetuximab with avelumab, which was based on their potential synergistic effects, since cetuximab-mediated immune activation could enhance tumor response to PD-L1 inhibition.[10-12] Findings of the single-arm phase II CAVE GOIM trial suggested a promising clinical activity of this combination.[13] Although there is no additional benefit of adding avelumab to cetuximab in the CAVE-2 GOIM trial, clinical signals of potential benefit were observed in the subgroup of patients without liver metastases. This observation is consistent with preclinical and clinical data indicating that MSS mCRC patients without liver metastatic involvement may derive benefit from immune checkpoint inhibition.[17,18] However, further clinical validation in larger, randomized trials in patients without liver involvement is required to determine the true contribution of cetuximab plus avelumab or other combinatory strategies with immune checkpoint inhibitors in refractory MSS mCRC. In this regard, the recently reported results of the large, multicenter, randomized phase III STELLAR-303 trial have shown that the combination of zanzalintinib with the anti-PD-L1 monoclonal antibody atezolizumab determines a small but statistically significant improvement in PFS and OS compared with regorafenib monotherapy in unselected refractory MSS mCRC patients.[30] Mature data on OS in patients without liver metastases will provide further evidence for the clinical activity of this combination.

While the KEYNOTE-158 study showed that pembrolizumab might exert antitumor activity in refractory solid tumors with TMB >10, the role of immunotherapy in patients with MSS/*POLE/POLD-1* WT tumors and high TMB remains controversial.[16,31,32] Recently, Yamaguchi and colleagues evaluated the clinical activity of pembrolizumab in MSS mCRC. Of note, patients with MSS-high TMB mCRC had worse outcomes if treated with pembrolizumab compared with trifluridine/tipiracil.[32] In the CAVE-2 GOIM study, the presence of high TMB was a negative prognostic factor and was not predictive of the antitumor activity of avelumab. Thus, other biomarkers rather than TMB should be investigated to identify mCRC patients with MSS tumors who could benefit from immune checkpoint inhibitors. In this scenario, the immunoscore-IC and TuLIS might represent putative biomarkers to identify patients who could benefit from immunotherapy in combination with chemotherapy plus bevacizumab as first-line treatment of mCRC, as suggested by translational analyses of the AtezoTRIBE and POCHI trials.[33,34]

In any case, the findings of the CAVE-2 GOIM trial strongly support the key role of anti-EGFR drug rechallenge patients with molecular hyperselected mCRC. VELO was the first randomized phase II clinical study to evaluate the combination of panitumumab with standard-of-care trifluridine/tipiracil as rechallenge for patients with refractory *RAS* WT mCRC.[22] The study was positive and demonstrated an advantage in PFS for the experimental arm compared

Table 2. Toxicity

	Arm A $n = 104$ (%)		Arm B $n = 52$ (%)	
	Any grade	G ≥ 3	Any grade	G ≥ 3
Skin disorders				
Rash	63 (61)	8 (8)	27 (52)	2 (4)
Dry skin	6 (6)	0 (0)	3 (6)	0 (0)
Skin ulceration	6 (6)	0 (0)	2 (4)	0 (0)
Mucositis	7 (7)	0 (0)	3 (6)	0 (0)
Nail disorders	7 (7)	0 (0)	3 (6)	0 (0)
Pruritus	18 (17)	0 (0)	4 (8)	0 (0)
Folliculitis	10 (10)	0 (0)	7 (13)	0 (0)
Conjunctivitis	9 (9)	0 (0)	1 (2)	0 (0)
Blepharitis	2 (2)	0 (0)	0 (0)	0 (0)
Eye disorder	3 (3)	0 (0)	1 (2)	0 (0)
Gastrointestinal disorders				
Diarrhea	8 (8)	0 (0)	3 (6)	1 (1)
Constipation	1 (1)	0 (0)	0 (0)	0 (0)
Nausea	4 (4)	0 (0)	0 (0)	0 (0)
Vomiting	2 (2)	0 (0)	0 (0)	0 (0)
AST/ALT increase	3 (3)	0 (0)	3 (6)	0 (0)
Blood bilirubin increase	2 (2)	1 (1)	0 (0)	0 (0)
Lipase and/or amylase increase	11 (11)	0 (0)	0 (0)	0 (0)
Hypomagnesemia	8 (8)	0 (0)	2 (4)	0 (0)
Others				
Fatigue	12 (11)	0 (0)	5 (10)	0 (0)
Immune-related disorders				
Hypothyroidism	3 (3)	0 (0)	0 (0)	0 (0)
Colitis	2 (2)	0 (0)	0 (0)	0 (0)
Hypophysitis	1 (1)	0 (0)	0 (0)	0 (0)
Pancreatitis	1 (1)	0 (0)	0 (0)	0 (0)
Pneumonitis	1 (1)	0 (0)	0 (0)	0 (0)

Data are in *n* (%). The table lists any-grade (1-2 and 3) adverse events that occurred. No grade 4 or 5 adverse events have been recorded so far in study population.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade.

with trifluridine/tipiracil (4 versus 2.5 months). Remarkably, by further refining patient selection through plasma ctDNA CGP, which included PVs in the EGFR pathway, mPFS reached 6.4 months following treatment with panitumumab plus trifluridine/tipiracil.[22] Recently, results of the CITRIC trial investigating rechallenge with cetuximab plus irinotecan were reported.[28] Similarly, in the subset of patients with 'negative hyperselected' tumors, a longer PFS was observed.

A key unresolved question is how to optimally integrate anti-EGFR rechallenge into the overall treatment sequence across the continuum of care following the first two lines of therapy. The randomized phase II PARERE trial has evaluated rechallenge with panitumumab compared with regorafenib versus the reverse strategy.[23] No difference in OS was observed; however, panitumumab rechallenge significantly improved ORR and PFS compared with regorafenib, regardless of the line of treatment. While the VELO and PARERE trials demonstrated that anti-EGFR rechallenge is associated with improved antitumor activity compared with trifluridine/tipiracil and regorafenib, so far, no direct comparison with trifluridine/tipiracil plus bevacizumab is available.

In this scenario, our research group has recently started the ROMANCE trial, a randomized phase II study in which mCRC patients with 'negative hyperselected' tumors by baseline plasma ctDNA CGP are randomly assigned to receive cetuximab plus irinotecan or standard-of-care trifluridine/tipiracil plus bevacizumab, as third-line therapy. This trial could help to clarify whether anti-EGFR drug rechallenge could be used in third line in these molecularly selected patients or should be considered as a subsequent therapeutic option.

In conclusion, the CAVE-2 GOIM study did not demonstrate that the addition of avelumab to cetuximab rechallenge is associated with improved survival. Nevertheless, within the limitations of a randomized phase II trial, these results highlight the need for comprehensive and accurate molecular stratification as the key determinant for predicting clinical efficacy of anti-EGFR drug rechallenge strategies. In this scenario, ctDNA assessment should be carried out at different time points across the therapeutic journey of patients with *RAS/BRAF* WT mCRC. When resistance alterations are not detected by liquid biopsy-based CGP, independently of the line of therapy (third versus later line), cetuximab monotherapy is an effective and valuable treatment option for refractory MSS mCRC. Collectively, these findings suggest that a subset of mCRC remains dependent on EGFR signaling and that this tumor dependency could allow the use of molecular targeted therapies also in refractory disease for appropriately selected patients.

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DISCLOSURE

DC reported receiving travel support from Merck KGaA, Sanofi, and BMS; advisory board Bayer, Roche, Merck KgA, and Amgen outside the submitted work. GM reported receiving honoraria from Servier, Incyte, and Pierre Fabre outside the submitted work. FP reported receiving research funding (to institution) from Lilly, BMS, Incyte, AstraZeneca, Amgen, Agenus, and Rottapharm; personal honoraria as an invited speaker from BeiGene, Daiichi-Sankyo, Seagen, Astellas, Ipsen, AstraZeneca, Servier, Bayer, Takeda, Johnson & Johnson, BMS, MSD, Amgen, Merck Serono, and Pierre Fabre; advisory/consultancy from BMS, MSD, Amgen, Pierre Fabre, Johnson & Johnson, Servier, Bayer, Takeda, Astellas, GSK, Daiichi-Sankyo, Pfizer, BeiGene, Jazz Pharmaceuticals, Incyte, Rottapharm, Merck Serono, Italfarmaco, Gilead, AstraZeneca, and Agenus. EMar reported serving as advisor and speaker for AstraZeneca, Eli Lilly, Servier, Sanofi Genzyme, Roche, Merck, Eisai, and Pfizer outside the submitted work. TT received travel grants from AstraZeneca and Pierre Fabre and is an advisory board member for AstraZeneca, Bayer, Amgen, Merck, Roche, Sanofi, Servier, and Pierre Fabre. ASB reported consulting or advisory role for Bayer, Novartis, Pierre Fabre, Servier, and Takeda; personal honoraria as an invited speaker from Amgen, Guardant Health, Pierre Fabre, and Seagen. GT reported consulting or advisory role for Bristol Myers Squibb, AstraZeneca, Merck, Merck Sharp & Dohme, and Servier. AA reported receiving personal fees from Amgen, AstraZeneca, Merck, Sharp & Dohme, Eisai, and Bristol Myers Squibb outside the submitted work. RBe reported serving as consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Novartis, MSD, Otsuka, Eli Lilly, and Roche outside the submitted work. EMai reported serving as advisor and speaker for AstraZeneca, Eli Lilly, Servier, Sanofi Genzyme, Roche, Merck, Eisai, and Pfizer outside the submitted work. NN reported receiving honoraria: Thermo Fisher Scientific, Lilly, MSD, Illumina, Merck Serono, Incyte, Biocartis, AstraZeneca, and MSD; consulting or advisory role: Biocartis, AstraZeneca, Bayer, Incyte, Novartis, and Roche; research funding: AstraZeneca (Inst), Biocartis (Inst), Illumina (Inst), Incyte (Inst), Merck Serono (Inst), Qiagen (Inst), Roche (Inst), and Thermo Fisher Scientific (Inst); travel, accommodations, expenses: Merck Serono. GS reported receiving research funds (to institution) from BMS, Mirati, and Nouscom; serving on an advisory board for Amgen and Bayer; and travel grants from AstraZeneca, Merck, and Servier outside the submitted work. RBo reported receiving honoraria: Novartis, AstraZeneca, Sanofi, Amgen, Roche, Pfizer, Janssen-Cilag, and Bristol Myers Squibb; consulting or advisory role: Novartis, Bayer, AstraZeneca, Sanofi, Amgen, Roche, Pfizer, Janssen-Cilag, and Bristol Myers Squibb; speakers' bureau: AstraZeneca, Sanofi, Novartis, Bayer, Amgen, Roche, Pfizer, Janssen-Cilag, and Bristol Myers Squibb. NF reported receiving research funds from and serving on an advisory board for Merck outside the submitted work. GC reported receiving honoraria for speaker's engagement: Roche, Seattle Genetics, Novartis, Lilly, Pfizer, Foundation Medicine, NanoString, Samsung, Celltrion, BMS, and MSD; honoraria for providing consultancy: Roche, Seattle Genetics, and NanoString; honoraria for participating in advisory board: Roche, Lilly, Pfizer, Foundation Medicine, Samsung, Celltrion, and Mylan; honoraria for writing engagement: Novartis and BMS; honoraria for participation in Ellipsis Scientific Affairs Group; institutional research funding for conducting phase I and II clinical trials: Pfizer, Roche, Novartis, Sanofi, Celgene, Servier, Orion, AstraZeneca, Seattle Genetics, AbbVie, Tesaro, BMS, Merck Serono, Merck Sharp Dohme, Janssen-Cilag, Philogen, Bayer, Medivation, and Medimmune. FC received institutional research grants from Amgen, Merck KGaA, Merck Sharp & Dohme, Pfizer, Pierre Fabre, Roche, and Servier; and service on advisory boards for Bayer, Merck KGaA, Merck Sharp & Dohme, Pierre Fabre, Roche, and Servier outside the submitted work. SN reported receiving personal fees from Novartis and a travel grant from Amgen outside the submitted work. All other authors have declared no conflicts of interest.

DATA SHARING

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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