Efficacy of Sym004 in Patients With Metastatic Colorectal Cancer With Acquired Resistance to Anti-EGFR Therapy and Molecularly Selected by Circulating Tumor DNA Analyses: A Phase 2 Randomized Clinical Trial

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**IMPORTANCE**
Acquired resistance to anti-EGFR therapy (epidermal growth factor receptor) is frequently due to RAS and EGFR extracellular domain (ECD) mutations in metastatic colorectal cancer (mCRC). Some anti-EGFR-refractory patients retain tumor EGFR dependency potentially targetable by agents such as Sym004, which is a mixture of 2 nonoverlapping monoclonal antibodies targeting EGFR.

**OBJECTIVE**
To determine if continuous blockade of EGFR by Sym004 has survival benefit.

**DESIGN, SETTING, AND PARTICIPANTS**
Multicenter, phase 2, randomized, clinical trial comparing 2 regimens of Sym004 with investigator’s choice from March 6, 2014, through October 15, 2015. Circulating tumor DNA (ctDNA) was analyzed for biomarker and tracking clonal dynamics during treatment. Participants had wild-type KRAS exon 2 mCRC refractory to standard chemotherapy and acquired resistance to anti-EGFR monoclonal antibodies.

**INTERVENTIONS**
Participants were randomly assigned in a 1:1:1 ratio to Sym004, 12 mg/kg/wk (arm A), Sym004, 9 mg/kg loading dose followed by 6 mg/kg/wk (arm B), or investigator’s choice of treatment (arm C).

**MAIN OUTCOMES AND MEASURES**
Overall survival (OS). Secondary end points included preplanned exploratory biomarker analysis in ctDNA.

**RESULTS**
A total of 254 patients were randomized (intent-to-treat [ITT] population) (median age, 63 [range, 34-91] years; 63% male; n = 160). Median OS in the ITT population was 7.9 months (95% CI, 6.5-9.9 months), 10.3 months (95% CI, 9.0-12.9 months), and 9.6 months (95% CI, 8.3-12.2 months) for arms A, B, and C, respectively (hazard ratio [HR], 1.31; 95% CI, 0.92-1.87 for A vs C; and HR, 0.97; 95% CI, 0.68-1.40 for B vs C). The ctDNA revealed high intrapatient genomic heterogeneity following anti-EGFR therapy. Sym004 effectively targeted EGFR ECD-mutated cancer cells, and a decrease in EGFR ECD ctDNA occurred in Sym004-treated patients. However, this did not translate into clinical benefit in patients with EGFR ECD mutations, likely owing to co-occurring resistance mechanisms. A subgroup of patients was defined by ctDNA (RAS/BRAF/EGFR ECD-mutation negative) associated with improved OS in Sym004-treated patients in arm B compared with arm C (median OS, 12.8 and 7.3 months, respectively).

**CONCLUSIONS AND RELEVANCE**
Sym004 did not improve OS in an unselected population of patients with mCRC and acquired anti-EGFR resistance. A prospective clinical validation of Sym004 efficacy in a ctDNA molecularly defined subgroup of patients with refractory mCRC is warranted.

**TRIAL REGISTRATION**
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Patients with histologically or cytologically confirmed mCRC that was exon 2 KRAS WT at the time of initial diagnosis and who gave written informed consent were screened for enrollment to this trial. Included patients were required to have prior intolerance to or failure of standard chemotherapy regimens including fluorouracil, oxaliplatin, and irinotecan, and were allowed to have received bevacizumab or ziv-afibercept. Prior therapy with regorafenib was not permitted. In addition, all included patients had acquired resistance to prior therapy with a marketed anti-EGFR mAb, as defined by having achieved either an objective partial response (PR), complete response (CR), or stable disease for more than 16 weeks followed by documented progressive disease (PD) during or within 6 months of completion of this therapy. Included patients were required to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment arms, 1 of 2 dose regimens of Sym004, 12 mg/kg/wk (arm A) or 9 mg/kg loading dose followed by 6 mg/kg/wk (arm B) compared with a control group, which included IC of capecitabine, fluorouracil, or BSC (arm C). Treatment continued until radiographically confirmed disease progression on standard imaging, unacceptable toxic effects, death, or the patient or physician decided to stop. Doses could be modified to manage treatment-related toxic effects.

Overall survival (OS), defined as time from randomization to date of death or censored at last day of contact, was the primary efficacy end point. Secondary end points included safety; progression-free survival (PFS), defined as time from randomization to date of disease progression or death from any cause; response rate; and exploratory biomarker analysis.

To establish a robust estimate of Sym004 survival benefit, a minimum of 240 patients were to be randomized based on 80% statistical power to differentiate assumed median OS of 6 months for arm C group19 and 9.2 months for arm A or B, with a 2-sided level of significance of P = .121. The primary analysis was to be performed when at least 181 events (deaths)
had been reported or 12 months after the last patient was randomized in the trial, whichever occurred later. The data cut-off was October 24, 2016. We used the Kaplan-Meier method to generate curves for OS and PFS. Hazard ratios (HRs) for treatment effects were estimated with an unstratified Cox proportional hazards model.

Baseline ctDNA profiles (Guardant360, version 2.9; Guardant Health) were obtained from blood samples collected from patients in the trial (eFigure 1 in Supplement 2). Serial samples obtained prior to and after 3 weeks of treatment were also analyzed for \textit{EGFR} ECD mutation dynamics. The ctDNA was amplified using droplet digital polymerase chain reaction (ddPCR) Supermix for Probes with \textit{EGFR} ECD mutation assays (Bio-Rad). This ddPCR was then performed according to the manufacturer’s protocol. We performed 3 independent ddPCR experiments for each of the point mutations assessed and for each longitudinal time point. Fractional abundances (%) were calculated as follows: fractional abundance $= \frac{\text{number of mutation events}}{\text{number of mutation + WT events}} \times 100$ and were Poisson corrected by QuantaSoft analysis software (BioRad).

Results

Between March 6, 2014, and October 15, 2015, of 299 patients screened, 254 were randomly assigned, and these made up the intent-to-treat (ITT) population (Figure 1). The study population was balanced at baseline (Table 1). Patients were heavily pretreated: 72%, 78%, and 72% in arms A, B, and C, respectively, had received at least 3 previous regimens.

Median OS in the ITT population was 7.9 (95% CI, 6.5-9.9) months, 10.3 (95% CI, 9.0-12.9) months, and 9.6 (95% CI, 8.3-12.2) months for arms A, B, and C, respectively (HR, 1.31; 95% CI, 0.92-1.87 for A vs C; and HR, 0.97; 95% CI, 0.68-1.4 for B vs C) (Table 2 and eFigure 2 in Supplement 2). Median PFS in the ITT population was 2.8 (95% CI, 1.8-3.2) months, 2.7 (95% CI, 2.6-3.3) months, and 2.6 (95% CI, 1.4-3.1) months for arms A, B, and C, respectively. Response rates for evaluable patients in the ITT population were 11 PRs (14.1%), 8 PRs (9.6%), and 1 CR and 1 PR (2.9%) in arms A, B, and C, respectively (eTable 1 in Supplement 2). The unexpectedly long median OS of 9.6 months in the IC arm led to evaluation of potential factors that might explain this finding. It became evident that a subgroup of patients (n = 30) had been subject to nonstandard medical practice in first- or second-line therapy that had an impact on the efficacy of rescue chemotherapy in the anti-EGFR refractory setting as well as in the molecular characterization of these patients (details provided in eMethods and eTable 2 in Supplement 2). This population was excluded from the genomic analysis.

Treatment with both regimens of Sym004 led to a higher frequency and severity of adverse events (AEs) than treatment administered to patients on the IC arm, and the Sym004 regimen of 12 mg/kg/wk (arm A) was more poorly tolerated than the Sym004 9 mg/kg loading dose followed by 6 mg/kg/wk (arm B) dosing schedule (eTable 3 in Supplement 2). The Sym004 AE profile was consistent with other anti-EGFR mAbs, although the frequency and severity of both dermatologic AEs (94.0% and 92.9% for arms A and B, respectively, compared with 10.3% in the IC arm) and hypomagnesemia (68.7% and 56.0% for arms A and B, respectively, compared with 7.7% in
the IC arm) were higher than those found with other approved anti-EGFR mAb therapies. In contrast, the frequency of gastrointestinal AEs appeared to be lower than has been reported for other anti-EGFR mAbs (51.8% and 48.8% for arms A and B, respectively, compared with 47.4% in IC arm). The frequency of treatment-emergent AEs leading to study treatment discontinuation (6.0% in arm B vs 7.7% in arm C) and related treatment-emergent AEs leading to study treatment discontinuation (2.4% in arm B vs 3.8% in arm C) was not different in patients treated with the lower Sym004 dose and IC.

Baseline ctDNA profiles of alterations in 70 genes (eFigure 1 in Supplement 2) were obtained from blood samples collected from 193 patients in the trial. Genotyping of baseline ctDNA captured high intratumor genomic heterogeneity and confirmed previously reported mechanisms of acquired resistance to cetuximab and panitumumab, including mutations in RAS (29.5% of patients), EGFR ECD (25% of patients), and BRAF V600E (6.7% of patients), as well as amplification of ERBB2/HER2 and MET (eFigures 3 and 4 in Supplement 2). Inactivation of APC and/or TP53 is an early event in the development of CRC and the APC/TP53 highest mutant allele frequency (MAF) alteration in a patient’s ctDNA can therefore serve as an arbitrary marker for clonal mutations (present in all tumor cells). The median MAF for the most prevalent TP53/ APC alterations was close to 20%. The median MAFs for KRAS, NRAS, EGFR ECD and BRAF were much lower than 20%, indicating that these mutations are primarily subclonal, al-

Table 1. Baseline Characteristics for the Intent-to-Treat Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A, Sym004 12 mg/kg (n = 83)</th>
<th>Arm B, Sym004 9/6 mg/kg (n = 86)</th>
<th>Arm C, Investigator’s Choice (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)*, y</td>
<td>62 (10)</td>
<td>64 (10)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>Male 52 (63) Female 31 (37)</td>
<td>Male 54 (63) Female 32 (37)</td>
<td>Male 54 (64) Female 31 (37)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td>White 72 (88) Other or NA 11 (13)</td>
<td>White 75 (87) Other or NA 11 (13)</td>
<td>White 73 (86) Other or NA 12 (14)</td>
</tr>
<tr>
<td>ECOG performance status, No. (%)</td>
<td>0 33 (40) 1 50 (60) 2 0</td>
<td>0 35 (41) 1 50 (58) 2 1 (1)*</td>
<td>0 35 (41) 1 50 (59) 2 0</td>
</tr>
<tr>
<td>Tumor site, No. (%)</td>
<td>Right colon 12 (15) Left colon/rectum 67 (81)</td>
<td>Right colon 10 (12) Left colon/rectum 72 (84)</td>
<td>Right colon 9 (11) Left colon/rectum 70 (82)</td>
</tr>
<tr>
<td>Prior mCRC treatments, No. (%)*</td>
<td>2 23 (28) 3 27 (33) 4 33 (40)</td>
<td>2 19 (22) 3 24 (28) 4 43 (50)</td>
<td>2 24 (28) 3 29 (34) 4 32 (38)</td>
</tr>
<tr>
<td>Prior anti-EGFR mAb therapies, No. (%)</td>
<td>Cetuximab only 55 (66) Cetuximab and panitumumab 12 (15) Panitumumab only 16 (19.3)</td>
<td>Cetuximab only 54 (63) Cetuximab and panitumumab 14 (16) Panitumumab only 18 (21)</td>
<td>Cetuximab only 53 (62) Cetuximab and panitumumab 14 (17) Panitumumab only 18 (21.2)</td>
</tr>
<tr>
<td>Time since last anti-EGFR mAb therapy, mean (SD), d</td>
<td>78 (48)</td>
<td>80 (51)</td>
<td>72 (46)</td>
</tr>
</tbody>
</table>

Table 2. Efficacy Data for the ITT Study Population and Population With Biomarker Data

<table>
<thead>
<tr>
<th>Study Group</th>
<th>OS (95% CI), mo</th>
<th>1-Year Survival, No. (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population (n = 254)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sym004 12 mg/kg (n = 83)</td>
<td>7.9 (6.5-9.9)</td>
<td>37 (26-47)</td>
<td>1.31 (0.92-1.87)</td>
</tr>
<tr>
<td>Sym004 9/6 mg/kg (n = 86)</td>
<td>10.3 (9.0-12.9)</td>
<td>44 (33-54)</td>
<td>0.97 (0.68-1.40)</td>
</tr>
<tr>
<td>Investigator’s choice</td>
<td>9.6 (8.3-12.2)</td>
<td>40 (29-51)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Population with biomarker data (n = 193)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sym004 12 mg/kg (n = 70)</td>
<td>7.7 (5.5-11.3)</td>
<td>38 (26-49)</td>
<td>1.03 (0.69-1.54)</td>
</tr>
<tr>
<td>Sym004 9/6 mg/kg (n = 67)</td>
<td>9.9 (7.1-12.9)</td>
<td>44 (32-56)</td>
<td>0.79 (0.52-1.20)</td>
</tr>
<tr>
<td>Investigator’s choice (n = 56)</td>
<td>8.5 (6.4-9.9)</td>
<td>27 (16-41)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NA, not available.
* Sixty-one patients are excluded from this population, 31 due to lack of biomarker data and 30 due to treatment and OS data inconsistent with the study population (see Supplement 2 for more information).
though a subset of 10 patients harbored RAS mutations at allele frequencies above 20% (Figure 2A). Six EGFR ECD mutations (V441D, V441G, S464L, G465E, G465R, and S492R) were the most frequent (each present in ≥5% of patients, totally detected in 25% of patients; Figure 2C and eFigure 5 in Supplement 2). Patients with EGFR ECD mutations had more genetic alterations (median number of alterations per patient, 14; interquartile range [IQR], 10.0-18.5) compared with the full biomarker patient population (median, 9; IQR, 5-14) (Figure 2C). The frequency and type of EGFR ECD mutations varied depending on previous treatment with cetuximab or panitumumab (Figure 2B). 6,7,20

As a predefined exploratory secondary objective of the study, we next aimed to investigate ctDNA-defined molecular subgroups that would predict Sym004 efficacy. A 20% RAS MAF cutoff accurately selected a subgroup of 10 patients in which RAS ctDNA mutations and other mutations of acquired resistance were virtually mutually exclusive, suggesting RAS clonality (Figure 2C and eFigure 10 in Supplement 2). In these patients, RAS mutations potentially existed at the time of diagnosis, before the patient received cetuximab or panitumumab therapy. In preclinical patient-derived xenograft CRC models with RAS and BRAF V600E mutations, poor or limited Sym004 activity was observed, indicating that clonal mut-
tations in these genes caused resistance to Sym004, as is the case for cetuximab and panitumumab (eFigure 11 in Supplement 2). Based on these data, we performed an exploratory analysis of efficacy in a genomically defined subpopulation, which excluded patients with clonal RAS (MAF >20%) and BRAF V600E mutation (named double-negative mCRC; 170 patients; eTable 3 in Supplement 2). Results showed an increase in OS for the Sym004 9/6 group (arm B) (11.9 vs 9.9 months) and a smaller increase in the Sym004 12 group (arm A) (8.9 vs 7.7 months) compared with the subpopulation of patients with biomarker data. Overall survival in the IC population (arm C) was unchanged (8.4 and 8.5 months in the subpopulation and double-negative mCRC subgroup, respectively). Thus, this exploratory biomarker-defined analysis showed an increase in median OS of 3.5 months in the double-negative mCRC population of patients treated with Sym004 9/6 (arm B; 11.9 months) compared with patients randomized to IC (arm 3; 8.4 months) (Figure 3A).
We then investigated the role of \textit{EGFR} ECD mutations as a biomarker of Sym004 activity. Preclinical studies showed that \textit{EGFR} ECD mutations negatively affected the binding and activity of cetuximab, panitumumab, and futuximab, all of which bind to surface-exposed amino acids in the V441-S492 region of domain III of \textit{EGFR}. The inhibitory activity of Sym004, however, was partially rescued by the modotuximab component of Sym004, which binds to a different region and retains full binding and activity toward the most frequent \textit{EGFR} ECD mutations (Figure 3B and eFigures 6, 7, 8, and 9 in Supplement 2). Unexpectedly, the presence of \textit{EGFR} ECD mutations in the ctDNA of patients was not linked to clinical benefit of Sym004 (eFigure 12 in Supplement 2). The most plausible explanation was the subclonal nature of the \textit{EGFR} ECD mutations in the patients and intrapatient heterogeneity (Figure 2C and eFigure 3 in Supplement 2). To study the molecular basis of these findings in more detail, we sought to analyze the dynamics of \textit{EGFR} ECD mutations in blood from patients during Sym004 treatment. The percentage of \textit{EGFR} ECD mutations decreased in the majority of patients treated with Sym004 (Figure 3C), suggesting that subclones carrying \textit{EGFR} ECD mutations might be targeted by the modotuximab component of Sym004, as shown in the preclinical studies (Figure 3B and eFigures 7, 8, and 9 in Supplement 2). However, this retained activity did not translate into a clinically meaningful OS benefit, likely owing to other co-occurring resistance mechanisms (Figure 2C and eFigures 13, 14, and 15 in Supplement 2) and subclonality of \textit{EGFR} ECD mutations (eFigure 3 in Supplement 2). Of note, in the 2 patients who experienced an increase in percentage of 1 \textit{EGFR} ECD mutation in ctDNA during Sym004 therapy, other \textit{EGFR} ECD mutations that were concomitantly detected in the same sample declined following Sym004 therapy (Figure 3C).

Most notably, we found that the molecular heterogeneity related to known resistance markers (which we defined as the number of resistance alterations, including \textit{RAS}, \textit{BRAF}, and \textit{EGFR} ECD mutations and \textit{ERBB2}/\textit{HER2} and \textit{MET} amplifications)\textsuperscript{21-23} was associated with worse OS (eFigure 12 in Supplement 2). This led us to postulate that the occurrence of heterogeneous resistance mutations (including \textit{EGFR} ECD mutations) might pinpoint a subset of patients in which high genomic complexity due to previous chemotherapy and \textit{EGFR} blockade impaired effectiveness of Sym004 treatment. To test this hypothesis, we assessed outcomes in patients with \textit{RAS} less than 20% MAF, \textit{BRAF} WT, and \textit{EGFR} ECD WT, which we named triple-negative mCRC (eTable 4 in Supplement 2). We found that the triple-negative mCRC population had markedly prolonged OS for Sym004 treatment arms: 12.8 (95% CI, 9.7-14.7) months in the Sym004 9/6 group (arm B; n = 46) and 10.6 (95% CI, 6.8-13.3) months in the Sym004 12 group (arm A; n = 47), compared with 7.3 (95% CI, 6.3-8.8) months in the IC group (arm C; n = 38) (Figure 3D and eTable 4 in Supplement 2).

**Discussion**

Sym004 is a mixture of 2 mAbs that target nonoverlapping epitopes on domain III with more efficient mediated down-modulation and subsequent degradation of cell-surface \textit{EGFR} than the clinically approved antibodies cetuximab and panitumumab, leading to more complete and durable pathway inhibition.\textsuperscript{16,17} Here, we report safety and efficacy data from a randomized, multicenter, phase 2 clinical trial of Sym004 investigating 2 Sym004 dose regimens vs IC (capcitabine, fluorouracil, or BSC) in patients with refractory mCRC and with acquired resistance to anti-\textit{EGFR} therapy.

In the ITT population, OS was similar for all arms of treatment. Based on historical data for last-line mCRC, the OS of 9.6 months in the IC arm is noteworthy. Currently, trifluridine/ tipiracil (TAS-102) and regorafenib are the only treatment options for last-line mCRC, based on an increase in median OS in randomized clinical trials.\textsuperscript{24,25} While patients in the control arms in these 2 earlier studies received placebo, those in the present Sym004 study had a potentially active control arm, in which patients were able to receive capecitabine (68 patients), fluorouracil (13 patients), or BSC (4 patients). It is therefore plausible that a potential benefit of Sym004 in the ITT population was masked by a control arm in which most patients received an active treatment.

Recently, \textit{EGFR} ECD mutations have emerged as a potential novel mechanism of acquired resistance to cetuximab and panitumumab in mCRC.\textsuperscript{6,7,10,26,27} In the present study, \textit{EGFR} ECD mutations were detected in approximately 25% of patients, and 6 ECD mutations were particularly abundant. A significantly higher number of \textit{EGFR} ECD mutations was found in patients treated with panitumumab than in those treated with cetuximab. The biology behind this apparent increased frequency of \textit{EGFR} ECD mutations in panitumumab-treated patients is currently unknown, but lack of secondary effector functions such as antibody-dependent, cell-mediated cytotoxic effects and the preference for monovalent binding of panitumumab could be part of the explanation.

While preclinical studies showed Sym004 efficacy in \textit{EGFR} ECD-mutated cells, and dynamic ctDNA analysis showed a decrease in \textit{EGFR} ECD MAF following Sym004 treatment, the presence of these mutations was not linked to clinical benefit of Sym004 in the present trial. The \textit{EGFR} ECD mutations were always subclonal and coexisted with other genetic alterations related to anti-\textit{EGFR} resistance, which suggests that although the \textit{EGFR} ECD-mutated cells are targeted by Sym004, Sym004-resistant clonal cell populations that fail to respond to Sym004 exist within the tumor. This finding provides a plausible explanation for the lack of clinical benefit of Sym004 in patients with \textit{EGFR} ECD mutations. Our data thus suggest that, in a subset of patients, treatment with the anti-\textit{EGFR} antibodies cetuximab and panitumumab results in the emergence of extremely heterogenous molecular landscapes in which subclones with distinct mechanisms of resistance coexist. These results are in agreement with evidence that genomic complexity following treatment pressure might be a poor prognostic factor and severely limit the impact of subsequent lines of treatment.\textsuperscript{28,29}

Evaluation of OS in the triple-negative mCRC population (patients with double-negative mCRC who are also without \textit{EGFR} ECD mutations) showed clinically meaningful increases in median OS in both Sym004 treatment arms. In this...
exploratory analysis, the definition of triple-negative mCRC appeared to be an effective method to enrich the patient population for responsiveness to Sym004.

Limitations

A potential limitation of the study is that the treatment in the control arm was by investigator’s choice, and 96% of patients in the control arm received chemotherapy. It is therefore plausible that a potential benefit of Sym004 in theITT population was masked by a control arm in which most patients received an active treatment. Second, the study was designed to assess OS in chemorefractory disease. However, patients were allowed to have discontinued previous lines of therapy because of intolerance without failure of that chemotherapy, and this potentially allowed for the recruitment of nonrefractory patients who could have benefited from chemotherapy in the control arm of the trial. Finally, although the increase in survival with Sym004 in the triple-negative population is promising, this is a retrospective hypothesis-generating analysis that has to be confirmed in a randomized clinical trial.

Conclusions

The results of this study showed that Sym 004 does not improve OS or PFS when used in an unselected group of patients with mCRC and acquired EGFR resistance. In a hypothesis-generating analysis, ctDNA profiling identified a subset of patients (clonal RAS, BRAF, and EGFR ECD WT) that gained clinically meaningful benefit from therapy with Sym004. These findings provide the rationale for a prospective clinical validation of Sym004 efficacy in a molecularly defined subgroup of patients for whom prior anti-EGFR therapy had failed. Moreover, these data support the use of liquid biomarker genomic profiling to guide treatment of patients with mCRC and to track cancer evolution.

ARTICLE INFORMATION

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Study supervision: Montagut, Argilés, Dienstmann, Koefoed, Pedersen, Nadler, Horak, Bardelli, Tabernero.

Conflict of Interest Disclosures: Dr Montagut is an advisory board member for Amgen, Merck-Serono, Bayer, Sanofi, and Symphogen, and has received a commercial research grant from Amgen and Symphogen. Dr Tabernero is an advisory board member for Amgen, Merck-Serono, Roche, Novartis, MSD, BMS, Ipsen, and Mundi Pharma, is speaker and consultant for Amgen, and has a commercial research grant from Merck. Dr Salazar is an advisory board member for Amgen, Merck-Serono, Roche, Novartis, MSD, BMS, Bayer, and Novartis. No other disclosures are reported.

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