Relationships Between Köhne Category/Baseline Tumor Load and Early Tumor Shrinkage, Depth of Response, and Outcomes in Metastatic Colorectal Cancer

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Abstract

In metastatic colorectal cancer, there are few data on associations between early tumor shrinkage (ETS), depth of response (DpR), and patient characteristics. We assessed ETS and DpR by baseline Köhne category and tumor load. High-risk patients or those with *BRAF* mutations have lower chances of achieving an ETS of 30% or greater or a high DpR. An ETS of 30% or greater and a high DpR were associated with prolonged survival. Baseline tumor load was not linked with achieving an ETS of 30% or greater or a high DpR.

Background: In metastatic colorectal cancer (mCRC), there are limited data on associations between early tumor shrinkage (ETS), depth of response (DpR), and patient characteristics. **Methods:** Data from patients with *RAS* wild-type mCRC who had participated in the PRIME (NCT00364013) and PEAK (NCT00819780) studies were analyzed retrospectively. ETS and DpR were assessed by baseline Köhne category/*BRAF* status (PRIME) and baseline tumor load (pooled PRIME and PEAK). **Results:** Analysis populations included 436 to 665 patients. Patients' chances of achieving ETS of 30% or greater were 63.8%, 50.4%, and 41.9% in the low-, medium-, and high-risk Köhne categories, and 21.7% in those with *BRAF* mutations. Corresponding percentages for the highest DpR classification (71%-100%) were 47.7% (low risk), 23.6% (medium risk), 10.0% (high risk), and 4.2% (*BRAF* mutant). No clear relationship was observed between baseline tumor load and ETS or DpR. An ETS of 30% or greater and higher DpR values were associated with statistically significant prolongation of median progression-free survival and overall survival. **Conclusion:** Patients with mCRC categorized at baseline by the Köhne criteria as high risk or with *BRAF* mutations have lower chances of achieving an ETS of 30% or greater or a high DpR. Baseline tumor load was not predictive of ETS or DpR. Favorable ETS or DpR is associated with improved progression-free and overall survival.

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Introduction

Globally in 2018, colorectal cancer (CRC) was reported to be the third most common form of cancer and the second leading cause of cancer death.[1,2] A high proportion of cases develop into metastatic disease (mCRC), with a 5-year survival rate of approximately 13%.[3,4] First-line treatment options for mCRC include chemotherapy, anti-vascular endothelial growth factor antibody (bevacizumab), and anti-epidermal growth factor receptor (EGFR) antibodies (panitumumab, cetuximab).[5-8] *RAS* mutations, which occur in 50% to 60% of patients with CRC, are predictive of

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resistance to anti-EGFR antibodies.[9] In Europe and the United States, panitumumab and cetuximab are therefore only approved for use in patients with wild-type *RAS* mCRC.[10-13] A meta-analysis has shown that in terms of overall survival (OS), first-line treatment with anti-EGFR therapy plus chemotherapy may be more effective than bevacizumab plus chemotherapy.[14]

A key treatment goal in mCRC is achieving an early, deep, and sustained response. This strategy may decrease tumor-related symptoms and increase eligibility for surgical resection.[15] Early tumor shrinkage (ETS) and depth of response (DpR) (maximum tumor shrinkage achieved) are parameters increasingly being used in mCRC studies.[15,16] These end points provide information on the timing and maximum level of response, which are variables not considered by Response Evaluation Criteria In Solid Tumors (RECIST).[15] ETS, usually determined as shrinkage within 6 or 8 weeks, may act as an early indicator of response and identify patients with high sensitivity to treatment.[16] Favorable ETS or DpR responses have been associated with prolonged survival.[17,18]

The efficacy of anti-EGFR agents in mCRC has been demonstrated in relation to ETS and DpR.[15,19-21] A pooled analysis, conducted using data from 3 major studies of panitumumab, suggested that treatment with panitumumab plus chemotherapy resulted in higher ETS rates and greater DpR in comparison with bevacizumab plus chemotherapy or chemotherapy alone.[15] The pooled analysis also indicated that ETS and greater DpR were associated with improved progression-free survival (PFS), OS, and resection rates, regardless of treatment.[15] In the phase II VOLFI trial, panitumumab plus modified FOLFOXIRI resulted in significantly higher rates of ETS and DpR, as well as an improved objective response rate, when compared with FOLFOXIRI alone.[22] Similarly, in a phase II, open-label study of panitumumab plus FOLFIRI in wild-type *RAS* mCRC, ETS (≥30% decrease within 8 weeks) was associated with improved PFS.[23] In an analysis of the phase II Valentino study of panitumumab plus FOLFOX followed by maintenance with panitumumab versus panitumumab plus 5-fluoracil/leucovorin, the ETS (≥20% decrease within 8 weeks) and a DpR of 34% or greater were associated with longer PFS and OS in wild-type *RAS* mCRC.[24] Further, in the phase III FIRE-3 study of cetuximab plus FOLFIRI in *KRAS* wild-type mCRC, ETS (≥20% decrease within 6 weeks) was associated with a longer OS.[25]

There are few data on the association between ETS, DpR, and baseline patient characteristics/prognostic factors. The Köhne prognostic category, which is based on clinical parameters, was designed to group patients with mCRC according to their risk of mortality.[26] Retrospective analysis of data from the PRIME study and Study 20050181 showed that the Köhne category is an accurate predictor of OS and PFS in first- and second-line mCRC.[27] Panitumumab plus chemotherapy led to improved PFS and OS versus chemotherapy alone, across all Köhne categories.[27] *BRAF* status represents another risk parameter in mCRC; patients with *BRAF* mutation-positive mCRC (particularly $BRAF^{V600E}$) have a higher mortality risk than patients with *BRAF* wild-type disease.[28,29] In the retrospective analysis mentioned elsewhere in this article,[27] PFS and OS were even shorter in patients with *BRAF* mutations than in any of the Köhne categories. Tumor load (sometimes referred to as volume of disease) has also been proposed as a potential prognostic marker in mCRC, with low tumor loads being associated with improved survival.[30] Out of the Köhne category, *BRAF* status, and baseline tumor load, it is unclear which would be the best predictor of whether a patient with mCRC will achieve ETS or a good DpR. Patients with liver-limited mCRC (liver-limited disease [LLD]) may be considered a distinct subgroup with improved prognosis on the basis of a higher chance of eligibility for surgical resection.[31] However, most patients with LLD require treatment for conversion to resectable disease, meaning that the baseline predictors of response to systemic therapy are also of interest in this group.[31, 32]

The objectives of the current retrospective analyses, conducted in patients with *RAS* wild-type mCRC from the PRIME and PEAK studies, were as follows. First, we sought to assess the relationship between Köhne category/*BRAF* status and ETS/DpR (this was explored in both the overall *RAS* wild-type population and in patients with LLD vs. without LLD). Second, the relationship between baseline tumor load/volume of disease and ETS/DpR was investigated. Third, associations between ETS/DpR and PFS/OS, regardless of baseline Köhne category or tumor load, were assessed.

Methods

Study Design and Treatment

This study was retrospective and not prespecified for either the PRIME study or the PEAK study. Details of the PRIME and PEAK studies have been reported previously.[33,34] Therefore, the study methods are described only briefly here. PRIME (NCT00364013) was a randomized, open-label, phase III study in which patients received panitumumab 6 mg/kg and FOLFOX4 every 2 weeks or FOLFOX4 alone every 2 weeks.[33] PEAK (NCT00819780) was a randomized, open-label, phase II study in which patients received mFOLFOX6 and either panitumumab 6 mg/kg or bevacizumab 5 mg/kg every 2 weeks.[34]

The PRIME and PEAK studies, including the additional analyses reported here, were performed in accordance with the Declaration of Helsinki. The protocol of each study was approved by the ethics committee at each participating site. All participants had provided written informed consent before undertaking any study-related procedures.

Patients

Both PRIME and PEAK were conducted in patients aged 18 years or older with previously untreated and unresectable mCRC and at least 1 measurable lesion of 20 mm or larger.[33,34] An Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 to 2 was required for the PRIME study, compared with a grade of 0 to 1 for the PEAK study. Prior adjuvant treatment with 5-fluorouracil was allowed in PRIME, provided that disease recurrence occurred 6 or more months after completion. No prior adjuvant chemotherapy was permissible in PEAK. The current analyses included patients with *RAS* wild-type mCRC (tumors without mutations in *KRAS* or *NRAS* exons 2 [codons 12/13], 3 [codons 59/61] and 4 [codons 117/146]).

Study End Points and Assessments

The end points analyzed in this study were ETS, DpR, PFS, and OS. An ETS response was defined as a 30% or greater decrease from

Table 1 Proportion of Patients With an ETS of 30% or Greater and Less Than 30% by Week 8 According to Köhne Prognostic Category/*BRAF* Status, and Median PFS and Median OS According to ETS and Köhne Prognostic Category/*BRAF* Status (Wild-Type *RAS* Efficacy Analysis Set; PRIME)

	Total (N = 436)			
Köhne Category	Low (n = 80)	Medium (n = 236)	High (n = 74)	*BRAF* Mutant (n = 46)
Patients, n (%)				
≥30% ETS[a]	51 (63.8)	119 (50.4)	31 (41.9)	10 (21.7)
<30% ETS[b]	29 (36.3)	117 (49.6)	43 (58.1)	36 (78.3)
Median PFS (Q1, Q3), months				
≥30% ETS[a]	15.4 (9.2, 27.7)	12.8 (8.8, 25.2)	13.9 (7.4, 21.0)	5.6 (5.4, 13.6)
<30% ETS[b]	9.2 (5.8, 11.1)	8.9 (3.9, 17.1)	6.1 (3.8, 13.1)	5.8 (2.8, 8.0)
Median OS (Q1, Q3), months				
≥30% ETS[a]	40.7 (19.8, 57.4)	32.5 (22.2, 58.8)	24.6 (15.7, 41.9)	9.6 (8.0, 30.3)
<30% ETS[b]	23.6 (13.1, 54.5)	19.3 (9.9, 36.1)	11.7 (6.9, 20.6)	10.4 (6.4, 18.9)

Patients with missing values of Köhne category or ETS are not included in this table.
Abbreviations: ETS = early tumor shrinkage; OS = overall survival; PFS = progression-free survival; Q = quartile.
[a] n = 211.
[b] n = 225.

baseline to week 8 in the sum of the longest diameters of measurable target lesions. The DpR was defined as the maximum percentage change in tumor size, from baseline to nadir, in patients who had tumor shrinkage, or from baseline to progressive disease in patients with tumor growth or no change. Positive DpR values represented tumor reductions and negative values represented tumor growth. DpR results were categorized as follows: less than 0%, 0% to 30%, 31% to 52%, 53% to 70%, and 71% to 100%.

ETS and DpR were assessed according to Köhne category/*BRAF* status (PRIME study only) and according to baseline tumor load (pooled PRIME and PEAK studies). The Köhne category (low, medium, or high risk) was based on 4 baseline clinical parameters: ECOG PS, white blood cell count, alkaline phosphatase levels, and number of metastatic sites. Patients with *BRAF* mutations were considered as a separate high-risk group. The baseline tumor load was defined as the sum of the longest diameters of target and nontarget lesions at baseline. Patients from the full pooled dataset were categorized into quartiles according to baseline tumor load: Q1, number of patients with baseline tumor load value of quartile 1 or less; Q2, number of patients with baseline tumor load value of more than quartile 1 and quartile 2 or less; Q3, number of patients with baseline tumor load value of more than quartile 2 and quartile 3 or less; and Q4, number of patients with baseline tumor load value of more than quartile 3. PFS and OS were assessed according to ETS, DpR, baseline Köhne category/*BRAF* status, and baseline tumor load.

Statistical Analyses and Analysis Set

The current analyses were conducted in the *RAS* wild-type efficacy analysis set, which comprised the subset of patients in the intent-to-treat efficacy analysis set whose tumors were confirmed as *RAS* wild type. To assess the relationship between LLD and an ETS of 30% or more versus less than 30% on outcomes, further analyses were performed in *RAS* wild-type patients with LLD, pooled across baseline Köhne category/*BRAF* status. An *ad hoc* analysis of ETS and DpR in the high-risk Köhne category according to ECOG PS was also carried out. For all analyses, study treatment groups were pooled to increase the sample size. For the assessment of end points according to the baseline tumor load, data from the PRIME and PEAK studies were pooled. The median PFS and OS were estimated using the Kaplan-Meier method. Statistical differences between groups were calculated using a log-rank test ($P < .05$ was considered statistically significant). No corrections were made for multiple comparisons. The statistical program used was SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Köhne Category/BRAF Status Analysis (PRIME)

ETS was analyzed in 436 participants from the PRIME study, of whom 216 received panitumumab plus FOLFOX4 and 220 received FOLFOX4 alone. The DpR was analyzed in 456 patients: 233 from the panitumumab plus FOLFOX4 arm and 223 from the FOLFOX4 arm. The number of patients differed between the 2 analyses because the ETS data were not available for patients with disease progression or who died before week 8.

The likelihood of patients achieving an ETS of 30% or higher or a high DpR decreased with increasing baseline Köhne risk and was even lower in patients with a *BRAF* mutation (Tables 1 and 2). The percentage of patients achieving an ETS of 30% or greater ranged from 63.8% in the low-risk Köhne category to 21.7% in the *BRAF*-mutant category. Similarly, 47.7% of low-risk patients had DpR of 71% to 100%, compared with only 4.2% of *BRAF*-mutant patients.

For patients with a high baseline Köhne risk, we also examined the subset of patients within this group who had an ECOG PS of 0 to 1. Differences were marginal with the overall high-risk subset. For 54 patients with a high baseline Köhne risk and an ECOG PS of 0 to 1, 26 (48.2%) achieved an ETS of 30% or greater and 28 (51.9%) achieved an ETS of less than 30%. In the DpR analysis, for 61 patients with a high baseline Köhne risk and an ECOG PS of 0 to 1, 5 (8.2%), 13 (21.3%), 15 (24.6%), 21 (34.4%), and 7

Table 2 Proportion of Patients in Each DpR Category According to Köhne Prognostic Category/*BRAF* Status, and Median PFS and Median OS According to DpR and Köhne Prognostic Category/*BRAF* Status (Wild-Type *RAS* Efficacy Analysis Set; PRIME)

	Total (N = 456)			
Köhne category	**Low (n = 86)**	**Medium (n = 242)**	**High (n = 80)**	***BRAF* mutant (n = 48)**
Patients, n (%)				
DpR <0%[a]	4 (4.7)	18 (7.4)	7 (8.8)	14 (29.2)
DpR 0%-30%[b]	8 (9.3)	41 (16.9)	20 (25.0)	20 (41.7)
DpR 31%-52%[c]	13 (15.1)	62 (25.6)	22 (27.5)	9 (18.8)
DpR 53%-70%[d]	20 (23.3)	64 (26.5)	23 (28.8)	3 (6.3)
DpR 71%-100%[e]	41 (47.7)	57 (23.6)	8 (10.0)	2 (4.2)
Median PFS (Q1, Q3), months				
DpR <0%[a]	4.0 (2.8, 5.0)	2.0 (1.9, 3.7)	2.4 (1.9, 3.0)	2.1 (1.9, 3.7)
DpR 0%-30%[b]	5.4 (5.3, 9.4)	5.4 (3.6, 11.1)	5.0 (3.7, 6.4)	6.0 (3.6, 9.4)
DpR 31%-52%[c]	8.5 (5.8, 17.6)	10.6 (6.0, 18.6)	10.2 (6.9, 13.8)	5.6 (5.4, 8.2)
DpR 53%-70%[d]	9.9 (8.9, 14.9)	11.5 (8.8, 16.6)	13.7 (9.2, 27.6)	14.9 (6.2, 23.5)
DpR 71%-100%[e]	17.7 (9.9, 42.6)	17.3 (10.8, 31.1)	22.4 (15.3, 35.1)	10.4 (7.2, 13.6)
Median OS (Q1, Q3), months				
DpR <0%[a]	10.7 (7.2, 17.8)	7.5 (4.8, 14.2)	5.5 (4.6, 11.0)	6.4 (4.9, 9.1)
DpR 0%-30%[b]	13.6 (7.3, 21.4)	14.3 (8.3, 27.2)	9.4 (6.5, 15.1)	10.9 (6.6, 21.8)
DpR 31%-52%[c]	20.0 (14.6, 36.1)	23.6 (14.0, 38.8)	13.8 (8.0, 21.7)	9.4 (8.2, 10.4)
DpR 53%-70%[d]	28.4 (18.0, 46.9)	30.9 (22.2, 37.6)	23.1 (18.0, 36.9)	39.5 (6.2, NE)
DpR 71%-100%[e]	47.4 (35.2, 62.2)	62.1 (34.6, NE)	33.2 (26.4, 44.1)	21.4 (18.8, 23.9)

Patients with missing values of Köhne category or DpR are not included in this table.
Abbreviations: DpR = depth of response; NE = not evaluable; OS = overall survival; PFS = progression-free survival; Q = quartile.
[a] n = 43.
[b] n = 89.
[c] n = 106.
[d] n = 110.
[e] n = 108.

(11.5%) had a DpR of less than 0%, 0% to 30%, 31% to 52%, 53% to 70%, and 71% to 100%, respectively.

Patients with an ETS of 30% or greater achieved a longer median PFS and OS than those with an ETS of less than 30%, in the low-, medium-, and high-risk Köhne categories (Table 1; Figure 1; Supplemental Figure 1). The differences between patients with an ETS of 30% or greater and those with an ETS of less than 30% were statistically significant in all 3 of these categories for PFS ($P < .005$), and in the medium- and high-risk categories for OS ($P < .0001$). Among patients with a *BRAF* mutation, there were no clear differences in PFS or OS between patients in the 2 ETS categories.

In the LLD analyses, having an ETS of 30% or greater was associated with a near doubling of PFS and OS versus having an ETS of less than 30%, and this effect was seen in patients both with and without LLD (Supplemental Figure 2). An analysis of the LLD results according to *BRAF* mutation or Köhne category was not possible owing to the limited numbers of patients (see Supplementary Table S1 for the breakdown according to LLD) in the *BRAF* mutation subgroups and because LLD patients are mostly, by definition, excluded from the high-risk Köhne group.

Similar to the ETS results, higher DpR values were associated with significantly longer median PFS and OS among patients in the low-, medium-, and high-risk Köhne categories ($P < .0001$; Table 2; Supplemental Figures 3 and 4). Patients with a *BRAF* mutation showed similar tendencies, although the relationships were less definite in this group and that between DpR and OS did not reach statistical significance.

Baseline Tumor Load Analysis (PRIME and PEAK)

ETS and DpR were analyzed in 665 patients from the PRIME and PEAK studies combined. Of these, 336 patients were treated with panitumumab plus FOLFOX4 or panitumumab plus mFOLFOX6, whereas 329 received FOLFOX4 alone or bevacizumab plus mFOLFOX6.

The percentage of patients achieving an ETS of 30% or greater was between approximately 40% and 50% in all baseline tumor load quartiles, with no clear trend from Q1 to Q4 (Table 3). The likelihood of achieving a high DpR decreased as the baseline tumor load increased; the percentage of patients achieving a DpR of 71% to 100% ranged from 32.9% (baseline tumor load Q1) to 17.9% (Q4; Table 4).

In all quartiles of tumor load, patients with an ETS of 30% or greater exhibited significantly longer PFS and OS than those with an ETS of less than 30% ($P < .01$; Table 3; Supplemental Figures 5 and 6). For patients with an ETS of 30% or greater, there were tendencies for both PFS and OS to decrease as the baseline tumor

Table 3 Proportion of Patients With ETS of 30% or Greater and Less than 30% by Week 8 in Each Baseline Tumor Load Quartile, and Median PFS and Median OS According to ETS and Baseline Tumor Load Quartile (Wild-Type *RAS* Efficacy Analysis Set; Pooled PRIME and PEAK)

	Baseline Tumor Load Total (N = 665)			
ETS category	Q1 (n = 167)	Q2 (n = 159)	Q3 (n = 160)	Q4 (n = 162)
Patients, n (%)				
≥30% ETS[a]	70 (41.9)	78 (49.1)	72 (45.0)	77 (47.5)
<30% ETS[b]	80 (47.9)	73 (45.9)	77 (48.1)	67 (41.4)
Median PFS (Q1, Q3), months				
≥30% ETS[a]	15.4 (9.0, 31.1)	12.9 (9.2, 22.5)	12.9 (7.7, 21.0)	11.5 (7.4, 21.5)
<30% ETS[b]	7.6 (5.3, 13.1)	7.5 (3.9, 16.6)	10.6 (5.4, 15.7)	7.2 (3.8, 13.1)
Median OS (Q1, Q3), months				
≥30% ETS[a]	42.9 (24.6, 62.1)	39.2 (25.3, 63.0)	29.9 (21.4, 56.0)	27.2 (17.6, 46.4)
<30% ETS[b]	20.7 (11.1, 48.0)	21.2 (9.3, 34.4)	18.0 (8.7, 30.4)	15.1 (7.3, 25.3)

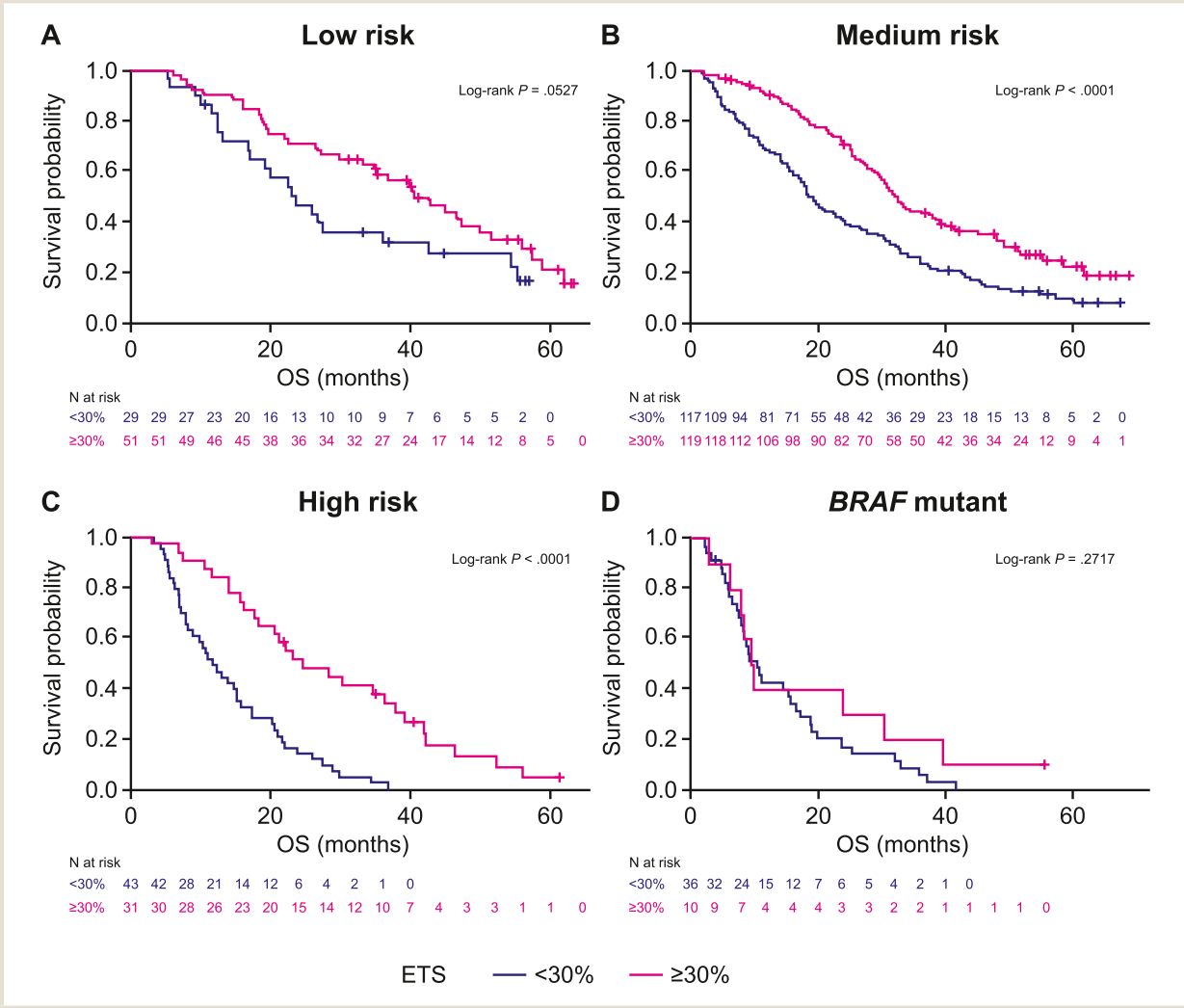
Patients with missing values of baseline tumor load or ETS are not included in this table.
Abbreviations: ETS = early tumor shrinkage; OS = overall survival; PFS = progression-free survival; Q = quartile.
[a] n = 297.
[b] n = 297.

Table 4 Proportion of Patients in Each DpR Category According to Baseline Tumor Load Quartile, and Median PFS and Median OS According to DpR and Baseline Tumor Load Quartile (Wild-Type *RAS* Efficacy Analysis Set; Pooled PRIME and PEAK)

	Baseline Tumor Load Total (N = 665)			
DpR category	Q1 (n = 167)	Q2 (n = 159)	Q3 (n = 160)	Q4 (n = 162)
Patients, n (%)				
DpR <0%[a]	13 (7.8)	9 (5.7)	13 (8.1)	11 (6.8)
DpR 0%-30%[b]	34 (20.4)	32 (20.1)	31 (19.4)	26 (16.0)
DpR 31%-52%[c]	28 (16.8)	35 (22.0)	35 (21.9)	50 (30.9)
DpR 53%-70%[d]	26 (15.6)	36 (22.6)	38 (23.8)	40 (24.7)
DpR 71%-100%[e]	55 (32.9)	40 (25.2)	37 (23.1)	29 (17.9)
Median PFS (Q1, Q3), months				
DpR <0%[a]	3.3 (2.0, 3.7)	3.7 (2.1, 3.9)	1.9 (1.8, 3.5)	1.9 (1.6, 2.7)
DpR 0%-30%[b]	7.4 (5.3, 9.5)	6.2 (3.7, 16.1)	5.8 (3.7, 12.7)	3.8 (3.5, 6.1)
DpR 31%-52%[c]	9.9 (6.0, 13.1)	9.7 (7.1, 17.2)	10.6 (5.7, 17.9)	7.7 (5.5, 13.7)
DpR 53%-70%[d]	10.0 (6.5, 16.6)	11.3 (9.2, 22.5)	13.0 (8.7, 20.5)	12.9 (9.2, 16.6)
DpR 71%-100%[e]	20.7 (10.9, 48.1)	16.8 (10.8, 27.3)	13.6 (10.7, 28.3)	19.8 (11.2, 28.9)
Median OS (Q1, Q3), months				
DpR <0%[a]	9.1 (7.5, 14.9)	12.6 (7.5, 25.3)	5.6 (4.8, 9.1)	5.5 (3.3, 11.5)
DpR 0%-30%[b]	20.1 (10.7, 35.6)	17.3 (7.9, 30.5)	12.4 (5.5, 18.2)	10.1 (6.1, 15.1)
DpR 31%-52%[c]	20.9 (13.7, 41.6)	27.7 (10.4, 39.2)	21.4 (15.3, 28.6)	15.4 (9.0, 25.3)
DpR 53%-70%[d]	31.4 (18.0, 42.1)	33.1 (25.4, 51.9)	28.2 (19.6, 37.6)	27.2 (19.8, 39.1)
DpR 71%-100%[e]	62.1 (42.9, NE)	51.7 (35.1, 63.0)	51.6 (35.0, NE)	46.1 (30.3, 62.2)

Patients with missing values of baseline tumor load or DpR are not included in this table.
Abbreviations: DpR = depth of response; NE = not evaluable; OS = overall survival; PFS = progression-free survival; Q = quartile.
[a] n = 46.
[b] n = 123.
[c] n = 148.
[d] n = 140.
[e] n = 161.

Figure 1 OS by ETS according to Köhne prognostic category/*BRAF* status. (A) Low-risk Köhne category, (B) medium-risk Köhne category, (C), high-risk Köhne category, and (D) *BRAF* mutant (wild-type *RAS* efficacy analysis set; PRIME). Abbreviations: ETS = early tumor shrinkage; OS = overall survival.



load increased. As shown in Table 4 and Supplemental Figures 7 and 8, the median PFS and OS became longer with increasing DpR in all baseline tumor load quartiles ($P < .0001$ for both PFS and OS in all quartiles).

Discussion

This study shows that patients with *RAS* wild-type mCRC who were in the high-risk Köhne category or who had *BRAF* mutations were less likely to achieve an ETS of 30% or greater or a high DpR than those in the low- or medium-risk Köhne categories. In the low-, medium-, and high-risk Köhne categories, patients achieving an ETS of 30% or greater showed improved OS and PFS when compared with those with an ETS of less than 30%. Similarly, higher DpR values were generally associated with longer PFS and OS across the 3 Köhne risk categories. Patients with *BRAF* mutations had a poor prognosis irrespective of ETS, while showing tendencies toward longer OS and PFS with increasing DpR. However, the number of patients with *BRAF* mutations was relatively small, meaning that the data are less robust in this group. Baseline tumor load was not clearly predictive of ETS or DpR, but patients with an ETS of at least 30% or a greater DpR had better survival outcomes, regardless of the original tumor load. It is not known why baseline tumor load was not predictive of ETS or DpR; this factor may be related to differences in underlying tumor biology (eg, molecular subtype)[35,36] and tumor location[37] potentially playing a larger role than tumor volume. Also, the measurement of tumor volume does not take into account the location of metastases, which can affect the prognosis.[38] Further, there can be challenges in accurately measuring low-volume disease, which may have affected the results.

It is vital to identify prognostic or predictive factors that can guide interventions for mCRC and thereby improve treatment

outcomes. There is a particular need for methods to determine the optimal treatment for patients with *RAS* wild-type mCRC. A range of patient and disease characteristics at baseline can greatly affect survival outcomes in patients with mCRC, and there is the potential for these factors to be used to inform treatment decisions.[27] Therefore, it is important to understand the prognosis of different patient subgroups and how they might respond to treatment. Although knowledge of the molecular mechanisms underlying tumor progression is evolving, current clinical practice is limited by a lack of reliable methods for identifying which patients will respond to therapy or develop resistance.[39] A recent analysis of the Valentino study of panitumumab in wild-type *RAS* mCRC suggested that a combined assessment of response dynamics and molecular hyperselection could be used to stratify PFS and OS. Maximal PFS and OS were achieved in patients who were negative for uncommon genomic alterations associated with anti-EGFR resistance (beyond *RAS* and *BRAF*), who also had ETS and a DpR of 34% or greater.[24] That study also showed that *BRAF* mutations were associated with significantly less tumor shrinkage within 8 weeks, and numerically lower DpR, broadly aligned with our study.[24] The data presented in our study initially suggested that more aggressive treatment options could be considered for patients shown at baseline to be in the high-risk Köhne category or to have *BRAF* mutations, assuming they are able to tolerate such treatment. However, when we examined a subset of patients with an ECOG PS of 0 to 1 (the group more likely to be able to undergo aggressive treatment), they were only slightly more likely to achieve ETS. Thus, such a strategy cannot be recommended at this time. A dedicated clinical trial would be needed to prospectively assess whether more aggressive treatment in high-risk patients translates to ETS and subsequent improved survival.

ETS and DpR are increasingly being used to monitor responses in mCRC clinical trials, because these parameters capture information beyond traditional end points, such as those included in RECIST, and allow early clinical characterization of response.[15] Early characterization of response can enable key treatment decisions to be taken sooner (eg, a change of therapy for nonresponders, particularly for right-sided disease, or early planning of surgical intervention, particularly in candidates for liver resection), potentially leading to less exposure to systemic therapy for patients. Early and deep responses to treatment may provide patients with relief from tumor-related symptoms[40] and enable surgical resection to be performed. There are major benefits to be gained from resecting tumors earlier: resection can provide long-term, relapse-free survival or cure, whereas decreased long-term cancer therapy lowers the occurrence of adverse effects such as liver toxicity and complications of surgery.[7,15] These considerations underline the importance of identifying at baseline which patients are likely to exhibit pronounced ETS and a high DpR. Thus, when choosing treatment, it is essential to know a patient's baseline clinical characteristics, in addition to their molecular marker status. In the current analyses, favorable ETS and DpR responses were associated with significantly prolonged PFS and OS. Similar results have been reported in several previous clinical studies.[15,17,18,21] Overall, as suggested in the European Society for Medical Oncology mCRC guidelines, these data seem to confirm that ETS and DpR may be predictive of long-term outcomes.[7]

A key strength of this study was the use of the PEAK and PRIME studies, providing well-annotated clinical data from prospective trials (including relatively mature OS data). The similar patient groups between studies allowed pooling of treatment groups, which also strengthened the study by providing a sufficiently large number of patients for stratification into the subgroups that were required. However, we acknowledge the relatively small numbers of patients in some subgroups as a limitation of the study. Further, the pooling of treatment groups did not allow potential treatment effects to be assessed (treatment may have been a confounding factor in these analyses). A number of other factors that could affect outcomes, such as tumor location (eg, left sided or right sided),[37] type of *BRAF* mutation (eg, $BRAF^{V600E}$), baseline carcinoembryonic antigen levels, lactate dehydrogenase levels, and human epidermal growth factor receptor 2 (HER2) status were not evaluated or accounted for in the current analyses. Another limitation was the retrospective nature of the analyses. Neither ETS nor DpR was included as a prespecified end point in the protocols for the PEAK or PRIME studies,[37] and there remains some uncertainty over the optimal cutoff for ETS (eg, a positive response could be defined as ≥20% instead of ≥30%).[15] Finally, patients in the PEAK and PRIME studies did not have identical baseline characteristics, meaning that the pooled data used for the tumor load analysis were heterogeneous.

Conclusions

This pooled, retrospective analysis shows that patients with mCRC categorized at baseline by the Köhne criteria as having high risk, or having *BRAF* mutations, have lower chances of achieving an ETS of 30% or greater or a high DpR when compared with low- or medium-risk patients. There were no clear trends between baseline tumor load and the likelihood of achieving an ETS of 30% or greater or a high DpR. An ETS of 30% or greater and high DpR were associated with significantly prolonged PFS and OS regardless of baseline Köhne category or tumor load.

Clinical Practice Points

- Studies of anti-EGFR agents in mCRC show that favorable ETS and DpR are associated with prolonged survival, but data on the association between ETS, DpR, and baseline patient characteristics/prognostic factors are limited.
- In particular, it remains unclear whether Köhne category, *BRAF* status, or baseline tumor load would be the best predictor of ETS or good DpR in these patients.
- A retrospective analysis of the PRIME (NCT00364013) and PEAK (NCT00819780) studies demonstrated that patients with *RAS* wild-type mCRC categorized at baseline as high risk by the Köhne criteria (or those with *BRAF* mutations) were less likely to achieve an ETS of 30% or greater or a high DpR than those in low- or medium-risk categories.
- The baseline tumor load was not predictive of ETS or DpR.
- An ETS of 30% or more and higher DpR values were associated with statistically significant prolongation of median PFS and OS.
- The early characterization of patients likely to exhibit pronounced ETS or high DpR should enable key treatment

decisions to be taken sooner, potentially leading to less exposure to systemic therapy and earlier surgical resection.

Data Statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/.

Disclosure

A.S.-B. has participated in consulting roles and/or advisory boards for Amgen, Bayer, Sanofi, and Servier. P.G.-A. has received honoraria from and served as a consultant for Amgen, Merck, Roche, Sanofi, and Servier. M.G. has received research funding from and acted in consultancy/advisory roles for Amgen, Bayer, Merck, Roche, and Sanofi. C.-H.K. has received honoraria from Amgen, Bayer, Merck, Pfizer, and Servier. M.P. has received research funding from Amgen and Roche, and honoraria from Amgen, Lilly, Merck Serono, Remedus, Roche, Sanofi-Aventis, Servier, Sirtex, and Terumo. T.P. has served on advisory boards for Amgen, Merck Serono, and Roche, and has received travel support from Amgen. M.V.-A. has served on advisory boards and received research funding from Amgen, Merck Serono, Roche, and Sanofi, and has received travel support from Roche. Y.Z. is an employee of Amgen Inc. and owns shares in Amgen. P.B. was an employee of Amgen (Europe) GmbH at the time the research was conducted and owns shares in Amgen, Guardant Health Inc., Mirati Therapeutics Inc., Novartis AG, and Verastem Inc.; he is currently an employee of MSD International GmbH. J.T. has participated in consulting roles and/or advisory boards for Amgen, Eli Lilly, Merck, MSD, Pierre Fabre, Roche, Sanofi, Servier, and Sirtex**.** D.P.M. has received honoraria from Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Merck, MSD, Roche, Servier, and Sirtex; has received grants for research from Amgen, Merck, and Roche; and has received travel support from Amgen, Bristol Myers Squibb, Merck, Roche, and Servier.

CRediT authorship contribution statement

Andrea Sartore-Bianchi: Data acquisition, Formal analysis, Writing – review & editing. **Pilar García-Alfonso:** Data acquisition, Formal analysis, Writing – review & editing. **Michael Geissler:** Data acquisition, Formal analysis, Writing – review & editing. **Claus-Henning Köhne:** Data acquisition, Formal analysis, Writing – review & editing. **Marc Peeters:** Data acquisition, Formal analysis, Writing – review & editing. **Timothy Price:** Data acquisition, Formal analysis, Writing – review & editing. **Manuel Valladares-Ayerbes:** Data acquisition, Formal analysis, Writing – review & editing. **Ying Zhang:** Data acquisition, Formal analysis, Writing – review & editing. **Peter Burdon:** Conceptualization, Formal analysis, Writing – review & editing. **Julien Taieb:** Data acquisition, Formal analysis, Writing – review & editing. **Dominik P. Modest:** Data acquisition, Formal analysis, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2021.05.007.

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