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ORIGINAL RESEARCH

Real-world first-line treatment of patients with BRAF^{V600E}-mutant metastatic colorectal cancer: the CAPSTAN CRC study☆

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Background: *BRAF*^{V600E} mutations occur in 8%-12% of metastatic colorectal cancer (mCRC) cases and are associated with poor survival. European guidelines recommend combination (doublet or triplet) chemotherapy plus bevacizumab in first line. However, an unmet need remains for more effective treatments for these patients.

Patients and methods: CAPSTAN CRC is a European, retrospective, multicenter, observational study evaluating real-world treatment practices for patients with *BRAF*^{V600E}-mutant mCRC treated between 1 January 2016 and 31 January 2020. The primary objective was to describe first-line treatment patterns. Secondary objectives included describing baseline demographics, mutational testing procedures, treatment effectiveness, and safety.

Results: In total, 255 patients (median age 66.0 years; 58.4% female) with *BRAF*^{V600E}-mutant unresectable mCRC from seven countries were included. Most had right-sided tumors (52.5%) and presented with synchronous disease at diagnosis (66.4%). Chemotherapy plus targeted therapy (68.7%) was preferred at first line over chemotherapy alone (31.3%). The main first-line treatments were FOLFOX plus bevacizumab (27.1%) and FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, irinotecan) with/without bevacizumab (27.1%/19.2%). Median duration of first-line treatment was 4.9 months. Overall, 52.5% received second-line treatment. Across all first-line regimens, progression-free survival (PFS) and overall survival were 6.0 [95% confidence interval (CI) 5.3-6.7] months and 12.9 (95% CI 11.6-14.1) months, respectively. Triplet plus targeted therapy was associated with more adverse events (75.0%) compared with triplet chemotherapy alone (50.0%) and doublet chemotherapy alone (36.1%). Multivariate analysis identified low body mass index and presence of three or more metastatic sites as significant prognostic factors for PFS.

Conclusions: This study is, to date, the largest real-world analysis of patients with BRAF^{V600E}-mutant mCRC, providing valuable insights into routine first-line treatment practices for these patients. The data highlight the intrinsic aggressiveness of this disease subgroup, confirming results from previous real-world studies and clinical trials, and stressing the urgent need for more effective treatment options in this setting.

Key words: metastatic colorectal cancer, observational, BRAF mutation, treatment practices, targeted therapy, real world

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide.[1] Approximately 20% of patients with CRC present with metastatic disease at the time of initial diagnosis, with 5-year survival rates <20% for metastatic CRC (mCRC) across Europe.[2,3] The identification of different tumor genomic mutations and profiles in recent years has proved to be pivotal in understanding tumor heterogeneity, guiding treatment and improving survival.[4]

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Mutations in the *BRAF* gene occur in 8%-12% of mCRC cases, >95% of which are $BRAF^{V600E}$.[5,6] $BRAF^{V600E}$ mutations represent an aggressive phenotype associated with a poor prognosis and resistance to standard chemotherapy regimens.[5-8] Given the importance of *BRAF* as a prognostic and predictive biomarker, the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network guidelines recommend the assessment of *BRAF* status alongside *RAS* at diagnosis of metastatic disease to better guide treatment decisions.[5,9]

Current international guidelines recommend treating patients with $BRAF^{V600E}$-mutant mCRC in first line using either a doublet or triplet combination chemotherapy regimen with or without the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, based on a small subgroup analysis of patients in the TRIBE studies and retrospective series.[5,9,10] The benefits of using anti-VEGF inhibitors, including aflibercept and ramucirumab, for patients with $BRAF^{V600E}$-mutant mCRC were initially reported in *post hoc* analyses of randomized trials in second line.[11,12] The results of individual patient data meta-analysis showed no increased benefit with folinic acid, 5-fluorouracil, oxaliplatin, irinotecan (FOLFOXIRI) plus bevacizumab versus doublet regimen plus bevacizumab among patients with BRAF-mutant tumors.[10]

Studies have suggested that $BRAF^{V600E}$ is a predictive marker for limited response to epidermal growth factor receptor (EGFR) inhibitors in patients with mCRC.[13-15] Although the role of EGFR inhibitors in combination with chemotherapy is controversial in the first-line setting, the EGFR inhibitor cetuximab recently received approval in combination with the BRAF inhibitor encorafenib for use in the second-line setting after prior systemic therapy in $BRAF^{V600E}$-mutant mCRC based on results from the pivotal BEACON CRC study.[16-20]

It is still unclear, however, what the optimal first-line treatment strategy is for this specific population, with local treatment practices and associated guidelines varying widely. Furthermore, although clinical trials provide valuable information regarding the safety and efficacy of therapies, a significant knowledge gap persists with regard to the real-world treatment practices for $BRAF^{V600E}$-mutant mCRC, and their effectiveness and safety in routine clinical practice.[5,6,9,17] Observational studies help to close this gap, complementing randomized controlled trials (RCTs) by putting clinical trial findings in real-world context.

CAPSTAN CRC (NCT04317599) is the largest observational study that collected real-world data to describe the baseline characteristics, treatment patterns, and treatment effectiveness and safety for patients with $BRAF^{V600E}$-mutant mCRC across Europe.

METHODS

Study design

The CAPSTAN CRC study (NCT04317599) is a retrospective, multicenter, observational study conducted in Europe for $BRAF^{V600E}$-mutant mCRC adult patients (aged ≥18 years). The study was approved by the independent ethics committee or institutional review board at each site and was conducted in accordance with the requirements of the regulatory authorities of each country and in accordance with the Declaration of Helsinki. All patients were informed of their data collection or a waiver was obtained, according to applicable regulations.

The study index date was defined as the date of initiation of first-line treatment for $BRAF^{V600E}$-mutant mCRC between 1 January 2016 and 31 December 2018. Patients were observed until death, loss to follow-up, or study cut-off date (31 January 2020), whichever occurred first.

Patient population and sample selection

Eligible patients had histologically or cytologically confirmed metastatic and unresectable CRC, with presence of a $BRAF^{V600E}$ mutation confirmed by a local tissue assay. Patients must have been ≥18 years at the time of mCRC diagnosis and started a registered first-line treatment for mCRC in their respective country during the study index period. Patients were excluded if they had concomitant cancer at the time of mCRC diagnosis (occurring <5 years since diagnosis) or participated in interventional trials on investigational drugs at the time of initiation of first-line treatment.

To obtain a representative sample of real-world patients undergoing treatment for $BRAF^{V600E}$-mutant mCRC in Europe, and to minimize selection bias, the eligibility criteria were kept broad, and sites were targeted across different medical specialties (oncology and gastroenterology), countries, and hospital type (academic and non-academic). Stratified random sampling was used to select 62 representative sites and an additional 12 backup sites if needed. For each participating site, all eligible patients' medical records were identified, and an enrollment list was pseudo-randomly generated (see Supplementary materials, available at https://doi.org/10.1016/j.esmoop.2022.100603).

Key study endpoints

The primary objective was to describe first-line treatment patterns in adult patients with $BRAF^{V600E}$-mutant mCRC, including the duration of treatment. First-line treatment for $BRAF^{V600E}$-mutant mCRC was defined as the systemic anticancer therapy initiated at first occurrence of unresectable, metastatic disease and received until first documented disease progression, treatment discontinuation, or treatment switch (whichever occurred first).

Secondary objectives included baseline demographic and clinical characteristics of patients with $BRAF^{V600E}$-mutant mCRC, mutational testing procedures, effectiveness [progression-free survival (PFS), overall survival (OS), and overall response rate (ORR)], and safety of first-line therapies (according to MedDRA 23.0). Treatments received after first disease progression (second- and third-line therapies) were further exploratory objectives. Definitions of effectiveness outcomes can be found in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.

2022.100603. Safety was described according to the proportion of patients with at least one relevant adverse event during first-line treatment and the frequencies of the most common events reported, both overall and by treatment regimen. A relevant adverse event was defined as an adverse event leading to first-line treatment modification, dose adaptation or discontinuation, or death.

Statistical analyses

To allow a 95% confidence interval (CI) precision of ±2.5%, ±3.4%, and ±4.5% for 5%, 10%, and 20% of patients, respectively, a target sample of 300 patients was set. The full analysis set (FAS) containing all patients who fulfilled the eligibility criteria was analyzed.

Analyses were descriptive, as no formal hypotheses were tested. Continuous variables were summarized by the median. Categorical variables were summarized by percentages and 95% CIs were provided as a measure of error. Where patients had missing data for a particular variable, they were excluded from that analysis. Median PFS and OS were assessed and Kaplan–Meier curves were generated. The reverse Kaplan–Meier method provided a measure of median follow-up, with corresponding 95% CIs estimated.[21,22]

Univariate analyses were carried out to identify prognostic factors for PFS and OS. Multivariate analyses for PFS and OS were then carried out, retaining factors at a $P < 0.15$ level from the univariate model. Cox proportional hazards models with a stepwise procedure were used to estimate the hazard ratio and corresponding 95% CIs.[23]

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline site and patient characteristics

Of the 74 sites approached, there were 13 refusals, 7 dropouts, 4 unable to participate due to COVID-19 restrictions, and 4 unable to participate due to conflicting ongoing data collection programs. A further 12 sites either could not be activated or included no patients. The final sample consisted of 34 medical centers in seven European countries: Austria, Belgium, France, Germany, Italy, Spain, and the United Kingdom. There was a relatively even distribution across academic ($n = 14$) and nonacademic ($n = 20$) institutions, and a dominance of medical oncology units ($n = 30$) over gastroenterology units ($n = 4$). Of the targeted 300 patients, 274 were included initially, of which 19 were proven ineligible, leaving 255 patients included in the FAS (Figure 1).

Of the 255 patients, 58.4% were female, with a median age at the start of first-line treatment of 66.0 years (range 27.0-89.0 years) across all regimens (Table 1). Most patients had right-sided primary tumors (52.5%) and presented with stage IV disease at diagnosis (66.4%). The median number of metastatic sites was two (32.2%) and the most common location of metastasis was the liver (58.0%), followed by the peritoneum (43.9%), lymph nodes (34.9%), and lungs (26.7%). The majority (63.9%) of patients had at least one prior surgery for either primary tumor (61.4%) or metastatic site (13.8%).

BRAF mutational testing

The majority (95.7%) of patients were tested for *BRAF* mutations once, with 89.8% tested before the start of first-line treatment, 9.3% during first-line treatment, 0.4% after first- but before second-line treatment, and 0.4% during second-line treatment. A small number of patients were tested two times (4.2%). Most of the testing procedures for *BRAF* mutational status used tissue tumor samples (98.8%), with only 1.2% utilizing a blood test to detect circulating tumor DNA. Most tumor samples were archival (76.8%) versus fresh (23.2%). PCR (46.0%) and next-generation sequencing (38.1%) were the most frequently used methods to detect *BRAF* mutations.

About 60% of patients were also tested locally for microsatellite instability (MSI), with the highest testing rate occurring in France (82.4%) and Belgium (82.1%). Of those tested, 24.4% were mismatch repair deficient.

RAS testing was carried out for 91.8% of patients at first-line treatment, with the lowest testing rate reported in Spain (77.1%). As expected, most of these patients were *RAS* wild type (92.7%); however, 6.8% had a *RAS* mutation, an unexpectedly high rate, which may be due to the heterogeneity of CRC, and 0.4% had an unknown status. Next-generation sequencing was the predominant testing method used in France (52.1%), Germany (50.0%), and Austria (50.0%), whereas PCR was used more frequently in Spain (84.0%) and Belgium (52.0%).

Treatment patterns by line of therapy

For first-line therapy, 74.5% of patients received doublet chemotherapy, either alone (28.2%) or in combination with a targeted therapy (46.3%). When combined with a targeted therapy, 38.8% of patients received anti-VEGF and 7.5% received anti-EGFR. Only 6.7% of patients received monotherapy with or without targeted therapy. Of the 18.8% who received triplet chemotherapy, most received anti-VEGF (14.9%) and 0.8% received anti-EGFR. The main first-line treatments were FOLFOX plus bevacizumab (27.1%), FOLFOX alone (19.2%), and FOLFOXIRI plus bevacizumab (13.3%). The median duration of treatment for the overall population was 4.9 months (95% CI 4.0-5.3 months).

Subsequently, 52.5% and 30.2% received second- and third-line treatments, respectively. The most frequently used second-line regimens were folinic acid, 5-fluorouracil, irinotecan (FOLFIRI) plus bevacizumab (14.9%), FOLFIRI alone (14.2%), and BRAF inhibitor/mitogen-activated protein kinase kinase (MEK) inhibitor/cetuximab (11.9%). BRAF inhibitor plus cetuximab was given to 5.2% of patients at second line. The most common third-line treatment regimens were FOLFIRI plus bevacizumab (11.7%), BRAF inhibitor/MEK inhibitor/EGFR inhibitor combination (7.8%), FOLFOX plus bevacizumab (6.5%), and BRAF inhibitor/cetuximab/irinotecan (6.5%). BRAF inhibitor plus cetuximab was given to 2.6% of patients at third line. Together, regorafenib, trifluridine plus

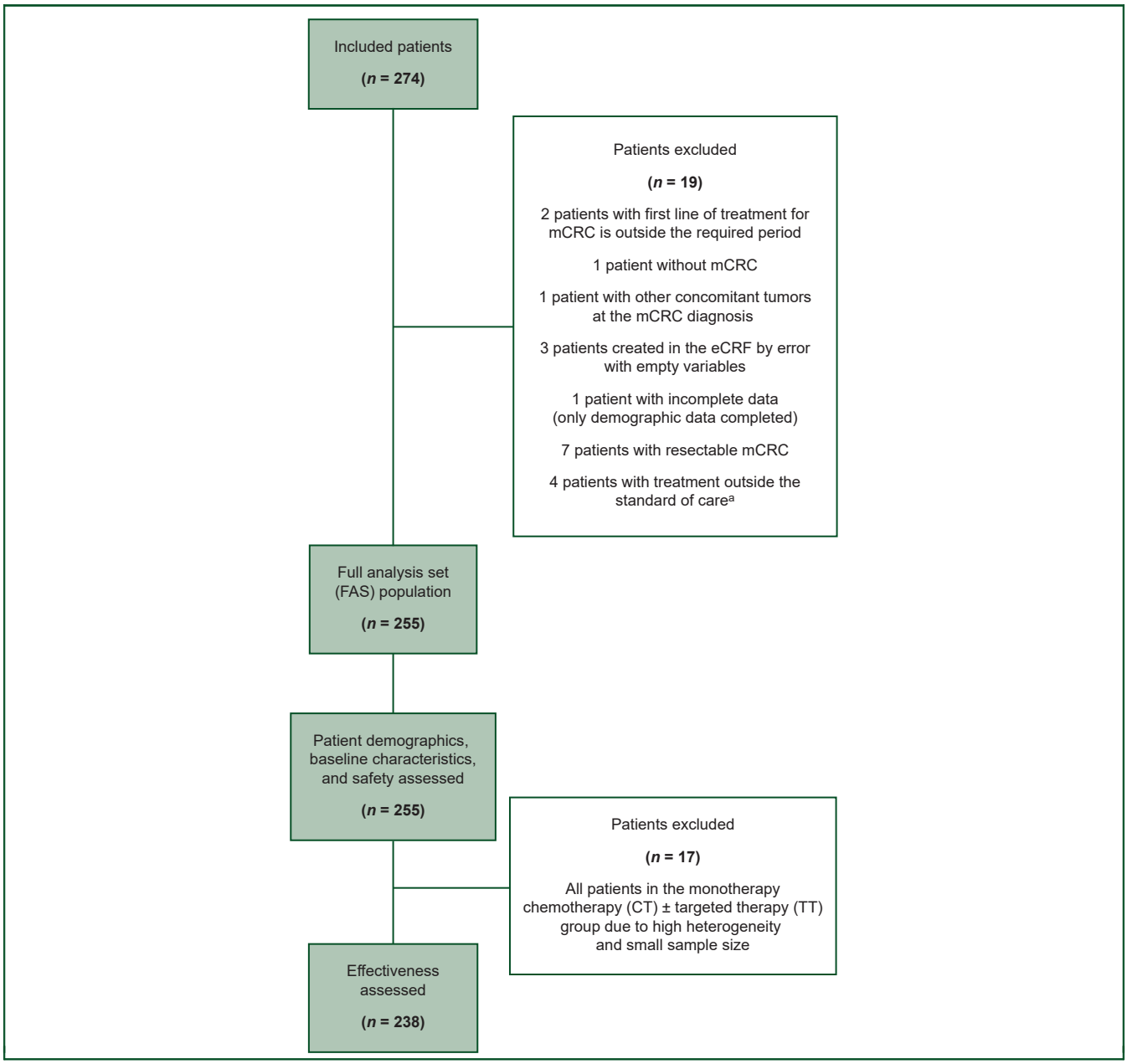

Figure 1. Population flow chart.
eCRF, electronic case report form; mCRC, metastatic colorectal cancer.
[a]Three patients in the monotherapy group were treated with irinotecan alone, bevacizumab alone, and panitumumab alone and one patient in the doublet chemotherapy group was treated with etoposide—carboplatin.

tipiracil (TAS-102), anti-programmed cell death protein 1 immunotherapy, and vinorelbine formed 26.0% of all third-line options prescribed.

Treatment patterns by country

Patient and tumor characteristics were similar between countries; however, first-line treatment patterns differ. In Belgium, Germany, and Italy, the main treatment received was doublet chemotherapy plus anti-VEGF (60.7%, 53.3%, and 51.9%, respectively; Figure 2). In France and Spain, doublet chemotherapy (29.7% and 37.1%, respectively) and doublet chemotherapy plus targeted therapy (32.4% and 40.0%) were equally common as a first-line treatment.

Effectiveness

Effectiveness objectives were assessed on a subset of the FAS population ($n = 238$). The monotherapy chemotherapy $\pm$ targeted therapy group ($n = 17$) was excluded due to the high heterogeneity and low number of patients who received this regimen (Figure 1). For the effectiveness analysis, the two chemotherapy alone groups [triplet ($n = 8$) and doublet ($n = 72$)] were combined due to the small number of patients.

Across all first-line regimens ($n = 238$), median PFS was 6.0 months (95% CI 5.3-6.7 months; Figure 3A). The median PFS was similar across all three treatment groups [4.4 (95% CI 2.8-6.7) months, 6.1 (95% CI 5.3-7.6) months, and 6.7

Table 1. Baseline demographic and clinical characteristics of patients

Variable	Monotherapy CT ± TT	Doublet CT	Doublet CT + TT	Triplet CT	Triplet CT + TT	Total
	n = 17	*n* = 72	*n* = 118	*n* = 8	*n* = 40	*N* = 255
Median age at start of first-line treatment						
n	16	72	117	8	40	253
Median (min–max), years	82.0 (69.0-89.0)	69.0 (29.0-88.0)	67.0 (27.0-87.0)	61.0 (46.0-70.0)	58.0 (34.0-74.0)	66.0 (27.0-89.0)
Sex						
Female, *n* (%)	10 (58.8)	42 (58.3)	72 (61.0)	5 (62.5)	20 (50.0)	149 (58.4)
TNM stage at initial diagnosis of CRC						
n	15	59	113	6	33	226
I/II/III/IV, %	0/20.0/26.7/53.3	1.7/11.9/16.9/69.5	1.8/8.8/23.0/66.4	0/0/33.3/66.7	3.0/12.1/18.2/66.7	1.8/10.6/21.2/66.4
ECOG assessment						
n	10	40	67	2	31	150
0/1/2/3, %	20.0/70.0/10.0/0.0	42.5/42.5/10.0/5.0	55.2/35.8/6.0/3.0	50.0/50.0/0.0/0.0	74.2/22.6/3.2/0.0	53.3/37.3/6.7/2.7
Primary tumor location						
n	17	72	118	8	40	255
Left ± rectum, %	11.8	23.6	35.6	87.5	37.5	32.5
Right only, %	76.5	58.3	49.2	12.5	50.0	52.5
Left + right/transverse or right + rectum or not applicable, %	11.8	18.1	15.3	0	12.5	14.9
At least one prior surgery for primary CRC						
n	17	71	118	8	40	254
Yes, %	70.6	62.0	58.5	75.0	62.5	61.4
At least one prior surgery for mCRC						
n	17	71	118	8	40	254
Yes, %	0	16.9	9.3	37.5	22.5	13.8
Number of metastatic sites						
Median (min–max)	1.0 (1.0-3.0)	1.0 (1.0-5.0)	2.0 (1.0-6.0)	1.5 (1.0-2.0)	2.0 (1.0-4.0)	2.0 (1.0-6.0)
1/2/≥3, %	64.7/29.4/5.9	51.4/23.6/25.0	42.4/29.7/28.0	50.0/50.0/0	32.5/52.5/15.0	45.1/32.2/22.7
Location of metastasis						
Liver, %	35.3	54.2	58.5	50.0	75.0	58.0
Liver only, %	11.8	25.0	16.9	12.5	17.5	18.8
Peritoneum, %	41.2	55.6	44.1	37.5	25.0	43.9
Lung, %	29.4	20.8	28.8	12.5	32.5	26.7
Lymph nodes, %	29.4	23.6	39.0	37.5	45.0	34.9
MSI tested						
n	11	36	69	6	31	153
Yes, %	64.7	50.0	58.5	75.0	77.5	60.0
MSI high, % of all tested	54.5	27.8	20.3	16.7	16.1	23.5

CRC, colorectal cancer; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; TNM, tumor–node–metastasis; TT, targeted therapy.

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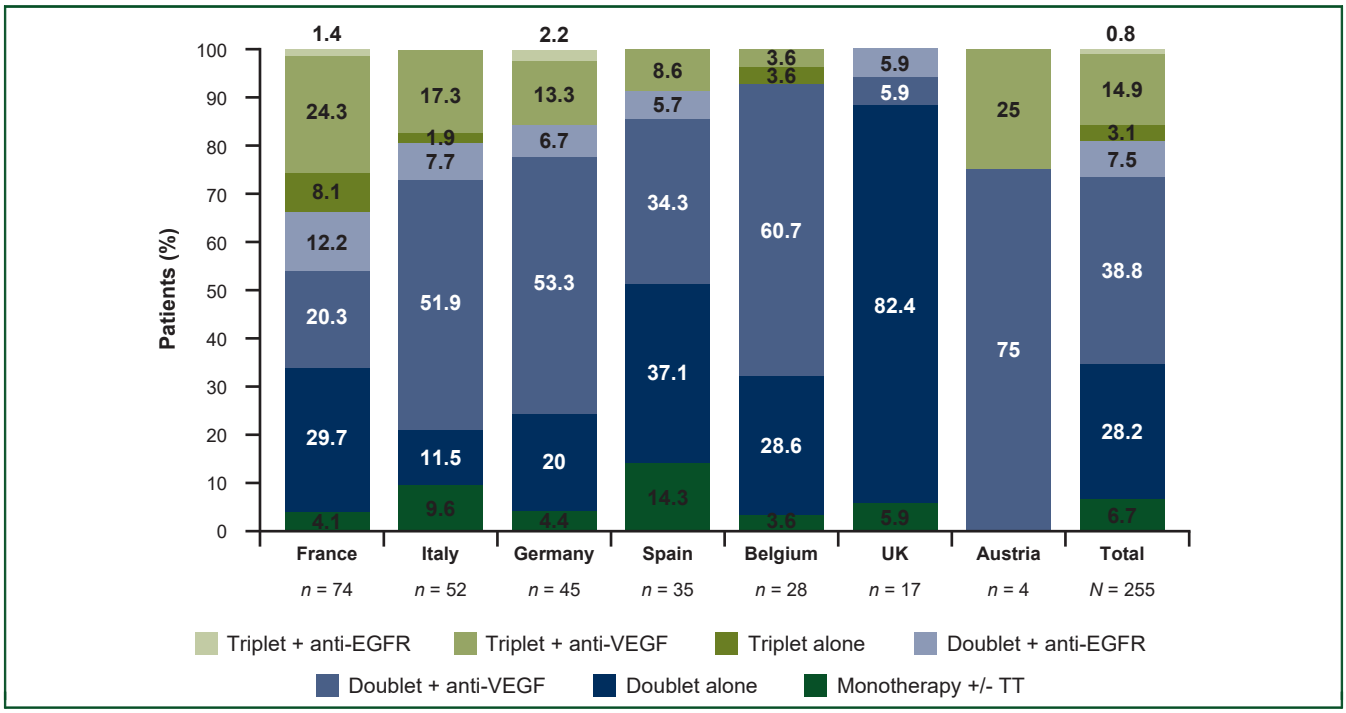


Figure 2. First-line mCRC treatment regimens by country.
The proportion of patients per country and across all countries ($N = 255$) in the full analysis set receiving each treatment type. The proportion of patients per treatment regimen is provided within each bar.
+, with; +/-, with or without; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; TT, targeted therapy; VEGF, vascular endothelial growth factor.

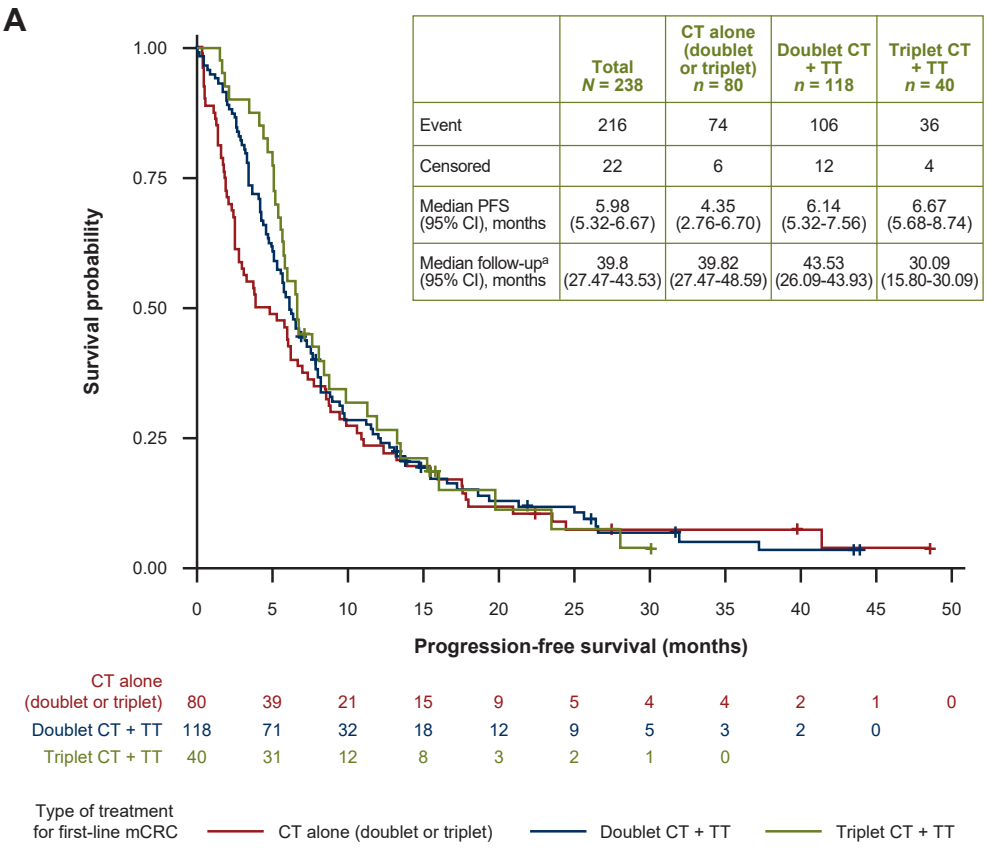
(95% CI 5.7-8.7) months for the chemotherapy alone, doublet chemotherapy plus targeted therapy, and triplet chemotherapy plus targeted therapy groups, respectively]. Subsequent multivariate analysis found that body mass index (both 25-30 and $\geq$30 kg/m^2) and the presence of $\geq$3 metastatic sites were significant prognostic factors of PFS ($P = 0.0092$, 0.0238, and 0.0025, respectively; Figure 4A). Interestingly, factors that may affect body mass index were not significant, including age ($P = 0.8597$) and peritoneal carcinomatosis ($P = 0.2130$), whereas performance status was not reliable due to missing data. Treatment choice was not assessed as a variable due to the dataset not being sufficiently robust. Univariate analysis data are provided in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100603.

The median OS across all regimens was 12.7 months (95% CI 11.6-14.1 months; Figure 3B). The median OS was similar for all three treatment groups [11.7 (95% CI 8.5-15.4) months, 12.9 (95% CI 11.4-15.7) months, and 13.5 (95% CI 10.1-15.7) months for the chemotherapy alone, doublet chemotherapy plus targeted therapy, and triplet chemotherapy plus targeted therapy groups, respectively]. By multivariate analysis, the presence of three or more metastatic sites and liver metastases were found to be significant predictors of OS ($P = 0.0020$ and 0.0009, respectively), each increasing risk of death by 84% and 72%, respectively (Figure 4B and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100603).

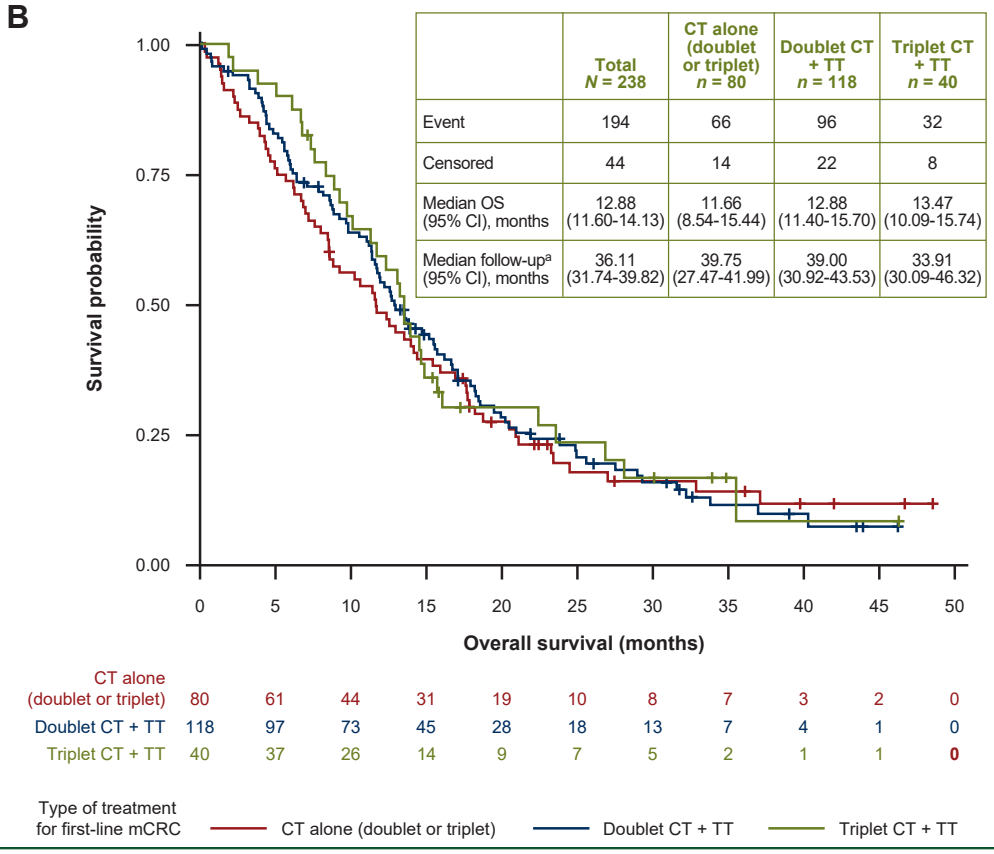
ORR was 32.9% (95% CI 26.9-38.9; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100603). The observed response rate was 52.5% in patients who received triplet chemotherapy plus targeted therapy (95% CI 37.0%-68.0%), 31.4% with doublet chemotherapy plus targeted therapy (95% CI 23.0%-39.7%), and 25.3% with doublet/triplet chemotherapy alone (95% CI 15.7%-34.9%). The complete response rate for all regimens was 2.1% and partial response rate was 30.8%, compared with stable disease (30.4%) and progressive disease (23.2%).

Exploratory analysis of the efficacy of first-line treatments was conducted by grouping patients who received doublet chemotherapy $\pm$ targeted therapy ($n = 190$) and comparing with patients who received triplet chemotherapy $\pm$ targeted therapy ($n = 48$; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100603). Median PFS was similar across both treatment groups [5.78 (95% CI 4.83-6.47) months versus 6.70 (95% CI 5.68-9.86) months]. A similar trend was seen for median OS [12.58 (95% CI 11.40-14.36) months versus 13.47 (95% CI 11.30-16.03) months]. A higher response rate was observed in patients who received triplet chemotherapy $\pm$ targeted therapy (50.0%; 95% CI 35.9%-64.1%), versus doublet chemotherapy $\pm$ targeted therapy (28.6%; 95% CI 22.1%-35.0%). However, limited conclusions can be drawn from these exploratory analyses due to the large difference in sample sizes between the two groups.

Additional exploratory analysis compared patients that received chemotherapy plus anti-EGFR, chemotherapy plus anti-VEGF, and chemotherapy alone. For patients who received chemotherapy plus anti-EGFR ($n = 21$) or



	Total N = 238	CT alone (doublet or triplet) n = 80	Doublet CT + TT n = 118	Triplet CT + TT n = 40
Event	216	74	106	36
Censored	22	6	12	4
Median PFS (95% CI), months	5.98 (5.32-6.67)	4.35 (2.76-6.70)	6.14 (5.32-7.56)	6.67 (5.68-8.74)
Median follow-up[a] (95% CI), months	39.8 (27.47-43.53)	39.82 (27.47-48.59)	43.53 (26.09-43.93)	30.09 (15.80-30.09)



	Total N = 238	CT alone (doublet or triplet) n = 80	Doublet CT + TT n = 118	Triplet CT + TT n = 40
Event	194	66	96	32
Censored	44	14	22	8
Median OS (95% CI), months	12.88 (11.60-14.13)	11.66 (8.54-15.44)	12.88 (11.40-15.70)	13.47 (10.09-15.74)
Median follow-up[a] (95% CI), months	36.11 (31.74-39.82)	39.75 (27.47-41.99)	39.00 (30.92-43.53)	33.91 (30.09-46.32)

Figure 3. Kaplan–Meier estimates for (A) PFS and (B) OS according to first-line mCRC treatment ($N = 238$).
+, with; CI, confidence interval; CT, chemotherapy; mCRC, metastatic colorectal cancer; PFS, progression-free survival; OS, overall survival; TT, targeted therapy.
[a]Follow-up was calculated using the reverse Kaplan–Meier method.

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chemotherapy alone ($n = 80$), median PFS was comparable (3.7; 95% CI 3.4-6.3 months versus 4.4; 95% CI 2.8-6.7 months). Median PFS was numerically higher for patients who received chemotherapy with anti-VEGF ($n = 137$; 6.7; 95% CI 5.8-8.0 months), with overlapping CIs for the three groups. Similarly, median OS was comparable across the chemotherapy plus anti-EGFR and chemotherapy alone groups (10.1; 95% CI 5.6-11.4 months versus 11.7; 95% CI 8.5-15.4 months), whereas median OS was higher for patients who received chemotherapy with anti-VEGF (13.7; 95% CI 12.6-16.0 months). CIs overlapped for all comparisons except for the chemotherapy plus anti-EGFR and chemotherapy plus anti-VEGF groups.

Safety

Safety objectives were assessed on the full FAS ($n = 255$). A total of 131 (51.4%) patients experienced at least one relevant adverse event during first-line treatment. For 49.0% of patients, at least one relevant adverse event was related to the mCRC therapy received during first-line treatment. The highest rate of adverse events was associated with triplet chemotherapy plus targeted treatment (75.0%) compared with triplet chemotherapy alone (50.0%), doublet chemotherapy alone (36.1%), doublet chemotherapy plus targeted treatment (49.2%), and monotherapy chemotherapy with or without targeted treatment (41.2%).

Across all first-line treatment regimens, the most frequent relevant adverse events were diarrhea (12.2%), peripheral neuropathy (7.5%), asthenia (7.1%), and neutropenia (7.1%). Triplet chemotherapy with targeted treatment resulted in higher rates of diarrhea (25.0%), peripheral neuropathy (25.0%; potentially due to oxaliplatin), and neutropenia (15.0%) compared with other first-line treatments. Rates of asthenia were higher for the triplet chemotherapy alone group.

DISCUSSION

To the best of our knowledge, CAPSTAN CRC is the first study to assess treatment patterns for *BRAF*^{V600E}-mutant mCRC in routine clinical practice across Europe. Although ESMO provides guidelines for the treatment of this subset of patients, these remain limited in scope and lack a clear consensus on therapeutic strategy in the first-line setting.[6,24] Furthermore, current treatment recommendations are based largely on evidence from RCTs including <100 patients with *BRAF*^{V600E}-mutant mCRC, except BEACON CRC ($n = 665$) and FIRE 4.5 ($n = 108$).[5,6,9,20,25-27] *BRAF*^{V600E}-mutant mCRC is a rare disease with an aggressive phenotype, making recruitment and patient retention challenging and preventing firm conclusions regarding best practices.[5] Therefore, characterization of real-world first-line treatment patterns for patients with *BRAF*^{V600E}-mutant mCRC in CAPSTAN CRC represents an important step.

The predominance of right-sided tumors and the high proportion of patients with metastatic disease at diagnosis, at >66% markedly higher than the 20% previously reported for CRC overall,[2] emphasizes the aggressive biology of the *BRAF*^{V600E} phenotype and the importance of early detection.

CAPSTAN CRC found most patients received doublet chemotherapy (with or without targeted therapy) in the first-line setting, with the most prescribed regimen being FOLFOX plus bevacizumab, followed by FOLFOX alone, and FOLFOXIRI plus bevacizumab. Just over half of patients received a second-line therapy. The notable variety of different treatments, in both first and second lines, perhaps reflects the heterogeneity of patients and complexity of the disease in real-world clinical practice.

It is unclear whether doublet or triplet chemotherapy regimens are superior for *BRAF*^{V600E}-mutant mCRC in first line, or what the optimal treatment sequence is. In CAPSTAN CRC, ORR was higher with first-line triplet chemotherapy plus targeted therapy compared with doublet chemotherapy plus targeted therapy. However, the nature of the study and the possibility of selection bias preclude definitive conclusions. In the phase III TRIBE2 study, sequential administration of doublet chemotherapies plus bevacizumab was compared with triplet FOLFOXIRI plus bevacizumab in patients with previously untreated mCRC.[28] Although triplet therapy improved survival overall, subgroup analyses of patients with *BRAF*^{V600E} or *RAS* mutations revealed no indisputable benefit of triplet over doublet chemotherapies. Similarly, a meta-analysis of five RCTs showed no benefit of FOLFOXIRI plus bevacizumab over doublet plus bevacizumab in *BRAF*-mutant mCRC.[10] Thus, the optimal choice of frontline chemotherapy regimen for these patients remains to be established.

In CAPSTAN CRC, most patients received first-line combination chemotherapy with bevacizumab, in line with European guidelines for *BRAF*^{V600E}-mutant mCRC.[5,9] Adding bevacizumab improved survival compared with chemotherapy alone in the subgroup analyses of patients with *BRAF*^{V600E}-mutant mCRC in previous clinical trials and a recent analysis of pooled individual patient data from the Analysis and Research in CAncers of the Digestive system (ARCAD) database.[8,29,30] Cetuximab and panitumumab have also demonstrated survival benefit in combination with FOLFIRI and FOLFOX for treatment-naive mCRC[17]; however, there is increasing evidence that the addition of cetuximab to chemotherapy is not effective in the first-line setting for patients with a *BRAF*^{V600E} mutation.[31] The recent phase II FIRE-4.5 study, which assessed FOLFOXIRI plus bevacizumab versus FOLFOXIRI plus cetuximab as first-line treatment for *BRAF*^{V600E}-mutant mCRC, showed a trend toward improved survival with bevacizumab in patients with right-sided tumors.[20] This further supports the use of bevacizumab in combination with chemotherapy in the first-line setting for these patients.

The median PFS in CAPSTAN CRC was 6.0 (95% CI 5.3-6.7) months and the median OS was 12.9 (95% CI 11.6-14.1) months across all first-line regimens. Median PFS and OS were similar for all three treatment groups. However, longer survival was seen in patients selected for clinical trials compared with our real-world population. FIRE 4.5 reported

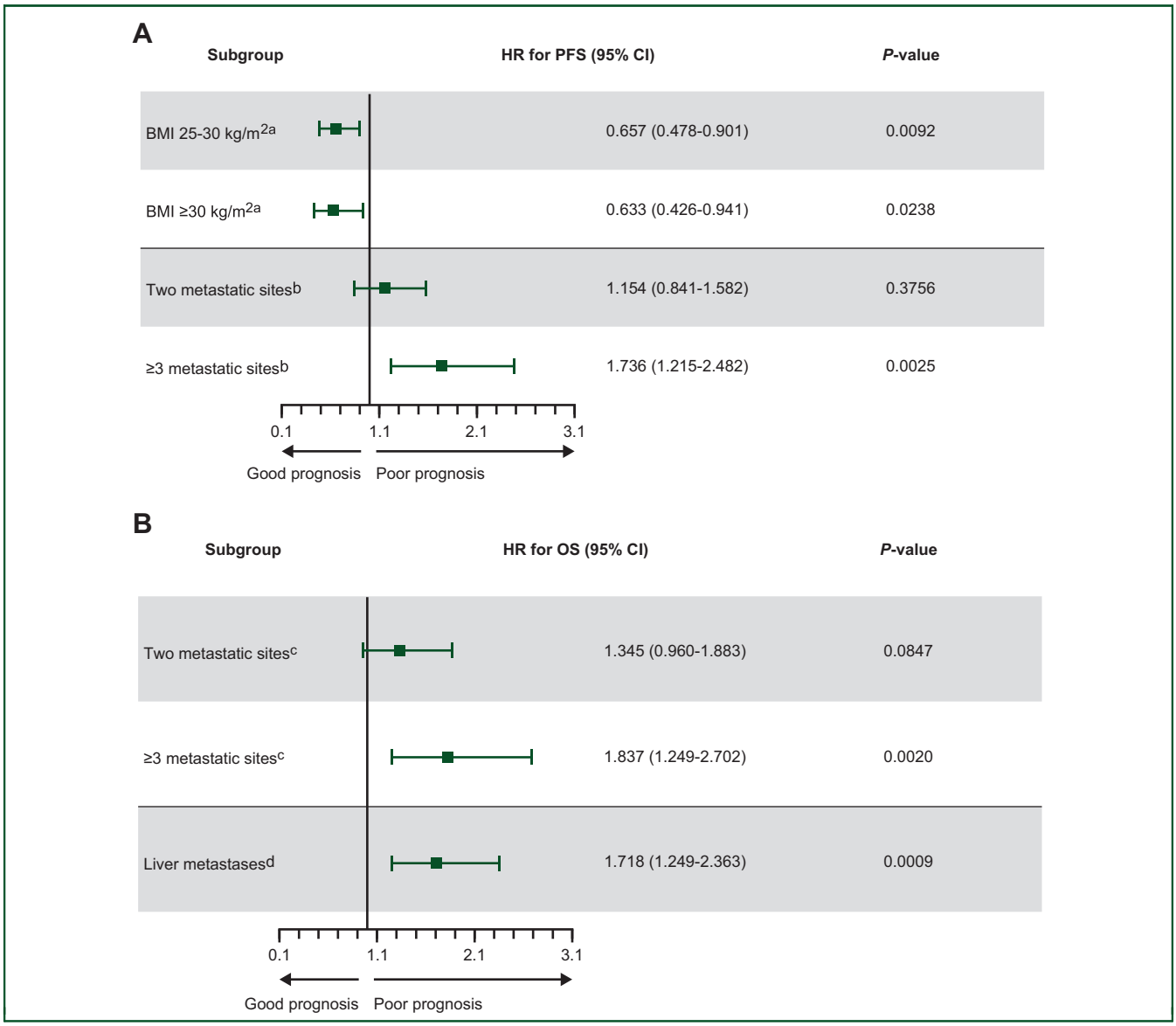

Figure 4. Multivariate analysis for (A) PFS and (B) OS according to first-line mCRC treatment ($P < 0.15$; $N = 238$).
BMI, body mass index; CI, confidence interval; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.
[a]Reference group was BMI <25 kg/m^2; [b]Reference group was one metastatic site. [c]Reference group was one metastatic site; [d]Reference group was the absence of liver metastasis.

an OS of 17.1 months with first-line FOLFOXIRI plus bevacizumab versus 15.2 months with FOLFOXIRI plus cetuximab in *BRAF*^{V600E}-mutant mCRC.[20] The single-arm, phase II ANCHOR CRC study in patients with previously untreated *BRAF*^{V600E}-mutant mCRC showed an OS of 17.2 months with encorafenib, binimetinib, and cetuximab.[32]

This study underscores the unmet need for more effective treatment strategies to improve the prognosis of patients with *BRAF*^{V600E}-mutant mCRC and allow more patients to receive subsequent lines of treatment. Unfortunately, only a very modest proportion were able to receive second- (52.5%) and third-line (30.2%) treatments, reaffirming that rapid disease progression is common. Therefore, optimization of first-line treatment is especially relevant in this patient population.[33]

As both *BRAF* and *RAS* mutations are significant negative prognostic factors in CRC, it was encouraging to observe that most patients were tested for each (89.8% and 91.8%, respectively) prior to first-line treatment.[5,9] However, while *BRAF* testing is standard of care in most European regions, with rates as high as 97% in Northern and Western Europe, testing at initial diagnosis (20%) trails behind East Asia (41%), Australasia (41%), and North America (35%).[34] Mutational status also guides appropriate therapeutic strategies for different biological mCRC subtypes.[5,24] Thus, improving testing rates further would greatly benefit optimization of treatment decisions.

In contrast to *BRAF* and *RAS*, MSI status was assessed much less frequently, in only 60.0% of patients overall. Variability of testing practices was high across Europe,

including regions without routine MSI testing during the study inclusion period (2016-2018). However, MSI screening is now recommended in the ESMO guidelines (2020) in both curative and palliative treatment settings.[24,35]

Surprisingly, 6.8% of *BRAF*^{V600E}-mutant patients in CAPSTAN CRC had a concomitant *RAS* mutation, although this is rare and these mutations are generally considered mutually exclusive.[36,37] The reasons are unclear, but may include the high heterogeneity of the *BRAF*^{V600E}-mutant population or reporting errors due to heterogeneous testing procedures across countries.[37]

There are some limitations to CAPSTAN CRC. First is the inherent issue of real-world evidence studies regarding low internal validity, human error, and quality control during data reporting. Despite this, real-world evidence can complement data from RCTs by providing valuable insights into routine clinical practices that guide treatment decisions.[38] Second, population size is relatively small compared with some cohort studies, and particularly small for the 'by country' analysis [UK ($n = 17$) and Austria ($n = 4$)]. However, CAPSTAN CRC provides further information regarding treatment practices, effectiveness, and safety in this often-overlooked subpopulation. Similarly, the study includes patients from only seven European countries. Surveys revealed, for example, that mCRC *BRAF* testing is far less commonly carried out in Eastern European than Northern and Western European countries.[34] Therefore, caution is required when extrapolating conclusions on treatment practices to the entirety of Europe. Finally, the treatment landscape for these patients is diverse and still evolving; this study is a snapshot of mCRC treatment practices and outcomes. The time frame in which the study was conducted should, therefore, be considered when evaluating the results.

A promising therapeutic avenue in *BRAF*^{V600E}-mutant mCRC lies in the development of targeted agents, and their combined use to inhibit multiple points in the mitogen-activated protein kinase signaling pathway and overcome mechanisms of treatment resistance.[39,40] BEACON CRC demonstrated the efficacy of combining BRAF and EGFR inhibition, using encorafenib and cetuximab, versus standard chemotherapy after prior systemic treatment.[27] ANCHOR CRC, which assessed the efficacy of encorafenib, binimetinib, and cetuximab as first-line treatment for patients with *BRAF*^{V600E}-mutant mCRC, reported an encouraging median PFS of 5.8 months and median OS of 17.2 months.[32] Further ongoing clinical trials in *BRAF*^{V600E}-mutant CRC evaluate different treatment combinations.[41,42] For example, the phase III BREAKWATER trial (NCT04607421) is assessing encorafenib in combination with cetuximab in *BRAF*^{V600E}-mutant, treatment-naive patients with or without chemotherapy.[16,43]

Immunotherapy is another promising treatment strategy in *BRAF*^{V600E}-mutant mCRC. In the phase III KEYNOTE-177 trial, first-line pembrolizumab in patients with mismatch repair deficient/MSI tumors significantly prolonged PFS versus chemotherapy, with a similar benefit observed in patients with *BRAF*^{V600E}-mutant and *BRAF* wild-type mCRC.[44] The phase II CheckMate-142 study found that the combination of nivolumab plus ipilimumab provided a robust and durable clinical benefit, including long-term survival, for patients with MSI-high mCRC, including those with *BRAF* mutations.[45-47]

Conclusions

The *BRAF*^{V600E} mutation is a biomarker for prognosis as well as treatment response, and screening is now recommended in combination with RAS and mismatch repair/MSI status determination. The CAPSTAN CRC study helps to elucidate the real-world European management of *BRAF*^{V600E}-mutant mCRC, demonstrating the aggressiveness of this disease where the median OS was 12.9 months and only 52.5% of patients were able to receive a potentially effective second-line therapy. The study's findings highlight the importance of testing for *BRAF*^{V600E} mutations to personalize and optimize treatment, and the close monitoring necessary for patients with this mutational status. There remains a clear unmet need to establish the best treatment strategies for this population in the first-line setting.

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