BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN THE BERING^{CRC} STUDY

REAL-WORLD STUDY IN BRAF^{V600E}-MUTANT METASTATIC COLORECTAL CANCER

Yael Bonnin-Gruber[1], Jan Schröder[2], Helmut Forstbauer[3], Jens Kisro[4], Manfred Welslau[5], Harald Müller-Huesmann[6], Dieter Bürkle[7], Beate Krammer-Steiner[8], Eyck von der Heyde[9], Frank Reichenbach[10], Dirk Arnold[11], Ralph Fritsch[12], Armin Gerger[13], Susanna Hegewisch-Becker[14], Arndt Vogel[15], Thomas Winder[16], Dieter Koeberle[17], Gerald Prager[18], Sebastian Stintzing[19]

1 Oho! Ostholstein-Onkologie, Oldenburg i.H./Eutin, Germany, 2 Outpatient Center for Hematology – Oncology – Palliative Care, Muelheim, Germany, 3 Practice Network Hematology/Oncology, Troisdorf, Germany, 4 Oncological Practice Lübeck, Lübeck, Germany, 5 Oncological Practice Aschaffenburg, Aschaffenburg, Germany, 6 MVZ im Medico, Paderborn, Germany 7 Oncological Practice Schorndorf, Schorndorf, German, 8 Department of Hematology and Oncology, Rostock South City Medical Center, Rostock, Germany. 9 Onkologische Praxis am Raschplatz, Hannover, Germany, 10 Pierre Fabre Pharma GmbH, Freiburg, Germany, 11 Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany, 12 Department of Medical Oncology and Hematology, University Hospital of Zurich, Zurich, Switzerland, 13 Medical University of Graz, Graz, Austria, 14 Hämatologisch-Onkologische Praxis Eppendorf (HOPE), Hamburg, Germany, 15 Hannover Medical School, Hannover, Germany, 16 Internal Medicine II, Landeskrankenhaus Feldkirch, Feldkirch, Austria, 17 Claraspital Basel, Switzerland, 18 Medical University of Vienna, Vienna, Austria, 19 Medical Department, Division of Hematology, Oncology, and Cancer Immunology (CCM), Charité Universitätsmedizin Berlin, Berlin, Germany

Background

- BRAF mutations are found in 8-12% of metastatic CRC (mCRC) patients with the majority being V600E.[1]
- BRAF^{V600E}-mutated mCRC is associated with a poor prognosis and limited clinical data.[1]
- Targeted treatment with the BRAF kinase inhibitor encorafenib and the anti-EGFR antibody cetuximab (E+C) represents a new standard of care for previously treated patients (pts) with BRAF^{V600E}-mutant mCRC.[2,3]
- The approval was based on the pivotal BEACON CRC study that demonstrated a clinically meaningful benefit with E+C vs. control, including significantly improved objective response rate (ORR; 19.5% vs. 1.8%) and median overall survival (OS; 9.3 months vs. 5.9 months).[2]
- The safety profile was consistent with the known profiles of the two compounds.[2]
- Data from controlled clinical trials are based on selected patient populations. Thus, BERING^{CRC} is the first non-interventional study to investigate the real-world use of E+C in a broader patient population with BRAF^{V600E}-mutant mCRC in Germany, Austria, and Switzerland (NCT04673955). As of August 22, 2022, 100 patients have been included and patient enrollment is ongoing.

Objectives

Primary objective

- Evaluation of the effectiveness of treatment with E+C based on the 12-months OS rate

Secondary objectives include

- Description of patient and disease profiles
- Description of prior and subsequent antineoplastic therapies
- Evaluation of reasons for selecting E+C
- Assessment of quality of life as well as physician's and patient's treatment satisfaction
- Evaluation of safety and tolerability

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Methods

Study design

- Prospective, longitudinal, multicentric, observational study in Germany, Austria, and Switzerland
- 300 adult pts are planned to be enrolled at 126 sites in accordance with the Summary of Product Characteristics specifications and treatment according to local clinical routine.

Key inclusion criteria

- Patients with BRAF^{V600E}-mutated mCRC, pretreated with systemic therapy
- Treatment with E+C has been started ≤ 3 months prior to providing written informed consent or is planned to be started

Key exclusion criteria

- > 2 prior systemic regimens in the metastatic setting (adjuvant systemic therapy with relapse ≤ 6 months will be counted as metastatic treatment line; maintenance treatment will not be counted as separate metastatic line)
- Prior treatment with any RAF-inhibitor or MEK-inhibitor
- Current or upcoming participation in an interventional clinical trial
- Current or upcoming systemic treatment of any other tumor than mCRC

Statistical analysis

- Here, we report results of the baseline analysis, which was performed using descriptive statistics.
- Patient and disease characteristics as well as prior antineoplastic therapies are given for all enrolled patients.
- Data on E+C treatment, except for dosages, were evaluated for patients who fulfilled the in-/exclusion criteria and had at least one administration of E/C documented (Full Analysis Set [FAS])
- Starting doses of E/C were analyzed for patients of the FAS for whom at least one safety assessment was documented (Safety Set [SAF]).

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Table 1: Patient and disease characteristics at inclusion, if not otherwise stated.

	n=40
Median age, years (min - max)	**67.7 (33.7-88.4)**
Female gender, n (%)	**15 (37.5)**
ECOG Performance Status, n (%)	
0	15 (37.5)
1	21 (52.5)
2	3 (7.5)
Not evaluated	1 (2.5)
Location of primary tumor, n (%) *	
Cecum	5 (12.5)
Colon	34 (85.0)
Rectum	3 (7.5)
Sidedness of primary tumor, n (%) #	
Right	26 (65.0)
Left	15 (37.5)
Missing	1 (2.5)
UICC stage at primary diagnosis, n (%)	
III	14 (35)
IV	25 (62.5)
Missing	1 (2.5)
Localization of metastases, n (%) *	
Liver	22 (55.0)
Peritoneum	16 (40.0)
Lung	13 (32.5)
Supra-regional lymph nodes	9 (22.5)
Other	9 (22.5)
Involvement of ≥3 organs, n (%)	**8 (20)**
Microsatellite instability, n (%)	
MSI-High	4 (10.0)
MSI-Low	2 (5.0)
MSS	22 (55.0)
No test reported	12 (30.0)

*Multiple answers per patient possible.
#Multiple answers due to multifocal primary tumor possible
MSI, Microsatellite Instability; MSS, Microsatellite Stable

Table 2: BRAF^{V600E} testing at inclusion, if not otherwise stated.

n (%)	n=40
BRAF^{V600E} testing	**40 (100.0)**
BRAF^{V600E} testing at primary diagnosis	25 (62.5)
Type of tissue used for BRAF^{V600E} testing*	
Archived tissue obtained from primary tumor	29 (72.5)
Tissue from metastasis	7 (17.5)
Unknown	4 (10)
Method of BRAF^{V600E} testing*	
Immune-histochemistry	9 (22.5)
Next generation sequencing	18 (45.0)
Single gene sequencing	1 (2.5)
Unknown	12 (30.0)

*Multiple answers per patient possible.

Table 3: Treatment regimens applied in the adjuvant and palliative setting prior to E+C.

Treatment regimen	Adjuvant (n=8)	1st-line (n=35)	2nd-line (n=9)
Chemotherapy			
FOLFOXIRI	2 (25.0)	8 (22.9)	1 (11.1)
FOLFOX	4 (50.0)	12 (34.3)	0
CAPOX	2 (25.0)	3 (8.6)	2 (22.2)
FOLFIRI	0	10 (28.6)	3 (33.3)
Capecitabine	0	5 (14.3)	0
5-FU + Folinic acid	0	1 (2.9)	3 (33.3)
Trifluridine / Tipiracil	0	0	1 (11.1)
Targeted therapy			
Bevacizumab	1 (12.5)	13 (37.1)	5 (55.6)
Cetuximab	0	2 (5.7)	1 (11.1)
Panitumumab	0	1 (2.9)	0

Percentages relative to the treatment setting. For 2 pts previous treatment had not been documented yet.
Targeted therapy with Bevacizumab, Cetuximab, or Panitumumab had been given in combination with chemotherapy.
If treatment regimen was changed for another reason than toxicity or disease progression, treatment was counted within the same line. Thus, multiple answers were possible and, accordingly, percentages do not always result in 100%.

Results

Patient population

- Between 3rd September 2020 and 14th August 2021, 40 pts were enrolled at 27 sites across Germany and Austria.
- For all included patients, baseline and disease characteristics are depicted in **Table 1** while details on BRAF^{V600E} testing are summarized in **Table 2**.
- For 25 pts (62.5%) results on KRAS/NRAS testing were also reported and one patient with BRAF mutation also had an overlapping RAS mutation.

Prior anticancer treatment

- Prior to E+C treatment, 3 pts (7.9%) had received adjuvant treatment only while for about two thirds (68.4%) and 23.7% of pts one or two prior lines of therapy were reported (**Figure 1**).
- While 87.5% of pts received chemotherapy alone for adjuvant treatment, the frequency of chemotherapy alone decreased in the 1st- and 2nd-line. Here, chemotherapy was commonly combined with a targeted therapy (i.e., anti-VEGF/R or anti-EGFR therapy) (**Figure 2**).
- Most pts (57.5%) received the combination of chemotherapy and targeted therapy with all pts receiving targeted therapy only once (**Figure 3**).
- Details on reported treatment regimens are summarized in **Table 3**.

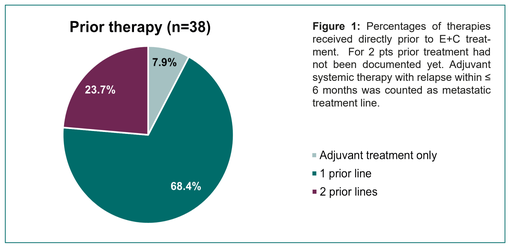

Figure 1: Percentages of therapies received directly prior to E+C treatment. For 2 pts prior treatment had not been documented yet. Adjuvant systemic therapy with relapse within ≤ 6 months was counted as metastatic treatment line.

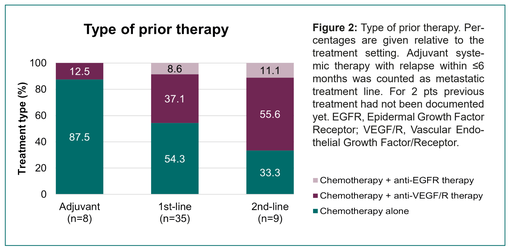

Figure 2: Type of prior therapy. Percentages are given relative to the treatment setting. Adjuvant systemic therapy with relapse within ≤6 months was counted as metastatic treatment line. For 2 pts previous treatment had not been documented yet. EGFR, Epidermal Growth Factor Receptor; VEGF/R, Vascular Endothelial Growth Factor/Receptor.

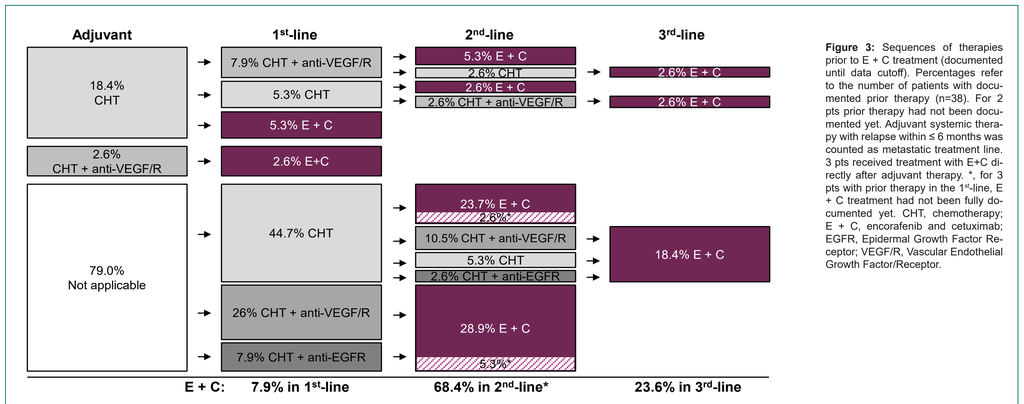

Figure 3: Sequences of therapies prior to E + C treatment (documented until data cutoff). Percentages refer to the number of patients with documented prior therapy (n=38). For 2 pts prior therapy had not been documented yet. Adjuvant systemic therapy with relapse within ≤ 6 months was counted as metastatic treatment line. 3 pts received treatment with E+C directly after adjuvant therapy. *, for 3 pts with prior therapy in the 1st-line, E + C treatment had not been fully documented yet. CHT, chemotherapy; E + C, encorafenib and cetuximab; EGFR, Epidermal Growth Factor Receptor; VEGF/R, Vascular Endothelial Growth Factor/Receptor.

Encorafenib and Cetuximab (E+C) treatment

- At the time of data cutoff, the median follow-up was 3.7 months (1st - 3rd quartile: 0.6 - 4.7 months).
- The predominant reason for E+C treatment was the presence of a BRAF mutation (69.4%) followed by physician's preference and remission pressure (each: 13.9%) (**Figure 4**).
- At this interim analysis, 23 patients (57.5%) were still under E+C treatment. For 6 pts (15%), treatment was stopped due to disease progression. For one patient each (2.5%), the reason for end of treatment was an adverse event, patient's decision, and the best benefit reached. Two pts (5.0%) each were lost to follow-up or died, respectively.
- Nearly all pts started encorafenib (91.7%) and cetuximab (80.6%) at the recommended dose. For 11.1% of patients an initial bi-weekly interval of cetuximab application was documented.

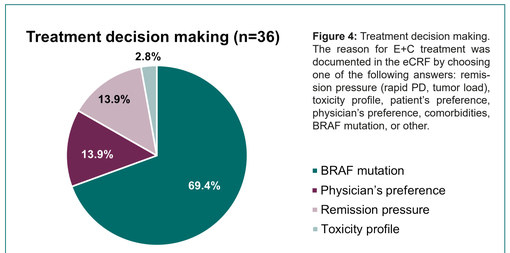

Figure 4: Treatment decision making. The reason for E+C treatment was documented in the eCRF by choosing one of the following answers: remission pressure (rapid PD, tumor load), toxicity profile, patient's preference, physician's preference, comorbidities, BRAF mutation, or other.

Conclusion

- Our real-world interim data reveal a study cohort, which was notably older, comprised more male patients, and had a higher ECOG performance status as compared to the BEACON CRC study population.[2]
- In most patients with BRAF^{V600E}-mutant mCRC, primary tumor was located on the right side of the colon, which is in line with prior publications
- Compared to the literature, synchronous metastasis was reported markedly more often and notably, one patient with a BRAF-mutated tumor in this initial real-word cohort presented with an overlapping RAS mutation.[1,4]
- Metastases were mainly located in the liver and peritoneum followed by the lung and distant lymph nodes.
- In most patients (88.0%) with mCRC at primary diagnosis, BRAF mutation status was determined at the time of diagnosis as recommended in guidelines.[1,5]

References

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Limitations

Considering the exploratory nature of this early interim analysis, with a limited number of patients and a short observational period, these results are considered preliminary and should be interpreted with caution.

Updated results regarding baseline characteristics and efficacy analyses including the 12-months OS rate will be reported after inclusion of the 80th and the 100th patient, respectively.

Conflicts of Interest:

Prager, G: Prager, G: Consulting and expert activities: Pierre Fabre, Servier, Bayer, Roche, Amgen, Sanofi, Lilly, Halozyme, BMS, MSD, Incyte; Honoraria: Pierre Fabre, Merck Serono, BMS, Roche, Amgen, Sanofi, Lilly, Servier, Taiho, Bayer, Halozyme, MSD, Celgene, Incyte; Funding of scientific research: Pierre Fabre, Merck, Incyte, Amgen, BMS, Roche.