UPDATED INTERIM RESULTS OF THE NON-INTERVENTIONAL STUDY VALIDATE

EVALUATION OF THE METASTATIC COLORECTAL CANCER SCORE (MCCS) IN PREDICTING OUTCOME FOR PATIENTS WITH RAS WILD-TYPE METASTATIC COLORECTAL CANCER TREATED WITH FIRST-LINE PANITUMUMAB PLUS FOLFIRI/FOLFOX

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BACKGROUND

The modified metastatic colorectal cancer (mCRC) prognostic score (mCCS) is designed to predict overall survival (OS) of RAS wild-type (WT) mCRC patients at the start of first-line (1L) therapy. The mCCS is based on 5 tumor characteristics that have been identified as independent negative prognostic factors for survival: tumor stage, tumor grading, lymph node ratio, primary tumor resection status, and number of metastatic sites at start of 1L therapy[1]. Patients are assigned into three prognostic risk groups with inferior prognosis for OS from low- to intermediate- and high-risk defined by the number of risk factors as shown in **Table 1**.

METHODS

Study design and participants

VALIDATE (NCT03043950) is a prospective, multicenter, real-world, non-interventional study to validate the mCCS in a large cohort of patients with RAS-WT mCRC and to evaluate real-world effectiveness, safety and quality of life in patients receiving 1L panitumumab in combination with FOLFIRI or FOLFOX according to SmPC in Germany and Austria. Patients were assigned into the three mCCS risk groups based on negative prognostic factors.

INTERIM ANALYSIS

This pre-planned second interim analysis (IA2) was performed 24 months after the last patient was enrolled. Patient characteristics and effectiveness were analyzed in patients who received at least one dose of panitumumab and were treated in-label (i.e., full analysis set), overall and for each of the three risk groups individually. Effectiveness variables were overall response rate (ORR), primary and secondary resection rates, progression-free survival (PFS) and 24-month OS rate. Safety was evaluated in patients who received at least one dose of panitumumab and had at least one post-baseline visit. Data were analyzed descriptively.

RESULTS

From January 2017 to June 2021, 621 patients were enrolled from 108 German and 5 Austrian sites and 611 patients were evaluated in this second interim analysis (cut-off date: November 17, 2022). Patient characteristics are depicted in **Table 2**. In total, 202 patients were assigned to the low-risk group, 198 patients to the intermediate-risk group and 211 patients to the high-risk group. The number of patients with ECOG performance status 0 or 1 was lower in the high-risk as compared to the low-risk, and intermediate-risk groups (78.7% vs. 84.2% and 87.4%, respectively). There were fewer colon tumors in the low-risk group compared to the intermediate- and high-risk groups (55.0% vs. 62.1% and 61.1%). More patients in the high-risk group (17.5%) had a right-sided tumor compared to patients in the low- (14.9%) and intermediate-risk (12.1%) groups. Other baseline patient characteristics such as age, sex, and histology were well balanced among the three risk groups **(Table 2)**. As expected, patients in the low- to intermediate- and high-risk group each had an increasing number of negative mCCS prognostic factors **(Figure 1)**.

Response under treatment with panitumumab and FOLFIRI/FOLFOX in terms of best response, ORR, PFS and 24-months OS rate are shown in **Table 3**. In the total population, the median PFS was 9.9 months (95% CI: 9.4-10.7 months) **(Figure 2)**. In the high-risk group, median PFS was shortest (9.0 months, 95% CI: 8.1-10.4 months) while a median PFS of 10.1 months (95% CI: 9.4-11.5 months) and 11.1 months (95% CI: 9.5-12.5 months) was reached in the low- and intermediate-risk groups, respectively. Yet, there was no clear separation between the three risk groups in the present analysis **(Figure 3)**. While the ORR was 62.4% in the total population, the ORR was lowest in the low-risk group (59.9%), followed by the high-risk group (62.6%), and highest in the intermediate-risk group (64.6%) **(Table 3)**. The 24-month OS rate was 54.2% (95% CI: 50.5%-58.3%) in the total population and lowest in the high-risk group (42.3%, 95% CI: 35.3-49.0%) **(Table 3)**. In the total population, 18.8% of patients underwent secondary metastasis resection following 1L panitumumab in combination with FOLFIRI or FOLFOX. As expected, the rate of secondary resection was lowest in the high-risk group (11.8%), followed by the low- (21.3%) and intermediate-risk groups (23.7%). Among patients with liver- (n=245) or lung- (n=51) limited disease, liver or lung metastases were resected in 29.0% and 5.9% of patients, respectively **(Table 4)**.

Safety results are shown in **Table 5**. Overall, the frequencies of reported treatment-emergent adverse drug reactions (TEADRs) in this study were lower as anticipated from the known safety profile of panitumumab. Especially the remarkably low rate of observed skin toxicity might be an indicator that current guidelines for prevention and management of dermatological toxicities have been translated well into routine clinical practice[2].

CONCLUSIONS

The VALIDATE IA2 showed favorable effectiveness of 1L panitumumab in combination with FOLFIRI or FOLFOX in patients with RAS-WT mCRC in routine clinical practice in Germany and Austria, irrespective of mCCS risk groups. The median PFS and ORR were similar to the results in RAS-WT patients of the pivotal PRIME trial[4] although real-world patients of the non-interventional study VALIDATE were older and in a worse general condition. Interestingly, the mCCS intermediate- and high-risk groups showed a better initial response than the low-risk group. This might be due to the higher proliferation rate and thus, the initially better response to study treatment. Almost 30% of patients with liver-limited disease underwent secondary resection. This is in line with current literature which reports approximately 22-40% of patients to become resectable after systemic therapy.[3] mCCS prediction of OS will be validated in the final analysis. No new safety signals emerged.

Table 2: Patient characteristics

	Total (N=611)	mCCS risk groups: Low-risk (N=202)	Intermediate-risk (N=198)	High-risk (N=211)
Age, years				
Median (min – max)	66.1 (32.0-87.0)	66.7 (32.3-87.0)	65.9 (32.0-84.9)	66.1 (36.8-85.8)
Sex, n (%)				
Female	190 (31.1%)	60 (29.7%)	61 (30.8%)	69 (32.7%)
Male	421 (68.9%)	142 (70.3%)	137 (69.2%)	142 (67.3%)
ECOG, n (%)				
0/1	509 (83.3%)	170 (84.2%)	173 (87.4%)	166 (78.7%)
≥2	36 (5.9%)	6 (3.0%)	8 (4.0%)	22 (10.4%)
Unknown	66 (10.8%)	26 (12.9%)	17 (8.6%)	23 (10.9%)
Tumor Location, n (%)				
Colon	363 (59.4%)	111 (55.0%)	123 (62.1%)	129 (61.1%)
Rectum	248 (40.6%)	91 (45.0%)	75 (37.9%)	82 (38.9%)
Tumor Sidedness, n (%)				
Left-sided	515 (84.3%)	169 (83.7%)	174 (87.9%)	172 (81.5%)
Right-sided	91 (14.9%)	30 (14.9%)	24 (12.1%)	37 (17.5%)
Colon unspecified	5 (0.8%)	3 (1.5%)	0 (0.0%)	2 (0.9%)
Histology, n (%)				
Adenocarcinoma	604 (98.9%)	198 (98.0%)	197 (99.5%)	209 (99.1%)
Other	7 (1.1%)	4 (2.0%)	1 (0.5%)	2 (0.9%)
Chemotherapy backbone, n (%)				
FOLFOX	192 (31.4%)	67 (33.2%)	56 (28.3%)	69 (32.7%)
FOLFIRI	419 (68.6%)	135 (66.8%)	142 (71.7%)	142 (67.3%)

Table 3: Response under treatment with panitumumab and FOLFIRI/FOLFOX

	Total (N=611)	mCCS risk groups: Low-risk (N=202)	Intermediate-risk (N=198)	High-risk (N=211)
Best overall response, n (%)				
Complete response	35 (5.7%)	13 (6.4%)	15 (7.6%)	7 (3.3%)
Partial response	346 (56.6%)	108 (53.5%)	113 (57.1%)	125 (59.2%)
Stable disease	107 (17.5%)	42 (20.8%)	33 (16.7%)	32 (15.2%)
Progressive disease	62 (10.1%)	19 (9.4%)	21 (10.6%)	22 (10.4%)
Not evaluable	6 (1.0%)	3 (1.5%)	0 (0.0%)	3 (1.4%)
Missing	55 (9.0%)	17 (8.4%)	16 (8.1%)	22 (10.4%)
Overall response rate, n (%)				
ORR	381 (62.4%)	121 (59.9%)	128 (64.6%)	132 (62.6%)
Progression-free survival				
Median PFS, months [95%-CI]	9.9 [9.4, 10.7]	10.1 [9.4, 11.5]	11.1 [9.5, 12.5]	9.0 [8.1, 10.4]
12-month PFS rate, % [95%-CI]	39.0% [34.9, 43.1]	40.1% [32.7, 47.3]	43.9% [36.4, 51.1]	33.5% [26.8, 40.2]
Overall survival				
24-month OS rate, % [95%-CI]	54.2% [50.0, 58.3]	60.0% [52.4, 66.8]	61.3% [53.8, 67.9]	42.3% [35.3, 49.0]

Table 1: Modified five-factor mCCS[1]

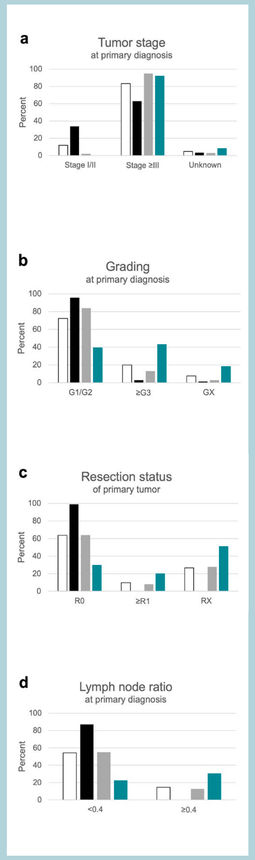
Risk factor		Low- risk	Intermediate-risk	High-risk
Tumor stage ≥III or unknown	Primary diagnosis	0-1 risk factors	2 risk factors	3-5 risk factors
Tumor grading ≥G3 or GX				
Lymph node ratio ≥0.4				
Resection status ≥R1 or RX	Primary tumor			
Number of metastatic sites ≥2	At start of 1L therapy			

Table 4: Secondary resections

Any metastases	Total (N=611)	Low -risk (N=202)	Intermediate-risk (N=198)	High-risk (N=211)
Patients with any secondary resections, n (%)	115 (18.8%)	43 (21.3%)	47 (23.7%)	25 (11.8%)
R0 resections, (%)	74 (12.1%)	33 (16.3%)	28 (14.1%)	13 (6.2%)
Liver-limited disease	Total (N=245)	Low-risk (N=121)	Intermediate-risk (N=91)	High-risk (N=33)
Patients with secondary resection of liver metastases, n (%)	71 (29.0%)	38 (31.4%)	25 (27.5%)	8 (24.2%)
R0 resections, n (%)	50 (20.4%)	30 (24.8%)	16 (17.6%)	4 (12.1%)
Lung-limited disease	Total (N=51)	Low-risk (N=35)	Intermediate-risk (N=12)	High-risk (N=4)
Patients with secondary resection of lung metastases, n (%)	3 (5.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)
R0 resections, n (%)	2 (3.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)
Liver- and lung-limited disease	Total (N=84)	Low-risk (N=11)	Intermediate-risk (N=31)	High-risk (N=42)
Patients with secondary resection of liver and lung metastases, n (%)	10 (11.9%)	0 (0.0%)	7 (22.6%)	3 (7.1%)
R0 resections, n (%)	3 (3.6%)	0 (0.0%)	2 (6.5%)	1 (2.4%)

Table 5: Summary of treatment-emergent adverse drug reaction (TEADR).

	Patients (N = 616)
TEADR, n (%)	425 (69.0%)
Serious TEADR, n (%)	50 (8.1%)
Non-serious TEADR, n (%)	410 (66.6%)
Grade 3/4 TEADR, n (%)	165 (26.8%)
TEADR leading to discontinuation of study treatment, n (%)	70 (11.4%)
Fatal TEADR, n (%)	1 (0.2%)
Most common grade 3/4 TEADRs (MedDRA v20.0)	
Acneiform dermatitis, n (%)	36 (5.8%)
Rash, n (%)	18 (2.9%)
Diarrhea, n (%)	20 (3.2%)



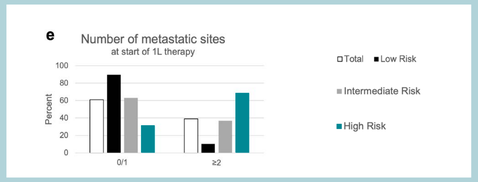


Figure 2: Progression-free survival

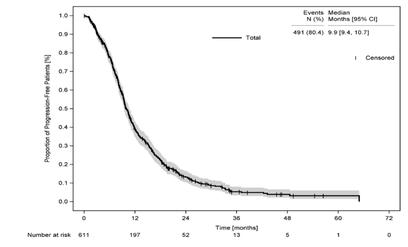
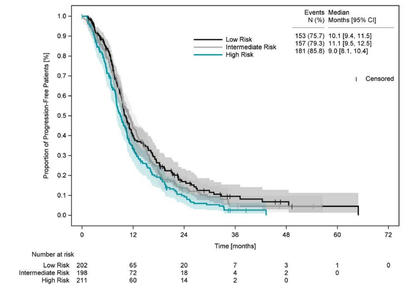


Figure 3: Progression-free survival by risk groups



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Conflicts of interest:
M. Reiser: No conflicts of interest.

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