FINAL RESULTS OF THE NON-INTERVENTIONAL STUDY VALIDATE

PROSPECTIVE VALIDATION OF THE METASTATIC COLON CANCER SCORE (MCCS) IN 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 prognostic score (mCCS) has been developed to predict the overall survival (OS) of patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC) at the start of first-line (1L) therapy. This scoring system stratifies patients into three prognostic risk groups with varying OS prognoses, ranging from low to intermediate and high risk, based on the number of identified risk factors. The risk factors integrate five 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 the number of metastatic sites at the initiation of 1L therapy **(Table 1)**[1].

CONCLUSION

The VALIDATE study investigated 1L treatment with panitumumab in combination with FOLFIRI or FOLFOX among patients with RAS WT mCRC in routine clinical practice in Germany and Austria. Compared to the pivotal PRIME trial[3], real-world patients in VALIDATE had a similar PFS and numerically higher OS and ORR, despite being of a higher age.

The prognostic value of the mCCS was prospectively validated by demonstrating a significantly shorter OS in patients in the high-risk group compared to those in the low-risk group. Therefore, the mCCS provides oncologists with a straightforward and readily applicable tool for routine clinical use, which may assist in identifying high-risk patients based on information available at the start of first-line therapy. The VALIDATE study thus offers a promising basis for future clinical trials evaluating the potential of risk-adapted treatment intensity and the mitigation of side effects.

METHODS

VALIDATE (NCT03043950) was a prospective, multicenter, non-interventional study observing patients with RAS WT mCRC who received 1L panitumumab in combination with FOLFIRI or FOLFOX according to SmPC in Germany and Austria. Real-world effectiveness such as overall response rate (ORR), secondary resection rates, progression-free survival (PFS) and overall survival (OS), safety and quality of life was analyzed descriptively in the total population and the three mCCS risk groups individually. The mCCS was validated by comparing OS in the mCCS risk groups high- and low-risk with a two-sided log-rank test at a significance level of 5%.

RESULTS

A total of 646 patients were enrolled across 108 German and 5 Austrian sites between January 2017 and June 2021 and observed until November 2023. Of these, 611 patients were evaluated in the final analysis. A total of 200 patients were classified as low-risk, 201 as intermediate-risk, and 210 as high-risk according to mCCS risk group. Overall, 418 patients received FOLFIRI and 193 patients FOLFOX as chemotherapy backbone. The baseline characteristics, such as age, gender, and histological features were evenly distributed among the three risk and both treatment groups **(Table 2)**. Notably, the high-risk group had the lowest proportion of patients with ECOG 0/1 (n=166, 79.0% vs. n=169, 84.5% and n=175, 87.1%) and the highest incidence of right-sided tumors (n=36, 17.1% vs. n=30, 15.0% and n=24; 11.9%) compared to the low- and intermediate-risk groups.

The effectiveness of 1L treatment with panitumumab and FOLFIRI/FOLFOX in terms of best response, ORR rate, PFS and OS is displayed in **table 3**. The median OS of the total population was 27.0 months (95% confidence interval (CI): 24.8-29.2 months) **(Figure 1)**. The high-risk group exhibited the shortest median OS duration of 20.1 months (95% CI: 15.0-23.9 months), while the low-risk and intermediate-risk groups achieved a median OS of 29.1 months (95% CI: 25.9-32.1 months) and 32.1 months (95% CI: 27.1-36.3 months), respectively **(Figure 2)**. The two-sided log-rank test confirmed a significant difference (p-value <0.001) in OS between the high- and low-risk groups **(Table 4)**. The median PFS in the total population was 10.1 months (95% CI: 9.5-10.8 months) and demonstrated mild variability between the risk groups **(Figure 3)**. The high-risk group exhibited the shortest median PFS duration of 9.0 months (95% CI: 8.1-10.4 months), while the low-risk and intermediate-risk groups achieved median PFS durations of 10.5 months (95% CI: 9.6-11.7 months) and 10.9 months (95% CI: 9.4-12.2 months), respectively **(Figure 4)**. Despite the observed variations in median PFS, the confidence intervals overlap and a clear separation between the three risk groups was not evident. The effectiveness of 1L treatment with panitumumab in combination with chemotherapy was comparable between the FOLFOX and FOLFIRI treatment groups **(Table 3)**.

In the total population, 19.6% (n=120) of patients underwent secondary resection. As anticipated, the incidence of secondary resection was lowest among patients with high-risk (n=25, 11.9%), followed by the low-risk (n=46, 23.0%) and intermediate-risk groups (n=49, 24.4%). In patients with liver-limited disease (n=246), surgical resection of liver metastases was performed in 29.3% (n=72) of patients, which is in line with existing literature indicating that 22 – 40% of patients may become eligible for resection following systemic therapy **(Table 5)**[2].

It is important to note that no new safety concerns or signals emerged during the study period **(Table 6)**.

LIMITATIONS

- The non-interventional study design in routine clinical practice is constrained by inherent limitations. These include the potential bias in patient selection and AE-reporting, as well as the risk of missing data due to non-mandatory assessments.
- The mCCS was designed as user-friendly prognostic tool based on easily available clinical parameters from patients with mCRC who started 1L treatment between 2006 and 2017[1]. Prognostic markers that initially were not clinically relevant, such as BRAF and tumor sidedness, are not included as parameters. The incorporation of these parameters could potentially enhance the score's prognostic capabilities.

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 2: Patient characteristics

	Total (N=611)	mCCS risk groups			Treatment groups	
		Low (N=200)	Intermediate (N=201)	High (N=210)	FOLFOX (N=193)	FOLFIRI (N=418)
Age, years						
Median (min – max)	66.1 (32.0 – 87.0)	66.7 (32.3 – 87.0)	66.0 (32.0 – 84.9)	65.9 (36.8 – 85.8)	66.0 (37.8 – 85.8)	66.2 (32.0 – 87.0)
Sex, n (%)						
Female	190 (31.1%)	60 (30.0%)	62 (30.8%)	68 (32.4%)	62 (32.1%)	128 (30.6%)
Male	421 (68.9%)	140 (70.0%)	139 (69.2%)	142 (67.6%)	131 (67.9%)	290 (69.4%)
ECOG, n (%)						
0/1	510 (83.5%)	169 (84.5%)	175 (87.1%)	166 (79.0%)	156 (80.8%)	354 (84.7%)
≥2	35 (5.7%)	6 (3.0%)	8 (4.0%)	21 (10.0%)	8 (4.1%)	27 (6.5%)
Unknown	66 (10.8%)	25 (12.5%)	18 (9.0%)	23 (11.0%)	29 (15.0%)	37 (8.9%)
Tumor location, n (%)						
Colon	362 (59.2%)	109 (54.5%)	126 (62.7%)	127 (60.5%)	114 (59.1%)	248 (59.3%)
Rectum	249 (40.8%)	91 (45.5%)	75 (37.3%)	83 (39.5%)	79 (40.9%)	170 (40.7%)
Tumor location, n (%)						
Left-sided	516 (84.5%)	167 (83.5%)	177 (88.1%)	172 (81.9%)	162 (83.9%)	354 (84.7%)
Right-sided	90 (14.7%)	30 (15.0%)	24 (11.9%)	36 (17.1%)	27 (14.0%)	63 (15.1%)
Colon unspecified	5 (0.8%)	3 (1.5%)	0 (0.0%)	2 (1.0%)	4 (2.1%)	1 (0.2%)
Histology, n (%)						
Adenocarcinoma	604 (98.9%)	196 (98.0%)	200 (99.5%)	208 (99.0%)	190 (98.4%)	414 (99.0%)
Other	7 (1.1%)	4 (2.0%)	1 (0.5%)	2 (1.0%)	3 (1.6%)	4 (1.0%)
Chemotherapy backbone, n (%)						
FOLFOX	193 (31.6%)	66 (33.0%)	58 (28.9%)	69 (32.9%)	193 (100.0 %)	0 (0.0%)
FOLFIRI	418 (68.4%)	134 (67.0%)	143 (71.1%)	141 (67.1%)	0 (0.0%)	418 (100.0%)

Figure 1: Overall survival

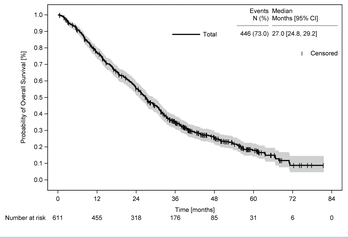

Figure 2: Overall survival by risk group

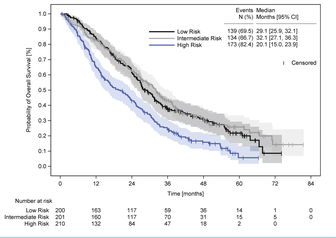

Figure 3: Progression-free survival

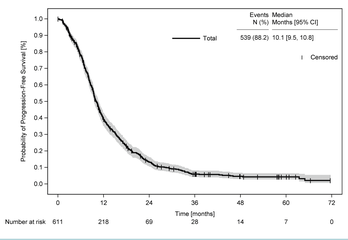

Figure 4: Progression-free survival by risk group

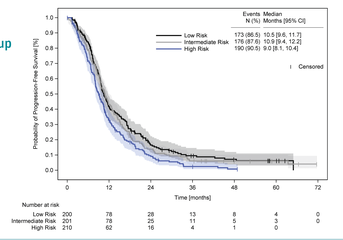

Table 3: Response under treatment with panitumumab and FOLFIRI/FOLFOX

	Total (N=611)	mCCS risk groups			Treatment groups	
		Low (N=200)	Intermediate (N=201)	High (N=210)	FOLFOX (N=193)	FOLFIRI (N=418)
Best overall response, n (%)						
Complete response	45 (7.4%)	16 (8.0%)	21 (10.4%)	8 (3.8%)	17 (8.8%)	28 (6.7%)
Partial response	358 (58.6%)	113 (56.5%)	116 (57.7%)	129 (61.4%)	112 (58.0%)	246 (58.9%)
Stable disease	94 (15.4%)	37 (18.5%)	28 (13.9%)	29 (13.8%)	35 (18.1%)	59 (14.1%)
Progressive disease	60 (9.8%)	18 (9.0%)	20 (10.0%)	22 (10.5%)	13 (6.7%)	47 (11.2%)
Not evaluable	2 (0.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.2%)
Missing	52 (8.5%)	15 (7.5%)	16 (8.0%)	21 (10.0%)	15 (7.8%)	37 (8.9%)
Overall response rate, n (%)						
ORR	403 (66.0%)	129 (64.5%)	137 (68.2%)	137 (65.2%)	129 (66.8%)	274 (65.6%)
Progression-free survival						
Median PFS, months [95% – CI]	10.1 [9.5, 10.8]	10.5 [9.6, 11.7]	10.9 [9.4, 12.2]	9.0 [8.1, 10.4]	9.9 [9.2, 10.8]	10.3 [9.4, 11.3]
12-month PFS rate, % [95% – CI]	39.1% [35.1, 43.1]	41.7% [34.6, 48.6]	43.2% [36.0, 50.1]	32.8% [26.4, 39.4]	34.8% [28.0, 41.7]	41.2% [36.3, 46.0]
Overall survival						
Median OS, months [95% – CI]	27.0 [24.8, 29.2]	29.1 [25.9, 32.1]	32.1 [27.1, 36.3]	20.1 [15.0, 23.9]	26.8 [22.1, 31.1]	27.0 [24.7, 30.0]
24-month OS rate, % [95% – CI]	55.5% [51.3, 59.4]	61.7% [54.5, 68.2]	62.3% [55.0, 68.7]	43.0% [36.1, 49.7]	54.1% [46.7, 60.9]	56.1% [51.1, 60.8]

Table 4: Testing of primary hypotheses

Two-sided log-rank test, p-value	
Overall survival: High-risk vs. low-risk	<0.001
Overall survival: Intermediate-risk vs. low-risk	0.495

Table 5: Secondary resections by mCCS risk group

Any metastases				
	Total (N=611)	**Low (N=200)**	**Intermediate (N=201)**	**High (N=210)**
Patients with any secondary resections, n (%)	120 (19.6%)	46 (23.0%)	49 (24.4%)	25 (11.9%)
R0 resections, n (%)	77 (12.6%)	35 (17.5%)	29 (14.4%)	13 (6.2%)
Liver-limited disease				
	Total (N=246)	**Low (N=119)**	**Intermediate (N=95)**	**High (N=32)**
Patients with secondary resection of liver metastases, n (%)	72 (29.3%)	39 (32.8%)	25 (26.3%)	8 (25.0%)
R0 resections, n (%)	49 (19.9%)	30 (25.2%)	15 (15.8%)	4 (12.5%)
Lung-limited disease				
	Total (N=51)	**Low (N=35)**	**Intermediate (N=12)**	**High (N=44)**
Patients with secondary resection of lung metastases, n (%)	4 (7.8%)	4 (11.4%)	0 (0.0%)	0 (0.0%)
R0 resections, n (%)	3 (5.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)

Table 6: Summary of treatment-emergent adverse drug reaction (TEADR)

	Patients (N = 617)
TEADR, n (%)	432 (70.0%)
Serious TEADR, n (%)	53 (8.6%)
Non-serious TEADR, n (%)	416 (67.4%)
Grade 3/4 TEADR, n (%)	170 (27.6%)
TEADR leading to discontinuation of study treatment, n (%)	100 (16.2%)
Fatal TEADR, n (%)	1 (0.2%)
Most common grade 3/4 TEADRs (MedDRA v26.0)	
Dermatitis acneiform, n (%)	37 (6.0%)
Diarrhea, n (%)	20 (3.2%)
Rash, n (%)	19 (3.1%)

References:

1. Marschner N, Frank M, Vach W, et al. Development and validation of a novel prognostic score to predict survival in patients with metastatic colorectal cancer: The metastatic colorectal cancer score (mCCS). Colorectal Dis Off J Assoc Coloproctology G B Irel. Published online March 4, 2019. doi:10.1111/codi.14650

2. Moehler M, Folprecht G, Heinemann V, et al. Survival after secondary liver resection in metastatic colorectal cancer: Comparing data of three prospective randomized European trials (LIVC , CELIM , FIRE-3). Int J Cancer. 2022;150(8):1341-1349. doi:10.1002/ijc.33881

3. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(7):1346-1355. doi:10.1093/annonc/mdu141

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Conflicts of Interest:
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