INTERIM RESULTS OF THE NON-INTERVENTIONAL STUDY VALIDATE

1ST-LINE PANITUMUMAB PLUS FOLFIRI OR FOLFOX FOR PATIENTS WITH RAS WILDTYPE METASTATIC COLORECTAL CANCER IN GERMANY

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BACKGROUND

The metastatic colorectal cancer prognostic score (mCCS) predicts overall survival of patients with metastatic colorectal cancer (mCRC) at start of 1st-line therapy[1]. The mCCS is based on five clinical routine parameters, i.e. tumor stage, tumor grading and lymph node ratio (affected lymph nodes / total number of resected lymph nodes) at primary diagnosis, primary tumor resectability and number of metastatic sites at start of 1st-line treatment. Based on the mCCS, patients were assigned to three prognostic risk groups with decreasing overall survival from low to intermediate and high risk group[1]. VALIDATE (NCT03043950) prospectively validates the mCCS in a large patient cohort with RAS wildtype mCRC.

METHODS

Study design and participants

In this prospective, multicenter, non-interventional study 606 patients with RAS wildtype mCRC without prior systemic therapy in the palliative setting will be enrolled in 112 sites in Germany and 10 sites in Austria. Patients receive panitumumab in combination with FOLFIRI or FOLFOX as 1st-line therapy according to the summary of product characteristics (SmPC).

The mCCS

The modified five-factor mCCS[1] for patients with RAS wildtype mCRC is based on five tumor characteristics that were identified as independent negative prognostic factors for survival. Low, intermediate and high risk groups are defined by the number of risk factors as shown in **Table 1**.

Interim analysis

This pre-planned interim analysis was performed 12 months after inclusion of the 250th patient. Based on the negative prognostic factors, patients were allocated to the three risk groups of the mCCS. Patient characteristics and effectiveness were analyzed in the full analysis set (patients having received at least on dose of panitumumab and who were treated in-label) in total and for each of the three risk groups. Effectiveness variables were overall response rate (ORR), secondary resection rate and progression-free survival (PFS) with 12-month PFS rate. Furthermore, safety was evaluated in the safety set (patients having received at least one dose of panitumumab and with at least one post-baseline information). Data were analyzed by descriptive analyses.

Table 1

		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				
Resectability ≥R1 or RX	Primary tumor			
Number of metastatic sites ≥2	At start of 1st-line therapy			

Table 1: Modified five-factor mCCS[1]

RESULTS

From January 2017 to December 2018 250 patients were recruited at 81 sites across Germany and analyzed in this interim analysis (cut-off date: January 14th, 2020). In the full analysis set (N=234 patients) the median age was 66.5 years, 73.5% of patients were male and 75.2% of patients had an ECOG performance status of 0 or 1. 62.0% of patients were diagnosed with a colon tumor, 82.9% of tumors were left-sided and 99.1% of tumors were adenocarcinomas. RAS was wildtype in 99.6% (0.4% RAS status missing). 83.8% of patients received FOLFIRI and 16.2% of patients received FOLFOX as 1st-line chemotherapy backbone (**Table 2**).

In the full analysis set 70 patients were assigned to the low mCCS risk group, 88 patients to the intermediate mCCS risk group and 76 patients to the high mCCS risk group. The median age was highest in the low risk group with 68.3 years, followed by the intermediate risk group with 66.5 years and lowest in the high risk group with 64.2 years. There were slightly more male patients in the low and intermediate risk group in comparison to the high risk group (75.7% and 75.0% vs. 69.7%). There were less colon tumors in the low risk group compared to the intermediate and high risk group (54.3% vs. 62.5% and 68.4%). The other baseline patient characteristics were well balanced between the 3 risk groups (**Table 2**).

As expected, there was an increase of the negative prognostic factors of the mCCS from low to intermediate and high risk group: Tumor stage ≥III was present in 52.9% of the low risk group and in 93.2% and 94.7% of the intermediate and high risk group. Tumor grading at primary diagnosis of ≥G3 increased from low to intermediate and high risk group (5.7% vs. 15.9% vs. 55.3%). Resections ≥R1 were lowest in the low risk group followed by the intermediate and high risk group (1.4% vs. 12.5% vs. 21.1%). In the low mCCS risk group, none of the patients had LNR ≥0.4, while in the intermediate and high risk group LNR was ≥0.4 in 12.5% and 30.3% of patients. Moreover, in the low, intermediate and high risk group the number of metastatic sites was ≥2 in 11.4%, 34.1% and 68.4% (**Figure 1**).

In the total population the ORR was 55.1%. Interestingly, the ORR was highest in the high risk group (61.8%) followed by the intermediate risk group (54.5%) and lowest in the low risk group (48.6%) (**Table 3**). Possibly, tumors of the high risk group are highly proliferative and therefore initially respond to the study treatment. However, an initial response does not necessarily have to be accompanied by longer PFS or OS.

In the total population the median PFS was 9.8 months (95% confidence interval (CI): 8.6-11.6 months) and the 12-month PFS-rate was 42.1% (95% CI: 35.0%-49.1%) (**Figure 2**). The median PFS was 9.5 months (7.2-11.6 months), 11.5 months (8.6-14.4 months) and 8.8 months (7.9-12.3 months) in the low, intermediate and high risk group. Moreover, the 12-month PFS-rates were 36.0% (23.6%-48.5%), 48.5% (36.3%-59.6%) and 40.7% (28.5%-52.5%) in the low, intermediate and high risk group (**Figure 3**).

16.2 % of patients of the total population underwent a secondary metastasis resection following FOLFIRI or FOLFOX plus panitumumab with 23 patients achieving RO status.. Of the patients with liver-limited (n=92) and lung-limited disease (n=17), liver and lung metastases were resected in 21.7% and 11.8% of patients, respectively. 3.6% of patients with liver and lung metastases only (n=28) underwent resection of liver and lung metastases (**Table 4**).

In the safety set 156 patients (67%) were reported with an adverse drug reaction (ADR) of any Common Terminology Criteria for Adverse Events (CTCAE) grade. Moreover, 27 patients (12%) were reported with a serious ADR and 68 patients (29%) with an ADR of CTCAE grade 3 or 4. In 18 patients (8%) an ADR led to discontinuation of study treatment. No fatal ADRs were reported. Most common ADRs (all CTCAE grades) are shown in **Figure 4**.

CONCLUSION

The VALIDATE interim analysis showed favourable effectiveness for panitumumab plus FOLFIRI or FOLFOX in the total population and in all mCCS risk groups in clinical routine in Germany. The secondary resection rate of about 16% was in line with recent study results[2]. No new safety signals emerged. mCCS predicting OS will be validated in the final analysis.

Table 2

	Total (N=234)	Low Risk (N=70)	Intermediate Risk (N=88)	High Risk (N=76)
Age (years)				
Median (min – max)	66.5 (36.8-87.0)	68.3 (39.2-87.0)	66.5 (40.2-83.9)	64.2 (36.8-81.7)
Gender				
Female	62 (26.5%)	17 (24.3%)	22 (25.0%)	23 (30.3%)
Male	172 (73.5%)	53 (75.7%)	66 (75.0%)	53 (69.7%)
ECOG				
0/1	176 (75.2%)	54 (77.1%)	66 (75.0%)	56 (73.7%)
≥2	17 (7.3%)	1 (1.4%)	5 (5.7%)	11 (14.5%)
Unknown	41 (17.5%)	15 (21.4%)	17 (19.3%)	9 (11.8%)
Tumor Location				
Colon	145 (62.0%)	38 (54.3%)	55 (62.5%)	52 (68.4%)
Rectum	89 (38.0%)	32 (45.7%)	33 (37.5%)	24 (31.6%)
Tumor Sidedness				
Left-sided	194 (82.9%)	58 (82.9%)	74 (84.1%)	62 (81.6%)
Right-sided	36 (15.4%)	11 (15.7%)	12 (13.6%)	13 (17.1%)
Colon unspecified	4 (1.7%)	1 (1.4%)	2 (2.3%)	1 (1.3%)
Histology				
Adenocarcinoma	232 (99.1%)	70 (100.0%)	86 (97.7%)	76 (100.0%)
Other	2 (0.9%)	0 (0.0%)	2 (2.3%)	0 (0.0%)
RAS status				
Wildtype	233 (99.6%)	70 (100.0%)	87 (98.9%)	76 (100.0%)
Mutation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.4%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
1st-line Chemotherapy				
FOLFIRI	196 (83.8%)	59 (84.3%)	71 (80.7%)	66 (86.8%)
FOLFOX	38 (16.2%)	11 (15.7%)	17 (19.3%)	10 (13.2%)

Table 2: Patient characteristics (full analysis set)

Table 3

	Total (N=234)	Low Risk (N=70)	Intermediate Risk (N=88)	High Risk (N=76)
Best Overall Response				
Complete response	18 (7.7%)	3 (4.3%)	10 (11.4%)	5 (6.6%)
Partial response	111 (47.4%)	31 (44.3%)	38 (43.2%)	42 (55.3%)
Stable disease	42 (17.9%)	15 (21.4%)	15 (17.0%)	12 (15.8%)
Progressive disease	27 (11.5%)	10 (14.3%)	9 (10.2%)	8 (10.5%)
Not evaluable	1 (0.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Missing	35 (15.0%)	10 (14.3%)	16 (18.2%)	9 (11.8%)
Overall Response Rate				
ORR	129 (55.1%)	34 (48.6%)	48 (54.5%)	47 (61.8%)

Table 3: Response (full analysis set)

Table 4

	Patients with secondary resections	Number of secondary resections	Resection status			
			RO	R1	R2	RX
Total population (n=234)	38 (16.2%)	43	23	2	2	16
Low Risk (N=70)	7 (10.0%)	8	5	0	0	3
Intermediate Risk (N=88)	21 (23.9%)	24	11	2	2	9
High Risk (N=76)	10 (13.2%)	11	7	0	0	4
Liver-limited disease (n=92)	20 (21.7%)	20	12	1	1	6
Lung-limited disease (n=17)	2 (11.8%)	2	1	0	0	1
Liver- and lung-limited disease (n=28)	1 (3.6%)	1	1	0	0	0

Table 4: Secondary resections (full analysis set)

Figure 1

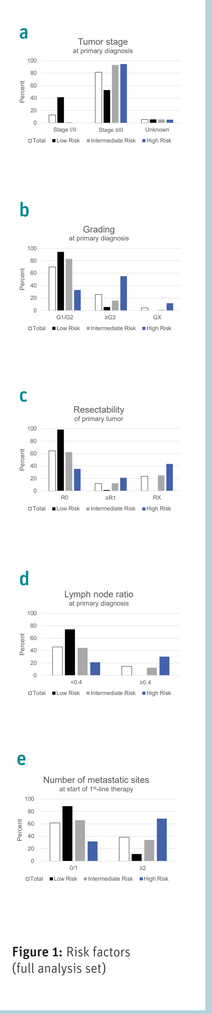
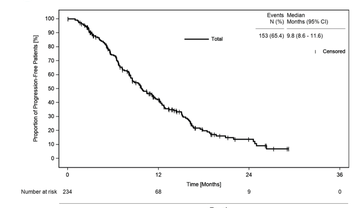


Figure 1: Risk factors (full analysis set)

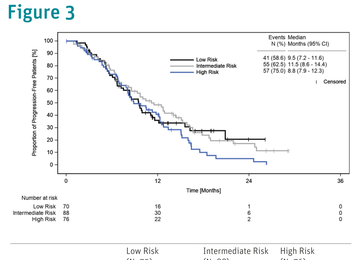
Figure 2



	Total (N=234)
12-month PFS rate [95%-CI]	42.1% [35.0, 49.1]

Figure 2: Progression-free survival (full analysis set)

Figure 3



	Low Risk (N=70)	Intermediate Risk (N=88)	High Risk (N=76)
12-month PFS rate [95%-CI]	36.0% [23.6, 48.5]	48.5% [36.3, 59.6]	40.7% [28.5, 52.5]

Figure 3: Progression-free survival by risk group (full analysis set)

Figure 4

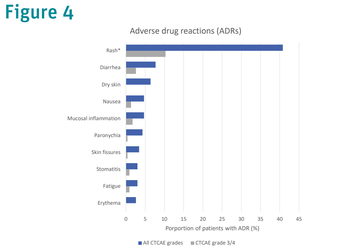


Figure 4: Most common adverse drug reactions ≥2.5% (patient based, safety set)

*Rash includes the MedDRA preferred terms: Dermatitis acneiform, Rash, Rash maculo-papular, Rash erythematous, Rash pustular, Rash generalized

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Conflicts of Interest:
A. Köhler: AMGEN GmbH: Advisory/Consultancy and Travel/Accommodation/Expenses

N. Marschner: AMGEN GmbH: Honorraria, Advisory/Consultancy and Travel/Accommodation/Expenses; iOMEDICO AG: Leadership Role

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