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Pembrolizumab (colorectal cancer with MSI-H or dMMR) –

Addendum to Commission A21-36[1]

Addendum

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Abbreviation	Meaning
AE	adverse event
dMMR	mismatch repair deficient
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-CR29	European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Colorectal 29
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PRO	patient-reported outcome
VAS	visual analogue scale

1 Background

On 10 August 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-36 (Pembrolizumab – Benefit assessment according to § 35a Social Code Book V) [1].

The KEYNOTE 177 randomized controlled trial (RCT) was included for the benefit assessment of pembrolizumab in patients with metastatic microsatellite instability - high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive therapy is appropriate (research question 1 of the benefit assessment).

In its dossier [2], the pharmaceutical company (hereinafter "company") presented responder analyses of time to deterioration for the patient-reported outcomes (PROs) on symptoms and health-related quality of life, surveyed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and EORTC QLQ Colorectal 29 (CR29), as well as on health status, surveyed with the visual analogue scale (VAS) of the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D). However, the results of the presented analyses were unusable because the treatment arms differed in survey time points within treatment cycles, leading to unequal representation of treatment burden (see dossier assessment A21-36 [1]). In its comment [3], the company presented further analyses (mixed models for repeated measurements, MMRM) for the PROs, but these analyses fail to remedy the problem of unequally represented treatment courses since the data of the corresponding survey time points are included in the calculations.

The dossier assessment additionally took into account the subgroup attribute of metastases (hepatic or pulmonary versus other metastases) [1]. In its dossier, however, the company presented subgroup analyses for this attribute only regarding the outcome of overall survival. As part of the commenting procedure, the company supplied the subgroup analyses for the outcomes of disease symptoms and health status, health-related quality of life, and for the total rates of adverse events (AEs).

The G-BA commissioned IQWiG with assessing the following additional data submitted by the company, taking into account the information provided in the dossier [2]:

- Time-to-event analyses (from the dossier) for the PROs EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D VAS
- Results for the subgroup of metastases for all relevant outcomes

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Time-to-event analyses for the PROs EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D VAS

For the PROs (surveyed with EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D), the company's dossier presented responder analyses on time to first deterioration. As supplementary information, the company also presented responder analyses on time to confirmed deterioration. A deterioration was deemed confirmed if it persisted for 2 consecutive measurements or if a deterioration was found at the last available survey time point.

Due to unequally represented treatment courses in the study arms and their potential influence on results, the PRO results do not supply any usable data. For details, see dossier assessment A21-36 [1].

Irrespective of the problem of unequally represented treatment courses, the results of the responder analyses on time to confirmed deterioration are unusable because of the differences in follow-up durations and the associated greater uncertainties. The outcomes on symptoms, health status, and health-related quality of life should be surveyed up to 30 days after treatment end. The median treatment duration was 5.7 months in the control arm and 11.1 months in the intervention arm. Hence, the treatment arms differ with regard to the potential follow-up surveys.

In accordance with the commission, this report presents the results of the responder analyses on time to first deterioration as supplementary information in Appendix A.

For EQ-5D VAS, it must be noted that the response thresholds used by the company (time to deterioration by ≥ 7 or ≥ 10 points; scale range 0100) do not fulfil the requirements for reflecting with sufficient certainty a change which is perceivable for patients [4,5]. The company did not submit any analyses on the response criterion of 15 points (corresponding to 15% of the scale range).

The return rates for the individual questionnaires are found in Appendix B.

2.2 Subgroup analyses for the attribute of metastases (hepatic or pulmonary versus other metastases)

For the attribute of metastases, the company's dossier presented subgroup analyses only for the outcome of overall survival [2]. No statistically significant interaction was found regarding this outcome. Likewise, the subgroup analyses subsequently submitted with the comment did not show any statistically significant interaction for the total rates of the side effects outcomes. In its comment, the company did not present any subgroup analyses for immune-mediated serious adverse events (SAEs) or for specific AEs with statistically significant difference.

For the PROs presented as per the commission, the subgroup analyses presented by the company showed isolated statistically significant interactions.

For both the EORTC QLQ-C30 symptom scale of nausea and vomiting and the EORTC QLQ-CR29 symptom scale of dysgeusia, a statistically significant interaction for the characteristic of metastases was found (interaction test $p = 0.024$ and $p = 0.004$, respectively). However, both subgroups exhibit statistically significant differences in favour of pembrolizumab. Therefore, these observed effect modifications are of lesser importance.

A statistically significant interaction was found for both health status, surveyed using the VAS of EQ-5D (time to first deterioration by ≥ 10 points), and the EORTC QLQ-C30 functioning scale of global health status. For each of them, there is a statistically significant difference in favour of pembrolizumab in the subgroup of "other metastases", but no statistically significant result for the subgroup of "metastases hepatic or pulmonary". The results for this subgroup analysis are presented as supplementary information in Appendix C.

2.3 Summary

The data presented in this addendum do not change the conclusion drawn in dossier assessment A21-36 on the added benefit of pembrolizumab.

Table 1 below shows the result of the benefit assessment of pembrolizumab in consideration of both dossier assessment A21-36 and the present addendum.

Table 1: Pembrolizumab – probability and extent of added benefit

Research question	**Indication**[a]	**ACT** [b]	**Probability and extent of added benefit**
1	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive therapy is appropriate; first line therapy	Individualized therapy depending on the AII-RAS mutation status, primary tumour location, and depending on the risk of bevacizumab-induced toxicity, selecting from ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and anti-EGFR therapy (cetuximab or panitumumab) – (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and anti-EGFR therapy (cetuximab or panitumumab) – (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab	Hint of considerable added benefit[c]
2	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive therapy is not appropriate; first line therapy	▪ 5-fluorouracil + folinic acid ± bevacizumab or ▪ capecitabine ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + (reduced-dose) oxaliplatin ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + (reduced-dose) irinotecan and bevacizumab	Added benefit not proven

a. For the present therapeutic indication, treatment with curative intent or primary resection is assumed not to be an option for patients with metastatic colorectal carcinoma.
b. Presented is the ACT specified by the G-BA.
c. Only patients with an ECOG-PS of 0 or 1 were included in the KEYNOTE 177 study. It remains unclear whether the observed effects can be assumed to occur also in patients with an ECOG-PS ≥ 2.

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; EGFR: Epidermal Growth Factor Receptor; FOLFIRI: folinic acid + 5-FU + irinotecan; FOLFOX: folinic acid + 5FU + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high; RAS: rat sarcoma viral oncogene homologue

The G-BA decides on the added benefit.

3 References

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Appendix A – Time-to-event analyses for the PROs EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D VAS

Table 2: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Outcome category Outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab / cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p value[c]
KEYNOTE 177					
Morbidity					
Symptoms (EORTC QLQ-C30, symptom scales)[d]					
Fatigue	141	2.1 [1.4; 3.0] 85 (60.3)	131	1.4 [0.7; 1.6] 97 (74.0)	0.62 [0.46; 0.83]; 0.001
Nausea and vomiting	141	NR [10.2; NC] 50 (35.5)	131	2.1 [1.4; 3.8] 82 (62.6)	0.37 [0.26, 0.54]; < 0.001
Pain	141	10.3 [4.2; NC] 60 (42.6)	131	3.3 [2.1; 8.1] 66 (50.4)	0.68 [0.48; 0.97]; 0.032
Dyspnoea	141	11.0 [8.3; NC] 53 (37.6)	131	6.2 [3.7; NC] 59 (45.0)	0.65 [0.45; 0.94]; 0.024
Insomnia	141	10.4 [6.2; NC] 56 (39.7)	131	10.3 [5.4; NC] 47 (35.9)	1.01 [0.69; 1.50]; 0.943
Appetite loss	141	10.8 [8.5; NC] 50 (35.5)	131	3.9 [2.0; 7.1] 66 (50.4)	0.49 [0.34, 0.71]; < 0.001
Constipation	141	11.1 [NC] 31 (22.0)	131	10.2 [5.1; NC] 49 (37.4)	0.46 [0.29, 0.73]; < 0.001
Diarrhoea	141	10.4 [8.3; NC] 56 (39.7)	131	2.7 [1.6; 5.3] 72 (55.0)	0.52 [0.36, 0.74]; < 0.001

Table 2: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Outcome category Outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab / cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p value[c]
Symptoms (EORTC QLQ-CR29, symptom scales)[d]					
Frequent urination	139	8.3 [4.2; NC] 63 (45.3)	132	3.9 [2.2; 10.6] 65 (49.2)	0.77 [0.55; 1.10]; 0.150
Blood and mucus in stool	139	NR 26 (18.7)	132	NR [9.0; NC] 36 (27.3)	0.56 [0.33; 0.93]; 0.024
Frequent bowel movements	139	8.5 [6.6; NC] 62 (44.6)	132	3.2 [2.4; 5.6] 76 (57.6)	0.59 [0.42; 0.82]; 0.002
Unintentional release of urine	139	NR [10.8; NC] 24 (17.3)	132	NR 22 (16.7)	0.86 [0.48; 1.55]; 0.619
Pain when urinating	139	NR 19 (13.7)	132	NR 20 (15.2)	0.80 [0.42; 1.50]; 0.482
Abdominal pain	139	NR 45 (32.4)	132	6.5 [4.8; 10.6] 55 (41.7)	0.67 [0.45; 0.99]; 0.045
Pain in the anal area	139	NR 33 (23.7)	132	5.1 [3.0; 9.9] 61 (46.2)	0.41 [0.27, 0.63]; < 0.001
Bloating	139	NR [10.4; NC] 46 (33.1)	132	10.6 [5.3; NC] 46 (34.8)	0.85 [0.56; 1.29]; 0.447
Dry mouth	139	8.2 [4.2; NC] 66 (47.5)	132	2.5 [1.4; 3.7] 78 (59.1)	0.61 [0.44; 0.85]; 0.003
Hair loss	139	NR [10.6; NC] 32 (23.0)	132	2.3 [1.9; 2.8] 86 (65.2)	0.22 [0.15, 0.34]; < 0.001
Dysgeusia	139	NR [10.6; NC] 40 (28.8)	132	1.9 [1.5; 2.5] 88 (66.7)	0.28 [0.19, 0.41]; < 0.001
Unintentional release of gas	139	9.2 [6.1; NC] 56 (40.3)	132	8.4 [3.3; NC] 57 (43.2)	0.79 [0.55; 1.15]; 0.219
Leakage of stools	139	10.8 [10.7; NC] 28 (20.1)	132	NR [9.9; NC] 31 (23.5)	0.75 [0.45; 1.25]; 0.272
Sore skin	139	NR [10.3; NC] 42 (30.2)	132	3.7 [2.8; 6.5] 65 (49.2)	0.41 [0.28, 0.61]; < 0.001
Problems caring for stoma				No usable data[e]	
Sexual symptoms in men[f]	64	NR [6.2; NC] 24 (37.5)	68	NR [8.5; NC] 22 (32.4)	1.00 [0.56; 1.78]; 0.995
Sexual symptoms in women [g]	67	NR [10.6; NC] 9 (13.4)	59	NR [10.3; NC] 8 (13.6)	0.71 [0.26; 1.92]; 0.502

Table 2: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Outcome category Outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab / cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p value[c]
Health status (EQ-5D VAS)[h]					
7 points	142	8.3 [3.1; NC] 61 (43.0)	133	2.9 [2.1; 4.4] 75 (56.4)	0.63 [0.45; 0.88]; 0.007
10 points	142	NR [6.6; NC] 54 (38.0)	133	3.6 [2.6; 6.2] 71 (53.4)	0.59 [0.42; 0.85]; 0.004
Health-related quality of life					
EORTC QLQ-C30 (functional scales and general health status scale)[i]					
Global health status	141	8.5 [4.2; NC] 64 (45.4)	131	2.9 [1.8; 4.2] 79 (60.3)	0.56 [0.40, 0.78]; < 0.001
Physical functioning	141	NR [8.5; NC] 51 (36.2)	131	3.3 [1.9; 4.8] 75 (57.3)	0.51 [0.35, 0.73]; < 0.001
Role functioning	141	6.6 [2.8; 10.6] 72 (51.1)	131	1.9 [1.4; 2.8] 87 (66.4)	0.54 [0.39, 0.74]; < 0.001
Emotional functioning	141	10.8 [10.8; NC] 39 (27.7)	131	10.6 [8.7; 11.3] 38 (29.0)	0.83 [0.53; 1.31]; 0.423
Cognitive functioning	141	8.3 [4.4; NC] 60 (42.6)	131	6.0 [3.0; 10.6] 59 (45.0)	0.77 [0.54; 1.11]; 0.164
Social functioning	141	10.6 [6.6; NC] 59 (41.8)	131	2.5 [1.5; 5.5] 74 (56.5)	0.53 [0.37, 0.74]; < 0.001
EORTC QLQ-CR29					
Embarrassment[d, j]	139	NR [10.8; NC] 33 (23.7)	132	NR [8.7; NC] 37 (28.0)	0.74 [0.46; 1.19]; 0.217
Body image[i]	139	6.2 [2.2; 8.3] 72 (51.8)	132	2.8 [1.6; 3.7] 78 (59.1)	0.69 [0.50; 0.95]; 0.022
Worries about health[i]	139	NR 42 (30.2)	132	NR 36 (27.3)	1.00 [0.64; 1.56]; 0.998
Worries about weight[i]	139	10.6 [8.5; 11.3] 52 (37.4)	132	8.5 [4.6; NC] 50 (37.9)	0.77 [0.52; 1.14]; 0.195
Interest in sex, men[i]	65	NR [6.2; NC] 24 (36.9)	68	NR [3.0; NC] 26 (38.2)	0.80 [0.46; 1.40]; 0.443
Interest in sex, women[i]	72	NR 6 (8.3)	63	NR 13 (20.6)	0.38 [0.14; 1.00]; 0.049

Table 2: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Outcome category Outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab / cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p value[c]

a. mFOLFOX or FOLFIRI
b. HR and CI: Cox proportional hazards model.
c. p-value: Wald test.
d. Time to first deterioration, defined as a score increase by at least 10 points over baseline.
e. The number of patients who had a stoma at study start is unclear. It is known that a stoma was present in 33 of the patients randomized to the intervention arm and 31 patients randomized into the control arm who received at least one dose of the study drug and for whom there is at least one data point for patient-reported outcomes.
f. A total of 71 men were randomized into the intervention arm and 82 men into the control arm.
g. A total of 82 women were randomized into the intervention arm and 72 women into the control arm.
h. Time to first deterioration, defined as a score decrease from baseline by at least 7 or 10 points.
i. Time to first deterioration, defined as a score decrease from baseline by at least 10 points.
j. In departure from the company's approach, this scale was assigned to the health-related quality of life category, rather than the symptoms category.

5-FU: 5-fluorouracil; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer 30; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Colorectal 29; FOLFIRI: folinic acid + 5-FU + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial

Appendix B – Return rates of the EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D VAS questionnaires

Table 3: Return rates for the instruments EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D VAS - RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Survey time point	Pembrolizumab N[b] = 153		Chemotherapy[a] ± bevacizumab / cetuximab N[b] = 154	
	Number of patients at the survey time point[c]	Percentage of patients with evaluable questionnaire n (%[d])	Number of patients at the survey time point[c]	Percentage of patients with evaluable questionnaire n (%[d])
KEYNOTE 177				
EORTC QLQ-C30				
Questionnaire before cycle 1 (baseline)	153	141 (92.2)	154	131 (85.1)
Week 2/3	149	132 (88.6)	154	125 (81.2)
Week 6	148	126 (85.1)	153	102 (66.7)
Week 9	147	119 (81.0)	152	58 (38.2)
Week 12	144	114 (79.2)	152	88 (57.9)
Week 18	143	102 (71.3)	150	82 (54.7)
Week 27	143	79 (55.2)	149	38 (25.5)
Week 36	143	80 (55.9)	149	35 (23.5)
Week 45	143	72 (50.3)	149	28 (18.8)
EORTC QLQ-CR29				
Questionnaire before cycle 1 (baseline)	153	131 (87.9)	154	132 (85.7)
Week 2/3	149	125 (84.5)	154	125 (81.2)
Week 6	148	119 (81.0)	153	100 (65.4)
Week 9	147	113 (78.5)	152	58 (38.2)
Week 12	144	102 (71.3)	152	88 (57.9)
Week 18	143	79 (55.2)	150	82 (54.7)
Week 27	143	80 (55.9)	149	38 (25.5)
Week 36	143	72 (50.3)	149	35 (23.5)
Week 45	143	131 (87.9)	149	27 (18.1)

Table 3: Return rates for the instruments EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D VAS - RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate) (multipage table)

Study Survey time point	Pembrolizumab N[b] = 153		Chemotherapy[a] ± bevacizumab / cetuximab N[b] = 154	
	Number of patients at the survey time point[c]	Percentage of patients with evaluable questionnaire n (%[d])	Number of patients at the survey time point[c]	Percentage of patients with evaluable questionnaire n (%[d])
EQ-5D VAS				
Questionnaire before cycle 1 (baseline)	153	142 (92.8)	154	133 (86.4)
Week 2/3	149	132 (88.6)	154	128 (83.1)
Week 6	148	126 (85.1)	153	102 (66.7)
Week 9	147	119 (81.0)	152	58 (38.2)
Week 12	144	114 (79.2)	152	89 (58.6)
Week 18	143	102 (71.3)	150	82 (54.7)
Week 27	143	79 (55.2)	149	39 (26.2)
Week 36	143	80 (55.9)	149	36 (24.2)
Week 45	143	72 (50.3)	149	28 (18.8)

a. mFOLFOX6 or FOLFIRI
b. Number of randomized patients.
c. Number of randomized patients minus patients for whom the company reported no data collection at the particular time point due to death (IQWiG calculation).
d. IQWiG calculations.

5-FU: 5-fluorouracil; n: number of patients with evaluable questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer 30; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Colorectal 29; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FOLFIRI: folinic acid + 5-FU + irinotecan; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); N: number of randomized patients; RCT: randomized controlled trial

Appendix C – Subgroup analyses for the characteristic of metastases (hepatic or pulmonary versus other metastases)

Table 4: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab vs. chemotherapy [a] ± bevacizumab or cetuximab (patients for whom intensive therapy is appropriate)

Study Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy[a] ± bevacizumab / cetuximab N	Chemotherapy[a] ± bevacizumab / cetuximab Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab HR [95% CI][b]	Pembrolizumab vs. chemotherapy[a] ± bevacizumab / cetuximab p-value[b]
KEYNOTE						
Morbidity						
EQ-5D VAS health status (10 points)[c]						
Metastases						
Hepatic or pulmonary	78	6.6 [2.8; NC] 34 (43.6)	62	4.4 [2.8; 11.3] 31 (50.0)	0.91 [0.56; 1.49]	0.708
Other metastases	64	NR [8.5; NC] 20 (31.3)	71	2.9 [1.8; 8.4] 40 (56.3)	0.38 [0.22; 0.66]	< 0.001
Total					Interaction:	0.017[d]
Health-related quality of life						
EORTC QLQ-C30 – functioning scales[e]						
Global health status						
Metastases						
Hepatic or pulmonary	78	6.3 [2.7; NC] 36 (46.2)	61	4.7 [2.1; 9.5] 32 (52.5)	0.80 [0.50; 1.29]	0.361
Other metastases	63	10.6 [2.8; NC] 28 (44.4)	70	1.8 [1.3; 2.9] 47 (67.1)	0.39 [0.24; 0.63]	< 0.001
Total					Interaction:	0.030[d]

a. mFOLFOX6 or FOLFIRI.
b. Cox proportional hazards model.
c. Time to first deterioration, defined as a score decrease from baseline by at least 10 points.
d. Interaction test: Cox proportional hazards model with corresponding interaction term.
e. Time to first deterioration, defined as a score increase from baseline by at least 10 points.

5-FU: 5-fluorouracil; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer 30; EQ-5D: European Quality of Life–5 Dimensions; FOLFIRI: folinic acid + 5-FU + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached ; RCT: randomized controlled trial; VAS: visual analogue scale