Nivolumab (colorectal cancer with dMMR or MSI-H, first line, combination with ipilimumab)

Addendum to Project A25-80 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma-isoform B
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
dMMR	mismatch repair deficiency
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
FOLFIRI	folinic acid + 5-FU + irinotecan
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IHC	immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
mFOLFOX6	folinic acid + 5-FU + oxaliplatin (modified regimen)
MSI-H	high microsatellite instability
NGS	next generation sequencing
NRAS	neuroblastoma rat sarcoma viral oncogene homologue
PCR	polymerase chain reaction
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Cancer 30
QLQ-CR29	Quality of Life Questionnaire-Colorectal 29
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	randomized controlled trial
SAE	serious adverse event

Abbreviation	Meaning
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
VAS	visual analogue scale

1 Background

On 28 October 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-80 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

Consistent with the findings of the company, no suitable data were available for the assessment of the added benefit of nivolumab + ipilimumab versus the appropriate comparator therapy (ACT), pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) [1].

In the commenting procedure, the company presented an adjusted indirect comparison of nivolumab + ipilimumab with pembrolizumab using chemotherapy as the common comparator [2]. The G-BA commissioned IQWiG to conduct an assessment of the adjusted indirect comparison presented, taking into account the information contained in the dossier [3].

In contrast to dossier assessment A25-80, this addendum required the use of information from Module 5 of the dossier in addition to the information in Modules 1 to 4 of the dossier. This concerned information on the methods and results of the company's CA209-8HW study. The relevant details were included in this addendum.

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

2 Assessment

This assessment addresses the following research question:

- Assessment of the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) compared with the ACT, pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H; see also dossier assessment A25-80 [1].

2.1 Presentation of an adjusted indirect comparison during the commenting procedure

In the dossier, the company presented the results of the pivotal RCT CA209-8HW. This study involves a direct comparison of nivolumab + ipilimumab with chemotherapy of physician's choice. As this study did not allow for a comparison versus the ACT pembrolizumab, in Module 4 Z the company presented the number of deaths per treatment arm and analyses of progression-free survival (PFS) as the best available evidence. The company also provided descriptive reports on the results relating to patient-reported outcomes and adverse events (AEs).

According to the company, it had not included an indirect comparison versus the ACT in Module Z because no analyses were available for the overall survival outcome in the data cut considered by the company (12 October 2023).

In its comments, the company presented an adjusted indirect comparison of nivolumab + ipilimumab versus pembrolizumab using the common comparator 'chemotherapy of physician's choice', based on the studies CA209-8HW and KEYNOTE 177, and used this to derive the added benefit. The data on the outcome overall survival presented for this comparison of nivolumab + ipilimumab were based on results of a recent interim analysis of the CA209-8HW study, with a data cut-off on 30 April 2025. According to the company's comments, this data had not yet been available at the time the dossier was submitted [2].

It is understandable that the data for the interim analysis, with a data cut-off on 30 April 2025, had not yet been sufficiently prepared when the dossier was submitted (15 June 2025). However, it should be noted that there was an additional prespecified data cut-off on 28 August 2024, which was between the data cut-off presented in the dossier (12 October 2023) and the current data cut-off provided in the comments (30 April 2025). According to the information in the study documents, this data cut was to be analysed in the same way as the 30 April 2025 data cut cited by the company in its comments (testing of the overall survival outcome, or at least an analysis of this outcome without testing).

It therefore remained unclear why analyses of overall survival were not available for the 28 August 2024 data cut and were not prepared in the dossier for an adjusted indirect comparison. A detailed explanation of the planned testing hierarchy and the changes during the course of the study can be found in Appendix A.

In compliance with the commission, the adjusted indirect comparison with the CA209-8HW data from the 30 April 2025 cut-off presented in the comments is assessed below.

2.2 Information retrieval and study pool

The study pool used for the assessment of the adjusted indirect comparison presented in the commenting procedure was compiled on the basis of the following information.

Sources used by the company in the comments:

- Bibliographical literature search on nivolumab + ipilimumab (last search on 8 September 2025)
- Search of trial registries for studies on nivolumab + ipilimumab (last search on 8 September 2025)
- Bibliographical literature search on the ACT (last search on 8 September 2025)
- Search of trial registries for studies on the ACT (last search on 8 September 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on nivolumab + ipilimumab (last search on 14 October 2025); for search strategies, see Appendix B
- Search of trial registries for studies on the ACT (last search on 14 October 2025); for search strategies, see Appendix B

In its comments, the company presented an adjusted indirect comparison according to Bucher [4] for the assessment of nivolumab + ipilimumab in comparison with the ACT, pembrolizumab as monotherapy, using chemotherapy of physician's choice as the common comparator. For the adjusted indirect comparison, the company identified the CA209-8HW study on the side of the intervention and the KEYNOTE 177 study on the side of pembrolizumab.

It should be noted that the company did not provide an updated list of studies for the information retrieval on which its comments were based. The company also did not conduct any searches in trial results databases; there is no information regarding the search on the G-BA website. Furthermore, it remained unclear whether the study selection was carried out by 2 people independently of each other. The review of the completeness of the study pool

identified no additional relevant studies for the indirect comparison of nivolumab + ipilimumab versus pembrolizumab, however.

2.2.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 1: Study pool – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
nivolumab + ipilimumab vs. chemotherapy[d] ± bevacizumab or cetuximab						
CA209-8HW	Yes	Yes	No	Yes [5-7]	Yes [8,9]	Yes [10]
pembrolizumab vs. chemotherapy[d] ± bevacizumab or cetuximab						
KEYNOTE 177	No	No	Yes	No	Yes [11,12]	Yes [13-18]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. mFOLFOX6 or FOLFIRI.

5-FU: 5-fluorouracil; FOLFIRI: folinic acid + 5-FU + irinotecan; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); RCT: randomized controlled trial

The study pool was consistent with that selected by the company. The KEYNOTE 177 study was already presented and assessed for a previous benefit assessment of pembrolizumab [16,19].

Figure 1 is a schematic representation of the adjusted indirect comparison.

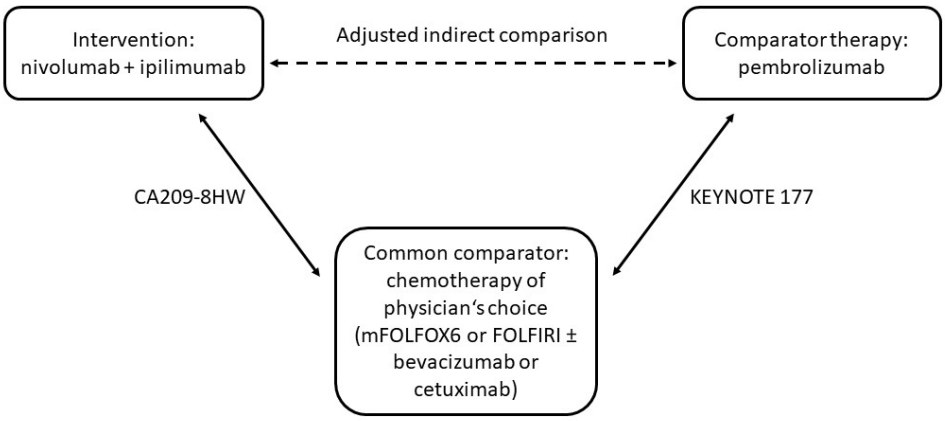

Figure 1 Study pool for the adjusted indirect comparison between nivolumab + ipilimumab and the ACT, pembrolizumab, via the common comparator 'chemotherapy of physician's choice' (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

2.2.2 Study characteristics

Table 2 and Table 3 describe the studies used for the benefit assessment.

Table 2: Characteristics of the studies included – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
nivolumab + ipilimumab vs. chemotherapy[b] ± bevacizumab or cetuximab						
CA209-8HW	RCT, open-label, parallel	Adults with metastatic or recurrent, unresectable colorectal cancer with dMMR or MSIH-, with or without prior treatment[c], ECOG PS 0 or 1	▪ nivolumab monotherapy: (N = 353)[d] ▪ nivolumab + ipilimumab (N = 354) ▪ chemotherapy[b] ± bevacizumab or cetuximab (N = 132) Relevant subpopulation thereof (in first line): ▪ nivolumab + ipilimumab (N = 202) ▪ chemotherapy[b] ± bevacizumab or cetuximab (N = 101)	Screening: ND Treatment: until disease progression[e], unacceptable toxicity, treatment discontinuation following the physician's or patient's decision, (nivolumab arms: maximum treatment duration of 2 years[f]) Observation[g]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	88 study centres in 22 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, Romania, Spain, Turkey, United Kingdom, United States 8/2019−ongoing Data cut-offs: 1st: 12 Oct 2023[h] 2nd: 28 Aug 2024[i] 3rd: 30 Apr 2025[j]	Primary: PFS (according to BICR) Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 2: Characteristics of the studies included – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
pembrolizumab vs. chemotherapy[b] ± bevacizumab or cetuximab						
KEYNOTE 177	RCT, open-label, parallel	Adults with metastatic colorectal cancer with MSI-H or dMMR in the first line[k], with ECOG PS 0 or 1	▪ pembrolizumab (N = 153) ▪ chemotherapy[b] ± bevacizumab or cetuximab (N = 154)	Screening: up to 42 days before start of treatment Treatment: until disease progression, unacceptable toxicity, occurrence of intercurrent diseases, treatment discontinuation following the physician's or patient's decision, (pembrolizumab: at most 24 months[l]) Observation[g]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	120 study centres in 23 countries: Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States 11/2015–7/2023[m] Data cut-offs: 1st: 19 Oct 2018[n] 2nd: 19 Feb 2020[o] 3rd: 19 Feb 2021[p] 4th: 17 Jul 2023[q]	Primary: overall survival, PFS (according to BICR) Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. mFOLFOX6 or FOLFIRI.
c. Recruitment took place in 2 consecutive phases: In part 1 of the study, patients were included regardless of their prior treatment (chemotherapy and/or targeted agents for metastatic disease). In part 2 of the study, only patients were included who had not previously received any treatment for metastatic disease. Prior adjuvant chemotherapy was allowed if disease progression occurred later than 6 months after completion of chemotherapy.
d. The arm is not relevant for this assessment and is no longer presented in the next tables.
e. Treatment beyond initial RECIST-defined progression was allowed provided the investigator found continued clinical benefit under certain conditions.

Table 2: Characteristics of the studies included – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
f. Patients with late response (during second year of treatment) were to continue treatment for up to an additional 12 months after onset of response, in the absence of disease progression and unacceptable toxicity. g. Outcome-specific information is provided in Table 4. h. Prespecified interim analysis of PFS for the comparison of nivolumab + ipilimumab vs. chemotherapy for all patients in first line (see Appendix A for details). i. Prespecified interim analysis of PFS for the comparison of nivolumab + ipilimumab vs. nivolumab for all patients in all treatment lines (see Appendix A for details) j. Prespecified final analysis of PFS for the comparison of nivolumab + ipilimumab vs. nivolumab for all patients in first line (see Appendix A for details). k. Patients had to be treatment-naive in the metastatic setting. Prior adjuvant chemotherapy completed at least 6 months prior to randomization was allowed. l. Patients who achieved complete response after at least 8 cycles of treatment with pembrolizumab were allowed to interrupt treatment after a further 2 cycles. Treatment could be continued for a further 17 cycles in the event of later confirmed disease progression. Patients who had tumour response after 24 months of treatment and did not receive any other subsequent therapy could also be treated with a further 17 cycles of pembrolizumab in the event of later confirmed disease progression. At the time of the 19 February 2020 data cut-off, 7 patients in the intervention arm were in the 2nd phase of treatment. No information on later data cut-offs is available. m. According to the study registry entry [11] the study was completed on 17 July 2023. n. Prespecified first interim analysis; this analysis was reviewed by an external data monitoring committee, which recommended to continue the study as planned. The company remained blinded for this data cut; relevant data are not available. o. Prespecified 2nd interim analysis after approx. 209 PFS events or an observation period of at least 24 months (for results, see [13,16]). p. Prespecified final analysis of overall survival after 190 deaths or 12 months after the 2nd interim analysis, whichever occurred first (for results, see [14]). q. Exploratory post-hoc analysis after > 5 years of follow-up (for results, see [15]). AE: adverse event; 5-FU: 5-fluorouracil; BICR: blinded independent central review; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-FU + irinotecan; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); MSI-H: high-frequency microsatellite instability; N: number of randomized patients; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours						

Table 3: Characteristics of the intervention – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
CA209-8HW	Weeks 1–12: nivolumab 240 mg IV, followed by ipilimumab 1 mg/kg BW IV as a 30-minute infusion every 3 weeks (4 doses in total) From Week 13: nivolumab 480 mg IV as a 30-minute infusion every 4 weeks	**Chemotherapy[b]:** <u>mFOLFOX6 every 2 weeks:</u> oxaliplatin 85 mg/m² BSA IV once folinic acid 400 mg/m² BSA IV once 5-FU 400 mg/m² BSA as single IV bolus, followed by 5-FU 2400 mg/m² BSA as continuous IV infusion over 46 hours or <u>FOLFIRI every 2 weeks:</u> irinotecan 180 mg/m² BSA IV once folinic acid 400 mg/m² BSA IV once 5-FU 400 mg/m² BSA as single IV bolus, followed by 5-FU 2400 mg/m² BSA as continuous IV infusion over 46 hours Each regimen (mFOLFOX6 or FOLFIRI) with or without the additional administration of <u>bevacizumab</u> 5 mg/kg BW IV once over 90 minutes; if well tolerated then over 60 minutes and then over 30 minutes every 2 weeks or <u>cetuximab</u> 500 mg/m² BSA once over 2 hours; if well tolerated then over 1 hour every 2 weeks
	Dose modifications: ▪ nivolumab and ipilimumab: dose modifications are not allowed; dose interruption / treatment discontinuation is allowed in case of immune-mediated or infusion-related AEs[c] ▪ mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab: dose modification/interruption or treatment discontinuation allowed in case of AEs[d]	
	Allowed prior treatment ▪ Adjuvant chemotherapy if disease progression occurred later than 6 months after completion of chemotherapy **Disallowed prior treatment** ▪ Systemic therapy for metastatic colorectal cancer (for the subpopulation of patients in first-line treatment) ▪ Other antineoplastic investigational products ≤ 4 weeks or 5 half-lives, whichever is longer, prior to randomization ▪ Systemic antineoplastic treatment ≤ 14 days ▪ Immune checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4) ▪ Focal palliative radiotherapy ≤ 2 weeks prior to randomization **Allowed concomitant treatment** ▪ Topical, ocular, intra-articular, intranasal and inhaled corticosteroids **Disallowed concomitant treatment** ▪ Immunosuppressants ▪ Immunosuppressant doses of systemic corticosteroids ▪ Any antineoplastic treatment	

Table 3: Characteristics of the intervention – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
KEYNOTE 177	pembrolizumab 200 mg IV as a 30-minute infusion every 3 weeks	**Chemotherapy[b]** mFOLFOX6 every 2 weeks: oxaliplatin 85 mg/m² BSA IV over 2 hours once folinic acid 400 mg/m² BSA[e] IV over 2 hours once 5-FU 400 mg/m² BSA as single IV bolus, followed by IV 5-FU 1200 mg/m² BSA/day on Days 1 and 2 (2400 mg/m² BSA over 46–48 hours) or FOLFIRI every 2 weeks: irinotecan 180 mg/m² BSA IV over 30–90 minutes once folinic acid 400 mg/m² BSA[e] IV over 30–90 minutes once 5-FU 400 mg/m² BSA as single IV bolus, followed by IV 5-FU 1200 mg/m² BSA/day on Days 1 and 2 (2400 mg/m² BSA over 46–48 hours) Each regimen (mFOLFOX6 or FOLFIRI) with or without the additional administration of bevacizumab 5 mg/kg BW IV over 30–90 minutes once every 2 weeks or cetuximab 400 mg/m² BSA IV once over 2 hours, then weekly 250 mg/m² BSA IV over 1 hour
	Dose modification: ▪ pembrolizumab: dose interruption/treatment discontinuation allowed in case of immune-mediated or infusion-related AEs[f] ▪ mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab: allowed in case of AEs[g]	
	Allowed prior treatment ▪ Adjuvant chemotherapy for the treatment of early-stage colorectal cancer, if this chemotherapy was completed at least 6 months before randomization **Disallowed prior treatment** ▪ Systemic therapy for metastatic colorectal cancer (stage IV) ▪ Other investigational treatments ≤ 4 weeks before randomization ▪ Systemic therapy for autoimmune disorders within 2 years before randomization ▪ Radiotherapy ≤ 4 weeks before randomization with existing side effects ▪ Immune checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 agent) **Allowed concomitant treatment** ▪ Any therapy that, at the investigator's discretion, is necessary for the patient's well-being (including palliative local therapy in consultation with the sponsor) **Disallowed concomitant treatment** ▪ Antineoplastic systemic chemotherapies or immunotherapies not predefined in the protocol ▪ Clinical investigational drugs other than pembrolizumab ▪ Glucocorticoids for purposes other than the regulation of symptoms of an event of clinical interest with suspected immunological aetiology	

Table 3: Characteristics of the intervention – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
a. mFOLFOX6 or FOLFIRI. b. Specified before randomization at the discretion of the investigator. c. Dose modifications were made in accordance with the protocol. d. Dose modifications were made in accordance with the protocol and local standards. e. or (L)-folinic acid 200 mg/m² BSA. f. Procedure in the event of immune-mediated AEs according to the recommendations in the protocol. g. Procedure in accordance with local standard. 5-FU: 5-fluorouracil; AE: adverse event; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; FOLFIRI: folinic acid + 5-FU + irinotecan; IV: intravenous; BSA: body surface area; BW: body weight; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial		

Study design

Study with nivolumab + ipilimumab: CA209-8HW

The CA209-8HW study is an ongoing open-label, 3-arm RCT comparing nivolumab, nivolumab + ipilimumab, and chemotherapy of physician's choice. The study included adult patients with metastatic or recurrent unresectable colorectal cancer with dMMR or MSI-H. The presence of MSI-H or dMMR was determined locally by polymerase chain reaction (PCR), immunohistochemistry (IHC) or next generation sequencing (NGS). The dMMR or MSI-H status for all patients was additionally confirmed by a central laboratory. Recruitment took place in 2 consecutive phases: In part 1, patients were included regardless of their prior treatment (chemotherapy and/or targeted agents for metastatic disease). In part 2, only patients were included who had not previously received any treatment for metastatic disease (first line). Prior adjuvant chemotherapy was allowed if disease progression occurred later than 6 months after completion of chemotherapy. Patients with active brain metastases and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of > 1 were excluded from the study.

A total of 839 patients were enrolled in the CA209-8HW study and were randomized in a 2:2:1 ratio to receive either nivolumab (N = 353) or nivolumab + ipilimumab (N = 354), or chemotherapy of physician's choice, with the option of folinic acid + 5-fluorouracil (5-FU) + oxaliplatin (modified regimen; mFOLFOX6) or folinic acid + 5-FU + irinotecan (FOLFIRI), each ± bevacizumab or cetuximab (N = 132). Assignment to the chemotherapy arm was restricted to patients who had previously received no systemic therapy or a maximum of one line of systemic therapy. Prior to randomization, the investigator determined which of the cited therapy options each patient should receive if assigned to the control arm.

Due to the given research question of nivolumab + ipilimumab as first-line treatment, the company used the results of the subpopulation of patients who received nivolumab +

ipilimumab compared with chemotherapy of physician's choice, each as first-line treatment, (N = 202 versus N = 101) for its adjusted indirect comparison.

The administration of nivolumab + ipilimumab in the intervention arm of the study concurred with the specifications set out in the summary of product characteristics (SmPC) [20,21]. During the first 12 weeks, patients received 240 mg nivolumab plus 1 mg/kg body weight ipilimumab every 3 weeks. From Week 13 onwards, they received 480 mg nivolumab monotherapy every 4 weeks. In the chemotherapy arm, patients received mFOLFOX6 or FOLFIRI, each ± bevacizumab or cetuximab, as chosen by the physician.

Treatment was continued until disease progression, unacceptable toxicity or treatment discontinuation following the physician's or patient's decision. Treatment with nivolumab was limited to a maximum treatment duration of 2 years. Treatment beyond initial Response Evaluation Criteria in Solid Tumours (RECIST)-defined progression was allowed provided the investigator found continued clinical benefit under certain conditions. If disease progression was confirmed, treatment with nivolumab + ipilimumab was permitted as subsequent therapy in the chemotherapy arm (referred to in the study as the 'crossover cohort') (see section on subsequent therapies).

The primary outcomes of CA209-8HW were PFS for the comparison of nivolumab + ipilimumab versus chemotherapy of physician's choice when administered as first-line treatment, and for the comparison of nivolumab + ipilimumab versus nivolumab when administered regardless of prior treatment for metastatic disease. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and AEs.

Study with pembrolizumab: KEYNOTE 177

The KEYNOTE 177 study was already described in the A21-36 benefit assessment procedure [16]; however, the company was not the sponsor of this study. The study is a completed open-label RCT comparing pembrolizumab with chemotherapy of physician's choice, selecting from mFOLFOX6 or FOLFIRI, each ± bevacizumab or cetuximab.

The study included adult patients with metastatic MSI-H or dMMR colorectal cancer. The presence of MSI-H or dMMR was determined locally by PCR or IHC. The patients were not allowed to have received prior systemic therapy for metastatic disease; any prior adjuvant chemotherapy for the treatment of an earlier stage of the colorectal cancer had to have been completed 6 months before the start of the study. The patients had to have a good general condition (ECOG PS ≤ 1) and adequate organ function. Patients with active brain metastases were excluded from participation in the study.

The KEYNOTE 177 study included a total of 307 patients, randomly allocated in a 1:1 ratio either to treatment with pembrolizumab (N = 153) or to chemotherapy, consisting of

mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab (N = 154). Prior to randomization, the investigator determined which of the cited therapy options each patient should receive if assigned to the control arm.

Treatment with pembrolizumab in the intervention arm was largely in compliance with the specifications of the SmPC [22]. In deviation from the SmPC [22], which recommends treatment until disease progression or unacceptable toxicity, treatment in KEYNOTE 177 was limited to a maximum duration of 35 cycles (approximately 2 years). However, the 2-year limit was in line with the recommendations in the current S3 guideline [23]. In the chemotherapy arm, patients received mFOLFOX6 or FOLFIRI, each ± bevacizumab or cetuximab, as chosen by the physician.

Overall, treatment in KEYNOTE 177 was continued until progression (determined using RECIST), unacceptable toxicity or intercurrent diseases that made further treatment impossible, or decision by the investigator or the patient. If disease progression was confirmed, treatment with pembrolizumab was permitted as subsequent therapy in the chemotherapy arm following a 30-day washout period (referred to in the study as the 'crossover phase') (see section on subsequent therapies).

Co-primary outcomes in the study were overall survival and PFS. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

Data cut-offs

CA209-8HW

Analyses on 3 data cuts were available for the CA209-8HW study:

- 1st data cut-off on 12 October 2023: prespecified interim analysis of PFS for the comparison of nivolumab + ipilimumab versus chemotherapy for all patients in first line
- 2nd data cut-off on 28 August 2024: prespecified interim analysis of PFS for the comparison of nivolumab + ipilimumab versus nivolumab for all patients in all lines of treatment
- 3rd data cut-off on 30 April 2025: prespecified final analysis of PFS for the comparison of nivolumab + ipilimumab versus nivolumab for all patients in first line

Data from the prespecified 3rd data cut-off provided by the company in its comments for the indirect comparison of nivolumab + ipilimumab versus pembrolizumab was taken into account for this assessment.

KEYNOTE 177

In the KEYNOTE 177 study, 4 data cut-offs were performed:

- 1st data cut-off on 19 October 2018: prespecified interim analysis 1 after approx. 162 PFS events and after an observation period of at least 6 months of all patients after randomization. No data were available for this data cut.
- 2nd data cut-off on 19 February 2020: prespecified interim analysis 2 after approx. 209 PFS events or an observation period of at least 24 months of all patients after randomization (for results, see benefit assessment A12-36 and the corresponding dossier [16,17]).
- 3rd data cut-off on 19 February 2021: prespecified final analysis for overall survival after 190 deaths or 12 months after interim analysis 2, whichever occurred first (for results, see the publication Diaz 2022 [14]).
- 4th data cut-off on 17 July 2023: exploratory post-hoc analysis after > 5 years of follow-up (for results, see publication Andre 2025 [15]).

The prespecified final analysis for overall survival was conducted for the data cut from 19 February 2021 [14]. An additional analysis was carried out for the data cut from 17 July 2023 [15]. Although the study register entry showed that the study was completed at this time [11], the analysis was described as an exploratory analysis (> 5-year follow-up) in the publication Andre 2025 [15]. There was also no sufficient information available to justify the time point as the end of the study. Therefore, this data cut-off was not considered prespecified [15].

For the overall survival outcome, the prespecified final analysis of overall survival dated 19 February 2021 was therefore used. Irrespective of this, the selection of the 3rd or 4th data cut of the KEYNOTE 177 study had no consequences for the assessment of overall survival in the adjusted indirect comparison, as the estimates in the indirect comparison differed only marginally.

It should be noted that, for the side effect outcomes, time-to-event analyses were only available for the 2nd data cut from the 19 February 2020 cut-off. However, compared with the 19 February 2020 data cut, only a few additional AEs appeared in the later data cuts. Based on the Kaplan-Meier curves for outcomes in the side effects category for the 19 February 2020 data cut, it was also assumed that the estimates for the later data cuts only changed marginally. For side effect outcomes, the 19 February 2020 data cut was therefore used.

Planned duration of follow-up

Table 4 shows the planned duration of follow-up of the patients in the studies CA209-8HW and KEYNOTE 177 for the individual outcomes.

Table 4: Planned duration of follow-up – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up**
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab	
CA209-8HW	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-CR29)	Up to 100 days after the last dose of the study medication[b]
Health status (EQ-5D VAS)	Until death, withdrawal of consent or end of study
Health-related quality of life	
EORTC-QLQ-C30 and EORTC-QLQ-CR29	Up to 100 days after the last dose of the study medication[b]
Side effects	
All outcomes in the side effects category	Up to 100 days after the last dose of the study medication[b, c]
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab	
KEYNOTE 177	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20), health status (EQ-5D VAS)	At most until Week 45 or until end of treatment, whichever is first, and 30 days after the last dose of the study medication
Health-related quality of life	
EORTC-QLQ-C30 and EORTC-QLQ-CR29	At most until Week 45 or until end of treatment, whichever is first, and 30 days after the last dose of the study medication
Side effects	
AEs/severe AEs[d]	Up to 30 days after the last dose of the study medication[e]
SAEs	Up to 90 days after the last dose of the study medication or 30 days in case of initiation of a subsequent therapy[e]

a. mFOLFOX6 or FOLFIRI.
b. For patients in the chemotherapy arm who received nivolumab + ipilimumab as subsequent therapy in the 'crossover cohort', follow-up continued until the last dose of nivolumab + ipilimumab (for the recording of AEs even beyond disease progression on nivolumab + ipilimumab).
c. AEs assessed by the investigator as related to the study treatment were recorded until death, withdrawal of consent or the end of the study.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. For patients in the chemotherapy arm who received pembrolizumab as subsequent therapy in the 'crossover phase', follow-up continued for up to 30 days after the last dose of pembrolizumab.

Table 4: Planned duration of follow-up – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up**
5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal 29; FOLFIRI: folinic acid + 5-FU + irinotecan; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened in both studies, with the exception of health status (recorded using the EQ-5D visual analogue scale [VAS]) in CA209-8HW.

In CA209-8HW, these outcomes were only recorded up to 100 days after the last dose of the study medication. In KEYNOTE 177, patient-reported outcomes on symptoms, health status and health-related quality of life were recorded only until Week 45 or until the end of treatment, whichever was first, as well as 30 days after the end of treatment. The outcomes on side effects were only recorded for the period of treatment with the study medication (plus 30 days or up to 90 days for serious adverse events [SAEs]) in KEYNOTE 177.

Only for the overall survival outcome in both studies, as well as the health status outcome recorded in CA2098HW, did recording continue until death, withdrawal of consent or the end of the study.

To draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to survey all outcomes over the total period in both studies, as was done for survival and for health status recorded in CA209-8HW.

Patient characteristics

Table 5 shows the characteristics of the patients in CA209-8HW and KEYNOTE 177.

Table 5: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study Characteristic Category	**nivolumab + ipilimumab vs. chemotherapy[a]**		**pembrolizumab vs. chemotherapy[a]**	
	CA209-8HW		**KEYNOTE 177**	
	nivolumab + ipilimumab	**Chemotherapy[a]**	**pembrolizumab**	**Chemotherapy[a]**
	N[b] = 202	**N[b] = 101**	**N[b] = 153**	**N[b] = 154**
Age [years], mean (SD)	61 (14)	62 (15)	62 (15)	61 (15)
Sex [F/M], %	53/47	55/45	54/46	47/53
Family origin, n (%)				
Asian	19 (9)	13 (13)	24 (16)	26 (17)
Black	2 (1)	2 (2)	9 (6)	5 (3)
White	176 (87)	85 (84)	113 (74)	116 (75)
Missing/other	5 (3)	1 (1)	7 (5)	7 (5)
Region, n (%)				
Asia	19 (9)	11 (11)	22 (14)	26 (17)
Western Europe[c] / North America	115 (57)	63 (62)	109 (71)	113 (73)
Rest of the world[d]	68 (34)	27 (27)	22 (14)	15 (10)
ECOG PS, n (%)				
0	111 (55)	52 (51)	75 (49)	84 (55)
1	91 (45)	49 (49)	78 (51)	70 (45)
dMMR, MSI-H status, n (%)				
Determined locally				
dMMR and/or MSI-H	200 (99)	101 (100)	153 (100)	153 (99)
dMMR	169 (84)	88 (87)	137 (90)[e]	137 (89)[e]
MSI-H	78 (39)	34 (34)	48 (31)[e]	56 (36)[e]
dMMR and MSI-H	ND	ND	32 (21[e])	40 (26[e])
Not determined locally	2 (1[e])	0 (0)	0 (0)	1 (< 1)
Centrally confirmed				
dMMR and/or MSI-H	171 (85)	84 (83)	-[f]	-[f]
dMMR	163 (81)	82 (81)	-[f]	-[f]
MSI-H	147 (73)	71 (70)	-[f]	-[f]
dMMR and MSI-H	ND	ND	-[f]	-[f]
Location of primary tumour, n (%)				
Right sided	139 (69)	68 (67)	102 (67)	107 (69)
Left sided	63 (31)	33 (33)	46 (30)	42 (27)
Both sided	0 (0)	0 (0)	4 (3)	5 (3)
Missing	0 (0)	0 (0)	1 (1)	0 (0)

Table 5: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study Characteristic / Category	nivolumab + ipilimumab vs. chemotherapy[a]		pembrolizumab vs. chemotherapy[a]	
	CA209-8HW		KEYNOTE 177	
	nivolumab + ipilimumab	Chemotherapy[a]	pembrolizumab	Chemotherapy[a]
	N[b] = 202	N[b] = 101	N[b] = 153	N[b] = 154
Metastases[g], n (%)				
Total	202 (100)	101 (100)	153 (100)	154 (100)
Liver or lung	100 (50)	55 (54)	86 (56)	73 (47)
Liver	75 (37)	42 (42)	71 (46)	54 (35)
Lungs	44 (22)	25 (25)	36 (24)	34 (22)
Peritoneal	84 (42)	42 (42)	ND	ND
Location not reported	3 (1)	1 (1)	ND	ND
Disease stage, n (%)				
Stage IV	202 (100)	101 (100)	153 (100)	154 (100)
Diagnosed stage, n (%)				
Initial diagnosis at stage IV in the course of disease	85 (42)	50 (49)	ND	ND
Newly diagnosed at baseline	ND	ND	73 (48)	80 (52)
Initial diagnosis at stage II–III in the course of disease	116 (57)	52 (51)	ND	ND
Recurrent at baseline	ND	ND	80 (52)	74 (48)
Stage not reported at the time of initial diagnosis	1 (< 1)	0 (0)	ND	ND
Mutation status (BRAF, KRAS, NRAS), n (%)[h]				
BRAF/KRAS and NRAS (all wild type)	49 (24)	25 (25)	34 (22)	35 (23)
KRAS or NRAS (± BRAF)	50 (25)	26 (26)	33 (22)	41 (27)
BRAF ± (KRAS or NRAS)				
BRAF V600E	ND	ND	34 (22)	43 (28)
Any BRAF mutation	60 (30)	27 (27)	ND	ND
(KRAS or NRAS) and BRAF				
BRAF V600E	ND	ND	0 (0)	3 (2)
Any BRAF mutation	7 (3)	2 (2)	ND	ND
Other				
Other[i] (including BRAF mutations other than V600E)	ND	ND	52 (34)	38 (25)
Unknown[j]	50 (25)	25 (25)	ND	ND

Table 5: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study Characteristic Category	**nivolumab + ipilimumab vs. chemotherapy[a]**		**pembrolizumab vs. chemotherapy[a]**	
	CA209-8HW		**KEYNOTE 177**	
	nivolumab + ipilimumab	**Chemotherapy[a]**	**pembrolizumab**	**Chemotherapy[a]**
	N[b] = 202	**N[b] = 101**	**N[b] = 153**	**N[b] = 154**
Lynch syndrome, n (%)				
Yes	22 (11)	17 (17)	28 (18)	36 (23)
No	135 (67)	49 (49)	114 (75)	104 (68)
Unknown/not reported	45 (22)[e]	35 (35)[e]	11 (7)	14 (9)
At least 1 prior line of systemic therapy, n (%)	67 (33)	32 (32)	38 (25)	45 (29)
Neoadjuvant	7 (3)	5 (5)	5 (3)	8 (5)
Adjuvant	60 (30)	27 (27)	36 (24)	42 (27)
Metastatic[k]	2 (1)	2 (2)	0 (0)	0 (0)
Prior lines of treatment for metastatic colorectal cancer according to CRF, n (%)				
0	190 (94)	91 (90)	ND	ND
1	10 (5)	8 (8)	ND	ND
≥ 2	1 (< 1)	1 (1)	ND	ND
Not reported	1 (< 1)	1 (1)	ND	ND
Disease duration: time from first diagnosis to randomization, n (%)				
< 1 year	117 (58)	64 (63)	ND	ND
1 to < 3 years	58 (29)	24 (24)	ND	ND
≥ 3 years	27 (13)	12 (12)	ND	ND
Not reported	0 (0)	1 (< 1)	ND	ND
Treatment discontinuation, n (%)	N = 200 99 (50)[l]	N = 88 88 (100)[l]	N = 153 94 (61)[m]	N = 143 141 (99)[m]
Study discontinuation, n (%)	N = 200 58 (29)[n]	N = 88 45 (51)[n]	ND[o]	ND[o]

a. mFOLFOX6 or FOLFIRI, each ± bevacizumab or cetuximab.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. In CA209-8HW, the 'Europe/North America' group was recorded for the region. For the comparison with KEYNOTE 177, the company subsequently allocated the countries Czech Republic and Romania from this group to the 'rest of the world' region.
d. CA209-8HW: Argentina, Australia, Brazil, Chile, Czech Republic, Romania, Turkey; KEYNOTE 177: Australia, Brazil, Israel, South Africa.
e. Institute's calculation.
f. In the KEYNOTE 177 study, no testing was carried out by a central laboratory to confirm dMMR/MSI-H.

Table 5: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Study Characteristic Category	nivolumab + ipilimumab vs. chemotherapy[a]		pembrolizumab vs. chemotherapy[a]	
	CA209-8HW		KEYNOTE 177	
	nivolumab + ipilimumab	Chemotherapy[a]	pembrolizumab	Chemotherapy[a]
	N[b] = 202	N[b] = 101	N[b] = 153	N[b] = 154

g. The data on metastases in the CA209-8HW study are based on an assessment by blinded and independent reviewers. No information on the type of assessment is available in the KEYNOTE 177 study.
h. KEYNOTE 177: small discrepancies between the information in Diaz 2022 [14] and the information in the dossier on pembrolizumab [17]. The information from the dossier and from benefit assessment A21-36 was used.
i. BRAF V600E, KRAS and NRAS mutated if at least one mutation status was not determined or is missing or the BRAF mutation was not of type V600E.
j. Patients whose BRAF, KRAS or NRAS mutation status could not be assessed or was missing.
k. 4 patients in the CA209-8HW study who had already received prior treatment for metastatic disease were incorrectly assigned to the group of patients without prior treatment for metastatic disease during randomization due to erroneous data in the interactive response technology.
l. Data on treatment discontinuation based on the data cut-off on 20 April 2025. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were the following (percentages refer to 200 vs. 88 patients who started treatment): disease progression 39 (20%) vs. 64 (73%) and toxicity related to the study medication 37 (19%) vs. 5 (6%). In addition, 2 (1%) vs. 13 (13%) of the randomized patients never started treatment. 101 (51%) vs. 0 (0) of the patients completed treatment as planned.
m. Data on treatment discontinuation based on the data cut-off on 19 February 2021. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were the following (percentages refer to 153 vs. 143 patients who started treatment, Institute's calculation): disease progression 50 (33%) vs. 85 (59%) and AEs 22 (14%) vs. 20 (14%). In addition, 0 (0%) vs. 11 (7%) of the randomized patients never started treatment. 59 (39%) vs. 0 (0%) of the patients completed treatment as planned. As of the data cut-off date of 19 February 2020, 94 (61%) patients in the intervention arm and 137 (96%) in the control arm had discontinued treatment.
n. Data on study discontinuations based on the data cut-off date of 20 April 2025. The figures include patients who died during the course of the study: intervention arm: 52 (26%) vs. control arm: 39 (44%).
o. No data on study discontinuation is available for the data cut-off date of 19 February 2021. As of the data cut-off date of 19 February 2020, 58 (38%) patients in the intervention arm and 75 (49%) in the control arm had discontinued from the study (the percentages refer to 153 vs. 154 of the randomized patients, respectively). The data include patients who died during the course of the study (intervention arm: 56 (37%) vs. control arm: 66 (43%).

5-FU: 5-fluorouracil; AE: adverse event; BRAF: rapidly accelerated fibrosarcoma-isoform B; CRF: case report form; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FOLFIRI: folinic acid + 5-FU + irinotecan; IRT: interactive response technology; KRAS: Kirsten rat sarcoma viral oncogene homologue; M: male; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); MSI-H: high microsatellite instability; NRAS: neuroblastoma rat sarcoma viral oncogene homologue; n: number of patients in the category; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; standard deviation

The patient characteristics in CA209-8HW were largely balanced between the study arms. The mean age of the patients was 61 and 62 years. The proportion of female patients (53% vs. 55%) and the proportion of patients of white family origin were similar in both study arms

(87% vs. 84%). 55% and 51% of the patients had an ECOG PS of 0. In nearly 70% of patients in both study arms, the primary tumour was located on the right side. While 24% versus 25% of patients had wild type regarding the rapidly accelerated fibrosarcoma-isoform B (BRAF) / Kirsten rat sarcoma viral oncogene homologue (KRAS) / neuroblastoma rat sarcoma viral oncogene homologue (NRAS) tumour mutation status, 25% of patients in the intervention arm and 26% of patients in the control arm had KRAS/NRAS mutations. A BRAF mutation was present in 30% of patients in the intervention arm and 27% of patients in the control arm.

The patient characteristics in KEYNOTE 177 were largely balanced between the study arms, pembrolizumab or chemotherapy ± bevacizumab or cetuximab. The mean age of the patients was 62 and 61 years. The proportion of female patients was similar in both arms (54% versus 47%). The proportion of patients with white family origin was similar in both study arms (74% vs. 75%). 49% and 55% of the patients had an ECOG PS of 0. In nearly 70% of patients, the primary tumour was located on the right side. While 22% versus 23% of patients had a wild type BRAF, KRAS and NRAS tumour mutation status, 22% of patients in the intervention arm and 27% of patients in the control arm had KRAS/NRAS mutations. A BRAF V600E mutation was present in 22% of patients in the intervention arm and 28% of patients in the control arm.

Information on the course of the study

Table 6 shows the mean and median treatment durations and observation periods of the patients in CA209-8HW and KEYNOTE 177 for individual outcomes.

Table 6: Information on the course of the study – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Duration of the study phase** **Outcome category/outcome**	**nivolumab + ipilimumab or pembrolizumab**	**Chemotherapy[a] ± bevacizumab or cetuximab**
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
CA209-8HW (data cut-off: 30 April 2025)	N = 202	N = 101
Treatment duration[b] [months]		
Median [min; max]	22.7 [0.0; 35.9]	4.0 [0.1; 32.8]
Mean (SD)	15.3 [ND]	5.7 [ND]
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	41.6 [26.3; 53.9]	29.5 [10.5; 46.8]
Mean (SD)	38.4 (18.9)	29.2 (20.0)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
KEYNOTE-177 (data cut-off: 19 February 2021)	N = 153	N = 154
Treatment duration[d] [months]		
Median [Q1; Q3]	11.1 [2.8; 23.8]	5.7 [2.7; 11.2]
Mean (SD)	13.3 (10.3)	8.3 (8.0)
Observation period [months]		
Overall survival[e]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (AEs / severe AEs[f]) (data cut-off: 19 February 2020)		
Median [Q1; Q3]	12.1 [ND]	6.6 [ND]
Mean (SD)	ND	ND
Side effects (SAEs) (data cut-off: 19 February 2020)		
Median [Q1; Q3]	14.1 [ND]	7.3 [ND]
Mean (SD)	ND	ND

Table 6: Information on the course of the study – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Duration of the study phase** **Outcome category/outcome**	**nivolumab + ipilimumab or pembrolizumab**	**Chemotherapy[a] ± bevacizumab or cetuximab**
a. mFOLFOX6 or FOLFIRI. b. Data are based on 200 patients in the intervention arm and 88 patients in the control arm. c. Time from randomization to the last patient contact or death. d. Data are based on 153 patients in the intervention arm and 143 patients in the control arm. e. For the data cut-off on 19 February 2021, the company stated that it had conducted its own calculation based on reconstructed individual patient data on overall survival (median observation period in months: 38.8 vs. 33.5); it remains unclear how these calculations were conducted. For the data cut-off date of 19 February 2020, the median observation periods were 27.9 vs. 25.9 months. f. Severe AEs are operationalized as CTCAE grade ≥ 3. 5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-FU + irinotecan; max: maximum; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); min: minimum; N: number of analysed patients; ND: no data; OS: overall survival; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation		

In the CA209-8HW study, the median treatment duration was 22.7 months in the intervention arm and 4.0 months in the control arm. The median observation period for the outcome overall survival was 41.6 months versus 29.5 months. No observation periods were available for the outcomes of morbidity, health-related quality of life and side effects. For these outcomes (with the exception of health status), the observation period can be estimated based on the data on median treatment duration, as follow-up was planned for 100 days after the last study medication (approx. 26 months versus 7 months).

In the KEYNOTE 177 study, the median treatment duration was 11.1 months in the pembrolizumab arm and 5.7 months in the control arm. No information on the observation period for the outcome overall survival was available for the 19 February 2021 data cut. As of the data cut-off date of 19 February 2020, the median observation period for overall survival was 27.9 months in the intervention arm versus 25.9 months in the control arm. No observation periods were available for the morbidity and health-related quality of life outcomes. At the data cut-off on 19 February 2020, the median observation period for AEs and severe AEs in the pembrolizumab arm compared to the control arm was 12.1 versus 6.6 months and for SAEs 14.1 vs. 7.3 months.

Subsequent therapies

Table 7 shows the subsequent antineoplastic therapies patients received in CA209-8HW and KEYNOTE 177 after discontinuing the study medication.

Table 7: Information on subsequent antineoplastic therapies – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Drug class or drug**	**Patients with subsequent therapy, n (%)**	
	nivolumab + ipilimumab or pembrolizumab	**Chemotherapy[a] ± bevacizumab or cetuximab**
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
CA209-8HW (data cut-off: 30 April 2025)[b, c]	N = 202	N = 101
Total	57 (28.2)	70 (69.3)
Radiotherapy	3 (1.5)	0 (0)
Surgical intervention	7 (3.5)	6 (5.9)
Systemic therapy	50 (24.8)	68 (67.3)
nivolumab + ipilimumab[d]	0 (0)	46 (45.5)
Other subsequent systemic therapy	50 (24.8)	22 (21.8)
CTLA-4 inhibitor	3 (1.5)	3 (3.0)
ipilimumab	3 (1.5)	3 (3.0)
PD-1 or PD-L1 inhibitor	17 (8.4)	21 (20.8)
pembrolizumab	11 (5.4)	15 (14.9)
nivolumab	6 (3.0)	5 (5.0)
tislelizumab	0 (0)	1 (1.0)
EGFR inhibitors	10 (5.0)	2 (2.0)
cetuximab	8 (4.0)	1 (1.0)
panitumumab	2 (1.0)	1 (1.0)
MEK, NRAS or BRAF inhibitor	2 (1.0)	1 (1.0)
encorafenib	2 (1.0)	1 (1.0)
Other systemic anticancer therapies	35 (17.3)	8 (7.9)
fluorouracil	27 (13.4)	5 (5.0)
irinotecan	18 (8.9)	5 (5.0)
capecitabine	5 (2.5)	1 (1.0)
irinotecan hydrochloride	1 (0.5)	1 (1.0)
tipiracil hydrochloride + trifluridine	2 (1.0)	0 (0)
Antineoplastic agents	1 (0.5)	0 (0)
pemetrexed	1 (0.5)	0 (0)
raltitrexed	1 (0.5)	0 (0)
tipiracil + trifluridine	1 (0.5)	0 (0)
Platinum compounds	23 (11.4)	3 (3.0)
oxaliplatin	21 (10.4)	3 (3.0)
carboplatin	1 (0.5)	0 (0)
fluorouracil + folinic acid + oxaliplatin	1 (0.5)	0 (0)

Table 7: Information on subsequent antineoplastic therapies – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison **Study** **Drug class or drug**	**Patients with subsequent therapy, n (%)**	
	nivolumab + ipilimumab or pembrolizumab	**Chemotherapy[a] ± bevacizumab or cetuximab**
VEGF/R inhibitor	18 (8.9)	5 (5.0)
bevacizumab	18 (8.9)	5 (5.0)
aflibercept	3 (1.5)	0 (0)
Other drugs	25 (12.4)	5 (5.0)
folinic acid	16 (7.9)	4 (4.0)
calcium folinate	5 (2.5)	0 (0)
dihydroquercetin	1 (0.5)	0 (0)
folinic acid	1 (0.5)	0 (0)
GAD20 209 FSP + MVA 209 FSP	1 (0.5)	0 (0)
Investigational product	0 (0)	1 (1.0)
moxifloxacin hydrochloride	1 (0.5)	0 (0)
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab		
KEYNOTE-177 (data cut-off: 19 February 2021)	N = 153	N = 154
Total[e]	ND	ND
anti-PD-1/anti-PD-L1 therapy	14 (9.2)	93 (60.4)
pembrolizumab according to protocol[f]	8 (5.2)	56 (36.4)
Off-protocol[g]	6 (3.9)	37 (24.0)
Other subsequent therapy	38 (24.8)	28 (18.2)
Chemotherapy	35 (22.9)	20 (13.0)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	9 (5.9)	5 (3.2)
Nucleoside analogue / thymidine phosphorylase inhibitor	2 (1.3)	2 (1.3)
CTLA-4 inhibitor	0 (0)	5 (3.2)
ICOS agonist	1 (0.7)	1 (0.6)
LAG-3 inhibitor	1 (0.7)	0 (0)
TIM3 inhibitor	1 (0.7)	1 (0.6)
Vaccine/viral therapy	0 (0)	2 (1.3)
BRAF inhibitor	0 (0)	1 (0.6)
CD-40 inhibitor	0 (0)	1 (0.6)

Table 7: Information on subsequent antineoplastic therapies – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Comparison Study Drug class or drug	Patients with subsequent therapy, n (%)	
	nivolumab + ipilimumab or pembrolizumab	Chemotherapy[a] ± bevacizumab or cetuximab
a. mFOLFOX6 or FOLFIRI. b. According to the CSR, for patients in the chemotherapy arm who received nivolumab + ipilimumab as subsequent therapy in the 'crossover cohort', further subsequent therapies from Day 1 of the nivolumab + ipilimumab administration were not taken into account. c. According to the information provided by the company in the comments, the only subsequent therapies taken into account were those administered after discontinuation of the study medication. In contrast, the CSR lists as subsequent therapy all treatments administered from the first dose of the study medication onwards. There are only marginal differences between the analysis presented in the CSR and the analysis shown here from the company's comments. The information from the company's comments is presented. d. Patients in the chemotherapy arm who received nivolumab + ipilimumab as subsequent therapy in the 'crossover cohort'. e. The data given in the running text of the publication Diaz 2022 [14] (intervention arm vs. control arm: 52 [34%] vs. 121 [79%]) are implausible, as the data for the comparator arm are higher than those reported at a later data cut-off. However, verifiable data is available for the data cuts of 19 February 2020: 44 (28.8%) vs. 100 (64.9%), and 17 July 2023: 54 (35.2%) vs. 105 (68.2%). f. Patients in the pembrolizumab arm who received a 2nd treatment phase with pembrolizumab, as well as patients in the chemotherapy arm who received pembrolizumab as subsequent therapy during the 'crossover phase'. g. The data are taken from the publication Diaz 2022 [14]; it is unclear whether they also include further subsequent therapies with pembrolizumab that did not take place during the 'crossover phase'. 5-FU: 5-fluorouracil; BRAF: rapidly accelerated fibrosarcoma-isoform B; CD: cluster of differentiation; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EGFR: epidermal growth factor receptor; EPAR: European Public Assessment Report; FOLFIRI: folinic acid + 5-FU + irinotecan; ICOS: inducible costimulator; LAG-3: lymphocyte-activation gene 3; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TIM: t-cell immunoglobulin mucin; VEGF: vascular endothelial growth factor		

In CA209-8HW, subsequent therapy was permitted for patients in both study arms. Overall, 50 (24.8%) patients in the intervention arm and 68 (67.3%) patients in the control arm received subsequent systemic therapy. It should be noted that, according to the clinical study report (CSR), for patients in the chemotherapy arm who received nivolumab + ipilimumab as subsequent therapy in the 'crossover cohort', further subsequent therapies from Day 1 of the nivolumab + ipilimumab administration were not taken into account.

In the intervention group, chemotherapy was the most common subsequent therapy. In the control arm, the most common subsequent therapy was nivolumab + ipilimumab (46 [45.5%]), followed by pembrolizumab (15 [14.9%]). Both therapies are approved for use in this therapeutic indication not only as first-line treatment but also following prior fluoropyrimidine-based combination therapy [20-22] and are recommended following prior chemotherapy treatment according to current S3 guidelines [23]. The dosing regimen used in

the study for the subsequent therapy with nivolumab + ipilimumab did not concur with the SmPC, however [20,21]. According to the SmPC, the combination of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) is administered every 3 weeks for the first 4 doses, followed by nivolumab monotherapy (240 mg) every 2 weeks (from Week 13). In CA209-8HW, however, combination therapy was administered throughout (up to Week 12: nivolumab [240 mg] every 2 weeks [6 doses] + ipilimumab 1 mg/kg every 6 weeks [2 doses]; from Week 13: nivolumab [480 mg] every 4 weeks + ipilimumab [1 mg/kg] every 6 weeks). Regardless of this, the subsequent therapies used largely concurred with the recommendations of the S3 guideline [23].

In KEYNOTE 177, subsequent therapy was permitted for patients in both study arms. No plausible data were available regarding the proportion of patients with subsequent therapy as of the data cut-off on 19 February 2021. The data given in the running text of the publication Diaz 2022 [14] are implausible, as the data for the comparator arm are higher than those reported at a later data cut-off. However, verifiable data were available on the proportion of patients with subsequent systemic therapy for the earlier data cut-off on 19 February 2020 (44 [29%] versus 100 [65%]), and for the later data cut-off on 17 July 2023 (54 [35%] versus 105 [68%]).

In the intervention arm, chemotherapy was the most common subsequent therapy. The most common subsequent therapy in the control arm was anti-programmed cell death 1 (PD-1) / programmed cell death ligand 1 (PD-L1) therapy. In the control arm, 56 (36.4%) patients received pembrolizumab as subsequent therapy during the ‘crossover phase’. In addition, 37 (24.0%) patients in the control arm received off-protocol treatment with anti-PD-1/PD-L1. It was unclear, however, whether this also included further subsequent therapies with pembrolizumab that were not administered as part of the ‘crossover phase’ following disease progression, but were instead used, for example, in later lines of treatment or due to reasons for discontinuation other than disease progression [14].

In the given therapeutic indication, pembrolizumab is approved not only as first-line treatment but also following prior fluoropyrimidine-based combination therapy [22]. Furthermore, according to the current S3 guideline, pembrolizumab or the combination of nivolumab + ipilimumab is used following pretreatment with chemotherapy [23]. However, it can be assumed that no more than 5 patients in the control arm received subsequent therapy with nivolumab and ipilimumab, as only 5 patients in the control arm received a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor at all. Overall, the subsequent therapies used largely concurred with the recommendations of the S3 guideline [23].

Transferability of the study results to the German health care context

The company did not provide any information on the transferability of the results of both studies to the German health care context. The dossier contained information only on study CA209-8HW.

2.2.3 Similarity of the studies for the adjusted indirect comparison

Similarity is a key requirement for the consideration of studies in an adjusted indirect comparison via a common comparator. The similarity of CA209-8HW and KEYNOTE 177 is assessed below.

Study design

Both of the included studies, CA209-8HW and KEYNOTE 177, are multicentre, open-label RCTs that enrolled adult patients with metastatic colorectal cancer with MSI-H or dMMR who were in good general health, concurring with an ECOG PS of ≤ 1. The study populations used by the company (the overall population of KEYNOTE 177 and the subpopulation of CA209-8HW) each comprise patients in first-line treatment.

The studies were conducted during different periods of time. Whilst the KEYNOTE 177 study recruited patients between 2015 and 2018 and was completed in 2023, the CA209-8HW study recruited patients between 2019 and 2023. Study CA209-8HW is still ongoing, with the most recent data cut from the 30 April 2025 cut-off presented in the comments. The implications of these differences are explained in Section 2.2.4.

Planned duration of follow-up

In both studies, the outcome of overall survival was observed until death, withdrawal of consent or the end of the study.

The planned duration of follow-up for the outcomes in the side effects category varied between the studies (see Table 4). For the adjusted indirect comparison, the company aligned the AEs included in the analysis for its study with the analysis conducted in the dossier for the benefit assessment of pembrolizumab for the KEYNOTE 177 study (data cut-off on 19 February 2020) [17]. In the KEYNOTE 177 study, all AEs and severe AEs occurring from the first dose to 30 days after the last dose of the study medication were taken into account. For the SAEs, the period from the first dose to 90 days after the last dose of the study medication was taken into account. For the indirect comparison, the company therefore used the same time periods when conducting the analysis of the AEs in study CA209-8HW.

A description of the differences in the planned observation of the patient-reported outcomes on morbidity and health-related quality of life is omitted, as the company did not conduct an adjusted indirect comparison for the outcomes of these categories. This is due to the fact that

no suitable data were available on at least one side of the indirect comparison (see Section 2.2.5).

Patient population

The demographic and clinical characteristics of the patients included, such as age, family origin, Eastern Cooperative Oncology Group Performance Status (ECOG PS), location of tumour and metastases, and mutation status (BRAF, KRAS and NRAS), were sufficiently comparable between the studies (see Table 5).

There were differences with regard to the regions in which the studies were conducted, but these did not call into question the comparability of the studies for the indirect comparison.

A key difference between the study populations was in the testing for dMMR and MSI-H status. This is explained in more detail in the next section.

Testing for dMMR and MSI-H

The CA209-8HW and KEYNOTE 177 studies differed notably in their approach to determine dMMR and MSI-H status.

According to the inclusion criteria of CA209-8HW, local testing for dMMR or MSI-H was carried out using IHC, PCR or NGS. A wide range of tests were available, as listed in Appendix 8 of the study protocol. Tissue samples from the patients included in the study were then sent to a central laboratory to confirm their MSI-H/dMMR status. However, participation in the study was not contingent on the results of the tests carried out at the central laboratory. The Biocartis Idylla test was used for the MSI testing in the central laboratory, whilst the Agilent MMR IHC Panel pharmDx (Dako Omnis) test was used for the MMR testing.

In the KEYNOTE 177 study, testing was only carried out locally, with no central confirmation of dMMR or MSI-H. Furthermore, the available sources did not provide any details regarding the tests used in the KEYNOTE 177 study.

It is described in the company's comments that the consideration of the prespecified primary outcomes of the CA209-8HW study related exclusively to the patient population with centrally confirmed dMMR or MSI-H. However, the company pointed out that it included all randomized/treated patients, regardless of whether dMMR or MSI-H had been confirmed by the central laboratory, for the results presented in the indirect comparison. Analogous to the KEYNOTE 177 study, the company therefore also considered the patient population with only local testing of dMMR or MSI-H.

With this adjustment, the company initially achieved comparability in the approach for both patient populations with regard to the exclusive consideration of local testing of dMMR or

MSI-H. However, the available analyses of the CA209-8HW study, among others, showed that a lack of confirmation by the central laboratory was a potential effect modifier for the outcome overall survival.

The available documents did not show to what extent the proportion of patients with centrally confirmed dMMR or MSI-H was comparable between the studies. Although it was stated for CA209-8HW that the locally detected dMMR/MSI-H status was centrally confirmed in 85% of patients in the intervention arm and 83% of patients in the comparator arm (see Table 5), no corresponding data were available for KEYNOTE 177 due to the lack of central confirmation. It can therefore not be ruled out that the patient populations considered by the company differed notably from each other in this characteristic.

The implications for the indirect comparison presented are described following the similarity test in Section 2.2.4.

Subsequent therapies

The information presented in Table 7 on the subsequent therapies used in CA209-8HW and KEYNOTE 177 largely concurred with the recommendations of the S3 guideline on colorectal cancer [23].

A key difference, arising from the study design and the time period during which each study was conducted, was that patients in the chemotherapy arm of each study received either predominantly nivolumab + ipilimumab (CA209-8HW) or predominantly pembrolizumab (KEYNOTE 177) as subsequent therapy. However, according to the current S3 guideline, both pembrolizumab and the combination of nivolumab and ipilimumab are treatment options after pretreatment with chemotherapy [23], although no criteria are specified for the use of either option, nor is one option recommended over the other.

The proportion of patients with subsequent systemic therapy who received nivolumab + ipilimumab or pembrolizumab was 90% in CA209-8HW and at least 60% in KEYNOTE 177. With regard to the KEYNOTE 177 study, it should be noted, firstly, that it was unclear whether the subsequent therapies listed under ‘off-protocol’ also included further subsequent therapies with pembrolizumab (see Table 7). Secondly, the proportion of patients who received nivolumab + ipilimumab was unclear; however, it was assumed that this applied to no more than 5 patients, as only 5 patients in the control arm received a CTLA-4 inhibitor at all. Overall, therefore, it was assumed that there was an important difference in subsequent therapies between the common comparator arms. It could therefore be concluded that, overall, the chemotherapy arms in both studies predominantly used immunotherapies recommended by the guidelines. However, the main drugs used differed from each other, i.e. nivolumab + ipilimumab in CA209-8HW and pembrolizumab in KEYNOTE 177. The relevance of these

differences was unclear. There were no comparative data available for nivolumab + ipilimumab versus pembrolizumab from the second-line setting onwards.

Common comparator

Treatment in the common comparator arms in CA209-8HW and KEYNOTE 177 was very similar in both studies, with the exception of the subsequent therapies mentioned above. Treatment in both studies was with chemotherapy of physician's choice with the options of folinic acid + 5-FU + oxaliplatin (modified regimen) (mFOLFOX6) or folinic acid + 5-FU + irinotecan (FOLFIRI), in each case ± bevacizumab or cetuximab. The distribution of the treatment regimens administered was also approximately the same between the studies (see Table 8). One difference between the studies was the dosage of cetuximab, which was administered at a dose of 500 mg every 2 weeks in CA209-8HW, and as a single dose of 400 mg followed by a weekly dose of 250 mg in KEYNOTE 177. However, this difference did not call into question the similarity of the common comparator arms, as only a small proportion of patients in both studies received cetuximab (11% in each study, see Table 8).

Table 8: Treatment regimens in the respective chemotherapy arm of CA209-8HW and KEYNOTE 177 – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab

Drug	Chemotherapy[a] ± bevacizumab or cetuximab	Chemotherapy[a] ± bevacizumab or cetuximab
	CA209-8HW	KEYNOTE 177
	N[b] = 88	N[b] = 143
Chemotherapeutics received, n (%)		
mFOLFOX6 ± bevacizumab/cetuximab	51 (58)	80 (56)
mFOLFOX6	9 (10)	11 (8)
mFOLFOX6 + bevacizumab	37 (42)	64 (45)
mFOLFOX6 + cetuximab	5 (6)	5 (3)
FOLFIRI ± bevacizumab/cetuximab	37 (42)	63 (44)
FOLFIRI	13 (15)	16 (11)
FOLFIRI + bevacizumab	19 (22)[c]	36 (25)
FOLFIRI + cetuximab	5 (6)	11 (8)

a. mFOLFOX6 or FOLFIRI.
b. Number of randomized patients who received at least one dose of the study medication.
c. Including one patient who received only the combination of fluorouracil + irinotecan + bevacizumab without leucovorin.

5-FU: 5-fluorouracil; FOLFIRI: folinic acid + 5-FU + irinotecan; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

Treatment duration

There were differences in the median treatment duration in the control arms of CA209-8HW and KEYNOTE 177 (4.0 versus 5.7 months) (see Table 6). However, the difference was not considered so substantial as to call into question the similarity of the common comparator.

Summary of the similarity of the studies

Overall, the CA209-8HW and KEYNOTE 177 studies were sufficiently comparable in terms of study design, patient characteristics and the common comparator. There were differences in treatment duration and subsequent therapies in the chemotherapy arms of the 2 studies.

However, there were notable differences between the studies regarding the testing of MSI-H or dMMR status. The implications for this indirect comparison are described in the following section.

2.2.4 Differences in MSI-H and dMMR testing between CA209-8HW and KEYNOTE 177

As described in Section 2.2.3, the CA209-8HW study included patients with locally confirmed dMMR or MSI-H. In addition, central testing was carried out after inclusion in the study to confirm this finding. In contrast, the KEYNOTE 177 study conducted only local testing – without central confirmation – of the tumour's dMMR or MSI-H status.

The particular importance of central confirmation of dMMR or MSI-H in addition to local testing was raised by clinicians during the hearing [24]. In the discussion section of its first CSR, the company also discussed the differences in the results of CA209-8HW and KEYNOTE 177, and also attributed these differences to the lack of central confirmation of dMMR/MSI-H. Furthermore, one of the authors of the CA209-8HW study emphasized the need for accurate testing of dMMR/MSIH for the efficacy of nivolumab/ipilimumab [25].

The results of the CA209-8HW study showed that whether or not dMMR/MSIH was centrally confirmed was a potential effect modifier for the comparison at hand (see Table 9).

Table 9: Overall survival (time to event) in CA209-8HW by subgroup based on central confirmation of dMMR or MSI-H

Study Outcome	nivolumab + ipilimumab		Chemotherapy[a] ± bevacizumab or cetuximab		nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or 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]; p-value
CA209-8HW (data cut-off: 30 April 2025)					
Overall survival					
dMMR/MSI-H Locally determined	202	NA 54 (26.7)	101	44.3 [26.3; NA] 50 (49.5)	0.44 [0.30; 0.65]; ND
Centrally confirmed	171	NA 32 (18.7)	84	57.5 [31.7; NA] 36 (42.9)	0.36 [0.22; 0.58]; ND
Not centrally confirmed	31[b]	ND 22 (71.0)[b]	17[b]	ND 14 (82.4)[b]	ND

a. mFOLFOX6 or FOLFIRI.
b. Institute's calculations.

5-FU: 5-fluorouracil; CI: confidence interval; 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; NA: not achieved; ND: no data; RCT: randomized controlled trial

For CA209-8HW, the data in Table 5 and Table 9 show that the previously locally detected dMMR/MSI-H status was centrally confirmed for 171 of 202 (85%) patients in the intervention arm and 84 of 101 (83%) patients in the comparator arm.

For patients in the nivolumab + ipilimumab arm, it was shown that there notably fewer deaths in the group of patients with centrally confirmed dMMR/MSI-H tumour status than in the group without central confirmation (19% versus 71%). This also applied to the chemotherapy arm, although the difference was smaller (43% versus 82%).

These differences in the results depending on whether the results were centrally confirmed were also reflected in the comparison between the 2 treatment groups. For example, for the patient group with centrally confirmed dMMR/MSI-H tumour status, there was a notably larger difference in the proportion of patients who died between the intervention arm and the control arm (19% versus 43%) in favour of nivolumab + ipilimumab than was the case for patients without central confirmation (71% versus 82%). The hazard ratios (HR) with 95% confidence intervals (CI) were available only for patients with local or central confirmation,

but not for patients without central confirmation. Overall, however, it became clear that even a comparatively small proportion of patients in whom the mutation was not confirmed had an influence on the overall result.

As the KEYNOTE 177 study used only local testing, it was unclear to what extent the patient populations in KEYNOTE 177 and CA209-8HW were similar in terms of the proportion of patients with centrally confirmed dMMR or MSI-H. In addition, it was unclear to what extent a comparably pronounced potential effect modification for the characteristic of central testing of dMMR/MSI-H was shown in KEYNOTE 177.

It could not be assumed per se that the KEYNOTE 177 study included a proportion of patients comparable to that in CA209-8HW who would have received central confirmation of the tumour's dMMR/MSI-H status if tested by a central laboratory. It should be taken into account that the test procedures are undergoing continuous further development. Thus it cannot be ruled out that the tests used for the local determination of dMMR/MSI-H in the CA209-8HW study, which started later, had better quality criteria than the tests used in KEYNOTE 177. According to the study documents for both studies, there were differences in the local tests used. For example, in the CA209-8HW study, testing using NGS was also possible to determine MSI-H, and more and different loci in the genome were tested to determine MSI-H than with the tests used in the KEYNOTE 177 study. It could therefore not be ruled out that local determination of dMMR/MSI-H was not confirmed by a central laboratory for a larger proportion of patients in the KEYNOTE 177 study than in the CA209-8HW study.

In the oral hearing, the company pointed out that by considering the entire patient population with local testing, a less favourable effect for nivolumab + ipilimumab was included in the indirect comparison than would have been the case if the patient population with central confirmation had been considered. This argument is not valid. Depending on the size of the proportion without central confirmation of dMMR or MSI-H and the magnitude of the potential effect modification in KEYNOTE 177, the impact on the estimate of the overall survival outcome in the indirect comparison would be correspondingly greater or smaller. Given this uncertainty, only a sufficiently large effect on overall survival could be interpreted in the present constellation. However, this is not the case.

The overall survival data from the adjusted indirect comparison (HR: 0.59; 95% CI: [0.36; 0.99]; p = 0.046) showed only a marginally statistically significant result and were therefore neither interpretable with sufficient certainty nor suitable for drawing conclusions on the added benefit.

2.2.5 Conclusions on added benefit based on the adjusted indirect comparison not possible

On the benefit side of the adjusted indirect comparison, there were no suitable data available on patient-relevant outcomes.

The results for the overall survival outcome were not suitable for the derivation of the added benefit due to a lack of information.

In both studies, in addition to the outcome overall survival, patient-reported outcomes from the categories morbidity and health-related quality of life were recorded (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Cancer 30 [QLQ-C30], EORTC Quality of Life Questionnaire-Colorectal 29 [QLQ-CR29] and EQ-5D VAS). However, the company pointed out in its comments that the data on the patient-reported outcomes recorded in the KEYNOTE 177 study were not interpretable according to IQWiG's benefit assessment of pembrolizumab (benefit assessment A21-36 [16]). This is due to the fact that the planned time points of recording in the pembrolizumab arm always fell at the beginning of a new cycle, while the time points of recording in the chemotherapy arm were sometimes in the middle of the cycle, so that the burden of treatment over the course of the cycle was represented unequally in the study arms. The company therefore did not provide an indirect comparison for these outcomes in its comments.

For all outcomes in the category of side effects, there was a high risk of bias on at least one side of the indirect comparison due to large differences between the treatment arms (> 5 percentage points) in the proportion of patients excluded from the analysis, and due to incomplete observations for potentially informative reasons (see benefit assessment A21-36 [16]), meaning that the requirement for the certainty of results for conducting an adjusted indirect comparison was not met.

Overall, it was not possible to weigh up benefits and harms. The results of the adjusted indirect comparison for the outcomes of overall survival, SAEs and severe AES in patients with locally determined dMMR/MSI-H are presented in Appendix C as supplementary information.

2.2.6 Further notes on the adjusted indirect comparison presented in the comments

Outcomes of immune-mediated SAEs and immune-mediated severe AEs

In its comments, the company did not present any results regarding immune-mediated SAEs or immune-mediated severe AEs, either for its CA209-8HW study or for the KEYNOTE 177 study. Immune-mediated SAEs and severe AEs are important patient-relevant outcomes for both PD-L1 inhibitors and CTLA-4 inhibitors, and were also presented by the company in previous benefit assessment procedures of nivolumab or ipilimumab (see, for example, [26-28]). Corresponding analyses would be necessary for an appropriate assessment of harm.

Outcome of discontinuation due to AEs

No suitable data for the indirect comparison were available for the outcome of discontinuation due to AEs. From the company's perspective, the results regarding treatment discontinuations due to AEs in KEYNOTE 177 referred to treatment discontinuations of all study drugs, whereas in CA209-8HW, treatment discontinuations due to AEs were defined as AEs that led to the discontinuation of at least one drug of the study medication. For the indirect comparison, the company therefore conducted analyses on treatment discontinuations due to AEs for the CA209-8HW study that deviated from the CSR and related to the discontinuation of all drugs. The operationalization considered by the company in the indirect comparison was not appropriate. An analysis on the discontinuation of all drug components alone could not be meaningfully interpreted in the given data situation (e.g. 1 or 2 drug components in the pembrolizumab / nivolumab + ipilimumab arm, and up to 4 drug components in the comparator arms). Rather, the assessment would require results for the analysis of time to discontinuation of at least one drug component, as any AE leading to discontinuation of any therapy component is relevant.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of nivolumab + ipilimumab from dossier assessment A25-80.

The following Table 10 shows the result of the benefit assessment of nivolumab + ipilimumab, taking into account dossier assessment A25-80 and this addendum.

Table 10: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H[b]	pembrolizumab as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for this therapeutic indication that treatment with curative intent or primary resection is not an option for patients with metastatic colorectal cancer. It is also assumed that antineoplastic therapy is indicated for patients in this therapeutic indication.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high microsatellite instability

The G-BA decides on the added benefit.

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Appendix A Test strategy and data cuts for study CA209-8HW

The CA209-8HW study is an ongoing open-label, 3-arm RCT comparing nivolumab, nivolumab + ipilimumab, and chemotherapy of physician's choice. According to the study protocol, the following comparisons were planned:

- i) nivolumab + ipilimumab versus nivolumab across all lines of treatment (i.e. regardless of prior treatment for metastatic disease)
- ii) nivolumab + ipilimumab versus nivolumab in first-line treatment
- iii) nivolumab + ipilimumab versus chemotherapy of physician's choice in first-line treatment

A common test hierarchy was planned for all 3 comparisons. In the primary protocol, the analysis dates for both the interim analysis and the final analysis of the primary outcome, PFS, were linked to the proportion of events for the outcome. According to the study design, the company assumed that these proportions of events for PFS would be reached at approximately the same time for all 3 comparisons. The final analysis of overall survival was originally planned for August 2024, 60 months after the first patient was randomized, for all 3 comparisons. Furthermore, the study documents showed that a consideration of overall survival was planned for both the interim analysis and the final analysis of PFS (referred to in the study protocol as an 'overall survival look').

The following list details which data cuts were available and when which changes were made in the study design with regard to the data cut-offs.

- Protocol amendment (Amendment 9) – 1 June 2023: The company stated that, given the heterogeneity of patient populations (first-line and all lines of treatment) and the different mode of action of the study drugs (nivolumab + ipilimumab, nivolumab and chemotherapy) the proportions of events of the 2 primary PFS outcomes might not be reached at identical time points for the 2 comparisons, nivolumab + ipilimumab versus chemotherapy in first line, and nivolumab + ipilimumab versus nivolumab across all lines. The company therefore amended the protocol so that the interim analyses for the primary outcomes (PFS) for the 2 comparisons were conducted at different time points.
- 1st data cut-off on 12 October 2023 (interim CSR [5]): The required proportion of PFS events was reached for the comparison of nivolumab + ipilimumab versus chemotherapy (first line). The interim analysis of the PFS was conducted as planned, and after consideration of the results for the PFS was declared the final analysis of the PFS. For the other comparisons (i and ii), the required proportions of PFS events had not yet been reached at that point in time. No results were available for any of the 3 comparisons

regarding the consideration of the overall survival outcome ('overall survival look') as outlined in the study documents.

- Protocol amendment (Amendment 10) – 1 July 2024: The company changed its planning again. The planned study-wide final analysis of the overall survival outcome, which was scheduled for 60 months after randomization of the first patient, i.e. in August 2024, was dropped. Instead, the company stipulated that the interim analysis for the primary outcome (PFS) across all lines of treatment was to take place at that time for the comparison of nivolumab + ipilimumab versus nivolumab. It also stipulated that, if the PFS results met the prespecified statistical significance in this interim analysis, the secondary outcomes including overall survival (interim analysis) were allowed to be tested according to the testing hierarchy. Furthermore, the company changed its plans for the final PFS analysis. This was now scheduled to be conducted approximately 2 years after randomization of the last patient (April 2025). The final analysis of overall survival was scheduled to occur 1 year later (April 2026). The company justified the described approach on the grounds that it would otherwise lead to deviations in the testing hierarchy.
- 2nd data cut-off on 28 August 2024 (primary CSR [6]): comparison of nivolumab + ipilimumab versus nivolumab (all lines of treatment); according to Amendment 10 of the study protocol, the planned interim analysis for the PFS outcome was conducted. After consideration of the results for the PFS this analysis was declared the final analysis of the PFS. In this case, according to Amendment 10, it would also have been possible to assess the secondary outcomes, including overall survival. Results on overall survival were not reported for this data cut, however.
- 3rd data cut-off on 30 April 2025 (addendum to the primary CSR [7]): In its comments [2], the company presented results of this interim analysis of CA209-8HW, which, according to the company, had not yet been available at the time of the dossier submission; comparison of nivolumab + ipilimumab versus nivolumab (first line); the final PFS analysis planned under Amendment 10. The company reported results on overall survival in the addendum to the CRS for all 3 comparisons without conducting a test. It referred to these analyses as interim analyses of overall survival.

Overall, it remained unclear why an analysis and testing of overall survival had not already been conducted at the data cut-off on 28 August 2024. At that time, the outcomes PFS and objective response rate had reached the specified threshold values, meaning that the criteria for the analysis of the overall survival outcome had already been met. In addition, according to the study protocol, overall survival was to be considered ('overall survival look') as part of both the interim PFS analysis and the final PFS analysis. It was not comprehensible why the company did not also conduct and report on overall survival evaluations at earlier time points (data cut-off in 2024 and 2023), as it did for the data cut-off on 30 April 2025.

Appendix B Search strategies

Trial registry

Search on nivolumab + ipilimumab

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Input interface: Expert Search

Search strategy
AREA[ConditionSearch](colorectal neoplasm OR CRC) AND AREA[InterventionSearch](nivolumab OR BMS-936558 OR MDX-1106 OR ONO-4538) AND AREA[InterventionSearch](ipilimumab OR MDX-010 OR MDX-CTLA-4)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Input interface: Basic Search

Search strategy
(colon* OR rectal* OR colorectal* OR CRC) AND (nivolumab* OR BMS-936558 OR BMS936558 OR "BMS 936558" OR MDX-1106 OR MDX1106 OR "MDX 1106" OR ONO-4538 OR ONO4538 OR "ONO 4538") AND (ipilimumab* OR MDX-010 OR MDX010 OR "MDX 010" OR MDX-CTLA-4 OR MDXCTLA4 OR "MDX CTLA 4")

3. Clinical Trials Information System (CTIS)

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials
- Input interface: Basic Search

Search strategy
Nivolumab, BMS-936558, BMS936558, MDX-1106, MDX1106, ONO-4538, ONO4538 [Contain any of these terms] AND colon [Contain all of these terms]
Nivolumab, BMS-936558, BMS936558, MDX-1106, MDX1106, ONO-4538, ONO4538 [Contain any of these terms] AND rectal [Contain all of these terms]
Nivolumab, BMS-936558, BMS936558, MDX-1106, MDX1106, ONO-4538, ONO4538 [Contain any of these terms] AND colorectal [Contain all of these terms]
Nivolumab, BMS-936558, BMS936558, MDX-1106, MDX1106, ONO-4538, ONO4538 [Contain any of these terms] AND CRC [Contain all of these terms]

Search on the ACT

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Input interface: Expert Search

Search strategy
AREA[ConditionSearch](colorectal neoplasm OR CRC) AND AREA[InterventionSearch](pembrolizumab OR MK-3475 OR SCH-900475) AND AREA[Phase](PHASE2 OR PHASE3 OR PHASE4 OR NA)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Input interface: Basic Search

Search strategy
(colon* OR rectal* OR colorectal* OR CRC) AND (pembrolizumab* OR MK-3475 OR (MK 3475) OR MK3475 OR SCH-900475 OR (SCH 900475) OR SCH900475)

3. Clinical Trials Information System (CTIS)

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials
- Input interface: Basic Search

Search strategy
pembrolizumab, MK-3475, MK3475, SCH-900475, SCH900475 [Contain any of these terms] AND colon [Contain all of these terms]
pembrolizumab, MK-3475, MK3475, SCH-900475, SCH900475 [Contain any of these terms] AND rectal [Contain all of these terms]
pembrolizumab, MK-3475, MK3475, SCH-900475, SCH900475 [Contain any of these terms] AND colorectal [Contain all of these terms]
pembrolizumab, MK-3475, MK3475, SCH-900475, SCH900475 [Contain any of these terms] AND CRC [Contain all of these terms]

Appendix C Supplementary information: results of the adjusted indirect comparison

Results for the outcomes of overall survival, SAEs and severe AEs in patients with local testing of dMMR/MSI-H

Table 11: Results (mortality and side effects, time to event, supplementary information) – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Outcome category Outcome Comparison Study	nivolumab + ipilimumab or pembrolizumab N	Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy[a] ± bevacizumab or cetuximab N	Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
Mortality					
Overall survival					
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
CA209-8HW (data cut-off: 30 April 2025)	202	NA 54 (26.7)	101	44.3 [26.3; NC] 50 (49.5)	0.44 [0.30; 0.65]; ND[b]
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
KEYNOTE 177 (data cut-off: 19 February 2021)	153	NA [49.2; NC] 62 (40.5)	154	36.7 [27.6; NC] 78 (50.6)	0.74 [0.53; 1.03]; 0.036[c]
Indirect comparison using common comparators[d]:					
nivolumab + ipilimumab vs. pembrolizumab					0.59 [0.36; 0.99]; 0.046
Side effects					
SAEs[e]					
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
CA209-8HW (data cut-off: 30 April 2025)	200	22.3 [11.9; NC] 95 (47.5)	88	8.2 [3.2; 19.5] 45 (51.1)	0.66 [0.46; 0.95]; ND[b]
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
KEYNOTE 177 (Data cut-off: 19 February 2020[f])	153	24.6 [14.0; NC][g] 62 (40.5)	143	8.0 [3.7; 20.6][g] 75 (52.4)	0.61 [0.43; 0.85]; 0.004[c]
Indirect comparison using common comparators[d]:					
nivolumab + ipilimumab vs. pembrolizumab					1.08 [0.66; 1.78]; 0.756

Table 11: Results (mortality and side effects, time to event, supplementary information) – RCT, indirect comparison: nivolumab + ipilimumab vs. pembrolizumab (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**nivolumab + ipilimumab or pembrolizumab** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Chemotherapy[a] ± bevacizumab or cetuximab** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Severe AEs (CTCAE ≥ 3)[e]					
nivolumab + ipilimumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
CA209-8HW (data cut-off: 30 April 2025)	200	12.5 [7.3; 18.9] 106 (53.0)	88	2.2 [1.4; 3.3] 59 (67.0)	0.41 [0.29; 0.57]; ND[b]
pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab					
KEYNOTE-177 (data cut-off: 19 February 2020[f])	153	10.8 [6.3; 14.1][g] 86 (56.2)	143	2.1 [1.5; 2.6][g] 111 (77.6)	0.41 [0.31; 0.55]; < 0.001[c]
Indirect comparison using common comparators[d]:					
nivolumab + ipilimumab vs. pembrolizumab					1.00 [0.64; 1.56]; > 0.999

a. mFOLFOX6 or FOLFIRI.
b. Cox proportional hazards model, stratified by tumour location (left- vs. right-sided).
c. Cox proportional hazards model; p-value: log-rank test (overall survival), Wald test (side effects).
d. Indirect comparison according to Bucher [4].
e. Overall rate without AEs assigned to the progression of the underlying disease, defined as the MedDRA terms 'neoplasm progression', 'malignant neoplasm progression' and 'disease progression'.
f. For the side effect outcomes, time-to-event analyses are only available for the 19 February 2020 data cut. It is assumed that the estimates for the later data cuts change only marginally.
g. Data from benefit assessment A21-36, with conversion of weeks to months conducted by IQWiG [16].

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-FU + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-FU + oxaliplatin (modified regimen); N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event

Kaplan-Meier curves for the outcomes of overall survival, SAEs and severe AEs

CA209-8HW

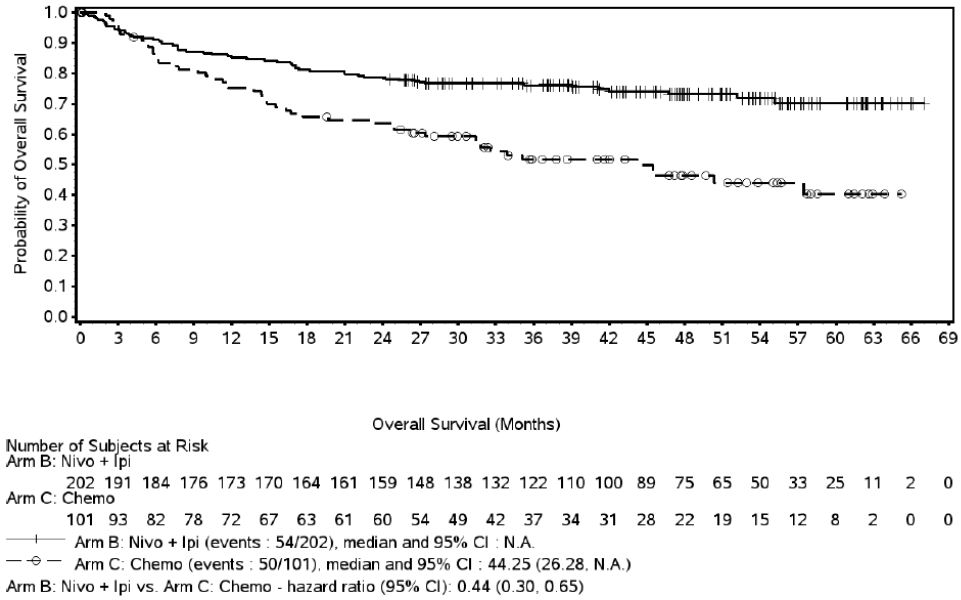

Figure 2: Kaplan-Meier curves for the outcome overall survival, CA209-8HW (data cut-off: 30 April 2025)

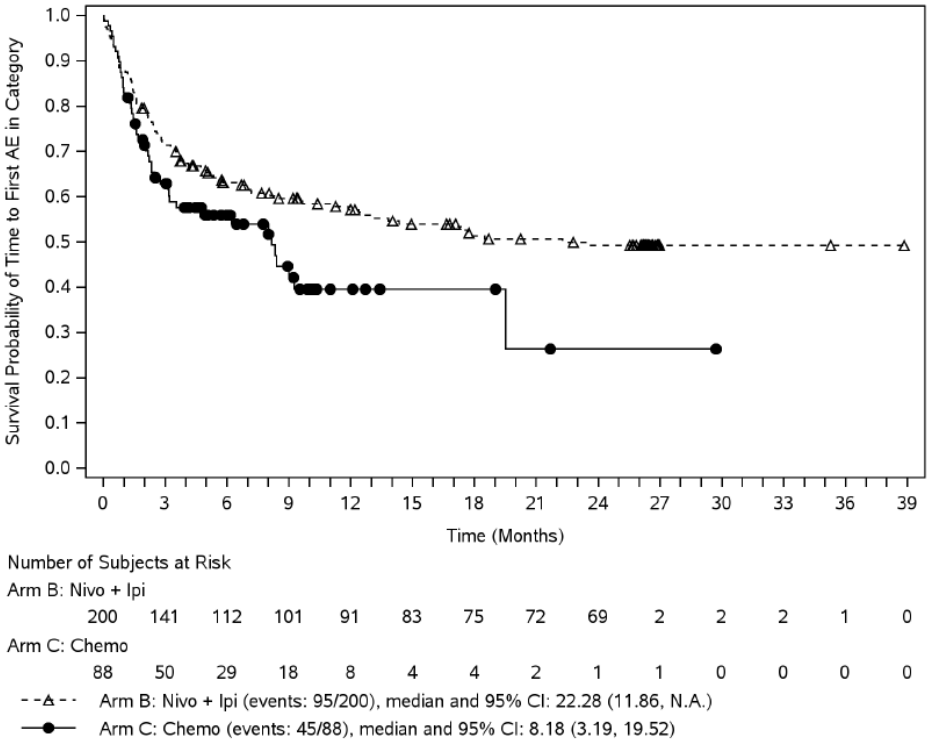

Figure 3: Kaplan-Meier curves for the outcome SAEs (excluding disease-related events); CA209-8HW (data cut-off: 30 April 2025)

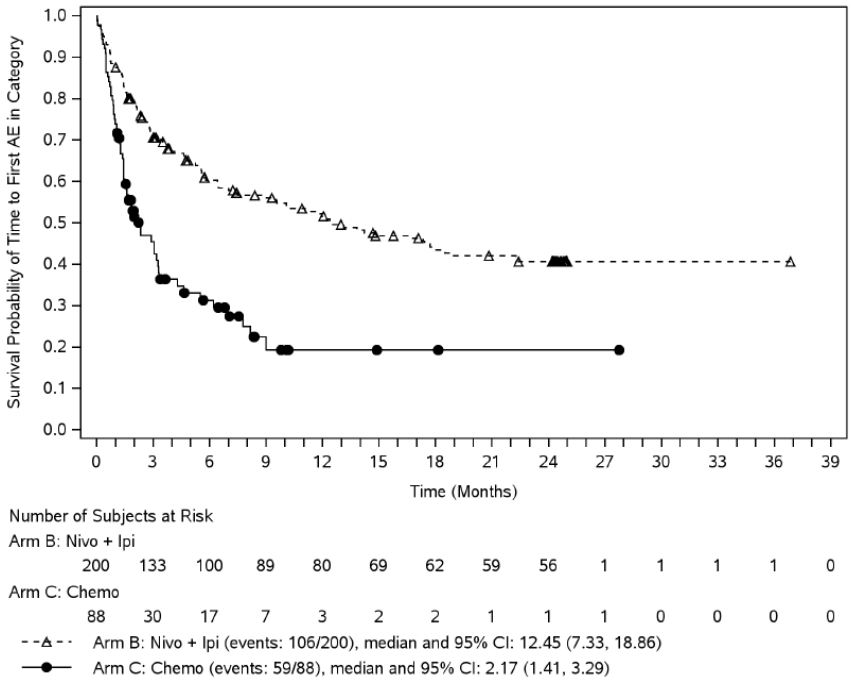

Figure 4: Kaplan-Meier curves for the outcome severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) (excluding disease-related events); CA209-8HW (data cut-off: 30 April 2025)

KEYNOTE 177

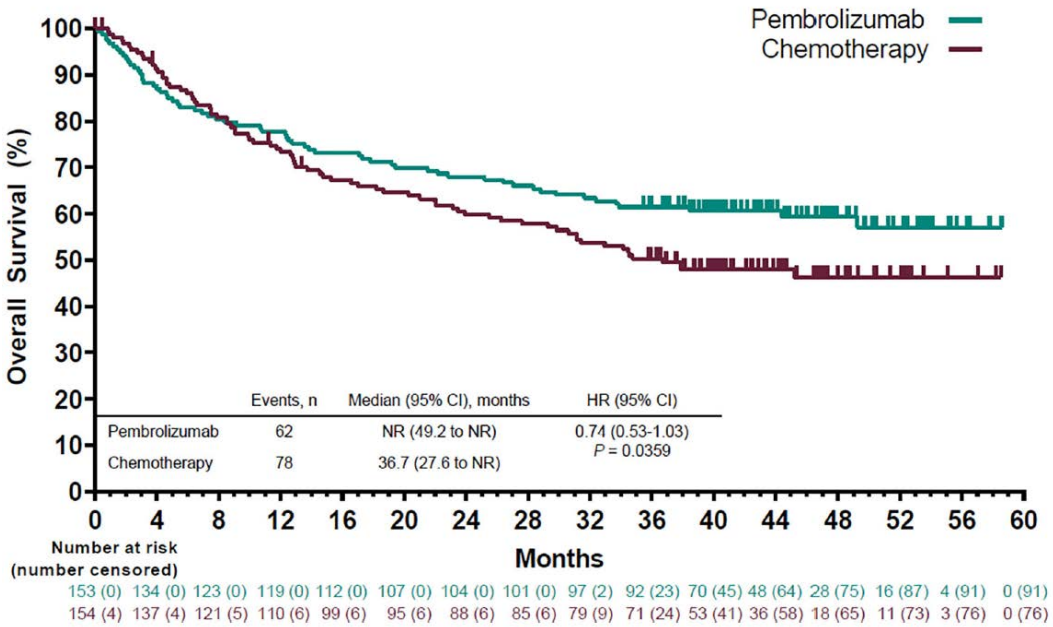

Figure 5: Kaplan-Meier curves for the outcome overall survival, KEYNOTE 177 (data cut-off: 19 February 2021)

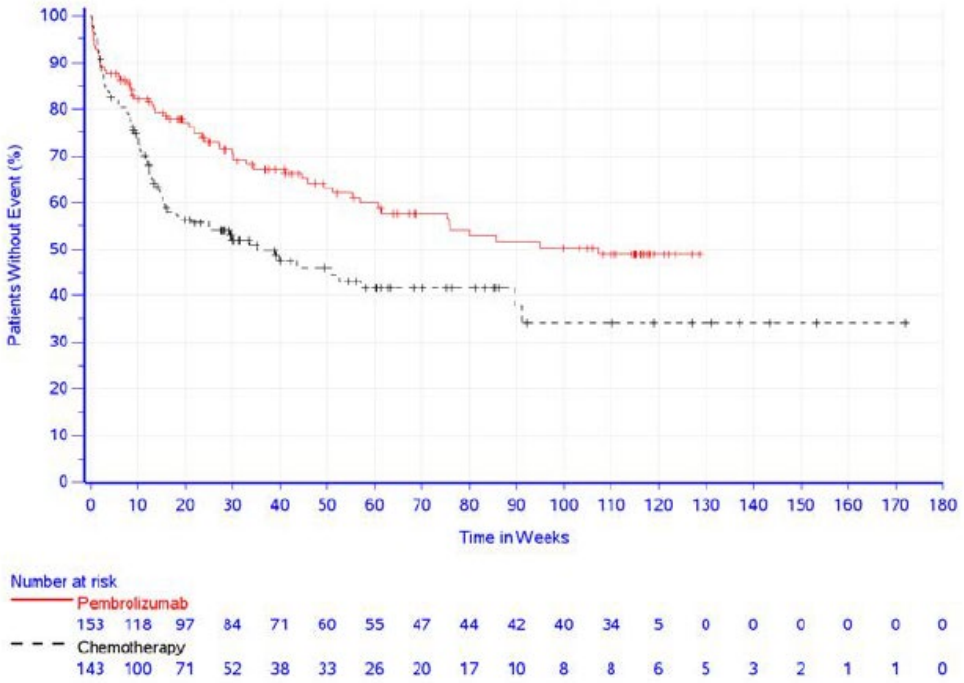

Figure 6: Kaplan-Meier curves for the outcome SAEs (excluding disease-related events); KEYNOTE 177 (data cut-off: 19 February 2020)

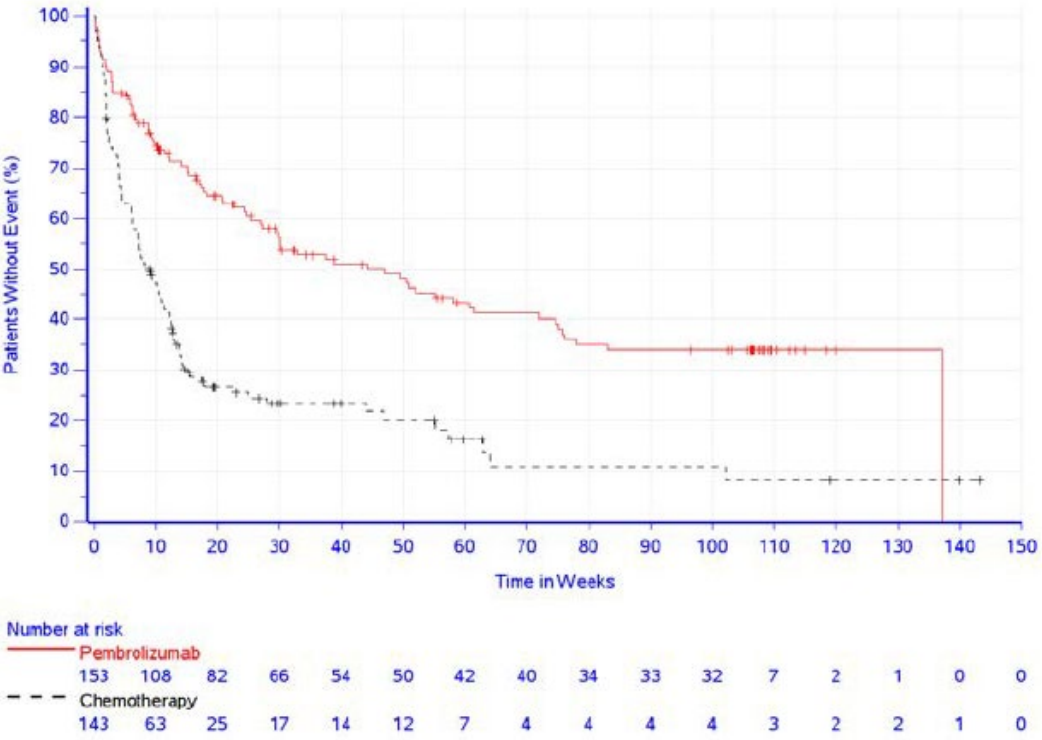

Figure 7: Kaplan-Meier curves for the outcome severe AEs (CTCAE grade ≥ 3) (excluding disease-related events); KEYNOTE 177 (data cut-off: 19 February 2020)