IQWiG Reports – Commission No. A21-99

Nivolumab (MSI-H or dMMR colorectal cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (Kolorektalkarzinom mit MSI-H oder dMMR) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Nivolumab (MSI-H or dMMR colorectal cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
27 July 2021

Internal Commission No.
A21-99

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Christoph Frank Dietrich, Bern

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Can Ünal
- Nadia Abu Rajab
- Stefan Kobza
- Petra Kohlepp
- Annika Orland
- Regine Potthast
- Anke Schulz
- Volker Vervölgyi

Keywords: Nivolumab, Ipilimumab, Colorectal Neoplasms, Benefit Assessment, NCT02060188

Table of contents

List of tables[2]

Page

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B
BW	body weight
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficiency
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FOLFIRI	5-fluorouracil + folinic acid + irinotecan
FOLFOX	5-fluorouracil + folinic acid + oxaliplatin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPD	individual patient data
IPTW	inverse probability of treatment weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
mCRC	metastatic colorectal cancer
MID	minimally important difference
mKRK	metastasiertes Kolorektalkarzinom
MSI-H	microsatellite instability-high
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 July 2021.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic colorectal cancer with microsatellite instability (MSI) or mismatch repair deficiency (dMMR) that has progressed after prior fluoropyrimidine-based combination therapy.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT[a]**
Adults with metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy[b]	Patient-specific treatment[c, d] depending on the type and number of prior therapies, the RAS and BRAF mutation status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR agents, choosing from the following options ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[e] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil ± folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[e] ▪ cetuximab monotherapy[e] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[e] ▪ encorafenib + cetuximab[f]

a. Presentation of the ACT specified by the G-BA.
b. It is assumed that there is no therapeutic indication for treatment with curative intent or for primary or secondary resectability.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Regorafenib is currently not marketed in Germany and therefore does not represent a treatment option in the context of the ACT at this time. Based on the available evidence, mitomycin is also not considered a suitable treatment option in the context of antineoplastic treatment of physician's choice.
e. Only for patients with RAS wild type.
f. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The company named patient-specific treatment under consideration of the respective Summaries of Product Characteristics (SPCs) as ACT, and thus followed the G-BA's specification. It referred to the ACT previously specified on 25 August 2020, which did not include the treatment options of irinotecan + cetuximab and encorafenib + cetuximab. This change in the ACT had no relevant consequence for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) for the comparison of nivolumab + ipilimumab with the ACT specified by the G-BA.

The company also did not identify any suitable studies for an adjusted indirect comparison via a common comparator.

The company mainly used the CA209-6EP study for the benefit assessment. This study is a comparison of individual arms from different studies (non-randomized retrospective study). The comparison was based on data on nivolumab + ipilimumab from a prospective cohort study (cohort 2 of the CA209-142 study) and data from the Flatiron Health database for representing the ACT. The study explicitly investigated the outcome of overall survival.

For conclusions on further outcome categories (morbidity, health-related quality of life), the company presented before-after comparisons of the prospective cohort study CA209-142 (cohort 2) with nivolumab + ipilimumab. For conclusions on the outcome category of side effects, the company considered a descriptive comparison by using freely available study data for 4 different options of the ACT. The company compared the resulting data on the ACT with the data on nivolumab + ipilimumab from the above-mentioned study CA209-142 (cohort 2).

None of the studies or analyses presented by the company are suitable for deriving an added benefit of nivolumab + ipilimumab in comparison with the ACT in adult patients with dMMR or MSI-high (MSI-H) metastatic colorectal cancer (mCRC) after prior fluoropyrimidine-based combination chemotherapy.

Study CA209-6EP – comparison of individual arms from different studies for the outcome of overall survival

The CA209-6EP study is a comparison of individual arms of different studies consisting of data on nivolumab + ipilimumab from a prospective cohort study (cohort 2 of study CA209-142) and data from the Flatiron Health database for representing the ACT. For this study, the company prepared a study protocol and a statistical analysis plan (SAP), but no entry was made in a study registry. The company did not submit a clinical study report (CSR). The following information on this study is limited to the information provided by the company in Module 4 O of the dossier.

Overall, the CA209-6EP study is not suitable for the derivation of an added benefit of nivolumab + ipilimumab in comparison with the ACT specified by the G-BA. This is mainly due to the following aspects:

- The information available in the data set on the confounders identified as relevant by the company is incomplete, which led to partial non-consideration of relevant confounders without the company drawing any conclusions from this.

- The included patient populations show a marked structural inequality with regard to the confounders recorded, which cannot be sufficiently compensated for by means of confounder adjustment.
- The company's information retrieval for identifying relevant confounders is unsuitable for ensuring the completeness of the results.

Results on morbidity and health-related quality of life

For conclusions on the outcome categories of morbidity and health-related quality of life, the company used the uncontrolled, prospective phase 2 cohort study CA209-142 (explicitly cohort 2). Using before-after comparisons, the company presented the proportions of patients with worsening or improvement by a minimally important difference (MID) of 7, 10 and 15 points compared with baseline. It can be seen that, in outcomes of disease-related symptoms, fatigue and pain, as well as health-related quality of life, role functioning and cognitive functioning, a higher proportion of patients experienced a worsening in the course of the study with an MID of 10.

This study did not include a comparison of nivolumab + ipilimumab against the ACT. The CA209-142 study is therefore not suitable for the research question of the present benefit assessment.

Comparison with individual arms of RCTs

The company did not conduct a confounder-adjusted comparison for the outcome category of tolerability as it did for the outcome of overall survival. Instead, it searched for RCTs in which one or more arms corresponded to the treatment options mandated by the G-BA in order to be able to estimate the harmful aspects of the intervention with nivolumab + ipilimumab. It limited its search to the 4 most common treatments administered in the Flatiron Health cohort. The information retrieval was non-systemic and is therefore not suitable for ensuring the completeness of the search results. The company did not submit a documentation of the search strategy. Besides, limiting the search to the 4 most common treatments in the cohort from the Flatiron Health database is not adequate. Irrespective of this, when comparing individual arms from different studies, conclusions can only be derived if large effects are present because of the large uncertainty. There were no such effects, however. A comparability of the therapies with regard to side effects in the sense of equivalence cannot be derived on this basis, either.

Summary

The company presented no suitable data for the assessment of the added benefit of nivolumab + ipilimumab in its dossier. This resulted in no hint of added benefit of nivolumab + ipilimumab in comparison with the ACT in adult patients with unresectable or metastatic colorectal cancer with MSI or dMMR that has progressed after prior fluoropyrimidine-based combination therapy. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of the added benefit of nivolumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy[b]	Patient-specific treatment[c, d] depending on the type and number of prior therapies, the RAS and BRAF mutation status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR agents, choosing from the following options ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[e] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil ± folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[e] ▪ cetuximab monotherapy[e] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[e] ▪ encorafenib + cetuximab[f]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b. It is assumed that there is no therapeutic indication for treatment with curative intent or for primary or secondary resectability.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Regorafenib is currently not marketed in Germany and therefore does not represent a treatment option in the context of the ACT at this time. Based on the available evidence, mitomycin is also not considered a suitable treatment option in the context of antineoplastic treatment of physician's choice.
e. Only for patients with RAS wild type.
f. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the ACT in adult patients with unresectable or metastatic colorectal cancer with MSI or dMMR that has progressed after prior fluoropyrimidine-based combination therapy.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT[a]**
Adults with metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy[b]	Patient-specific treatment[c, d] depending on the type and number of prior therapies, the RAS and BRAF mutation status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR agents, choosing from the following options ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[e] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil ± folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[e] ▪ cetuximab monotherapy[e] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[e] ▪ encorafenib + cetuximab[f]

a. Presentation of the ACT specified by the G-BA.
b. It is assumed that there is no therapeutic indication for treatment with curative intent or for primary or secondary resectability.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Regorafenib is currently not marketed in Germany and therefore does not represent a treatment option in the context of the ACT at this time. Based on the available evidence, mitomycin is also not considered a suitable treatment option in the context of antineoplastic treatment of physician's choice.
e. Only for patients with RAS wild type.
f. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The company named patient-specific treatment under consideration of the respective SPCs as ACT. It referred to the ACT specified by the G-BA on 25 August 2020. In the course of the benefit assessment, the G-BA adjusted the ACT and included the treatment options of irinotecan + cetuximab as well as encorafenib + cetuximab as additional options. This change in the ACT had no relevant consequence for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on nivolumab + ipilimumab (status: 14 June 2021)
- bibliographical literature search on nivolumab + ipilimumab (last search on 13 June 2021)
- search in trial registries/trial results databases for studies on nivolumab + ipilimumab (last search on 13 June 2021)
- search on the G-BA website for nivolumab + ipilimumab (last search on 14 June 2021)
- bibliographical literature search on the ACT (last search on 13 June 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 13 June 2021)
- search on the G-BA website for the ACT (last search on 14 June 2021)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab + ipilimumab (last search on 23 August 2021); for search strategies, see Appendix A of the full dossier assessment

Direct comparison

Concurring with the company, the check of the completeness of the study pool produced no RCTs for the comparison of nivolumab + ipilimumab with the ACT specified by the G-BA.

Adjusted indirect comparison

The company also did not identify any suitable studies for an adjusted indirect comparison via a common comparator.

Further investigations

The company mainly used the CA209-6EP study for the benefit assessment. This study is a comparison of individual arms from different studies (non-randomized retrospective study). The comparison was based on individual patient data on nivolumab + ipilimumab from a

prospective cohort study (cohort 2 of the CA209-142 study) and individual patient data from the Flatiron Health database for representing the ACT. The study explicitly investigated only the outcome of overall survival.

For conclusions on further outcome categories (morbidity, health-related quality of life), the company presented before-after comparisons of the prospective cohort study CA209-142 (cohort 2) with nivolumab + ipilimumab [3-5]. For conclusions on the outcome category of side effects, the company considered a descriptive comparison by using freely available study data for 4 different options of the ACT. The company compared the resulting data with the data on nivolumab + ipilimumab from the above-mentioned study CA209-142 (cohort 2).

None of the studies or analyses presented by the company are suitable for deriving an added benefit of nivolumab + ipilimumab in comparison with the ACT in adult patients with dMMR or MSI-H mCRC after prior fluoropyrimidine-based combination chemotherapy. This is explained in the following sections.

It should be noted that an additional investigation on nivolumab + ipilimumab was identified in the completeness check of the company's study pool (study NIPICOL). The company had identified this study, but excluded it from its study pool. The exclusion of this study is not conclusive. This is explained in Section 2.3.1.4.

2.3.1 Evidence provided by the company

2.3.1.1 Study CA209-6EP – comparison of individual arms from different studies

The CA209-6EP study is a comparison of individual arms of different studies consisting of individual patient data on nivolumab + ipilimumab from a prospective cohort study (cohort 2 of study CA209-142) and individual patient data from the Flatiron Health database for representing the ACT. For this study, the company prepared a study protocol and a statistical analysis plan (SAP), but no entry was made in a study registry. The company did not submit a CSR. The following information on this study is limited to the information provided by the company in Module 4 O of the dossier.

Overall, the CA209-6EP study is not suitable for the derivation of an added benefit of nivolumab + ipilimumab in comparison with the ACT specified by the G-BA, however. This is mainly due to the following aspects:

- The company's information retrieval for identifying relevant confounders is unsuitable for ensuring the completeness of the results.
- The information available in the data set on the confounders identified as relevant by the company is incomplete, which led to partial non-consideration of relevant confounders without the company drawing any conclusions from this.

- The included patient populations show a marked structural inequality with regard to the confounders recorded, which cannot be sufficiently compensated for by means of confounder adjustment.

The CA209-6EP study presented by the company is described below, providing detailed reasons as to why the analyses do not allow an assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT. Further information on the study characteristics is presented in Appendix B of the full dossier assessment.

Data sources for the CA209-6EP study

The company stated that a systematic search did not identify any suitable interventional clinical studies for conducting an adjusted indirect comparison with a common comparator. Therefore, the company set up its own study in which the comparator arm was compiled from individual patient data (IPD) from the Flatiron Health database and was compared with the data from the CA209-142 study. This comparison of individual arms from different studies was limited to the outcome of overall survival, for which, according to the company, completely collected data were available in both data sources. From the perspective of the company, the data on side effects in the CA209-6EP study cannot be assessed due to the lack of available suitable registry data.

The studies and data sources used for the CA209-6EP study as well as the patient populations used from them are described below.

Study CA209-142 (data source for the intervention arms of the CA209-6EP study)

The ongoing CA209-142 study is an open-label, uncontrolled, prospective phase 2 cohort study with a total of 7 cohorts. It included adults with metastatic or recurrent colorectal cancer (mCRC) who had progressed on or after, or been intolerant of, previous fluoropyrimidine-based chemotherapy (Eastern Cooperative Oncology Group [ECOG] Performance Status ≤ 1). The administration of nivolumab as monotherapy or in combination with various other drugs is investigated in the 7 cohorts. For the CA209-6EP study, the company considered exclusively cohort 2, where patients received nivolumab + ipilimumab after at least one prior therapy.

The patients received intravenous (IV) nivolumab 3 mg/kg body weight (BW) every 3 weeks for 4 cycles, followed by IV ipilimumab 1 mg/kg BW and then IV nivolumab 3 mg/kg BW every 2 weeks (Table 10 of the full dossier assessment). Treatment was conducted until disease progression, toxicity or withdrawal of consent. The dosing of nivolumab in the monotherapy phase deviates from the specifications of the SPC, which recommends a BW-independent dosage of 240 mg every 2 weeks [6]. This deviation is deemed acceptable by the European Medicines Agency (EMA) [7].

The primary outcome of the study was the objective response rate assessed by the investigator. Further patient-relevant outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs). European approval was granted based on data from a data cut-

off on 19 February 2019 supplemented by results from an updated data cut-off from October 2020 [7]. In the dossier, the company presented data from the most recently updated data cut-off from October 2020.

For the CA209-6EP study, the company considered all patients of cohort 2 of the CA209-142 study, which comprised 119 patients with locally recorded dMMR/MSI-H status.

Flatiron Health database (data source for the comparator arm of the CA209-6EP study)

From the Flatiron Health database, the company extracted data for adult patients (ECOG ≤ 1) with dMMR and/or MSI-H mCRC who had received at least one prior therapy with a fluoropyrimidine combined with oxaliplatin or irinotecan and had received standard chemotherapy in the subsequent line of treatment (see Table 9 of the full dossier assessment).

The company referred to the patient-specific treatment defined by the G-BA as the ACT and stated that it had implemented these comparator therapies by extracting corresponding patient data from the Flatiron Health database. In Module 4 O, the company presented a list of the used drugs (see text below for details).

The data retrospectively extracted by the company from the Flatiron Health database refer to patients who were diagnosed with the disease between January 2013 and January 2021.

According to the information provided by the company in the dossier, the patients were observed for the outcome of overall survival until death, last contact date or treatment with an immuno-oncological or investigational therapy.

From the Flatiron Health database, the company included a cohort of 146 patients meeting the criteria listed above for the CA209-6EP study.

Confounders: identification, completeness and adjustment in the CA209-6EP study

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors that are related to both the treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The first prerequisite for this is that relevant confounders are systematically identified. Then it must be ensured that the data set used contains the necessary information on the identified confounders. Based on this, a possible biasing effect of confounders must then be taken into account adequately using suitable adjustment methods (e.g. propensity score weighting).

For the primary analysis of the outcome of overall survival, the company applied an inverse probability of treatment weighting (IPTW) method based on the propensity score.

As sensitivity analyses, the company presented an unadjusted comparison using a univariate regression model, a multivariate regression model using the confounders determined by the company as covariates, a propensity score matching, and an IPTW complete cases analysis

(taking into account only those patients for whom complete information on the confounders was available). Furthermore, it calculated the IPTW analysis, the unadjusted comparison and the propensity score matching for the outcome of overall survival without censoring the patients with subsequent immuno-oncological therapy. Already due to the present situation of a non-randomized study, the unadjusted calculations of the company are not suitable for deriving a conclusion, and can therefore only serve as a starting point for the assessment of overall survival.

The following text describes the procedure of the company as well as the deficiencies regarding the identification, completeness and adjustment of the confounders, which led to the exclusion of the CA209-6EP study.

Identification of confounders in the CA209-6EP study

The company stated that it had conducted a systematic literature search for the CA209-6EP study to identify indirect comparisons or network meta-analyses in the therapeutic indication of mCRC, identifying the confounders it considered relevant.

The company's information retrieval for searching for relevant confounders (Appendix 4 G2 of the dossier) is unsuitable for ensuring the completeness of the results, however. This is due, among other things, to the fact that the company named the inappropriate reason for exclusion "systematic literature searches", which potentially also take into account observational studies, which are important sources for identifying the relevant confounders. Furthermore, the composition of the study pool of the company is not comprehensible, as not all studies completely fulfil the inclusion and exclusion criteria. For example, the 2 observational studies Fujii 2019 [8] and Quan 2017 [9] were included, although the company had formulated this type of study as a reason for exclusion.

Completeness of the relevant confounders

The choice of relevant confounders is essential for the adequate adjustment and analysis of non-randomized comparisons.

In Appendix 4 G of the dossier, the company described that its systematic literature search revealed 13 publications in which indirect comparisons with confounder adjustment were conducted. According to the company, 6 of the 13 publications were based on clinical studies; the other 7 publications referred to retrospective patient information from clinical databases.

The company explained that, of the confounders identified in the systematic literature search, only those that are mentioned in at least 3 publications were considered for the propensity score in the CA209-6EP study. This procedure resulted in 9 potential confounders. However, of these 9 confounders, the company subsequently did not consider 3 confounders: On the one hand, this was the confounder "region". It justified this by stating that all patients from the Flatiron Health database came from the United States. On the other hand, this concerned the confounder "number of metastatic sites/organs" and "primary tumour resection". In the opinion of the

company, these could not be taken into account, as the Flatiron Health database did not provide any information on them. This initially left 6 confounders.

In Module 4 O, Section 4.2.5.6, of the dossier, the company explained that, in addition to the confounders identified in the systematic literature search, it also used the confounders rated as relevant in a consultation with the G-BA for the propensity score of the indirect comparison in the CA209-6EP study [10]. The company's approach resulted in a total of 10 confounders that it used for the propensity score.

The company's approach in the choice of relevant confounders is not appropriate in several aspects. For example, it did not explain why potential confounders that were named in fewer than 3 publications identified by the company were not taken into account or were not considered relevant by the company. This apparently arbitrary limit can lead to the exclusion of potentially relevant confounders. An indication of this is that, for example, 2 of the additional confounders included by the company (rapidly accelerated fibrosarcoma – isoform B [BRAF] mutation status, family origin) were also identified in the systematic search of the company, but were mentioned in ≤ 2 publications.

The company did not draw any conclusions from the non-consideration of the confounders "number of metastatic sites/organs", "primary tumour resection" and "region" identified as relevant by the company. This is not appropriate, as the possible influence that the missing information on relevant confounders has on the certainty of results and on the observed effects of the outcome of overall survival of the CA209-6EP study was thus not addressed. For example, there is no assessment of how a missing adjustment for potentially relevant confounders could affect the effect estimation of this outcome and of the extent of an observed effect at which a sufficiently reliable conclusion, for example on an added benefit, is still possible.

Insufficient overlap of the propensity score of the groups to be compared

In the IPTW analysis used by the company as the primary analysis (and also the IPTW complete cases analysis), weighting is carried out according to propensity scores based on the confounders taken into account by the company. A prerequisite for the application of the method is sufficient overlap, measured by the propensity score of the cohorts compared (cohort 2 of study CA209-142 and the cohort from the Flatiron Health database) [11].

However, the propensity score graph of the IPTW analysis shows that the 2 populations differ notably in this respect (Figure 1). This means that the 2 interventions to be compared were used in completely different patient populations. The results of this analysis are therefore not usable and cannot be used to answer the original research question [12]. The same can be seen in the propensity score graph for the IPTW complete cases analysis.

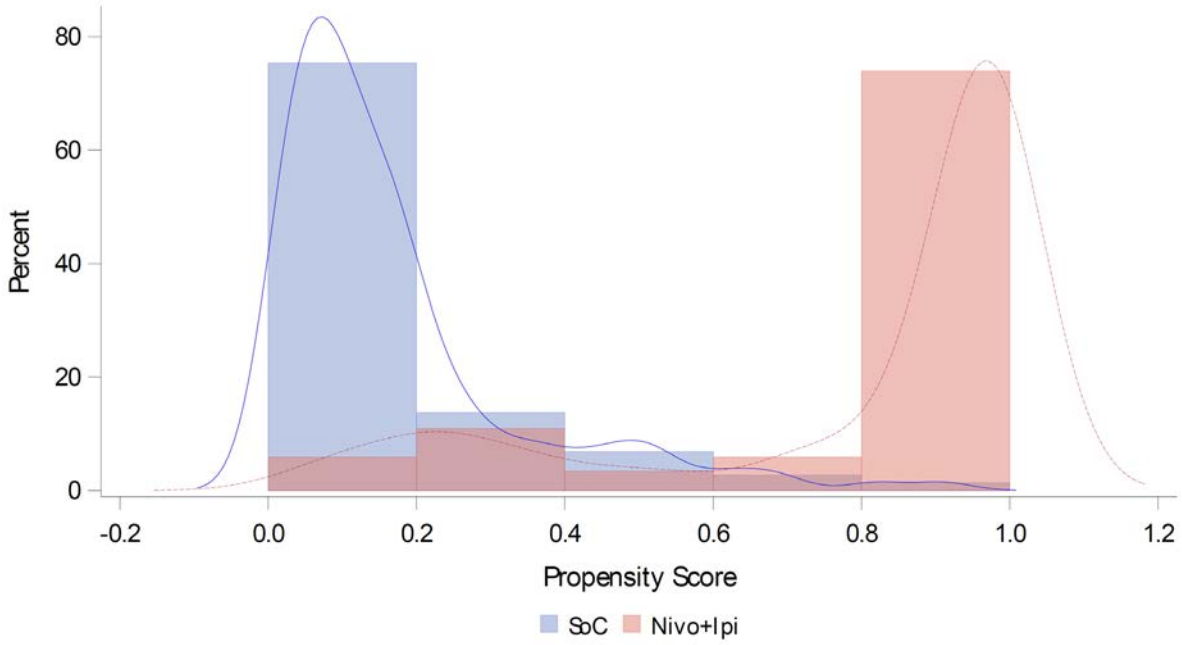

Figure 1: Propensity score graph of the IPTW analyses for the non-randomized comparison of the CA209-6EP study

If there is insufficient overlap between the groups to be compared, the application of a regression model is also not meaningful. In this case, a regression model would work with extrapolations that are not valid, since associations are transferred to areas where no observations are available at all [13]. Thus, the multiple regression of the company, in which adjustments are made for the final confounder list, does not provide a robust result.

Although the propensity score matching achieves a good overlap of the compared populations, only 29 patients remain in each cohort. The company did not provide any patient characteristics for these, so that it cannot be assessed which patients were included in the analysis and for which population conclusions on the added benefit would be possible. Irrespective of this, no statistically significant difference between the interventions can be observed in this analysis with regard to the outcome of overall survival.

Summary

In summary, key aspects regarding the comparison of individual arms from different studies (non-randomized retrospective study) [11] were not taken into account, which is why the analyses presented by the company for the CA209-6EP study do not allow an adequate comparison of nivolumab + ipilimumab with the ACT.

Further deficiencies of the CA209-6EP study

Appropriate implementation of the ACT

The company stated that, from the Flatiron Health database, it extracted the data of the patient population that received the ACT of a patient-specific therapy specified by the G-BA. A list of

the drugs considered by the company was provided by the company in Module 4 O. This shows that 39 of the 146 (26.7%) patients identified as relevant cohort by the company had received a treatment option that deviates from the specification of the G-BA (Table 11 of the full dossier assessment). The treatment options used in deviation from the specification included both combinations of approved drugs and combinations of drugs that are not approved for the therapeutic indication of mCRC (daratumumab, lenalidomide, binimetinib or vemurafenib). Regorafenib, which is not marketed in Germany and is currently not a treatment option, was also used in 5 (3.4%) patients. For the population resulting from the propensity score matching, information on the therapies used is also missing, so that it is possible that the proportions of therapies that do not correspond to the ACT are even higher.

Besides, on the basis of the available data, it is not possible to check to what extent the remaining drugs, which correspond to the ACT, were administered in accordance with the respective SPCs.

Overall, it is therefore questionable whether the CA209-6EP study included an appropriate implementation of the ACT.

Time point of preparation of the statistical analysis plan

The company described key aspects and methods of analysis of the CA209-6EP study in a study protocol and SAP. Even in retrospective study designs, these documents should be prepared without knowledge of the data. However, the study protocol is dated 12 March 2021. Since both data cut-offs used by the company were before the preparation of the study protocol, it is questionable whether the study protocol and the SAP were prepared without knowledge of the data.

2.3.1.2 Before-after comparisons of the CA209-142 study

For conclusions on the outcome categories of morbidity and health-related quality of life, the company used the uncontrolled, prospective phase 2 cohort study CA209-142 (explicitly cohort 2) (see Section 2.3.1.1). This study recorded outcomes on symptoms and health-related quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) as well as the general health status using the EQ-5D visual analogue scale (VAS). The company carried out before-after comparisons on the basis of the CA209-142 study by calculating the proportions of patients with an MID of 7, 10 or 15 points for the individual outcomes of the EORTC QLQ-C30 and the EQ-5D VAS, both with regard to an improvement and a worsening compared with baseline.

The before-after comparisons used by the company for the assessment of morbidity and health-related quality of life are unsuitable for the derivation of an added benefit, as they do not allow a comparison with the ACT.

2.3.1.3 Comparison with individual arms of RCTs

In contrast to the outcome of overall survival, the company did not conduct a confounder-adjusted comparison for the outcome category of side effects. The company justified this by stating that most IPD in the Flatiron Health database were from oncology clinics and that therefore outcomes in the side effects category were not recorded as systematically as in clinical studies.

In order to nevertheless obtain an overview of the side effects of the ACT, the company used freely available study data. For this purpose, the company used the 4 most common treatments used in the patients from the Flatiron Health database. This corresponds to a total proportion of 39.7% of the Flatiron Health cohort considered by the company.

For these 4 treatments, the company conducted a targeted bibliographic literature search as well as a search for studies in the therapeutic indication in trial registries and on the G-BA website, without differentiating between MSI-H and non-MSI-H.

With this approach, the company identified the following 4 studies:

- ML18147 (arm: 5-fluorouracil [5-FU] + folinic acid + oxaliplatin [FOLFOX] + bevacizumab **or** 5-FU + folinic acid + irinotecan [FOLFIRI] + bevacizumab, depending on prior therapy) [14];
- RAISE (arm: FOLFIRI) [15];
- ECOG E3200 (arm: FOLFOX + bevacizumab) [16]
- CRYSTAL (arm: FOLFIRI + cetuximab) [17].

The company conducted a descriptive comparison of the data on the overall rates of AEs, serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), as well as AEs that led to treatment discontinuation, from the respective arms of these 4 studies against the data from the CA209-142 study (cohort 2). From this comparison, the company concluded that the side effects of nivolumab + ipilimumab are comparable overall with the ACT.

The approach of the company is not appropriate. The information retrieval was non-systemic and is therefore not suitable for ensuring the completeness of the search results. The company did not submit a documentation of the search strategy. Besides, limiting the search to the 4 most common treatments in the cohort from the Flatiron Health database is not adequate, particularly as these only constitute about 40% of the treatment options in this cohort and therefore do not provide a comprehensive reflection of the ACT. In addition, each of these 4 studies has further arms potentially corresponding to the ACT, which the company excluded from its analysis without justification.

Irrespective of this, when comparing individual arms from different studies, conclusions can only be derived if large effects are present because of the large uncertainty. There were no such effects, however. A comparability of the therapies with regard to side effects in the sense of equivalence cannot be derived on this basis, either.

For the reasons mentioned, the descriptive comparison presented by the company is unsuitable for drawing conclusions on the added benefit of nivolumab + ipilimumab in comparison with the ACT.

2.3.1.4 Exclusion of the NIPICOL study unclear

The check of the completeness of the study pool of the company for nivolumab + ipilimumab identified the NIPICOL study [18-20].

This study is a single-arm, open-label phase 3 study conducted in 8 centres in France. It included adult patients (ECOG ≤ 1) with histologically confirmed mCRC and locally determined MSI-H/dMMR with measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

The patients were treated with IV nivolumab 3 mg/kg BW every 3 weeks for 4 cycles, followed by IV ipilimumab 1 mg/kg BW, and then with a maximum of 20 infusions of IV nivolumab 3 mg/kg BW every 2 weeks.

Primary outcome was the disease control rate after 12 weeks according to RECIST 1.1 and to iRECIST, the instrument modified for immunotherapeutics. Overall survival and AEs were recorded as patient-relevant outcomes.

Apart from differences in the primary outcome and the mandated duration of treatment, among other things, the characteristics of the NIPICOL study and the approval study CA209-142 used by the company are very similar.

Module 4 O shows that the company identified the NIPICOL study in its search for further investigations with the drug to be assessed in the EU Clinical Trials Register, but excluded it due to missing results on patient-relevant outcomes. Results on the patient-relevant outcomes of overall survival and AEs had been published before the date of the company's search, however [18]. The company's reason for exclusion is therefore not appropriate. However, since the company did not present any suitable data for the derivation of the benefit overall, this had no consequence.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of nivolumab + ipilimumab in its dossier. This resulted in no hint of added benefit of nivolumab + ipilimumab in comparison with the ACT in adult patients with dMMR or MSI-H mCRC that has progressed

after prior fluoropyrimidine-based combination chemotherapy. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT is summarized in Table 5.

Table 5: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability after prior fluoropyrimidine-based combination chemotherapy[b]	Patient-specific treatment[c, d] depending on the type and number of prior therapies, the RAS and BRAF mutation status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR agents, choosing from the following options ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[e] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil ± folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[e] ▪ cetuximab monotherapy[e] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[e] ▪ encorafenib + cetuximab[f]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b. It is assumed that there is no therapeutic indication for treatment with curative intent or for primary or secondary resectability.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Regorafenib is currently not marketed in Germany and therefore does not represent a treatment option in the context of the ACT at this time. Based on the available evidence, mitomycin is also not considered a suitable treatment option in the context of antineoplastic treatment of physician's choice.
e. Only for patients with RAS wild type.
f. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The assessment described above deviates from that of the company, which claimed a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Bristol-Myers Squibb. An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread [online]. 2019 [Accessed: 27.08.2021]. URL: https://ClinicalTrials.gov/show/NCT02060188.

4. Bristol-Myers Squibb International. A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite High (MSI-H) Colon Cancer [online]. [Accessed: 27.08.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003939-30.

5. Overman MJ, Lonardi S, Wong KYM et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol 2018; 36(8): 773-779. https://dx.doi.org/10.1200/JCO.2017.76.9901.

6. Bristol Myers Squibb. OPDIVO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 11.08.2021]. URL: https://www.fachinfo.de/.

7. European Medicines Agency. Opdivo; Assessment Report [online]. 2021 [Accessed: 03.08.2021]. URL: https://www.ema.europa.eu/documents/variation-report/opdivo-h-c-3985-ws-1840-epar-assessment-report-variation_en.pdf.

8. Fujii H, Matsuhashi N, Kitahora M et al. Bevacizumab in Combination with TAS-102 Improves Clinical Outcomes in Patients with Refractory Metastatic Colorectal Cancer: A Retrospective Study. Oncologist 2019; 25(3): e469-e476. https://dx.doi.org/10.1634/theoncologist.2019-0541.

9. Quan Q, Huang Y, Chen Q et al. Impact of Serum Apolipoprotein A-I on Prognosis and Bevacizumab Efficacy in Patients with Metastatic Colorectal Cancer: a Propensity Score-Matched Analysis. Transl Oncol 2017; 10(2): 288-294. https://dx.doi.org/10.1016/j.tranon.2017.01.006.

10. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV - Beratungsanforderung 2020-B-208 - Nivolumab zur Behandlung des metastasiertem Kolorektalkarzinoms [unpublished]. 2020.

11. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

12. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ 2019; 367: l5657. https://dx.doi.org/10.1136/bmj.l5657.

13. Williamson E, Morley R, Lucas A et al. Propensity scores: from naive enthusiasm to intuitive understanding. Stat Methods Med Res 2012; 21(3): 273-293. https://dx.doi.org/10.1177/0962280210394483.

14. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013; 14(1): 29-37. https://dx.doi.org/10.1016/S1470-2045(12)70477-1.

15. Lilly Deutschland. Ramucirumab (Cyramza): Modul 4A - Kombinationstherapie mit FOLFIRI zur Behandlung von erwachsenen Patienten mit einem metastasierten Kolorektalkarzinom mit Tumorprogress während oder nach vorausgangener Therapie mit Bevacizumab, Oxaliplatin und einem Fluoropyrimidin [online]. 2016 [Accessed: 18.06.2021]. URL: https://www.g-ba.de/downloads/92-975-1398/2016-02-23_Modul4A_Ramucirumab.pdf.

16. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25(12): 1539-1544. https://dx.doi.org/10.1200/JCO.2006.09.6305.

17. Van Cutsem E, Kohne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360(14): 1408-1417. https://dx.doi.org/10.1056/NEJMoa0805019.

18. Cohen R, Bennouna J, Meurisse A et al. RECIST and iRECIST criteria for the evaluation of nivolumab plus ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the GERCOR NIPICOL phase II study. J Immunother Cancer 2020; 8(2). https://dx.doi.org/10.1136/jitc-2020-001499.

19. GERCOR. RECIST 1.1 and iRECIST evaluation for patients with deficient MMR and/or MSI Metastatic Colorectal Cancer treated with nivolumab and ipilimumab. A GERCOR open-label phase II study NIPICOL C17-01 [online]. [Accessed: 27.08.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002442-72.

20. GERCOR - Multidisciplinary Oncology Cooperative Group. Interest of iRECIST Evaluation for DCR for Evaluation of Patients With Deficient MMR and /or MSI Metastatic Colorectal Cancer Treated With Nivolumab and Ipilimumab [online]. 2021 [Accessed: 27.08.2021]. URL: https://ClinicalTrials.gov/show/NCT03350126.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-99.html.