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## Nivolumab (Opdivo®) for metastatic DNA mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

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# Abstract


## Introduction

Colorectal cancer (CRC) arises in the tissue that lines the inner surface of the intestine (colon and rectum). Nivolumab received accelerated approval by the US Food and Drug Administration (FDA) in July 2017 for the following indication: as monotherapy for the treatment of patients that are 12 years and older with DNA mismatch repair-deficient (dMMR) and microsatellite instability-high (MSI-H) metastatic CRC that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The FDA approval was based on one part of the CheckMate 142 study. Currently, nivolumab is not approved for CRC in Europe.

## Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer (overall: 125 references). Quality assessment to assess the risk of bias at the study level based on the EUnetHTA internal validity was not conducted, since this tool is only for randomised controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from nivolumab was evaluated based on the Magnitude of Clinical Benefit Scale v1.1 (MCBS) developed by the European Society for Medical Oncology (ESMO).

## Results from the CheckMate 142 study

The CheckMate 142 study is separated into two parts, investigating nivolumab monotherapy or nivolumab in combination with ipilimumab. The part of the study examined in the present report was conducted to assess the activity and safety of nivolumab monotherapy in 74 patients with metastatic dMMR/MSI-H CRC. At the time of data cut-off (3 January 2017), 23 (31.1%) of the 74 included patients demonstrated an objective response (OR) – all responses were partial (investigator-assessed). An OR assessed by blinded independent central review (BICR) occurred in 24 (32%) patients (dMMR/MSI-H per local assessment); out of those, 2 (3%) patients had a complete response and 22 (30%) a partial one. After 36 investigator-assessed progression events had happened, the median progression-free survival (PFS) was 14.3 months, but was not mature at the time of data cut-off. In addition, median overall survival (OS) (23 deaths) had not been reached at the time of interim analysis. In regard to safety outcomes, drug-related adverse events (AEs) occurred in 70% of patients; out of those, 20% of patients had grade ≥3 AEs (most frequent: increased lipase and amylase). Serious AEs related to the study treatment of grade 3 or higher occurred in 12% of patients.

## Conclusion

In conclusion, the treatment of nivolumab offers durable responses; 31.1% demonstrated partial responses with an acceptable safety profile at high costs. However, the immature OS data, in combination with the lack of evidence for the actual patient population affected most by CRC in clinical practice, highlight the requirement for long-term data. Moreover, head-to-head comparisons will be necessary to identify the best treatment option for CRC patients with dMMR/MSI-H. Finally, trustworthy biomarker testing will be needed to select those patients who benefit most from nivolumab.

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# 1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

**EUnetHTA HTA Core Model®**

| Element ID | Research question |
|---|---|
| **Description of the technology** | |
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# 2 Drug description

## Generic/Brand name/ATC code:

Nivolumab/Opdivo®/L01XC17

### B0001: What is nivolumab?

nivolumab is a human IgG4 monoclonal antibody against PD-1

The programmed cell death receptor-1 protein (PD-1) is expressed on several cell types such as T-cells, B-cells, monocytes and natural killer cells [2]. The binding of the two known ligands of PD-1, PD-L1 and PD-L2, results in the inhibition of T-cell proliferation and cytokine production [2, 3]. Therefore, the interaction of PD-1 with its ligands inhibits T-cell receptor signalling as well as downregulates T-cell response [2]. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that blocks binding of PD-1 to PD-L1 and PD-L2. Since PD-L1 is upregulated in some tumours, the blockade of these interactions can retrieve T-cell activity and cell-mediated immune response against these tumour cells [2, 3].

intravenous infusion every two weeks

Nivolumab monotherapy is administered as an intravenous infusion over 60 minutes at a dose of 3 mg per kilogram of body weight every two weeks [4]

### A0022: Who manufactures nivolumab?

Bristol-Myers Squibb

# 3 Indication

### A0007: What is the target population in this assessment?

dMMR/MSI-H metastatic CRC

Nivolumab is indicated for the treatment of patients with DNA mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic CRC, who have progressed on or after, or been intolerant of at least one previous line of treatment, including fluoropyrimidine and oxaliplatin or irinotecan.

# 4 Current regulatory status

**A0020: For which indications has nivolumab received marketing authorisation?**

not approved for metastatic CRC by the EMA, but for various other indications

To date, nivolumab is not approved for the treatment of patients with dMMR and MSI-H metastatic CRC by the European Medicines Agency (EMA). The EMA granted marketing authorisation of nivolumab for the following indications [5]:

- for the treatment of NSCLC that has spread locally or to other parts of the body, in patients who have previously been treated with chemotherapy (February 2016)
- for the treatment of advanced RCC as monotherapy in previously treated patients (April 2016)
- for the treatment of advanced melanoma as monotherapy or in combination with ipilimumab (May 2016)
- for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant and treatment with brentuximab vedotin (October 2016)
- for the treatment of SCCHN as monotherapy in adults progressing on or after platinum-based therapy (April 2017)
- for the treatment of locally advanced unresectable or metastatic UC as monotherapy in adults after failure of prior platinum-containing therapy (June 2017)

accelerated FDA approval for CRC in July 2017

additional approved indications of nivolumab in the US

In July 2017, the US Food and Drug Administration (FDA) granted accelerated approval for nivolumab for the treatment of patients who are 12 years and older with dMMR and MSI-H metastatic CRC that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The approval was based on the CheckMate 142 study. Moreover, nivolumab has received marketing authorisation by the FDA for several other indications [3]:

- for the treatment of BRAF V600 wild-type unresectable or metastatic melanoma as monotherapy (September 2015)
- for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma as monotherapy (September 2015)
- for the treatment of unresectable or metastatic melanoma in combination with ipilimumab (September 2015)
- for the treatment of metastatic NSCLC patients, who have progressed on or after receiving platinum-based chemotherapy (October 2015)
- for the treatment of advanced RCC patients, who have received prior anti-angiogenic therapy (November 2015)
- for the treatment of patients with cHL who relapsed or progressed after:

  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - three or more lines of systemic therapy that includes autologous HSCT (May 2016)
- for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy (November 2016)
- for the treatment of previously treated locally advanced or metastatic UC (February 2017)

# 5 Burden of disease

### A0002: What is colorectal cancer?

CRC arises in the tissue of the inner surface of the colon or rectum

CRC is a malignancy that arises in the tissue that lines the inner surface of the intestine (colon and rectum). More than half (62%) of all bowel cancers arise from the colon and almost one-third (29%) arise from the rectum (including the anus) [6, 7]. Histologically, CRC can be differentiated into: adenocarcinomas, squamous cell carcinomas, carcinoid tumours, sarcomas, and lymphomas [7].

various genetic subtypes of CRC

Generally, a large proportion of CRC tumours are characterised by the activation of the wnt/B-catenin pathway. In cases of metastatic diseases over 50% of patients carry RAS (KRAS or NRAS) mutations and in 5–10% of patients BRAF mutations are present. Furthermore, HER-2 amplifications occur in 2–5% of CRCs [8]. A subset of CRCs demonstrate markedly elevated mutational rates; these are mainly tumours characterised by MSI-H, which is associated with inactivating alterations in MMR genes [8, 9]. In general, MSI-H tumours account only for a minority of CRCs, whereby the frequency decreases in more advanced stages of the disease. A small proportion of hyper-mutated CRC tumours are seen to have polymerase mutations, especially within the catalytic domain of DNA polymerase epsilon (POLE) or delta (POLD1) [8].

### A0004: What is the natural course of colorectal cancer?

commonly CRC arises as a flat or raised polyp in the colon or rectum

Mostly, CRC starts as a flat or raised polyp in the tissue that lines the inner surface of the colon or rectum. It can spread by lymphatic and haematogenous dissemination, as well as by contiguous and transperitoneal routes. In the majority of instances metastatic sites occur in the regional lymph nodes, liver, lungs, and the peritoneum [6].

prevalence of MSI-H:
22% stage II
12% stage III
3% stage IV

The preferred staging system for CRC is the tumour, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC). It classifies tumours on the basis of primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The final stage (ranging from I to IV) is dependent on the particular combination of T, N, and M characteristics [10].

The prevalence of MSI-H in the stages II, III and IV for CRC is 22%, 12%, and 3%, respectively [8].

MSI arises from germline or somatic mutations

MSI results from germline (inherited) or somatic (sporadic; acquired) mutations. DNA mismatch errors are usually repaired by mismatch repair protein complexes. If these do not function, DNA errors accumulate, which is a condition of genetic hypermutability, like in the case of MSI [11]. On the contrary, dMMR deficiency is not a direct transforming event, since most oncogenic alterations found in dMMR patients have originated from somatic mutation events occurring as a result of MSI [9].

### A0006: What are the consequences of colorectal cancer for the society?

increasing incidence of CRC

association with the socioeconomic status

Due to the ageing population and in combination with the fact that higher age is related to increased CRC risk, the incidence of cancer will grow over time [12, 13]. Globally, CRC is the third most common cancer, with almost 1.4 million new cases diagnosed in 2012 [14]. In addition, low socioeconomic status is associated with an increased risk for the development of CRC. The incidence of CRC varies more than tenfold worldwide. Socioeconomic disparity particularly in the new-onset risk of CRC may be due to modifiable behaviours like physical inactivity, unhealthy diet, smoking, and obesity [13].

### A0023: How many people belong to the target population?

incidence rate of CRC: 55.0 per 100,000 persons/year (European Standard Population)

median age at diagnosis in years:
♂ 73
♀ 75

Carcinomas of the colon and rectum are the third leading cause of death in men (13%) and the second leading cause of death in women (11%) due to cancer in Austria (2014). Two-thirds of all diagnosed intestine cancers occurred in the colon, 30% in the rectum, and all others in the transition of the colon and rectum or the anal canal (small intestine carcinomas are not included). In 2014, 4,567 new cases of colon and rectum cancer (men: 2,585; women: 1,982) were diagnosed in Austria, with a corresponding age standardised incidence rate for the European Standard Population of 55.0 cases per 100,000 persons [15]. The median age at diagnosis of CRC is 73 years in men and 75 in women (range: 70–75) [16].

metastatic disease: 20%
MSI-H: 15%
MMR: 3%

One in five patients with CRC (20%) is present with metastatic disease at the time of diagnosis and the survival rate of CRC patients with distant metastasis is about 12% [10, 17]. In approximately 15% of CRCs the tumour subtype MSI-H is represented, and only 3% of all CRCs have a germline MMR mutation (Lynch syndrome) [8, 9]. As a result, about 700 of the 4,567 persons diagnosed with CRC in 2014 in Austria were affected by dMMR and/or MSI-H.

### A0005: What are the symptoms and the burden of colorectal cancer?

early stage of cancer is often asymptotic

The majority of CRC patients with an early stage of cancer do not show any characteristic symptoms or signs [10, 16]. If symptoms are present, they typically occur because of the tumour growth into the lumen or nearby structures; therefore, a symptomatic representation usually reflects relatively advanced cancer. However, CRC patients may be presented in the following three ways: suspicious symptoms and/or signs, asymptomatic individuals discovered by routine screening, and emergency admission with intestinal obstruction, peritonitis or, rarely, acute gastrointestinal bleeding [10].

### A0003: What are the known risk factors for colorectal cancer?

generally, environmental & genetic risk factors

In general, environmental as well as genetic factors can increase the probability of developing CRC. The predominant risk factors for developing CRC are the following: hereditary forms of CRC, age, personal or family history of sporadic CRC, inflammatory bowel disease, and a history of abdominal irradiation [13]. Further, factors that may have an impact on the risk of CRC are cigarette smoking, alcohol, and obesity [18].

### A0024: How is colorectal cancer currently diagnosed according to published guidelines and in practice?

initial diagnosis: colonoscopy (+ biopsy), rectoscopy/ sigmoidoscopy (+ biopsy), and virtual colonoscopy

CRC may be suspected due to the aforementioned symptoms (A0005) or in cases of asymptomatic CRC it may be detected by routine screening [10]. Initial diagnosis is a digital rectal examination, primarily via a colonoscopy (including biopsy); if this is not applicable a rectoscopy/sigmoidoscopy (including biopsy), or virtual colonoscopy may be applied. To evaluate the spread of the disease and to plan the next steps of treatment, a sonography, a computed tomography (CT) or a magnetic resonance imaging (MRI) of the abdomen or the thorax can be used [10, 16]. After an established diagnosis, the determination of the extent of the primary tumour and of the metastasis is based on the TNM staging system. Additionally, serum carcinoembryonic antigen (CEA) levels may be obtained preoperatively and postoperatively in patients with demonstrated CRC to support surgical treatment planning and prognosis assessment [16].

# 6 Current treatment

### A0025: How is colorectal cancer currently managed according to published guidelines and in practice?

factors for therapeutic decision

Certain factors have to be taken into account for the therapeutic decision on CRC [16, 19]:

- Localisation of the primary tumour
- Stage of cancer (TNM staging system)
- Mutations in certain genes (e.g., MSI, BRAF, Lynch syndrome)
- Health condition of the patient (Eastern Cooperative Oncology Group [ECOG] performance scale)

stage I, II, III treatment

Stage I, II or III CRC is commonly treated by surgical resection with curative intent. Adjuvant chemotherapy (5-fluorouracil, folinic acid, capecitabine, oxaliplatin) should be considered if a higher risk of recurrence is present. This includes mostly patients with stage III (node-positive) CRC, whereas in cases of CRC patients with MSI, no adjuvant chemotherapy is recommended.

therapy options for stage IV CRC:

Therapy options for stage IV CRC patients are [16, 19]:

for resectable and unresectable metastasis

- Resectable metastasis
  - Chemotherapy (FOLFOX in combination with oxaliplatin or irinotecan)

- Unresectable metastasis
  - RAS or BRAF mutation
    - fluoropyrimidine plus oxaliplatin and/or irinotecan with or without bevacizumab
  - RAS or BRAF wild-type
    - fluoropyrimidine plus oxaliplatin or irinotecan in combination with an anti-EGFR antibody (cetuximab, panitumumab)
  - Patients with severe comorbidities
    - 5-fluorouracil or capecitabine in combination with bevacizumab or best supportive care

- ≥Second-line therapy options (dependent on prior therapy and the RAS mutation status) [16, 19]:

≥Second-line therapy options:

  - Prior irinotecan-based therapies → oxaliplatin in combination with fluoropyrimidine; if prior irinotecan therapy did not include bevacizumab → FOLFOX in combination with bevacizumab

prior irinotecan-based therapy

  - Prior oxaliplatin → fluoropyrimidine in combination with irinotecan

prior oxaliplatin

  - Prior oxaliplatin-based therapies → FOLFIRI chemotherapy in combination with aflibercept
  - Prior bevacizumab- or oxaliplatin-based therapy → ramucirumab in combination with FOLFIRI

prior bevacizumab

  - RAS wild-type patients who have not received an EGFR antibody → EGFR antibody in combination with chemotherapy

RAS wild-type

  - Failure of all established chemotherapies and monoclonal antibodies → regorafenib or fluoropyrimidine TAS 102

chemotherapy/ monoclonal antibodies

  - BRAF mutation → vemurafenib in combination with cetuximab/irinotecan

BRAF mutation

  - MSI mutations → off-label use of pembrolizumab and nivolumab (both approved by the FDA), as well as trastuzumab/lapatinib

MSI mutation

# 7 Evidence

A literature search was conducted on 19 October 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “nivolumab”, “Opdivo”, “L01XC17”, “colon cancer”, “colorectal cancer” and “bowel cancer”. The manufacturer was also contacted and submitted two references (one of which had already been identified by systematic literature search). A manual search identified 17 additional references (web documents and journal articles).

systematic literature search in 5 databases: 108 hits

manual search: 17 additional references

overall: 125 references included: 1 study

Overall, 125 references were identified. Included in this report is the following study to assess outcomes on clinical efficacy and safety:

- One phase II study (two parts), assessing nivolumab or nivolumab in combination with ipilimumab in patients with metastatic dMMR/MSI-H CRC [20-22].

study level risk of bias assessment based on EUnetHTA internal validity not conducted

The assessment of the risk of bias at the study level and the assessment of the methodological quality of the evidence based on the EUnetHTA internal validity has not been conducted, since this tool is only for randomised controlled trials (RCTs) [23].

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS version 1.1) was used [24, 25]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

## 7.1 Clinical efficacy and safety – phase II study

CheckMate 142: open-label, ongoing, single-arm, multicentre phase II study

CheckMate 142 (open-label, ongoing, multicentre, single-arm phase II study) was conducted to assess the efficacy and safety of nivolumab or nivolumab in combination with ipilimumab in patients with metastatic dMMR/MSI-H CRC, who have progressed on or after, or been intolerant of at least one previous line of treatment, including fluoropyrimidine and oxaliplatin or irinotecan [21, 22]. Reported in the current study are only the interim results for nivolumab monotherapy. At the time of data cut-off (3 January 2017), 74 patients with locally determined dMMR/MSI-H metastatic CRC were receiving nivolumab, with a median follow-up of 12.0 months (interquartile range [IQR] 8.6–18.0). Additionally, 36 (49%) of the 74 patients were still receiving the study treatment at the time of data cut-off; 38 patients (51%) discontinued (27 progressed, six had treatment-related toxic effects, one had adverse events [AEs] unrelated to study drug, one had a maximum clinical benefit, one due to patient decision, one due to withdrawal of consent, and one due to other reasons).

74 patients with dMMR/ MSI-H CRC

A total of 74 patients were enrolled to receive 3 mg/kg dose of nivolumab every two weeks until disease progression, death, unacceptable toxic effects, withdrawal from the study or study end. Out of these 74 patients who had been locally assessed as having dMMR/MSI-H metastatic CRC, 53 (72%) patients were centrally determined to have MSI-H tumours and 14 (19%) to have non-MSI-H (microsatellite-stable [MSS]/MSI-low) tumours. For seven patients (9%) insufficient adequate tumour tissue or DNA was available. Therefore, these patients had no centrally determined results. 29 (39%) of 74 patients were both BRAF and KRAS wild-type, and 12 (16%) had tumours with a BRAF mutation.

centrally determined status:
72% MSI-H
19% MSS/ MSI-low
9% undefined

median age of 52.5 years and ECOG performance status of 0–2

Enrolled patients were at least 18 years old and had a median age of 52.5 (ranging from 44.0–64.0); 57 (77%) of the 74 enrolled patients were younger than 65 years. The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 1 and measurable disease defined by the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) guidelines. Detailed patient characteristics, including inclusion and exclusion criteria, can be found in Table 4.

The primary outcome of CheckMate 142 was investigator-assessed objective response (OR) as per RECIST 1.1; secondary outcomes included duration of response, rate of complete response and masked independent central review-assessed OR. Other exploratory endpoints included safety and tolerability of nivolumab monotherapy; progression-free survival (PFS); overall survival (OS); the association between biomarkers, such as PD-L1 expression, with nivolumab activity; and quality of life (QoL) changes from baseline.

primary outcome: OR assessed by investigators

## 7.1.1 Clinical efficacy

**D0001: What is the expected beneficial effect of nivolumab on mortality?**

At the time of interim analysis, median OS (23 deaths) had not been reached (95% CI 18.0–not estimable [NE]). The 12-month OS was 73% (95% CI 62–82).

median OS had not been reached, 12-month OS: 73%

**D0006: How does nivolumab affect progression (or recurrence) of colorectal cancer?**

Median PFS was 14.3 (95% CI 4.30–NE) months, after 36 investigator-assessed progression events had happened. The 12-month PFS was 50% (95% CI 38–61).

median PFS 14.3 months (after 36 events)

**D0005: How does nivolumab affect symptoms and findings (severity, frequency) of colorectal cancer?**

Per investigator assessment, 23 (31.1%, 95% CI 20.8–42.9) of the 74 patients who had locally assessed dMMR/MSI-H CRC demonstrated an OR; all of them were partial. In total, three responders had experienced progression. In 51 (69%, 95% CI 57–79) patients a disease control for at least 12 weeks was present. An OR assessed by the blinded independent central review (BICR) occurred in 24 (32%, 95% CI 22–44) patients (dMMR/MSI-H per local assessment); out of those, 2 (3%) patients had a complete response and 22 (30%) a partial one. 19 (36%, 95% CI 23–50) patients out of 53 centrally identified to have dMMR/MSI-H CRC showed an OR, independent of their assessment (by investigator or central review). Out of the 14 patients assessed as having non-MSI-H by the central review, three (21%, 95% CI 5–51) had an OR (all partial).

investigator-assessed OR: 31.1% (all partial)

BICR assessed OR: 32% (3% complete & 30% partial response)

The median time to response was 2.8 months (IQR 1.4–3.2) for investigator-assessed patients with locally determined dMMR/MSI-H metastatic CRC. All responders were alive at the time of data cut-off and the median duration of response had not yet been reached (95% CI NE).

median time to response 2.8 months

duration of response was not reached

**D0011: What is the effect of nivolumab on patients'body functions?**

Nivolumab may affect body functions by causing the following immune-mediated AEs: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, and skin adverse reactions. Furthermore, after the

immune-mediated AEs

complications during allogeneic HSCT

administration of nivolumab, complications can occur due to allogeneic hematopoietic stem cell transplantation (HSCT) [3].

**D0012: What is the effect of nivolumab on generic health-related quality of life?**

**D0013: What is the effect of nivolumab on disease-specific quality of life?**

**≥50% of patients had no clinically meaningful deterioration in functioning or worsening of symptoms, global health status/QoL**

Until week 97, patient-reported outcomes were measured. Questionnaire completion rates ranged from 68% to 100%. No clinically meaningful deterioration (≥10 point change) in functioning or worsening of symptoms and global health status or QoL, as per EORTC QLQ-C30, was experienced by 50% or more patients. At week 13, clinically meaningful improvements could be observed in functioning (emotional, role, and social), symptoms (fatigue, pain, insomnia, appetite loss, constipation, and diarrhoea), and global QoL. No meaningful improvements in physical functioning, nausea and vomiting, or dyspnoea occurred. In addition, clinically relevant worsening in cognitive functioning was observed at week 67. 12% of patients reported health problems at baseline as per EQ-5D, ranging from 12% (eight of 67 patients for self-care) to 57% (38 of 67 patients for pain). Notable (>10%) reductions in health problems occurred at week 13 for all dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression.

*Table 1: Efficacy results of CheckMate 142 study*

| | | | | | | |
|---|---|---|---|---|---|---|
| **Descriptive statistics and estimate variability** | Treatment group | | Nivolumab (dMMR/MSI-H per local assessment) | | Nivolumab (dMMR/MSI-H per central assessment) | |
| | Number of subjects (n) | | 74 | | 53 | |
| | Assessment | | Investigator | Blinded independent central review | Investigator | Blinded independent central review |
| | Objective response, n (%, 95% CI) | | 23 (31.1, 20.8–42.9) | 24 (32, 22–44) | 19 (36, 23–50) | 19 (36, 23–50) |
| | BOR | CR, n (%) | 0 (0) | 2 (3) | 0 (0) | 1 (2) |
| | | PR, n (%) | 23 (31) | 22 (30) | 19 (36) | 18 (34) |
| | | Stable disease, n (%) | 28 (38) | 25 (34) | 20 (37) | 19 (36) |
| | | Progressive disease, n (%) | 19 (26) | 21 (28) | 11 (21) | 12 (23) |
| | | Not determined, n (%) | 4 (5) | 4 (5) | 3 (6) | 3 (6) |
| | Disease control for ≥12 weeks, n (%, 95% CI) | | 51 (69, 57–79) | 47 (64, 52–74) | 39 (74, 60–85) | 37 (70, 56–82) |
| | PFS | Median PFS, months (95% CI) | 14.3 (4.30–NE) | NA | NA | NA |
| | | 12-month PFS, % (95% CI) | 50 (38-61) | NA | NA | NA |
| | OS | Median OS, months (95% CI) | NR (18.0–NE) | NA | NA | NA |
| | | 12-month OS, % (95% CI) | 73 (62-82) | NA | NA | NA |

*Abbreviations: BOR = best overall response, CI = confidence interval, CR = complete response, dMMR/MSI-H = DNA mismatch repair-deficient/microsatellite instability-high, NA = not available, NE = not estimable, NR = not reached, PFS = progression-free survival, PR = partial response, OS = overall survival*

## 7.1.2 Safety

**C0008: How safe is nivolumab in relation to the comparator(s)?**

Since the CheckMate 142 study was a single-arm study, no results comparing nivolumab to a comparator are available. However, in 52 patients (70%) drug-related AEs occurred; out of those, 15 (20%) patients had grade ≥3 AEs. Increased lipase (n = 6) and amylase (n = 2) were the only grade ≥3 AEs that were present in more than one patient. Serious AEs related to the study treatment of grade 3 or higher occurred in nine (12%) patients; including adrenal insufficiency, increased ALT levels, colitis, diarrhoea, gastritis, stomatitis, acute kidney injury, pain, and arthritis.

20% of patients had grade ≥3 AEs

most common grade ≥3 AEs: Increased lipase and amylase

One serious AE of sudden death from an unknown cause was observed, but was not related to toxic effects of nivolumab. In addition, 20 (27%) patients died because of disease progression, three (4%) due to unknown cause, and 12 (16%) patients died within 100 days after receiving their last dose of nivolumab. None of the deaths occurred because of toxic effects of the study drug. Discontinuation due to drug-related AEs were present in five (7%) patients, including increased ALT level, colitis, duodenal ulcer, acute kidney injury, and stomatitis.

none of the deaths occurred due to toxic effects of nivolumab

7% of patients discontinued because of treatment-related AEs

**C0002: Are the harms related to dosage or frequency of applying nivolumab?**

No dose reductions were permitted in the CheckMate 142 study. Dose interruptions were allowed for treatment-related AEs, but if the interruption lasted longer than six weeks, the patient was discontinued from the study. However, no dose interruptions of any patient were reported in the trial.

dose reductions were not allowed & no dose interruptions are reported

**C0005: What are the susceptible patient groups that are more likely to be harmed through the use of nivolumab?**

Nivolumab may cause foetal harm, resulting in increased abortions or premature infant deaths, due to its mechanism of action. It is advised that females use effective contraception when they receive nivolumab, and for at least five months after the last dosage. In addition, breastfeeding should be discontinued during the treatment [3].

susceptible patient group: pregnant or breastfeeding women

*Table 2: Most frequent treatment-related adverse events[1] in patients locally assessed as having dMMR/MSI-H*

| **Adverse event** (according to CTCAE version 4.03) | **Nivolumab** (n = 74) | | |
|---|---|---|---|
| | Grade 1–2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| Any event | 36 (49) | 13 (18) | 2 (3) |
| Fatigue | 16 (22) | 1 (1) | 0 (0) |
| Diarrhoea | 15 (20) | 1 (1) | 0 (0) |
| Pruritus | 10 (14) | 0 (0) | 0 (0) |
| Rash | 8 (11) | 0 (0) | 0 (0) |
| Nausea | 7 (10) | 0 (0) | 0 (0) |
| Hypothyroidism | 7 (10) | 0 (0) | 0 (0) |
| Asthenia | 5 (7) | 0 (0) | 0 (0) |
| Increased aspartate aminotransferase | 5 (7) | 0 (0) | 0 (0) |
| Arthralgia | 4 (5) | 0 (0) | 0 (0) |
| Pyrexia | 4 (5) | 0 (0) | 0 (0) |
| Dry skin | 4 (5) | 0 (0) | 0 (0) |
| Maculopapular rash | 4 (5) | 1 (1) | 0 (0) |
| Increased alanine aminotransferase | 3 (4) | 1 (1) | 0 (0) |
| Lipase increased | 3 (4) | 4 (5) | 2 (3) |
| Amylase increase | 2 (3) | 2 (3) | 0 (0) |
| Stomatitis | 2 (3) | 1 (1) | 0 (0) |
| Abdominal pain | 1 (1) | 1 (1) | 0 (0) |
| Increased creatinine | 1 (1) | 1 (1) | 0 (0) |
| Decreased lymphocyte count | 1 (1) | 1 (1) | 0 (0) |
| Colitis | 0 (0) | 1 (1) | 0 (0) |
| Acute kidney injury | 0 (0) | 1 (1) | 0 (0) |
| Adrenal insufficiency | 0 (0) | 1 (1) | 0 (0) |
| Oesophagitis | 0 (0) | 1 (1) | 0 (0) |
| Increased gamma-glutamyltransferase | 0 (0) | 1 (1) | 0 (0) |
| Gastritis | 0 (0) | 1 (1) | 0 (0) |
| Pain | 0 (0) | 1 (1) | 0 (0) |

*Abbreviations: AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, dMMR/MSI-H = DNA mismatch repair-deficient/microsatellite instability-high*

[1] Reported are grade 1–2 AEs occurring in at least 10% of patients in any treatment cohort and all grade 3–4 AEs.

## 7.2 Clinical effectiveness and safety – further studies

There is no further study available that has investigated nivolumab for the treatment of patients with dMMR/MSI-H metastatic CRC. However, the second part of the CheckMate 142 study investigates the combination of nivolumab and ipilimumab for the treatment of CRC patients with MSI-H and non-MSI-H. Data for this combination regimen is only available in abstract form, since the study is still ongoing [20]. Included were 27 patients who received four doses of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg), followed by nivolumab monotherapy until disease progression or other discontinuation, ≥6 months before the database lock (September 2016). The primary endpoint was investigator-reported objective response rate (ORR) by RECIST 1.1; secondary endpoints were OS and PFS.

**Part 2 of the CheckMate 142 study: ipilimumab in combination with nivolumab (ongoing)**

At the time of database lock 44% of patients still remained on treatment, and 14 patients had discontinued therapy due to disease progression (n = 8) or treatment related AEs (n = 6). The ORR was 41% and the disease control rate was 78%. Median time to response was 2.7 months, and 82% of responses (9/11) were still ongoing at 6 months. Median duration of response, PFS as well as OS had not been reached. Grade 3–4 treatment related AEs were present in 10 patients (37%).

**ORR: 41% patients**

**grade ≥3 AEs: 37%**

# 8 Estimated costs

**A0021: What is the reimbursement status of nivolumab?**

In Austria, nivolumab is available as 4 mg and 10 mg concentrated infusion solutions. The ex-factory price of 40 mg is € 572; therefore, based on the recommended dose of 3 mg/kg intravenously every two weeks, assuming an average body weight of 70 kg, costs of € 6,006 per treatment cycle (four weeks) would incur [26]. In the CheckMate 142 trial patients received a median number of 22 nivolumab doses, according to this dosage number costs of € 66,066 would arise [21]. Additional costs associated with MSI testing and the treatment of AEs will also occur.

**costs per treatment cycle (4 weeks): € 6,006**

**22 nivolumab doses: € 66,066**

# 9 Ongoing research

**no phase III or IV studies are ongoing, investigating nivolumab in patients with colon cancer**

In November 2017, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. No ongoing phase III or IV trials investigating nivolumab in colon cancer could be identified. However, several phase II studies are ongoing in different treatment lines of colon cancer, either using nivolumab monotherapy or combination treatment:

**ongoing phase II studies in different treatment lines and regimens**

- **NCT03104439:** A phase II study investigating nivolumab and ipilimumab and radiation therapy in microsatellite stable (MSS) and microsatellite instability (MSI) high colorectal and pancreatic cancer. Estimated primary completion date is October 2024.
- **NCT02860546:** A phase II study with safety lead-in, evaluating TAS-102 plus nivolumab in patients with microsatellite stable refractory metastatic colorectal cancer. Estimated primary completion date is March 2018.
- **NCT03271047:** An open-label phase Ib/II study of binimetinib administered in combination with nivolumab or nivolumab plus ipilimumab in patients with previously treated microsatellite-stable (MSS) metastatic colorectal cancer with RAS mutation. Estimated primary completion date is January 2020.
- **NCT03026140:** A phase II study investigating nivolumab, ipilimumab and COX2-inhibition in early stage colon cancer: an unbiased approach for signals of sensitivity: The NICHE TRIAL. Estimated primary completion date is January 2020.
- **NCT03233711:** A randomized phase II study of nivolumab after combined modality therapy (CMT) in high risk anal cancer. Estimated primary completion date is December 2019.
- **NCT02948348:** A Phase Ib/II multicentre study to investigate the safety, efficacy and proof of concept (POC) of nivolumab monotherapy as a sequential therapy following preoperative chemoradiotherapy patients with locally advanced resectable rectal cancer. Estimated primary completion date is June 2020.

**numerous ongoing studies investigating nivolumab**

In addition, nivolumab is currently being investigated in several other indications, like thymic carcinoma, renal cell carcinoma, transitional cell carcinoma, myeloma, biliary tract cancer and head and neck neoplasms.

# 10 Discussion

**nivolumab approved for CRC by the FDA, but not by the EMA**

In July 2017, nivolumab has been granted accelerated approval for the treatment of patients at the age of 12 or older with dMMR and MSI-H metastatic CRC, who progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan in the US [3]. However, nivolumab has not yet re-

ceived marketing authorisation by the EMA for the treatment of metastatic CRC [5].

CheckMate 142
investigator-assessed
OR: 31.1% (all partial)

BICR assessed
OR: 32% (3% complete & 30% partial response)

immature at data cut-off:
median PFS 14.3 months
median OS was not reached

The FDA approval was based on an open-label, ongoing, multicentre, single-arm phase II study, the CheckMate 142 [21, 22]. The study is separated into two parts, investigating nivolumab monotherapy or nivolumab in combination with ipilimumab. The part of the study examined in the present report was conducted to assess the activity and safety of nivolumab monotherapy in 74 patients with metastatic dMMR/MSI-H CRC. The results showed that 23 (31.1%) of the 74 included patients demonstrated an OR – all responses were partial (investigator-assessed). An OR assessed by BICR occurred in 24 (32%) patients (dMMR/MSI-H per local assessment); out of those, 2 (3%) patients had a complete response and 22 (30%) a partial one. At the time of data cut-off (3 January 2017), all responders were alive. However, the median duration of response was not reached. After 36 investigator-assessed progression events had happened, the median PFS was 14.3 (95% CI 4.30–NE) months, but was not mature at the time of data cut-off. In addition, median OS (23 deaths) had not been reached, at the time of interim analysis. Regarding QoL no clinically meaningful deterioration (≥10 point change) in functioning or worsening of symptoms and global health status was experienced by 50% or more of the patients (EORTC QLQ-C30).

mature OS data and further follow-up is necessary

Since only interim results are present, mature OS data and further follow-up data are needed to ensure a clinical relevant patient benefit over time. In addition, since 57 (77%) of the 74 patients were younger than 65 years and the median age at diagnosis of CRC is 73 years in men and 75 in women (range: 70–75), the study population reflects younger patients than those common in clinical practice [16]. In addition, none of the patients had an ECOG performance-status higher than 1. Durable responses were observed in metastatic CRC patients –however, not only in a younger, but also in a less diseased population (ECOG 0–1) – and might not be reached in the general patient population. Therefore, this patient population should be further analysed in future trials to identify any advantages or disadvantages for older patients with more comorbidities when treated with nivolumab.

age and disease status of the study population was not representative for the actual patient population

grade ≥3 drug-related AEs: 20%

In regard to safety outcomes, drug-related AEs occurred in 70% of patients; out of those, 20% of patients had grade ≥3 AEs (most frequent: increased lipase and amylase). Serious AEs related to the study treatment of grade 3 or higher occurred in 12% of patients. Moreover, 27% of patients died because of disease progression and 4% due to unknown cause. None of the deaths occurred because of toxic effects of the study drug. 7% of the patients discontinued treatment due to drug-related AEs (increased ALT level, colitis, duodenal ulcer, acute kidney injury, and stomatitis). At the time of data cut-off 38 patients (51%) were discontinued from the study.

discontinuation due to drug-related AEs: 7%

ESMO-MCBS v1.1:
form 3 → grade 3
(based on immature PFS)

Given the single-arm design of the CheckMate 142 study, we applied form 3 (scores 1–3) of the ESMO-MCBS v1.1 in order to assess the clinical benefit of nivolumab [24, 25]. The form 3 was introduced into the updated ESMO-MCBS v1.1 framework to assess studies in orphan diseases and for diseases with high unmet need. However, since the scale only ranges from score 1 to 3, the criteria for a "meaningful clinical benefit" (score 4 or 5) cannot be satisfied by these therapies. The application of the ESMO-MCBS v1.1 to the CheckMate 142 study resulted in a grade 3, though it should be emphasised that this grade is based on the median PFS (14.3 months), which was not mature at the time of data cut-off (36 events, 95% CI 4.30–NE).

**various limitations inherent to the single-arm study design**

Moreover, due to the single-arm design of the trial, several limitations have to be considered, especially in regard to the interpretation of the treatment effect. Not only is a positive effect of the treatment with nivolumab missing, but also the comparative efficacy of the treatment. In addition, responses may be influenced by an effect of the natural history of the disease [27]. Furthermore, the high discontinuation rate and the single-arm and open-label design of the study can also lead to various biases besides the treatment effect (e.g., bias from patient attrition), that can affect clinical outcomes [28]. Nivolumab should therefore be compared to other treatment options (e.g., pembrolizumab). This could have the additional advantage of yielding information as to which treatment option the patients benefit the most from and thus enable the establishment of treatment recommendations based on direct head-to-head comparison data.

**reliable biomarker testing is needed for patient selection**

Furthermore, there was a high discordance of 20% between the local and the central assessment of dMMR and MSI. This could be due to the investigation of tissues at different time points and the use of different methods and analyses. In addition, no association between the treatment effect and PD-L1 expression, KRAS or BRAF mutation or history of Lynch syndrome was shown. This highlights the challenges of dMMR and MSI assessments and the need of repetitive testing. Furthermore, the establishment of a reliable dMMR and MSI biomarker testing will be crucial in the future to select those patients who benefit most from nivolumab [29].

**resistance to nivolumab monotherapy**

In a current study, PD-1 therapy-resistant melanoma patients demonstrated unique signatures of upregulated genes involved in immunosuppression, angiogenesis, monocyte and macrophage chemotaxis, extracellular matrix remodelling, and epithelial–mesenchymal transition. The factor of resistance may be eliminated by combined targeting of these pathways with PD-1 and other agents, thus producing effective antitumor immunity [30].

**results from the second part of the CheckMate 142 study are crucial**

Therefore, results from the second part of the CheckMate 142 study, which investigates the addition of ipilimumab to nivolumab, are of high importance to further elucidate the issue of resistance.

**nivolumab treatment costs for 4 weeks: € 6,006**

The costs of a four-week treatment cycle would be (assuming an average body weight of 70 kg) € 6,006 [26]. Costs for about 22 doses may arise, since this was the median number of nivolumab doses in the CheckMate 142 study. According to this, the total costs for 22 doses of nivolumab would be € 66,066. However, additional costs for the treatment of AEs, as well as costs associated with MSI testing, would arise.

**durable response with an acceptable safety profile at high costs**

**longer follow-up necessary**

**need of randomised controlled trials – head-to-head comparisons**

Overall, the treatment of nivolumab offers durable responses; 31.1% demonstrated partial responses with an acceptable safety profile at high costs. However, the immature OS data, in combination with the lack of evidence for the actual patient population affected most by CRC in clinical practice and the potential resistance mechanism, highlight the requirement for long-term data. Moreover, head-to-head comparisons (e.g., pembrolizumab) will be necessary to identify the best treatment option for CRC patients with dMMR/MSI-H and to be able to reliably interpret the actual treatment effect. Finally, trustworthy biomarker testing will be needed to select those patients who benefit most from nivolumab.

*Table 3: Benefit assessment based on the ESMO-MCBS v1.1 [24, 25]*

| ESMO-MCBS | Active substance | Indication | Intention | PE | Form | MG-ST | Efficacy | | | | Safety | | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *MG months* | *HR (95% CI)* | *Score calculation* | *PM* | *Toxicity* | *QoL* | | |
| **Original ESMO-MCBS** | nivolumab | CRC | NC | ORR | 3 | x | ORR: 31.1%<br>**PFS: 14.3** | **PFS: 4.30–NE** | PFS ≥6 months | 3 | x | ND | x | **3** |

*Abbreviations: [A] = co-primary endpoints, AJ = Adjustments, CCR = colorectal cancer, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, ORR = objective response rate, PE = primary endpoint, PFS = progression-free survival, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life, ST = standard treatment*

**DISCLAIMER**

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

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# 12 Appendix

*Table 4: Characteristics of CheckMate 142 study*

| **Title:** Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer: an open-label, multicentre, phase 2 study [21, 22] | | | |
|---|---|---|---|
| **Study identifier** | NCT02060188, EudraCT number 2013-003939-30, CA209-142 | | |
| **Design** | Phase II, single-arm, open-label, multicentre | | |
| | Duration | | Enrolment: March 2014 to March 2016<br>Median follow-up: 12.0 months (range: 8.6-18.0)<br>Data cut-off: 2017-01-03 |
| **Hypothesis** | Exploratory<br>The study was designed as a phase II trial to investigate the activity and safety of nivolumab monotherapy or nivolumab in combination with ipilimumab in patients with MSI-H and non-MSI-H metastatic colorectal cancer. If fewer than seven of the first 19 patients with centrally confirmed MSI-H metastatic colorectal cancer had an objective response (complete response or partial response) with nivolumab, enrolment would end; if seven or more patients had a response, 29 additional centrally confirmed patients would be treated in stage 2. | | |
| **Funding** | Bristol-Myers Squibb | | |
| **Treatments group** | Investigation (n = 74) | | Dose of 3 mg/kg nivolumab monotherapy intravenously every 2 weeks until disease progression, death, unacceptable toxic effects, withdrawal of consent or study end |
| **Endpoints and definitions** | Objective response (primary endpoint) | - | Assessed by the investigator according to RECIST criteria |
| | Overall response | OR | Best response between the date of first dose and progression or subsequent treatment, whichever occurred first, divided by the number of those treated |
| | Investigator-assessed objective response | - | Characterised by the investigator-assessed duration of response and rate of complete response |
| | Duration of response | DOR | Time from first confirmed response (complete response or partial response) to the date of tumour progression or death due to any cause, whichever occurred first |
| | Masked independent central review-assessed objective response | - | Number of patients with a best overall response of confirmed complete response or partial response, according to RECIST criteria, divided by the number of those treated |
| | Progression-free survival | PFS | Time from first dosing date to the date of the first documented progression, or death due to any cause, whichever occurred first |
| | Overall survival | OS | Time from first dosing date to the date of death, |
| | Quality of life | QoL | Changes from baseline functioning (emotional, role, and social), symptoms (fatigue, pain, insomnia, appetite loss, constipation, and diarrhoea), cognitive functioning and global quality of life |
| **Results and analysis** | | | |
| **Analysis description** | **Primary analysis**<br>An adequate number of objective responses (n = 7) was achieved in the first 19 patients with centrally confirmed dMMR/MSI-H metastatic colorectal cancer given nivolumab in stage 1; therefore, enrolment into stage 2 was initiated and is now complete. | | |

| **Title:** Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer: an open-label, multicentre, phase 2 study [21, 22] | | |
|---|---|---|
| **Study identifier** | NCT02060188, EudraCT number 2013-003939-30, CA209-142 | |
| **Analysis population** | Inclusion | ✪ Histologically confirmed metastatic or recurrent colorectal cancer with tumours locally assessed as dMMR or MSI-H<br>✪ Age ≥ 18 years<br>✪ ECOG performance status of 0 or 1<br>✪ Measurable disease defined by the RECIST, version 1.1<br>✪ Patients must have progressed on or after, or been intolerant of at least one previous line of treatment, including fluoropyrimidine and oxaliplatin or irinotecan.<br>✪ Baseline laboratory tests required to assess eligibility included with blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), lipase and amylase |
| | Exclusion | ✪ Active brain metastases or leptomeningeal metastases<br>✪ Any serious or uncontrolled medical disorder that might have resulted in an increased risk associated with participation in the study or study drug administration, that impaired the ability of the patient to receive nivolumab, or that interfered with the interpretation of study results<br>✪ Previous cancer active within the previous 3 years<br>✪ Active, known, or suspected autoimmune disease (except for vitiligo, type 1 diabetes mellitus, residual hyperthyroidism due to autoimmune condition requiring only hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger)<br>✪ Need for immunosuppressive doses of systemic corticosteroids or other immunosuppressive drugs 2 weeks before nivolumab administration<br>✪ Previous treatment with other therapy targeting T-cell costimulation or immune checkpoint pathways<br>✪ Acute or chronic hepatitis B or hepatitis C virus infection or history of positive testing for HIV or known AIDS<br>✪ Previous palliative radiotherapy allowed if completed at least 2 weeks before study drug administration per the protocol |

| Characteristics | dMMR/MSI-H per local assessment (n = 74) |
|---|---|
| Age | |
| Median, years (range) | 52.5 (44.0-64.0) |
| <65 years, n (%) | 57 (77) |
| Sex | |
| Male, n (%) | 44 (59) |
| Female, n (%) | 30 (41) |
| Race | |
| White, n (%) | 65 (88) |
| Black, n (%) | 7 (9) |
| Asian, n (%) | 1 (1) |
| Other, n (%) | 1 (1) |
| ECOG performance status | |
| 0, n (%) | 32 (43) |
| 1, n (%) | 42 (57) |
| Disease stage at diagnosis (TNM stage) | |
| I-II, n (%) | 15 (20) |
| III, n (%) | 26 (35) |
| IV, n (%) | 33 (45) |
| Number of previous regimens received | |
| 0, n (%) | 1 (1) |
| 1, n (%) | 11 (15) |
| 2, n (%) | 22 (30) |
| ≥3, n (%) | 40 (54) |

| **Title:** Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer: an open-label, multicentre, phase 2 study [21, 22] | | |
|---|---|---|
| **Study identifier** | NCT02060188, EudraCT number 2013-003939-30, CA209-142 | |
| **Analysis population** *(continuation)* | Previous treatments received<br>Fluoropyrimidine (fluorouracil or capecitabine), n (%)<br>Oxaliplatin, n (%)<br>VEGF inhibitors, n (%)<br>Irinotecan, n (%)<br>EGFR inhibitors, n (%)<br>Regorafenib, n (%)<br>Other, n (%) | <br>73 (99)<br>71 (96)<br>57 (77)<br>55 (74)<br>31 (42)<br>12 (16)<br>11 (15) |
| | Previous radiotherapy, n (%) | 27 (36) |
| | Mutation status<br>Both BRAF and KRAS wild-type, n (%)<br>BRAF mutation, n (%)<br>KRAS mutation, n (%)<br>Unknown, n (%) | <br>29 (39)<br>12 (16)<br>26 (35)<br>7 (9) |
| | Tumour PD-L1 expression quantifiable at baseline<br>≥1%, n (%)<br><1%, n (%)<br>Unknown, n (%) | <br>21 (28)<br>47 (64)<br>6 (8) |
| | Clinical history of Lynch syndrome<br>Yes, n (%)<br>No, n (%)<br>Unknown, n (%) | <br>27 (36)<br>28 (38)<br>19 (26) |
| **Study strengths** | ✿ The study represents the largest cohort of patients with dMMR/MSI-H metastatic colorectal cancer given an immune checkpoint inhibitor.<br>✿ Responses were recorded across all patient subgroups, including those with (≥1%) and without (<1%) tumour PD-L1 expression.<br>✿ Responses were reported in patients with and without a clinical history of Lynch syndrome, or KRAS or BRAF mutations.<br>✿ dMMR/MSI-H status was determined locally before inclusion based on archival tissue using PCR or immunohistochemistry and assessed centrally by PCR (modified Bethesda criteria) using tumour tissue collected at baseline.<br>✿ Patient population of the study also represents a young metastatic colorectal cancer population. | |
| **Study limitations** | ✿ Insufficient follow-up to determine intended effects (immature median PFS and OS)<br>✿ Patient subgroups were small, which could limit the interpretation of the subgroup analyses.<br>✿ The study population reflects younger patients with less comorbidities than those common in clinical practice.<br>✿ Absence of a comparator group | |

*Abbreviations: dMMR/MSI-H = DNA mismatch repair-deficient/microsatellite instability-high, DOR = duration of response, ECOG =Eastern Cooperative Oncology Group, EGFR =Epidermal Growth Factor Receptor, OR = overall response, OS = overall survival, PFS = progression-free survival, QoL = quality of life, RECIST = Response Evaluation Criteria in Solid Tumours, TNM = Classification of Malignant Tumours, VEGF = Vascular Endothelial Growth Factor*