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REVIEW

The EMA assessment of pembrolizumab as monotherapy for the first-line treatment of adult patients with metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer

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On 21 January 2021, the European Commission amended the marketing authorisation granted for pembrolizumab to include the first-line treatment of microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC) in adults. The recommended dose of pembrolizumab was either 200 mg every 3 weeks or 400 mg every 6 weeks by intravenous infusion. Pembrolizumab was evaluated in a phase III, open-label, multicentre, randomised trial versus standard of care (SOC: FOLFOX6/FOLFIRI alone or in combination with bevacizumab/cetuximab) as first-line treatment of locally confirmed mismatch repair-deficient or microsatellite instability-high stage IV CRC. Subjects randomised to the SOC arm had the option to crossover and receive pembrolizumab once disease progressed. Both progression-free survival (PFS) and overall survival were primary endpoints. Pembrolizumab showed a statistically significant improvement in PFS compared with SOC, with a hazard ratio of 0.60 [95% confidence interval (CI): 0.45-0.80], $P = 0.0002$. Median PFS was 16.5 (95% CI: 5.4-32.4) versus 8.2 (95% CI: 6.1-10.2) months for the pembrolizumab versus SOC arms, respectively. The most frequent adverse events in patients receiving pembrolizumab were diarrhoea, fatigue, pruritus, nausea, increased aspartate aminotransferase, rash, arthralgia, and hypothyroidism. Having reviewed the data submitted, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) considered that the benefit–risk balance was positive. This is the first time the CHMP has issued an opinion for a target population defined by DNA repair deficiency biomarkers. The aim of this manuscript is to summarise the scientific review of the application leading to regulatory approval in the European Union.

Key words: EMA, MSI-high, dMMR, pembrolizumab, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) ranks fourth in terms of incidence and second in terms of mortality worldwide.[1] Mismatch repair proteins (e.g. MLH1, MSH2, MSH6, and PMS2) repair insertions or deletions in microsatellites, which are repetitive DNA motifs scattered across the entire genome. Dysfunction of this system—mismatch repair-deficient (dMMR)—leads to the accumulation of mutations in these repetitive regions in what is called microsatellite instability (MSI). High MSI (MSI-H)/dMMR has been observed in malignancies including CRC, gastric, endometrial, biliary and urinary tract, and ovarian cancer. Some tumours have noticeably higher MSI-H prevalence than others (endometrial and colon cancer in particular).[2] Approximately 12%-15% of patients with CRC and 4% of patients with metastatic CRC (mCRC) are classified as MSI-H/dMMR,[3] which is generally associated with favourable prognosis.[4]

Approximately 25% of newly diagnosed patients with CRC present with metastases and 50% of initially non-metastatic patients eventually develop metastatic disease.[5] The outcome of patients with mCRC has clearly improved during recent years with median survival now reaching 30 months in clinical trials. The treatment of mCRC patients should encompass a continuum of care in which the goals may vary over time: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression, and/or maintaining quality of life (QoL). Patients are treated

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according to international guidelines for CRC.[5] Combination schemes such as FOLFOX (oxaliplatin, 5-fluorouracil, and folinic acid) or FOLFIRI (irinotecan, 5-fluorouracil, and folinic acid) are established first-line options for patients with mCRC, and can be combined with monoclonal antibodies (mAbs) against vascular endothelial growth factor (bevacizumab) and the epidermal growth factor receptor (cetuximab, panitumumab).

On 29 June 2020, Merck Sharp & Dohme B.V. applied for an extension of indication via the European Medicines Agency (EMA) centralised procedure for pembrolizumab (Keytruda®) as monotherapy for the first-line treatment of adult patients with unresectable or metastatic MSI-H/dMMR CRC. The review was conducted by EMA's Committee for Medicinal Products for Human Use (CHMP) and a positive opinion was issued on 10 December 2020, this being the first European Union (EU) approval for a population defined by a DNA-repair deficiency biomarker.

NONCLINICAL ASPECTS AND CLINICAL PHARMACOLOGY

Pembrolizumab is a humanised monoclonal antibody (mAb) directed against the programmed cell death protein 1 (PD-1) that has been previously approved for the treatment of a variety of solid tumours and Hodgkin's lymphoma. By blocking the interaction between PD-1 and programmed cell death ligand 1/2 (PD-L1/2), pembrolizumab enhances T-cell lymphocyte activity with consequent stimulation of immune-mediated antitumour activity. The dose and schedule of pembrolizumab investigated for treatment of MSI-H/dMMR mCRC was the same as for other monotherapy indications: 200 mg by intravenous infusion over 60 min every 3 weeks. The marketing authorisation holder (MAH) proposed an additional dosing regimen of 400 mg every 6 weeks. This new regimen had been already approved in the EU for all monotherapy indications at the time of this application and, therefore, the 400 mg every 6 weeks dosing regimen was assumed to have a similar benefit–risk profile in patients with MSI-H/dMMR mCRC.[6] The clinical pharmacology profile of pembrolizumab in patients with MSI-H/dMMR mCRC was consistent with findings in patients with other malignancies.

TRIAL DESIGN

The marketing authorisation application for the extension of indication was based on the results of the pivotal study KEYNOTE-177, which followed upon the results obtained in the KEYNOTE-164 trial (a phase II trial evaluating the efficacy and safety of pembrolizumab in patients with treatment-refractory dMMR/MSI-H mCRC).[7] KEYNOTE-177 was an open-label, multicentre, randomised phase III trial evaluating the efficacy and safety of pembrolizumab monotherapy (200 mg every 3 weeks) versus standard of care (SOC) chemotherapy (FOLFOX or FOLFIRI alone or in combination with bevacizumab or cetuximab) as first-line treatment of locally confirmed dMMR/MSI-H mCRC.[8] FOLFOX (mFOLFOX6) chemotherapy consisted of 5-fluorouracil (400 mg/m^2 bolus followed by 1200 mg/m^2/day continuous infusion for 2 days), oxaliplatin (85 mg/m^2), and folinic acid (400 mg/m^2) every 2 weeks, while FOLFIRI comprised 5-fluorouracil and folinic acid as before plus irinotecan (180 mg/m^2) every 2 weeks. Doses for bevacizumab and cetuximab were 5 mg/kg every 2 weeks and 400 mg/m^2 (followed by 250 mg/m^2) every week, respectively. Treatment was stopped in case of progressive disease, unacceptable toxicity, intercurrent illness preventing further treatment administration, consent withdrawal, investigator's decision, positive pregnancy test, or the patient completing 35 courses of pembrolizumab. Patients could undergo resection of primary tumours or metastases with curative intent after responding to treatment, and then could resume the same preoperative scheme if clinically appropriate.

Randomisation was not stratified, and subjects randomised to SOC had the option to receive pembrolizumab (up to 17 administrations) after disease progression confirmed by blinded independent central review (BICR) if eligibility criteria for the crossover phase were met. MSI-H/dMMR status was determined locally by either PCR or immunohistochemistry (IHC). The primary endpoints were: (i) progression-free survival (PFS) per RECIST version 1.1 as assessed by BICR; and (ii) overall survival (OS). The study was considered to meet its primary objective if pembrolizumab was superior to SOC in either of the two endpoints. Objective response rate (ORR) was a secondary endpoint, and PFS2 and duration of response were among the exploratory endpoints. The submission was based on the second interim analysis (i.e. final PFS and interim OS analysis) results with cut-off date of 19 February 2020, 24 months after the last subject was randomised and a median follow-up of about 28 months.

CLINICAL EFFICACY

A total of 307 patients were randomised to pembrolizumab ($n = 153$) or SOC ($n = 154$). In the intention-to-treat population, pembrolizumab showed a statistically significant improvement in PFS compared with SOC, with a hazard ratio (HR) of 0.60 [95% confidence interval (CI): 0.45-0.80), $P = 0.0002$. Median PFS was 16.5 (95% CI: 5.4-32.4) versus 8.2 (95% CI: 6.1-10.2) months for the pembrolizumab versus SOC arms, respectively (Table 1, Figure 1). There was no statistically significant difference in OS, with a trend towards a survival advantage for pembrolizumab over SOC: HR 0.77 (95% CI: 0.54-1.09), $P = 0.0694$ (Figure 2). ORR was also in favour of pembrolizumab compared with SOC, but statistical significance was not reached: 43.8% (95% CI: 35.8-52.0) versus 33.1% (95% CI: 25.8-41.1), respectively, including a higher complete response rate (11.1% versus 3.9%). A total of 14 versus 13 patients allocated to the pembrolizumab and SOC arms, respectively, underwent curative surgery after treatment.

In an exploratory non-alpha controlled analysis of the subgroup of patients with KRAS/NRAS mutations ($n = 74$), there was no apparent PFS advantage of pembrolizumab over SOC (HR 1.19), though with no detriment in OS (HR

Table 1. Effects table for pembrolizumab versus standard of care in first-line treatment of patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer (cut-off date: 19 February 2020)

Effect	Short description	Unit	Treatment pembrolizumab 200 mg every 3 weeks	Control SOC	Uncertainties/strength of evidence
PFS (by BICR per RECIST 1.1)	Time from randomisation to first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.	Months (95% CI)	16.5 (5.4-32.4) HR 0.60 (95% CI: 0.45-0.80) *P* value: 0.0002 (boundary ≤0.0117)	8.2 (6.1-10.2)	Statistically significant and clinically relevant advantage in PFS. Consistent sensitivity analyses.
OS	Time from randomisation to death due to any cause.	Months (95% CI)	NR (NR-NR) HR 0.77 (95% CI: 0.54-1.09) *P* value: 0.0694 (boundary ≤0.0053)	34.8 (26.3-NR)	Trend towards OS benefit although not statistically significant (59% of crossover in SOC arm) and early crossing of OS curves.
ORR	Confirmed CR or PR by BICR per RECIST 1.1.	% (95% CI)	43.8 (35.8-52.0)	33.1 (25.8-41.1)	
DOR	Time from first response to PD or death due to any cause, whichever occurred first, in subjects who achieved a PR or CR.	Months (range)	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)	
PFS2	Time from randomisation to disease progression on the next line of therapy, or death from any cause, whichever occurred first.	Months (95% CI)	NR (NR-NR)	23.5 (16.6-32.6)	
AE Summary	AEs	%	97.4	99.3	Pembrolizumab safety profile compared favourably with SOC. Higher discontinuation due to AE in pembrolizumab than SOC arm possibly due to longer exposure. Safety profile comparable to the reference safety dataset except for a higher incidence of colitis. No new safety concerns identified.
	Drug-related AEs	%	79.7	98.6	
	Grade 3-5 AEs	%	56.2	77.6	
	Drug-related grade 3-5 AEs	%	21.6	65.7	
	SAEs	%	40.5	52.4	
	Drug-related SAEs	%	16.3	28.7	
	Death due to AEs	%	3.9	4.9	
	Death due to drug-related AEs	%	0	0.7	
	Discontinuation due to AEs	%	13.7	11.9	
	Discontinuation due to drug-related AEs	%	9.8	5.6	
AEOSI	Hypothyroidism	%	12.4	2.1	
	Colitis	%	6.5	0	

AE, adverse event; AEOSI, adverse events of special interest; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SAE, serious adverse event; SOC, standard of care.

0.89) and a similar ORR. In patients with Lynch syndrome ($n = 64$), the HRs were 0.57 (95% CI: 0.27-1.20) for PFS and 0.42 (95% CI: 0.15-1.17) for OS.

No significant deterioration in health status was observed in patients treated with pembrolizumab, with a trend towards improvement in QoL and most functioning and symptom scores compared with SOC.

CLINICAL SAFETY

Safety data were presented side by side with the reference safety dataset (RSD, $n = 5884$). The median drug exposure was longer for the pembrolizumab arm than the SOC arm (11.1 versus 5.7 months) and the RSD (11.1 versus 4.9 months).

The incidence of adverse events (AEs) was similar for the pembrolizumab versus SOC arms (97.4% versus 99.3%) or the RSD (96.5%). The most frequent (>20% incidence) AEs in the pembrolizumab arm were diarrhoea, fatigue, nausea, abdominal pain, decreased appetite, and vomiting. Diarrhoea, nausea, and fatigue were also the most common AEs in the SOC arm. AEs with a ≥10% difference between pembrolizumab and SOC were arthralgia, hypothyroidism, and increased alkaline phosphatase. When compared with the RSD, AEs more frequently reported in the pembrolizumab arm (≥10% difference) were diarrhoea (44.4% versus 20.3%), abdominal pain (24.2% versus 8.1%), and nausea (30.7% versus 20.4%).

The incidence of grade 3-5 AEs was lower in the pembrolizumab arm compared with the SOC arm (56.2% versus 77.6%), mostly driven by the higher incidence of haematological toxicity in patients assigned to SOC, but it was higher when compared with the RSD (48.7%). However, the difference between the pembrolizumab arm and the RSD was no longer evident after adjusting for exposure. The most common grade 3-5 AE was hypertension (7.2% versus 4.9% in the pembrolizumab versus SOC arms, respectively, and 1.7% in the RSD).

The incidence of serious AEs (SAEs) was lower in the pembrolizumab than in the SOC arm (40.5% versus 52.4%) and in line with the RSD (38.3%). The most frequently reported (>2%) SAEs in the pembrolizumab arm were

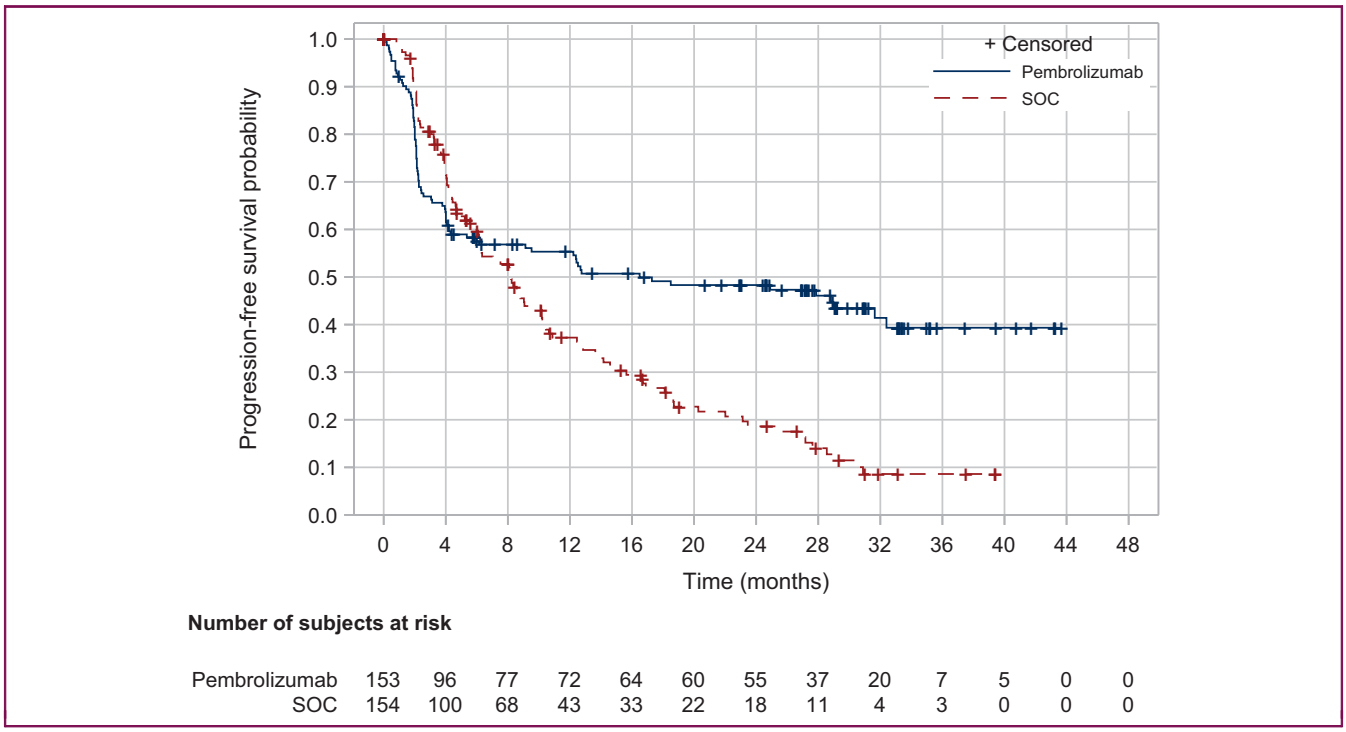

Figure 1. Kaplan–Meier estimates of progression-free survival by blinded independent review committee as per RECIST 1.1 (intention-to-treat population, cut-off date: 19 February 2020).
SOC, standard of care.

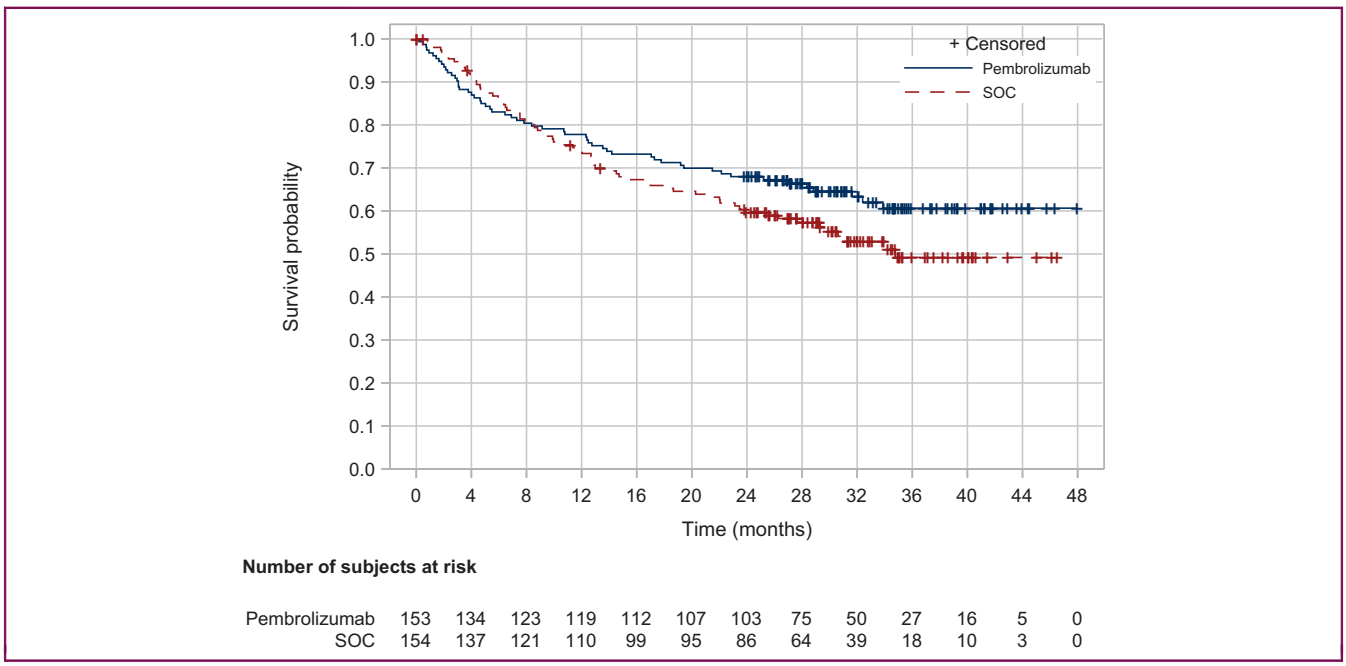

Figure 2. Kaplan–Meier estimates of overall survival (intention-to-treat population, cut-off date: 19 February 2020).
SOC, standard of care.

abdominal pain, diarrhoea, and pyrexia. The overall incidence of AEs of special interest (AEOSI) was higher in the pembrolizumab compared with the SOC arm (30.7% versus 12.6%), the most common being hypothyroidism, colitis, hyperthyroidism, pneumonitis, adrenal insufficiency, hepatitis, and infusion reactions. The frequency of AEOSI was higher for the pembrolizumab arm compared with the RSD (30.7% versus 24.9%), but this trend reverted when adjusted for drug exposure.

Treatment was stopped more often due to AEs in the pembrolizumab arm than the SOC arm or the RSD (9.8% versus 5.6% versus 6.9%, respectively). However, after adjusting for exposure, discontinuations in the pembrolizumab arm were less frequent than in the other two

datasets. The proportion of participants with AEs resulting in death was similar in both the pembrolizumab and SOC arms [six participants (3.9%) versus seven participants (4.9%)].

BENEFIT–RISK ASSESSMENT

Pembrolizumab demonstrated a statistically significant and clinically relevant improvement in PFS compared with SOC therapy as first-line treatment of patients with MSI-H/dMMR mCRC in the KEYNOTE-177 study. Kaplan–Meier curves for PFS demonstrated an increasingly pronounced separation after 6 months of follow-up (PFS rates at 12 months: 55.3% versus 37.3%; PFS rates at 24 months: 48.3% versus 18.6%) (Figure 1, Table 1). A trend towards a prolonged OS for patients treated with pembrolizumab was considered supportive of the PFS results. The median OS was not reached in the pembrolizumab arm versus 34.8 months (95% CI: 26.3-not reached) in the control arm, the latter being far longer than expected for SOC (normally around 24 months). The 59% crossover rate to anti-PD-L1 therapy may explain the latter finding, as sensitivity analyses assessing the impact of crossover revealed lower HRs compared with the primary OS analysis. As repeatedly observed in phase III trials comparing anti-PD-L1 mAbs versus chemotherapy, HRs for OS favoured the SOC arm for the first 4 months, after which the curves crossed and diverged with a 5%-10% difference in favour of the pembrolizumab arm (Figure 2). Baseline characteristics of the 32 participants who died within 4 months (19 in the pembrolizumab group and 13 in the SOC group) did not reveal any obvious risk factor for early death in patients treated with pembrolizumab. An updated section 4.4 of the summary of product characteristics (SmPC) now reports that 'in the KEYNOTE-177 study, the hazard ratios for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab'. The final OS analysis for this trial is expected on Q3 2021.

Overall, the safety profile of pembrolizumab remained unchanged as no new safety concerns were identified in the KEYNOTE-177 study (Table 1). Pembrolizumab showed a favourable safety profile relative to SOC, with a distinct AE profile as expected. Compared with the RSD, a trend towards a worse safety profile and a higher discontinuation rate was observed in patients with MSI-H/dMMR mCRC treated with pembrolizumab, but this was due to a longer exposure in most cases. Specifically, a higher incidence of gastrointestinal toxicity (diarrhoea and abdominal pain) was observed compared with the known pembrolizumab safety profile. As such, the incidence of immune-related colitis observed in the KEYNOTE-177 study was included in section 4.8 of the SmPC.

No significant deterioration in health status was observed in patients receiving pembrolizumab, with a trend towards an improved QoL supporting the benefit of pembrolizumab over SOC in terms of efficacy and safety. However, the open-label design of the study and the lack of multiplicity control did not permit formal superiority claims.

Patient inclusion was based on locally determined MSI/MMR testing by PCR or IHC, which was accepted considering that these tests are recommended by international guidelines for routine clinical practice.[5,9] Moreover, the use of imaging central review was endorsed in view of the study's open-label design. The comparator arm consisted of an investigator's choice among six different regimens, all acceptable as first-line therapy: FOLFOX + bevacizumab (45%), FOLFIRI + bevacizumab (25%), chemotherapy alone (<20%), and chemotherapy + cetuximab (11%),[5] but a consistent benefit was observed for pembrolizumab versus each SOC (alone or grouped).

The MAH had applied for an indication in patients with 'unresectable or metastatic' CRC but only patients with stage IV disease (i.e. metastatic) were included in KEYNOTE-177. The indication was consequently updated during the procedure to include 'metastatic' patients only. Having reviewed the data submitted by the MAH, the CHMP considered that the benefit–risk balance of pembrolizumab monotherapy was positive for first-line treatment of patients with MSI-H/dMMR mCRC.

CONCLUSIONS

The CHMP recommended approval of pembrolizumab as monotherapy for first-line treatment of metastatic MSI-H or mismatch repair-deficient (dMMR) CRC in adults, this being the first approval for a target population defined by a DNA-repair deficiency biomarker in the EU. This new indication was added to the list of approved indications for Keytruda.

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DISCLOSURE

The authors have declared no conflicts of interest.

DISCLAIMER

This publication is based on the European Public Assessment Report (EPAR) available in the public domain, on the summary of product characteristics (SmPC) and other product information on the EMA website (www.ema.europa.eu). The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the author(s) is/are employed/affiliated.

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