Pembrolizumab (Keytruda®) as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer

General information

Drug description [1]	Indication [2]
Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody.	Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic MSI-H or dMMR colorectal cancer in adults.

Current treatment [3]

- Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care.
- When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered.
- Treatment for metastatic colorectal cancer aims to prolong survival, improve QoL and/or make the primary tumour or metastases suitable for resection.
- Chemotherapy options include:
  - folinic acid plus fluorouracil plus oxaliplatin (FOLFOX),
  - folinic acid plus fluorouracil plus irinotecan (FOLFIRI),
  - capecitabine plus oxaliplatin (XELOX),
  - single-agent irinotecan, capecitabine or tegafur with uracil (in combination with folinic acid).
- Chemotherapy may be combined with biological agents such as EGFR inhibitors (cetuximab or panitumumab) or VEGF inhibitors (bevacizumab).
- If standard therapies are unsuccessful, not tolerated or contraindicated, people are treated with supportive care to manage the symptoms and complications of the condition.

Regulatory status

EMA [2]

Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

<u>The CHMP adopted a new indication as follows:</u>

- Keytruda® as monotherapy is indicated for the first-line treatment of metastatic MSI-H or dMMR colorectal cancer in adults.

Other indications: Keytruda®

- as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

FDA [4, 5]

Approval status for this indication: On 29 June 2020, the FDA approved pembrolizumab for intravenous injection for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer.

Other indications: Pembrolizumab is indicated in

- Melanoma
  - for the treatment of patients with unresectable or metastatic melanoma.
  - for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- NSCLC
  - in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
  - in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
  - as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
  - as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- Small Cell Lung Cancer (SCLC)
  - for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy (indication approved under accelerated approval based on tumor response rate and durability of response).
- HNSCC
  - in combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.

❖ in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. ❖ in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. ❖ as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab. ❖ as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. ❖ as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma (UC) in adults who have received prior platinum-containing chemotherapy. ❖ as monotherapy is indicated for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. ❖ as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC	• as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. • as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. ❖ cHL • for the treatment of adult patients with relapsed or refractory cHL. • for the treatment of paediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. ❖ Primary Mediastinal Large B-Cell Lymphoma (PMBCL) • for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. • Limitations of Use: Pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy. ❖ UC • for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status (indication approved under accelerated approval based on tumor response rate and durability of response). • for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. ❖ MSI-H or dMMR Cancer • for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR o solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (indication approved under accelerated approval based on tumor response rate and durability of response), or o colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (indication approved under accelerated approval based on tumor response rate and durability of response). • Limitations of Use: The safety and effectiveness of pembrolizumab in paediatric patients with MSI-H central nervous system cancers have not been established. ❖ Gastric Cancer • for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy (indication approved under accelerated approval based on tumor response rate and durability of response). ❖ Esophageal Cancer • for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS) ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. ❖ Cervical Cancer • for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS) ≥1) as determined by an FDA-approved test (indication approved under accelerated approval based on tumor response rate and durability of response) . ❖ Hepatocellular Carcinoma (HCC) • for the treatment of patients with HCC who have been previously treated with sorafenib (indication approved under accelerated approval based on tumor response rate and durability of response). ❖ Merkel Cell Carcinoma (MCC)

in adults whose tumours express PD-L1 with a ≥50% TPS and progressing on or after platinum-containing chemotherapy. ❖ in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. ✓ **Medicine under additional monitoring**	• for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (indication approved under accelerated approval based on tumor response rate and durability of response). ❖ RCC • in combination with axitinib, for the first-line treatment of patients with advanced RCC. ❖ Endometrial Carcinoma • in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation (indication approved under accelerated approval based on tumor response rate and durability of response). ❖ Tumor Mutational Burden-High (TMB-H) Cancer • for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H ≥10 mutations/megabase (mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (indication approved under accelerated approval based on tumor response rate and durability of response). • Limitations of Use: the safety and effectiveness of pembrolizumab in paediatric patients with TMB-H central nervous system cancers have not been established. ❖ Cutaneous Squamous Cell Carcinoma (cSCC) • for the treatment of patients with recurrent or metastatic cSCC that is not curable by surgery or radiation. ❖ Triple-Negative Breast Cancer (TNBC) • in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test (indication approved under accelerated approval based on progression-free survival). ❖ Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks • for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications (indication approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety).

Costs

4 ml Keytruda® concentrate for solution for infusion 25mg/ml = € 3,428.00 [6]
KEYNOTE-177 trial patients received pembrolizumab at a dose of 200 mg every 3 weeks; the median treatment exposure was 11.1 months in the pembrolizumab group [7] → costs of € 6,856/dose

Disease-specific precautions [1]

❖ Use of pembrolizumab for first-line treatment of patients with MSI-H/dMMR CRC
- In KEYNOTE-177, the hazard rates for OS events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab.

Study characteristics [1, 7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-177 NCT02563002	307	pembrolizumab at a dose of 200 mg every 3 weeks	chemotherapy (5-fluorouracil–based therapy with or without bevacizumab or cetuximab) every 2 weeks	PFS + OS	randomized, open-label, phase 3 trial	PD-L1	Merck Sharp and Dohme and Stand Up to Cancer	Link

Efficacy (I vs. C)	**Safety** (I vs. C)
Primary end point: **Median PFS[1]:** 16.5 months (95% CI, 5.4-32.4) vs. 8.2 months (95% CI, 6.1-10.2), HR 0.60 (95% CI, 0.45 to 0.80; p=0.0002)	**Grade ≥3 AEs**: n=86/153 (56%) vs. n=111/143 (78%)

[1] Second interim analysis data

Estimated percentages of patients alive and PFS at 12 months and at 24 months: 55.3% (95% CI, 47.0-62.9) and 48.3% (95% CI, 39.9-56.2) vs. 37.3% (95% CI, 29.0-45.5) and 18.6% (95% CI, 12.1-26.3)

Estimated restricted mean survival time for PFS after 24 months of follow-up: 13.7 months (95% CI, 12.0-15.4) vs. 10.8 months (95% CI, 9.4-12.2). PFS was consistently longer with I than with C across key pre-specified **subgroups** tested.

Radiographic Response

Overall response (complete or partial response): in 43.8% (95% CI, 35.8-52.0) vs. 33.1% (95% CI, 25.8-41.1); **CR**: in 11% vs. 4%; PR: 33% vs. 29%

Progressive disease: 29.4% vs. 12.3%

Patients could **not be evaluated** for best response or a radiographic assessment was **not performed**: n=9 vs. n=19

Duration of Response

Of patients with a **complete or partial response** at 24 months, 83% in I had ongoing responses, as compared with 35% in C.

Median duration of response: not reached vs. 10.6 months; Patients with duration ≥ 12 months: 85% vs. 44%

Patients who had **surgery with curative intent** during the initial treatment phase: 9% vs. 8%

OS: At the time of data cutoff, data on OS were still evolving, with 125 of the required 190 events for the final analysis of OS having occurred. Patients who had died as of the data cutoff date: 56 and 69 patients. The independent data monitoring committee recommended that the trial continue without changes to the final analysis for assessment of OS until 190 overall deaths have occurred or until 12 months after the second interim analysis.

Crossover will be a factor in the assessment of OS. At the time of data cutoff, 56 of 154 patients **(36%)** randomly assigned to the chemotherapy group had **crossed over** to the pembrolizumab group after disease progression was confirmed. An additional **35 patients** in the chemotherapy group received anti–PD-1 or anti–PD-L1 therapies outside the trial, for an **effective crossover rate** to anti–PD-1 or anti–PD-L1 therapy of **59%** in the intention-to-treat population.

QoL analysis [11]:

- The HRQoL analysis population comprised 294 patients (152 receiving pembrolizumab and 142 receiving chemotherapy)
- LSM change from baseline to prespecified week 18 showed a clinically meaningful improvement in EORTC QLQ-C30 GHS/QoL scores with I vs. C (between-group LSM difference 8.96, 95% CI, 4.24–13.69); two-sided nominal p=0.0002.
- Median time to deterioration was longer with pembrolizumab vs. chemotherapy for GHS/QoL (hazard ratio 0.61, 95% CI 0.38–0.98; one-sided nominal p=0.019), physical functioning (0.50, 95% CI 0.32–0.81); one-sided nominal p=0.0016), social functioning (0.53, 95% CI 0.32–0.87); one-sided nominal p=0.0050), and fatigue scores (0.48, 95% CI 0.33–0.69); one-sided nominal p<0.0001).

Treatment-related AEs grade ≥3[2]: n=33/153 (22%) vs. n=94/143 (66%)

Immune-mediated AEs and infusion reactions: n=47/153 (31%) vs. n=18/143 (13%)

AEs attributed to treatment by the investigator: n=122/153 (80%) vs. n=141/143 (99%)

Grade 5 AEs: n=6/153 (4%) vs. n=7/143 (5%)

Discontinuation[3]: n=21/153 (14%) vs. n=17/143 (12%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	>6 m	PFS: +8.3 m	0.60 (0.45 to 0.80)	HR≤0.65 AND gain ≥3 m	3	x	improvement	+1	4
Adapted	NC	2b	>6 m	PFS: +8.3 m	0.60 (0.45 to 0.80)	HR≤0.65 AND gain ≥3 m	3	+18% immune-mediated adverse events and infusion reactions +2% discontinuation	improvement	-/+1	3

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	no	no, open label	unclear[4]	yes[5]	unclear

First published: 12/2020
Last updated: 04/2021

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT= autologous stem cell transplant, BV=brentuximab vedotin, C=comparator, CHMP=Committee for Medicinal Products for Human Use, cHL=classical Hodgkin lymphoma, CI=confidence interval, CPS=combined positive score, cSCC=cutaneous squamous cell carcinoma, dMMR= mismatch repair deficient, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FOLFIRI= folinic acid plus fluorouracil plus irinotecan, FOLFOX= folinic acid plus fluorouracil plus oxaliplatin, GHS=global health status, HCC=hepatocellular carcinoma, HER2=human epidermal growth factor

[2] Including one death in the chemotherapy group

[3] Discontinuation due to AE(s)

[4] Interim analysis data; KEYNOTE-177 trial is ongoing until 12/2021; QoL (exploratory endpoint) results not (yet) reported; impact of crossover needs to be considered.

[5] The trial was designed by academic investigators and employees of the sponsor. The first draft was written by the lead author and senior author with assistance from a medical writer employed by the sponsor.

receptor 2, HNSCC= head and neck squamous cell carcinoma, HR=hazard ratio, HRQoL=Health-related quality of life, I=intervention, Int.=intention, LSM=Least squares mean, MCC=Merkel cell carcinoma, MG=median gain, MSI-H= microsatellite instability-high, n=number of patients, NA=not available, NMIBC= non-muscle invasive bladder cancer, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=Programmed cell death protein 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-Cell lymphoma, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, SCLC=small cell lung cancer ST=standard treatment, TMB-H=tumour mutational burden-high, TNBC=triple-negative breast cancer, TPS=tumour proportion score, UC=urothelial carcinoma, VEGF=vascular endothelial growth factor, XELOX= capecitabine plus oxaliplatin

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