Pembrolizumab (Keytruda®) in combination with platinum and fluoropyrimidine-based chemotherapy for the treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma

General information

Drug description [1]	Indication [2]
Pembrolizumab is a high-affinity, highly selective, humanised immunoglobulin G4-κ monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.	Pembrolizumab, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥10.

Current treatment [3]

- The NICE recommendation about first-line palliative chemotherapy for locally advanced or metastatic oesophagogastric cancer treatment includes:
  - Trastuzumab (in combination with cisplatin and capecitabine or 5-fluorouracil) as a treatment option to people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:
    - have not received prior treatment for their metastatic disease and
    - have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).
  - First-line palliative combination chemotherapy to people with advanced oesophagogastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:
    - doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
    - triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

Regulatory status

EMA [2]

Approval status for this indication: On 20 May 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

The CHMP adopted a new indication as follows:

- Keytruda®, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.

Other indications: Keytruda® is indicated:

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

FDA [4, 5]

Approval status for this indication: On March 22, 2021, the FDA approved pembrolizumab (Keytruda®) in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced oesophageal or gastroesophageal (tumours with epicentre 1 to 5 centimetres above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

Other indications: Keytruda® is indicated:

- 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.
- Non-Small Cell Lung Cancer (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 tumour 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 tumour 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 tumours 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 tumour aberrations

- ❖ in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
- ❖ as monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma 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 Keytruda.
- ❖ as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- ❖ as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- ❖ as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10.
- ❖ as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
- ❖ as monotherapy for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.
- ❖ in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma in adults.
- ❖ as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

✓ **Medicine under additional monitoring**

should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda®.

- ❖ Head and Neck Squamous Cell Cancer (HNSCC)
  - in combination with platinum and FU for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC.
  - as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumours 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.
- ❖ Classical Hodgkin Lymphoma (cHL)
  - for the treatment of adult patients with relapsed or refractory cHL.
  - for the treatment of pediatric 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: Keytruda® is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy.
- ❖ Urothelial Carcinoma
  - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours 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 (accelerated approval).
  - for the treatment of patients with locally advanced or metastatic urothelial carcinoma 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 with carcinoma in situ with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.
- ❖ MSI-H or dMMR
  - for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR
    - o solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options (accelerated approval) or
    - o colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval).
  - Limitations of Use: The safety and effectiveness of Keytruda® in pediatric patients with MSI-H central nervous system cancers have not been established.
- ❖ MSI-H or dMMR Colorectal Cancer (CRC)
  - for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC.
- ❖ Gastric Cancer
  - in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma (accelerated approval).
  - as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours 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 (accelerated approval). ❖ Oesophageal Cancer • for the treatment of patients with locally advanced or metastatic oesophageal or gastroesophageal junction (tumours with epicentre 1 to 5 centimetres above the gastroesophageal junction) carcinoma that is not amenable to surgical resection or definitive chemoradiation as a single agent after one or more prior lines of systemic therapy for patients with tumours of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test. ❖ Cervical Cancer • for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test (accelerated approval). ❖ Hepatocellular Carcinoma (HCC) • for the treatment of patients with HCC who have been previously treated with sorafenib (accelerated approval). ❖ Merkel Cell Carcinoma (MCC) • for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (accelerated approval). ❖ Renal Cell Carcinoma (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 (accelerated approval). ❖ Tumour Mutational Burden-High (TMB-H) Cancer • for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥10 mutations/megabase) solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (accelerated approval). • Limitations of Use: The safety and effectiveness of Keytruda® in pediatric 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) • for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. • in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS) ≥10) as determined by an FDA approved test ❖ 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 (accelerated approval).
Costs	
4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = **€ 3,428.00 (ex-factory price)** [6]	
Warnings and precautions [4]	
❖ **Immune-Mediated Adverse Reactions:**	

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
- Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- Withhold or permanently discontinue based on severity and type of reaction.

❖ **Infusion-related reactions**:
- Interrupt, slow the rate of infusion, or permanently discontinue Keytruda® based on the severity of the reaction.

❖ **Complications of allogeneic HSCT**: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.

❖ **Treatment of patients with multiple myeloma** with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

❖ **Embryo-Foetal toxicity**:
- Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use an effective method of contraception.

Study characteristics [1, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
Keynote-590 NCT03189719	749	pembrolizumab 200 mg IV every 3 weeks (Q3W) in combination with chemotherapy [1]	Placebo + chemotherapy	OS + PFS as assessed by the investigator according to RECIST 1.1	a randomized, double-blind, placebo-controlled Phase III study	-	Merck Sharp & Dohme Corp.	[1] (Clinical Trial Protocol) [7] (Abstract)

Efficacy (I vs. C)

Median OS in months (all patients): 12.4 (95% CI: 10.5-14.0) vs. 9.8 (95% CI: 8.8-10.8); HR 0.73, 95% CI: 0.62-0.86; p<0.0001
Median OS in patients with ESCC CPS ≥10: 13.9 vs. 8.8 months; HR 0.57; 95% CI: 0.43-0.75; p<0.0001
Median OS in patients with ESCC: 12.6 vs. 9.8 months; HR 0.72; 95% CI: 0.60-0.88; p=0.0006
Median OS in patients with CPS ≥10: 13.5 vs. 9.4 months; HR 0.62; 95% CI: 0.49-0.78; p<0.0001
Median PFS in months (all patients): 6.3 (95% CI: 6.2-6.9) vs. 5.8 (95% CI: 5.0-6.0); HR 0.65; 95% CI: 0.55-0.76; p<0.0001
Median PFS (ESCC): 6.3 vs. 5.8 months; HR 0.65; 95% CI: 0.54-0.78; p<0.0001
Median PFS (CPS ≥10): 7.5 vs. 5.5 months; HR 0.51; 95% CI: 0.41-0.65; p<0.0001
Confirmed ORR (in all patients): 45.0% vs. 29.3%; p<0.0001)
Median DOR in months (in all patients): 8.3 (1.2-31.0) vs. 6.0 (1.5-25.0)

HRQoL [9]:
- ❖ QLQ-C30, QLQ-OES18 and EQ-5D-5L **compliance** was ≥90% in both arms at baseline and at week 18.
- ❖ There was **no significant difference in LSM change** from baseline to week 18 in GHS/QoL status between arms; LSM difference,95% CI: -0.10 (-3.40-3.20); p=0.9530
- ❖ **Median TTD** in GHS/QoL was similar between arms; HR 0.86 (95% CI: 0.66-1.13); p=0.2864
- ❖ Outcomes were **similar** in ESCC PD-L1 CPS ≥10, ESCC, and PD-L1 CPS ≥10 patient populations.

Safety (I vs. C) [4, 7]

Grade 3-5 drug-related AE rates: 72% vs. 68%
Discontinuation rates from drug-related AEs: 19% vs. 12%.
The most common adverse reactions resulting in permanent discontinuation of the study drug: pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%)
Adverse reactions leading to interruption of the study drug: 67%

[1] Chemotherapy regimen for both arms will consist of cisplatin 80 mg/m^2 IV every 3 weeks (maximum six doses) plus 5-fluorouracil 800 mg/m^2 continuous iv. infusion on days 1–5 every 3 weeks.

❖ LSM change from baseline to week 18 for QLQ-OES18 **pain** subscale was **better for I** vs. C (-1.85) (-2.94, -5.86 to -0.02; p = 0.0487). ❖ There was **no significant difference** in LSM change from baseline to week 18 between arms for **reflux** (-1.19; -4.49-2.10; p= 0.4781) or **dysphagia** (-2.35; -7.78-3.07; p=0.3945). ❖ VAS LSM change from baseline to week 18 was similar between arms (1.20, -1.61-4.01; p=0.4016). ❖ HRQoL was **stable and similar** over 18 weeks in the pembrolizumab + chemotherapy and chemotherapy arms.	

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +2.6 months	0.73 (0.62-0.86)	HR ≤0.65 AND gain ≥2.0-<3 months	3	-	-	-	3
Adapted	NC	2a	≤12 months	OS: +2.6 months	0.73 (0.62-0.86)	>0.70 OR gain <1.5 months	1	+4% Grade 3-5 drug-related AEs +7% discontinuation from drug-related AEs	-	-	1

Risk of bias (study level) [11]

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	yes	yes	unclear[2]	yes[3]	unclear

First published: 06/2021
Last updated: 08/2021

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, CRC=colorectal cancer, cSCC=cutaneous squamous cell carcinoma, dMMR=mismatch repair deficient, DOR=Duration of response, EMA=European Medicines Agency, EGFR=epidermal growth factor receptor, EQ-5D-5L=EuroQol 5-dimension 5-level, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GHS=global health status, HCC=hepatocellular carcinoma, HER2= human epidermal growth factor receptor 2, HNSCC=head and neck squamous cell cancer, 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, NICE=National Institute for Health and Care Excellence, NSCLC=non small cell lung cancer, ORR=objective response rate, OS=overall survival, PD-L1=programmed death- ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-Cell lymphoma, QLQ-C30=quality of life questionnaire, QLQ-OES18=QLQ-esophageal module, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, ST=standard treatment, TMB-H=tumor mutational burden-high, TNBC=triple-negative breast cancer, TPS= tumour proportion score, TTD= time to deterioration, VAS=visual analogue scale

References:

1. Kato K, Shah MA, Enzinger P, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Clinical trial Protocol. Future Oncol (2019) 15(10) Published online: 8 February 2019. [Available from: https://doi.org/10.2217/fon-2018-0609].
2. European Medicines Agency (EMA). Medicines. Keytruda. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-3].

[2] The Keynote-590 trial is ongoing until 06/2022; Efficacy results: only abstracts available.
[3] Industry-funded

3. National Institute for Health and Research (NIHR). Pembrolizumab in addition to cisplatin and fluorouracil for recurrent locally advanced or metastatic oesophageal cancer – First-lin. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2020/01/23790-TSID_10209-Pembrolizumab-for-Oesophageal-Cancer-V1.0-DEC2019-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). Keytruda. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves pembrolizumab for esophageal or GEJ carcinoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Kato K, et al. LBA8_PR Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study. Abstract. [Available from: https://doi.org/10.1016/j.annonc.2020.08.2298].
8. U.S.National Library of Medicine, ClinicalTrials.gov. First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590). [Available from: https://clinicaltrials.gov/ct2/show/NCT03189719].
9. Mansoor W, et al. Health-related quality of life (HRQoL) of pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase III KEYNOTE-590 study. [Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.168].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
11. European Network for Health Technology Assessment (EUnetHTA). LEVELS OF EVIDENCE. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].