Pembrolizumab (Keytruda®) in combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC)

General information

Drug description [1]	Indication [1]
Pembrolizumab (Keytruda®) is an anti-PD-1 monoclonal antibody.	Pembrolizumab (Keytruda®), in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 and who have not received prior chemotherapy for metastatic disease.

Current treatment [2]

- NICE recommends for patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), single-agent docetaxel should be offered as first-line.
- NICE recommends gemcitabine in combination with paclitaxel, within its licensed indication, as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.
- European guidelines recommend that in advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.

Regulatory status

EMA [1]

Approval status for this indication: On 16 September 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 chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

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.
- 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 ≥

FDA [3, 4]

Approval status for this indication: On 13 November 2020, the FDA granted accelerated approval to pembrolizumab (Keytruda®) 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.

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

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 (cHL) 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 (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ as monotherapy for the treatment of recurrent or metastatic HNSCC 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 (RCC) in adults. ❖ in combination with lenvatinib for the first-line treatment of advanced RCC 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. ❖ in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of 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. ❖ in combination with Lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. ✓ **Medicine under additional monitoring**	❖ 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 paediatric 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: o are not eligible for any platinum-containing chemotherapy, or o 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 Cancer • for the treatment of adult and paediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options. • Limitations of Use: The safety and effectiveness of Keytruda® in paediatric patients with MSI-H central nervous system cancers have not been established. ❖ Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC) • for the 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 (GEJ) adenocarcinoma (indication approved under accelerated approval based on tumour response rate and durability of response). • as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ 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 (indication approved under accelerated approval based on tumour response rate and durability of response). ❖ Oesophageal Cancer • for the treatment of patients with locally advanced or metastatic oesophageal or GEJ (tumours with epicentre 1 to 5 centimetres above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: o in combination with platinum- and fluoropyrimidine-based chemotherapy, or o 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

	• in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer 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 cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. ❖ Hepatocellular Carcinoma (HCC) • for the treatment of patients with HCC who have been previously treated with sorafenib (indication approved under accelerated approval based on tumour response rate and durability of response). ❖ Merkel Cell Carcinoma (MCC) • for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic MCC (indication approved under accelerated approval based on tumour response rate and durability of response). ❖ RCC • in combination with axitinib, for the first-line treatment of adult patients with advanced RCC. • in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC. • for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following. • nephrectomy, or following nephrectomy and resection of metastatic lesions. ❖ 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 in any setting and are not candidates for curative surgery or radiation. ❖ Tumour Mutational Burden-High (TMB-H) Cancer • for the treatment of adult and paediatric 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 (indication approved under accelerated approval based on tumour response rate and durability of response). • 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 or locally advanced cSCC that is not curable by surgery or radiation. ❖ 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. <u>Adult Indications:</u> 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 is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety).
Costs	
Keytruda® concentrate for solution for infusion 25 mg/ml 4 ml = €3,428.00 (ex-factory price) [5]	
Warnings and precautions [3]	
❖ **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

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-355 NCT02819518	847: 566 vs. 281	Pembrolizumab (200 mg) every 3 weeks plus chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin)	Placebo plus chemotherapy	PFS + OS[1]	randomised, double-blind, placebo- controlled, phase 3 trial	PD-L1	Merck Sharp & Dohme Corp	[7]

Efficacy (I vs. C)

Patients with CPS of ≥10:

Median PFS: 9.7 months vs. 5.6 months; HR for progression or death 0.65, 95% CI 0.49–0.86; one-sided p=0.0012
PFS at 6 months: 65.0% vs. 46.9%
PFS at 12 months: 39.1% vs. 23.0%
OS/patients with event: 70% vs. 82%, HR 0.73, 95% CI, 0.55-0.95, p=0.0093
Median OS: 23.0 months vs. 16.1 months
Objective response rate: 53% vs. 41%
Complete response: 17% vs. 14%
Partial response: 36% vs. 27%
Median response duration: 12.8 months vs. 7.3 months
% with duration ≥ 6 months: 82% vs. 60%
% with duration ≥ 12 months: 56% vs. 38%

Patients with CPS of ≥1:

Median PFS: 7.6 months vs. 5.6 months; HR 0.74, 95% CI 0.61–0.90; one-sided p=0.0014
PFS at 6 months: 56.4% vs. 46.6%
PFS at 12 months: 31.7% vs. 19.4%

Safety (I, n=562 vs. C, n=281)

Any AE grade ≥3: 78% vs. 74%
AEs of any grade related to study treatment by the investigator: 96% vs. 95%
AEs grade ≥3 related to study treatment: 68% vs. 67%
Treatment-related AEs led to death: <1% vs. 0%
Immune-mediated AEs of grade ≥3: 5% vs. 0%
Infusion reactions of grade ≥3: 1% vs. 0%

[1] Assessed in the PD-L1 CPS of 10 or more, CPS of 1 or more, and ITT populations.

Intention-to-treat population: **Median PFS:** 7.5 months vs. 5.6 months; HR 0.82, 95% CI 0.69–0.97 **PFS at 6 months:** 55.4% vs. 47.8% **PFS at 12 months:** 29.8% vs. 20.9% **Patients with PD-L1 CPS of <1:** **Median PFS:** 6.3 months vs. 6.2 months; HR 1.08, 95% CI 0.77–1.53	

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: +4.1 months	0.65 (0.49–0.86)	HR ≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2B	≤6 months	PFS: +4.1 months	0.65 (0.49–0.86)	HR ≤0.65 AND gain ≥1.5 months	3	-	-	-	3

Risk of bias (RCT) [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

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BRCA=breast cancer gene, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, 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, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GEJ=gastroesophageal junction, HNSCC= head and neck squamous cell cancer, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, 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, OS=overall survival, PD-1=programmed cell death protein 1, PD-L1=programmed cell death 1 ligand 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, ST=standard treatment, TMBH=tumor mutational burden-high, TNBC=triple-negative breast cancer, TPS=tumour proportion score

References:

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5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].

[2] The KEYNOTE-355 trial is ongoing until 01/2022.

[3] The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report.

6. Supplement to: Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396: 1817–28.
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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].