Pembrolizumab (Keytruda®) as monotherapy for the adjuvant treatment of renal cell carcinoma (RCC)

General information

Drug description [1]	Indication [2]
Pembrolizumab (Keytruda®) is a humanised monoclonal antibody, which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2.	Pembrolizumab (Keytruda®) as monotherapy is indicated for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Current treatment

- There are several different types of biological therapy used for the treatment of advanced kidney cancer, including immunotherapy, targeted therapies, and monoclonal antibodies. However, currently, there is no NICE recommended adjuvant therapy after nephrectomy for RCC [3].
- For adjuvant therapy in clear cell RCC (ccRCC) the ESMO recommends [4]:
  - Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC (as defined by the study) after careful patient counselling regarding immature OS and potential long-term AEs. Further data are required in the future including positive OS data. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
  - Regarding the M1 NED population, systemic therapy with PD-1-based combination therapy is the standard of care for patients who relapse within 1 year of nephrectomy.
  - Metastasectomy as an alternative to this systemic therapy in patients with synchronous or early oligometastatic disease is not usually recommended and requires a multidisciplinary team decision.
  - Adjuvant pembrolizumab can be offered to these patients after complete resection of their oligometastatic disease.
  - Incomplete resection should not be offered to patients with oligometastatic disease.

Regulatory status

EMA [2]

Approval status for this indication: On 16 December 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

<u>The CHMP adopted an extension to the existing indication as follows:</u>

- Keytruda® as monotherapy is indicated for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Other indications: Pembrolizumab (Keytruda®) is indicated:

- Melanoma
  - 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.
- Non-small cell lung carcinoma (NSCLC)
  - as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK-positive tumour mutations.

FDA [5, 6]

Approval status for this indication: On 17 November 2021, the FDA approved pembrolizumab (Keytruda®) 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.

Other indications: Keytruda® is indicated:

- Melanoma
  - for the treatment of patients with unresectable or metastatic melanoma.
  - for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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 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 pemetrexed and platinum chemotherapy, 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 for the first-line treatment of metastatic squamous NSCLC in adults.
- as monotherapy 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 Keytruda®.

❖ Classical Hodgkin lymphoma (cHL)
- as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory cHL who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

❖ Urothelial carcinoma
- 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 combined positive score (CPS) ≥ 10.

❖ Head and neck squamous cell carcinoma (HNSCC)
- as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of metastatic or unresectable recurrent 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.

❖ RCC
- in combination with axitinib for the first-line treatment of advanced RCC in adults.
- in combination with lenvatinib for the first-line treatment of advanced RCC in adults.

❖ Colorectal cancer (CRC)
- as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC in adults.

❖ Oesophageal carcinoma
- in combination with platinum and fluoropyrimidine based chemotherapy for the first-line treatment of locally advanced
- in combination with platinum and FU for the first-line treatment of patients with metastatic or with 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.

❖ 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 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 any platinum-containing chemotherapy, or
  - 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.

❖ MSI-H or dMMR 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).

❖ Oesophageal Cancer
- for the treatment of patients with locally advanced or metastatic oesophageal or GEJ (tumours with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - 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

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.

- ❖ Triple-negative breast cancer (TNBC)
  - in combination with chemotherapy 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.
- ❖ Endometrial carcinoma (EC)
  - in combination with lenvatinib for the treatment of advanced or recurrent EC 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**

- 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 tumours 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.
- ❖ EC
  - in combination with lenvatinib, for the treatment of patients with advanced EC 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 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 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.
  - 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 (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 25 mg/ml = € 3,428.00 (ex-factory price) [7]

Warnings and precautions [6]

- ❖ **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 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 effective method of contraception.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-564 NCT03142334	994 (496 vs. 498)	pembrolizumab 200 mg IV once every 3 weeks for up to 17 cycles	placebo (carrier saline)	disease-free survival	**ongoing**[1], phase 3, randomised, double-blind, international trial	-	Merck Sharp and Dohme	[10]

Efficacy (I vs. C)**; Interim analysis data**

Pre-specified interim analysis data (median time from randomisation to the data-cutoff date was 24.1 months)

Median disease-free survival: not reached in either group

The **risk of disease recurrence or death** was 32% lower with adjuvant pembrolizumab therapy than with placebo (HR for recurrence or death 0.68, 95% CI, 0.53-0.87; p=0.002 (two-sided)

Estimated percentage of patients who remained alive and recurrence-free at 24 months: 77.3% (95% CI, 72.8-81.1) vs. 68.1% (95% CI, 63.5-72.2)

Estimated percentage of patients who remained alive and recurrence-free at 12 months: 85.7% (95% CI, 82.2-88.5) vs. 76.2% (95% CI, 72.2-79.7)

Local recurrence: 3.4% vs. 6.4%

Distant recurrence: 17.3% vs. 23.5%)

Median OS: not reached in either group (HR for death 0.54, 95% CI, 0.30-0.96)

Estimated percentage of patients who were alive at 24 months: 96.6% (95% CI, 94.3-98.0) vs. 93.5% (95% CI, 90.5-95.6)

Estimated percentage of patients who were alive at 12 months: 98.6% (95% CI, 97.0-99.3) and 98.0% (95% CI, 96.3-98.9)

Patient-Reported Outcomes

❖ The full analysis population for patient-reported outcomes included 483 patients in the pembrolizumab group and 493 patients in the placebo group for the FKSI-DRS tool and 484 and 493 patients, respectively, for the EORTC QLQ-C30 tool.

Safety (I vs. C)**; As-treated population**[2]

Any cause AEs

AE of any grade: n=470/488 (96.3%) vs. n=452/496 (91.1%)

AE of grade 3 to 5: n=158/488 (32.4%) vs. n=88/496 (17.7%)

Discontinuation of pembrolizumab or placebo due to AE: n=101/488 (20.7%) vs. n=10/496 (2.0%)

Death due to AE: n=2/488 (0.4%) vs. n=1/496 (0.2%)

Serious AE: n=100/488 (20.5%) vs. n=56/496 (11.3%)

Discontinuation of pembrolizumab or placebo due to serious AE: n=49/488 (10.0%) vs. n=5/496 (1.0%)

Treatment-related AEs, as assessed by investigator

AE of any grade: n=386/488 (79.1%) vs. n=265/496 (53.4%)

AE of grade 3 to 5: n=92/488 (18.9%) vs. n=6/496 (1.2%)

Discontinuation of pembrolizumab or placebo due to AE: n=86/488 (17.6%) vs. n=3/496 (0.6%)

Death due to AE: n=0 vs. n=0

Serious AE: n=59/488 (12.1%) vs. n=1/496 (0.2%)

[1] The KEYNOTE-564 trial is currently ongoing; estimated study completion date is 12/2025.

2 The as-treated population included all the patients who received at least one dose of pembrolizumab or placebo.

❖ At baseline in the pembrolizumab group, 435 patients (90.1%) completed the FKSI-DRS assessment and 438 patients (90.5%) completed the EORTC QLQ-C30 assessment; the corresponding values in the placebo group were 447 patients (90.7%) and 450 patients (91.3%). ❖ At 52 weeks into the treatment phase, in the pembrolizumab group, 300 patients (62.1%) completed the FKSI-DRS assessment and 301 patients (62.2%) completed the EORTC QLQ-C30 assessment; the corresponding values in the placebo group were 328 patients (66.5%) and 325 patients (65.9%). ❖ The least-squares mean change from baseline to week 52 in the FKSI-DRS score was −1.12 (95% CI, −1.53 to −0.71) in the pembrolizumab group and −0.45 (95% CI, −0.84 to −0.05) in the placebo group. The least-squares mean change from baseline to week 52 in the EORTC QLQ-C30 physical functioning score was −1.81 (95% CI, −3.19 to −0.43) in the pembrolizumab group and −0.90 (95% CI, −2.23 to 0.44) in the placebo group.	**Discontinuation of pembrolizumab or placebo due to serious AE:** n=37/488 (7.6%) vs. n=0 **Immune-mediated AEs of any grade:** 34.6% vs. 5.8% **Immune-mediated AEs of grade 3 or 4:** 8.6% vs. 0.6%

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	-	0.68 (0.53-0.87)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A
Adapted	adjuvant	1	-	-	0.68 (0.53-0.87)	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	B	-	-	-	B

Risk of bias (RCT) [13]

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[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, C=comparator, ccRCC=clear cell RCC, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, CRC=colorectal carcinoma, cSCC=cutaneous squamous cell carcinoma, dMMR=mismatch repair deficient, EC=endometrial carcinoma, EGFR=endothelial growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FKSI-DRS=Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms, FM=final magnitude of clinical benefit grade, GEJ=gastroesophageal junction, HCC=hepatocellular carcinoma, HNSCC=head and neck squamous cell carcinoma, 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, NED=no evidence of disease, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=programmed cell death-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,

[3] Trial is ongoing.

[4] The trial was designed by academic advisors and employees of the sponsor. The sponsor participated in the trial design; the collection, analysis, and interpretation of the data; and the writing of the manuscript. The first draft of the manuscript was written by the first and last authors, with assistance from a medical writer employed by the sponsor.

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