Pembrolizumab (Keytruda®) in combination with Lenvatinib (Lenvima®) for the treatment of advanced or recurrent endometrial carcinoma (EC)

General information

Drug description [1]	Indication [2, 3]
Pembrolizumab (Keytruda®) is a monoclonal antibody targeting programmed death receptor-1 (PD-1). Lenvatinib (Lenvima®) is an oral multikinase inhibitor that targets vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor-a, RET, and KIT.	Pembrolizumab (Keytruda®), in combination with lenvatinib (Lenvima®), is indicated 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.

Current treatment [4]

- There are currently no NICE recommended second-line medicinal therapies for advanced EC.
- The current British Gynaecological Cancer Society guidelines for EC recommend chemotherapy-naïve patients who relapse with systemic disease or those with late relapse after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel.
- For metastatic and/or relapsed disease, ESMO guidelines recommend endocrine therapy or cytotoxic chemotherapy. Hormonal therapy mainly involves the use of progestational agents, however, tamoxifen and aromatase inhibitors are also used.

Regulatory status

EMA [2, 3]

Pembrolizumab (Keytruda®)

Approval status for this indication: On 14 October 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 lenvatinib, is indicated 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**

Other indications: 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)

FDA [5-7]

Approval status for this indication: On 21 July 2021, the FDA approved pembrolizumab (Keytruda®) in combination with lenvatinib (Lenvima®) for 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. FDA granted accelerated approval on 17 September 2019 to pembrolizumab with lenvatinib for advanced EC.

- ✓ Priority review
- ✓ Breakthrough therapy designation

Pembrolizumab (Keytruda®)

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.
- 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 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.
- 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.

❖ Renal cell carcinoma (RCC)
- in combination with axitinib, for the first-line treatment of advanced RCC in adults.
- 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 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 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 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 pediatric 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 (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 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).
- 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).

❖ Oesophagal Cancer

- 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 MSI-H or dMMR CRC in adults.

❖ Oesophageal carcinoma
- 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.

❖ 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.

Lenvatinib (Lenvima®)

Approval status for this indication: On 14 October 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lenvima®.

The CHMP adopted a new indication as follows:

❖ Lenvima® in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

✓ **Medicine under additional monitoring**
✓ **Accelerated assessment**

Other indications: Lenvima® is indicated

❖ Differentiated Thyroid Carcinoma (DTC)
- as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

❖ Hepatocellular Carcinoma (HCC)
- as monotherapy for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy.
- for the treatment of patients with locally advanced or metastatic oesophagal or GEJ (tumours with epicentre 1 to 5 centimetres 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
- 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.

❖ 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 pediatric 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.

❖ Tumor 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 (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.
- 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).

Lenvatinib (Lenvima®)

Other indications: Lenvima® is indicated

	❖ DTC • for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC. ❖ RCC • in combination with pembrolizumab, for the first-line treatment of adult patients with advanced RCC. • in combination with everolimus, for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy. ❖ HCC • for the first-line treatment of patients with unresectable HCC.

Costs [8]

4 ml **Keytruda®** concentrate for solution for infusion 25mg/ml = €3,428.00 (ex-factory price)
30 **Lenvima®** hard capsules 10 mg = € 1,670.00 (ex-factory price)

Posology [5, 6]

Pembrolizumab (Keytruda®)

- **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.
- **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.

Lenvatinib (Lenvima®)

- **Hypertension**: Control blood pressure prior to treatment and monitor during treatment. Withhold for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for Grade 4 hypertension.
- **Cardiac Dysfunction:** Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold or discontinue for Grade 3 cardiac dysfunction. Discontinue for grade 4 cardiac dysfunction.
- **Arterial thromboembolic events:** Discontinue following an arterial thromboembolic event.
- **Hepatotoxicity**: Monitor liver function prior to treatment and periodically during treatment. Withhold or discontinue for Grade 3 or 4 hepatotoxicity. Discontinue for hepatic failure.
- **Renal failure or Impairment**: Withhold or discontinue for Grade 3 or 4 renal failure or impairment.
- **Proteinuria**: Monitor for proteinuria prior to treatment and periodically during treatment. Withhold for 2 or more grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome.
- **Diarrhoea**: May be severe and recurrent. Promptly initiate management for severe diarrhoea. Withhold or discontinue based on severity.
- **Fistula formation and gastrointestinal perforation**: Discontinue in patients who develop Grade 3 or 4 fistula or any Grade gastrointestinal perforation.
- **QT interval prolongation**: Monitor and correct electrolyte abnormalities. Withhold for QT interval greater than 500 ms or for 60 ms or greater increase in baseline QT interval.
- **Hypocalcemia**: Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold or discontinue based on severity.

- **Reversible posterior leukoencephalopathy syndrome (RPLS)**: Withhold for RPLS until fully resolved or discontinued.
- **Hemorrhagic events**: Withhold or discontinue based on severity.
- **Impairment of thyroid-stimulating hormone suppression/thyroid dysfunction**: Monitor thyroid function prior to treatment and monthly during treatment.
- **Impaired wound healing:** Withhold Lenvima® for at least 1 week before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Lenvima® after resolution of wound healing complications has not been established.
- **Osteonecrosis of the jaw**: Consider preventive dentistry prior to treatment with Lenvima®. Avoid invasive dental procedures, if possible, particularly in patients at higher risk.
- **Embryo-foetal toxicity**: Can cause foetal harm. Advise of potential risk to a foetus and use of effective contraception.

Study characteristics [7, 9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)[1]
Study 309/ KEYNOTE-775 NCT03517449	827	**pembrolizumab** 200 mg IV every 3 weeks for up to 35 cycles in + **lenvatinib** 20 mg orally once daily	**chemotherapy** treatment of physician's choice[2]	**PFS** (per RECIST v1.1 by BICR) and **OS**	multicenter, randomised, open-label, phase 3 study	-	Eisai Inc.	[9] [10]

Efficacy (I vs. C)

Median PFS: 6.6 months vs. 3.8 months; HR 0.60; 95% CI 0.50-0.72; p<0.0001
Median OS: 17.4 months vs. 12.0 months; HR 0.68; 95% CI 0.56-0.84; p=0.0001
ORR: 30% vs. 15%; p<0.0001
Median DOR: 9.2 months vs. 5.7 months

Efficacy results (median follow-up time 11.4 months) [12]:
Median OS: 18.3 months (95% CI, 15.2-20.5) vs. 11.4 months (10.5-12.9); HR 0.62, 95% CI 0.51-0.75, p<0.0001
Median PFS: 7.2 months (95% CI, 5.7-7.6) vs. 3.8 months (3.6-4.2), HR 0.56, 95% CI 0.47-0.66, p<0.0001
Objective Response Rate: 32% vs. 15%
Complete response: 7% vs. 3%
Partial response: 25% vs. 12%, p<0.0001
Median duration of response: 14.4 months vs. 5.7 months
Not dMMR patients (n=697):
OS HR 0.68, 95% CI, 0.56-0.84, p=0.0001
Median OS:17.4 months vs. 12 months for chemotherapy
dMMR patients (n=130):
OS HR 0.37, 95% CI, 0.22-0.62
Median OS: not reached vs. 8.6 months

QoL [13]:
- Completion and compliance rates of EORTC QLQ-C30 were >95% in both groups at baseline.
- Primary analysis was conducted at week 12 as completion rate was 80% for I and 62% for C; compliance rate was 93% for I and 87% for C.

Safety (I vs. C)

SAEs: occurred in 50% of patients most commonly hypertension (4.4%) and urinary tract infection (3.2%).
Discontinuation of pembrolizumab due to AEs**:** 15%
Discontinuation of lenvatinib due to AEs: 26%.
Fatal AEs occurred in 4.7% of patients.

[1] The KEYNOTE-775 trial is currently ongoing; only abstracts available.

[2] Consisting of either doxorubicin at 60 mg/m² every 3 weeks up to a maximum cumulative dose of 500 mg/m², or paclitaxel at 80 mg/m² on a 28-day cycle.

❖ Baseline GHS/QoL scores were similar between the I and C: mean (SD) of 65.74 (21.87) vs. 65.69 (22.71), respectively. ❖ Over 12 weeks of follow-up, patients in both groups had slight decreases in GHS/QoL. Similar decreases were observed for patients receiving I vs. C: -5.97 (95% CI: -8.36, -3.58) vs. -6.98 (95% CI: -9.63, -4.33). ❖ The between-group difference in least-squares mean score change from baseline to week 12 for I vs. C was 1.01 points (95% CI: -2.28, 4.31). Over time, QoL scores were generally similar across treatments. ❖ No significant differences were observed in HRQoL scores between treatment groups.	

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +6.9 months	0.62 (0.51-0.75)	HR ≤0.65 AND gain ≥3 months	4	-	-	-	4
Adapted	NC	2a	≤12 months	OS: +6.9 months	0.62 (0.51-0.75)	HR ≤0.65 AND gain ≥3 months	4	-	-	-	4

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
Unclear	-	no, open-label	unclear	unclear	unclear[3]

First published: 11/2021
Last updated: 01/2022

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BICR=blinded independent central review, C=comparator, 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, DOR=duration of response, DTC=differentiated thyroid cancer, EC=endometrial carcinoma, ECOG=Eastern Cooperative Oncology Group, EGFR=epidermal 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, FM=final magnitude of clinical benefit grade, FU=fluorouracil, GEJ= gastroesophageal junction, GHS=global health status. HCC=hepatocellular carcinoma, HER2=human epidermal growth factor receptor 2, HNSCC=head and neck squamous cell carcinoma, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, IV=intravenous, MCC=Merkel cell carcinoma, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health Care Excellence, 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, RECIST= Response Evaluation Criteria in Solid Tumors, RPLS=reversible posterior leukoencephalopathy syndrome, SAE=serious adverse event, SD=standard deviation, ST=standard treatment, TMB-H=tumor mutational burden-high TNBC=triple-negative breast cancer, TPS=tumour proportion score, VEGF=vascular endothelial growth factor

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[3] The KEYNOTE-775 trial is currently ongoing, estimated study completion date is 11/2023. Currently only abstracts available.

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