Pembrolizumab (Keytruda®) with chemoradiotherapy (CRT) for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer

General information

Drug description

Pembrolizumab (Keytruda®) is an anti-PD-1 monoclonal antibody.

Indication [1]

Pembrolizumab (Keytruda®), in combination with CRT (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

Incidence [2]

In Austria, in 2022, a total of 439 women were newly diagnosed with cervical cancer; the age-standardised[1] incidence rate was 9.2/100,000 women.

Current treatment[2] [3]

Management of locally advanced cervical cancer (T1b3-T4a) according to the ESGO/ESTRO/ESP Guidelines:

- Definitive radiotherapy should include concomitant chemotherapy whenever possible [I, A].
- IGBT is an essential component of definitive radiotherapy and should not be replaced with an external boost (photon or proton). If BT is not available, patients should be referred to a centre where this can be done [III, B].
- General recommendations for the prescription of CRT and IGBT are as follows [III, B]:
  - 3D imaging (preferentially both MRI and (PET-CT) with the patient in the treatment position should be used for target contouring.
  - External beam radiotherapy (EBRT) with a dose of 45 Gy/25 fractions or 46 Gy/23 fractions is recommended by the use of intensity-modulated or volumetric arc technique.
  - An additional dose of radiation should be applied to pathological lymph nodes on imaging, preferentially using a simultaneous integrated boost (60 Gy EQD2, combined EBRT and estimated dose from IGBT).
  - Concomitant weekly cisplatin is standard. However, weekly carboplatin or hyperthermia can be considered as an alternative option for patients not suitable for cisplatin.
  - Image-guided adaptive brachytherapy (preferentially MRI), including access to intracavitary/interstitial techniques, is needed to obtain a sufficiently high dose to ensure a high rate of local control in advanced cases with poor response to initial CRT. This is especially important for nonsquamous histology.
  - Boosting of the primary tumour and/or the parametria by use of EBRT should be avoided.
  - The overall treatment time, including both CRT and IGBT should aim to not exceed 7 weeks.
- PALND (at least up to the inferior mesenteric artery) may be used to assess the need for elective para-aortic EBRT in patients with negative para-aortic lymph nodes (PALN) and positive PLN on imaging [IV, C].
- If PALND is not performed, risk assessment for microscopic para-aortic nodal involvement and the indication for elective para-aortic irradiation can be based on the number of level 1 positive nodes (external iliac, interiliac, internal iliac) on imaging (e.g. >2 positive nodes). However, elective para-aortic radiation should always be applied in patients who on imaging, have even one positive node at level 2 (common iliac) and above. The groin should also be included in the elective target for patients with tumour involvement of the lower third of the vagina [IV, B].
- Surgical removal of large pathological pelvic and/or para-aortic nodes before definitive CRT is not routinely recommended [IV, D].
- NACT in patients who are otherwise candidates for upfront definitive CRT and IGBT is not recommended outside clinical trials [II, D].
- Adjuvant chemotherapy following definitive CRT and IGBT does not improve survival and enhances toxicity and should not be used outside clinical trials [IV, D].
- Adjuvant/completion hysterectomy after definitive CRT and IGBT should not be performed since it does not improve survival and is associated with both increased perioperative and late morbidities [II, E].

[1] European Standard Population 2013.

[2] There are no recent Onkopedia- or ESMO-guidelines available.

❖ Patients with a persistent tumour 3–6 months after definitive CRT and BT and without evidence of regional or metastatic disease should be referred to specialised centers for evaluating the necessity and the possibility of performing salvage surgery ([IV, B].

Regulatory status

EMA [1, 4]	FDA [5, 6]
Approval status for this indication: On 19 September 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Keytruda®. The CHMP adopted an extension to an existing indication as follows: ❖ Keytruda®, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy. **Other indications**: Keytruda® is indicated: ❖ as monotherapy for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. ❖ as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection. ❖ in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment for the treatment of resectable non-small cell lung carcinoma (NSCLC) at high risk of recurrence in adults. ❖ as monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. ❖ as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% TPS with no EGFR or ALK positive tumour mutations. ❖ in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic nonsquamous 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®. ❖ 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.	**Approval status for this indication**: On 12 January 2024, the FDA approved pembrolizumab (Keytruda®) with chemoradiotherapy (CRT) for patients with FIGO 2014 Stage III-IVA cervical cancer [5]. **Other indications**: Keytruda® is indicated: ❖ for the treatment of patients with unresectable or metastatic melanoma. ❖ for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection. ❖ in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous 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®. ❖ for the treatment of patients with resectable (tumours ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. ❖ as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC. ❖ in combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma. ❖ 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.

- ❖ in combination with enfortumab vedotin, for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.
- ❖ 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 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 adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
- ❖ as monotherapy for adults with MSI-H or dMMR colorectal cancer in the following settings:
    - first-line treatment of metastatic colorectal cancer;
    - treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.
- ❖ as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with:
    - advanced or recurrent endometrial carcinoma, 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;
    - unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.
- ❖ in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10.
- ❖ in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early-stage TNBC at high risk of recurrence.
- ❖ 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.
- ❖ 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.
- ❖ in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer.
- ❖ as a single agent 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.
- ❖ as a single agent 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.
- ❖ for the treatment of adult and paediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- ❖ for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- ❖ in combination with trastuzumab, fluoropyrimidine-and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumour response rate and durability of response.
- ❖ in combination with fluoropyrimidine-and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.
- ❖ 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.
- ❖ 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.

❖ 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. ❖ in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy. ❖ 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. ❖ in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ in combination with gemcitabine and cisplatin, for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.	❖ 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. ❖ for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD1/PD-L1-containing regimen. ❖ in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer. ❖ for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. ❖ 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. ❖ in combination with carboplatin and paclitaxel, followed by Keytruda® as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma. ❖ in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. ❖ as a single agent, for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. ❖ 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. This indication is 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 CNS cancers have not been established. ❖ for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation. ❖ 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 Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

	• for use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL in adults. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety.

Marketing authorisation holder in EU

Merck Sharp & Dohme B.V.

Costs [7]

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = € 3,428.00 (ex-factory price)

Posology [8]

- If specified in the indication, a validated test should confirm patient selection for treatment with Keytruda® based on the tumour expression of PD-L1.
- Keytruda®, as monotherapy or combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions unless specified in the product information.
- For locally advanced cervical cancer, patients should be treated with Keytruda® concurrent with chemoradiotherapy, followed by Keytruda® as monotherapy. Keytruda® can be administered as
  either 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity or up to 24 months.

Warnings and precautions [4]

- Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- Assessment of PD-L1 status
  - When assessing the PD-L1 status of the tumour, a well-validated and robust methodology must be chosen to minimise false negative or false positive determinations.
- Immune-mediated adverse reactions
  - Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-mediated adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of pembrolizumab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.
  - For suspected immune-mediated adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
  - Pembrolizumab may be restarted within 12 weeks after the last dose of Keytruda® if the adverse reaction recovers to Grade ≤ 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.
  - Pembrolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones.
  - For a detailed description of immune-mediated pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and skin adverse reactions, please see Product Information.
- Transplant-related adverse reactions
  - Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.
- Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)
  - Allogeneic HSCT after treatment with pembrolizumab

- Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to pembrolizumab. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case.

- Allogeneic HSCT prior to treatment with pembrolizumab
  - In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

❖ Infusion-related reactions
- Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab. For Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with Grades 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

❖ Use of pembrolizumab in combination with chemotherapy
- Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

❖ Patients excluded from clinical studies
- Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection (except for BTC); active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks.
- Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.
- There are limited data on the safety and efficacy of Keytruda® in patients with ocular melanoma
- After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

❖ Patient card
- All prescribers of Keytruda® must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Keytruda® therapy with the patient. The patient will be provided with the patient card with each prescription

Study characteristics [9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ENGOT-cx11/ GOG-3047/ KEYNOTE-A18) NCT04221945	1060 (1:1)	5 cycles of pembrolizumab 200 mg every 3 weeks + CRT followed by 15 cycles of pembrolizumab 400 mg every 6 weeks	5 cycles of placebo every 3 weeks + chemoradiotherapy followed by 15 cycles of placebo every 6 weeks	PFS per RECIST 1.1 by investigator or by histopathological confirmation of suspected disease progression + OS	median follow-up was 29.9 months (IQR 23.3–34.3)	**ongoing**[3], randomised, double-blind, placebo-controlled, phase 3 trial	PD-1	Merck Sharp & Dohme	KEYNOTE-A18 [9]

[3] KEYNOTE-A18 is ongoing until 01/2026.

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline (n=529 vs. n=531)
❖ High-risk locally advanced cervical cancer: FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stages III-IVA ❖ Histologically-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix. ❖ No previous definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents and immunotherapy-naïve. ❖ Female participants must not be pregnant or breastfeeding and agree to use highly effective contraception during the treatment period and for at least 120 days after the last dose of pembrolizumab or placebo and 180 days following the end of chemoradiotherapy and agree not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. ❖ Female participants must abstain from breastfeeding during the study intervention period and for at least 120 days after the last dose of pembrolizumab or placebo and 180 days following the end of chemoradiotherapy. ❖ ECOG PS of 0 or 1 within 7 days prior to the first dose of study treatment. ❖ A tissue sample from a core incisional or excisional biopsy of a tumour lesion provided. ❖ Radiographically evaluable disease, either measurable or non-measurable per RECIST 1.1, as assessed by the local site investigator/radiology. ❖ Adequate organ function within 7 days prior to the start of study treatment.	❖ Excluded subtypes of locally advanced cervical cancer. ❖ FIGO 2014 Stage IVB disease. ❖ Has undergone a previous hysterectomy defined as removal of the entire uterus or will have a hysterectomy as part of their initial cervical cancer therapy. ❖ Bilateral hydronephrosis, unless at least one side has been stented or resolved by the positioning of nephrostomy or considered mild and not clinically significant in the opinion of the investigator. ❖ Anatomy or tumour geometry or any other reason or contraindication that cannot be treated with intracavitary brachytherapy or a combination of intracavitary and interstitial brachytherapy. ❖ Received a live vaccine within 30 days prior to the first dose of study treatment. ❖ Received treatment with systemic immunostimulatory agents, colony-stimulating factors, interferons, interleukins and vaccine combinations within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1. ❖ Received prior therapy with a PD-1, PD-L, or PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor. ❖ Received prior systemic anticancer therapy, including investigational agents within 4 weeks prior to randomisation. ❖ Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomisation. ❖ Any contraindication to the use of cisplatin. ❖ Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. ❖ Known additional malignancy that is progressing or has required active treatment within the past 3 years. ❖ Severe hypersensitivity to pembrolizumab and/or any of its excipients. ❖ Active autoimmune disease that has required systemic treatment in past 2 years. ❖ History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. ❖ Active infection requiring systemic therapy. ❖ Known history of Human Immunodeficiency Virus infection	❖ Median age (IQR): 49 (40–57) vs. 50 (41–59) years ❖ ≥65 years: 11% vs. 15% ❖ Race: • White: 48% vs. 50% • Asian: 29% vs. 28% • Multiple: 15% vs.16% • American Indian or Alaska Native: 5% vs. 4% • Black or African American: 3% vs. 2% • Native Hawaiian or other Pacific Islander: <1% vs. <1%) • Missing: <1% vs. <1% ❖ ECOG status score: • 0: 72% vs. 75% • 1: 28% vs. 25% ❖ FIGO 2014 stage at screening: • IB2 to IIB: 44% vs. 43% • III to IVA: 56% vs. 57% ❖ Lymph node involvement: • Positive pelvic only: 62% vs. 61% • Positive para-aortic only: 3% vs. 2% • Positive pelvic and paraaortic: 20% vs. 20% • No positive pelvic or paraaortic: 16% vs. 18% ❖ Histology: • Nonsquamous: 18% vs. 15% • Squamous: 82% vs. 85% ❖ Planned type of external beam radiation therapy: • IMRT or VMAT: 89% vs. 89% • Non-IMRT and non-VMAT: 11% vs. 11% ❖ Planned total radiotherapy dose (Gy in equivalent dose in 2 Gy fractions) • <70 Gy: 9% vs. 9% • ≥70 Gy: 91% vs. 91%

[4] For detailed in- and exclusion criteria, please see Trial Protocol.

	❖ Known history of Hepatitis B or known active Hepatitis C virus infection. ❖ History or current evidence of any condition, therapy, lab abnormality, or other circumstance that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results, and in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this study. ❖ Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study. ❖ Allogenic tissue/solid organ transplant. ❖ Evidence of metastatic disease per RECIST 1.1 including lymph nodes above the first lumbar vertebra (L1) cephalad body, in the inguinal region.	❖ PD-L1 combined positive score • <1: 4% vs. 5% • ≥1: 95% vs. 94% ❖ Missing: 1% vs. 1%

Efficacy (I vs. C)	**Safety** (I vs. C)
2nd interim analysis 8 January 2024; median follow-up 29.9 months: **Median OS**: was not reached in either treatment group **Estimated OS at 36 months**: 82.6% (95% CI 78.4–86.1) vs. 74.8% (70.1–78.8) **HR for death**: 0.66 (0.49–0.89) in the subgroup of patients with **PD-L1-positive** (CPS ≥1) tumours (n=1000) **HR for death**: 1.06 (0.26–4.29) in the small subgroup of patients with **PD-L1–negative** (CPS <1) tumours **HR for disease-specific survival**: 0.64 (0.46–0.89) **Estimated disease-specific survival at 36 months**: 86.8% (95% CI 83.1–89.7) vs. 79.0% (74.6–82.8) **PFS events**: 29% vs. 40%, HR 0.68 (95% CI 0.56–0.84) **Median PFS**: not reached in either group **HR for disease progression or death**: 0.69 (95% CI, 0.56–0.85) in the subgroup with **PD-L1-positive** (CPS ≥1) tumours and 0.57 (0.19–1.71) in the subgroup with **PD-L1-negative** (CPS <1) tumours **Patients who received immunotherapy as post-progression treatment**: 11% vs. 26%; of those, 7% and 21%, respectively, had received pembrolizumab. **PFS 2 event**: 15% vs. 24%; HR 0.60 (95% CI 0.46–0.80). HR for disease progression or death was <1 in all the protocol-specified subgroups. **Median duration of response**: not reached in either group **Response duration of at least 12 months**: 83% vs. 78%	**TEAE:** 100% vs. 99% **TEAEs grade ≥3:** 78% vs. 70% **AEs grade ≥3 considered related to study treatment by the study investigator:** 69% vs. 61% **Serious TRAE:** 19% vs. 13% **TRAEs leading to discontinuation of any treatment component:** 19% vs. 13% **TRAEs leading to death[5]:** <1% vs. <1% **Potentially immune-mediated AEs:** 39% vs. 17% **Potentially immune-mediated AEs grade ≥3:** 5% vs. 1% **Serious immune-mediated AEs:** 4% vs. 1% **Death from immune-mediated AEs**: <1% vs. 0 **Infusion-related reactions:** 2% vs. 2% **Infusion-related reactions ≥grade 3:** <1% vs. <1%

Patient-reported outcomes
QoL analysis showed no clinically meaningful between-group differences at week 36 by using the EORTC QOL Questionnaire Core 30 [11].

ESMO-MCBS version 1.1 [12, 13]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[5] Immune-mediated gastritis and large intestine perforation in the pembrolizumab–chemoradiotherapy group and bone marrow failure and neutropenic colitis in the placebo–chemoradiotherapy group.

Original	Curative	1	-	OS at 36 months: +7.8 months	0.67 (0.50–0.90)	>5% improvement of survival at ≥3 years follow-up	A	-	-	-	A
Adapted	curative	1	-	OS at 36 months: +7.8 months	0.67 (0.50–0.90)	>5% improvement of survival at ≥3 years follow-up	A	-	-	-	A

Risk of bias (RCT) [14]

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 low risk	yes low risk	yes low risk	unclear[6] unclear risk	yes[7] high risk	Unclear risk

Ongoing trials [15]

NCT number/trial name	Description	Estimated study completion date
NCT04221945 / ENGOT-cx11/GOG-3047/KEYNOTE-A18)	Please see above.	01/2026

Available assessments

- NIHR published "Pembrolizumab with chemoradiotherapy for treating high-risk locally advanced cervical cancer" in May 2022 [16].
- No further assessments were found via NICE, G-BA, ICER and CDA-AMC.

Other aspects and conclusions

- In September 2024, the **CHMP adopted an extension** to an existing indication for Keytruda®, in combination with CRT (external beam radiation therapy followed by brachytherapy), for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy. In January 2024, the **FDA approved** pembrolizumab (Keytruda®) with chemoradiotherapy (CRT) for patients with FIGO 2014 Stage III-IVA cervical cancer.
- **ENGOT-cx11/GOG-3047/KEYNOTE-A18 is an ongoing**, randomised, double-blind, placebo-controlled, **phase 3 trial** assessing the addition of pembrolizumab to chemoradiotherapy in patients with locally advanced cervical cancer. The patient eligibility criteria included age of ≥18 years, newly diagnosed, high-risk (FIGO 2014 stage IB2–IIB with node-positive disease or stage III–IVA regardless of nodal status), locally advanced, histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix; an ECOG PS score of 0 or 1;16 evaluable diseases per RECIST version 1.1; provision of a tumour tissue sample collected from a core, incisional, or excisional biopsy; and adequate organ function. Key exclusion criteria included other histological cervical
  cancer subtypes; FIGO 2014 stage IVB disease; previous hysterectomy; and previous systemic therapy, immunotherapy, definitive surgery, or radiation.
- Primary endpoints were **PFS per RECIST 1.1** by the investigator or by histopathological confirmation of suspected disease progression and **OS**. Median OS was not reached in either group; 36-month OS was 82.6% (95% CI 78.4–86.1) vs. 74.8% (70.1–78.8); HR for death was 0.67 (95% CI 0.50–0.90; p=0.0040). Median PFS was not reached in either group; HR for disease progression or death was 0.69 (95% CI, 0.56–0.85) in the subgroup with PD-L1-positive (CPS ≥1) tumours and 0.57 (0.19–1.71) in the subgroup with PD-L1-negative (CPS <1) tumours.
- **QoL** analysis showed **no clinically meaningful between-group differences**.
- The **original and adapted ESMO-MCBS** were applied, resulting in a **magnitude of clinical benefit grade of A** each.
- The risk of bias was considered unclear due to the ongoing status of the trial; however, the risk is increased by the industry-funded background.
- Besides KEYNOTE-A18, **no further ongoing trials** were identified for the assessed indication.
- To sufficiently assess the addition of pembrolizumab to CRT for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer, **final analysis data is required**.

First published: 12/2024

[6] The KEYNOTE-A188 trial is currently ongoing; currently, only interim analysis data is available.
[7] The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report.

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ALT alanine aminotransferase, AST=aspartate aminotransferase, ASCT=autologous stem cell transplant, BTC=biliary tract cancer, C=comparator, CDA-AMC=Canada´s Drug Agency, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=Combined Positive Score, CRC=colorectal cancer, CRT=chemoradiotherapy, cSCC= Cutaneous Squamous Cell Carcinoma, CT=computed tomography, dMMR=mismatch repair deficient, EBRT=external beam radiotherapy, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EORTC=European Organization for the Research and Treatment of Cancer, ESGO=European Society of Gynecological Oncology, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, ESP=European Society of Pathology, ESTRO=European Society for Radiotherapy and Oncology, EU=European Union, FDA=Food and Drug Administration, FIGO=International Federation of Gynaecology and ObstetricsFM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ= gastroesophageal junction, GVHD=Graft-versus-Host disease, HNSCC=head and neck squamous cell cancer, HR=hazard ratio, HSCT=haematopoietic stem cell transplant, I=intervention, ICER=Institute for Clinical and Economic Review, IGBT=image-guided brachytherapy, IMRT=intensity-modulated radiation therapy. Int.=intention, IQR=interquartile range, MG=median gain, MRI=magnetic resonance imaging, MSI-H=microsatellite instability-high, n=number of patients, NACT=Neoadjuvant chemotherapy, NICE=National Institute for Health Care Excellence, NSCLC=non small cell lung cancer, ORR=objective response rate, OS=overall survival, PALND=Para-aortic lymph node dissection, PD-1=programmed death receptor-1, PD-L1=programmed death-ligand 1, PE=primary endpoint, PET-CT=positron emission tomography-computed tomography, PFS=progression-free survival, PM=preliminary grade, PMBCL= Primary Mediastinal Large B-Cell Lymphoma QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, ST=standard treatment, TMB-H=Tumor Mutational Burden-High, TPS= Tumor Proportion Score, TRAE=treatment-related adverse event, TNBC=triple-negative breast cancer, ULN=upper limit of normal, VMAT=volumetric modulated arc therapy

References:

[1] European Medicines Agency (EMA). Summary of opinion (post authorisation). Keytruda. [cited 2024-11-21]. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda-ii-145_en.pdf.

[2] Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [cited 2024-11-26]. Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen.

[3] Cibula D, Raspollini MR, Planchamp F and et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023. Int J Gynecol Cancer 2023;33:649–666 doi:101136/ijgc-2023-004429.

[4] European Medicines Agency (EMA). Keytruda: EPAR - Product Information. [cited 2024-11-21]. Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf.

[5] U.S. Food and Drug Administration. FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer. [cited 2024-11-26].

[6] U.S. Food and Drug Administration. Keytruda. Label Information. [cited 2024-11-26].

[7] Österreichischer Apothekerverlag. Warenverzeichnis Online, . [cited 2024-11-26]. Available from: https://warenverzeichnis.apoverlag.at/.

[8] European Medicines Agency (EMA). Keytruda: EPAR - Product Information. [cited 2024-11-27]. Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf.

[9] Lorusso D, Xiang Y, Hasegawa K, et al. and on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2024. Volume 403(10434):1341-1350

[10] U.S. National Library of Medicine and ClinicalTrials.gov. Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer (MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047).

[11] Rosa K. KEYNOTE-A18 Data Support Pembrolizumab Plus Chemoradiotherapy as New SOC in High-Risk Locally Advanced Cervical Cancer. Available from: https://www.onclive.com/view/keynote-a18-data-support-pembrolizumab-plus-chemoradiotherapy-as-new-soc-in-high-risk-locally-advanced-cervical-cancer.

[12] Cherny NI, Dafni U, Bogaerts J. and et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.

[13] Grössmann N, Del Paggio JC, Wolf S, Sullivan R, Booth CM, Rosian K, et al. Five years of EMA-approved systemic cancer therapies for solid tumours—a comparison of two thresholds for meaningful clinical benefit. European Journal of Cancer Volume 82, September 2017, Pages 66-71.

[14] 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.

[15] U.S. National Library of Medicine and ClinicalTrials.gov. [cited 2024-11-27]. Available from: https://clinicaltrials.gov/.

[16] National Institute for Health Reseach (NIHR). Pembrolizumab with chemoradiotherapy for treating high-risk locally advanced cervical cancer. [cited 2024-11-27]. Available from: https://io.nihr.ac.uk/wp-content/uploads/2022/05/29563-TSID_10690-Pembrolizumab-Chemoradiotherapy-for-Cervical-Cancer-V1.0-MAY2022-NON-CONF.pdf.