

Pembrolizumab (Keytruda®) in combination with chemotherapy with or without bevacizumab for the treatment of persistent, recurrent, or metastatic cervical cancer

General information

Drug description [1]	Indication [2]
Pembrolizumab (Keytruda®) is an anti-programmed death 1 (PD-1) monoclonal antibody.	Pembrolizumab (Keytruda®), in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥ 1 .

Current treatment [3]

- ❖ In the UK, chemotherapy is offered to patients with advanced, metastatic or recurrent cervical cancers. These include:
 - Cisplatin
 - Carboplatin
 - Paclitaxel (Taxol)
 - Paclitaxel-carboplatin
 - Topotecan (Hycamtin, postactasol)
 - Carboplatin-etoposide
- ❖ NICE recommends topotecan in combination with cisplatin for women with recurrent or stage IVb cervical cancer if they have not previously received cisplatin.
- ❖ The British Gynaecological Cancer Society recommends that those patients who are WHO performance status 0/1 should be considered for systemic treatment whereas for those with lower performance status should be carefully risk assessed.
- ❖ Since 2014, bevacizumab has been FDA approved and SMC and NICE approved from 2016 to be used with either platinum/paclitaxel or platinum/topotecan.

Regulatory status

EMA [2]	FDA [4, 5]
<p>Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.</p> <p><u>The CHMP adopted a new indication as follows:</u></p> <ul style="list-style-type: none"> ❖ Keytruda®, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1. <p>Other indications: Keytruda® is indicated:</p> <ul style="list-style-type: none"> ❖ Melanoma <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a $\geq 50\%$ 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 	<p>Approval status for this indication: On 13 October 2021, the FDA approved pembrolizumab (Keytruda®) in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥ 1), as determined by an FDA-approved test.</p> <ul style="list-style-type: none"> ✓ Priority review designation <p>Other indications: Keytruda is indicated:</p> <ul style="list-style-type: none"> ❖ Melanoma <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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 $\geq 1\%$) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and is: <ul style="list-style-type: none"> ○ 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 $\geq 1\%$) 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®

<p>in adults whose tumours have no EGFR or ALK positive mutations.</p> <ul style="list-style-type: none"> • 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 $\geq 1\%$ 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®. <p>❖ Classical Hodgkin lymphoma (cHL)</p> <ul style="list-style-type: none"> • 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. <p>❖ Urothelial carcinoma</p> <ul style="list-style-type: none"> • 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. <p>❖ Head and neck squamous cell carcinoma (HNSCC)</p> <ul style="list-style-type: none"> • 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 $\geq 50\%$ TPS and progressing on or after platinum-containing chemotherapy. <p>❖ Renal cell carcinoma (RCC)</p> <ul style="list-style-type: none"> • 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. • 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. <p>❖ Colorectal cancer (CRC)</p> <ul style="list-style-type: none"> • as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC in adults. 	<p>❖ HNSCC</p> <ul style="list-style-type: none"> • 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. <p>❖ cHL</p> <ul style="list-style-type: none"> • 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. <p>❖ Primary mediastinal large B-cell lymphoma (PMBCL)</p> <ul style="list-style-type: none"> • 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. <p>❖ Urothelial carcinoma</p> <ul style="list-style-type: none"> • for the treatment of patients with locally advanced or metastatic urothelial carcinoma who: <ul style="list-style-type: none"> ○ 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. <p>❖ MSI-H or dMMR cancer</p> <ul style="list-style-type: none"> • 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 (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 paediatric patients with MSI-H central nervous system cancers have not been established. <p>❖ MSI-H or dMMR CRC</p> <ul style="list-style-type: none"> • for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC. <p>❖ Gastric cancer</p> <ul style="list-style-type: none"> • 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 (this indication is approved under accelerated approval based on tumour response rate and durability of response). • 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: <ul style="list-style-type: none"> ○ 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. <p>❖ Cervical Cancer</p>
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<ul style="list-style-type: none"> ❖ MSI-H or dMMR cancer <ul style="list-style-type: none"> • as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with: <ul style="list-style-type: none"> ○ unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy; ○ 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. ❖ Oesophageal carcinoma <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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. <p>✓ Medicine under additional monitoring</p>	<ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • for the treatment of patients with HCC who have been previously treated with sorafenib (this indication is approved under accelerated approval based on tumour response rate and durability of response). ❖ Merkel Cell Carcinoma (MCC) <ul style="list-style-type: none"> • for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic MCC (this indication is approved under accelerated approval based on tumour response rate and durability of response). ❖ RCC <ul style="list-style-type: none"> • 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. ❖ EC <ul style="list-style-type: none"> • 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. • as a single agent, for the treatment of 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. ❖ Tumour Mutational Burden-High (TMB-H) Cancer <ul style="list-style-type: none"> • for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high 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 paediatric patients with TMB-H central nervous system cancers have not been established. ❖ Cutaneous Squamous Cell Carcinoma (cSCC) <ul style="list-style-type: none"> • for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation. ❖ TNBC <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications (this indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.
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Costs [6]

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



Warnings and precautions [4]

- ❖ **Immune-mediated adverse reactions**
 - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
 - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
 - Withhold or permanently discontinue based on severity and type of reaction.
- ❖ **Infusion-related reactions**
 - Interrupt, slow the rate of infusion, or permanently discontinue Keytruda® based on the severity of 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 [1, 7-9]

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-826 NCT03635567	617 (1:1)	pembrolizumab (200 mg) every 3 weeks for up to 35 cycles + platinum-based chemotherapy ¹ ± bevacizumab ²	placebo every 3 weeks for up to 35 cycles + platinum-based chemotherapy ± bevacizumab	PFS + OS (dual primary end points)	ongoing ³ , multicentre, randomized, double-blind, phase 3 trial	PD-L1	Merck Sharp and Dohme	[1]
Efficacy (I vs. C); interim analysis data							Safety (I vs. C), interim analysis data	
<p>Median PFS in patients with a PD-L1 combined positive score of ≥1 (n=548): 10.4 months (95% confidence interval, 9.7-12.3) vs. 8.2 months (95% CI, 6.3-8.5); HR for disease progression or death 0.62; 95% CI, 0.50-0.77; p<0.001</p> <p>Median PFS in the ITT population (n=617): 10.4 months (95% CI, 9.1-12.1) vs. 8.2 months (95% CI, 6.4-8.4); HR 0.65; 95% CI, 0.53-0.79; p<0.001</p> <p>Median PFS in patients with a PD-L1 CPS≥10 (n=317): 10.4 months (95% CI, 8.9-15.1) vs. 8.1 months (95% CI, 6.2-8.8); HR 0.58; 95% CI, 0.44-0.77; p<0.001</p> <p>24-month estimate of patients alive among patients with a PD-L1 CPS≥1: 53.0% (95% CI, 46.0-59.4) vs. 41.7% (95% CI, 34.9-48.2); HR for death 0.64; 95% CI, 0.50-0.81; p<0.001</p> <p>24-month estimate of patients alive among patients in the ITT-population: 50.4% (95% CI, 43.8-56.6) vs. 40.4% (95% CI, 34.0-46.6); HR 0.67; 95% CI, 0.54-0.84; p<0.001</p>							<p>Any AEs of grade 3 to 5: n=251/307 (81.8%) vs. 232/309 (75.1%)</p> <p>Serious AEs: 49.8% vs. 42.4%</p> <p>AEs that led to discontinuation of any trial agent: 37.5% vs. 26.5%</p> <p>AEs that led to discontinuation of all trial agents: 5.9% vs. 4.9%</p> <p>AEs that led to death: 4.6% vs. 4.5%; of these, 0.7% vs. 1.3% were considered by the investigator to be related to any trial agent</p>	

¹ Paclitaxel (175 mg per m² of BSA) and the investigator's choice of cisplatin (50 mg per m²) or carboplatin (area under the concentration–time curve, 5 mg per milliliter per minute) every 3 weeks.

² Patients could receive bevacizumab at a dose of 15 mg per kilogram of body weight every 3 weeks according to local practice at the investigator's discretion.

³ The KEYNOTE-826 trial is currently ongoing; the estimated study completion date is 11/2022.



24-month estimate of patients alive among patients with a PD-L1 CPS ≥ 10 : 54.4% (95% CI, 45.5-62.4) vs. 44.6% (95% CI, 36.3-52.5); HR 0.61; 95% CI, 0.44-0.84; p=0.001

Median OS in either PD-L1–selected population for pembrolizumab: not reached

Median OS in the ITT-population: 24.4 months vs. 16.3-16.5 months

Confirmed response (according to investigator review) among patients with a PD-L1 CPS ≥ 1 : 68.1% vs. 50.2%, **complete response:** 22.7% vs. 13.1%, **median duration of response:** 18.0 vs. 10.4 months

Confirmed response (according to investigator review) among patients in the ITT-population: 65.9% vs. 50.8%, **complete response:** 21.4% vs. 12.9%, **median duration of response:** 18.0 vs. 10.4 months

Confirmed response (according to investigator review) among patients with a PD-L1 CPS ≥ 10 : 69.6% vs. 49.1%, **complete response:** 22.2% vs. 11.3%, **median duration of response:** 21.1 vs. 9.4 months

Patient-Reported Outcomes

- ❖ Compliance with the EQ-5D-5L questionnaires between baseline and week 30 was 94.0% or more in the pembrolizumab group and 88.9% or more in the placebo group.
- ❖ Time to deterioration in the EQ-5D-5L VAS score was longer with pembrolizumab than with placebo (12-month estimate of patients free from deterioration, 58.2% vs. 44.8%; HR 0.75; 95% CI, 0.58-0.97).
- ❖ During 30 weeks of follow-up, more patients who received pembrolizumab had improved or stable EQ-5D-5L VAS scores than patients who received placebo (78.3% vs. 71.7%).

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	+2.2 months	0.62 (0.50-0.77)	HR ≤ 0.65 AND gain ≥ 1.5 months	3	-	-	-	3
Adapted	NC	2b	>6 months	+2.2 months	0.62 (0.50-0.77)	HR ≤ 0.65 AND gain ≥ 1.5 months	3	-	-	-	3

Risk of bias (RCT) [12]

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 ⁴	yes ⁵	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BSA=body-surface area, 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, EC=endometrial carcinoma, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EQ-5D-5L=EuroQoL Group 5-Dimension 5-Level 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, GEJ=gastroesophageal junction, HCC=hepatocellular carcinoma, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, HSCT=Hematopoietic 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 death 1, PD-L1=programmed death 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, SMC=Scottish Medicines Consortium, ST=standard treatment, TMB-H=Tumor Mutational Burden-High, TNBC=triple-negative breast cancer, TPS=tumour proportion score, VAS=visual analogue scale, WHO=World Health Organization

⁴ The KEYNOTE-826 trial is ongoing; currently only interim analysis data is available.

⁵ The trial was designed by academic advisors and employees of the sponsor. Assistance with manuscript preparation was provided by a medical writer who was employed by the sponsor.



References:

1. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med* 2021;385:1856-67. [Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2112435>]
2. European Medicines Agency (EMA). Medicines. Keytruda. [Available from: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-7>].
3. National Institute for Health and Research (NIHR). Pembrolizumab in addition to chemotherapy for persistent, recurrent or metastatic cervical cancer – first line. [Available from: <https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/26907-Pembrolizumab-Chemo-for-Cervical-Cancer-V1.0-APR2020-NON-CONF.pdf>].
4. U.S. Food and Drug Administration (FDA). Keytruda. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s110lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves pembrolizumab combination for the first-line treatment of cervical cancer. [Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-combination-first-line-treatment-cervical-cancer>].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: <https://warenverzeichnis.apoverlag.at/>].
7. Protocol for: Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021;385:1856-67.
8. Supplement to: Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021;385:1856-67.
9. U.S. National Library of Medicine, ClinicalTrials.gov. Efficacy and Safety Study of First-line Treatment With Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Women With Persistent, Recurrent, or Metastatic Cervical Cancer (MK-3475-826/KEYNOTE-826). [Available from: <https://clinicaltrials.gov/ct2/show/NCT03635567>].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28: 2340–2366, 2017.
11. European Society of Medical Oncology (ESMO). ESMO-MCBS Scorecards. Pembrolizumab. [Available from: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-306-1>].
12. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: <https://www.eunetha.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf>].

