Pembrolizumab (Keytruda®) for the treatment of adults with endometrial carcinoma

General information

Drug description [1]

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

Indication [1]

Pembrolizumab (Keytruda®) is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

Incidence [2]

In Austria, in 2022, a total of 1034 women were newly diagnosed with ovarian cancer. The age-standardised incidence rate[1] in Austria was in 2022 for females 20.5 per 100,000. As of 2022, the prevalence in absolute numbers was 14,632.

Current treatment [3]

The Onkopedia treatment recommendation for the treatment of ovarian cancer is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [4]	FDA [5]
Approval status: On September 19 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the extension of indication for the medicinal product Keytruda®. Extension of indication for Keytruda® is as follows: Keytruda®, 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. **Other indications** [1]: Melanoma Keytruda® as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. Keytruda® as monotherapy is indicated 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. Non-small cell lung carcinoma Keytruda®, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults. Keytruda® as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.	**Approval status**: On June 17 2024, the FDA approved pembrolizumab (Keytruda®, Merck) with carboplatin and paclitaxel, followed by single-agent pembrolizumab, for adult patients with primary advanced or recurrent endometrial carcinoma. The indication is as follows: Endometrial Carcinoma ❖ 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 (pMMR) 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. **Other indications** [6]: Melanoma ❖ for the treatment of patients with unresectable or metastatic melanoma. ❖ for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. Non-Small Cell Lung Cancer (NSCLC) ❖ in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

[1] European Standard Population 2013.

Keytruda® as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score with no EGFR or ALK positive tumour mutations. Keytruda®, in combination with pemetrexed and platinum chemotherapy, is indicated for the firstline treatment of metastatic nonsquamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations. Keytruda®, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults. Keytruda® as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma 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®. <u>Classical Hodgkin lymphoma</u> Keytruda® as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. <u>Urothelial carcinoma</u> Keytruda®, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults. Keytruda® as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Keytruda® as monotherapy is indicated 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. <u>Head and neck squamous cell carcinoma</u> Keytruda®, as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. Keytruda® as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.	❖ 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 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor 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 tumors 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 tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda®. Small Cell Lung Cancer (SCLC) ❖ for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Head and Neck Squamous Cell Cancer (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 tumors express PD-L1 [Combined Positive Score (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. Classical Hodgkin Lymphoma (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 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 cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. ❖ for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinumcontaining 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 tumors who are ineligible for or have elected not to undergo cystectomy. Microsatellite Instability-High or Mismatch Repair Deficient Cancer

Renal cell carcinoma Keytruda®, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. Keytruda®, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. Keytruda® as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers *Colorectal cancer* Keytruda® as monotherapy is indicated 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. *Non-colorectal cancers* Keytruda® as monotherapy is indicated 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. Oesophageal carcinoma Keytruda®, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated 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. Triple-negative breast cancer Keytruda®, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence. Keytruda®, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease. Endometrial carcinoma	❖ for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. • Limitations of Use: The safety and effectiveness of Keytruda® in pediatric patients with MSI-H central nervous system cancers have not been established. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer ❖ for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer. Gastric Cancer ❖ for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (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. Esophageal Cancer ❖ for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: o in combination with platinum- and fluoropyrimidine-based chemotherapy, or o as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test. Cervical Cancer ❖ for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. Hepatocellular Carcinoma (HCC) ❖ for the treatment of patients with HCC who have been previously treated with sorafenib. Merkel Cell Carcinoma ❖ for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. Renal Cell Carcinoma (RCC) ❖ in combination with axitinib, for the first-line treatment of patients with advanced RCC. Tumor Mutational Burden-High Cancer ❖ for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. ❖ Limitations of Use: The safety and effectiveness of Keytruda® in pediatric patients with TMB-H central nervous system cancers have not been established.

Keytruda®, in combination with lenvatinib, is indicated 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.

Cervical cancer

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.

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.

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

Keytruda®, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated 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.

Keytruda®, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated 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.

Biliary tract carcinoma

Keytruda®, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Cutaneous Squamous Cell Carcinoma

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (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.
- This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- 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.

Marketing authorisation holder in EU [1]

Merck Sharp & Dohme B.V.

Costs [7]

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

Posology [1]

- If specified in the indication, patient selection for treatment with KEYTRUDA based on the tumour expression of PD-L1 should be confirmed by a validated test.
- The recommended dose of Keytruda® in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Warnings and precautions [1]

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, it is important that a well-validated and robust methodology is 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 last dose of Keytruda® if the adverse reaction recovers to Grade ≤ 1 and 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.

Immune-mediated pneumonitis

Pneumonitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.

Immune-mediated colitis

Colitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis. The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued.

Immune-mediated nephritis

Nephritis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.

Immune-mediated endocrinopathies

Severe endocrinopathies, including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab
treatment. Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.

Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Hypophysitis has also been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. Pembrolizumab should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone

replacement. Pembrolizumab should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement. Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of type 1 diabetes associated with Grade ≥ 3 hyperglycaemia or ketoacidosis until metabolic control is achieved.
Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement. For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.

<u>Immune-mediated skin adverse reactions</u>
Immune-mediated severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving pembrolizumab. For suspected SJS or TEN, pembrolizumab
should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued. Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anti-cancer agents.

<u>Other immune-mediated adverse reactions</u>
The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective and hypoparathyroidism.

Based on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids administered. Pembrolizumab may be restarted within 12 weeks after last dose of Keytruda® if the adverse reaction recovers to Grade ≤ 1 and 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. For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, pembrolizumab should be permanently discontinued.

<u>Transplant-related adverse reactions</u>
Solid organ transplant rejection
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 (VOD) 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.

Disease-specific precautions

Use of pembrolizumab in urothelial carcinoma patients who have received prior platinum-containing chemotherapy Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial carcinoma, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy. Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in urothelial carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy. No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. KEYNOTE-052 also included patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, no safety and efficacy data are available in frailer patients (e.g. ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

Use of pembrolizumab for first-line treatment of patients with NSCLC

In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components. A direct comparison of pembrolizumab when used in combination with chemotherapy to pembrolizumab monotherapy is not available. Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in previously untreated patients with NSCLC whose tumours express PD-L1. In KEYNOTE-042, a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy.

Use of pembrolizumab for first-line treatment of patients with HNSCC

In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components. Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in patients with HNSCC whose tumours express PD-L1. Use of pembrolizumab for treatment of patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma.

A direct comparison of pembrolizumab when used in combination with lenvatinib to pembrolizumab monotherapy is not available. Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with lenvatinib) before initiating treatment in patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma.

Use of pembrolizumab for adjuvant treatment of patients with melanoma

A trend toward increased frequency of severe and serious adverse reactions in patients ≥ 75 years was observed. Safety data of pembrolizumab in the adjuvant melanoma setting in patients ≥ 75 years are limited.

Use of pembrolizumab in combination with axitinib for first-line treatment of patients with RCC

When pembrolizumab is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC. Liver enzymes should be monitored before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes as compared to when the medicines are used in monotherapy may be considered. Medical management guidelines for both medicines should be followed. Use of pembrolizumab for first-line treatment of patients with MSI-H/dMMR CRC In KEYNOTE-177, the hazard rates for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab.

Use of pembrolizumab for first-line treatment of patients with BTC

Cholangitis and biliary tract infections are not uncommon in patients with BTC. Cholangitis events were reported in KEYNOTE-966 in both treatment groups (11.2% [n=59] of participants in the pembrolizumab plus chemotherapy arm and 10.3% [n=55] of participants in the placebo plus chemotherapy arm). Patients with biliary stents and drains (n=74) were at increased risk of cholangitis and biliary tract infections in KEYNOTE-966 (39.4% [n=13] of participants in the pembrolizumab plus chemotherapy arm vs. 29.3% [n=12] of participants in the placebo plus chemotherapy arm). Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

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 [8]

Trial name/ NCT number	*n*	Intervention (I)[2,3]	Comparator (C)[4,3]	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NCT03914612	816 (1:1)	Paclitaxel plus carboplatin along with pembrolizumab.	Paclitaxel plus carboplatin along with placebo.	PFS	12 months in dMMR cohort, 7.9 months in the pMMR cohort.[5]	Double-blind, placebo-controlled, randomised, phase 3 trial.	MMR	National Cancer Institute, Merck	KEYNOTE-868, NRG-GY018 [8]

Inclusion criteria[6]	Exclusion criteria[6]	Patient characteristics at baseline

[2] 6 cycles followed by pembrolizumab maintenance every 6 weeks for up to 14 cycles. 200 mg of pembrolizumab administered i.v. in a 30-minute infusion every 3 weeks in combination with chemotherapy, followed by 400 mg of pembrolizumab maintenance, administered i.v. in a 30-minute infusion every 6 weeks.

[3] Chemotherapy consisted of paclitaxel administered i.v. in a 3-hour infusion (175 mg / m^2 of body-surface), carboplatin at an area under the curve of 5 mg/mL/min administered i.v. over 30 to 60 minutes.

[4] 6 cycles followed by placebo maintenance every 6 weeks for up to 14 cycles. Placebo administered i.v. in a 30-minute infusion every 3 weeks in combination with chemotherapy, placebo maintenance, administered i.v. in a 30-minute infusion every 6 weeks.

[5] The patients were stratified into two cohorts according to whether they had mismatch repair–deficient (dMMR) or mismatch repair– proficient (pMMR) disease on immunohistochemical (IHC) assessment.

[6] For detailed in-and exclusion criteria, please see trial protocol.

		dMMR Cohort I (n=112) vs. C (n=113) vs pMMR Cohort I (n=293) vs. C (n=295)
❖ Measurable stage III, measurable stage IVA, stage IVB (with or without measurable disease) or recurrent (with or without measurable disease) endometrial cancer. ❖ Patients with the following histologic types: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified. ❖ Lesions defined and monitored by RECIST v 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension. Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. ❖ Prior Therapy: • Patients may have received either ▪ NO prior chemotherapy for treatment of endometrial cancer OR ▪ Prior adjuvant chemotherapy (e.g., paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥ 12 months prior. • Prior radiation therapy, including pelvic radiation therapy, extended field pelvic/para aortic radiation therapy, and/or intravaginal brachytherapy. All radiation therapy must be completed at least 4 weeks prior. • Prior hormonal therapy for treatment of endometrial cancer. All hormonal therapy must be discontinued at least three weeks prior. ❖ Age ≥ 18. ❖ Performance Status of 0, 1 and 2. ❖ Adequate hematologic function defined as follows: • Platelets ≥ 100,000/mcl • Absolute neutrophil count ≥ 1,500/mcl ❖ Adequate renal function defined as follows: • GFR ≥50 mL/min/1.73m^2 • GFR will be estimated using the Cockcroft and Gault equation for females: CLcr (mL/min) = 0.85 x (140-age[years]) x weight (kg)/ (creatinine (mg/dL) x 72).	❖ Patients with prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibodies or other similar agents. ❖ Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. ❖ Patients who are currently participating and receiving cancer-directed study therapy or have participated in a study of an investigational agent and received cancer-directed study therapy within 4 weeks prior to Step 1 registration. ❖ Patients who have a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Step 1 registration. ❖ Patients with treated brain metastases are eligible if follow-up brain imaging after CNSdirected therapy shows no evidence of progression, and they have been off steroids for at least 4 weeks prior to Step 1 registration and remain clinically stable. ❖ Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. This includes, but is not limited to, patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be	**Demographic** ❖ Median age (range) — yr: 67 (38–81) vs 66 (37–85) vs 66 (31–93) vs 65 (29–90) ❖ Race or ethnic group — no. (%) • White: 82.1 vs 76.1 vs 79.1 vs 71.9 vs 72.1 • Black: 9.8 vs 8.0 vs 15.4 vs 17.3 • Asian: 2.7 vs 3.5 vs 5.8 vs 4.7 • American Indian or Alaska Native: 0 vs 1.8 vs 0.7 vs 0.7 • Native Hawaiian or other Pacific: 0 vs 0 vs 0.3 vs 1.0 • Unknown: 2.7 vs 8.0 vs2.7 vs 2.4 • Not reported: 2.7 vs 2.7 vs 2.4 vs 1.7 • Multiracial: 0 vs 0 vs 0.3 vs 0.3 ❖ Hispanic ethnic group — no. (%) • No: 94.6 vs 87.6 vs 89.8 vs 92.5 • Yes: 4.5 vs 5.3 vs 7.2 vs 5.4 • Unknown: 0.9 vs 3.5 vs 1.4 vs 1.0 • Not reported: 0 vs 3.5 vs 1.7 vs 1.0 **Medical history** ❖ ECOG performance-status score —no. (%) • 0: 64.3 vs 64.6 vs 66.9 vs 67.1 • 1: 34.8 vs 31.0 vs 30.0 vs 29.8 • 2: 0.9 vs 4.4 vs 3.1 vs 3.1 ❖ Histologic analysis — no. (%) • Adenocarcinoma, NOS: 0.7 vs 12.4 vs 8.2 vs 11.2 • Clear cell : 0.9 vs 0 vs 5.8 vs 6.8 • Dedifferentiated or undifferentiated: 3.6 vs 3.5 vs 2.4 vs 2.0 • Endometrioid: ▪ G1: 18.8 vs 31.0 vs 18.4 vs 15.6 ▪ G2: 46.4 vs 36.3 vs 17.4 vs 19.7 ▪ G3: 13.4 vs 14.2 vs 18.1 vs 14.2 • Mixed epithelial: 2.7 vs 1.8 vs 2.0 vs 3.7 • Serous: 3.6 vs 0.9 vs 26.6 vs 24.4 • Pending: 0 vs 0 vs 1.0 vs 2.4 **Previous therapy** ❖ Chemotherapy — no. (%) • Yes: 4.5 vs 7.1 vs 24.6 vs 26.1 • No: 95.5 vs 92.9 vs 75.4 vs 73.9

Followed by conversion to a value normalised to 1.73m^2 with the patient's BSA ❖ Adequate hepatic function defined as follows: • Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled) • AST and ALT ≤ 3 x ULN ❖ TSH within normal limits (TSH <ULN allowed in euthyroid patients on thyroid replacement therapy). ❖ HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial. ❖ For patients of child bearing potential: negative urine or serum pregnancy test within 72 hours prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. ❖ Women of childbearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from up to 14 days prior to Step 2 registration (for oral contraceptives), during treatment, and for 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. ❖ The patient or a legally authorised representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorisation permitting release of personal health information.	evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. ❖ Patients who have a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis. ❖ Uncontrolled intercurrent illness including, but not limited to: ongoing or active infection, interstitial lung disease or active, non-infectious pneumonitis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. ❖ Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; and cirrhosis. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load. ❖ Pregnant or lactating patients.	❖ Radiotherapy — no. (%) • Yes: 36.6 vs 48.7 vs 38.9 vs 40.3 • No: 63.4 vs 51.3 vs 61.1 vs 59.7 ❖ Surgery — no. (%) • Yes: 87.5 vs 92.9 vs 89.1 vs 83.1 • No: 12.5 vs 7.1 vs 9.9 vs 15.6 • Missing data: 0 vs 0 vs 1.0 vs 1.4
Efficacy (I vs. C)		**Safety** (I vs. C, n=218 vs. n=207)
Data cutoff date (December 16, 2022) **PFS:** dMMR cohort: Kaplan–Meier estimates, 74% vs 38%, HR, 0.30 (95% CI, 0.19-0.48); P<0.001; pMMR cohort: median, 13.1 months vs 8.7 months, HR, 0.54 (95% CI, 0.41-0.71); P<0.001. **OS:** not reported.		**AEs of any grade:** dMMR cohort: 98.2% vs 99.1%; pMMR cohort: 93.5% vs 93.4% **Grade ≥3 AEs**: dMMR cohort: 63.3% vs 47.2%; pMMR cohort: 55.1% vs 45.3% **Discontinuation:** 57% of patients overall **Adverse event leading to death:** dMMR cohort: 1 vs 2; pMMR cohort: 6 vs 2 **Treatment-related adverse event leading to death:** 1 (0.5%) vs 1 (0.5%)
Patient-reported outcomes (I vs. C) **[8]**		
Quality of life was assessed in 588 patients in the pMMR cohort at baseline and in similar percentages of patients in the pembrolizumab and placebo groups (86% and 87%, respectively) at 6 weeks after randomisation. Quality of life assessments were preplanned at the following intervals: weeks 18, 30, and 54. The analysis of the data is not available yet.		
ESMO-MCBS version 1.1 [9, 10]		

Subgroup	Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
pMMR	Original	NC	2b	≥6 - <12 months	PFS: 4.4 months	0.54 (0.41-0.71)	HR ≤0.65 AND gain ≥3 months	3		NA	+1[7]	4
	Adapted	NC	2b	≥6 - <12 months	PFS: 4.4 months	0.54 (0.41-0.71)	HR ≤0.65 AND gain ≥3 months	3		NA	-	3
dMMR	An ESMO-MCBS score was not calculated since the median PFS was not reached in the intervention group.											

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear[8] unclear risk	unclear[9] unclear risk	yes low risk	yes low risk	yes[10] high risk	unclear[11]

Ongoing trials [12]

For the assessed indication, no ongoing trials were identified via ClinicalTrials.gov

Available assessments

No assessments were found via NICE, G-BA, ICER and CDA-AMC.

Other aspects and conclusions

- On **September 19 2024**, the CHMP adopted a new indication for Keytruda®, 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. On June 17, 2024, the FDA approved Keytruda® with carboplatin and paclitaxel, followed by single-agent pembrolizumab, for adult patients with primary advanced or recurrent endometrial carcinoma.
- **NRG-GY018** (NCT03914612) is a **phase 3, double-blind, placebo-controlled, randomised** trial comparing the efficacy and safety of paclitaxel plus carboplatin along with pembrolizumab with the paclitaxel plus carboplatin along with placebo in the treatment of endometrial cancer. The eligibility criteria included: stage III, IVA, IVB or recurrent endometrial cancer, histologic types: endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma, age ≥ 18 and Performance Status of 0, 1, 2. Key exclusion criteria included prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibodies or other similar agents, active autoimmune disease or history of autoimmune disease that might recur.
- **The primary endpoint, PFS,** was in dMMR cohort: Kaplan–Meier estimates, 74% vs 38%, HR, 0.30 (95% CI, 0.19-0.48); P<0.001 and in pMMR cohort: median, 13.1 months vs 8.7 months, HR, 0.54 (95% CI, 0.41-0.71); P<0.001.
- The **original and adapted ESMO-MCBS** were applied, resulting in a magnitude of clinical benefit of grade 4 with the original scale and grade 3 with the adapted version.
- The **risk of bias was unclear** since the randomisation method and allocation concealment of the trial were unknown. The risk was further increased by the industry-funded background.
- Based on the analysis, the efficacy of pembrolizumab has been shown as an improved PFS in combination with carboplatin and paclitaxel for the first-line treatment of primary advanced or recurrent endometrial carcinoma. It has to be, however, noted that in each group, the majority (~65%) of the patients had an ECOG performance score of 0.

First published: 12/2024

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, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=Combined Positive Score, dMMR= mismatch repair–deficient, ECOG=Eastern Cooperative Oncology Group, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FU=fluorouracil, G-BA=Gemeinsamer Bundesausschuss, GEJ= gastroesophageal junction, GFR= glomerular filtration rate, GVHD=Graft-versus-Host disease, HCC =Hepatocellular Carcinoma, HNSCC=head and neck squamous cell cancer, HR=hazard ratio, HSCT=haematopoietic stem cell transplant, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, i.v.=intravenously, MG=median gain, MMR=mismatch repair, MRI=magnetic resonance imaging, MSI-H=microsatellite instability-high, n=number of patients, NOS= not otherwise specified, NSCLC=non-small cell lung

[7] Long-term plateau in the PFS curve: 7 patients (2.4%) available at 24 months.
[8] The specific randomization method is not described in detail.
[9] The study protocol does not describe whether the allocation sequence was concealed.
[10] The study was sponsored by Merck.
[11] Due to unclear allocation concealment.

cancer, PE=primary endpoint, PD-1=programmed death receptor-1, PD-L1=programmed death-ligand 1, PFS=progression-free survival, PM=preliminary grade, PMBCL= Primary Mediastinal Large B-Cell Lymphoma, pMMR= mismatch repair– proficient, PRO= patient reported outcome, RCC =Renal Cell Carcinoma, SAE=serious adverse event, SCLC =Small Cell Lung Cancer, SJS=Stevens-Johnson syndrome, ST=standard treatment, TEN=toxic epidermal necrolysis, TNBC=Triple-Negative Breast Cancer, TPS= Tumor Proportion Score, TSH=thyroid stimulating hormone, ULN=Upper Normal Limits, VOD=veno-occlusive disease

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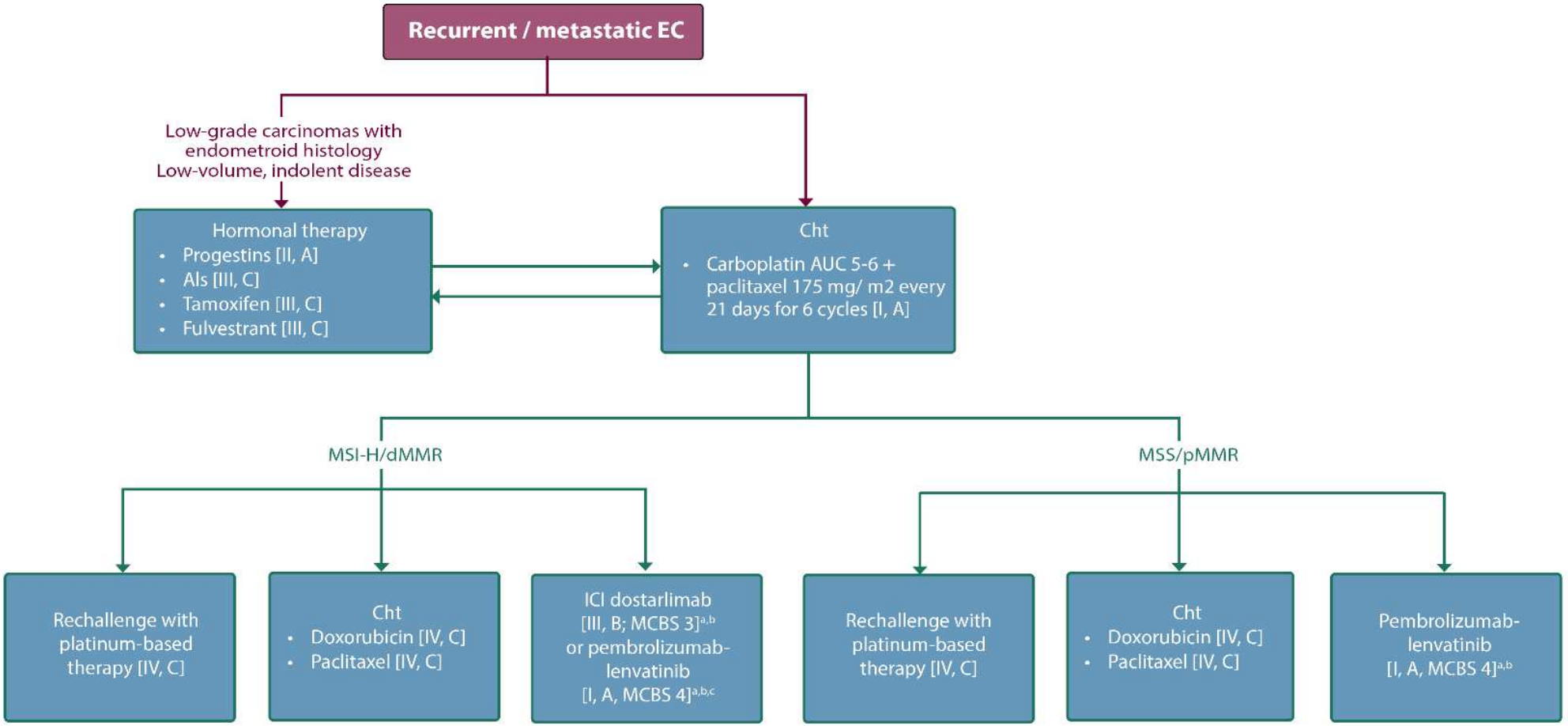
[12] U.S. National Library of Medicine, ClinicalTrials.gov [cited 21.11.2024]. Available from: https://clinicaltrials.gov/.

Appendix – Figure 1:



AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; dMMR, mismatch repair deficient; EC, endometrial cancer; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient.

[a] In patients eligible for further treatment after failure of platinum-based therapy.

[b] ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the European Medicines Agency or Food and Drug Administration (FDA). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[c] FDA approval is restricted to patients whose tumours are not MSI-H or dMMR.