Durvalumab (Imfinzi®) in combination with carboplatin and paclitaxel for the first-line treatment of primary advanced or recurrent endometrial cancer (EC), followed by maintenance treatment durvalumab (Imfinzi®) as monotherapy in EC that is mismatch repair deficient (dMMR) or in combination with olaparib (Lynparza®) in EC that is mismatch repair proficient (pMMR)

General information

Drug description [1, 2]

Durvalumab (Imfinzi®) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80.
Olaparib (Lynparza®) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3).

Indication [3, 4]

Durvalumab (Imfinzi®) in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:

- Durvalumab (Imfinzi®) as monotherapy in EC that is mismatch repair deficient (dMMR)
- Durvalumab (Imfinzi®) in combination with olaparib in EC that is mismatch repair proficient (pMMR).

Incidence [5]

In Austria, in 2022, 1,034 women were newly diagnosed with EC; the age-standardised[1] incidence rate was 20.5 per 100,000 women.

Current treatment [6]

The ESMO treatment recommendation for the treatment of recurrent/metastatic EC is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [3, 4]

Durvalumab (Imfinzi®)

Approval status for this indication: On 27 June 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imfinzi®.

The CHMP adopted a new indication as follows:

- Imfinzi® in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:
  - Imfinzi® as monotherapy in endometrial cancer that is dMMR.
  - Imfinzi® in combination with olaparib in endometrial cancer that is pMMR.

Other indications: Imfinzi® is indicated:

- as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
- in combination with tremelimumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations.

FDA [7-9]

Durvalumab (Imfinzi®)

Approval status for this indication: On 14 June 2024, the FDA approved durvalumab (Imfinzi®) with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent EC that is dMMR.

Other indications: Imfinzi® is indicated:

- for the treatment of adult patients with unresectable Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- in combination with tremelimumab-actl and platinum-based chemotherapy for the treatment of adult patients with metastatic NSCLC with no sensitising EGFR mutations or ALK genomic tumour aberrations.
- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with ES-SCLC.
- in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic BTC.
- in combination with tremelimumab-actl, for the treatment of adult patients with unresectable HCC.

[1] European Standard Population 2013.

- ❖ in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).
- ❖ in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).
- ❖ as monotherapy for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
- ❖ in combination with tremelimumab for the first line treatment of adults with advanced or unresectable HCC.

Olaparib (Lynparza®)

Approval status for this indication: On 27 June 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lynparza®.

The CHMP adopted a new indication as follows:

- ❖ Lynparza® in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

Other indications: Lynparza® is indicated

- ❖ as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- ❖ As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- ❖ in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.
- ❖ monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.
- ❖ monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

Olaparib (Lynparza®)

Approval status for this indication: not approved

Other indications: Lynparza® is indicated:

- ❖ for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- ❖ in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either:
  - a deleterious or suspected deleterious BRCA mutation, and/or
  - genomic instability.

  Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- ❖ for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- ❖ for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm HER2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- ❖ for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- ❖ for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line

- as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.
- as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

Manufacturer

Imfinzi® and Lynparza® are manufactured by AstraZeneca AB.

Costs [10]

Imfinzi® concentrate for solution for infusion 50 mg/ml 2.4 ml = **€ 741.00** (ex-factory price)
2x56 Lynparza® film tablets 100 mg = **€ 4,123.92** (ex-factory price)

Warnings and precautions [1, 2]

Durvalumab (Imfinzi®)

- For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate etiologies. Based on the severity of the adverse reaction, Imfinzi® Imfinzi® in combination with tremelimumab should be withheld or permanently discontinued. Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing the dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.
- **Immune-mediated pneumonitis**
  - Immune-mediated pneumonitis or interstitial lung disease, defined as requiring the use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. For Grade 2 events, an initial dose of 1-2 mg/kg/day prednisone or equivalent should be initiated, followed by a taper. For Grade 3 or 4 events, an initial dose of 2-4 mg/kg/day methylprednisolone or equivalent should be initiated, followed by a taper.
- **Pneumonitis and radiation pneumonitis**
  - Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung, and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the study, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the Imfinzi®-treated group and 58 (24.8%) in the placebo group, including Grade 3 (3.4% vs. 3.0%) and Grade 5 (1.1% vs. 1.7%).
  - Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging, and other infectious and disease-related aetiologies should be excluded. It should be managed as recommended in Product Information.
- **Immune-mediated hepatitis**
  - Immune-mediated hepatitis, defined as requiring the use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving Imfinzi® or Imfinzi® in combination with
    Tremelimumab.

- Monitor alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for all grades.

❖ **Immune-mediated colitis**

- Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Adverse drug reactions of intestinal perforation and large intestine perforation were reported in patients receiving Imfinzi® in combination with tremelimumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in Product Information. Corticosteroids should be administered at an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4. Consult a surgeon immediately if intestinal perforation of ANY grade is suspected.

❖ **Immune-mediated endocrinopathies**

- **Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis**
  - Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed as recommended in Product Information. For immune-mediated hypothyroidism, initiate thyroid hormone replacement as clinically indicated for Grades 2-4. For immune-mediated hyperthyroidism/thyroiditis, symptomatic management can be implemented for Grades 2-4.
- **Immune-mediated adrenal insufficiency**
  - Immune-mediated adrenal insufficiency occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2-4.
- **Immune-mediated type 1 diabetes mellitus**
  - Immune-mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in Product Information. Treatment with insulin can be initiated as clinically indicated for Grades 2-4.
- **Immune-mediated hypophysitis/hypopituitarism**
  - Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2-4.
- **Immune-mediated nephritis**
  - Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with Imfinzi® or Imfinzi® in combination with tremelimumab and managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.
- **Immune-mediated rash**
  - Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grade 2 > 1 week or Grade 3 and 4.
- **Immune-mediated myocarditis**
  - Immune-mediated myocarditis, which can be fatal, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 2-4

mg/kg/day prednisone or equivalent followed by taper for Grades 2-4. If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month.

- **Immune-mediated pancreatitis**
  - Immune-mediated pancreatitis, occurred in patients receiving Imfinzi® in combination with tremelimumab and chemotherapy. Patients should be monitored for signs and symptoms of immune-mediated pancreatitis and managed as recommended in Product Information.
- **Other immune-mediated adverse reactions**
  - Given the mechanism of action of Imfinzi® or Imfinzi® in combination with tremelimumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with Imfinzi® monotherapy or Imfinzi® in combination with tremelimumab: myasthenia gravis, myelitis transverse, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, immune-mediated arthritis, uveitis and cystitis noninfective. Patients should be monitored for signs and symptoms and managed as recommended in Product Information. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.

❖ **Infusion-related reactions**

- Patients should be monitored for signs and symptoms of infusion-related reactions. Severe infusion-related reactions have been reported in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab. Infusion-related reactions should be managed as recommended in Product Information. For Grade 1 or 2 severity, may consider pre-medications for prophylaxis of subsequent infusion reactions. For Grade 3 or 4, manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines.

❖ **Patients with pre-existing autoimmune disease**

- In patients with pre-existing autoimmune disease, data from observational studies suggest an increased risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy as compared with patients without pre-existing autoimmune disease. In addition, flares of the underlying autoimmune disease were frequent, but the majority were mild and manageable

❖ **Disease-specific precaution**

- Cholangitis and biliary tract infections
  - Cholangitis and biliary tract infections are not uncommon in patients with advanced BTC. Cholangitis events were reported in TOPAZ-1 in both treatment groups (14.5% Imfinzi® + chemotherapy vs. 8.2% placebo + chemotherapy); these were mostly in association with biliary stents and were not immune-mediated in aetiology. 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.
- Metastatic NSCLC
  - Limited data are available in elderly patients (≥75 years) treated with Imfinzi® in combination with tremelimumab and platinum-based chemotherapy. Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended.

❖ **Patients excluded from clinical studies**

- Patients with the following were excluded from clinical studies: a baseline ECOG performance score ≥ 2; active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent); uncontrolled intercurrent illnesses; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of Imfinzi®. In the absence of data, durvalumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. The safety of concurrent prophylactic cranial irradiation with Imfinzi® in patients with ES-SCLC is unknown.

<u>Olaparib (Lynparza®)</u>

❖ **Haematological toxicity**

- Haematological toxicity has been reported in patients treated with Lynparza®, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Lynparza® until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet and neutrophil levels should be ≤CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

- If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with Lynparza should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza® dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

❖ **Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML)**

- The overall incidence of MDS/AML in patients treated in clinical trials with Lynparza® monotherapy, including long-term survival follow-up, was <1.5%, with higher incidence in patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years. The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >4 years.
- If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Lynparza® should be discontinued and the patient treated appropriately.

❖ **Venous Thromboembolic Events (VTE)**

- VTEs, predominantly events of pulmonary embolism, have occurred in patients treated with Lynparza® and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer, who also received androgen deprivation therapy, compared with other approved indications. Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.
- Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored appropriately.

❖ **Pneumonitis**

- Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza® in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza® treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza® treatment should be discontinued and the patient treated appropriately.

❖ **Hepatotoxicity**

- Cases of hepatotoxicity have been reported in patients treated with olaparib. If clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected drug-induced liver injury (DILI), treatment should be interrupted. In case of severe DILI treatment discontinuation should be considered as clinically appropriate.

❖ **Embryofoetal toxicity**

- Based on its mechanism of action (PARP inhibition), Lynparza® could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg twice daily.

❖ **Pregnancy/contraception**

- Lynparza® should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting Lynparza® treatment, during therapy and for 6 months after receiving the last dose of Lynparza®. Two highly effective and complementary forms of contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of Lynparza®.

❖ **Interactions**

- Lynparza® co-administration with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of Lynparza® should be reduced. Lynparza® co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza® requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza® may be substantially reduced.

❖ **Sodium**

- This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg or 150 mg tablet, that is to say essentially "sodium-free".

Study characteristics [11, 12]

Trial name	*n*	Intervention (I)	Intervention2 (I2)	Comparator (C)	PE	Median follow-up (I/I2/C)	Characteristics	Biomarker	Funding	Publication(s)

DUO-E GOG-3041 ENGOT-EN10 NCT04269200	718 (1:1:1)	carboplatin/paclitaxel + durvalumab followed by maintenance durvalumab + olaparib placebo (**durvalumab arm**)	carboplatin/paclitaxel + durvalumab followed by maintenance durvalumab + olaparib **(durvalumab + olaparib arm)**	carboplatin/paclitaxel + durvalumab placebo followed by placebo maintenance **(control arm)**	PFS in the durvalumab arm vs. control and the durvalumab+olaparib arm vs. control	15.4/15.4/12.6 months	**ongoing**[2], randomised, double-blind, placebo-controlled multicentre phase III trial	MMR	AstraZeneca in collaboration with the authors and academic groups under the GOG Foundation and the ENGOT groups	DUO-E [12]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (n=239 vs. n=238 vs. n=241)
❖ Age ≥18 years at the time of screening and female. ❖ Histologically confirmed diagnosis of epithelial endometrial carcinoma. All histologies, including carcinosarcomas, will be allowed. Sarcomas will not be allowed. ❖ Patient must have endometrial cancer in one of the following categories: • Newly diagnosed Stage III disease (measurable disease per RECIST 1.1 following surgery or diagnostic biopsy), • Newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy) • Recurrence of disease (measurable or non-measurable disease per RECIST 1.1) where the potential for cure by surgery alone or in combination is poor. ❖ Naïve to first-line systemic anticancer treatment. For patients with recurrent disease only, prior systemic anticancer treatment is allowed only if it was administered in the adjuvant setting and there is at least 12 months from the date of	❖ History of leptomeningeal carcinomatosis. ❖ Brain metastases or spinal cord compression. ❖ Prior treatment with PARP inhibitors. ❖ Any prior exposure to immune-mediated therapy, including (but not limited to) other anti CTLA-4, anti-PD-1, anti-PD-L1, or anti-programmed-cell-death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.	❖ Median age (range): 63 (27-86) vs. 64 (22-84) vs. 64 (31-85) years ❖ Geographic region: • Asia: 28.0% vs. 28.6% vs. 28.2% • Non-Asia: 72.0% vs. 71.4% vs. 71.8% ❖ Race: • White: 55.6% vs. 57.1% vs. 59.3% • Asian: 29.3% vs. 30.3% vs. 30.3% • Black/African American: 5.9% vs. 4.6% vs. 4.1% • American Indian or Alaska Native: 2.% vs. 2.5% vs. 0 • Native Hawaiian or Other Pacific Islander: 0.4% vs. 0 vs. 0.8% • Other: 5.0% vs. 3.4% vs. 4.1% • Not reported: 1.3% vs. 2.1% vs. 1.2% ❖ Ethnicity: • Not Hispanic or Latino: 86.2% vs. 87.4% vs. 90.5% • Hispanic or Latino: 13.4% vs. 11.8% vs. 9.3% • Missing: 0.4% vs. 0.8% vs. 1.2% ❖ ECOG performance status, No. (%) • 0: 69.5% vs. 65.5% vs. 64.7% • 1: 30.5% vs. 34.0% vs. 35.3% ❖ Disease status: • Recurrent: 52.3% vs. 52.5% vs. 52.3% • Newly diagnosed: 47.7% vs. 47.5% vs. 47.7% ❖ FIGO stage in newly diagnosed patients • I: 0.9% vs. 0 vs. 0 • II: 0% vs. 0% vs. 0.4% • III: 5.0% vs. 7.1% vs. 5.0%

[2] DUO-E is currently ongoing; the estimated study completion date is 08/2027.

last dose of systemic anticancer treatment administered to date of subsequent relapse ❖ FPPE tumour sample must be available for MMR evaluation. ❖ ECOG PS of 0 or 1 within 7 days of starting study treatment.		• IV: 41.4% vs. 40.3% vs. 41.9% ❖ Histology type: • Endometrioid: 63.6% vs. 59.2% vs. 57.7% • Serous: 17.6% vs. 24.4% vs. 22.4% • Carcinosarcoma: 7.5% vs. 5.0% vs. 8.7% • Mixed, epithelial: 3.8% vs. 3.8% vs. 4.6% • Clear cell: 3.3% vs. 1.7% vs. 2.9% • Undifferentiated: 2.1% vs. 1.7% vs. 1.2% • Mucinous: 0 vs. 0.4% vs. 0 • Other: 2.1% vs. 3.8% vs. 2.5% ❖ MMR status: • Proficient: 79.9% vs. 80.7% vs. 79.7% • Deficient: 20.1% vs. 19.3% vs. 20.3% ❖ HRRm status: • HRRm: 16.3% vs. 10.9% vs. 13.3% • Non-HRRm: 59.0% vs. 58.0% vs. 54.8% • Unknown: 24.7% vs. 31.1% vs. 32.0% ❖ PD-L1 expression: • Positive: 62.8% vs. 71.4% vs. 67.6% • Negative: 34.3% vs. 25.6% vs. 31.1% • Unknown: 2.9% vs. 2.9% vs. 1.2% ❖ Previous chemotherapy: • Yes: 22.6% vs. 21.4% vs. 21.2% • No: 77.4% vs. 78.6% vs. 78.8% ❖ Previous surgery: • Yes: 86.6% vs. 86.1% vs. 83.8% • No: 13.4% vs. 13.9% vs. 16.2% ❖ Previous radiotherapy • Yes: 35.6% vs. 30.7% vs. 29.5%

Efficacy (I vs. I2 vs. C)	**Safety** (I vs. I2 vs. C)
<u>Data cutoff date (12 April 2023); median duration of follow-up: 15.4 vs. 15.4 vs. 12.6 months;</u> **<u>ITT subgroup (n=239 vs. n=238 vs. n=241)</u>** Progression events or death: 52.7% vs. 58.4% vs. 71.8% Median PFS: 15.1 (95% CI, 12.6-20.7) vs. 10.2 (95% CI, 9.7-14.7) vs. 9.6 (95% CI, 9.0-9.9) months HR (95% CI) vs. control arm: 0.55 (0.43-0.69), p< .0001; 0.71 (0.57-0.89), p=.003 HR (95% CI) vs. durvalumab arm: 0.78 (0.61-0.99) 6-month PFS rate: 83.9% (95%CI, 78.6-88.0) vs. 83.8% (95% CI, 78.4-88.0) vs. 82.5% (95% CI, 76.9-86.8) 12-month PFS rate: 61.5% (95% Ci, 54.9-67.4) vs. 48.5% (95% CI, 41.8-54.9) vs. 41.1% (95% CI, 34.6-47.5) 18-month PFS rate: 46.3 % (95% CI, 39.2-53.0) vs. 37.8% (95% CI, 31.0-44.5) vs. 21.7% (95% CI, 16.0-27.9) **<u>dMMR subgroup (n=48 vs. n=46 vs. n=49)</u>** Progression events or death: 37.5% vs. 32.6% vs. 51.0%	**<u>Overall (chemotherapy phase + maintenance phase); n=238 vs. n=235 vs. n=236</u>** **Any-grade AE**: 99.6% vs. 98.7% vs. 100% **Any grade ≥3 AEs**: 67.2% vs. 54.9% vs. 56.4% **MDS/AML**: 0 vs. 0 vs. 0 **New primary malignancies**: 0.8% vs. 0.4% vs. 1.3% **Pneumonitis**: 5.0% vs. 1.7% vs. 0.4% **Immune-mediated AEs**: 23.5% vs. 28.1% vs. 6.8% **AEs leading to discontinuation of any study treatment**: 24.4% vs. 20.9% vs. 18.6%

Median PFS: 31.8 (95% CI, 12.4-NR) vs. NR (95%CI, NR-NR) vs. 7.0 (95% CI, 6.7-14.8) months
HR (95% CI) vs. control arm: 0.41 (0.21-0.75) vs. 0.42 (0.22-0.80)
HR (95% CI) vs. durvalumab arm: 0.97 (0.49-1.98)
6-month PFS rate: 87.2 % (95% CI, 73.8-94.1) vs. 90.6% (95% CI, 76.9-96.4) vs. 73.1% (95% CI, 56.6-84.2)
12-month PFS rate: 70.0% (95% CI, 54.7-81.0) vs. 67.9% (95% CI, 51.1-80.0) vs. 43.3% (95% CI, 27.3-58.3)
18-month PFS rate: 62.7% (95% CI, 46.9-75.0) vs. 67.9% (95%CI, 51.1-80.0) vs. 31.7% (95% Ci,16.7-47.9)

pMMR (n=191 vs. n=192 vs. n=192)

Progression events or death: 56.5% vs. 64.6% vs. 77.1%
Median PFS: 15.0 (95% CI, 12.4-18.0) vs. 9.9 (95% CI, 9.4-12.5) vs. 9.7 (9.2-10.1) months
HR (95% CI) vs. control arm: 0.57 (0.44-0.73) vs. 0.77 (0.60-0.97)
HR (95% CI) vs. durvalumab arm: 0.76 (0.59-0.99)
6-month PFS rate: 83.1% (95% CI, 77.0-87.7) vs. 82.4% (95% CI, 76.1-87.1) vs. 84.4% (95% CI, 78.4-88.9)
12-month PFS rate: 59.4 % (95% CI, 52.0-66.0) vs. 44.4% (95% CI, 37.1-51.4) vs. 40.8% (95% CI, 33.6-47.8)
18-month PFS rate: 42.0% (95% CI, 34.1-49.6) vs. 31.3% (95% CI, 24.2-38.6) vs. 20.0% (95% CI, 14.1-26.7)

PD-L1–positive (n=150 vs. n=170 vs. n=163)

Progression events or death: 45.3% vs. 57.1% vs. 69.9%
Median PFS: 20.8 (95% CI, 15.1-NR) vs. 11.3 (95% CI, 9.7-15.4) vs. 9.5 (95% CI, 7.9-9.9) months
HR (95% CI) vs. control arm: 0.42 (0.31-0.57) vs. 0.63 (0.48-0.83)
HR (95% CI) vs. durvalumab arm: 0.67 (0.49-0.91)
6-month PFS rate: 85.2 % (95% CI, 78.3-90.0) vs. 89.0% (95% CI, 83.1-92.9) vs. 81.7% (95% CI, 74.6-87.0)
12-month PFS rate: 67.3% (95% CI, 59.0-74.2) vs. 48.8% (95% CI, 40.8-56.3) vs. 38.6% (95% CI, 30.7-46.4)
18-month PFS rate: 54.8% (95% CI, 45.7-63.0) vs. 40.2% (95% CI, 32.1-48.2) vs. 21.5% (95% CI, 14.7-29.3)

PD-L1–negative (n=82 vs. n=61 vs. n= 75

Progression events or death: 67.1% vs. 62.3% vs. 76.0%
Median PFS: 10.1 (95% CI, 9.5-15.0) vs. 9.7 (95% CI, 7.0-14.7) vs. 9.9 (95%CI, 7.6-12.5)
HR (95% CI) vs. control arm: 0.80 (0.55-1.16) vs. 0.89 (0.59-1.34)
HR (95% CI) vs. durvalumab arm: 0.93 (0.61-1.41)
6-month PFS rate: 81.5% (71.2-88.4) vs. 71.0 (95% CI, 57.5-80.8) vs. 84.7% (95% CI, 74.0-91.2)
12-month PFS rate: 49.9% (95% CI, 38.5-60.3) vs. 44.9% (95% CI, 31.8-57.1) vs. 46.6% (95% CI, 34.7-57.6)
18-month PFS rate: 30.4% (95% CI, 19.8-41.6) vs. 31.1% (95% CI, 18.9-44.1) vs. 22.7% (95% CI, 13.2-33.7)

- Durvalumab/placebo: 9.2% vs. 11.1% vs. 8.1%
- Olaparib/placebo: 8.8% vs. 4.7% vs. 2.1%
- Chemotherapy: 13.0% vs. 13.2% vs. 13.6%

Maintenance phase; n=192 vs. n=183 vs. n=169

Any-grade AEs: 95.8% vs. 86.3% vs. 84.6%
Any grade ≥3 AE: 41.1% vs. 16.4% vs. 16.6%
MDS/AML: 0 vs. 0 vs. 0
New primary malignancies: 0.5% vs. 1.1% vs. 1.2%
Pneumonitis: 4.2% vs. 1.6% vs. 0
Immune-mediated AEs: 14.1% vs. 14.8% vs. 3.6%
AEs leading to discontinuation of any study treatment: 14.1% vs. 6.0% vs. 4.1%

- Durvalumab/placebo: 8.3% vs. 4.9% vs. 2.4%
- Olaparib/placebo: 10.9% vs. 5.5% vs. 3.0%
- Chemotherapy: 0.5% vs. 1.1% vs. 0.6%

Patient-reported outcomes

Analyses of patient-reported outcomes are ongoing.

ESMO-MCBS version 1.1 [13]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: +5.6 months	0.55 (0.43-0.69)	HR ≤0.65 AND gain ≥1.5 months	3	-	NA	-	3
Adapted	NC	2B	≤6 months	PFS: +5.6 months	0.55 (0.43-0.69)	HR ≤0.65 AND gain ≥1.5 months	3	+10.8% AEs grade ≥3	NA	-1[3]	2

[3] Toxicity adjustment.

								+16.7% immune-mediated AEs			

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[4] unclear risk	yes[5] high risk	unclear

Ongoing trials [15]

NCT number/trial name	Description	Estimated study completion date
NCT04269200 / DUO-E	Please see above.	08/2027

Available assessments

- In March 2023, NIHR published a Health Technology Briefing "Durvalumab with carboplatin and paclitaxel with or without olaparib for newly diagnosed advanced or recurrent endometrial cancer" [16].
- No assessments were identified via NICE (project in progress); CDA-AMC, G-BA and ICER.

Other aspects and conclusions

- In June 2024, the **CHMP adopted a new indication** for **Imfinzi®** in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with Imfinzi® as monotherapy in EC that is dMMR or Imfinzi® in combination with olaparib in EC that is pMMR. In June 2024, the **CHMP adopted a new indication for Lynparza®** in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. Also, in June 2024, the **FDA approved** durvalumab (Imfinzi®) with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent EC that is dMMR.
- **DUO-E (NCT04269200)** is an **ongoing**, randomised, double-blind, placebo-controlled multicentre **phase 3 trial** assessing durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced EC. Eligible patients were ≥18 years with newly diagnosed advanced (FIGO stage III/newly diagnosed stage IV) or recurrent EC of epithelial histology. Patients were required to have known MMR status.
- The **primary endpoints** of DUO-E were **PFS** in the durvalumab arm vs. control and the durvalumab + olaparib arm vs. control. In the ITT population, statistically significant PFS benefit was observed in the durvalumab (HR 0.71; 95% CI, 0.57-0.89; p=.003) and durvalumab + olaparib arms (HR 0.55; 95% CI, 0.43-0.69; p< .0001) vs. control.
- According to the authors of DUO-E trial, analyses of patient-reported outcomes are ongoing.
- The original and adapted ESMO-MCBS were applied, resulting in a final adjusted magnitude of clinical benefit of 3 and 2, respectively.
- Due to the ongoing status of the trial and, thus, the lack of final analysis data, the **risk of bias is considered unclear**. However, it is increased by the industry-funded background (the sponsor was responsible for overseeing the collection, analysis, and interpretation of data) of the trial.
- Besides DUO-E, no further phase 3 trial was identified for the indication assessed herein.
- Final analysis data from the DUO-E trial and patient-reported outcomes analysis are required to determine the role of durvalumab with carboplatin and paclitaxel with or without olaparib for the treatment of patients with newly diagnosed advanced or recurrent EC.

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Abbreviations: ADP=adenosine diphosphate, AE=adverse event, AJ=adjustment, ALK= anaplastic lymphoma kinase, AML=acute myeloid leukaemia, BRCA=breast cancer gene, BTC=biliary tract cancer, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTCAE=Common Terminology Criteria for Adverse Events, dMMR= mismatch repair deficient, EC=endometrial cancer, ECOG PS=Eastern Cooperative Oncology Group performance status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ENGOT= European Network of Gynecological Oncological Trial, ES-SLCL=extensive-stage small cell lung cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO=International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HCC=hepatocellular carcinoma, HER2=human epidermal growth factor receptor, HR=hazard ratio, HRD= homologous recombination deficiency, HRRm=homologous recombination repair mutation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, mCRPC=metastatic castration-resistant prostate cancer, IV=intravenous, MDS=myelodysplastic

[4] The DUO-E trial is currently ongoing.

[5] The trial was designed and sponsored by AstraZeneca in collaboration with the authors and academic groups under the GOG Foundation and the ENGOT groups. The sponsor was responsible for overseeing the collection, analysis, and interpretation of data. Medical writing assistance was funded by the sponsor.

syndrome, MG=median gain, MMR=mismatch repair, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, NR=not reached, NSCLC=non-small cell lung cancer, OS=overall survival, PARP= poly-ADP ribose polymerase, PD-L1= programmed Cell Death Ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, pMMR= mismatch repair proficient, QoL=quality of life, RECIST= Response Evaluation Criteria, SAE=serious adverse event, ST=standard treatment, TAP=tumour area positivity, VTE= venous thromboembolism

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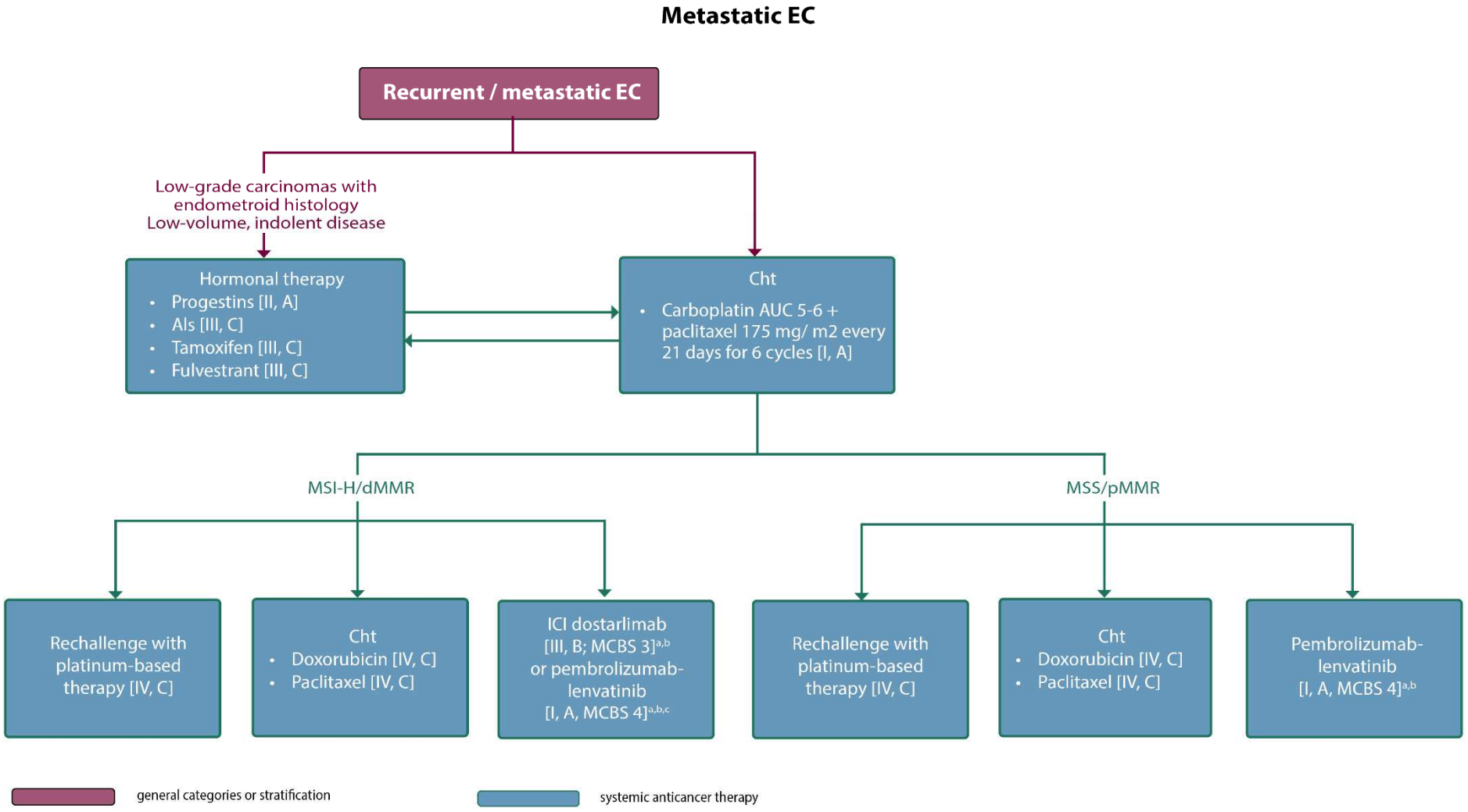
Appendix – Figure 1:



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.