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HEALTH TECHNOLOGY BRIEFING MAY 2020

Lenvatinib in combination with pembrolizumab for advanced endometrial cancer – second line

NIHRIO ID	5245	NICE ID	10110
Developer/Company	Eisai Co Ltd	UKPS ID	649794

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Lenvatinib in combination with pembrolizumab is in clinical development for the treatment of advanced endometrial cancer. Endometrial cancer is the most common form of womb cancer and originates from the lining of the womb (endometrium). The most common symptoms of this cancer are post-menopausal or irregular vaginal bleeding. For patients with advanced endometrial cancers who progress on platinum-based chemotherapy, there are few treatment options available.

Lenvatinib is a drug that targets several different growth factor receptors including vascular endothelial growth factor (VEGFR) and fibroblast growth factor receptors (FGFR). By blocking these receptors, lenvatinib can reduce tumour growth. Pembrolizumab is a drug that binds to the programmed cell death-1 (PD-1) receptor improve the activity of the immune system to kill cancer cells. If licenced, lenvatinib in combination with pembrolizumab will provide a second line treatment for adults with advanced endometrial cancer who have few therapies available.

PROPOSED INDICATION

Second line systemic treatment of advanced endometrial carcinoma.[1]

TECHNOLOGY

DESCRIPTION

Lenvatinib (Kisplyx; Lenvima) is a multiple receptor tyrosine kinase inhibitor (TKI) with a novel binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor receptors (VEGFR), in addition to other proangiogenic and oncogenic pathway-related RTKs including all fibroblast growth factor receptors (FGFR), the platelet-derived growth factor (PDGF) receptor PDGFRα, KIT and RET that are involved in tumour proliferation.[2,3]

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal antibody, which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[4]

Lenvatinib in combination with pembrolizumab is in clinical development for the treatment of advanced endometrial cancer. The dose proposed in the phase III trial (NCT03517449) for advanced endometrial cancer consists of 20mg of lenvatinib administered orally once daily during each 21-day cycle and 200mg of pembrolizumab administered by intravenous infusion on day 1 of each 21-day cycle for up to 35 cycles until disease progression.[1]

INNOVATION AND/OR ADVANTAGES

For patients with advanced endometrial cancer there is currently no NICE recommended second-line treatment, representing an unmet medical need.

Pembrolizumab and lenvatinib are both anti-tumour drugs with different mechanisms of action and are approved as monotherapies for several cancer indications in the UK.[2,5] The decision to combine the agents was based on preclinical data, which suggested co-inhibition of VEGF and PD-1 signalling—e.g., the combination of an immune checkpoint inhibitor (pembrolizumab) and simultaneous inhibition of angiogenesis and VEGF-mediated immune suppression (lenvatinib)—could be an efficacious anti-tumour strategy.[6]

In a phase II trial (NCT02501096), the combination of lenvatinib and pembrolizumab demonstrated a manageable safety profile and encouraging antitumor activity in patients with selected advanced solid tumours.[7] In the trial, there were 12 evaluable patients from the endometrial cancer cohort (n = 23), the 24-week Objective Response Rate of 52% (95% CI, 30.6%-73.2%). The median Progression Free Survival achieved in patients with endometrial cancer was 9.7 months (95% CI, 4.2 months-NE). The study investigators concluded from this study that the combination of lenvatinib and pembrolizumab is effective and tolerable for patients with selected advanced solid tumours.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lenvatinib is currently licenced as a monotherapy for treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) and for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.[2] It is also currently licenced in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.[3]

Pembrolizumab is currently licenced as a monotherapy for:[4]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- 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
- first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- 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
- 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.

Pembrolizumab is currently licenced in combination with:[4]

- axitinib, for the first-line treatment of advanced renal cell carcinoma in adults
- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
- as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, 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.

Very common adverse events (occurs in ⩾ 1 in 10 patients) of lenvatinib include: urinary tract infection, hypothyroidism, hypocalcaemia, thrombocytopenia, decreased weight and appetite, insomnia, headache, dysgeusia, dizziness, hypertension, haemorrhage, diarrhoea, vomiting, oral pain and inflammation, constipation, dyspepsia, dysphonia, dry mouth, rash, alopecia, pain, palmar erythema, palmar-plantar erythrodysaesthesia syndrome, myalgia, proteinuria, arthralgia, peripheral oedema, fatigue and asthenia.[2]

Very common adverse events (frequency ⩾ 1/10) of pembrolizumab as monotherapy include: anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.[4]

In August 2018, the FDA granted Breakthrough Therapy designation for lenvatinib in combination with pembrolizumab for the potential treatment of patients with advanced and/or metastatic non–microsatellite instability high (MSI-H)/proficient mismatch repair (pMMR) endometrial carcinoma that has progressed following at least one prior systemic therapy.[8]

Lenvatinib in combination with pembrolizumab is in phase III clinical development for malignant melanoma, hepatocellular carcinoma, renal cell carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer and urothelial carcinoma. This combination is also in phase II clinical development for advanced solid tumours like gastric, thyroid and breast cancer.[9]

PATIENT GROUP

DISEASE BACKGROUND

Endometrial cancer is the most common type of uterine cancer.[10] Endometrial means that the cancer starts in the lining of the womb, called the endometrium. The majority of cases (95%) are adenocarcinomas. Less common types of endometrial cancer include uterine serous carcinoma and clear cell carcinomas.[11] The International Federation of Gynecology and Obstetrics (FIGO) system is used to stage endometrial cancer from stage I (cancer confined to the uterus) to stage IV (cancer that has spread to another body organ).[10]

The most common symptom of endometrial cancer is post-menopausal or irregular vaginal bleeding. About 90% of womb cancers are picked up because of this bleeding, which is why womb cancer is so often diagnosed early. Other symptoms may include lower abdominal pain or discomfort, pain during intercourse, and haematuria.[12]

The cause of endometrial cancer in most women remains unknown. However, there are several risk factors that increase the chance of this cancer developing such as; increasing age, longer exposure to oestrogen (exogenous or endogenous), increased weight, treatment with tamoxifen, endometrial hyperplasia, factors relating to menstruation including starting early, late menopause and polycystic ovary syndrome, and Lynch syndrome, also known as hereditary non-polyposis colorectal cancer.[12] The single greatest risk factor is age, with 99% of cases being diagnosed in women aged over 40 years.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Endometrial cancer is the 4th most common cancer among women in the UK, accounting for 5% of all new cases of cancer in females.[13] In 2017, there were 7,605 new cases of endometrial cancer in England.[14] In England, most cases of endometrial cancer are diagnosed at an early stage with about 18-19% being diagnosed at stage III or IV. Between 7% and 8% of uterine cancer patients have metastases at diagnosis (stage IV).[13] The 5 year survival rate for advanced endometrial cancer (stage III and IV) is approximately 50% and 15% respectively.[15]

In 2018-19, there were 16,262 hospital admissions for malignant neoplasm of endometrium (ICD-10 C54.1), resulting in 30,741 bed days and 17,431 finished consultant episodes.[16] In 2018, there were 1,702 deaths from malignant neoplasm of endometrium in England and Wales.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Endometrial cancer is treated in the first instance by surgery to remove the uterus (hysterectomy). This surgery can be more extensive in later stages and by stage IV no longer has a curative aim, referred to as debulking surgery. Younger women who have not already reached the menopause may not want to have their womb and ovaries removed if they wish to have children, In this case, it may be possible, under very specific circumstances, to treat the cancer using hormone therapy to reduce tumour size and control symptoms. Additionally radiotherapy or chemotherapy may be used in the adjuvant setting to reduce the chance of the cancer returning.[18] Chemotherapy is also a systemic treatment for advanced womb cancer.[19]

CURRENT TREATMENT OPTIONS

There are currently no NICE recommended second-line medicinal therapies for advanced endometrial cancer.[20]

The current British Gynaecological Cancer Society guidelines for endometrial cancer recommend chemotherapy-naïve patients who relapse with systemic disease or those with late relapse after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel.[21] For metastatic and/or relapsed disease, European Society for Medical Oncology (ESMO) guidelines recommend endocrine therapy or cytotoxic chemotherapy. Hormonal therapy mainly involves the use of progestational agents, however tamoxifen and aromatase inhibitors are also used.[22]

PLACE OF TECHNOLOGY

If licenced, lenvatinib in combination with pembrolizumab would provide a second-line treatment for advanced endometrial carcinoma in patients that have progressed following 1 prior systemic, platinum-based chemotherapy (and up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting) and have very limited treatment options available.

CLINICAL TRIAL INFORMATION

Trial	**KEYNOTE-775, NCT03517449; A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer** **Phase III - ongoing** **Location:** EU countries (inc UK), United States, Canada and other countries.
Trial design	Open label, parallel assignment, randomised.
Population	N = 780, aged 18 years and older, advanced, recurrent or metastatic endometrial carcinoma, disease progression after 1 prior systemic, platinum-based chemotherapy regimen.
Intervention(s)	Pembrolizumab 200mg administered by intravenous infusion on day 1 of each 21-day cycle plus lenvatinib 20 mg administered orally once daily during each 21-day cycle, for up to 35 cycles.

Comparator(s)	Treatment of physician's choice (doxorubicin or paclitaxel)
Outcome(s)	Primary Outcome(s): • Progression Free Survival (PFS) [Time frame: up to approximately 24 months] • Overall Survival (OS) [Time frame: up to approximately 27 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**E7080-A001-111, NCT02501096, 2017-000300-26; A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumours** **Phase Ib/II** **Location: Norway, Spain, and United States.**
Trial design	Open label, single group assignment.
Population	N = 357, aged 18 years and older, non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, squamous cell carcinoma of the head and neck, or melanoma with 0-2 prior lines of systemic therapy.
Intervention(s)	Patients received 20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks.
Comparator(s)	None.
Outcome(s)	Primary Outcome(s): • Determine maximum tolerated dose (MTD) (Phase 1b) [Time frame: cycle 1 (21 Days)] • Objective response rate (ORR) at Week 24 [Time frame: week 24] • Dose Limiting Toxicity (DLT) (Phase 1b) [Time frame: cycle 1 (21 Days)] See trial record for full list of other outcomes.
Results (efficacy)	• At the cut-off date for anti-tumour activity data, median study follow-up was 13·3 months (IQR 6·7–20·1) and 21 (39·6% [95% CI 26·5–54·0]) patients had an objective response at week 24.[6]
Results (safety)	• Serious treatment-related adverse events occurred in 16 (30%) patients, and one treatment-related death was reported (intracranial haemorrhage). • The most frequently reported any-grade treatment-related adverse events were hypertension (31 [58%]), fatigue (29 [55%]), diarrhoea (27 [51%]), and hypothyroidism (25 [47%]). • The most common grade 3 treatment-related adverse events were hypertension (18 [34%]) and diarrhoea (four [8%]). • No grade 4 treatment-related adverse events were reported. Five (9%) patients discontinued study treatment because of treatment-related adverse events.[6]

ESTIMATED COST

Lenvatinib is already marketed in the UK. The NHS indicative price for 4 mg and 10 mg capsules (30 units) is £1,437.[23]

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[24]

- A 100 mg/4 ml concentrate for solution for infusion vial costs £2630.00

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for previously treated endometrial cancer (GID-TA10243). Publication date: TBC.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology: specialist gynaecological cancers. E10/S/f.

OTHER GUIDANCE

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- Royal College of Obstetricians and Gynaecologists. Management of Endometrial Hyperplasia. 2016.[25]
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ADDITIONAL INFORMATION

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