

HEALTH TECHNOLOGY BRIEFING MAY 2020

Selinexor for advanced or recurrent endometrial cancer - maintenance therapy

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| NIHRIO ID | 25498 | NICE ID | 10256 |
| Developer/Company | Karyopharm Therapeutics Inc | UKPS ID | Not available |

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| Licensing and market availability plans | Currently in phase III clinical trial |
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SUMMARY

Selinexor is in clinical development for the endometrial cancer maintenance therapy after combination chemotherapy. Endometrial cancer (uterine cancer) is a common cancer that affects the female reproductive system and starts when cells in the endometrium (the inner lining of the uterus) start to grow out of control. It is more common in women who have been through the menopause. Signs and symptoms of endometrial cancer may include vaginal bleeding after menopause, pelvic pain, loss of appetite, tiredness, and nausea. The exact cause of the disease is not clear, but some factors can increase the risk of developing it. One of the main risk factors for endometrial cancer is higher levels of oestrogen in the body.

Selinexor works by selectively inhibiting nuclear export (SINE) compounds. By blocking exportin 1 (XPO1), selinexor blocks the nuclear export of tumour suppressor, growth regulatory, and anti-inflammatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. If licensed, selinexor will offer a maintenance treatment option for endometrial cancer after combination chemotherapy.

PROPOSED INDICATION

Maintenance therapy for advanced or recurrent endometrial cancer (Stage IV) after combination chemotherapy.¹

TECHNOLOGY

DESCRIPTION

Selinexor (KPT-330) is a selective inhibitor of nuclear export (SINE) compound which works by binding with and inhibiting the nuclear export protein XPO1 (also called CRM1), leading to the accumulation of tumour suppressor proteins in the cell nucleus.² XPO1 is a nuclear export protein that mediates the transport of ≥ 200 cargo proteins through the nuclear pore complex to the cytoplasm. The anti-tumour activity of tumour suppressor proteins (TSPs) requires nuclear localisation, and XPO1 is the sole nuclear exporter of key TSPs such as p53, p21, BRCA1 and 2, I κ B and Rb.³

Selinexor is currently in phase III clinical development as maintenance therapy for advanced or recurrent endometrial cancer (Stage IV) after combination chemotherapy. In phase III clinical trial (SIENDO; NCT03555422), participants were randomised to receive oral selinexor 80 mg (once weekly), 60 mg if BMI < 20 kg/m².¹

INNOVATION AND/OR ADVANTAGES

In nearly all cancers studied to date, XPO1 expression is elevated, leading to functional inactivation of TSPs and increased translation of oncoproteins. Furthermore, the elevated levels are correlated with poor prognosis and reduced survival. Preclinical studies using selinexor showed nuclear retention of TSPs and oncogenic mRNAs in ovarian cancer cell lines.³

Selinexor is a first-in-class orally bioavailable selective inhibitor of nuclear export (SINE) compound that specifically blocks XPO1 by forming a slowly reversible covalent bond at cysteine-528 in the cargo-binding groove of XPO1. By inhibiting XPO1, selinexor forces the nuclear retention and functional activation of TSPs and prevents the translation of oncoprotein mRNAs. This leads to the selective induction of apoptosis in malignant cells, but largely sparing normal cells.⁴

In the phase II clinical trial, the Selinexor demonstrated single-agent activity and disease control in patients with heavily pre-treated ovarian and endometrial cancers. Side effects were a function of dose level and treatment frequency, similar to previous reports, reversible and mitigated with supportive care.³

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selinexor does not currently have Marketing Authorization in the EU/UK for any indication.

Selinexor is in phase III clinical development for dedifferentiated multiple myeloma.⁵ Selinexor is also in phase II clinical development for several indication such as diffuse large B-cell lymphoma, ovarian carcinoma, endometrial carcinoma, cervical carcinoma, breast cancer, glioblastoma, glioma, acute myeloid leukaemia, dedifferentiated liposarcoma, primary myelofibrosis, post-essential thrombocythemia myelofibrosis, post-polycythemia vera myelofibrosis, thymoma, advanced thymic epithelial tumour, non-small cell lung cancer, leukaemia, and myelodysplastic syndromes.⁶

DISEASE BACKGROUND

Endometrial cancer begins in the layer of cells that form the lining (endometrium) of the uterus. Endometrial cancer or carcinoma is sometimes called uterine cancer.⁷ Two main clinic pathological types of endometrial carcinoma have been recognised, corresponding to estrogen-dependent endometrioid (Type 1) and estrogen-independent nonendometrioid carcinomas (Type 2). Endometrioid adenocarcinomas represent 80% of endometrial carcinomas; at least in well-differentiated form, are composed of glands that resemble those of the normal endometrium and can be associated with, or preceded by, endometrial hyperplasia.⁸

Signs and symptoms of endometrial cancer may include vaginal bleeding after menopause, bleeding between periods and pelvic pain. The causes of endometrial cancer remain unclear. Factors that increase the risk of endometrial cancer include changes in the balance of female hormones in the body, more years of menstruation, never having been pregnant, older age, obesity, hormone therapy for breast cancer, and an inherited colon cancer syndrome.⁷

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, uterine cancer was the 4th most common cancer in the UK. There were approximately 9,500 new cases of uterine cancer in the UK in 2017.⁹ The age-standardised incidence rate in England for uterine cancer, in 2017, was 28.9 per 100,000 in females.¹⁰

Uterine cancer patients with a known stage are diagnosed at an early stage (81-83% are diagnosed at stage I or II), than a late stage (18-19% are diagnosed at stage III or IV). Between 7% and 8% of uterine cancer patients have metastases at diagnosis (stage IV).¹¹ According to 2010-2012 data in the UK, most uterine cancer cases occur in the endometrium, with much smaller proportions in the myometrium, fundus uteri and isthmus uteri.¹²

In England in 2018-2019, there were 17,431 finished consultant episodes (FCE) and 16,262 hospital admissions for malignant neoplasm of endometrium (ICD 10: C54.1), resulting in 30,741 FCE bed days and 8,107 day cases.¹³

According to 2013-2017 data, 75.6% women diagnosed with uterine cancer in England survive their disease for five years or more.¹⁴ Around 15 out of every 100 women (around 15%) will survive their cancer for 5 years or more after they are diagnosed with advanced uterine cancer.¹⁵

Uterine cancer is the 8th most common cause of cancer death in females in the UK in 2017. The age-standardised mortality rate in England was 3.8 per 100,000 in 2017.¹⁶ Uterine cancer mortality is strongly related to age, with the highest mortality rates being in older women.¹⁷ In the 2017 death registration in England and Wales, there were 2,101 deaths due to malignant neoplasm of other and unspecified parts of uterus (C54-C55) with the higher proportions in aged 65 and above.¹⁸

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For endometrial cancer, the main treatment is surgery, which usually involves a total hysterectomy with bilateral salpingo-oophorectomy. Radiotherapy, hormone therapy and chemotherapy are also used, depending on the type, stage and grade of cancer.

There is no agreement on the standard treatment of women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy and/or chemotherapy is employed. Systemic treatment of metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy.⁸

CURRENT TREATMENT OPTIONS

The most common type of chemotherapy drugs for endometrial cancer are paclitaxel, carboplatin, cisplatin, doxorubicin, and cyclophosphamide. Patient may have a single drug or a combination of two or three drugs.¹⁹

PLACE OF TECHNOLOGY

If licensed, selinexor will offer a maintenance therapy option for patients with endometrial cancer after combination chemotherapy that have very limited treatment options available.

CLINICAL TRIAL INFORMATION

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| Trial | SIENDO, NCT03555422 ; A Randomized, Double-Blind, Phase 3 Trial of Maintenance With Selinexor/ Placebo After Combination Chemotherapy for Patients With Advanced or Recurrent Endometrial Cancer Phase III - ongoing Location(s): EU (not including the UK), US, and Canada |
| Trial design | Randomised, double-blind, placebo-controlled |
| Population | n=192 (planned); aged 18 and older with a histological confirmed endometrial cancer of the endometrioid, serous, or undifferentiated type. Carcinosarcoma of the uterus is also allowed. Completed a single line of at least 12 weeks of taxane-platinum combination therapy for Stage IV disease or at first relapse and is in partial or complete remission according to RECIST v1.1. This includes patients who received taxane-platinum combination therapy for primary Stage IV disease and patients who received taxane-platinum combination therapy for recurrent disease. |
| Intervention(s) | Selinexor 80 mg (once weekly) orally, 60 mg if BMI <20 Kg/m ² |
| Comparator(s) | Placebo |
| Outcome(s) | Progression Free Survival (PFS) [Time frame: 30 months after FPI] |
| Results (efficacy) | - |
| Results (safety) | - |

ESTIMATED COST

The cost of selinexor is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for previously treated endometrial cancer (ID1205). Expected date of issue to be confirmed.
- NICE interventional procedures guidance. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer (IPG356). September 2010.
- NICE guideline (NG88). Heavy menstrual bleeding: assessment and management. March 2018, updated March 2020.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 2013-2014 NHS Standard Contract for Complex Gynaecology: Specialist Gynaecological cancers. E10/S/f
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Sociedad Española de Oncología Médica. SEOM clinical guidelines for endometrial cancer (2017). 2018.²⁰
- British Gynaecological Cancer Society. BGCS uterine cancer guidelines: Recommendations for practice. 2017.²¹
- European Society for Medical Oncology. Endometrial cancer: ESMO clinical practice guidelines. 2013.⁸

ADDITIONAL INFORMATION

Karyopharm Therapeutics Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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