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HEALTH TECHNOLOGY BRIEFING
MAY 2020

Selinexor for advanced unresectable dedifferentiated liposarcoma

NIHRIO ID	12227	**NICE ID**	10253
Developer/Company	Karyopharm Therapeutics Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II/III clinical trial

SUMMARY

Selinexor is in clinical development for the treatment of adults with advanced unresectable dedifferentiated liposarcoma (DDLS). Liposarcoma is a malignancy of fat cells and represents the most common form of soft tissue sarcoma. The prognosis varies depending on tumour site, size, grade, and histologic subtype. DDLS occurs when a low-grade tumour changes and newer cells with higher grade arise in the tumour. DDLS is frequently found in the retroperitoneum and the extremities (arms and legs) and is characterised as a painless mass, though it can cause symptoms of obstruction, decrease in appetite and abdominal distention.

Selinexor works by selectively inhibiting nuclear export (SINE) compounds. By blocking a protein called Exportin 1 (XPO1), responsible for the transport of the major tumour suppressor proteins from the nucleus to the cytoplasm, the 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 treatment option for patients with advanced unresectable DDLS.

PROPOSED INDICATION

Treatment of adults with advanced unresectable dedifferentiated liposarcoma (DDLS).[1, a]

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] Selinexor also significantly decreased cell proliferation as well as induced cell cycle arrest and apoptosis of liposarcoma cells. Importantly, selinexor inhibits insulin-like growth factor 1 (IGF1) activation of IGF-1R/AKT pathway through upregulation of insulin-like growth factor binding protein 5 (IGFBP5). Further, overexpression and knockdown experiments showed that IGFBP5 acts as a tumour suppressor and its expression was restored upon selinexor treatment of liposarcoma cells.[3]

Selinexor is currently in phase II/III clinical development for the treatment of adults with advanced unresectable DDLS. In phase II/III clinical trial (SEAL; NCT02606461), participants were randomised to receive oral selinexor 60 mg (twice weekly), 42 days cycle until progression disease or intolerability.[1,4]

INNOVATION AND/OR ADVANTAGES

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 tumour suppressor proteins (TSPs) and prevents the translation of oncoprotein messenger Ribonucleic acid (mRNAs). This leads to the selective induction of apoptosis in malignant cells, but largely sparing normal cells.[5]

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 and endometrial cancer.[6] Selinexor is also in phase II clinical development for several indications 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.[7]

[a] Information provided by Karyopharm Therapeutics Inc

PATIENT GROUP

DISEASE BACKGROUND

Liposarcoma is the most common type of soft tissue tumour. According to the World Health Organisation and others, liposarcoma is currently sub-classified into five subtypes including (1) well-differentiated; (2) dedifferentiated; (3) myxoid; (4) pleomorphic; and (5) round/mixed.[3]
DDLS is defined as the transition from a well-differentiated liposarcoma to non-lipogenic sarcoma of variable histological grade, usually measuring at least several millimetres in diameter. There is no sex predilection. It is much more common to arise de novo than as a recurrence. The most common site is the retroperitoneum followed by the extremities. It is extremely rare in subcutaneous tissue. The clinical presentation is usually of a large painless mass, which radiologically has a fatty and non-fatty component. Histologically, it is characterised by the presence of a sarcoma, usually high grade, in close association with a well-differentiated liposarcoma component. DDLS have a better prognosis than other types of pleomorphic sarcoma. Key features of dedifferentiated liposarcoma include the polymorphous population of round or spindle cells, including multinucleated forms; occasional lipoblasts; and myxoid matrix and arborizing vascular structures rarely seen.[8]

CLINICAL NEED AND BURDEN OF DISEASE

According to European Orphanet data, in 2020 the reported incidence for dedifferentiated liposarcoma was 0.27 per 100,000.[9] Applying the UK 2018 mid-year population estimate, this would be equate to approximately 160 cases in England and Wales.[10]

In England in 2018-2019 there were 1,201 finished consultant episodes (FCE), 1,119 hospital admissions with a primary diagnosis of malignant neoplasm: Connective and soft tissue, unspecified (ICD-10 code C49.9), resulting in 1,180 FCE bed days and 904 day cases.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Surgical resection remains the definitive management for operable DDLS disease. However, in the metastatic or unresectable setting, DDLS is considered relatively chemotherapy-resistant and there is no consensus to warrant the use of systemic treatment currently in the adjuvant or neoadjuvant setting.[12]

CURRENT TREATMENT OPTIONS

Benefit from chemotherapy for DDLS has been reported to be minimal and limited.[13]

The chemotherapy drugs used for soft tissue sarcoma include doxorubicin, ifosfamide, cisplatin, carboplatin, etoposide, vincristine, gemcitabine, gemcitabine, and trabectedin.[14]

PLACE OF TECHNOLOGY

If licensed, selinexor will offer an additional therapy option for patients with advanced unresectable DDLS.

CLINICAL TRIAL INFORMATION

Trial	**SEAL,** NCT02606461, EudraCT 2015-003594-14; A Phase 2-3, Multicenter, Randomized, Double-blind Study of Selinexor (KPT-330) Versus Placebo in Patients With Advanced Unresectable Dedifferentiated Liposarcoma (DDLS) **Phase II/III - ongoing** **Location(s):** EU (including the UK), US, Canada, and other countries
Trial design	Randomised, double-blind, placebo-controlled, multicentre, crossover assignment
Population	n=334; aged 12 and older with a histological evidence of DDLS at any time prior to randomization AND current evidence of DDLS requiring treatment; must have measurable disease per RECIST v1.1 response criteria; radiologic evidence of disease progression within 6 months prior to randomization; must have had at least two (2) prior lines of systemic therapy for liposarcoma (not to exceed 5 prior lines).
Intervention(s)	Selinexor 60 mg (twice weekly) oral, 42-day cycle until progression disease or intolerability.[4]
Comparator(s)	Placebo, twice weekly, 42-day cycle until progression disease or intolerability.[4]
Outcome(s)	Assess and compare Progression-free Survival (PFS) of patients with advanced unresectable DDLS treated with selinexor (60 milligrams [mg]) or placebo. [Time frame: from the date of randomization until the first date of disease progression, per RECIST v1.1 Response Criteria, or death due to any cause; up to approximately 30 months.]
Results (efficacy)	There was no difference in median PFS by WHO. By RECIST v1.1, median PFS on selinexor: 5.6 months; placebo: 1.8 months, hazard ratio of 0.64 (p 0.21, not powered in Phase 2). Some patients ended treatment early with small changes in tumour burden due to progression disease by WHO criteria.[4]
Results (safety)	Common adverse events Grade 1/2 (Selinexor: Placebo) were: nausea (85%: 31%), anorexia (62%: 14%), and fatigue (58%: 45%). Grade 3/4 adverse events were: hyponatremia (15%: 0%), anaemia (15%: 7%), and thrombocytopenia (12%: 0%). 12 pts on selinexor had dose reductions due to adverse events.[4]

ESTIMATED COST

The cost of selinexor is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Trabectedin for the treatment of advanced soft tissue sarcoma (TA185). February 2010.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 2013/14 NHS Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.

OTHER GUIDANCE

- Casali PG, et al., Soft Tissue and Visceral Sarcomas: ESMO-EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. 2018.[15]
- Adam D, et al., UK guidelines for the management of soft tissue sarcomas. 2016.[16]

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.

REFERENCES

1 Clinicaltrials.gov. *Selinexor in Advanced Liposarcoma (SEAL). Trial ID*. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT02606461 [Accessed 10 March 2020].

2 Karyopharm Therapeutics. *Karyopharm Announces Successful Outcome from Phase 2 Portion of Phase 2/3 SEAL Study Evaluating Selinexor in Patients with Previously Treated Advanced Dedifferentiated Liposarcoma*. Available from: https://investors.karyopharm.com/news-releases/news-release-details/karyopharm-announces-successful-outcome-phase-2-portion-phase-23 [Accessed 10 March 2020].

3 Garg, M., Kanojia D., Mayakonda A., Said J. W., Doan N. B., Chien W., et al. *Molecular mechanism and therapeutic implications of selinexor (KPT-330) in liposarcoma*. Oncotarget. 2017 Jan 31;8(5):7521-32. Available from: 10.18632/oncotarget.13485 https://www.ncbi.nlm.nih.gov/pubmed/27893412

4 Gounder, M. M., Somaiah N., Attia S., Chawla S. P., Villalobos V. M., Chmielowski B., et al. *Phase 2 results of selinexor in advanced de-differentiated (DDLS) liposarcoma (SEAL) study: A phase 2/3, randomized, double blind, placebo controlled cross-over study*. Journal of Clinical Oncology. 2018;36(15_suppl):11512-. Available from: 10.1200/JCO.2018.36.15_suppl.11512 https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.11512

5 Chen, C., Siegel D., Gutierrez M., Jacoby M., Hofmeister C. C., Gabrail N., et al. *Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia*. Blood. 2018 Feb 22;131(8):855-63. Available from: 10.1182/blood-2017-08-797886 https://www.ncbi.nlm.nih.gov/pubmed/29203585

6 ClinicalTrials.gov. *Selinexor - Phase III clinical trial*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Selinexor+&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=Karyopharm+Therapeutics&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 22 April 2020].

7 ClinicalTrials.gov. *Selinexor - Phase II clinical trial*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Selinexor+&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=Karyopharm+Therapeutics&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 22 April 2020].

8 Oscar L; Maureen F. *Cytology of Soft Tissue, Bone, and Skin.* Available from: https://reader.elsevier.com/reader/sd/pii/B9781416042082100181?token=3DA0AC6309D29023D0FCB69424D74B2B0C9A2C7832AF7A1B27D3D3CA46C56FA0E7836D4397703ECC4BAFB7039DECBF45 [Accessed 13 March 2020].
9 Orphanet. *Prevalence and incidence of rare diseases: Bibliographic data.* Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed 12 March 2020].
10 Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2018: 2019 LA boundaries.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed 22 April 2020].
11 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 12 March 2020].
12 McGovern, Y., Zhou C. D., Jones R. L. *Systemic Therapy in Metastatic or Unresectable Well-Differentiated/Dedifferentiated Liposarcoma*. Front Oncol. 2017;7:292. Available from: 10.3389/fonc.2017.00292 https://www.ncbi.nlm.nih.gov/pubmed/29250486
13 Livingston, J. A., Bugano D., Barbo A., Lin H., Madewell J. E., Wang W. L., et al. *Role of chemotherapy in dedifferentiated liposarcoma of the retroperitoneum: defining the benefit and challenges of the standard*. Sci Rep. 2017 Sep 19;7(1):11836. Available from: 10.1038/s41598-017-12132-w https://www.ncbi.nlm.nih.gov/pubmed/28928422
14 Cancer Research UK. *Soft tissue sarcoma - Chemotherapy drugs.* Available from: https://www.cancerresearchuk.org/about-cancer/soft-tissue-sarcoma/treatment/chemotherapy/drugs [Accessed 22 April 2020].
15 Casali, P. G., Abecassis N., Aro H. T., Bauer S., Biagini R., Bielack S., et al. *Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv51-iv67. Available from: 10.1093/annonc/mdy096 https://www.ncbi.nlm.nih.gov/pubmed/29846498
16 Dangoor, A., Seddon B., Gerrand C., Grimer R., Whelan J., Judson I. *UK guidelines for the management of soft tissue sarcomas*. Clin Sarcoma Res. 2016;6:20. Available from: 10.1186/s13569-016-0060-4 https://www.ncbi.nlm.nih.gov/pubmed/27891213

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