Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Onfekafusp alfa in addition to doxorubicin for advanced or metastatic soft tissue sarcoma – first line

NIHRIO ID	13279	**NICE ID**	9539
Developer/Company	Philogen S.p.A	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III trials

SUMMARY

Onfekafusp alfa in addition to doxorubicin is in clinical development for the treatment of advanced or metastatic soft tissue sarcoma. Soft tissue sarcomas are a group of rare cancers affecting the tissues that connect, support and surround other body structures and organs. Tissues that can be affected by soft tissue sarcomas include fat, muscle, blood vessels, deep skin tissues, tendons and ligaments. Soft tissue sarcomas can develop in almost any part of the body, including the legs, arms and torso. Doxorubicin is used as a standard-of-care drug in sarcoma and is commonly administered in combination with other chemotherapy drugs. These combinations do not significantly increase survival rates and are associated with substantial toxicities.

Onfekafusp alfa consists of an anti-body that selectively targets tumour blood vessels, and an anti-tumour agent which exerts toxic effects on tumour-associated blood vessels and causes an increase of the antitumour immune response. Doxorubicin is a chemotherapy drug which slows or stops cancer cell growth. This treatment may address the need for improved therapies for people who cannot have surgery and currently have limited options.

PROPOSED INDICATION

Advanced or metastatic soft tissue sarcoma – first line.[1]

TECHNOLOGY

DESCRIPTION

Onfekafusp alfa (Fibromun; L19-TNF) is a fully-human tumour-targeting human antibody-cytokine fusion protein consisting of the anti- extra domain-B (EDB) human antibody L19, fused to human tumour necrosis factor (TNF), a strong pro-inflammatory cytokine.[2] TNF is a naturally occurring vasodisruptive cytokine. It induces apoptosis of endothelial cell in newly formed blood vessels and haemorrhagic tumour necrosis in animal models and in extremity melanoma patients undergoing isolated limb perfusion. TNF rapidly increases permeability of tumour blood vessels and decreases the interstitial fluid pressure of tumour tissues, leading to an increased uptake of concomitantly applied anti-cancer drugs and synergistic anti-cancer activity. L19 antibody is able to localize to tumour lesions; it binds to the EDB of fibronectin, a well characterized marker of tumour angiogenesis, thereby selectively targeting human TNF to EDB-fibronectin on tumour blood vessels.[3]

Onfekafusp alfa in addition to doxorubicin is in clinical development for the treatment of advanced or metastatic soft tissue sarcoma. In the phase III trial (EudraCT Number: 2016-003239-38), subjects with advanced or metastatic soft tissue sarcoma will be administered 13 µg/ kg onfekafusp alfa as intravenous (iv) infusion and 60mg/m^2,[a] doxorubicin as iv infusion, or doxorubicin alone. Patients with partial response or stable disease after the maximum of 6 cycles of treatment will receive maintenance therapy with infusions of onfekafusp alfa every 3 weeks for up to 18 months, toxicity or until progression occurs.[4]

In the phase II clinical trial (FIBROSARC USA; NCT03420014), subjects with metastatic soft tissue sarcoma will be administered 13 µg/kg onfekafusp alfa as iv infusion on day 1, 3 and 5 of every 21-days cycle in combination with 60 mg/m^2 doxorubicin iv infusion on day 1 of every 21-days cycle.[1] Patients with partial response or stable disease after the maximum of 6 cycles of treatment will receive maintenance therapy with infusions of onfekafusp alfa every 3 weeks for up to 18 months, toxicity or until progression occurs.[a]

INNOVATION AND/OR ADVANTAGES

Doxorubicin is used as a standard-of-care drug in sarcoma and is commonly administered in combination with ifosfamide or dacarbazine, which enhances the response rates, but does not lead to a significant survival benefit compared to the monotherapy. Additionally, these combination treatments are associated with substantial toxicities. Thus, there is a clear need of improved agents for the therapy of soft-tissue sarcomas. Recombinant human TNF has been found to be efficacious for the treatment of patients with large sarcomas of the limb. The therapeutic activity of pro-inflammatory cytokines is often hindered by substantial toxicity at low doses, which prevents the escalation to therapeutically active doses. However, recent research has shown that suitable tumour-targeting antibodies can be used for the construction of 'immunocytokine' fusion proteins and can mediate the selective delivery of cytokines to the site of disease. The antibody-based pharmacodelivery of TNF in sarcoma-bearing mice leads to complete and long-lasting tumour eradications when administered in combination with doxorubicin, the first-line drug for the treatment of sarcomas in humans.[5]

[a] Information provided by Philogen S.p.A

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Onfekafusp alfa in additon to doxorubicin does not currently have Marketing Authorisation in the EU/UK for any indication.

Onfekafusp alfa is in the phase I/ II clinical development for glioma of the brain.[6]

Onfekafusp alfa has an orphan drug designation in the EU granted in October 2016 for the treatment of soft tissue sarcoma.[7]

PATIENT GROUP

DISEASE BACKGROUND

Soft tissue sarcomas are a group of rare cancers affecting the tissues that connect, support and surround other body structures and organs. Tissues that can be affected by soft tissue sarcomas include fat, muscle, blood vessels, deep skin tissues, tendons and ligaments. Soft tissue sarcomas can develop in almost any part of the body, including the legs, arms and trunk (torso). There are many different types of soft tissue sarcoma, depending on where in the body it develops. Examples include: leiomyosarcoma – develops in muscle tissue; liposarcoma – develops in fat tissue; angiosarcoma – develops in the cells of the blood or lymph glands; gastrointestinal stromal tumours – develop in the connective tissues that support the organs of the digestive system.[8]

Cancer occurs when cells multiply uncontrollably, forming growths called tumours. In the vast majority of soft tissue sarcomas it is unclear what causes this to happen, but there are a number of things known to increase the risk, such as:[8]

- Age: soft tissue sarcomas can occur at any age, including in children, but are more common in middle-aged or elderly people and the risk increases with age; around 4 in 10 (43%) soft tissue sarcoma cases are diagnosed in people over 65 years old.[9] However, as a proportion of paediatric malignancies, soft tissue sarcomas are are relatively common, comprising 7–10% of all childhood cancers. They are an important cause of death in the 14–29 years' age group.[10]
- Certain genetic conditions: neurofibromatosis type 1 and retinoblastoma, are associated with an increased risk of soft tissue sarcomas.
- Previous radiotherapy for another type of cancer.
- Exposure to certain chemicals, including vinyl chloride, dioxins and phenoxyacetic herbicides, has been associated with increased rates of soft tissue sarcomas
- Human herpesvirus type 8 (HHV-8): this causes Kaposi's sarcoma when the virus infects someone with a weakened immune system (such as people with HIV).

Soft tissue sarcomas often have no obvious symptoms in the early stages. They can cause symptoms as they get bigger or spread. The symptoms depend on where the cancer develops. For example: cancer in the tissue under the skin may cause a soft, painless lump that cannot easily be moved around and gets bigger over time; cancer near the stomach may cause tummy (abdominal) pain, a persistent feeling of fullness and constipation; cancer near the lungs may cause a cough or breathlessness.[8]

Soft tissue sarcoma patients can be affected by the effects of cancer treatment, including: breathlessness, tiredness, fertility problems, hair loss and eating problems.[11] A study from 2011 found that locally advanced "inoperable"/metastatic soft tissue sarcoma patients have a median number of symptoms ranging from 2 (range 0-5) before first-line chemotherapy (n = 50) to 3 (range

1-6) at the time of best supportive care decision (n = 48). Pain and dyspnoea were the commonest symptoms.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2016, there were 134 registrations of newly diagnosed cases of Kaposi sarcoma (ICD code C46) and 1,687 registrations of newly diagnosed cases of malignant neoplasm of other connective and soft tissue (ICD code C49).[13]The most common subtypes of soft tissue sarcoma in the UK in 2008-2010 were: leiomyosarcoma (18%), fibroblastic sarcoma (14%) and liposarcoma (13%). One-fifth (20%) of soft tissue sarcoma cases were not recorded as a specific subtype. The age-standardised relative survival rates for for adults (aged 15-85+) with soft tissue sarcoma in the UK, based on data from 1996-2009, are 75% (one-year survival), 53% (five year survival) and 45% (ten year survival).[9,14]

According to HES data for England, there were 8,525 finished consultant episodes (FCE), 7,948 hospital admissions, 4,909 day cases and 20,093 FCE bed days for ICD-10 codes C49 (malignant neoplasm of connective and soft tissue) and C46 (Kaposi sarcoma).[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the UK, any patient with a suspected soft tissue sarcoma should be referred to one of the specialist regional soft tissues sarcoma services, to be managed by a specialist sarcoma multidisciplinary team. Once the diagnosis has been confirmed using appropriate imaging, plus a biopsy, the main modality of management is usually surgical excision performed by a specialist surgeon. In tumours at higher risk of recurrence or metastasis pre- or post-operative radiotherapy should be considered. Systemic anti-cancer therapy may be utilized in some cases where the histological subtype is considered more sensitive to systemic treatment. Regular follow-up is recommended to assess local control, development of metastatic disease, and any late-effects of treatment. For local recurrence, and more rarely in selected cases of metastatic disease, surgical resection would be considered. Treatment for metastases may include radiotherapy, or systemic therapy guided by the sarcoma subtype. In some cases, symptom control and palliative care support alone will be appropriate.[10]

CURRENT TREATMENT OPTIONS

Olaratumab in combination with doxorubicin is recommended for use within the Cancer Drugs Fund as an option for advanced soft tissue sarcoma in adults, if:[16]

- they have not had any previous systemic chemotherapy for advanced soft tissue sarcoma
- they cannot have curative treatment with surgery or their disease does not respond to radiotherapy
- the conditions in the managed access agreement for olaratumab are followed

PLACE OF TECHNOLOGY

If licensed, onfekafusp alfa in addition to doxorubicin will offer an additional treatment option for patients with advanced/ metastatic soft tissue sarcoma.

CLINICAL TRIAL INFORMATION

Trial	EudraCT Number: 2016-003239-38; **onfekafusp alfa plus doxorubicin vs doxorubicin; phase III**
Sponsor	Philogen S.p.A.
Status	Ongoing
Source of Information	Trial registry[4,a]
Location	Germany
Design	Randomised, parallel assignment, open label
Participants	N= 60 (planned) in the European Economic Area and 102 (planned) in whole clinical trial; aged 18 years and over; histological evidence of high-grade metastatic soft tissue sarcoma (grade 2 – 3) according to the FNLCC grading system.
Schedule	Patients randomised to receive 13 µg/kg onfekafusp alfa as intravenous (iv) infusion and 60 mg/m^2 doxorubicin as iv infusion or doxorubicin alone. Patients with partial response or stable disease after the maximum of 6 cycles of treatment will receive maintenance therapy with infusions of onfekafusp alfa every 3 weeks for up to 18 months, toxicity or until progression occurs
Follow-up	18 months
Primary Outcomes	Median progression-free survival [Time Frame: End of Study)
Secondary Outcomes	To assess the efficacy, the following measurements will be considered: - Median overall survival (mOS) - Overall response rate (ORR, consisting of CR and PR). - Progression-free survival (PFS) rate at 3, 6, 9, 12 and 18 months - Overall survival (OS) rate at 12 and 18 months To assess the safety profile of onfekafusp alfa combined with doxorubicin. The following safety endpoints will be considered: - Adverse events (AEs) assessment based on CTCAE v.4.03 - Standard laboratory (haematology, biochemistry and urinalysis) parameters. - Physical examination findings including assessment of vital signs and physical measurements
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

Trial	**FIBROSARC USA, NCT03420014**; onfekafusp alfa plus doxorubicin vs doxorubicin; phase II
Sponsor	Philogen S.p.A.
Status	Ongoing
Source of Information	Trial registry[1,a]
Location	USA
Design	Randomised, parallel assignment, open label

Participants	N= 114 (planned); aged 16-75 years; histological evidence of advanced unresectable and/or metastatic high-gradesoft tissue sarcoma (grade 2 - 3 according to the FNLCC grading system) not amenable to curative treatment with surgery or radiotherapy
Schedule	Patients will be randomised in a 1:1 ratio to receive a fixed dose of 75 mg/m^2 doxorubicin, administered as a 15 ± 5 minutes i.v. infusion once every 3 weeks (day 1 of every 21-days cycle); or fixed dose of 13 µg/kg onfekafusp alfa administered on day 1, 3 and 5 of every 21-days cycle in combination with 60 mg/m^2 doxorubicin. Doxorubicin will be administered as a 15 ± 5 minutes i.v. infusion on day 1 of each 21-day cycle followed by at least 30 minutes pause before starting infusion of onfekafusp alfa
Follow-up	Follow-up 144 weeks
Primary Outcomes	Progression free survival (PFS) [Time Frame: from randomization up to week 72]
Secondary Outcomes	Time frame: at day 1, 2 ,3 and 5 of week 1 • Area under the drug concentration-time curve, extrapolated to infinity • Terminal half-life [t1/2] • Time to reach maximum drug concentration [Tmax] • Maximum drug concentration [Cmax] • Area under the drug concentration-time curve, extrapolated to infinity [AUC] • Terminal half-life [t1/2] • Time to reach maximum drug concentration [Tmax] • Maximum drug concentration [Cmax] Time frame: at day 1 of week 1 and week 2; at day 1 from week 4 up to week 18, every 3 weeks; at week 22-23 (EoT); at week 23-24 (first follow-up visit) • Human anti-fusion protein antibodies (HAFA) levels against onfekafusp alfa Time frame: from week 1 up to week 72 • Number of participants With clinically significant physical examination abnormalities (general appearance, skin, eyes, ears-nose-throat, breast, head and neck, lungs, heart, abdomen, lymph nodes, musculoskeletal) • Number of Participants With Clinically Significant Abnormalities in Vital Signs (Systolic and Diastolic Blood Pressure, Temperature, Heart Rate) • Percentage of participants with worst on-study hematological and chemistry abnormalities • Number of patients with adverse events (AEs) Time frame: from week 1 up to week 72, every 6 weeks • Percentage of participants with electrocardiogram (ECG) and echocardiogram (ECHO) abnormality findings Time frame: from week 1 up to week 144 •Overall survival (OS) rates

	Time frame: 1) from week 1 up to week 18, every 6 weeks; 2) from week 19 up to week 72, every 12 weeks (maintenance); 3) EoT: at week 22/23 (only Induction) and at week 72 (maintenance); 4) follow-up: from week 22/23 (EoT) up to week 72, every 12 weeks •Progression-free survival (PFS) rate •Duration of response (DOR) •Overall response rate (ORR) Time frame: from week 1 up to week 72, every 6 weeks; from week 73 up to week 144, every 12 weeks •Overall survival (OS)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study estimated completion date reported as September 2021

ESTIMATED COST

The cost of onfekafusp alfa is not yet known.

Doxorubicin is already marketed in the UK under different commercial brands. A 20mg/10ml concentrate for solution for infusion vials (2mg/mL) price starts from £360.23.[17]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Soft tissue or bone sarcoma (metastatic) – ridaforolimus (maintenance) (ID415). Expected date of issue to be confirmed.
- NICE technology appraisal in development. NBTXR-3 for treating soft tissue sarcoma (ID1050). Expected October 2019.
- NICE Technology appraisal. Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma (TA465). August 2017.
- NICE Technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (TA86). Last updated November 2010.
- NICE Technology appraisal. Trabectedin for the treatment of advanced soft tissue sarcoma (TA185). February 2010.
- NICE cancer service guideline. Improving outcomes for people with sarcoma (CSG9). March 2006.
- NICE guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). Last updated June 2018.
- NICE guideline. Suspected cancer: recognition and referral (NG12). Last updated July 2017.
- NICE clinical guideline. Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (CG75). November 2008.

- NICE quality standard. Suspected cancer (QS124). Last updated December 2017.NICE quality standard. Sarcoma (QS78). January 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- The European Cancer Organisation. ECCO essential requirements for quality cancer care: soft tissue sarcoma in adults and bone sarcoma. 2017.[18]
- British Sarcoma Group, NHS England Sarcoma Clinical Reference Group. UK guidelines for the management of soft tissue sarcomas. 2016.[10]
- The Spanish Society for Medical Oncology. SEOM Clinical Guideline of management of soft-tissue sarcoma 2016.[19]
- National Comprehensive Cancer Network. Soft Tissue Sarcoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. 2016.[20]
- Spanish Group for Research on Sarcoma. Clinical practice guidelines for the diagnosis and treatment of patients with soft tissue sarcoma by the Spanish group for research in sarcomas (GEIS). 2016.[21]
- The European Society for Medical Oncology. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014.[22]

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