NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Bifikafusp alfa-onfekafusp alfa neoadjuvant therapy for treating resectable stage IIIB and IIIC melanoma

Company/Developer	Sun Pharmaceutical Industries Europe BV

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 6380	NICE TSID: 9865	UKPS ID: 670945

Licensing and Market Availability Plans

Currently in phase III clinical trial

Summary

Bifikafusp alfa-onfekafusp alfa is currently in clinical development for the neoadjuvant treatment of resectable stage IIIB and IIIC melanoma. Melanoma is a type of skin cancer. The stage of a cancer tells how big it is and how far it has spread. Stage IIIB and IIIC melanomas are regional, meaning the cancer has spread beyond the primary tumour (local) to the closest lymph nodes, but not to distant sites. Despite the introduction of advanced treatments (immunotherapies and targeted therapies), there is still an unmet medical need for melanoma patients with surgically resectable disease, especially those that are at high risk for relapse or progression to stage IV (distant organ involvement), for which the outcome is particularly poor. Neoadjuvant therapy (delivered before surgery) has the potential to provide a more robust immune response (either instead of, or in addition to adjuvant therapy) and also represents a new treatment option for patients not amenable for adjuvant therapy (delivered after surgery).

Bifikafusp alfa-onfekafusp alfa is an immuno-oncology drug (a drug which uses the body's own immune system) which consists of two active proteins (L19IL2 and L19TNF), which act cooperatively to directly kill tumour cells while also inducing a systemic anti-tumour immune response. Bifikafusp alfa-onfekafusp alfa is administered directly into the tumour (intralesionally or intratumourally). If licensed, bifikafusp alfa-onfekafusp alfa would offer an additional neoadjuvant therapeutic option for patients with surgically resectable stage IIIB and IIIC melanoma.

Proposed Indication

For neoadjuvant treatment of adult patients with resectable stage IIIB and IIIC melanoma.[1]

Technology

Description

Bifikafusp alfa-onfekafusp alfa (Nidlegy) is a combination of darleukin (L19-IL2), an immunocytokine consisting of the recombinant form of interleukin-2 (IL-2). Bifikafusp alfa-onfekafusp alfa is fused to a human single-chain variable fragment (scFv) directed against the extra-domain B (ED-B) of fibronectin (L19), and fibromun (L19-TNFalpha), an immunocytokine consisting of human tumour necrosis factor alpha (TNFalpha) fused to a human scFv antibody fragment directed against the ED-B of L19, with potential antineoplastic and immunostimulating activities.[2] Upon administration, the L19 moieties of each immunocytokine bind to the extra-domain (ED)-B domain of fibronectin on tumour cells in the tumour neo vasculature. In turn, the IL-2 and TNF-alpha moieties of darleukin and fibromun, respectively, may locally induce an immune response against ED-B fibronectin-expressing tumour cells.[3]

Bifikafusp alfa-onfekafusp alfa is in clinical development for neoadjuvant treatment of patients with resectable stage IIIB and IIIC melanoma. In the phase III clinical trial (NCT02938299), bifikafusp alfa and onfekafusp alfa will be administered via intertumoural administrations into injectable cutaneous, subcutaneous, and nodal tumours, once weekly for up to 4 weeks, followed by surgery.[4]

Key Innovation

Despite recent advances in therapeutic options for patients with advanced melanoma, there is still an unmet medical need for melanoma patients with local recurrence, who are candidates for surgical resection. These patients are at a high risk of further recurrences until the disease becomes inoperable (unresectable), or progresses to stage IV (distant organ involvement), for which the prognosis is particularly poor.[5] In addition, evidence suggests that not all stage III melanoma patients are amenable for adjuvant treatment with currently licensed therapies.[6] In a phase II clinical study conducted in stage III/IVM1a melanoma patients, bifikafusp alfa-onfekafusp alfa led to complete responses not only on the injected tumour lesions but also on the majority of non-injected lesions (proving the onset of a systemic immune response induced after the intralesional injection of the product).[7,8] If licensed, bifikafusp alfa-onfekafusp alfa will offer an additional therapeutic option for patients with resectable stage IIIB and IIIC melanoma.

Regulatory & Development Status

Bifikafusp alfa-onfekafusp alfa does not currently have Marketing Authorisation in the UK for any indication.

Bifikafusp alfa-onfekafusp alfa is also in phase II clinical development for basal cell and cutaneous squamous cell carcinoma.[9]

Bifikafusp alfa-onfekafusp alfa has an orphan drug designation status in the USA in 2018 for melanoma stages IIb through IV.[10]

Patient Group

Disease Area and Clinical Need

Melanoma, also called malignant melanoma, is a cancer that usually starts in the skin and is responsible for 90% of skin cancer-related mortality.[11] It can start in a mole or in normal-looking skin. Melanoma develops from skin cells called melanocytes. These cells make melanin which gives the skin its colour. UV radiation from sunlight, sunbeds or sunlamps can build up and damage the DNA in melanocytes. They then start to grow and divide more quickly than usual and can develop into melanomas.[12] Stage III melanomas are tumours that have spread beyond the primary tumour to regional lymph nodes or have developed in-transit deposits of disease, but there is no evidence of distant metastasis. There are four subgroups of stage III melanoma, namely IIIA, IIIB, IIIC, IIID. A change in the shape, colour or size of a mole is usually the first sign of melanoma. A melanoma can start either: as a new mole or in a mole you already have.[13]

Melanoma is the 5th most common cancer in the UK. In 2025, 3,119 people are expected to die from melanoma and 19,513 people are expected to be diagnosed with melanoma in the UK.[14] In the UK (2016-18) there are an average of 16,744 new cases of melanoma diagnosed each year, with 2,341 deaths between 2017-19 attributable to melanoma.[15] In England (2021-22), there were 25,760 finished consultant episodes (FCE) for melanoma (ICD-10 code: C43), with 25,186 hospital admissions that resulted in 21,827 day cases and 10,379 FCE bed days.[16]

Recommended Treatment Options

Surgery is the main treatment for melanoma. Radiotherapy is sometimes used to reduce the size of large melanomas and help control and relieve symptoms.[17] There are currently no NICE recommended treatment options for neoadjuvant treatment for stage IIIB and IIIC resectable melanoma.

Clinical Trial Information

Trial	NCT02938299; 2015-002549-72; A Pivotal Phase III, Open-label, Randomized, Controlled Multi-center Study of the Efficacy of L19IL2/L19TNF Neoadjuvant Intratumoural Treatment Followed by Surgery Versus Surgery Alone in Clinical Stage III B/C Melanoma Patients **Phase III** – Recruiting **Location(s):** 4 EU countries **Primary completion date:** December 2023
Trial Design	Randomised, parallel assignment, open label
Population	N=214 (estimated); subjects with a diagnosis of malignant melanoma of the skin with locally advanced disease as defined by clinical stage III B and III C, eligible for complete surgical resection; aged 18 years and older.
Intervention(s)	Mixture of bifikafusp alfa and onfekafusp alfa (intratumoural) once weekly for up to 4 weeks + surgery (+ adjuvant therapy as per investigator choice).[18]
Comparator(s)	Surgery (+ adjuvant therapy as per investigator choice).[18]
Outcome(s)	Primary outcome measure: Recurrence Free Survival (RFS) [Time frame: from date of randomisation until the date of the first recurrence or date of death from any cause, whichever occurs first assessed up to 60 months].[a]

[a] Information provided by Sun Pharmaceutical Industries Europe BV

Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**NeoDREAM**; NCT03567889; 2021-003064-27; An Open-Label, Randomized, Controlled Multi-Center Study of The Efficacy of Bifikafusp alfa and onfekafusp alfa (L19IL2 + L19TNF) Neoadjuvant Intratumoural Treatment Followed by Surgery and Adjuvant Therapy Versus Surgery and Adjuvant Therapy in Clinical Stage IIIB/C Melanoma Patients **Phase III** – Recruiting **Location(s):** USA, Spain and Switzerland **Primary completion date:** June 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=186 (estimated); subjects who have diagnosis of clinical stage IIIB and IIIC (AJCC v7) melanoma, eligible for complete surgical resection of all metastases; aged 18 years and older
Intervention(s)	Bifikafusp alfa-onfekafusp alfa (intratumoural) once weekly for up to 4 weeks + surgery (+ adjuvant therapy as per investigator choice).[18]
Comparator(s)	Surgery (+ adjuvant therapy as per investigator choice).[18]
Outcome(s)	Primary outcome measure: Recurrence Free Survival (RFS) [Time frame: from date of randomisation until the date of the first recurrence or date of death from any cause, whichever occurs first assessed up to 60 months].
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT02076633; A Phase II Study of Intratumoral Application of L19IL2/L19TNF in Melanoma Patients in Clinical Stage III or Stage IV M1a With Presence of Injectable Cutaneous and/or Subcutaneous Lesions **Phase II** – Completed **Location**: Italy **Study completion date**: May 2015
Trial Design	Single group assignment, open Label
Population	N= 21 (actual); subjects with histologically confirmed malignant melanoma of the skin in clinical stage III or stage IV M1a; aged 18 years and older
Intervention(s)	L19IL2 + L19TNF (intratumoural) once weekly for up to 4 weeks

Comparator(s)	No comparator.
Outcome(s)	Primary outcome measure: Rate of patients with complete response (CR) of L19IL2 treated Index/non-index lesions at week 12 [Time frame: week 12].
Results (efficacy)	L19IL2 + L19TNF was reported to have efficient regional control of disease progression, increased time to distant metastasis and evidence of effect on circulating immune cell populations.[11]
Results (safety)	Overall, the treatment was well tolerated, with mostly grade 1 and 2 drug-related adverse events recorded.[11]

Estimated Cost

The cost of bifikafusp alfa-onfekafusp alfa is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Melanoma: assessment and management. NG14. July 2015
- NICE quality standard. Skin cancer. QS130. September 2016

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for NHS Standard Service Specification Template for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/s/b

Other Guidance

- European Society for Medical Oncology (ESMO). ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. 2020.[19]
- British Associated of Dermatologists (BAD). Stage 3 melanoma. 2019.[20]

Additional Information

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