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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Lifileucel for unresectable or metastatic melanoma – second-line or greater

NIHRIO ID	10808	**NICE ID**	10425
Developer/Company	Iovance Biotherapeutics, Inc.	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Lifileucel is being developed for the treatment of patients with unresectable or metastatic melanoma who have previously been treated with at least one systemic therapy. Melanoma is characterised by the uncontrolled growth of melanocytes, which are cells that protect against ultraviolet radiation through the production of the dark pigment melanin. Advanced or metastatic (stage IV) melanoma is cancer that has spread to distant areas or other organs such as the lungs, liver or brain. The general symptoms of advanced melanoma can include weight loss, loss of appetite and fatigue.

Lifileucel uses a novel mechanism of action to treat stage IV melanoma for which there are currently no autologous tumour-infiltrating lymphocytes (TIL)-based therapies recommended. It is composed of a patient's own naturally occurring immune cells TIL, which are prepared from a sample of cancerous tumour removed from the patient and multiplied in a laboratory until billions of TIL are obtained. The expanded TIL are then administered via intravenous infusion back to the patient with the intention that TIL will target and infiltrate cancer in the patient and attack the cancer in greater number. If licensed, lifileucel will offer an additional treatment option for patients with previously treated unresectable or metastatic melanoma and for patients who have progressed on multiple therapies, who are currently without additional effective options.

PROPOSED INDICATION

Treatment of patients with unresectable or metastatic melanoma who have previously been treated with at least one systemic therapy, including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor.[1,a]

TECHNOLOGY

DESCRIPTION

Lifileucel (Contego; LN-144) is an autologous adoptive cell therapy that utilizes tumour infiltrating lymphocytes (TIL) for the treatment of patients with metastatic melanoma.[1,2] The adoptive cell therapy procedure involves patients receiving a lymphocyte depleting preconditioning regimen prior to infusion of lifileucel.[1] Upon re-introduction of lifileucel into the patient after lymphodepletion, the TIL infiltrate the tumour, specifically recognize tumour-specific neoantigens, and initiate tumour cell killing.[2]

Lifileucel is being evaluated in a registrational phase II clinical trial for treatment of metastatic melanoma (NCT02360579).[1] The treatment regimen used involves patients receiving a standard nonmyeloablative lymphodepletion (NMA-LD), followed by infusion of the autologous TIL product, and the administration of IL-2 at 600,000 IU/kg approximately every eight hours for up to a maximum of six doses, starting 3-24 hours after cell infusion. TIL therapy is a one-time treatment.[a]

INNOVATION AND/OR ADVANTAGES

Lifileucel uses a novel mechanism of action to treat unresectable or metastatic melanoma (stage IV melanoma) for which there are currently no autologous TIL-based therapies recommended.[3]

Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors and targeted therapies such as v-raf murine sarcoma viral oncogene homolog B1 (BRAF)/mitogen-activated protein kinase kinase (MEK) inhibitors (if BRAF-V600E mutated). Adoptive cell therapy utilizing autologous TIL has shown antitumour efficacy with durable long-term responses in heavily pre-treated melanoma patients.[4] A naturally occurring feedback mechanism that prevents excess immune activation is through the expression of negative costimulatory molecules. These negative costimulatory molecules, also known as "immune checkpoints", such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), T cell immunoglobulin 3, and lymphocyte-activation gene 3, act as "brakes" on T cell activation and serve as negative feedback mechanism. TIL in many tumour types express high levels of negative costimulatory markers, suggesting a tumour-derived mechanism of suppressing antitumour immunity and providing rationale for T-cell checkpoint blockade.[5]

Through the lifileucel manufacturing procedure, the ex vivo expanded TIL reacquire the capacity for anti-tumour activity irrespective of the presence of immune checkpoint molecules on residual tumour. Lifileucel has a mechanism of action that provides advantages over other forms of T cell therapy (e.g., CAR-T), such as recognition of a diverse array of tumour antigens and the potential for persistence of therapeutic benefit for months to years after a single infusion. An additional advantage associated with the single treatment regimen is the limited

[a] Information provided by Iovance Biotherapeutics, Inc.

and well-defined administration timeframe and period for potential treatment-associated adverse events.[b]

Lifileucel may meet the criteria for classification as an advanced therapy medicinal product (ATMP) by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lifileucel does not currently have Marketing Authorisation in the EU/UK for any indication.

Lifileucel is currently in phase II and III clinical development for metastatic melanoma, cervical cancer, squamous cell carcinoma of the head and neck, and non-small cell lung cancer.[7]

Lifileucel was granted the following regulatory designations by the US FDA for the treatment of patients with metastatic melanoma:[8-10]

- A Regenerative Medicine Advanced Therapy (RMAT) designation in September 2018
- A Fast Track designation in August 2017
- An Orphan Drug designation in June 2015.

PATIENT GROUP

DISEASE BACKGROUND

Melanoma (also called malignant melanoma) is a type of skin cancer that develops from cells called melanocytes when they start to grow and divide more quickly than usual. About half of all melanomas start with a new, abnormal-looking mole in normal-looking skin.[11] The first sign of a melanoma is often a new mole or a change in the appearance of an existing mole, including asymmetry, border, colour, diameter and an evolving appearance.[12,13] Melanoma can appear anywhere on your body, but they most commonly appear on the back in men and on the legs in women. It can also develop underneath a nail, on the sole of the foot, in the mouth and eye or in the genital area, but these types of melanoma are rare.[12]

The main risk factor for developing melanoma is exposure to UV radiation. This can be through natural sunlight or the artificial light used in sunbeds or sunlamps.[11] In the UK, around 85 out of 100 melanomas (around 85%) are caused by too much ultraviolet radiation.[14] You have an increased risk of melanoma if you have lots of moles on your body, particularly if they're large (more than 5mm) or unusually shaped.[15] Increasing age is also one of the main risk factors for melanoma.[16] Other risk factors include family history and genetic factors, other medical conditions (such as inflammatory bowel disease, diabetes and weakened immune system), pale skin that does not tan easily, red or blonde hair, blue eyes, several freckles, previously damaged skin through sunburn or radiotherapy, a previous diagnosis of skin cancer, and body weight.[14,15]

Advanced or metastatic melanoma describes disease which has spread to distant areas of the skin or other organs such as the lungs, liver or brain.[17] The general symptoms of advanced melanoma can include weight loss, loss of appetite and fatigue. More than a quarter of melanomas are diagnosed in people aged over 75.[16]

The mitogen-activated protein kinase (MAPK) pathway is one of the mechanisms by which basic cellular processes such as growth, proliferation and apoptosis are controlled.[18,19] The

[b] Information provided by Iovance Biotherapeutics, Inc.

MAPK pathway is overactive in the majority of melanomas, most often as a result of mutations in the following: BRAF, neuroblastoma RAS viral oncogene homolog (NRAS) and neurofibromatosis type 1 (NF1).[18]

The most prevalent driver in melanoma is mutant BRAF, found in 40–50% of patients with metastatic disease.[18] Over 70–90% of BRAF mutations (BRAFm) involve a missense mutation at position 600, resulting in a substitution from valine to glutamic acid at amino acid 600 (termed V600E), creating a constitutively active protein that binds MEK. The V600K is the second most common BRAFm (10–30%), occurring more frequently in older patients and those with chronic sun-damaged skin. The disease-free interval between primary and metastatic disease is shorter in patients with V600K compared with V600E BRAF melanoma; however, the evidence on overall survival in established metastatic disease is conflicting.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the 5th most common cancer in the UK, accounting for accounting for 4% of all new cancer cases (2017). There are around 16,200 new melanoma skin cancer cases in the UK every year, that's 44 every day (2015-2017). Since the early 1990s, melanoma skin cancer incidence rates have more than doubled (135%) in the UK. Rates in females have increased by around two times (101%) and rates in males have almost tripled (182%) (2015-2017).[20]

In England in 2017, there were 13,740 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[21] Across the UK, the European age-standardised incidence rate for malignant melanoma is expected to increase by 7% between 2014 and 2035 from 30 cases per 100,000 to 32 cases per 100,000 people. It is projected that 22,175 cases of melanoma skin cancer (11,897 males, 10,278 females) will be diagnosed in the UK in 2035.[22]

In England and Wales in 2017 there were 2,106 deaths with malignant melanoma of skin (ICD10 code C43) recorded as the underlying cause.[23] The latest published survival statistics for melanoma of skin (2017, patients diagnosed between 2013 and 2017) report 1-year survival rate of 98.2% and 5-year survival rate of 91.3% (age-standardised). The reported overall 1-year age-standardised survival rate for stage IV melanoma of the skin is 53%, with 50.8% for men and 55.6% for women.[24] In England in 2018/2019, there were 21,595 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), 22,116 finished consultant episodes (FCE), resulting in 11,063 FCE bed days and 18,417 day cases.[25]

More melanoma skin cancer patients with a known stage are diagnosed at an early stage (91% are diagnosed at stage I or II), than a late stage (9% are diagnosed at stage III or IV). Late stage at diagnosis is associated with higher deprivation. Among adults aged 15-99 years in England, 10% of those in the most deprived areas are diagnosed at stage III or IV, versus 8% in the least deprived areas. Late stage melanoma is more common in adults aged 60-79 years (10% diagnosed at stage III or IV) versus those aged 15-59 years (8% diagnosed at stage III or IV). Late stage diagnosis is more common in males in England. Among adults aged 15-99 years, 10% of males are diagnosed at stage III or IV versus 7% of females.[26]

BRAFm are found in just under half of patients with metastatic melanoma. The incidence of BRAFm decreases with age. Almost all patients <30 years with cutaneous melanoma have BRAFm melanoma.[18]

The number of patients eligible to receive this technology could not be found from published literature.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Advanced or metastatic melanoma is currently treated using systemic anticancer treatments such as targeted therapies, immunotherapy or cytotoxic chemotherapy. Completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases should be considered in addition to therapeutic lymph node dissection for people with palpable stage IIIB-IIIC melanoma or nodal disease detected by imaging.[27]

Management of unresectable or metastatic BRAF V600 mutant melanoma is changing rapidly with the availability of new immunotherapy and other treatments, however, it is difficult to determine the position of immunotherapy and targeted therapies in the care pathway for mutation-positive melanoma. There is no consensus on whether first-line treatment should be targeted therapies or immunotherapies.[28]

CURRENT TREATMENT OPTIONS

The following immunotherapies are recommended by NICE for treating previously treated advanced melanoma:[29]

- Ipilimumab
- Pembrolizumab after ipilimumab - after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor

For unresectable or metastatic BRAF V600 mutation-positive melanoma, NICE guidelines recommend the following targeted therapy options in adults:[30]

- Encorafenib with binimetinib
- Trametinib with dabrafenib
- Dabrafenib
- Vemurafenib

Cytotoxic chemotherapy with dacarbazine may be considered for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable. Further cytotoxic chemotherapy for stage IV metastatic melanoma should not be routinely offered to people previously treated with dacarbazine except in the context of a clinical trial.[29]

PLACE OF TECHNOLOGY

If licensed, lifileucel will offer a treatment option for patients with previously treated unresectable or metastatic melanoma and for patients who have progressed on multiple therapies, who currently are without additional effective therapeutic options.

CLINICAL TRIAL INFORMATION

Trial	**C-144-01;** NCT02360579; EudraCT 2017-000760-15; A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients With Metastatic Melanoma **Phase II –** Active, not recruiting **Location(s):** EU (incl UK), USA and Switzerland **Primary completion date:** Jul 2020
Trial design	Non-randomized, parallel assignment, open label

Population	N=178 (actual), adults with unresectable or metastatic melanoma (Stage IIIc or Stage IV); aged 18 years and over
Intervention(s)	Lifileucel by IV, followed by 600,000 IU/kg of IL-2 approximately every 8 hours for up to a maximum of 6 doses, starting 3-24 hours after cell infusion
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Objective Response Rate (ORR) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) [Time frame: every 6 weeks for 6 months, then every 3 months for a maximum of 54 months] See trial record for full list of other outcomes
Results (efficacy)	Lifileucel resulted in a 36.4% ORR in heavily pre-treated metastatic melanoma patients with high baseline disease burden. At a median follow up of 18.7 months, median Duration of Response (DOR) had not been reached (Cohort 2 data).[31]
Results (safety)	Lifileucel demonstrated an acceptable safety and efficacy profile.[31]

ESTIMATED COST

The cost of lifileucel is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (TA562). February 2019.
- NICE technology appraisal guidance. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). November 2015. Updated September 2017.
- NICE technology appraisal guidance. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). October 2015. Updated September 2017.
- NICE technology appraisal guidance. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA414). October 2016.
- NICE technology appraisal guidance. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal guidance. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (TA396). June 2016.
- NICE technology appraisal guidance. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016.
- NICE technology appraisal guidance. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012. Updated January 2015.
- NICE technology appraisal guidance. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.

- NICE technology appraisal guidance. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.
- 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: Skin (Adult). A12/S/b.

OTHER GUIDANCE

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ADDITIONAL INFORMATION

Iovance Biotherapeutics, 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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