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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Talimogene laherparepvec in addition to pembrolizumab for metastatic melanoma

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Developer/Company	Amgen Ltd.	**UKPS ID**	647588

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Talimogene laherparepvec is licensed for the treatment of melanoma skin cancer, and is proposed for the treatment of melanoma skin cancer in combination with pembrolizumab. Melanoma is the commonest skin cancer in the UK and is characterised by changes to mole size or shape. Metastatic melanoma is when the cancer has spread outside the original tumour site and is not usually curative. Unresectable cancer means that the tumour cannot be removed by surgery. As survival is poor in those with unresectable or metastatic melanoma skin cancer, additional treatment options are needed.

Talimogene laherparepvec is a type of gene therapy called an oncolytic virus that is administered intralesionally. It is derived from herpes simplex virus 1 (the cold sore virus), and is modified so that it can infect melanoma cells and multiply inside the cells until it overwhelms and kills them. Pembrolizumab is an antibody (protein) that binds to programmed death-1 receptor (PD-1) to block the binding of programmed death-ligand (PD-L) 1 and PD-L2, increasing the response of a type of immune cell called T-cells, which are then able to kill the cancer cells. Pembrolizumab is administered intravenously. Both treatments have been shown to be effective monotherapies for the treatment of melanoma and it is anticipated that their complementary mechanisms of action could enhance their tumour-killing capacity. Therefore, if licenced, talimogene laherparepvec in combination with pembrolizumab could offer an additional treatment option for patients with unresectable or metastatic melanoma.

PROPOSED INDICATION

Talimogene laherparepvec, in combination with pembrolizumab, is proposed for the adjuvant treatment of patients following disease progression on prior anti-PD-1 therapy in unresectable/metastatic melanoma (stage IIIB-IVM1d) or prior anti-PD-1 therapy.[1]

TECHNOLOGY

DESCRIPTION

Talimogene laherparepvec (Imlygic, T-Vec) is an oncolytic immunotherapy that is derived from herpes simplex virus 1 (HSV-1). Talimogene laherparepvec has been modified to replicate within tumours and to produce the immune stimulatory protein human granulocyte-macrophage colony-stimulating factor (GM-CSF). Talimogene laherparepvec causes the death of tumour cells and the release of tumour-derived antigens. It is thought that together with GM-CSF, it will promote a systemic anti-tumour immune response and an effector T-cell response.[2]

The modifications to talimogene laherparepvec from HSV-1 include deletion of ICP34.5 and ICP47. Whereas anti-viral immune responses defend normal cells following infection by talimogene laherparepvec, tumours have been shown to be susceptible to injury and cell death from ICP34.5-deficient HSV-1 viruses, including talimogene laherparepvec. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, thereby enhancing viral replication in tumour cells.[2]

Pembrolizumab is a humanised monoclonal antibody which binds to PD-1. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[3]

Both talimogene laherparepvec and pembrolizumab have shown efficacy as monotherapies in advanced unresectable melanoma, and it is expected that their complementary mechanisms of action could enhance anti-tumour activity in combination compared to either treatment alone.[4]

Talimogene laherparepvec in addition to pembrolizumab is in clinical development for metastatic melanoma. The phase IIb/III clinical trial, MASTERKEY-115/KEYNOTE-034 (NCT04068181), is designed to evaluate the efficacy as assessed by progression-free survival and overall survival of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with unresectable, stage IIIB to IVM1c melanoma. Talimogene laherparepvec will be administered by intralesional injection at day one on weeks 0, 3, 5 and 7 and then every three weeks starting at week nine. The initial dose of talimogene laherparepvec is 4.0mL of 10^6 plaque forming units (PFU)/mL. Subsequent doses of talimogene laherparepvec are given at a dose of up to 4.0 mL of 10^8 PFU/mL. Pembrolizumab at a dose of 200mg is administered intravenously every three weeks.[1,5]

INNOVATION AND/OR ADVANTAGES

Talimogene laherparepvec is an advanced therapy medicinal product (ATMP) within the definition of a gene therapy medicinal product. [6,7] The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[8]

Oncolytic viruses are a novel class of intratumoural immunotherapies that show promise for treating solid tumours. Talimogene laherparepvec is a first-in-class, genetically modified, herpes simplex virus type 1–based oncolytic immunotherapy.[9]

The aim of intratumoural immunotherapy is to inhibit tumour growth by locally priming the human T-cell immune response against tumour-derived antigens for loco-regional control in the injected site and to initiate a durable systemic clinical response in non-injected distant metastases through lymphatic and blood circulation. The needle-based injection of intratumoural immunotherapy into multiple lesions can lead to the generation of a polyclonal immune response against antigens expressed across different cancer cell subclones, potentially providing a means to address intratumoural heterogeneity. This approach avoids the need for manual antigen identification and isolation and reduces the delays and costs associated with exogenous production of a personalised vaccine while harnessing the patient's immune system to create a personalised treatment and response. It may also reduce the potential for disease relapse and/or the development of treatment resistance associated with other tumour-targeted treatments, such as monoclonal antibodies.[9]

Pembrolizumab is a type of immunotherapy drug known as a 'checkpoint inhibitor', which acts systemically to enhance T-cell recruitment and prevent exhaustion of activated T cells by blocking the interaction of PD-1 and PD-L1/PD-L2. It is expected that the combination of talimogene laherparepvec and pembrolizumab will enhance anti-tumour activity, compared to either treatment alone.[4]

In the phase Ib portion of MASTERKEY-265/KEYNOTE-034 (NCT02263508), a combination of talimogene laherparepvec and pembrolizumab was associated with clinical benefit in unresectable advanced melanoma, as assessed by objective response rate (ORR) and complete response (CR) rate. The data suggested that talimogene laherparepvec may provide a combinatorial effect when administered alongside pembrolizumab. In this study, the number of patients with tumours with low baseline CD8+ density and a low interferon (IFN)-γ signature who had an ORR to combined therapy was high compared with prior trials of single-agent pembrolizumab.[10,11]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Talimogene laherparepvec is currently licenced as a monotherapy in the EU/UK for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.[2]

Common or very common side effects of talimogene laherparepvec monotherapy (reported in $\geqslant$ 25% of patients) include: abdominal discomfort; abdominal pain; anaemia; anxiety; arthralgia; cellulitis; chills; confused state; contusion; constipation; cough; deep vein thrombosis; dermatitis; dehydration; depression; diarrhoea; dizziness; dyspnoea; ear pain; fatigue; fever; flushing; headache; hypertension; immune-mediated events; infected neoplasm; influenza like illness; injection site reactions; insomnia; malaise; myalgia; nausea; oral herpes; oropharyngeal pain; pain; peripheral oedema; procedural pain; pyrexia; rash; tachycardia; tumour pain; upper respiratory tract infection; vitiligo; vomiting; weight decreased; wound complication; wound secretion.[2,12]

Selected adverse events include: cellulitis; immune-mediated events; influenza-like symptoms; plasmacytoma.[2]

Talimogene laherparepvec is currently in several phase II/III clinical trials, including the treatment of:[13]

- Unresected melanoma

- Classic or endemic Kaposi sarcoma
- Recurrent breast cancer that cannot be treated by surgery

Pembrolizumab is licenced in the UK for:[3]

- Melanoma
    - As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults
    - As monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- Non-small cell lung cancer
    - As monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a $\geqslant$ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
    - In combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
    - In combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
    - As monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a $\geqslant$ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab
- Urothelial carcinoma
    - As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
    - As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) $\geqslant$ 10
- Classical Hodgkin lymphoma (cHL): as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- Head and neck squamous cell carcinoma
    - As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS $\geqslant$ 1
    - As monotherapy for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a $\geqslant$ 50% TPS and progressing on or after platinum-containing chemotherapy
- Renal cell carcinoma: in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma in adults

Common or very common side effects of pembrolizumab monotherapy include: abdominal pain; alopecia; anaemia; appetite decreased; arthralgia; arthritis; asthenia; cardiac arrhythmia; chills; colitis; constipation; cough; dermatitis acneiform; diarrhoea; dizziness; dry eye; dry mouth; dry skin; dysgeusia; dyspnoea; eczema; erythema; fatigue; headache; hypertension; hyperthyroidism; hypocalcaemia; hypokalaemia; hyponatraemia; hypothyroidism; influenza-like illness; infusion-related reaction; insomnia; lethargy; lymphopaenia; musculoskeletal pain; myositis; nausea; oedema; pain; peripheral neuropathy; pneumonia; pneumonitis; pruritus; pyrexia; rash; thrombocytopaenia; severe skin reactions; vitiligo; vomiting.[3,14]

Selected adverse events include: immune-related adverse reactions; Complications of allogeneic HSCT in cHL; laboratory abnormalities; immunogenicity.[3]

Talimogene laherparepvec, in combination with Pembrolizumab, is currently in phase II/III clinical trials for the treatment of:[15]

- Stage III-IV melanoma
- Metastatic and/or locally advanced sarcoma
- As a neoadjuvant for stage III melanoma

PATIENT GROUP

DISEASE BACKGROUND

Melanoma is a type of skin cancer. It starts in cells in the skin called melanocytes. There are two main types of skin cancer: non melanoma skin cancer (which includes basal cell skin cancer, squamous cell skin cancer and other rare types) and melanoma skin cancer.[16] The first sign of a melanoma is normally a new mole or a change in the appearance of an existing mole. For example, increasing size, changing shape, changing colour, bleeding, itchiness or soreness.[17]

Risk factors associated with skin cancer include: repeated sunburn, use of artificial sources of light, high number of moles, pale skin that does not tan easily, red or blonde hair, blue eyes, several freckles, previously damaged skin through sunburn or radiotherapy, immunosuppressive diseases, a family history of melanoma and/or a previous diagnosis of skin cancer.[18,19]

When diagnosed, melanomas are staged:[20]

- Stage 0 – the melanoma is on the surface of the skin
- Stage 1A – the melanoma is less than 1mm thick
- Stage 1B – the melanoma is 1mm to 2mm thick, or less than 1mm thick and the surface of the skin is broken (ulcerated) or its cells are dividing faster than usual
- Stage 2A – the melanoma is 2mm to 4mm thick, or it's 1mm to 2mm thick and ulcerated
- Stage 2B – the melanoma is thicker than 4mm, or it's 2mm to 4mm thick and ulcerated
- Stage 2C – the melanoma is thicker than 4mm and ulcerated
- Stage 3A – the melanoma has spread into 1 to 3 nearby lymph nodes, but they're not enlarged; the melanoma is not ulcerated and has not spread further
- Stage 3B – the melanoma is ulcerated and has spread into 1 to 3 nearby lymph nodes but they're not enlarged, or the melanoma is not ulcerated and has spread into 1 to 3 nearby lymph nodes and they are enlarged, or the melanoma has spread to small areas of skin or lymphatic channels, but not to nearby lymph nodes
- Stage 3C – the melanoma is ulcerated and has spread into 1 to 3 nearby lymph nodes and they're enlarged, or it's spread into 4 or more nearby lymph nodes
- Stage 4 – the melanoma cells have spread to other parts of the body, such as the lungs, brain or other areas of the skin

Unresectable cancer means that the cancer cannot be removed with surgery.[21] Therefore, chemotherapy is the first treatment option for metastatic disease when tumour lesions are not fully resectable at presentation.[22]

Metastatic cancer is when cancer cells break away from where they first formed (primary cancer), travel through the blood or lymph system, and form new tumours (metastatic tumours) in other parts of the body. The metastatic tumour is the same type of cancer as the primary tumour.[23]

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the fifth most common cancer in the UK.[24] In England, in 2017 there were 13,740 registrations of newly diagnosed cases of melanoma of the skin (ICD-10, code C43).[23]

In England in 2018/2019 there were 22,116 finished consultant episodes, 21,595 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), resulting in 11,063 bed days and 18,417 day cases.[25] In England and Wales in 2017 there were 2,106 deaths with malignant melanoma of skin (ICD-10 code C43) recorded as the underlying cause.[26]

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 associated with male sex in England. Among adults aged 15-99 years, 10% of males are diagnosed at stage III or IV versus 7% of females.[27]

Survival statistics fall with more advanced stages of melanoma. Around 94.7% of people diagnosed with stage III melanoma will survive for one year; 70.6% of people will be alive 5 years later. For those diagnosed at stage IV, one year survival is 53.0%.[28]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment depends on the stage of the disease. Advanced cancer is not usually curative, and therefore treatment aims to alleviate symptoms, improve quality of life and sometimes prolong life.[29]

NICE recommends patients with stage III melanoma undergo lymphadenectomy or lymph node dissection. If palliative surgery is not feasible for people with in-transit metastasis, the following may be offered:[30]

- Systemic therapy (chemotherapy, immunotherapy)
- Isolated limb infusion
- Isolated limb perfusion
- Radiotherapy
- Electrochemotherapy in line with NICE's interventional procedure guidance
- CO_2 laser
- Topical agent e.g. imiquimod

NICE recommends patients with stage IV melanoma receive targeted treatments, immunotherapy or cytotoxic chemotherapy.[30]

CURRENT TREATMENT OPTIONS

Targeted cancer drugs and immunotherapies that may be used for the treatment of unresectable or metastatic melanoma skin cancer include:[31,32]

- Vemurafenib
- Dabrafenib
- Pembrolizumab

- Ipilimumab
- Nivolumab
- Talimogene laherparepvec
- Ipilimumab and nivolumab
- Encorafenib and binimetinib
- Dabrafenib and trametinib

Chemotherapy may also be offered to patients with advanced melanoma; dacarbazine is currently licenced for the treatment of advanced melanoma.[33,34]

PLACE OF TECHNOLOGY

If licensed, talimogene laherparepvec, in combination with pembrolizumab, would offer an adjuvant treatment for patients following disease progression on prior anti-PD-1 therapy in unresectable/metastatic melanoma (stage IIIB-IVM1d) or prior anti-PD-1 therapy.[1]

CLINICAL TRIAL INFORMATION

Trial	**MASTERKEY-265 /KEYNOTE-034** (NCT02263508), A Phase 1b/3, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265/KEYNOTE-034) **Phase III** – active, not recruiting **Location(s):** Europe (including the UK), US and other countries **Primary completion date:** July 2022
Trial design	Randomised, parallel assignment, double-blinded
Population	- N = 713 - Melanoma, stage IIIB to IVM1c for whom surgery is not recommended - Adults aged 18 to 95 years old
Intervention(s)	Talimogene laherparepvec Phase 1b: administered by intralesional injection at Day 1, Week -5; then every 2 weeks starting at Day 1, Week -2 Phase 3, Arm 1: administered by intralesional injection at Day 1 Week 0, 3, 5, 7 then every 3 weeks starting at Day 1 Week 9 Pembrolizumab Phase 1b: administered intravenously every 2 weeks starting at Day 1 Week 0 Phase 3: administered intravenously on Day 1 Week 0, then every 3 weeks starting at Day 1 Week 3
Comparator(s)	No comparator for phase 1b. Phase 3: Placebo Administered by intralesional injection at Day 1 Week 0, 3, 5, 7 then every 3 weeks starting at Day Week 9 Pembrolizumab - Administered intravenously on Day 1 Week 0, then every 3 weeks starting at Day 1 Week 3

Outcome(s)	Primary outcome(s); - Incidence of dose limiting toxicities (DLT) [Time Frame: Start of treatment until 6 weeks from the initial administration of pembrolizumab (MK-3475)] - Progression Free Survival (PFS) (response evaluation by blinded central review assessed modified RECIST 1.1) [Time Frame: up to 44 months] - Overall Survival [Time Frame: up to 62 months] See trial record for full list of other outcomes
Results (efficacy)	Of the 21 patients enrolled from Dec 2014 – Mar 2015, 48% had IIIB-IVM1a, 52% IVM1b/c, 76% HSV-1+, and 19% BRAFmut+. Median follow-up at data cut was 33 w. All patients received at least one dose of talimogene laherparepvec+pembro. Tx-related adverse events (AEs) occurred in all patients: 33% G3/4, and no G5. A combination of talimogene laherparepvec and pembrolizumab was associated with clinical benefit in advanced melanoma, as assessed by ORR and CR rate[11]
Results (safety)	Most common AEs were fatigue (62%), pyrexia (52%), and chills (48%). Per immune-related response criteria, in 21 patients, confirmed/not yet confirmed objective response rate (ORR) was 48%/57%; CR rate was 14%/24%. Median time to response was 17 wks. Circulating CD8+ T cells including those expressing defined immune modulatory receptors (e.g. Tim3, BTLA) became elevated during tx with Talimogene laherparepvec initially but decreased after pembrolizumab began on day 36[11]

Trial	**MASTERKEY-115** (NCT04068181), Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti PD-1 Based Therapy **Phase II –** recruiting **Location(s):** Europe (excluding the UK), US and other countries **Primary completion date:** May 2021
Trial design	Single group assignment, open label
Population	- N = 100 (planned) - Unresectable/metastatic stage IIIB-IVM1d melanoma who have progressed on prior anti PD-1 based therapy - Adults aged 18 to 99 years old
Intervention(s)	On day 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. The second dose of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec will be administered 21 days after the initial dose. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec will be given every 3 weeks

	Pembrolizumab will be administered intravenously at a fixed dose of 200 mg every 3 weeks
Comparator(s)	No comparator
Outcome(s)	Overall response (Complete Response [CR] plus partial response [PR] by investigator assessment using modified Response Evaluation Criteria in Solid Tumour [RECIST v1.1]) [Time Frame: Up to 4 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02965716, A Phase II Study of Combining Talimogene Laherparepvec (T-VEC) (NSC-785349) and MK-3475 (Pembrolizumab) (NSC-776864) in Patients With Advanced Melanoma Who Have Progressed on Anti-PD1/L1 Based Therapy **Phase II** - recruiting **Location(s):** USA **Primary completion date:** June 2023
Trial design	Single group assignment, open label
Population	- N= 47 (planned) - Advanced (unresectable stage III or stage IV) melanoma who have progressed on anti-PD1/L1 based therapy - Adults aged 18 years and older
Intervention(s)	Patients receive talimogene laherparepvec IL and pembrolizumab IV over 30 minutes on day 1. Treatment repeats every 21 days for up to 36 cycles in the absence of disease progression or unacceptable toxicity.
Comparator(s)	No comparator
Outcome(s)	Objective response rate (ORR) (Cohort A and B) [Time Frame: Up to 180 days] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price of talimogene laherparepvec is £1,670 per 1 ml vial of either 1,000,000 plaque forming units (PFU) per ml or 100,000,000 PFU per ml.[35,36]

Pembrolizumab costs £2630.00 per 25mg/mL vial of concentrate for solution infusion or £1315.00 for a 50mg vial of powder for concentrate for solution for infusion.[14]

RELEVANT GUIDANCE

NICE GUIDANCE

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- NICE Technology Appraisal Guidance. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. [TA366]. November 2015 (Last updated: September 2017)
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- 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. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. [TA268]. December 2012.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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