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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in combination with lenvatinib for advanced melanoma – first line

NIHRIO ID	27088	**NICE ID**	10280
Developer/Company	Merck Sharp & Dohme Ltd and Eisai Ltd	**UKPS ID**	655841, 655874

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pembrolizumab in combination with lenvatinib is in clinical development for the first-line treatment of patients with advanced melanoma (skin cancer), which is unresectable or metastatic (stage III and IV). Malignant melanoma occurs due to the uncontrolled division of skin cells (melanocytes). Cancer is metastatic when it has spread to other parts of the body and unresectable if it cannot be removed via surgery. Melanoma is characterised by the appearance of a new mole or a change in an existing mole, and general symptoms include weight loss, loss of appetite, and fatigue.

Pembrolizumab is an immunotherapy, meaning it stimulates the body's immune system by triggering T-cells (a type of white blood cells) to find and kill cancer cells. Lenvatinib is a targeted therapy drug that inhibits cancer growth by preventing the formation of new blood vessels. These drugs modulate different aspects of tumour biology, combining them, may result in improved efficacy and help overcome resistance to immunotherapy. Pembrolizumab in combination with lenvatinib (pembrolizumab administered intravenously and lenvatinib administered orally) would offer an additional first-line treatment option for previously untreated and unresectable advanced melanoma.

PROPOSED INDICATION

Pembrolizumab in combination with lenvatinib as first-line treatment of patients with advanced melanoma.[a]

[a] Information provided by Merck and Sharp Dohme Ltd on UK Pharmascan

TECHNOLOGY

DESCRIPTION

Pembrolizumab (MK-3475; KEYTRUDA®), is a type of immunotherapy that stimulates the body's immune system to fight cancer cells.[1] Specifically, it is an anti-programmed death-1 (PD-1) monoclonal antibody which triggers the T-cells to find and kill cancer cells.[1,2]
Lenvatinib (MK-7902/E7080; LENVIMA®) is a mutlireceptor tyrosine kinase inhibitor.[3] Specifically, it is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptor (FGF)1-4, platelet-derived growth factor receptor (PDGF) α, rearranged during transfection (RET), and tyrosine protein kinase KIT.[2]

Pembrolizumab in combination with lenvatinib is currently in phase III clinical development for treatment of adults (≥18 years old) with advanced melanoma (NCT03820986; LEAP-003). During the trials patients are provided with a 200mg of pembrolizumab intravenous infusion on day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years), plus 20mg of Lenvatinib orally (capsule) daily until progressive disease or unacceptable toxicity.[4]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab and lenvatinib are both approved monotherapies for several cancer indications in the UK. The combination of the drugs is based on a strong mechanistic rationale. Specifically, the combination of lenvatinib and an anti-PD1 (pembrolizumab) antibody produced greater reduction in tumour volume and a higher response rate than either agent alone, based on pre-clinical data.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lenvatinib is currently licenced as a monotherapy for the treatment of:[6]

- Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
- Adult patients with progressive locally advanced or metastatic, differentiated thyroid carcinoma (DTC), refractory to radioactive iodine.

It is also currently licensed in combination with everolimus for the treat of:[7]

- Adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Pembrolizumab is currently licenced as a monotherapy for:[8]

- advanced (unresectable or metastatic) melanoma in adults.
- adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection.
- locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 1% tumour proportion score (TPS) and who have received at least one prior chemotherapy regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic or anaplastic lymphoma kinase (ALK) positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
- first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.
- 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.
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

- 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) ≥ 10.
- first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥1.
- recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum containing chemotherapy.
- First-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Pembrolizumab is currently licenced in combination with:[8]

- axitinib, for the first-line treatment of advanced renal cell carcinoma (RCC) in adults
- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations
- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults
- in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, 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 ≥ 1.

Very common adverse events (frequency ≥ 1/10) of pembrolizumab as monotherapy include: anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, and pyrexia.[8]

Very common adverse events (occurs in ⩾ 1 in 10 patients) of lenvatinib include: urinary tract infection, hypothyroidism, hypocalcaemia, thrombocytopenia, decreased weight and appetite, insomnia, headache, dysgeusia, dizziness, hypertension, haemorrhage, diarrhoea, vomiting, oral pain and inflammation, constipation, dyspepsia, dysphonia, dry mouth, rash, alopecia, pain, palmar erythema, palmar-plantar erythrodysaesthesia syndrome, myalgia, proteinuria, arthralgia, peripheral oedema, fatigue and asthenia.[6]

Pembrolizumab in combination with lenvatinib is in phase III clinical development for hepatocellular, head and neck squamous cell, urothelial, non-small cell lung, advanced gastric, and renal cancers, and endometrial neoplasms. This combination is also in phase II clinical development for melanoma, advanced gastric, kidney, thyroid, and ovarian cancers.[9]

PATIENT GROUP

DISEASE BACKGROUND

Malignant melanoma occurs from the uncontrolled division of melanocytes; pigment producing cells.[10]

The American Joint Committee on Cancer (AJCC) provides staging criteria (stage I-IV) for melanoma based on the thickness (depth of penetration), and degree to which it has metastasised (spread). Higher stages (i.e. III and IV) have metastasised to other parts of the body and is commonly termed advanced malignant melanoma.[11]

Symptoms of advanced melanoma can develop years after the original melanoma was diagnosed and removed. For some people, a change to an existing mole or freckle, or a change in normal-looking

skin is the first sign. The symptoms also depend on which parts of the body the melanoma has spread to. Generally, patients with advanced melanoma may experience weight loss, loss of appetite, and fatigue.[12]

Most melanoma is caused by ultraviolet (UV) light damaging the DNA in skin cells. Exposure to artificial sources of light (such as sunlamps or tanning beds) as well as repeated sunburn, increases risk of melanoma in all ages. Other risk factors include large numbers of moles; having a close relative with skin cancer; having pale skin, blonde hair, blue eyes and freckles; previous radiotherapy treatment; diabetes; immunosuppressants or a previous diagnosis of skin cancer. The risk of developing skin cancer also increases with age.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the fifth most common cancer in the UK with over 16,000 new melanoma skin cancers in the UK between 2015-2017.[14] In England 13,740 new diagnoses were made in 2017, with 1,984 deaths (ICD-10 code: C43).[15,16] Incidence rates are predicted to rise by 7% in the UK up to 2035, leading to 32 cases per 100,000 people by 2035. These rates are due to vary by sex, with male incidence rates projected to be 35 cases per 100,000 by 2035, and females projected to be 30 cases per 100,000 by 2035; leading to a projected 22,175 cases of melanoma diagnoses in the UK in 2035.[15]

Data suggests that this may have already been surpassed in England, with 25,219 malignant melanoma diagnoses recorded in 2019-2020; males: 13,236 and females: 11,974 (ICD code: C43). Resulting in 11,492 bed days and 21,367 day cases.[17]

More melanoma skin cancer patients are diagnosed at an early stage (91% stage I or II), than later stages (9% are diagnosed at stage III or IV). Late stage 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 less deprived areas. Late stage melanoma is more common in adults aged 60-79 years (10% diagnosed at stage III or IV) compared to those aged 15-59 years (8% diagnosed at stage III or IV). Late stage diagnosis is associated with the male sex in England. Among adults (15-99 years) 10% of males are diagnosed with stage III or IV versus 7% in females.[15]

Survival statistics for melanoma of skin (2018, patients diagnosed between 2013-2017) report a 1-year survival rate of 98.2% (95% CI: 98.0-98.3%) and a 5-year survival rate of 91.3% (95% CI: 90.8-91.7%).[18] Survival statistics fall in advanced stages of melanoma. Stage III survival is 94.7% at 1-year and 70.6% at 5-years. Stage IV survival rate is 53.0% at 1-year.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Advanced or metastatic melanoma is currently treated using surgery or through the use of systemic anticancer treatments such as targeted therapies, immunotherapy or cytotoxic chemotherapy. Completion lymphadenectomy for people whose sentinel lymph node biopsy shows micrometastases should be considered in addition to therapeutic lymph node dissection for people with palpable stage IIIB-IIIC melanoma or nodal disease detected by imaging.[19]

CURRENT TREATMENT OPTIONS

For previously untreated Stage III unresectable or metastatic melanoma NICE recommendations advise the following:[20]

- Intralesional treatment:
  - Talimogene laherparepvec is recommended for adults as an option for treating unresectable stage IIIB and IIIC melanoma; that has not spread to bone, brain, lungs or other internal organs. Only if treatment with systemically administered immunotherapies is not suitable and the company provides treatment with the agreed discounts in the patient access scheme.
- Systemic immunotherapy
  - Nivolumab with ipilimumab is recommended for unresectable or metastatic melanoma in adults only when the company provides ipilimumab with agreed discount.
  - Nivolumab as a monotherapy is recommended for unresectable or metastatic melanoma in adults.
  - Pembrolizumab is recommended as an option for treating unresectable or metastatic melanoma that has not been previously treated with ipilimumab. Only when the company provides it in line with the commercial access agreement with NHS England.
  - Ipilimumab is recommended as an option for treating adults with unresectable or metastatic melanoma, only if the agreed discounts are applied.
- Targeted therapy for BRAF V600-positive melanoma
  - Encorafenib with binimetinib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according to the commercial agreements.
  - Trametinib with dabrafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according the agreed discounts in the patient access schemes.
  - Dabrafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according the agreed discounts in the patient access schemes.
  - Vemurafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according the agreed discounts in the patient access schemes.

For previously untreated stage IV unresectable or metastatic melanoma NICE recommendations advise the following:[21]

- Intralesional treatment:
  - Talimogene laherparepvec is recommended for adults as an option for treating unresectable stage IVM1a melanoma; that has not spread to bone, brain, lungs or other internal organs. Only if treatment with systemically administered immunotherapies is not suitable and the company provides treatment with the agreed discounts in the patient access scheme.
- Cytotoxic chemotherapy:
  - Dacarbazine can be offered to people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable.
- Immunotherapy
  - Nivolumab with ipilimumab is recommended for treating unresectable or metastatic melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.
  - Nivolumab as a monotherapy is recommended for adults with advanced (unresectable or metastatic) melanoma in adults.
  - Pembrolizumab is recommended as an option for treating unresectable or metastatic melanoma that has not been previously treated with ipilimumab, in adults. Only when the company provides it in line with the commercial access agreement with NHS England.
  - Ipilimumab is recommended as an option for treating adults with unresectable or metastatic melanoma, only if the agreed discounts are applied.
- Targeted therapy for BRAF V600-positive melanoma

- Encorafenib with binimetinib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according to the commercial agreements.
- Trametinib with dabrafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according to the agreed discounts in the patient access schemes.
- Dabrafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according to the agreed discounts in the patient access schemes.
- Vemurafenib is recommended when the melanoma is BRAF V600 mutation-positive, if the company provides it according to the agreed discounts in the patient access schemes.

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with lenvatinib would offer an alternative first-line treatment option for previously untreated and unresectable advanced melanoma.

CLINICAL TRIAL INFORMATION

Trial	**LEAP-003;** NCT03820986**; A phase 3 randomized, placebo-controlled trial to evaluate the safety and efficacy of pembrolizumab (MK-3475) and Lenvatinib (E78080/MK-7902) versus pembrolizumab alone as first-line intervention in participants with advanced melanoma.** **Phase III** – Recruiting **Location(s)** – Europe (incl UK), USA, Canada, and other countries. **Estimated primary completion date:** April 2024
Trial design	Randomised, parallel assignment, quadruple blinding.
Population	*N* = 660 (planned); unresectable stage III or IV melanoma, not amenable to local therapy, has been untreated for advanced or metastatic disease (apart from BRAF V600 mutation positive melanoma may have received standard target first-line therapy; prior adjuvant or neoadjuvant therapy such as CTLA-4 or anti-PD-1, as long as relapse did not occur during active treatment or within 6 months of treatment completion); Aged 18 years and older.
Intervention(s)	Participants receive 200mg of pembrolizumab intravenously on day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years) plus lenvatinib 20mg oral capsule.
Comparator(s)	Participants receive 200mg of pembrolizumab intravenously on day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years) plus placebo for Lenvatinib oral capsules daily
Outcome(s)	- Progression free survival [time frame: up to approximately 2 years] - Overall survival [time frame: up to approximately 2 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK. The NHS indicative price for a 100mg/4 ml concentrate of solution for infusion vial costs £2,630.[22]

Lenvatinib is already marketed in the UK. The NHS indicative price for 4mg and 10mg capsules (30 units) is £1,437.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

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- NICE technology appraisal guidance. Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410). September 2016.
- NICE technology appraisal guidance. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). November 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. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. July 2014.
- NICE technology appraisal guidance. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
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- 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.
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- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
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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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