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Newcastle University

Health Technology Briefing
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Dabrafenib with Trametinib with adjuvant therapy for treating advanced BRAF V600 mutation-positive melanoma in adolescents

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34835	NICE TSID: 11839	UKPS ID: 666018

Licensing and Market Availability Plans

Currently in phase I/II clinical trials.

Summary

Dabrafenib in combination with trametinib is currently in clinical development for the treatment of advanced BRAF V600 mutation-positive melanoma in adolescents. Melanoma is a type of skin cancer. Common signs include the appearance of a new mole or a change in an existing mole. This can happen anywhere on the body, but the most commonly affected areas are the back in men and the legs in women. It is caused by ultraviolet (UV) light damaging the DNA in skin cells. Despite being rare, melanoma is the most common cancer in children, and is more common in adolescents aged 15 – 19 years. Adjuvant therapy is a therapy that is given in addition to the primary or initial therapy to maximise its effectiveness. Current treatment options are limited and often include surgical interventions. Adjuvant therapy options are crucial because more than half of patients have a recurrence after surgery.

Dabrafenib inhibits a protein called BRAF which prevents tumour cells from growing. Trametinib blocks the activation of BRAF thereby slowing down the growth and spread of the cancer. Dabrafenib in combination with trametinib has been approved for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation. Dabrafenib and trametinib are administered orally. If licensed, dabrafenib with trametinib will offer a novel treatment option for BRAF V600 mutation-positive advanced melanoma in adolescent patients.

Proposed Indication

Treating advanced BRAF V600 mutation-positive melanoma in adolescents.[1,2]

Technology

Description

Dabrafenib (Tafinlar, DRB436) is an inhibitor of rapidly accelerated fibrosarcoma (RAF) kinases. Oncogenic mutations in BRAF (B-Raf serine-threonine kinase) lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations. Dabrafenib has demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) and inhibited cell growth of BRAF V600 mutant melanoma cell lines, in vitro and in animal models.[3]

Trametinib (Mekinist, TMT212) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib has been shown to inhibit growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.[4]

Dabrafenib in combination with trametinib is currently in clinical development for treatment of advanced BRAF V600 mutation-positive solid tumours in adolescents. In the phase I/II clinical trial (NCT02124772), dabrafenib was administered orally as a single dose on day 1 and twice daily from day 2 based on weight at the appropriate study dose level, and trametinib was administered orally at a dose of 0.0125 mg/kg/day, 0.025 mg/kg/day, 0.032 mg/kg/day, or 0.04 mg/kg/day once daily.[1,2]

Key Innovation

The purpose of adjuvant therapy is to improve recurrence-free and overall survival in patients with melanoma. Adjuvant therapy options are crucial because more than half of patients have a recurrence after surgery. Dabrafenib in combination with trametinib was the first adjuvant treatment of resected Stage III BRAF V600 mutation-positive melanoma.[5] Targeted therapy for advanced melanoma blocks the activity of certain molecules within cancer cells that control cell growth. Dabrafenib and trametinib shrink tumours and help patients with advanced melanoma live longer.[6]

If licensed, dabrafenib in combination with trametinib will provide a novel treatment option for advanced BRAF V600 mutation-positive melanoma in adolescents.

Regulatory & Development Status

Dabrafenib and trametinib are currently licensed in the UK for the following indications:[3,4]

- either as monotherapy or in combination for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
- in combination for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection
- in combination for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

Dabrafenib in combination with trametinib is in phase II and III clinical development for multiple rare cancers such as the following:[7]

- differentiated thyroid cancer
- glioma
- non-small cell lung cancer
- ameloblastoma
- astrocytoma
- metastatic colorectal cancer

Dabrafenib in combination with trametinib has the following regulatory designations:[8,9]

- an orphan drug in the USA in 2012 for the treatment of stage IIb through stage IV melanoma
- Breakthrough Therapy by the US FDA for the adjuvant treatment of adult patients with melanoma with BRAF V600E or V600K mutations in October 2017

Patient Group

Disease Area and Clinical Need

Melanoma is a type of skin cancer that can spread to other organs in the body. The most common sign of melanoma is the appearance of a new mole or a change in an existing mole. This can happen anywhere on the body, but the most commonly affected areas are the back in men and the legs in women. Most melanomas are caused by exposure to ultraviolet (UV) light from the sun. People mostly at risk of melanoma tend to have lots of moles or freckles, pale skin that burns easily, red or blonde hair, or have a family history of melanoma.[10] Stage III melanoma, also known as regional melanoma, has metastasized (spread) to nearby lymph nodes, lymph vessels, or skin.[11] The BRAF gene makes a protein that helps regulate cell growth, and a mutation in it can result in uncontrolled cell growth. BRAF mutation melanoma can lead to the cancer growing at a faster rate.[12] The most commonly observed BRAF mutation is V600E which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.[3]

Melanoma skin cancer is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases (2016-2018).[13] Even though melanoma is rare, it is the most common skin cancer in children, occurring most often in adolescents aged 15 to 19 years.[14] In the UK (2021), among young people aged 15-24, malignant melanoma was twice as frequent in females as it was in males. Melanoma accounted for 10% of all cancer registrations in this age group, and skin carcinomas for a further 5%.[15]

Recommended Treatment Options

Surgical treatment for stage III melanoma usually requires wide excision of the primary tumour, along with lymph node dissection. After surgery, (additional) adjuvant treatment with immune checkpoint inhibitors or with targeted therapy drugs (for cancers with BRAF gene changes) may help lower the risk of the melanoma coming back.[16]

NICE currently recommends the following treatment options for advanced BRAF V600 mutation-positive melanoma for adults and the committee agreed that the following treatment should not differ for young people/adolescents:[17,18]

- Vemurafenib
- Dabrafenib with trametinib
- Encorafenib with binimetinib

Clinical Trial Information	
Trial	NCT01677741, EudraCT:2012-001499-12, Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced BRAF V600-Mutation Positive Solid Tumours **Phase I/II:** Completed **Location(s):** 5 EU countries, UK, USA, Canada and other countries **Study completion date:** December 2020
Trial Design	Non-randomised, parallel assignment, open label
Population	N=85; aged 12 months to 17 years; Subjects with recurrent disease, refractory disease, or progressive disease after having received at least one standard therapy for their disease; BRAF V600 mutation-positive tumour
Intervention(s)	Dabrafenib (oral) administered as a single dose on day 1 and twice daily from day 2, based on weight at the appropriate study dose level
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of treatment emergent adverse events in Part 1 (dose escalation) [time frame: from study treatment start date till 28 days safety follow-up, assessed up to approximately 90 months] • Maximum concentration of dabrafenib [time frame: week 1 day 1, week 3 day 15] • Area under the concentration-time curve over the dosing interval and AUC from zero to infinity of dabrafenib (time frame: week 1 day 1) See trial record for full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Clinical Trial Information	
Trial	NCT02124772, Eudra CT:2013-003596-35, An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor Trametinib in Children and Adolescents Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Children and Adolescents With Cancers Harbouring V600 Mutations **Phase I/II:** Completed **Location(s):** France, UK, USA, Canada and Australia **Study completion date:** December 2020
Trial Design	Non-randomised, parallel assignment, open label
Population	N=139; aged 1 month to 17 years; subjects with a disease that is relapsed/refractory to all potentially curative standard treatment regimens or must have a current disease for which there is no known curative therapy, or

	therapy proven to prolong survival with an acceptable quality of life; BRAF V600 mutant tumours
Intervention(s)	• Trametinib (oral) administered once daily at a dose of 0.0125 mg/kg/day, 0.025 mg/kg/day, 0.032 mg/kg/day or 0.04 mg/kg/day • Dabrafenib (oral) administered twice daily. The daily dose was divided into two equal doses
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of treatment emergent adverse events in subjects treated with trametinib monotherapy [time frame: from the day of the first dose of trametinib up to 30 days after the last dose, up to maximum duration of 64 months] • Average steady state plasma concentration of trametinib when administered alone (monotherapy) [time frame: pre dose, 1, 2, 4, 7, 10 and 24 hours post trametinib dose on cycle 1 day 15. The duration of 1 cycle was 28 days] See trial record for full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

Dabrafenib is already marketed in the UK; a pack of 28 x 50mg capsules costs £933.33 and a pack of 28 x 75mg capsules costs £1,400.[19]

Trametinib is already marketed in the UK; a pack of 7 x 0.5mg tablets costs £280, a pack of 30 x 0.5mg tablets costs £1,200, a pack of 7 x 2mg tablets costs £1,120 and a pack of 30 x 2mg tablets costs £4,800.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (TA544). October 2018.
- NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). January 2015.
- NICE guideline. Melanoma: assessment and management (NG14). July 2022.
- 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

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma, Version 2. 2019.[21]
- American Academy of Dermatology (ADD). ADD clinical practice guideline: Guidelines of care for the management of primary cutaneous melanoma. 2018.[22]
- European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016. 2016.[23]
- European Society for Medical Oncology (ESMO). Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2015.[24]

Additional Information

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