Health Technology Briefing
February 2022

Dabrafenib with trametinib for treating paediatric BRAF V600 mutated high-grade or low-grade glioma

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28728	NICE ID: 10688	UKPS ID: 662881

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Dabrafenib in combination with trametinib is currently in clinical development for the treatment of paediatric BRAF V600 mutant relapsed or refractory high-grade glioma (HGG), or BRAF V600 mutant low grade glioma (LGG) with progressive disease. Brain tumours in children arise from different types of cells in the brain. Gliomas are the most common type of central nervous system tumours. Symptoms of glioma are non-specific and include headache, nausea and vomiting. Current treatment options are very limited and include surgery, radiotherapy and chemotherapy for which the best drugs are still under investigation.

The proposed formulation for dabrafenib is a dispersible tablet for oral suspension and for trametinib a powder for oral solution. Dabrafenib inhibits a protein called BRAF which prevents tumour cells from growing. Trametinib inhibits the growth of cell lines with a mutation in BRAF protein. If licensed, dabrafenib with trametinib will offer an additional option for BRAF V600 mutant HGG and LGG in paediatric patients.

Proposed Indication

Dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive low-grade glioma (LGG) or relapsed or refractory high grade glioma (HGG).[1]

Technology

Description

Dabrafenib (Tafinlar, DRB436) is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers. 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 in animal models.[1,2]

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.[1,3]

Dabrafenib in combination with trametinib is currently in clinical development for BRAF V600 refractory or relapsed HGG tumours after having received one previous frontline therapy, or BRAF V600 LGG with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic therapy.[1] In the phase II clinical trial NCT02684058, dabrafenib will be administered orally twice daily (BID) plus trametinib orally once daily (QD) based on age and weight, in the HGG cohort. In the LGG cohort, patients will be randomised 2:1 to receive either dabrafenib (BID) plus trametinib (QD) or comparator treatment.[1,4] The combination will be liquid formulations of dabrafenib and trametinib.[a]

Key Innovation

Conventional therapies including neurosurgical intervention, radiotherapy, and chemotherapy often provide poor post-treatment quality of life, and survival of glioma patients is still devastating in several cases. In general, LGGs have more than 90% overall survival rate; on the contrary, HGGs have less than 10% long-term survival rate, despite the aggressive treatment regimens.[5]

Activation of the MAPK pathway via the BRAF V600 mutation has been observed in several tumours. This mutation is observed in a subset of paediatric brain tumours, including HGG and LGG for which limited therapeutic options are currently available. In a phase I/II clinical trial of paediatric patients with recurrent or refractory BRAF V600–mutant relapsed tumours, the BRAF inhibitor dabrafenib demonstrated its efficacy, including complete responses, in paediatric patients with HGG and LGG.[4] BRAF inhibitor plus MEK inhibitor combination therapy has proved to be effective in the treatment of BRAF mutated malignancies. Investigations of combination therapy in murine models of BRAF V600 mutated HGG have demonstrated sustained MAPK pathway inhibition, prolonged survival and decreased cutaneous toxicity

[a] Information provided by Novartis Pharmaceuticals UK Ltd

when compared to monotherapy.[6] There is a lack of consensus regarding the best treatment for people with high-grade glioma. In the UK, treatment usually consists of surgical resection where possible, followed by radiotherapy.[7] If licensed, dabrafenib in combination with trametinib will offer an additional treatment option for paediatric patients with HGG or LGG.

Regulatory & Development Status

Dabrafenib in combination with trametinib is currently licensed in the UK for the following indications:[2,3]

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

Dabrafenib in combination with trametinib and various other medicinal products is currently in phase II and III trials for the treatment of melanoma, thyroid gland carcinoma, colorectal cancer, non-small cell lung cancer, ameloblastoma, hematopoietic and lymphoid cell neoplasm, malignant neoplasms of digestive organs and pyrexia.[8]

Dabrafenib and trametinib were both separately granted EU orphan drug designation in 2020 for glioma.[9,10]

Patient Group

Disease Area and Clinical Need

Brain tumours in children arise from different types of cells in the brain.[5] There are more than 100 different types, most of which are very rare.[11] Gliomas are the most common type of central nervous system (CNS) tumours. Paediatric gliomas consist of World Health Organization (WHO) histological grade 1–2, LGGs (e.g., pilocytic astrocytomas, diffuse gliomas, and WHO histological grade 3–4, paediatric HGGs (e.g., anaplastic astrocytoma, GBM (glioblastoma), DIPG (diffuse intrinsic pontine glioma)).[5] Clinical manifestations of gliomas may be entirely nonspecific, and present only as sequelae resulting from the effects of increased intracranial pressure, such as headache, nausea and vomiting.[12]

Over 400 children a year are diagnosed with brain, CNS or intracranial tumours in Great Britain. They are the second most common group of cancers and the most common group of solid tumours that occur in this age group, accounting for more than a quarter (26%) of all childhood cancers in Great Britain.[11] There are about 150 cases of childhood LGG a year in the UK.[13] Less than 30 children a year develop HGG in the UK, which represents about 8% of all childhood brain and spinal cord tumours.[14] Survival outcomes for paediatric LGGs are generally excellent; lesions are typically slow growing and may even have protracted periods of growth arrest over a patient's lifespan. Nevertheless, prognosis is influenced by many factors including the degree of tumour resection achieved, histological and molecular tumour classification, presence of disseminated disease or concurrent diencephalic syndrome. Long term cure rates of over 90% have been reported for cases achieving complete or near total tumour removals.[15]

Recommended Treatment Options

Paediatric HGG are very difficult tumours to treat due to the problems in completely removing the tumour and their resistance to radiotherapy and chemotherapy. As there is no ideal treatment, patients are often

treated on clinical trials investigating new therapies. Common treatments include surgery, radiotherapy and chemotherapy although the best drugs and schedules are still being investigated.[14]

Treatment for LGG depends on location of the tumour and the age of the child, but common treatments include surgery, radiotherapy and chemotherapy given together with surgery and/or radiotherapy to treat the tumour.[13]

Clinical Trial Information

Trial	NCT02684058, 2015-004015-20; Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG). **Phase II:** Active, not recruiting **Location(s):** Twelve EU countries, UK, US, Canada and other countries **Primary completion date:** August 2021
Trial Design	Non-randomised, single group assignment, open label.
Population	N = 149; age 12 months to 17 years; BRAF V600 mutant HGG that has relapsed, progressed or failed to respond to frontline therapy or BRAF V600 mutant LGG with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression.
Intervention(s)	Dabrafenib orally twice daily in combination with trametinib orally once daily
Comparator(s)	Active comparator chemotherapy
Outcome(s)	• HGG cohort: Overall response rate [Time frame: within the first 32 weeks of treatment • LGG cohort: Overall response rate [Time Frame: within the first 32 weeks of treatment]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS list price (hospital only) of dabrafenib is £933.33 for 28 50mg capsules, and £1,400 for 28 75mg capsules.[16]

The NHS indicative price of trametinib is £280 or £1,200 for 7 or 30 0.5mg tablets respectively, and £1,120 or £4,800 for 7 or 30 2mg tablets respectively.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23). March 2016.

- NICE guideline. Suspected cancer: recognition and referral (NG12). December 2021.
- NICE guideline. Suspected neurological conditions: recognition and referral (NG127). May 2019.
- NICE quality standard. Suspected neurological conditions: recognition and referral (QS198). January 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- SIOPE Brain tumour group. SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. May 2019.[18]

Additional Information

References

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.