Dabrafenib (Tafinlar) with trametinib (Mekinist) for BRAF V600 mutation positive melanoma – adjuvant therapy

NIHR HSRIC ID: 8622

Lay summary

Dabrafenib and trametinib are two drugs that are taken together to treat melanoma that has been caused by a mutation called BRAF V600. Melanoma is a type of skin cancer that usually develops from abnormal moles. Dabrafenib and trametinib are given as two separate tablets that are taken together each day. They target the BRAF V600 mutation to stop the tumours growing. This may offer a new treatment option for patients who are at risk of their melanoma returning, despite having already had surgery to remove the disease.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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**TARGET GROUP**

- Malignant melanoma: stage III; BRAF V600 mutation positive – adjuvant therapy; after surgical resection.

**TECHNOLOGY**

**DESCRIPTION**

Dabrafenib (Tafinlar; dabrafenib mesylate; GSK-2118436) is a potent and selective reversible ATP competitive BRAF kinase inhibitor. Trametinib (Mekinist; GSK1120212; JTP-74057) is an allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). Mutations at the V600 codon in the serine-threonine kinase BRAF gene induces constitutive activation of the mitogen-activated protein kinase (MAPK) signalling pathway and have been identified in 40-50% of cutaneous melanomas. Suppression of MAPK signalling by inhibiting BRAF or the downstream partner, MEK, has the potential to be an effective therapeutic strategy in BRAF V600 mutant melanoma¹. Dabrafenib in combination with trametinib is intended for the treatment of melanoma that is BRAF V600-mutation positive. Dabrafenib is administered orally at 150mg twice daily in combination with trametinib, administered orally at 2mg daily following surgery to excise the melanoma².

Dabrafenib as monotherapy, or in combination with trametinib, is licensed in the EU for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib as monotherapy is also licensed in the EU for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Very common (>10%) reported adverse events associated with dabrafenib and trametinib combination therapy include urinary tract infection, nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, hypertension, haemorrhage, cough, abdominal pain, constipation, diarrhoea, nausea, vomiting, arthralgia, myalgia, fatigue, asthenia, pyrexia and peripheral oedema².

Dabrafenib and trametinib as combination therapy is in phase II clinical trials for BRAF V600E positive rare cancers, BRAF V600 positive colorectal cancer and advanced BRAF mutated non-small cell lung cancer.

Dabrafenib is also in phase II clinical trials for BRAF V600 positive rare cancers, BRAF V600 positive high grade glioma, brain metastases from BRAF V600 positive melanoma and BRAF V600 positive colorectal cancer. Trametinib is in phase II clinical trials for BRAF V600 positive rare cancers, biliary tract cancer, BRAF V600 positive colorectal cancer, BRAF V600 positive non-small cell lung cancer, relapsed or refractory leukaemias, and metastatic pancreatic cancer.

**INNOVATION and/or ADVANTAGES**

If licensed, dabrafenib and trametinib combination therapy will offer an additional oral adjuvant therapy after surgical resection of stage III BRAF V600 mutation positive melanoma.

¹ Company provided information.
DEVELOPER

Novartis Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

The combination use of dabrafenib and trametinib is a designated orphan drug in the USA for the treatment of stage IIb-IV melanoma.

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Melanoma is a type of skin cancer that arises from melanocytes – cells derived from the neural crest that make the pigment melanin. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate, including the uveal tract, upper digestive tract, anal canal, rectum and vagina.

A typical melanoma starts as a small dark patch on the skin, which can develop from previously normal-looking skin, or from existing nevi. Signs of melanoma arising from previously existing nevi may include asymmetry, change of shape, change in colour and/or diameter or an evolving appearance (including the area becoming raised or dome-shaped), itchiness, pain, bleeding or crustiness. The most common place for a melanoma to develop in a woman is on the legs, whereas for men it is on the chest or back. The main risk factor for developing melanoma is exposure to ultraviolet radiation from natural or artificial sources, e.g. the sun or sunbeds. People with very fair skin, sun-sensitive skin, large numbers of nevi, dysplastic nevi, reduced immunity or a family history of malignant melanoma have an increased risk of disease.

CLINICAL NEED and BURDEN OF DISEASE

Melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cases. Over the last decade, the incidence of melanoma has increased by almost half (46%) in the UK. This increase is strongly associated with an increased diagnosis of early melanomas, possibly due to secondary prevention efforts. In 2013, there were 12,246 new diagnoses of melanoma in England, equating to an age-standardised incidence rate of 25.1 per 100,000 population. Incidence increases with age, however melanoma rates are disproportionately higher in younger people; in 2013 approximately one third of new cases occurred in people under the age of 55. Patients diagnosed with melanoma with a known stage most commonly present at stage I or II (91%), with only 6% of patients diagnosed at stage III. Approximately 50% of melanomas harbour BRAF mutations and among these over 90% are at codon 600.

In 2014-15, there were 15,820 hospital admissions for malignant neoplasm of the skin, resulting in 12,500 bed days and 16,269 finished consultant episodes. In 2014, there were 2,237 deaths from malignant neoplasm of skin in England and Wales; 1,307 (58%) in males and 930 (42%) in females.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Melanoma (untreated, advanced, unresectable, metastatic) - nivolumab (with ipilimumab) [ID848]. Anticipated September 2016.
- NICE technology appraisal in development. Melanoma (BRAF V600, advanced, unresectable, metastatic) - cobimetinib (with vemurafenib) [ID815]. Anticipated October 2016.
- NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). January 2015.
- NICE technology appraisal. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.
- NICE interventional procedure guidance. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446). March 2013.
- NICE public health guidance. Skin cancer prevention: information, resources and environmental changes (PH32). January 2011.

NHS England Policies and Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

Standard treatment options for resectable stage III melanoma includes:

• Excision with or without lymph node management
  o The primary tumour may be treated with wide local excision with 1-3 cm margins, depending on tumour thickness and location.
  o Sentinel lymph node biopsy can be considered to assess the presence of metastases in regional lymph nodes.
  o Complete lymphadenectomy can be considered for people whose sentinel lymph node biopsy shows micro-metastases.

• Adjuvant therapy and immunotherapy
  o There is currently no clear guidance on adjuvant drug therapy in the treatment of melanoma.
  o Ipilimumab (not currently licensed for this indication), high-dose interferon alpha-2b, or pegylated interferon may improve relapse-free survival when used as adjuvant therapy in patients at high risk for relapse after surgical resection of tumours.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>COMBI-AD, NCT01682083, 115532; dabrafenib in combination with trametinib vs placebo; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>GlaxoSmithKline.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=852 (planned); aged 18 yrs and older; high-risk stage III V600E/K mutation positive cutaneous melanoma; surgically rendered free of disease; no known mucosal or ocular melanoma; no evidence of distant metastatic disease; no prior systematic anti-cancer treatment or radiotherapy for melanoma.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to dabrafenib 150mg oral twice daily in combination with trametinib 2mg oral once daily; or matched placebo, oral.</td>
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<td>Follow-up</td>
<td>Active treatment for 1 yr, follow-up 5 yrs.</td>
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<td>Primary outcome</td>
<td>Relapse-free survival.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Overall survival, distant metastasis-free survival; freedom from relapse; safety; health-related quality of life measured using EuroQoL five dimensions questionnaire.</td>
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<tr>
<td>Expected reporting date</td>
<td>Study completion date July 2018.</td>
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ESTIMATED COST and IMPACT

COST

Dabrafenib is already marketed in the UK for the treatment of unresectable or metastatic BRAF V600 mutation positive melanoma; the unit price for a pack of 28x75mg tablets is £1,400, and treatment with 150mg twice daily for 12 months would cost £73,00023.

IMPACT - SPECULATIVE

Impact on Patients and Carers
☐ Reduced mortality/increased length of survival  ☐ Reduced symptoms or disability
☐ Other  ☐ No impact identified

Impact on Health and Social Care Services
☐ Increased use of existing services: adjuvant treatment option  ☐ Decreased use of existing services
☐ Re-organisation of existing services  ☐ Need for new services
☐ Other  ☐ None identified

Impact on Costs and Other Resource Use
☐ Increased drug treatment costs  ☐ Reduced drug treatment costs
☐ Other increase in costs  ☐ Other reduction in costs
☐ Other  ☐ None identified

Other Issues
☐ Clinical uncertainty or other research question identified  ☐ None identified

REFERENCES