National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing April 2017

Vemurafenib (Zelboraf) for BRAF V600 mutation positive melanoma; completely resected but at high risk of recurrence

NIHRIO (HSRIC) ID: 8738 NICE ID: 8798

LAY SUMMARY

Vemurafenib is a drug targeting a specific gene mutation (called BRAF V600) seen in some melanomas. Melanoma is a type of skin cancer. Vemurafenib is a type of cancer treatment called a cancer growth blocker. The gene mutation (BRAF V600) seen in some melanomas leads to the production of a mutated (BRAF) protein, by blocking the mutated protein the treatment stops the melanoma cells from growing and dividing.

Vemurafenib is given orally as a tablet. It is already licenced for certain melanoma patients, but is currently being trialled as a new treatment option for patients who have had surgery but are at high risk of their melanoma returning. Vemurafenib could potentially improve the survival time of these patients.

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.

TARGET GROUP

Vemurafenib for BRAF V600 mutation positive melanoma; adjuvant therapy for completely resected melanoma at high risk of recurrence – first line after surgery

TECHNOLOGY

DESCRIPTION

Vemurafenib (Zelboraf) is a potential adjuvant therapy for patients whose stage IIC-III (cf. Background) cutaneous melanoma (BRAF V600 mutation positive) has been surgically resected, but is at a high risk of reoccurring.[1] It is a small molecule BRAF kinase inhibitor, originally developed by Plexxikon (Daiichi Sankyo) for the treatment of cancer.[2] BRAF V600 positive mutations, which have been identified in 40-70% of all melanomas, lead to continual downstream signalling, causing unchecked cell proliferation and decreased cell death.[1] Vemurafenib binds to and inhibits the active conformation of the V600 mutated BRAF protein.[1] As BRAF targeting has improved overall survival in advanced melanoma, clinical trials are exploring whether this approach could potentially also eliminate residual microscopic melanoma remaining after surgery.[3] Adjuvant chemotherapy and immunotherapy following tumour removal are not currently standard practice in the UK.[4]

Vemurafenib was licenced in the EU in 2012 for the treatment of unresectable or metastatic BRAF V600 positive melanoma,[5] and was recommended by NICE for this indication based on a patient access scheme discount, agreed with the company.[6] Vemurafenib is administered orally. For the already licenced indication and in a phase III trial for adjuvant therapy, 960mg of vemurafenib was administered twice daily and in the trial this regimen was continued for one year.[1]

The most common (>30%) adverse drug reactions reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus.[7] Very common (>10%) adverse effects reported include: headache, dysgeusia, decreased appetite, SCC of the skin, seborrheic keratosis, skin papilloma, cough, diarrhoea, vomiting, nausea, constipation, photosensitivity reaction, actinic keratosis, rash, rash maculo-papular, rash papular, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn, arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain, fatigue, pyrexia, oedema peripheral, asthenia.[7]

Vemurafenib is currently in phase II trials for other types of cancer (brain, colorectal, thyroid and myeloma).[2]

INNOVATION and/or ADVANTAGES

If licensed for this indication, vemurafenib could offer an oral adjuvant therapy for post-surgical patients whose melanoma is at a high risk of recurring.

DEVELOPER

Roche Products Ltd (originator: Plexxicon)

AVAILABILITY, LAUNCH or MARKETING

Vemurafenib is currently in phase III clinical trials for this indication.

PATIENT GROUP

BACKGROUND

Melanoma starts in melanocytes, skin cells that make the pigment melanin, between the dermis and epidermis.[8] Risk factors for melanoma include exposure to UV light, sun exposure, sunburn, having fair skin, moles, and family history of melanoma.[9]

Melanoma is classified into various stages from 0 (in situ/contained) to IV (advanced). At stage II, melanoma is only found in the skin and there is no sign that it has spread to lymph nodes or other parts of the body, whereas at stage III, cancer cells have spread into skin, lymph vessels, or lymph glands close to the melanoma.[10]

CLINICAL NEED and BURDEN OF DISEASE

Cutaneous melanoma is one of the deadliest types of skin cancer, with rising incidence in all Western countries.[11] In the UK, melanoma is the 5th most common cancer, with 14,500 people diagnosed each year.[8] It is the second most common cancer in adults aged below 50 in the UK.[9] In 2015-16 there were 17,230 admissions for malignant melanoma in England, resulting in 12,090 bed days and 17,649 finished consultant episodes.[12]

Melanoma survival is dependent on the stage of disease at diagnosis. Variability in survival is also impacted by the possible microscopic spread of the melanoma prior to the resection of the primary lesion.[13] While no UK-wide statistics for survival are available, Cancer Research UK reports that in one area of England (between 2002 and 2006), people diagnosed at stage II had 80-90% five-year survival rates, this reduced to 50% when diagnosed at stage III.[14] Following surgical resection and in the absence of metastatic disease, prognosis is variable, resulting in 40-90% five-year survival of patients, as cited in a Cochrane Review.[11] Between 40-70% of stage IIB and IIC and more than 50% of stage III melanomas will recur.[15] [16] Prognosis of resectable high-risk melanomas remains poor.[17] The Cochrane review suggests that adjuvant (postoperative) interferon alpha might improve survival in patients with more aggressive tumours.[11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ipilimumab for the adjuvant treatment of completely resected high risk stage III or IV melanoma. (GID-TAG479). Expected date of issue to be confirmed.
- NICE technology appraisal. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA414). October 2016.

- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (TA396). June 2016.
- NICE technology appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016.
- NICE technology appraisal. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). November 2015.
- NICE technology appraisal. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). October 2015.
- NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012 – updated 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 untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.

- NICE guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE interventional procedure guidance. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446). March 2013.
- NICE guideline. Skin cancer prevention: information, resources and environmental changes. NICE public health guidance (PH32). February 2016 (updated).

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/S/b.
- 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

- Scottish Intercollegiate Guidelines Network. Cutaneous melanoma (SIGN 146). January 2017.
- British Association of Dermatologists. Revised UK guidelines for the management of cutaneous melanoma. 2010.
- Sun A., Souter L.H., Hanna T.P., et al. (2016) The use of adjuvant radiation therapy for curatively resected melanoma. Program in Evidence-based Care Guideline No.: 8-9. Cancer Care Ontario; January 4.
- Dummer, R., Hauschild, A., Lindenblatt, N., et al., on behalf of the ESMO Guidelines Committee (2015) Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (Supplement 5): v126–v132.

CURRENT TREATMENT OPTIONS

No standard practice or guidance currently exists for adjuvant drug therapy following melanoma surgery in the UK. Chemotherapy, immunotherapy, interferon alpha, and vaccines are all areas that are currently being explored for treatment of patients at this stage of disease.[17] For example, ipilimumab, a monoclonal antibody, has demonstrated improvement in postoperative survival in trials, but was associated with a much higher number of adverse events compared to a placebo.[18]

In the USA, interferon alpha treatment is the only FDA-approved agent for adjuvant therapy in high risk melanoma.[19] Roferon A is a form of interferon alpha that has UK marketing authorisation for patients with AJCC stage II malignant melanoma (Breslow tumour thickness > 1.5 mm, no lymph node involvement or cutaneous spread) who are free of disease after surgery.[20] A systematic review by the Cochrane Skin Group has reported high quality evidence in support of interferon alpha therapy, improving overall survival by 9% and disease-free survival by 17%.[11] Any treatments must however balance potential toxicity against benefits in a relatively young patient population (compared to other cancers).[16] Due to its high toxicity, the role of interferon alpha in adjuvant melanoma treatment remains a matter for debate, with treatment not routinely recommended by international guidelines.[11]

EFFICACY and SAFETY

Trial	BRIM8, NCT01667419, GO27826; vemurafenib vs. placebo in patients with resected BRAF V600+ tumors; phase III
Sponsor	Hoffman-La Roche
Status	Ongoing/unpublished, final data collection date was reported as June 2016
Source of Information	Trial registry entry[21]
Location	EU (including UK), USA, Canada and other countries
Design	Randomised, double blind, placebo-controlled
Participants	N=503; aged ≥18; histologically confirmed melanoma of cutaneous origin; surgically free of disease within 90 days of randomization and fully recovered from effects of surgery prior to the first study dose
Schedule	Oral doses of vemurafenib 960mg twice daily or film-coated placebo tablets; treatment time 52 weeks
Follow-up	Primary outcome assessed every 13 weeks during treatment; up to approx. 50 months. Follow-up: up to 6 years.
Primary Outcomes	Disease-free survival
Secondary Outcomes	Overall survival, distant metastasis-free survival, safety, quality of life, plasma concentration of vemurafenib
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as June 2016 in the trial registry.

ESTIMATED COST and IMPACT

COST

Vemurafenib is currently supplied via a patient access scheme for another indication, as agreed between the company and the Department of Health; a cost of £1,750 for a week's supply (56 x 240mg tablets) was quoted by NICE in 2012.[6]

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
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☒ Other: *prescribed in hospital care by consultant oncologists; referral and follow-up pathways may need to be reviewed*
- ☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- ☒ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☒ Other increase in costs: *new mode of adjuvant therapy.*
- ☐ Other reduction in costs
- ☐ Other
- ☐ None identified

OTHER ISSUES

- ☐ Clinical uncertainty or other research question identified
- ☒ None identified

REFERENCES

[1] UK Pharmascan. *Vemurafenib/Zelboraf*. [Accessed 28 March 2017, log-in required]

[2] Pharmaprojects. *Vemurafenib/Zelboraf*. [Accessed 28 March 2017, log-in required]
[3] Melanoma International Foundation. *Stage III adjuvant therapy*. Available from: http://melanomainternational.org/2016/12/adjuvant-therapy-decisions/#.WNpHVYMrKUk [Accessed 28 March 2017]
[4] NICE. *Proposed Health Technology Appraisal Ipilimumab for the adjuvant treatment of completely resected high risk stage III or IV melanoma. Draft scope (pre-referral) – Appendix B*. Available from: https://www.nice.org.uk/guidance/gid-tag479/documents/melanoma-resected-stage-iv-high-risk-stage-iii-ipilimumab-adjuvant-draft-scope-for-consultation-prereferral-january-2014-2 [Accessed 28 March 2017]
[5] European Medicines Agency. *Zelboraf. EPAR summary for the public*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002409/WC500124320.pdf [Accessed 28 March 2017]
[6] NICE. *Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma – technology appraisal TA269. Updated January 2015*. Available from: https://www.nice.org.uk/Guidance/TA269 [Accessed 28 March 2017]
[7] EMC. *Zelboraf 240mg film-coated tablets*. Available from: http://www.medicines.org.uk/emc/medicine/26056#UNDESIRABLE_EFFECTS [Accessed 28 March 2017]
[8] Cancer Research UK. *About melanoma*. Available from: http://www.cancerresearchuk.org/about-cancer/melanoma/about [Accessed 28 March 2017]
[9] Cancer Research UK. *Risks and causes of melanoma*. Available from: http://www.cancerresearchuk.org/about-cancer/melanoma/risks-causes [Accessed 28 March 2017]
[10] Cancer Research UK. *Melanoma – stages and types*. Available from: http://www.cancerresearchuk.org/about-cancer/melanoma/stages-types [Accessed 28 March 2017]
[11] Mocellin, S., Lens, M.B., Pasquali, S., Pilati, P. and Chiarion Sileni, V. 2013. Interferon alpha for the adjuvant treatment of cutaneous melanoma. *The Cochrane Library*. DOI: 10.1002/14651858.CD008955.pub2
[12] NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 28 March 2017]
[13] Harcharik, S., Bernardo, S., Moskalenko, M., Pan, M., Sivendran, M., Bell, H., Hall, L.D., Castillo-Martín, M., Fox, K., Cordon-Cardo, C. and Chang, R. Defining the role of CD2 in disease progression and overall survival among patients with completely resected stage-II to-III cutaneous melanoma. *Journal of the American Academy of Dermatology*, 2014, *70*(6), pp.1036-1044.
[14] Cancer Research UK. *Melanoma - survival*. Available from: http://www.cancerresearchuk.org/about-cancer/melanoma/survival [Accessed 28 March 2017]
[15] Melanoma UK. *Stage 2 and stage 3 melanoma.* Available from: http://www.melanomauk.org.uk/stage-2-two-melanoma/ [Accessed 28 March 2017]
[16] Coens, C., Suciu, S., Chiarion-Sileni, V., Grob, J.J., Dummer, R., Wolchok, J.D., Schmidt, H., Hamid, O., Robert, C., Ascierto, P.A. and Richards, J.M.. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *The Lancet Oncology*, 2017, *18*(3), pp.393-403.
[17] van Zeijl, M.C.T., van den Eertwegh, A.J., Haanen, J.B. and Wouters, M.W.J.M.. (Neo) adjuvant systemic therapy for melanoma. *European Journal of Surgical Oncology (EJSO)*, 2017, *43*(3), pp.534-543.
[18] Eggermont, A.M., Chiarion-Sileni, V., Grob, J.J., Dummer, R., Wolchok, J.D., Schmidt, H., Hamid, O., Robert, C., Ascierto, P.A., Richards, J.M. and Lebbé, C. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *New England Journal of Medicine*, 2016, *375*(19), pp.1845-1855.
[19] Grossmann, K. and Christiansen, S. Advances in Adjuvant Therapy for the Treatment of High-risk Melanoma. *Oncology & Hematology Review*, 2013, 9(2):132–7.
[20] EMC. *Roferon-A 3 million international units (IU) solution for injection in pre-filled syringe.* Available from: Available from: https://www.medicines.org.uk/emc/medicine/1730 [Accessed 21 April 2017]
[21] ClinicalTrials.gov. *BRIM8: A Study of Vemurafenib Adjuvant Therapy in Patients with Resected Cutaneous BRAF Mutant Melanoma*. Available from: https://clinicaltrials.gov/ct2/show/record/NCT01667419 [Accessed 28 March 2017]