Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of dabrafenib in combination with trametinib within their marketing authorisations for adjunctive treatment of resected BRAF V600 mutation-positive malignant melanoma.

Background

Cutaneous melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn.

There were 12,993 new diagnoses of melanoma in 2014 and 2,080 deaths registered in the England.[1] In the UK in 2012-2014, on average half of cases were diagnosed in people aged 65 and over.[1]

A mutated form of the BRAF gene is found in about 50% of melanomas; over 90% of these are BRAF V600 mutations.[2] Mutated BRAF genes activate the RAF-MEK-ERK pathway, leading to uncontrolled cell division and growth of the tumour.

The stage of melanoma describes how deeply it has grown into the skin, and whether it has spread. At stage I and II, there is no evidence that the tumour has spread anywhere else in the body, although there is a possibility of microscopic spread. Stage III melanoma means that the melanoma cells have spread into skin, lymph vessels, or lymph glands close to the melanoma. Stage III melanomas are considered intermediate to high risk as they more likely to spread to other distant parts of the body (stage IV melanoma) than in earlier melanoma stages. In 2012, the proportion of people in the UK diagnosed with melanoma at stage III disease was 3%.[2] Five-year survival rates are approximately 50-55% for stage III disease.[3] Advanced melanoma (stage IV) means the cancer has spread from where it started to another part of the body.

Surgery (tumour removal and wide local excision) is the main treatment for early (stage I) and medium stage (stage II and III) melanoma. Surgical removal of the nearly lymph nodes is also considered if there is evidence of microscopic spread. Early recognition of melanoma and accurate diagnosis

present the best opportunities for cure. Adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in UK practice.

The technology

Dabrafenib (Taflinlar, Novartis Pharmaceuticals) is a BRAF kinase inhibitor and trametinib (Mekinist, Novartis Pharmaceuticals) is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2. Consequently, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and BRAF, with the combination of these therapies providing concomitant inhibition of the pathway. Dabrafenib and trametinib are administered orally.

Dabrafenib with trametinib does not have a marketing authorisation in the UK for the adjuvant treatment of BRAF V600 mutation-positive melanoma after surgical resection. It has been studied in a placebo controlled clinical trial, in adults with BRAF V600E/K mutation-positive, resected confirmed high-risk melanoma.

Intervention(s)	Dabrafenib in combination with trametinib
Population(s)	People with completely resected, stage III melanoma with BRAF V600 positive mutations
Comparators	Routine surveillance
Outcomes	The outcome measures to be considered include: • overall survival • relapse-free survival • distant metastases free survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.

Appendix B

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Appraisals in development: None Related Guidelines: 'Melanoma: assessment and management' (2015) NICE guideline NG14. Review date to be confirmed. 'Improving outcomes for people with skin tumours including melanoma' (2006) NICE Cancer Service guideline CSG8. Review date March 2018. Related Interventional Procedures: 'Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma' (2013). NICE interventional procedures guidance 446. Related Diagnostics Guidance: 'VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions' (2015). NICE diagnostics guidance 19. Related Quality Standards: 'Skin cancer' (2016). NICE quality standard 130. Related NICE Pathways: Melanoma (2016) NICE pathway.

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Related National Policy	Department of Health (2016) NHS outcomes framework 2016 to 2017: Domains 1–5. Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy NHS England (2016) Manual for Prescribed Specialised Services 2016/17. Chapter 105. Specialist cancer services (adults). NHS England (2013) NHS standard contract for cancer: skin (adult) A12/S/b.

References

1. Cancer Research UK (2014) Skin cancer statistics. Accessed August 2017
2. Ascierto PA, Kirkwood JM, Grob J-J, et al. (2012) The role of BRAF V600 mutation in melanoma. Journal of Translational Medicine 10:85.
3. National Cancer Intelligence Network and Cancer Research UK (2015) Routes to diagnosis by stage 2012-2013 workbook. Accessed August 2017
4. Cancer Research UK (2014) Skin cancer survival statistics. Accessed August 2017