NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA321; Dabrafenib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma.

Original publication date:	October 2014
Review date	October 2017
Existing recommendations:	Recommended with a Patient Access Scheme To see the complete existing recommendations and the original remit for TA321, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

There are no new cost or clinical effectiveness data for dabrafenib, which would warrant reconsideration of the existing recommendations. Since technology appraisal 321 was issued, dabrafenib has been recommended in combination with trametinib for the same indication (technology appraisal 396). Because the combination therapy has been demonstrated to be more clinically effective than dabrafenib monotherapy it is anticipated that in clinical practice, combination therapy will replace monotherapy in the majority of cases. However, there will be some people for whom dabrafenib monotherapy, but not combination therapy, will be suitable. As such NICE technology appraisal guidance on dabrafenib monotherapy remains relevant. Technology appraisal 321 has been incorporated in NICE guideline 14 Melanoma: assessment and management (2015).

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?
A patient access scheme is in place for dabrafenib. The price of dabrafenib has not increased since TA321.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
There were no trials directly comparing dabrafenib with vemurafenib (the comparator) at the time of TA321. BREAK-3 compared dabrafenib with darcarbazine and this trial was used in an indirect comparison of dabrafenib with vemurafenib. There was a high level of crossover in BREAK-3 and this meant there was uncertainty in the overall survival results from this trial (the magnitude of the treatment effect). Additionally there were differences in when crossover was allowed in BREAK-3 and in the vemurafenib trial (BRIM-3) in the indirect comparison, which added to the uncertainty of the indirect comparison. The committee concluded that there was no evidence to suggest that there was a difference between the clinical effectiveness of dabrafenib and vemurafenib. There are no new trials (comparing dabrafenib directly with vemurafenib or trials enabling a new indirect comparison) and therefore no new data to support changing this conclusion.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
The company notified NICE that the majority of patients with Stage IV metastatic unresectable BRAF mutant melanoma now receive combination dabrafenib/trametinib treatment as opposed to BRAF monotherapy (dabrafenib). It stated there are however, a small proportion of patients who remain on BRAF monotherapy due to stable disease, or are they unable to tolerate the MEK inhibitor trametinib due to adverse events or existing ocular/ cardiac complications.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from October 2013 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: **Meindert Boysen, 11 October 2017**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of dabrafenib within its licensed indication for the treatment of unresectable, advanced or metastatic BRAFV600 mutation-positive melanoma.

6. Current guidance

Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

The list price of dabrafenib is £1400 for a pack of 75-mg capsules (28 capsules per pack) and £933.33 for a pack of 50-mg capsules (28 capsules per pack) (excluding VAT; 'British national formulary' [BNF] edition 67). It is taken orally at a recommended dose of 150 mg twice daily. Novartis has agreed a patient access scheme with the Department of Health that makes dabrafenib available with a discount applied at the point of purchase or invoice. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Melanoma (2016) NICE pathway

Skin cancer (2016) NICE quality standard 130

Melanoma: assessment and management of melanoma (2015) NICE guidelines NG14

Improving outcomes for people with skin tumours including melanoma (2010) NICE Cancer Service Guideline (CSG8).

Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2016) NICE technology appraisal guidance 414

Talimogene laherparepvec for treating unresectable metastatic melanoma (2016) NICE technology appraisal guidance 410

Nivolumab in combination with ipilimumab for treating advanced melanoma (2016) NICE technology appraisal guidance 400

Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (2016) NICE technology appraisal guidance 396

Nivolumab for treating advanced (unresectable or metastatic) melanoma (2016) NICE technology appraisal guidance 384

Pembrolizumab for advanced melanoma not previously treated with ipilimumab (2015) NICE technology appraisal guidance 366

Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (2015) NICE technology appraisal guidance 357

Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (2014) NICE technology appraisal guidance 319

Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (2012) NICE technology appraisal guidance 269

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (2012) NICE technology appraisal guidance 268

Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (2013) NICE interventional procedure guidance 446

VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions (2015) NICE diagnostics guidance 19

In progress

Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226] NICE technology appraisals guidance. Publication expected December 2018

Ipilimumab for the adjuvant treatment of completely resected stage IV or high risk stage III melanoma [ID721] NICE technology appraisals guidance. Publication date to be confirmed

Electrochemotherapy for the treatment of malignant melanoma NICE interventional procedures guidance. Publication date to be confirmed.

Suspended/terminated

Binimetinib for treating melanoma [ID833] NICE technology appraisals guidance. Publication date to be confirmed. Status: to be confirmed

Paclitaxel (as albumin-bound nanoparticles) for the first-line treatment of metastatic melanoma [ID570] NICE technology appraisals guidance. Publication date to be confirmed. Status: removed from work programme as the company has advised that regulatory approval for this technology is not being sought.

Temozolomide for the treatment of advanced and metastatic melanoma [ID316] NICE technology appraisals guidance. Publication date to be confirmed. Status: removed from work programme as the company has advised that regulatory approval for this technology is not being sought.

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Eltrapuldencel-t (NeoStem)	Phase III Clinical Trials UK launch: [redacted]	[redacted]
Encorafenib (Pierre Fabre)	Phase III Clinical Trials UK launch: [redacted]	[redacted]
Immunicell (TC Biopharm)	Phase III Clinical Trials UK launch: [redacted]	[redacted]
Pelareorep (Oncolytics Biotech)	Phase II Clinical Trials UK launch: [redacted]	[redacted]
Pembrolizumab with epacadostat (Incyte)	Phase II Clinical Trials UK launch: [redacted]	[redacted]
PDR001 (Novartis)	Phase III Clinical Trials UK launch: [redacted]	[redacted]
Pv 10 (Provectus Pharmaceuticals)	Phase II Clinical Trials UK launch: [redacted]	[redacted]

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Current indication and price
Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or	Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult

Indication and price considered in original appraisal	Current indication and price
metastatic melanoma with a BRAF V600 mutation. The list price of dabrafenib is £1400 for a pack of 75-mg capsules (28 capsules per pack) and £933.33 for a pack of 50-mg capsules (28 capsules per pack) (excluding VAT; 'British national formulary' [BNF] edition 67).	patients with unresectable or metastatic melanoma with a BRAF V600 mutation Source: SPC (June 2017) No change to the list price. Source: BNF (July 2017) [redacted] Source: Novartis email to NICE (10 July 2017)

4. Registered and unpublished trials

No ongoing trials specific to TA321 identified.

5. Relevant services covered by NHS England specialised commissioning

NHS England (2016) Manual for prescribed specialised services 2016/17

Chapter 105: Specialist cancer services - NHS England commissions specialist cancer services for adults, including services delivered on an outreach basis as part of a provider network. Specialist cancer services include… Section D. Certain specified interventions provided by defined Specialist Cancer Centres (including assessment if performed at the Specialist Centre). Includes skin cancer interventions.

NHS England (2013) 2013/14 NHS Standard contract for cancer: skin (adult) A12/S/b

6. Additional information

ESMO (2015) Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

European Dermatology Forum, European Association of Dermato-Oncology, European Organisation of Research and Treatment of Cancer (2017) Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – update 2016

Scottish Medicines Consortium (2015) Dabrafenib 1023/15 – accepted for restricted use in NHS Scotland