

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA269; Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

This guidance was issued in December 2012.

The review date for this guidance is November 2014.

1. Recommendation

The guidance should be incorporated into an on-going clinical guideline. The current Patient Access Scheme for vemurafenib will remain in place. That we consult on this proposal.

2. Original remit(s)

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

3. Current guidance

- 1.1 Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.

4. Rationale¹

Further follow-up data from the studies originally included in the appraisal have been published. These additional data are not inconsistent with the results used for the appraisal and would not be expected to change the decision.

5. Implications for other guidance producing programmes

NICE is currently developing a clinical guideline for the assessment and management of melanoma, which is due to be published in July 2015. The draft scope for the guideline indicates that TA269 should be incorporated in the guideline.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2011

¹ A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

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 See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for vemurafenib at the time of developing technology appraisal 269 was for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'. The marketing authorisation is currently the same although the manufacturer has confirmed that there may be an extension to the licence into the adjuvant setting in 2018/19.

The literature searches identified 15 relevant references, since the development of NICE technology appraisal 269. Three of the references, (McArthur et al., 2014, McArthur et al., 2012; a conference abstract and Chapman et al., 2012), contained data from extended follow-up studies for the BRIM3 study, which was the key clinical evidence for vemurafenib in technology appraisal 269. Two references were for studies comparing vemurafenib with treatments other than dacarbazine (the comparator in technology appraisal 269), 2 were observing the cost effectiveness or budget impact of vemurafenib treatment, 1 health technology assessment, 2 safety studies of vemurafenib treatment, 1 non-comparative study and 2 references were outside the remit of advanced or metastatic BRAF V600 mutation-positive malignant melanoma.

The Committee for technology appraisal 269 noted the short-term nature of the results from the BRIM3 study and the uncertainty of the long-term benefits of vemurafenib treatment. The BRIM3 extended follow-up studies (McArthur et al., 2014 and Chapman et al., 2012) observed patients with advanced BRAFV600 mutation-positive melanoma treated with vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg/m² of body surface area intravenously every 3 weeks). In the McArthur et al., 2014 study (n=675) the median overall survival for the 598 (91%) patients with BRAF V600E mutation-positive disease, in the vemurafenib group was 13.3 months (95% confidence interval [CI] 11.9 to 14.9) compared with 10.0 months (95% CI 8.0 to 14.0) in the dacarbazine group (HR 0.75 [95% CI 0.60 to 0.93]; p=0.0085). Median progression-free survival was 6.9 months (95% CI 6.2-7.0) and 1.6 months (95% CI 1.6 to 2.1) for vemurafenib and dacarbazine respectively (HR 0.39 [95% CI 0.33 to 0.47]; p<0.0001). For the 57 (9%) patients with BRAF V600K mutation-positive disease, median overall survival in the vemurafenib group was 14.5 months (95% CI 11.2 to not estimable) compared with 7.6 months (95% CI 6.1 to 16.6) in the dacarbazine group (hazard ratio 0.43 [95% CI 0.21 to 0.90]; p=0.024). The median progression-free survival was 5.9 months (95% CI 4.4 to 9.0) and 1.7 months (1.4 to 2.9), respectively (hazard ratio 0.30 [95% CI 0.16 to 0.56]; p<0.0001). The Chapman et al., 2012 study also reported follow-up results for the BRIM3 study with the median length of follow-up for vemurafenib and dacarbazine being 10.5 months (range 0.4-18.1 months) and 8.4 months (range <0.1-18.3 months), respectively. Median overall survival rates with vemurafenib and dacarbazine were 13.2 months (95% CI 12.0 to 15.0) and 9.6 months (95% CI 7.9 to 11.8), respectively. Overall survival rates at 12 months were 55% for vemurafenib and 43% for dacarbazine with a hazard ratio for death of 0.62 (95% CI 0.49 to 0.77) in favour of vemurafenib. There were 334 deaths.

The current list price specified in the British National Formulary 68 for vemurafenib and the comparator dacarbazine have not altered since the development of NICE technology appraisal 269. In July 2014 NICE technology appraisal 319 recommended ipilimumab as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. This could be considered a comparator for vemurafenib as ipilimumab is licensed for both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients.

The clinical effectiveness evidence identified from the literature searches, registered trials and current list prices of the technologies do not suggest the recommendations of technology appraisal 269 need reviewing.

Based on the above information, it is proposed that technology appraisal guidance 269 is transferred to the 'static guidance list'.

8. Implementation

A submission from Implementation is included in Appendix 3.

Data is available on the volume of vemurafenib prescribing in hospitals in England between January 2012 and January 2013. The ePACT data suggests that the use of vemurafenib slowly increased until Q3 2013, when the use started to decrease.

There is insufficient evidence to make any firm conclusions on the adherence to NICE technology appraisal guidance 269, or whether there is any regional variation in clinical practice in England.

9. Equality issues

No equality issues were raised during the scoping exercise or the course of the appraisal.

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Appendix 1 – 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.	<p>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.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	Yes

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>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.</p> <p>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).</p>	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.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment
 - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. TA319. Published: July 2014. Review date: June 2017

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. TA268. Published: December 2012. Review date: November 2014.

Improving outcomes for people with skin tumours including melanoma. Cancer Service Guidance CSGSTIM. Published: May 2006. In May 2010 NICE published a partial update of this guidance. See also: Improving outcomes for people with skin tumours including melanoma: Evidence Update (October 2011).

Skin cancer prevention: information, resources and environmental changes. PH32 Published: January 2011. Review date: 3 years from publication

In progress

Melanoma: assessment and management of melanoma. Anticipated publication date: July 2015.

Diagnosis of skin cancer: the VivaScope imaging system (and other alternative technologies identified in scoping). Anticipated publication date: November 2015.

Dabrafenib for the treatment of BRAF V600 mutation positive, unresectable, advanced or metastatic melanoma. [ID605]. Anticipated publication date: December 2014. [Note this topic incorporated trametinib in combination with dabrafenib until the manufacturer withdrew its Marketing Authorisation Application]

Ipilimumab for the adjuvant treatment of completely resected stage IV or high risk stage III melanoma. [ID721]. Referred: July 2014. Publication date: TBC.

Referred - QSs and CGs


Skin cancer (including melanoma). Referred

Suspended/terminated

Temozolomide for the treatment of advanced and metastatic melanoma. [ID316]. Referred: June 2008. Status: suspended. The manufacturer is not seeking regulatory approval.

Paclitaxel (as albumin-bound nanoparticles) for the first-line treatment of metastatic melanoma. [ID570]. Referred: October 2013. Status: suspended. The manufacturer will no longer be pursuing a licensing application for this indication.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
<p>Vemurafenib has a UK marketing authorisation for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.</p> <p>Vemurafenib costs £1750 for 1 pack of 56 x 240 mg tablets (1 week's supply) (excluding VAT; 'British national formulary' [BNF] September 2012). Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of vemurafenib has agreed a patient access scheme with the Department of Health, in which a discount on the list price of vemurafenib is offered. The size of the discount is commercial-in-confidence.</p>	<p>Currently unchanged.</p> <p>Source: SPC (July 2014) and BNF (Sept 2014)</p> <p>Roche do not anticipate any changes to the marketing authorisation for vemurafenib in the short term. There is the possibility of an application for a license extension being made in 2018/19. The marketing authorisation for vemurafenib may be extended to the adjuvant setting in 2018/19.</p> <p>The marketing authorisation for a MEK inhibitor (cobimetinib), expected in </p> <p>Source: Roche letter to NICE, 19 August 2014</p>

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date)
Astuprotimut-R (zumagev), GSk - MAGE-A3 positive, stage III after surgery	Phase III Clinical Trials ██████████
Binimetinib, Novartis - NRAS mutant, 1st & 2nd line	Phase III Clinical Trials ██████████
Cobimetinib, Roche - 1st line in combination with vemurafenib	Phase III Clinical Trials ██████████
Encorafenib, Novartis - monotherapy, and in combination with binimetinib	Phase III Clinical Trials ██████████
Masitinib, AB Science - non-resectable or metastatic Stage 3 or Stage 4 melanoma carrying a mutation in the juxta membrane domain of c-kit	Phase III Clinical Trials
Nivolumab (opdivo), Bristol-Myers Squibb - unresectable or metastatic BRAF-positive, 1st line	Phase III Clinical Trials ██████████
Nivolumab (opdivo), Bristol-Myers Squibb - unresectable or metastatic, 2nd line after ipilimumab	Phase III Clinical Trials ██████████
Paclitaxel + XR 17 (paclical), Oasmia Pharmaceutical AB	
Pembrolizumab (keytruda), Merck Sharp & Dohme - unresectable or metastatic, advanced, 1st, 2nd or 3rd line	Approved in the US ██████████
PV10, Provectus Pharmaceuticals - Malignant melanoma	Phase II clinical trials
Talimogene laherparepvec (oncovex, Amgen - stage IIIc and IV disease - 1st & 2nd line therapy	Phase III Clinical Trials ██████████

Registered and unpublished trials

Trial name and registration number	Details
A Phase 3 Study Comparing GDC-0973 (Cobimetinib), a MEK Inhibitor, in Combination With Vemurafenib vs Vemurafenib Alone in Patients With Metastatic Melanoma coBRIM NCT01689519	Multicenter, randomized, double-blind, placebo-controlled phase 3 study Sponsor: Roche Patients: 499 Status: ongoing, not recruiting Start date: January 2013 Expected completion: December 2017
An Observational Safety Study in Zelboraf (Vemurafenib)-Treated Patients With BRAF-V600 Mutation-Positive Unresectable or Metastatic Melanoma ZeSS NCT01990248	Multi-center, prospective, observational safety study to evaluate the safety and effectiveness of vemurafenib in a real-world setting Sponsor: Roche Patients: 400 Status: recruiting Start date: March 2013 Expected completion: March 2016

Relevant services covered by NHS England specialised commissioning

NHS England (2013) 2013/14 NHS standard contract for cancer: skin (adult). Section B Part 1 - service specifications. A12/s/b.

Cancer Drugs Fund - Dabrafenib for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and intolerance to vemurafenib where certain criteria are met.

Additional information

████████████████████ however it should be noted that stakeholders (including NICE and NHS) have been notified that Roche will cease funding for BRAF testing from 1st Jan 2015. This has no impact the cost-effectiveness of vemurafenib in TA268. Source: Roche letter to NICE, 19 August 2014

References

McArthur GA et al. (2014) Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncology* 15 (3): 323-332

McArthur G et al. (2012) Efficacy of vemurafenib in BRAFV600K mutationpositive melanoma disease-results from the phase 3 clinical study BRIM3. *Pigment Cell and Melanoma Research* 25 (6): 871

Chapman PB et al. (2012) Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. *Journal of Clinical Oncology* 30 (15 SUPPL. 1)

Appendix 3 – Implementation submission

1. Routine healthcare activity data

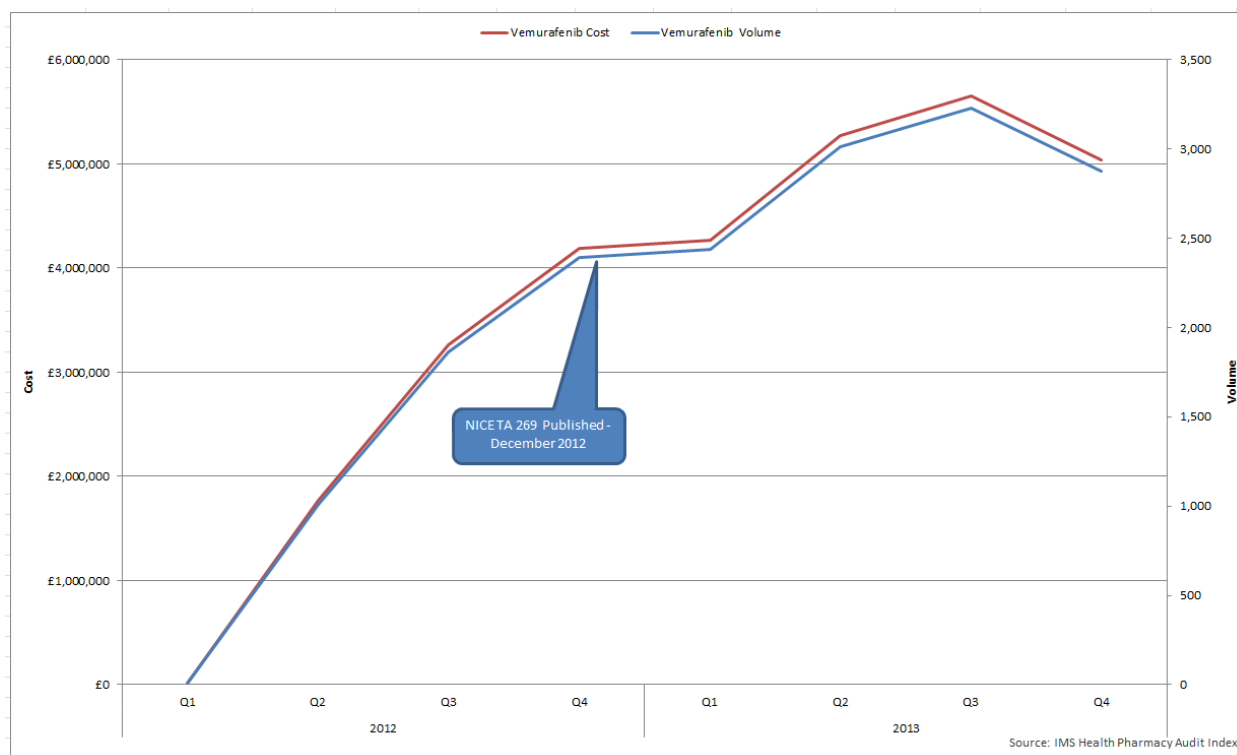
ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of drugs prescribed in hospitals and or the community and dispensed in the community in England. Vemurafenib was not dispensed in the community during April 2009 to March 2014.

Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of vemurafenib prescribed and dispensed in hospitals in England between January 2012 and January 2013.

Figure 1 Cost and volume of vemurafenib prescribed in hospitals in England between January 2012 and December 2013.



2. Implementation studies from published literature

No uptake information was found on the uptake database website for TA 269.

3. Qualitative input from the field team

The implementation field team have not recorded any feedback in relation to this guidance.

4. Implementation studies from shared learning

A search of the [shared learning](#) website highlighted no examples of TA269 being implemented.

Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals, mental health units and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines

supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.