Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 45 p. (Technology appraisal guidance; no. 269).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

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.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Dermatology

Family Practice

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Target Population

Patients with locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Interventions and Practices Considered

Vemurafenib

Major Outcomes Considered

- Clinical effectiveness
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Joint outcome of OS and PFS
  - Best overall response rate
  - Duration of response
  - Time to response
  - Adverse events
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of the Clinical Reviews

Two separate systematic literature searches were carried out to identify relevant studies of vemurafenib used as monotherapy in the treatment of malignant melanoma. The first was designed to identify randomised controlled trials (RCTs) and the second to identify non-randomised studies. Appropriate search strategies and inclusion criteria were utilised. All identified studies had been sponsored by the manufacturer.

Identified Studies

A total of three studies that examined the use of vemurafenib as monotherapy were identified by the searches conducted by the manufacturer. Details of these studies are reported in the manufacturer's submission (MS) and are presented in Table 4 of the ERG report (see the "Availability of Companion Documents" field). The only direct evidence used in the MS for this Single Technology Appraisal (STA) comes from the BRIM 3 trial. Therefore data from the other two studies are not considered in any depth by the ERG. Reports of all three trials have been published.

Cost-Effectiveness

Objective of the Manufacturer's Cost-Effectiveness Literature Review

The manufacturer's search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem set out in the scope. A full systematic review of cost-effectiveness studies in melanoma was conducted in support of the NICE technology appraisal for ipilimumab and the manufacturer focused their search on papers published from 9 December 2010 onwards.

On 17 January 2012 ProQuest was searched for databases Medline, EMBASE, and EMBASE Alert; EconLit was searched via the American Economic Association website; and National Health Service Economic Evaluation Database (NHS EED) was searched using the University of York's Centre for Reviews and Dissemination website. All five databases were searched with the same set of search terms.

The manufacturer appears not to have undertaken any searches of the unpublished literature; however, the ERG considers that finding any relevant studies from such sources is unlikely and concludes that the search strategy used by the manufacturer was appropriate.

Inclusion and Exclusion Criteria Used in Study Selection

The inclusion/exclusion criteria used in study selection are presented in the table below (see Table 16 in the Evidence Review Group [ERG] report).

Table: Economic Evaluation Search Inclusion and Exclusion Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population	BRAF V600 mutation positive advanced or metastatic melanoma patients	Non-melanoma patients; Non BRAF mutated patients
Intervention	Vemurafenib	
Comparator	Dacarbazine; best supportive care, ipilimumab	
Outcome	Cost per quality-adjusted life year (QALY) gained; Cost per life year (LY) gained	
Study design*	Economic evaluation (cost-effectiveness analyses, cost utility analyses, cost minimisation analyses)	Randomised controlled trials (RCTs), observational data, budget impact assessments

*During the record sifting process records were excluded if they were not a cost-utility analysis.

Conclusions of the Review

The manufacturer's search of the published cost-effectiveness literature describing the use of vemurafenib for the treatment of locally advanced or

metastatic BRAF V600 mutation positive malignant melanoma did not identify any relevant cost-effectiveness studies. The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

Number of Source Documents

Clinical Effectiveness

A total of three studies that examined the use of vemurafenib as monotherapy were identified by the searches conducted by the manufacturer. The only direct evidence comes from the BRIM 3 trial. Therefore data from the other two studies are not considered in any depth by the Evidence Review Group.

Cost-Effectiveness

An economic model was submitted by the manufacturer.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

BRIM 3 Quality and Validity Assessment

The quality assessment of the BRIM 3 trial is presented in the manufacturer's submission (MS). The assessment demonstrates that it was generally a well designed international, multi-centre trial. There are however some areas of trial design that should be noted.

Although there was appropriate concealment of allocation and randomisation, the trial was not blinded. The MS appropriately presents a case that given the poor prognosis in these patients it would have been inappropriate to subject participants to unnecessary additional clinical visits and treatments.

Important changes to the study design and data analysis were required by the U.S. Food and Drug Administration (FDA) regulatory system as the trial progressed. These included a change in the primary outcome (from overall survival [OS] to joint primary outcomes of OS and progression-free survival [PFS]) and the crossover of patients from the dacarbazine group. The effects of these changes are discussed in the statistical analysis section (see below and in the ERG report). The most recent data cut was in October 2011 and the data remain immature. Analysis of OS was due again at the end of May 2012 for review by the European Medicines Agency (EMA).

The randomisation process produced equivalent groups; however, 14% (48/338) of patients randomised to receive dacarbazine did not receive treatment. The most common reasons were withdrawal of consent or refusal of treatment (37/48). It is not known what impact this may have had on data analysis related to the intention to treat (ITT) and per protocol (PP) populations.

Data related to health-related quality of life (HRQoL) were collected using the FACT-M questionnaire. However, the MS reports that completion rates were low following the reporting the results of the interim analysis. In addition, the MS points out that the tool is not preference based and therefore does not conform to the NICE reference case.

Description and Critique of the Statistical Approach

Blinding and Concealment

The BRIM 3 trial was an open-label study; investigators, patients and sponsor were all aware of treatment allocations after randomisation had taken place. One of the co-primary endpoints was PFS which is a subjective outcome and therefore the lack of blinding could lead to potential bias, especially as there was no independent review committee to reinforce the assessments made by investigators. The other co-primary endpoint, OS, is objective so the ERG has no concerns about any bias introduced by the lack of blinding for this outcome.

It is still important to have allocation concealment in an open-label study, whereby the investigators are not aware of the treatment that the patient will be assigned before randomisation takes place. This was achieved in the BRIM 3 study by randomising patients centrally using an interactive voice response system. The ERG is satisfied that allocations were adequately concealed in this trial.

Randomisation

According to the statistical analysis plan (SAP), patients were randomised (1:1) to receive treatments based on a minimisation algorithm using the following balancing factors:

- Geographic region (North America, Western Europe, Australia/New Zealand, others)
- ECOG performance status (0,1)
- Metastatic classification (unresectable stage IIIC, M1A, M1B, M1C)
- Serum lactate dehydrogenase (LDH) (normal, elevated)

Minimisation is a method of treatment allocation whereby the first patient is truly randomly allocated and then for subsequent patients, the treatment that minimises the imbalance on the selected factors between the groups at that time is identified. This allocation may then be used or a random element may be introduced so that although there is a heavy weighting (commonly 80%) towards the treatment that minimises the imbalance, there is still a chance that the patient may be allocated to the other treatment. The approach where a random element is incorporated is generally preferred. It is not clear whether the minimisation algorithm adopted by the manufacturer utilised a random element but the ERG is satisfied with the approach taken as it is stated in the CONSORT statement that "in general, trials that use minimisation are considered to be methodologically equivalent to randomised trials, even when a random element is not incorporated".

See Section 4 of the ERG report (see the "Availability of Companion Documents" field) for details on clinical effectiveness evaluation.

<u>Cost-Effectiveness</u>

NICE Reference Case Checklist

Table 17 of the ERG report (see the "Availability of Companion Documents" field) tests how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist, and Table 18 of the ERG report summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond checklist.

Model Structure

A schematic of the manufacturer's model is shown in Figure 3 of the ERG report. It comprises three health states: PFS, progressed disease (PD) and death. All patients enter the model in the PFS health state. At the beginning of each time period patients can either remain in the same health state or progress to a 'worse' health state, i.e., from PFS to PD or death; or from PD to death.

The model has been developed in MS Excel and has a one week cycle length. It includes a half-cycle correction and the time horizon is set at 30 years. A discount rate of 3.5% has been used for both costs and outcomes and the perspective is stated to be that of the National Health Service (NHS) and Personal Social Services.

Sensitivity Analyses

Deterministic Sensitivity Analyses

The manufacturer varied transition probabilities (± 10%), with the exception of the monthly hazard of death from month 46 onwards which was varied ± 50%, utilities (± 10%), costs (between upper and lower confidence interval (CI) assuming the standard error = 1/4 base case value),

patient characteristics (age ± 10 years) and BRAF mutation incidence 40-60%), and general parameters (time horizon [-20 years] and discount rates [0% and 6%]). The results, presented in Table 27 of the ERG report, for the ten parameters showing the greatest variability, demonstrate that the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained for vemurafenib in the modelled patients is most sensitive to discount rates and hazard of death between months 9 and 14.

Probabilistic Sensitivity Analyses

The manufacturer undertook probabilistic sensitivity analysis (PSA) to derive the mean ICER of vemurafenib versus dacarbazine. The manufacturer notes that OS, the parameter subject to the most uncertainty, was not varied probabilistically as they were not able to determine which potential extrapolations should be given a higher likelihood of occurring. The manufacturer highlights that this omission means that the PSA significantly understates the uncertainty associated with the incremental QALY gain provided by vemurafenib.

See Section 5 of the ERG report (see the "Availability of Companion Documents" field) for details on manufacturer's cost-effectiveness analysis and its critique by ERG.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The manufacturer presented an economic model comparing vemurafenib with dacarbazine using effectiveness data from the February 2012 data cut-off of the BRIM3 study (that is, up to 14 months of treatment), and assumed an equal chance of death (hazard ratio of 1) for both treatment arms after disease progression at 14 months.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee considered the manufacturer's use of the rank preserving structural failure time (RPSFT) to adjust the survival estimate for people who switched from dacarbazine to vemurafenib in its revised analysis, and the use of external data from the Bedikian et al. (2011) trial to model the clinical effectiveness of dacarbazine in a sensitivity analysis. It noted that both the manufacturer and the evidence review group (ERG) agreed that the effect of vemurafenib treatment on mortality changes over time and that applying a single acceleration factor (a factor that 'speeds up' the time for people receiving vemurafenib after disease progression) may therefore be an oversimplification, and that the results should be viewed with caution.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The manufacturer's economic model used utility values sourced from the literature.

The Committee acknowledged a higher utility value for long-term survival (that is, survival greater than 5 years estimated to be 0.767) is reasonable and was persuaded that an improved utility value for the progressed disease stage after 5 years of survival was justified.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

Not applicable

What Are the Key Drivers of Cost Effectiveness?

The Committee discussed whether the benefit of vemurafenib over dacarbazine was likely to continue once treatment was stopped, or conversely whether there may be accelerated disease progression. It heard from the clinical specialists that people whose disease progresses after treatment with vemurafenib may have a smaller tumour burden compared with those treated with dacarbazine because of the higher disease response rate seen with vemurafenib, and may have a survival advantage. The Committee acknowledged that the existence or magnitude of continued benefit from vemurafenib after treatment is stopped is uncertain, but recognised there is no evidence currently available to suggest that people who stop vemurafenib treatment will experience accelerated disease progression compared with those who have been treated with dacarbazine.

Most Likely Cost-Effectiveness Estimate (Given as an Incremental Cost-Effectiveness Ratio [ICER])

The manufacturer's revised cost-effectiveness estimate was £51,800 per quality-adjusted life-year (QALY) gained when using the RPSFT adjusted February 2012 data cut-off and £44,400 when using the Bedikian trial data to represent the dacarbazine arm. These estimates take into account the evidence review group's (ERG) suggested amendments to discounting and costs.

The Committee considered the cost-effectiveness estimates for the additional scenario analysis (comparing vemurafenib with dacarbazine, in which exponential hazards were applied separately to each arm of the BRIM3 study from 14 months onward) provided by the ERG, but was aware of the manufacturer and clinical specialists' opinion that such an analysis was inappropriate; the manufacturer noted this extrapolation gave a post-progression survival after treatment with vemurafenib that was 2.2 months shorter than post-progression survival after dacarbazine. The manufacturer considered that this implausible result may be a result of an under-adjustment of the acceleration factor used in the RPSFT method. The ERG disagreed with the manufacturer's comments, and reported a cost-effectiveness estimate of £121,000 per QALY gained using the February 2012 data cut-off.

The Committee noted that it was unlikely that a single acceleration factor would capture the benefit of vemurafenib, which meant that the resulting

ICER of £51,800 should be interpreted with caution and was higher than the ICER of £44,000 per QALY gained that resulted from using external data. The Committee was not satisfied that the alternative ICER (based on the Committee's requested scenario) of £121,000 per QALY gained represented the true benefit of vemurafenib. The Committee concluded that the most plausible ICER was in the range of £44,000 to £51,800 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, one randomised controlled trial was the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Potential Harms

Vemurafenib is most commonly associated with the following adverse reactions: arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. It can also lead to the formation of cutaneous squamous-cell carcinomas.

For full details of adverse reactions and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/.

Contraindications

Contraindications

For full details of side effects and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The technology in this appraisal may not be the only treatment for unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. If a NICE technology appraisal recommends use of a technology, it is an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with the section above) when the clinician concludes that the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.
- NICE has developed tools to help organisations put this guidance into practice. These are available on the NICE Web site (http://guidance.nice.org.uk/TA269).
    - Costing template and report to estimate the national and local savings and costs associated with implementation.
- The Department of Health and the manufacturer have agreed that vemurafenib will be offered to the NHS under a patient access scheme that makes vemurafenib available with a discount on the list price. The size of the discount is commercial-in-confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Roche Products (0800 731 5711, Welwyn.rx_commercial_group@roche.com).

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 45 p. (Technology appraisal guidance; no. 269).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Dec

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. Evidence Review Group report. Liverpool (UK): Liverpool Reviews and Implementation Group, University of Liverpool; 2012 Apr 12. 66 p. (Technology appraisal guidance; no. 269) Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. (Technology appraisal guidance; no. 269). Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Vemurafenib for unresectable or metastatic melanoma with the BRAF V600 mutation. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 6 p. (Technology appraisal guidance; no. 269). Electronic copies: Available

in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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