NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Vismodegib for treating basal cell carcinoma [ID1043]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Roche**
     - **Updated PAS submission**
   - **NCRI-ACP-RCP joint response**

3. **NICE request and comments received on additional evidence from experts:**
   - **Dr John Lear**, Clinical Expert, nominated by Roche
   - **Professor Ruth Plummer**, Clinical Expert, nominated by Roche

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **ERG critique** prepared by BMJ Group

6. **ERG additional analysis** prepared by BMJ Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Vismodegib for treating basal cell carcinoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Consultee	Comment [sic]	NICE Response
Roche	**Justification of the Landmark analysis** Vismodegib received conditional marketing authorisation in 2013 on the basis of the phase II, single arm ERIVANCE (NCT00833417) study.[1] A control group was not used, given there was no accepted standard of care and no data suggesting spontaneous responses in advanced BCC. Full marketing authorisation was gained with data from the ongoing STEVIE (NCT01367665) study (primary objective: safety assessment).[2] Data from the STEVIE study was used in the landmark analysis and comparator data needed to be generated. Economic and clinical experts were consulted and possible approaches were suggested: the construction of a match-adjusted indirect comparison (MAIC); and the use of a relative treatment effect from a published vismodegib randomised controlled trial (RCT) in a different but related therapeutic setting. MAIC would involve sourcing and using data for patients with aBCC who have received BSC only. The aim would be to combine this data on overlapping comparator groups and use multiple direct and indirect comparisons to build a network meta-analysis that summarises comparative evidence for all treatments in the therapeutic area. This approach is advantageous as it addresses the lack of comparator data by allowing the assessment of relative efficacy across comparable patient groups. Overall survival (OS) and progression-free survival (PFS) data from published observational literature, disease registries, or clinical studies are required. Roche considered the RONNIE (NCT02100111) study which includes aBCC patients receiving supportive or palliative care. However, only 8 of the 121 eligible patients in RONNIE received palliative/supportive care as their first therapy option and this sample size is not large enough to power a MAIC; secondly, the type of supportive care received points to an end-of-life setting, which is not representative of the supportive care that patients eligible for the STEVIE study would receive. A MAIC was deemed	Comments noted. The committee fully considered the landmark analysis but was concerned that the data were at high risk of bias (see section 3.6 in the FAD).

Consultee	Comment [sic]	NICE Response
	unfeasible.[3] Consulted experts also suggested using relative treatment effect from a published vismodegib RCT. In 2012, a study was published by Tang et al. reporting vismodegib in Gorlin's syndrome.[4] From September 2009 through January 2011, 42 patients were enroled at three clinical centres. Patients were randomly assigned to receive either vismodegib or placebo for a planned duration of 18 months. Disease burden differs between patients with Gorlin's syndrome and those with aBCC; best supportive care is likely to differ significantly.[4] This modelling strategy was not adopted as Roche was unable to gain access to the complete dataset and suitability could not be assessed. After discussion with experts, a landmark analysis was believed to be the most methodologically robust option. Stakeholders, including the evidence review group (ERG) have not suggested alternative methodology to date. For further information on data limitations and methodological rationale refer to page 280 of the Committee Papers for this appraisal: https://www.nice.org.uk/guidance/gid-ta10090/documents/committee-papers.	
Roche	**Selection of Landmark point** The submitted landmark analysis included 6 months and 3 months as the base case and scenario analyses, respectively; additional time-points were not evaluated. The Committee stated that further exploration around the landmark would have increased its confidence in the overall analysis. Roche and the ERG agreed that the 3-month landmark was inappropriate as it is too close to the median time to first response of (2.76 months) and is less than the mean (3.40 months) for the combined aBCC population.[5] A 3-month landmark (or shorter) is likely to misclassify a large proportion of subsequent responders as non-responders and thus overestimate the efficacy for non-responders. The 3-month landmark was included as a conservative scenario to explore general sensitivity around the parameter. Time-points between 3 and 6 months may have been appropriate to explore but did not align with the assessment schedule in the STEVIE study and data was therefore not available. It is reasonable to assume that a 4-month landmark would be no more robust than a 3-month landmark. The results of 4- or 5-month landmarks can be assumed to lie between the	Comments noted (see section 3.6 in the FAD).

Consultee	Comment [sic]	NICE Response
	3- and 6-month results reported. Landmarks beyond 6-months were not explored because the majority of patients in the non-responder group would have progressed or died by this point; leading to a higher number of exclusions, a lower number of patients in the final analysis and hence a less robust analysis.	
Roche	**Extrapolation of time to treatment discontinuation (TTD)** Roche submitted the Weibull function believing it to be the most appropriate TTD extrapolation choice. The ERG disagreed and preferred the log-logistic function. This issue was not discussed in open Committee on 28Jun2017 and Roche did not have the opportunity to support its choice. Akaike information criterion (AIC) values influenced the ERG's selection of the log-logistic distribution. An AIC value is designed to show how well a parametric function fits to the Kaplan-Meier (KM) data, relative to the other functions in question – the AIC value says nothing of the appropriateness of the extrapolation beyond the KM data. The STEVIE KM data accounts for a very small proportion of the overall time horizon of the model and therefore Roche believes the AIC values should not be over-interpreted.[5] The ERG argues that the Weibull function proves to be a worse fit than the log-logistic when visually inspecting the curves despite the KM data accounting for approximately 13% of the model time horizon. Roche feels the closeness of the fit should not be over-interpreted as it does not address the appropriateness of the overall extrapolation beyond the observed KM data. Roche would also argue that the difference in fit between the Weibull and the log-logistic throughout the observed time period is negligible—the difference in proportion of patients still on treatment in the Weibull and log-logistic curves remains <5% for 40 months. The submitted model includes the facility to use KM data for the observed period and then use a parametric extrapolation for the remainder of the time horizon. Data artefacts result in the TTD curves crossing the PFS curves when certain parametric extrapolations are used, implying that patients continue treatment after progressing (off-protocol). To address this, Roche artificially capped the TTD curve to ensure it was unable to exceed the PFS curve i.e. for a period of time, patients only discontinue treatment as	Comments noted. The committee discussed the comments about the most appropriate model to extrapolate TTD extrapolation and concluded that the log-logistic function is the best fit for laBCC and mBCC data based on AIC and BIC values as well as the smoother drop in the tail of the log-logistic curve, which reflects the typically slow progression of the disease more accurately. Please see section 3.9 of FAD for the committee's full considerations.

Consultee	Comment [sic]	NICE Response
	a result of either progression or death and not adverse events. If using the log-logistic curve to model TTD, the curve must be capped (to prevent exceeding PFS) from year 5 to year 8. This implies that from year 5 onwards, the 7% of patients left on treatment are only able to discontinue due to progression or death. This is clinically implausible. Using the Weibull extrapolation results in all patients having discontinued before the TTD curve exceeds PFS, and no artificial capping is required. The appendices report updated cost-effectiveness results, in which both distributions discussed here are used. For further information and graphical illustration of these issues, please refer to page 272 of the committee papers for this appraisal: https://www.nice.org.uk/guidance/gid-ta10090/documents/committee-papers	
Roche	**Intensity of the post-progression BSC regimen in the economic analysis** The ERG and the committee feel that the majority of patients will eventually receive the same post-progression BSC regimen, regardless of whether or not they were treated with vismodegib. Clinical experience and trial data (see ERIVANCE photo appendix) demonstrate that vismodegib reduces tumour burden in the majority of patients (in some cases visual improvement is seen in patients not meeting study defined response). Expert opinion is that patients who receive vismodegib can expect a delay before having the same BSC requirements as a patient who is not treated. The ERG suggested 6-months as a plausible delay and this was discussed by the Committee. The clinical expert in attendance on 28Jun2017 stated that this delay could be significantly longer (6-10 years) reflecting the views of clinical advisors to Roche that long term responses to vismodegib are seen in clinical practice. The intensity of BSC is highly variable. Roche feels this issue was not explored sufficiently by the Committee and the decision to adopt the highly conservative ERG estimate was not scrutinised adequately by clinical experts and patient groups. Given the uncertainty around this parameter, Roche feels it inappropriate to suggest an alternative point estimate. Instead, scenario analysis has been conducted and the results are presented in the appendices of this	Comments noted. The committee acknowledged that the length of the delay in re-starting BSC after progression on vismodegib is highly variable in clinical practice. After hearing from the clinical experts and taking into consideration that vismodegib has only been available for 4 years, it concluded that a delay of 3 years in re-starting BSC after vismodegib is most plausible. Please see section 3.13 of the FAD for the committee's full considerations.

Consultee	Comment [sic]	NICE Response
	document.	
Roche	**<u>Underestimation of health-related quality of life (HRQoL) in the economic analysis</u>** The Committee note and Roche recognises that the economic analysis underestimates the true HRQoL impact of aBCC and treatment. The model applies health-state utilities across treatment arms and is likely to underestimate the HRQoL benefit associated with vismodegib therapy—assuming that: HRQoL in 'PFS on vismodegib' is equal to HRQoL in 'PFS on BSC'; and that 'Progressive disease (PD) after vismodegib' has the same utility associated as 'PD after BSC'. Utilities were applied across treatment arms because the sample size of the SF-36 data was already too small (n=35 at end of treatment assessment) to support further stratification by response.[5] The progression free state on vismodegib will contain patients who have responded to treatment and have smaller tumours with a probable improvement in HRQoL. This is unlikely to be the case for progression free patients in the BSC arm of the model. Similarly, patients who have progressed after vismodegib treatment may have smaller tumours than those who progress without treatment, hence the delay discussed in comment four. It can be argued that vismodegib treated patients should have higher utilities than BSC patients in each equivalent health state. Roche believes this underestimation is having a significant impact on the results of the economic model. To illustrate this, a scenario analysis has been implemented whereby differential health-state utilities have been applied in the two treatment arms. No evidence exists regarding health-related quality of life in BSC patients. Therefore, Roche applied a factor to the utilities derived from the ERIVANCE SF-36 data and assigned those figures to the BSC health states. Results of this analysis are presented in the results section (and PAS appendix). This exercise is purely academic and has little clinical grounding. The analysis is designed to highlight the sensitivity of the model to this difference in HRQoL. As can be seen from the results, the application of health-state utilities across treatment arms in the original submission is highly conservative. This gain in HRQoL for vismodegib patients is unlikely to be meaningfully diminished by the disutility associated with treatment-related adverse	Comments noted. The committee recognised that the quality-of-life benefits may have been underestimated in the model, but was mindful that in the absence of robust evidence vismodegib's effect on quality of life is uncertain. Please see section 3.12 of the FAD for the committee's full considerations.

Consultee	Comment [sic]	NICE Response
	events (AE) because the overall costs and HRQoL impact associated with AEs can be seen to be negligible in the economic analysis. Utility decrements related to AEs have been applied in the model. These values were taken from a publication by Beusterien *et al.*:[6] • Grade 3 = 1-day in-/outpatient stay for severe toxicity (for 7 days) • Grade 4 = 2 – 5-day hospitalisation for severe toxicity (for 14 days) The assumed AE treatment in our analysis primarily consisted of over the counter medication. Roche believes our analysis overestimates the disutility associated with vismodegib-related AEs. HRQoL data (SF-36) was collected in ERIVANCE and it can be reasonably assumed that AE-related disutility is already implicit in the SF-36 responses. The inclusion of additional disutility values could be seen as "double-counting". Roche, and other HTA bodies,[7,8] recognise that the SF-36 instrument may not be sensitive enough to capture the HRQoL impact in the aBCC population unsuitable for surgery or radiotherapy. Lesions are often visible and close to critical structures in the neck and facial area; a significant impact on self-esteem and social interaction is suggested by clinical experts. These aspects are encompassed in certain domains of the SF-36 but are not a focus of the questionnaire. Similarly following a treatment-response the SF-36 is likely to underestimate the associated HRQoL gain.	
Roche	**<u>Unmet clinical need and suitability of process</u>** Vismodegib has been available to patients in England through the CDF from marketing authorisation in July 2013; if access is not maintained, patients with aBCC inappropriate for radiotherapy or surgery will have extremely limited treatment options. Clinical experience of vismodegib through the Cancer Drugs Fund (CDF) in England, and the ERIVANCE and STEVIE studies has demonstrated clinical utility in a UK population, including important subsets such as those with Gorlin's syndrome. The CDF Panel recognised the demonstrable clinical effect for a medicine unsuitable for NICE processes at that time (vismodegib had not been topic selected). The Panel accepted the Phase II non-comparative ERIVANCE study as a valid study design for the population of patients in question. The Panel scored PFS improvement and noted that for aBCC, OS would	Comments noted. Please see sections 3.1 and 3.2 of the final appraisal determination (FAD) for the committee's considerations on unmet clinical need; section 3.4 on clinical benefit associated with vismodegib, and sections 3.10 and 3.11 on overall survival benefit.

Consultee	Comment [sic]	NICE Response
	be unlikely to be a relevant outcome. The Panel also agreed that as no active systemic treatment would be the likely standard practice in NHS England, vismodegib satisfied the criteria for a degree of unmet need. Data from the post-authorisation safety (STEVIE) study was not available in July 2013; final data analysis and clinical trial report for STEVIE is expected in December 2017. The CDF transition process does not consider the health utilities that would be lost if vismodegib, which has become a standard of care for specialist multidisciplinary skin cancer teams, is decommissioned. Roche disagree with the Committee's view that the clinical benefit associated with vismodegib is uncertain. Clinical experience continues to be documented—a very recent example is the publication by Wong et al which reported clinical utility where orbital exenteration was the only possible surgical course (Plast Reconstr Surg Glob Open 2017; 5:e1424; doi 10.1097/GOX.0000000000001424, published online 24 July 2017). The vismodegib development programme was designed with input from regulators and led to marketing authorisation. A phase 3 programme was not required and therefore clinical data limitations introduce sizable uncertainty in pharmacoeconomic modelling and consequently make it extremely difficult to create a robust case for cost-effectiveness. Vismodegib was introduced in an indication with no previous treatment options to address a high unmet need of a very small patient group with a condition that may rarely contribute to death, making OS benefit difficult to measure. The heterogeneous nature of these disfiguring tumours meaning there is no recognised protocol of best supportive care. Treatment is individualised, defined by patient, tumour, and social characteristics. Roche agrees that the size of the OS benefit associated with vismodegib is uncertain. For the purposes of economic analysis, necessitated by the NICE review, Roche modelled survival benefit using innovative methodology. A survival benefit was predicted by the model but the nature of this exercise does make the magnitude of benefit uncertain (the primary end-point of the pivotal clinical trial (ERIVANCE) was response; survival was a secondary endpoint as it was in the post-license safety study STEVIE).[1,2] The NICE Committee discussed the plausibility of an OS benefit between responders and non-responders in the STEVIE study being true of the	

Consultee	Comment [sic]	NICE Response
	general aBCC population. Clinical advice to Roche and a review of the literature imply that aBCC rarely contributes directly to death. However, although not demonstrated directly in studies, a survival benefit is plausible. Clinical advisers state aBCC may occur in very elderly patients, who present late with extensive physically disfiguring tumours exacerbated by poor physical health, self-care and social isolation. Dramatic tumour responses have been demonstrated - as evidenced in the photo appendix supplied (includes photographs of all patients treated in the ERIVANCE study). Such responses can plausibly lead to an improvement in general health status and reversal of social isolation with a possible morbidity impact. aBCC is rare and patient advocacy is low, both NICE and the AWMSG have been unable to involve patient groups in their decision making. Roche is concerned that the Committee is making a decision, in a situation where all parties acknowledge significant uncertainty, without adequate expert opinion. NICE is considering an evidence base that the technology appraisal process was not specifically designed to address – where the primary outcome of the pivotal clinical trial was response and not survival. Indeed, vismodegib was not topic selected by NICE in 2013.	
NCRI-AC-RCP	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts believe that the NICE ACD is very disappointing. Vismodegib definitely meets an unmet need in patients with locally advanced or metastatic BCCs. Attached is the proof of a publication from Cambridge and Manchester which shows 10/15 patients being able to avoid orbital exenteration following temporary use of vismodegib. The guidance states: `However, all patients will eventually go on to have best supportive care as their disease progresses, and this regimen will be the same irrespective of prior vismodegib treatment.' Our experts argue that this is not necessarily true. Vismodegib can induce long term responses in patients after around 6 months of treatment. Some patients will die of other causes before their disease progresses; some go into long term complete responses. Patients do not have to be treated continuously long term to get benefits.	Comments noted. The committee acknowledged that the length of the delay in re-starting BSC after progression on vismodegib is highly variable in clinical practice. After hearing from the clinical experts and taking into consideration that vismodegib has only been available for 4 years, it concluded that a delay of 3 years in re-starting BSC after vismodegib is most plausible. The committee concluded that although the clinically relevant benefits associated with vismodegib are plausible, the evidence presented was associated with substantial uncertainty. Additionally, the ICERs remained substantially above a level that could be considered a cost-effective use of NHS resources.

Consultee	Comment [sic]	NICE Response
NCRI-AC-RCP	Short term or intermittent treatment with vismodegib would significantly reduce the costs associated with it. Particularly in Gorlin's patients, they can avoid 20-30 operations and procedures a year, and can get long term benefit with intermittent therapy. The statement 'There are also no trials directly comparing vismodegib with best supportive care' is not strictly true; there is a vismodegib vs placebo double blind study in patients with Gorlins (Tang, attached) which showed very high efficacy. tHe Mikie trial also showed that intermittent treatment is effective.	Comment noted. The committee is only able to make a recommendation for vismodegib within its marketing authorisation, which is: 'adult patients with: - symptomatic metastatic basal cell carcinoma - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy'. The recommended dose is 1×150 mg capsule taken once daily. Treatment should be continued until disease progression or unacceptable toxicity.
NCRI-AC-RCP	It would be a significant backward step if vismodegib were to become unavailable. Our experts note that it has transformed many patients' lives, and avoided mutilating surgery for many patients.	Comment noted and was considered by the Appraisal Committee when formulating its recommendations. The committee concluded that although the clinically relevant benefits associated with vismodegib are plausible, the evidence presented was associated with substantial uncertainty. Additionally, the ICERs remained substantially above a level that could be considered a cost-effective use of NHS resources.
Patient	As a patient who used vismodegib for about 30 months I believe it should be available on the NHS. At the time I was diagnosed again with basal cell carcinoma having already been through major surgery and radiotherapy. It was such a relief for an alternative at that stage. It should be made available to every one and also not as a last resort. Please reconsider your outcome. Thank you.	Comments noted. The committee concluded that although the clinically relevant benefits associated with vismodegib are plausible, the evidence presented was associated with substantial uncertainty. Additionally, the ICERs remained substantially above a level that could be considered a cost-effective use of NHS resources.
NHS professional	Because of the constraints of the NICE Appraisal process, we do not believe that the committee have fully appreciated the impact of this novel and innovative treatment on the lives of a small group of patients. The treatment will never be able to demonstrate an improvement in survival, because metastatic BCC is exceedingly rare, and death from	Please see sections 3.2, 3.4 and 3.11 of the final appraisal determination (FAD) for the committee's full considerations on unmet clinical need and overall survival benefit. The committee concluded that although the clinically relevant benefits associated with vismodegib are

Consultee	Comment [sic]	NICE Response
	locally advanced BCC or it's complications are relatively rare (although they do occur). The comparator of best supportive care is misleading; many patients are in fact avoiding life changing and mutilating surgery, for example removal of a nose, eye or ear. The surgery is very expensive and can involve protracted hospital stays. In particular, we have shown in a recent publication that patients can avoid orbital exenteration. It is important that the committee appreciate that this operation involves removing the entire orbit, leaving a large defect ,and patients cannot have a prosthetic eye. The alternative â€˜best supportive careâ€™ is in reality living with a disfiguring, painful, weeping, smelly tumour. Many of these patients, but by no means all, are elderly; the committee need to be confident that there is no element of age discrimination in their decision. Vismodegib is not always used strictly according to the label, a fact which Roche would not be able to present to the committee. The drug is in fact frequently used for short periods of treatment, for example 6 months; patients are not on therapy life-long. Remissions after a few months of treatment can be long lasting; and the drug can be stopped and potentially used again for a short period when the cancer recurs. This approach is both better palliation for the patient in terms of side effects, and more cost effective. It is also useful in patients with advanced Gorlin syndrome who may otherwise be having 30 plus procedures per year. The Mikie study (Rogers G et al, proc ASCO 2016) provides good data on this, as does the randomised trial of vismodegib vs placebo (Tang Y et al, NEJM 2012;366:2180-2). Pictures can speak louder than words; we would be delighted to present some case histories to the NICE committee of patients who have benefitted from vismodegib. We believe that making this breakthrough drug unavailable on the NHS would be a retrograde step; it fulfils a unique role in cancer management.	plausible, the evidence presented was associated with substantial uncertainty. Additionally, the ICERs remained substantially above a level that could be considered a cost-effective use of NHS resources. The committee is only able to make a recommendation for vismodegib within its marketing authorisation.

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 10 August 2017 **email:** jenna.dilkes@nice.org.uk / NICE DOCS

Dear Jenna,

Many thanks for providing the opportunity to comment on the above ACD.

Whilst we are disappointed with the decision reached we are fully cognisant of the fact that any comparison of vismodegib to a best supportive care (BSC) regimen is extremely challenging and highly uncertain. This is primarily due to the absence of evidence on the relative effectiveness of vismodegib versus BSC in the population of interest (adults with advanced basal cell carcinoma (aBCC)).

Roche has provided formal comments on the ACD in the table below. Several of these issues centre on the committees preferred assumptions in the cost-effectiveness analysis, namely: the choice of time to treatment discontinuation (TTD) extrapolation function and the intensity of the post-progression BSC regimen received by patients who were originally treated with vismodegib. As part of the discussion around these assumptions, revised base case results and additional scenario analyses have been provided in the appendices of this document. Remaining comments focus on issues that we believe are not being accurately quantified under the rigours of this appraisal process.

In addition to the comments in the table, an increased patient access scheme (PAS) discount of [redacted] has also been agreed with the Department of Health. As such, revised base case results and budget impact figures have been provided in a confidential PAS appendix, which has been submitted separately to this document.

Roche's preferred base case assumptions include the use of the Weibull function in the extrapolation of TTD data, and also a six-year delay period before receiving an equivalent BSC regimen following vismodegib-progression. When the updated PAS discount is also applied, a revised base case ICER of [redacted] is generated.

Patients with aBCC, unsuitable for surgery or radiotherapy have no other treatment options other than best supportive care. Clinical experience of vismodegib through the CDF, the ERIVANCE, and the STEVIE study has demonstrated sizable clinical utility in a UK population. In light of the evidence below, Roche would ask the committee to reconsider its list of preferred assumptions and re-evaluate its overall decision on the reimbursement of vismodegib.

If any further information is required we would be happy to provide it in order to aid the Committee's decision making.

Kind regards

Tom Loughran

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 10 August 2017 **email:** jenna.dilkes@nice.org.uk / NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Roche Products Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Tom Loughran *Health Economist at Roche Products Ltd.*

Please return to: **jenna.dilkes@nice.org.uk** / NICE DOCS

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 10 August 2017 **email:** jenna.dilkes@nice.org.uk / NICE DOCS

Comment number	Comments
1	**Justification of the Landmark analysis** Vismodegib received conditional marketing authorisation in 2013 on the basis of the phase II, single arm ERIVANCE (NCT00833417) study.[1] A control group was not used, given there was no accepted standard of care and no data suggesting spontaneous responses in advanced BCC. Full marketing authorisation was gained with data from the ongoing STEVIE (NCT01367665) study (primary objective: safety assessment).[2] Data from the STEVIE study was used in the landmark analysis and comparator data needed to be generated. Economic and clinical experts were consulted and possible approaches were suggested: the construction of a match-adjusted indirect comparison (MAIC); and the use of a relative treatment effect from a published vismodegib randomised controlled trial (RCT) in a different but related therapeutic setting.q MAIC would involve sourcing and using data for patients with aBCC who have received BSC only. Overall survival (OS) and progression-free survival (PFS) data from published observational literature, disease registries, or clinical studies are required. The aim would be to combine this data on overlapping comparator groups and use multiple direct and indirect comparisons to build a network meta-analysis that summarises comparative evidence for all treatments in the therapeutic area. This approach is advantageous as it addresses the lack of comparator data by allowing the assessment of relative efficacy across comparable patient groups. Overall survival (OS) and progression-free survival (PFS) data from published observational literature, disease registries, or clinical studies are required. Roche considered the RONNIE (NCT02100111) study which includes aBCC patients receiving supportive or palliative care. However, only 8 of the 121 eligible patients in RONNIE received palliative/supportive care as their first therapy option and this sample size is not large enough to power a MAIC; secondly, the type of supportive care received points to an end-of-life setting, which is not representative of the supportive care that patients eligible for the STEVIE study would receive. A MAIC was deemed unfeasible.[3] Consulted experts also suggested using relative treatment effect from a published vismodegib RCT. In 2012, a study was published by Tang et al. reporting vismodegib in Gorlin's syndrome.[4] From September 2009 through January 2011, 42 patients were enroled at three clinical centres. Patients were randomly assigned to receive either vismodegib or placebo for a planned duration of 18 months. Disease burden differs between patients with Gorlin's syndrome and those with aBCC; best supportive care is likely to differ significantly.[4] This modelling strategy was not adopted as Roche was unable to gain access to the complete dataset and suitability could not be assessed. After discussion with experts, a landmark analysis was believed to be the most methodologically robust option. Stakeholders, including the evidence review group

	(ERG) have not suggested alternative methodology to date. Further information on data limitations and methodological rationale refer to page 280 of the Committee Papers for this appraisal: https://www.nice.org.uk/guidance/gid-ta10090/documents/committee-papers.
2	**Selection of Landmark point** The submitted landmark analysis included 6 months and 3 months as the base case and scenario analyses, respectively; additional time-points were not evaluated. The Committee stated that further exploration around the landmark would have increased its confidence in the overall analysis. Roche and the ERG agreed that the 3-month landmark was inappropriate as it is too close to the median time to first response of (2.76 months) and is less than the mean (3.40 months) for the combined aBCC population.[5] A 3-month landmark (or shorter) is likely to misclassify a large proportion of subsequent responders as non-responders and thus overestimate the efficacy for non-responders. The 3-month landmark was included as a conservative scenario to explore general sensitivity around the parameter. Time-points between 3 and 6 months may have been appropriate to explore but did not align with the assessment schedule in the STEVIE study and data was therefore not available. It is reasonable to assume that a 4-month landmark would be no more robust than a 3-month landmark. The results of 4- or 5-month landmarks can be assumed to lie between the 3- and 6-month results reported. Landmarks beyond 6-months were not explored because the majority of patients in the non-responder group would have progressed or died by this point; leading to a higher number of exclusions, a lower number of patients in the final analysis and hence a less robust analysis.
3	**Extrapolation of time to treatment discontinuation (TTD)** Roche submitted the Weibull function believing it to be the most appropriate TTD extrapolation choice. The ERG disagreed and preferred the log-logistic function. This issue was not discussed in open Committee on 28Jun2017 and Roche did not have the opportunity to support its choice. Akaike information criterion (AIC) values influenced the ERG's selection of the log-logistic distribution. An AIC value is designed to show how well a parametric function fits to the Kaplan-Meier (KM) data, relative to the other functions in question – the AIC value says nothing of the appropriateness of the extrapolation beyond the KM data. The STEVIE KM data accounts for a very small proportion of the overall time horizon of the model and therefore Roche believes the AIC values should not be over-interpreted.[5] The ERG argues that the Weibull function proves to be a worse fit than the log-logistic when visually inspecting the curves despite the KM data accounting for approximately 13% of the model time horizon. Roche feels the closeness of the fit

	should not be over-interpreted as it does not address the appropriateness of the overall extrapolation beyond the observed KM data. Roche would also argue that the difference in fit between the Weibull and the log-logistic throughout the observed time period is negligible—the difference in proportion of patients still on treatment in the Weibull and log-logistic curves remains <5% for 40 months. The submitted model includes the facility to use KM data for the observed period and then use a parametric extrapolation for the remainder of the time horizon. Data artefacts result in the TTD curves crossing the PFS curves when certain parametric extrapolations are used, implying that patients continue treatment after progressing (off-protocol). To address this, Roche artificially capped the TTD curve to ensure it was unable to exceed the PFS curve i.e. for a period of time, patients only discontinue treatment as a result of either progression or death and not adverse events. If using the log-logistic curve to model TTD, the curve must be capped (to prevent exceeding PFS) from year 5 to year 8. This implies that from year 5 onwards, the 7% of patients left on treatment are only able to discontinue due to progression or death. This is clinically implausible. Using the Weibull extrapolation results in all patients having discontinued before the TTD curve exceeds PFS, and no artificial capping is required. The appendices report updated cost-effectiveness results, in which both distributions discussed here are used. For further information and graphical illustration of these issues, please refer to page 272 of the committee papers for this appraisal: https://www.nice.org.uk/guidance/gid-ta10090/documents/committee-papers
4	**Intensity of the post-progression BSC regimen in the economic analysis** The ERG and the committee feel that the majority of patients will eventually receive the same post-progression BSC regimen, regardless of whether or not they were treated with vismodegib. Clinical experience and trial data (see ERIVANCE photo appendix) demonstrate that vismodegib reduces tumour burden in the majority of patients (in some cases visual improvement is seen in patients not meeting study defined response). Expert opinion is that patients who receive vismodegib can expect a delay before having the same BSC requirements as a patient who is not treated. The ERG suggested 6-months as a plausible delay and this was discussed by the Committee. The clinical expert in attendance on 28Jun2017 stated that this delay could be significantly longer (6-10 years) reflecting the views of clinical advisors to Roche that long term responses to vismodegib are seen in clinical practice. The intensity of BSC is highly variable. Roche feels this issue was not explored sufficiently by the Committee and the decision to adopt the highly conservative ERG estimate was not scrutinised adequately by clinical experts and patient groups. Given the uncertainty around this parameter, Roche feels it inappropriate to suggest an alternative point estimate. Instead, scenario analysis has been conducted and

	the results are presented in the appendices of this document.
5	**Underestimation of health-related quality of life (HRQoL) in the economic analysis** The Committee note and Roche recognises that the economic analysis underestimates the true HRQoL impact of aBCC and treatment. The model applies health-state utilities across treatment arms and is likely to underestimate the HRQoL benefit associated with vismodegib therapy—assuming that: HRQoL in 'PFS on vismodegib' is equal to HRQoL in 'PFS on BSC'; and that 'Progressive disease (PD) after vismodegib' has the same utility associated as 'PD after BSC'. Utilities were applied across treatment arms because the sample size of the SF-36 data was already too small (n=35 at end of treatment assessment) to support further stratification by response.[5] The progression free state on vismodegib will contain patients who have responded to treatment and have smaller tumours with a probable improvement in HRQoL. This is unlikely to be the case for progression free patients in the BSC arm of the model. Similarly, patients who have progressed after vismodegib treatment may have smaller tumours than those who progress without treatment, hence the delay discussed in comment four. It can be argued that vismodegib treated patients should have higher utilities than BSC patients in each equivalent health state. Roche believes this underestimation is having a significant impact on the results of the economic model. To illustrate this, a scenario analysis has been implemented whereby differential health-state utilities have been applied in the two treatment arms. No evidence exists regarding health-related quality of life in BSC patients. Therefore, Roche applied a factor to the utilities derived from the ERIVANCE SF-36 data and assigned those figures to the BSC health states. Results of this analysis are presented in the results section (and PAS appendix). This exercise is purely academic and has little clinical grounding. The analysis is designed to highlight the sensitivity of the model to this difference in HRQoL. As can be seen from the results, the application of health-state utilities across treatment arms in the original submission is highly conservative. This gain in HRQoL for vismodegib patients is unlikely to be meaningfully diminished by the disutility associated with treatment-related adverse events (AE) because the overall costs and HRQoL impact associated with AEs can be seen to be negligible in the economic analysis. Utility decrements related to AEs have been applied in the model. These values were taken from a publication by Beusterien *et al.*:[6] • Grade 3 = 1-day in-/outpatient stay for severe toxicity (for 7 days) • Grade 4 = 2 – 5-day hospitalisation for severe toxicity (for 14 days) The assumed AE treatment in our analysis primarily consisted of over the counter

	medication. Roche believes our analysis overestimates the disutility associated with vismodegib-related AEs. HRQoL data (SF-36) was collected in ERIVANCE and it can be reasonably assumed that AE-related disutility is already implicit in the SF-36 responses. The inclusion of additional disutility values could be seen as "double-counting". Roche, and other HTA bodies,[7,8] recognise that the SF-36 instrument may not be sensitive enough to capture the HRQoL impact in the aBCC population unsuitable for surgery or radiotherapy. Lesions are often visible and close to critical structures in the neck and facial area; a significant impact on self-esteem and social interaction is suggested by clinical experts. These aspects are encompassed in certain domains of the SF-36 but are not a focus of the questionnaire. Similarly following a treatment-response the SF-36 is likely to underestimate the associated HRQoL gain.
6	**Unmet clinical need and suitability of process** Vismodegib has been available to patients in England through the CDF from marketing authorisation in July 2013; if access is not maintained, patients with aBCC inappropriate for radiotherapy or surgery will have extremely limited treatment options. Clinical experience of vismodegib through the Cancer Drugs Fund (CDF) in England, and the ERIVANCE and STEVIE studies has demonstrated clinical utility in a UK population, including important subsets such as those with Gorlin's syndrome. The CDF Panel recognised the demonstrable clinical effect for a medicine unsuitable for NICE processes at that time (vismodegib had not been topic selected). The Panel accepted the Phase II non-comparative ERIVANCE study as a valid study design for the population of patients in question. The Panel scored PFS improvement and noted that for aBCC, OS would be unlikely to be a relevant outcome. The Panel also agreed that as no active systemic treatment would be the likely standard practice in NHS England, vismodegib satisfied the criteria for a degree of unmet need. Data from the post-authorisation safety (STEVIE) study was not available in July 2013; final data analysis and clinical trial report for STEVIE is expected in December 2017. The CDF transition process does not consider the health utilities that would be lost if vismodegib, which has become a standard of care for specialist multidisciplinary skin cancer teams, is decommissioned. Roche disagree with the Committee's view that the clinical benefit associated with vismodegib is uncertain. Clinical experience continues to be documented—a very recent example is the publication by Wong et al which reported clinical utility where orbital exenteration was the only possible surgical course (Plast Reconstr Surg Glob Open 2017; 5:e1424; doi 10.1097/GOX.0000000000001424, published online 24 July 2017). The vismodegib development programme was designed with input from regulators and led to marketing authorisation. A phase 3 programme was not required and therefore clinical data limitations introduce sizable uncertainty in pharmacoeconomic modelling and consequently make it extremely difficult to create a robust case for

	cost-effectiveness. Vismodegib was introduced in an indication with no previous treatment options to address a high unmet need of a very small patient group with a condition that may rarely contribute to death, making OS benefit difficult to measure. The heterogeneous nature of these disfiguring tumours meaning there is no recognised protocol of best supportive care. Treatment is individualised, defined by patient, tumour, and social characteristics. Roche agrees that the size of the OS benefit associated with vismodegib is uncertain. For the purposes of economic analysis, necessitated by the NICE review, Roche modelled survival benefit using innovative methodology. A survival benefit was predicted by the model but the nature of this exercise does make the magnitude of benefit uncertain (the primary end-point of the pivotal clinical trial (ERIVANCE) was response; survival was a secondary endpoint as it was in the post-license safety study STEVIE).[1,2] The NICE Committee discussed the plausibility of an OS benefit between responders and non-responders in the STEVIE study being true of the general aBCC population. Clinical advice to Roche and a review of the literature imply that aBCC rarely contributes directly to death. However, although not demonstrated directly in studies, a survival benefit is plausible. Clinical advisers state aBCC may occur in very elderly patients, who present late with extensive physically disfiguring tumours exacerbated by poor physical health, self-care and social isolation. Dramatic tumour responses have been demonstrated - as evidenced in the photo appendix supplied (includes photographs of all patients treated in the ERIVANCE study). Such responses can plausibly lead to an improvement in general health status and reversal of social isolation with a possible morbidity impact. aBCC is rare and patient advocacy is low, both NICE and the AWMSG have been unable to involve patient groups in their decision making. Roche is concerned that the Committee is making a decision, in a situation where all parties acknowledge significant uncertainty, without adequate expert opinion. NICE is considering an evidence base that the technology appraisal process was not specifically designed to address – where the primary outcome of the pivotal clinical trial was response and not survival. Indeed, vismodegib was not topic selected by NICE in 2013.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See

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the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

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Cost-effectiveness results

As part of Roche's response to this ACD, updated results and scenario analyses have been provided in the following subsections. The majority of results presented here have been generated without the updated PAS applied. Results with the new PAS ([redacted]) applied are provided in the confidential PAS appendix that has been separately submitted as part of this response.

ERG's preferred results

The ICERs generated using the assumptions preferred by the ERG (and the committee) are reported in Table 1, Table 2, and Table 3, below:

Table 1 ERG's preferred ICERs - No PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	£101,538	1.25	0.95	£106,810
Vismodegib	£192,264	10.54	8.11				

Table 2 ERG's preferred ICERs - Original PAS ([redacted]) applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Table 3 ERG's preferred ICERs - Updated PAS ([redacted]) applied

-	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

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Roche assumptions

In accordance with the comments in the table above, Roche accepts the ERG's preferred base case assumptions, with the exception of the following:

1. **The use of the log-logistic parametric extrapolation as opposed to the Weibull**
2. **Assuming that vismodegib patients move to BSC six months after progression**

The following subsections report the corresponding results relating to these issues.

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

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TTD extrapolation choice

As documented in comment 3, Roche disagrees with the ERGs choice of TTD extrapolation function. While the committee argues that a log-logistic function should have been used in the base case analysis, Roche maintains that the Weibull extrapolation was the most appropriate choice.
Table 4 and Table 5 below report the economic results when using the log-logistic extrapolation (ERG and Committee) and the Weibull (Roche) extrapolation, respectively.

Table 4 Results generated using Log-logistic TTD extrapolation - No PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	£101,538	1.25	0.95	£106,810
Vismodegib	£192,264	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

Table 5 Results generated using Weibull TTD extrapolation - No PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	£91,845	1.25	0.95	£96,611
Vismodegib	£182,572	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

Assuming that vismodegib patients move to BSC six months after progression

As per comment 4 above, Roche believes that a six month delay period is extremely conservative and not reflective of the entire evidence base available. However, Roche acknowledges that this parameter is highly uncertain and has therefore undertaken sensitivity analysis. The resulting ICERs are presented below.

Table 6 Scenario analysis results - BSC delay – No PAS applied

Months	ICER (Log-logistic TTD extrapolation)	ICER (Weibull TTD extrapolation)
0	£109,120	£98,921
6	£106,810	£96,611
12	£104,593	£94,394
24	£100,413	£90,214
36	£96,548	£86,349
48	£92,983	£82,785
60	£89,683	£79,485
72	£86,557	£76,359
84	£83,691	£73,493
96	£81,004	£70,806
108	£78,484	£68,286
120	£76,121	£65,923

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.

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Application of differential health-state utilities across the two treatment arms

As discussed in comment 5, Roche undertook scenario analysis in which differential health-state utilities were applied in the vismodegib and BSC treatment arms. The utilities corresponding to the BSC health states were derived by multiplying the SF-36 utilities by a user-modifiable factor. Results of this analysis are presented below.

Table 7 Application of differential health-state utilities across vismodegib and BSC arms - No PAS applied

Factor applied to SF-36 vismodegib utilities	ICER (Log-logistic TTD extrapolation)	ICER (Weibull TTD extrapolation)
1.0	£106,810	£96,611
0.95	£77,585	£70,177
0.90	£60,917	£55,101
0.85	£50,144	£45,357
0.80	£42,609	£38,541
0.75	£37,043	£33,506

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.

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Revised base case

Based on the assumptions preferred by the ERG and the evidence highlighted in the committee meeting, Roche has developed a revised base case.

As mentioned at the beginning of this results section, Roche accepts many of the assumptions stipulated in the ERG's preferred base case. However, Roche maintains that the most appropriate choice of TTD extrapolation function is the Weibull.

In addition, we disagree with the ERG's choice of a six month delay period before patients receive an equivalent BSC regimen following vismodegib progression. The clinical expert present at the first committee meeting reported that patients could expect to receive a reduced BSC regimen for up to 6-10 years in some cases. As such, we have produced revised base case result using a six year delay period. It should also be noted that this value could be considered conservative and in some cases may even be higher.

Finally, it has been documented by both the ERG and Roche that the original economic analysis underestimated the HRQoL impact associated with vismodegib therapy. Hence the scenario analysis in which differential health-state utilities are applied across the vismodegib and BSC treatment arms. However, there is no clinical evidence to support the use of a specific factor value by which to derive the BSC health-state utilities. The scenario analysis was purely an academic exercise to illustrate the sensitivity of the model to this parameter, and portray the conservative impact that this underestimation of HRQoL had on the initial cost-effectiveness results. Therefore the revised base case results have been generated using a factor of 1 (i.e. we have assumed equal health-state utilities in both treatment arms). Nevertheless, Roche would ask the committee to remain conscious of the underestimation of HRQoL impact even in these revised results.

The assumptions that differ in Roche's revised base case, compared to the ERG's, are reported below.

- Use of the Weibull function as opposed to the log-logistic in the extrapolation of TTD
- A 6 year delay period before receiving an equivalent BSC regimen following vismodegib progression

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Table 8 Roche's revised base case results - No PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	£72,592	1.25	0.95	£76,359
Vismodegib	£163,318	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

Table 9 Roche's revised base case results - PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

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Confidential Appendix. With-PAS results

[redacted]

Appendix 1: Confidential patient access scheme appendix

ERG's preferred results

The ICERs generated using the assumptions preferred by the ERG are reported in **Error! Reference source not found.** and below.

[redacted]

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

[redacted]

-	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

TTD extrapolation choice

[redacted]

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

[redacted]

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, Quality adjusted life years.

Assuming that vismodegib patients move to BSC six months after progression

[redacted]

Months	ICER (Log-logistic TTD extrapolation)	ICER (Weibull TTD extrapolation)
0	[redacted]	[redacted]
6	[redacted]	[redacted]
12	[redacted]	[redacted]
24	[redacted]	[redacted]
36	[redacted]	[redacted]
48	[redacted]	[redacted]
60	[redacted]	[redacted]
72	[redacted]	[redacted]
84	[redacted]	[redacted]
96	[redacted]	[redacted]
108	[redacted]	[redacted]
120	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.

Application of differential health-state utilities across the two treatment arms

[redacted]

Factor applied to SF-36 vismodegib utilities	ICER (Log-logistic TTD extrapolation)	ICER (Weibull TTD extrapolation)
1.0	[redacted]	[redacted]
0.95	[redacted]	[redacted]
0.90	[redacted]	[redacted]
0.85	[redacted]	[redacted]
0.80	[redacted]	[redacted]
0.75	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.

[redacted]

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
	2018	2019	2020	2021	2022	2023
Total eligible patients (England and Wales)	426	438	451	464	477	489
Market uptake	35%	35%	35%	35%	35%	35%
Vismodegib treated patients	155	159	164	168	173	178
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 10 August 2017 **email:** jenna.dilkes@nice.org.uk / NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **jenna.dilkes@nice.org.uk** / NICE DOCS

Vismodegib for treating basal cell carcinoma

NICE National Institute for Health and Care Excellence

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
2	Our experts believe that the NICE ACD is very disappointing. Vismodegib definitely meets an unmet need in patients with locally advanced or metastatic BCCs. Attached is the proof of a publication from Cambridge and Manchester which shows 10/15 patients being able to avoid orbital exenteration following temporary use of vismodegib. The guidance states: `However, all patients will eventually go on to have best supportive care as their disease progresses, and this regimen will be the same irrespective of prior vismodegib treatment.' Our experts argue that this is not necessarily true. Vismodegib can induce long term responses in patients after around 6 months of treatment. Some patients will die of other causes before their disease progresses; some go into long term complete responses. Patients do not have to be treated continuously long term to get benefits. Short term or intermittent treatment with vismodegib would significantly reduce the costs associated with it. Particularly in Gorlin's patients, they can avoid 20-30 operations and procedures a year, and can get long term benefit with intermittent therapy. The statement 'There are also no trials directly comparing vismodegib with best supportive care' is not strictly true; there is a vismodegib vs placebo double blind study in patients with Gorlins (Tang, attached) which showed very high efficacy. tHe Mikie trial also showed that intermittent treatment is effective. It would be a significant backward step if vismodegib were to become unavailable. Our experts note that it has transformed many patients' lives, and avoided mutilating surgery for many patients.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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Vismodegib for treating basal cell carcinoma

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- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Question to clinical experts:

Please could you help clarify what is the general time frame in clinical practice for people who have progressed on vismodegib to move from a monitoring regimen (lighter BSC) to the same full BSC regimen as patients who have progressed and not received vismodegib? Is there any evidence available for this?

Prof Plummer:
So we are trying to predict how quickly an advanced BCC which has responded to visomdegib but then become resistant (as they do appear to) would re-grow and therefore need more intense BSC as if it had not responded in the first place

In my clinical experience recurrence will occur, but it does seem to have the same slow natural history as the original BCC – very unlike BRAF mutant melanoma becoming resistant to drugs where progression is rapid.

So if a patient has responded well but has residual tumour which starts to progress it is usually many months before they are facing the advanced stage again. 6 months, as suggested below, would be unusually short, and I would expect this to be approaching 1-2 years at least – as these are elderly patients many will not get into significant problems again in their life time

With a good response and a slow growing tumour it could be 6-10 years, my struggle with using this as a bench mark is we have no data as the drug has not been around long enough for many patients to have reached this point.

As ever the problem is there is great variation in the degree of response, what we do know is that growth is slow with these tumours, so there is a good symptomatic control duration of benefit with slow progression. And for multiple years in some patients

Dr Lear:
Tricky one as all the patients are so different, don't think there is that much hard data on this, to my mind the question you are asking is: when do the patients return to the pre vismo treatment baseline levels of size of lesion, ulceration, pain, bleeding, effect on quality of life, etc following cessation of vismo. BCC is generally a slow growing tumour and we know that the lesions have often been present for many years (indeed decades) before they are labelled as locally advanced and are considered for vismo therapy. It follows therefore, and I see in my clinical practice, that it can take a considerable amount of time for the lesions to get back to where they were after treatment, with many of my patients taking years rather than months to get back to the baseline. In my experience, it takes a lot longer than 6 months, ie the patients get the benefit for a considerable amount of time after stopping, certainly much longer than 6 months. There are of course some exceptions with occasional aggressive tumours but they are unusual, <10% of the population.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	CONSULTANT CLINICAL ONCOLOGIST
Organisation	Anglia Skin Cancer Network (Cambridge, Norwich and Ipswich)
Location	England
Conflict	No
Notes	[redacted] HAVE RECEIVED HONORARIA FOR ADVISORY BOARDS AND SPEAKER FEES FROM ROCHE. [redacted] has also received honoraria from other pharma companies for research costs, advisory boards, speaker fees and travel assistance.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We are a consultant oncologists, plastic surgeons and dermatologists from the Anglian Cancer Network. In the Anglian region we have treated over 60 patients since 2012, including 19 in the STEVIE trial and have very wide experience of vismodegib. Because of the constraints of the NICE Appraisal process, we do not believe that the committee have fully appreciated the impact of this novel and innovative treatment on the lives of a small group of patients. The treatment will never be able to demonstrate an improvement in survival, because metastatic BCC is exceedingly rare, and death from locally advanced BCC or it's complications are relatively rare (although they do occur). The comparator of best supportive care is misleading; many patients are in fact avoiding life changing and mutilating surgery, for example removal of a nose, eye or ear. The surgery is very expensive and can involve protracted hospital stays. In particular, we have shown in a recent publication that patients can avoid orbital exenteration. It is important that the committee appreciate that this operation involves removing the entire orbit, leaving a large defect ,and patients cannot have a prosthetic eye. The alternative â€˜best supportive careâ€™ is in reality living with a disfiguring, painful, weeping, smelly tumour. Many of these patients, but by no means all, are elderly; the committee need to be confident that there is no element of age discrimination in their decision. Vismodegib is not always used strictly according to the label, a fact which Roche would not be able to present to the committee.

	The drug is in fact frequently used for short periods of treatment, for example 6 months; patients are not on therapy life-long. Remissions after a few months of treatment can be long lasting; and the drug can be stopped and potentially used again for a short period when the cancer recurs. This approach is both better palliation for the patient in terms of side effects, and more cost effective. It is also useful in patients with advanced Gorlin syndrome who may otherwise be having 30 plus procedures per year. The Mikie study (Rogers G et al, proc ASCO 2016) provides good data on this, as does the randomised trial of vismodegib vs placebo (Tang Y et al, NEJM 2012;366:2180-2). Pictures can speak louder than words; we would be delighted to present some case histories to the NICE committee of patients who have benefitted from vismodegib. We believe that making this breakthrough drug unavailable on the NHS would be a retrograde step; it fulfils a unique role in cancer management. ref: Vismodegib for locally advanced periocular and orbital basal cell carcinoma: A review of 15 consecutive cases KY Wong, K Fife, JT Lear, RD Price, AJ Durrani Plastic and Reconstructive Surgery Open Access 2017;5:e1424
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a patient who used vismodegib for about 30 months I believe it should be available on the NHS. At the time I was diagnosed again with basal cell carcinoma having already been through major surgery and radiotherapy. It was such a relief for an alternative at that stage. It should be made available to every one and also not as a last resort. Please reconsider your outcome. Thank you.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Vismodegib for treating basal cell carcinoma

ERG critique on company's reply to the first Appraisal Committee Document

This report was commissioned by the NIHR HTA Programme as project number 16/51/16

BMJ Technology Assessment Group

1 SUMMARY

The company has provided comments on the Appraisal Consultation Document (ACD) resulting from the first Appraisal Committee Meeting (ACM) on 28 June 2017. This document summarises the ERG's critique on the company's comments (Section 3) and highlights some of the issues previously raised by the ERG, which remain relevant for this appraisal and have not been mitigated by the company's reply to the ACD (Section 2).

As part of their response to the ACD, the company also submitted an updated economic model in Microsoft Excel® to assess the cost-effectiveness of vismodegib in comparison with BSC. The ERG reports the results of the company's updated analysis (Section 4) and provides the results of the additional analysis undertaken by the ERG (Section 5).

2 ISSUES PREVIOUSLY RAISED BY THE ERG

2.1 Clinical

The main clinical issues previously raised by the ERG are listed below:

- A key limitation of the submission is the lack of direct randomised evidence comparing vismodegib versus BSC. The ERG's preference would have been for a comparative RCT with standard care defined as physician's choice. The number of patients recruited to STEVIE suggest that sample size would be unlikely to be prohibitive.

- The ERG notes that there are no data on the long-term safety and efficacy of vismodegib, data on OS in laBCC are immature and data on mBCC are based on small patient numbers (96 patients in STEVIE and 33 patients in ERIVANCE).

- The ERG has concerns around the generalisability of ERIVANCE and STEVIE to the UK population most likely to be eligible for treatment with vismodegib as limited information was provided on the location of the patients enrolled. The ERG also considers a high proportion of patients in both studies had Gorlin syndrome, the ERIVANCE study had a lower median age than expected in UK patients and there was no information on subsequent treatments received following study drug discontinuation.

- Based on guidance from the FDA, the ERG is concerned that single-arm studies shouldn't be used for capturing time-to-event data such as OS and PFS. In addition, the ERG considers that OS data in the landmark analysis are likely confounded by the use of subsequent treatment,

although no data on subsequent treatments were recorded as part of either ERIVANCE or STEVIE.

- The ERG notes that there were high levels of AEs in ERIVANCE and STEVIE (100% and 98% of patients, respectively). In addition, compared with background mortality in the general population there appears to be an increase in mortality in STEVIE, which has not been explained by the company. While this may be due to unaccounted for comorbidities in the STEVIE population and differences in the life expectancy of patients from some of the countries from which patients were enrolled, the ERG cannot rule out the possibility that vismodegib may increase mortality in laBCC patients.

- The ERG has concerns around the validity of the methods used by the company to carry out the landmark analysis that was used to estimate the clinical effectiveness of vismodegib non-responders versus vismodegib responders. In particular, the ERG is concerned that important covariates may have been omitted from the landmark analysis due to the non-systematic approach taken by the company and the limited number of covariates included. The ERG considers that results of the landmark analysis should be interpreted with caution because they are associated with an extremely high degree of uncertainty and they are based on non-randomised data which is at a high risk of bias.

- The company's assumption that PH holds in the analysis is also likely to introduce further uncertainty in the results, particularly for OS data. For laBCC patients, the only statistically significant HR resulting from the landmark analysis is for OS. The fact that the OS HR for laBCC is statistically significant in favour of vismodegib and the fact that the PFS HR for laBCC is not statistically significant needs to be caveated by the uncertainty in the HR introduced by the methods used to estimate clinical effectiveness. It is difficult to anticipate the direction and the extent of the methodological uncertainty associated with the estimation of the HRs for PFS and OS.

- The results for mBCC from the landmark analysis are based on small patient numbers (<100 patients) and thus the evidence base is extremely limited for drawing any conclusions relating to vismodegib in mBCC.

- The ERG does not consider the Gorlin syndrome subgroup to have been addressed adequately in the CS. The ERG notes that Gorlin syndrome patients in STEVIE differed from the non-Gorlin syndrome patients in key prognostic factors, having a lower median age, a more favourable ECOG performance status and higher median number of target lesions. The Gorlin

subgroup results from the landmark analysis are not however, adjusted for differences in baseline characteristics.

2.2 Economic

The ERG discusses below the particularities of the STA and its outstanding issues following from the first ACM in more detail:

- To obtain survival curves for BSC, the HRs derived from the landmark approach were applied to the estimated vismodegib PFS and OS survival curves. The company's base case model assumes that the PH assumption holds for the responders compared with non-responders in STEVIE. Considering the methodological approach undertaken to estimate relative treatment effectiveness (i.e. recreating two treatment groups from a single arm study) and the extremely small number of patients in the mBCC analysis, it is difficult to evaluate if the assessment of PH could produce meaningful results in this case. With regards to laBCC patients, the conclusion that PH does not seem to hold for OS at a 6-month landmark is based on a more robust sample size, nonetheless the assessment suffers from the same underlying study design issue. The ERG concludes that there is too much uncertainty related with the analysis of relative effectiveness, which, in turn, adds substantial uncertainty to the final ICERs.

- The company decided to include age and ECOG as covariates in the estimation of the landmark HRs. During the clarification process, the company indicated that the approach taken to select covariates for the analysis was not systematic and that no other prognostic factors were tested for OS and PFS outcomes. The ERG is concerned with the potentially flawed selection process of prognostic factors to be included as covariates in the estimation of the HRs. A systematic approach to selecting covariates should have been taken to avoid the introduction of selection bias in the analysis and ensure that all relevant and statistically significant prognostic factors were captured. Clinical experts advising the ERG noted that other baseline characteristics are likely to be relevant prognostic factors, such as Gorlin syndrome, nerve infiltration and BCC location (i.e. head, neck, etc.).

- The ERG has some concerns regarding the estimation of TTD curves in the laBCC and mBCC vismodegib models. These are discussed in Section 3.1 of this report.

- The ERG agrees with the company's assessment regarding the lack of mature OS data. The OS KM curve for laBCC patients shows that 16% of patients had died at the end of the 44-month follow-up period, while 25% of mBCC patients had died at the end of the 38-month follow-up

period in STEVIE. Therefore, the curve fitting and extrapolation exercises using these data will carry a high degree of uncertainty. With regards to laBCC related mortality, the clinical experts advising the ERG reported that they would expect the OS curve for vismodegib to be closer (if not the same) to the age and gender matched background survival curve for the average UK population. Clinical experts stated that patients are highly unlikely to die from laBCC, as acknowledged by the company several times in the CS and reinforced by the clinical expert attending the ACM. The CS did not provide any rationale for why laBCC death events in STEVIE were considerably higher than those observed for the age and gender-matched average UK population. It is therefore difficult to understand the extent to which the company's analysis is generalizable to laBCC patients in the UK. During the ACM, the committee noted that although vismodegib was unlikely to have a direct impact on survival for laBCC, it could not rule out survival benefits altogether.

With regards to mBCC-related mortality, the ERG's view is consistent with that of the Economic Guidance Panel (EGP) in Canadian Health Technology Assessment (HTA) body, which considered that mBCC patients were expected to survive for less than 10 years. During the ACM, the committee agreed that mortality with mBCC was underestimated by the assumption in the model that people with mBCC would survive for more than 10 years.

- The quality of life data incorporated in the model is discussed in Section 3.2. of this report.
- The ERG's concerns surrounding the company's assumptions for estimating disease management costs are discussed in Section 3.3.

Overall, it is the ERG's opinion that the lack of comparative data allied to the methods used to estimate the relative treatment effectiveness of vismodegib compared with BSC, makes it impossible to mitigate the uncertainty related to the existence of a potential benefit of vismodegib from a clinical and economical point of view.

3 SPECIFIC COMMENTS RAISED BY THE COMPANY

3.1 Time to treatment discontinuation

Originally, the ERG disagreed with the company's approach to modelling time to treatment discontinuation (TTD) in the economic analysis with a Weibull distribution. The ERG considered that there was no robust evidence to suggest using a Weibull over a log-logistic distribution to estimate TTD in the model given that the log-logistic curve provides a better fit to the KM data and that the use of the

Weibull curve brings no benefits to the modelling exercise. Therefore, the ERG provided alternative analyses using a log-logistic, instated of a Weibull distribution, to model TTD in the economic analysis.

The company states that the Weibull and the log-logistic distributions are very similar in their appropriateness of fit and that using a log-logistic curve implies having to cap the TTD curve to the PFS curve earlier in the model's time horizon. Therefore, the company's updated model uses the Weibull distribution to model TTD for vismodegib patients.

The ERG's opinion remains that the most appropriate distribution to model TTD, despite the repeated assertion of the company, is the log-logistic. The ERG agrees with the company on the fact that TTD curves for vismodegib should not cross the PFS curves as treatment beyond progression was not allowed for patients in STEVIE. However, the non-crossing of the curves should be reflected in the KM curves, and should only be a curve fitting problem in the case where KM curves do not cross themselves. Nonetheless, the PFS and TTD KM curves from STEVIE cross for both laBCC and mBCC patients. The company has dealt with the issue of TTD and PFS KM curves crossing by capping the estimated TTD curves to the PFS curves. This implies that from the moment the TTD and PFS curves overlap, patients discontinue treatment because of progression or death only.

For laBCC patients, the fact that the KM TTD and the PFS curves cross at around month 38 (Figure 1) could be an artefact of the small number of patients in the PFS curve at this point in time (three patients). In the company's base case approach, where a Weibull was used to model TTD, the TTD and PFS curves cross at 141 months (12 years). Therefore, the TTD curve is capped to the PFS curve from month 141 to the end of the analysis. If a log-logistic model is used to estimate TTD, then the curves cross at month 56 (5 years). Even though using a log-logistic model leads to capping the TTD curve to the PFS curve earlier in the model time horizon, the proportion of patients left in the log-logistic TTD curve (and the PFS curve) at 5 years is only 7%. Considering the small percentage of patients, and the intrinsic uncertainty in the long-term predictions of the economic analysis, the ERG's preferred approach would still be to use a better fitting curve to the available data, and cap it to the PFS curve instead of using a Weibull model. The caveat in the ERG's use of the log-logistic model is that it assumes that from year 5 to year 8 the 7% of patients left in the TTD curve only discontinue treatment due to death or progression.

With regards to mBCC patients, the long tails of the KM TTD curves suggest that metastatic patients continued treatment after progression in STEVIE (Figure 2). The TTD and PFS KM curves cross at about month 15 when there are 30 patients at risk in the TTD curve (corresponding to 34% of patients) and 26 patients at risk (corresponding to 29% of patients) in the PFS curve. This is difficult to explain

as STEVIE patients could not continue treatment after progression as per the trial protocol. Not surprisingly, this leads to crossing fitted curves early in the model's time horizon whether a Weibull or a log-logistic curve is used to model TTD. Given that vismodegib cannot be given beyond disease progression, the fact that the KM TTD curves cross the PFS curves is not easily explainable. However, this is not a problem related with the fitting of survival curves, and therefore cannot be used as a justification for choosing one model over another. The company neglected to acknowledge this problem in the CS and in their reply to the ACD and so no clinical rationale was given for this. It remains uncertain if the crossing of the KM TTD and PFS curves is an artefact of the data or if the curves reflect the clinical reality in STEVIE. Nonetheless, using a log-logistic model in the mBCC case actually leads to capping the TTD by the PFS curve slightly later (14 months) than using a Weibull model (12 months). The company fails to acknowledge the mBCC model is their reply and so does not address the inconsistency in their argument for using a Weibull distribution across both models.

Based on the AIC and BIC criteria reported (Table 44 in the ERG report), the log-logistic model is the best statistical fit for the laBCC and mBCC data. Furthermore, the AIC and the BIC statistics show that the Weibull distribution is one of the worst fitting curves for the laBCC data. Moreover (as discussed in Section 5.4.5.4 of the ERG report), the tails of the KM curves show a plateau from month 30 for laBCC patients and month 22 for mBCC patients. As per the company's clarification, this plateau reflects a period of time (about 15 months) during which patients did not discontinue treatment. Even though the tails of the KM curves are less reliable due to the limited number of patients at risk (26 for laBCC and 8 for mBCC), the log-logistic curves are a better representation in terms of portraying a smoother drop in the TTD curve than a Weibull curve which exhibits a sharper drop in the tail (Figure 1). Figure 1 also shows (through visual inspection of the curves) how the Weibull curve is a worse fit throughout the observed data period in the KM curve for TTD, when compared with the log-logistic curve. The ERG considers that there is no robust evidence for choosing a Weibull over a log-logistic curve to estimate TTD in the economic analysis given that the log-logistic curve provides a better fit to the KM data and that the argument for using a Weibull curve is based on the extrapolated portion of the curve and therefore on unobserved data.

Figure 1. TTD and PFS curves for laBCC

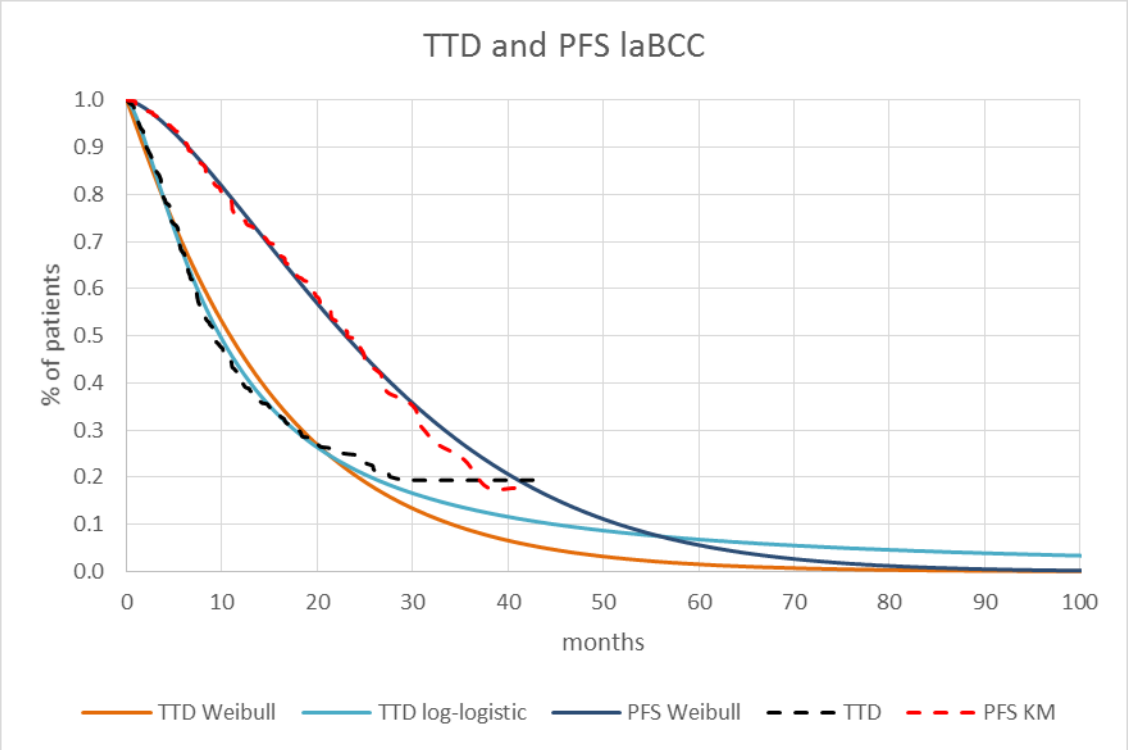
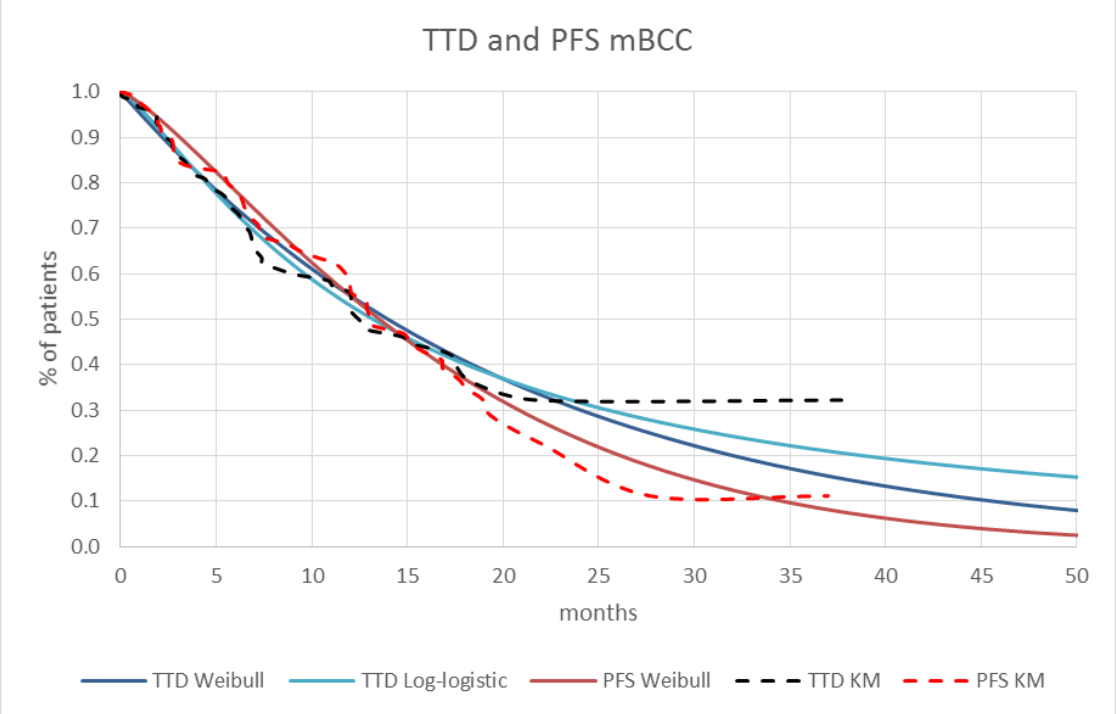


Figure 2. TTD and PFS curves for mBCC



3.2 Quality of life with vismodegib

The quality of life data used in the model are based on SF-36 data collected in the ERIVANCE trial, which were mapped by the company to EQ-5D tariff scores. In the ERG's original report, several concerns with the estimation of quality of life in the company's economic analysis were raised. The most relevant issues, relating to the comments raised by the company on the ACD, are as follows:

- The ERG's clinical experts explained that the baseline age of patients in the ERIVANCE trial is not reflective of aBCC patients encountered in UK clinical practice. Clinical experts reported that aBCC patients are typically 70 years old, which compares to a baseline median age of 62 years in ERIVANCE and 72 years in STEVIE. This leads to a potential overestimation of utility values in the economic analysis, when compared with those observed in clinical practice, but also when compared with the STEVIE population, which was on average 10 years older than the population in ERIVANCE;

- According to the descriptive statistics provided by the company at clarification stage (Table 49 in the ERG report), the mean change from baseline in SF-36 values for all the dimensions is not statistically significant at Week 12 and Week 24 (with the exception of the increase in the social functioning domain at Week 12). The reduction in SF-36 values observed at the end of the study (compared with baseline) in all dimensions (except for physical functioning and vitality) were also not statistically significant. The lack of statistical significance in the results might be related with the small sample size of the population (35 patients at the end of the study), and the lack of sensitivity of the SF-36 scale to depict changes in aBCC patients' quality of life. Even though the mapping method employed by the company was robust, the underlying SF-36 data seems to carry a lot of uncertainty. The company used SF-36 values which mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values which suggest a decrease in patients' quality of life upon progression.

The ACD reports that, *"the company highlighted that the quality of life benefits* [associated with vismodegib] *may not be fully captured because the SF-36 lacks sensitivity. However, the committee recalled that it contains domains on social functioning, anxiety and depression. Nonetheless the committee acknowledged that the results may not fully reflect the feedback from clinical experts that the main benefit of vismodegib is on the quality of life of patients".*

In their reply to the ACD, the company states that using the same health state utility values (HSUVs) across treatment arms in the economic model is likely to underestimate the quality of life benefits

associated with vismodegib. The company adds that vismodegib patients in the progression-free survival (PFS) and in the progressed disease (PD) states are likely to have smaller tumours than PFS and PD patients receiving BSC, hence experiencing a better quality of life. Therefore, the company conducted a scenario analysis whereby a differential factor was applied to the utilities used in the BSC arms of the laBCC and mBCC models. The company acknowledges that this is a purely academic exercise to explore the impact of having different HSUVs across treatment arms on the final ICER, and states that there is little clinical grounding and no available evidence to substantiate the analysis. The company explored the impact of applying a 0.95; 0.90; 0.85; 0.80 and 0.75 factors to the utility values experienced in the vismodegib arm of the model, in order to estimate the utility values for the PFS and the PD states in the BSC models. This is the equivalent to assuming, for example when the 0.95 factor is used, that patients in the BSC arm of the model will experience a 5% reduction in their utility values in the PFS and the PD states, when compared with patients receiving vismodegib. Results of the company analysis are reported in Table 7 of the company's consultation document on the ACD.

Overall, the ERG agrees with the company that using the same HSUVs for vismodegib and BSC might potentially lead to an underestimation of patients' quality of life on vismodegib. Nonetheless, the ERG disagrees with the company's rationale that the benefit with vismodegib would last forever (thus applying a higher utility value to the PD state for vismodegib patients, when compared to the BSC PD state. Once vismodegib patients progress to the point where they will need full BSC, then effectively these patients become BSC patients and would not have any incremental gain in their quality of life compared with progressed BSC patients. This issue is intrinsically linked to when in time vismodegib patients become the equivalent of BSC patients, and incur the same costs (Section 3.3) and the same quality of life. Therefore, the ERG notes that the company exploratory analysis is an overestimation of the impact of using treatment-specific HSUVs on the final ICERs.

In summary, it is the ERG's opinion that the company's exploratory analysis should be taken, as suggested by the company, as an academic exercise. The SF-36 utility data used to estimate HSUVs in the model is too uncertainty and using a non-evidence based differential factors only adds to this uncertainty.

Furthermore, the company points out that the potential gain in quality of life associated with vismodegib is unlikely to be meaningfully diminished by the disutility associated with treatment related adverse events (AEs) as these have a negligible impact on the economic analysis. However, the reason why the impact of AEs is negligible in the economic analysis is because the AEs related with vismodegib are not easily quantifiable in terms of impact on costs to the NHS and impact on patients' quality of life. For example, clinical experts advising the ERG explained that vismodegib causes hair and appetite loss,

which has a considerable impact on patients' quality of life, despite not being costly or captured through the QALY analysis. Although difficult to quantify, it could be argued that the underestimation of the negative impact of vismodegib-related AEs on patients' quality of life somewhat attenuates the underestimation of the positive impact of vismodegib which the company is concerned with.

3.3 Disease management costs

Most of the issues raised by the ERG in its original report were acknowledged by the company after the first ACM, and have been appropriately addressed in the updated economic model submitted by the company. The main outstanding issue is at what point in time progressed vismodegib patients move on to receive the same BSC regimen as patients who have progressed and have never received vismodegib (i.e. BSC patients in the model).

Clinical expert opinion sought by the ERG indicated that the duration of the watchful waiting period is highly volatile and depends on the location and type of the BCC and other factors, but that it would be reasonable to assume that, on average, between three to six months after the monitoring regimen begins, vismodegib progressed patients will move to BSC. The ERG took a conservative approach and presented a scenario analysis where vismodegib patients who progress stay on watchful waiting for six months and then switch to a BSC regimen.

The ACD states that, *"The clinical experts explained that an initial delay in restarting BSC after vismodegib was plausible because these patients may initially only need monitoring or a less intensive regimen of BSC because they will have a lower disease burden. However, all patients will eventually go on to have BSC as their disease progresses, and this regimen will be the same irrespective of prior vismodegib treatment. The committee noted that the ERG explored the impact of assuming that patients on vismodegib moved to BSC 6 months after progression and had the same treatment as people on BSC whose disease has progressed; the committee concluded that this was appropriate."*

The company comments that the delay brought on by vismodegib could be longer and could be between six to 10 years, according to the company's clinical experts. Therefore, the company explored further scenario analyses, where the duration of the watchful waiting period varied from zero months; six months; and yearly after that, up to10 years. The results of the company analysis are reported in Section 4.

Overall, the ERG acknowledges the volatility in clinical practice and the dependence on the type and location of aBCC lesions as determining factors for the duration of the watchful waiting period. Nonetheless, the ERG points to the extremely large discrepancy in the clinical expert opinion provided to the ERG (an estimate of three to six months) and the one provided to the company (between six to

10 years) and adds that the 10-year estimate seems somewhat implausible, especially when considering mBCC patients, who have an average life expectancy of 10 years. The ERG's preferred assumption is still to assume that, on average, vismodegib patients switch to the full BSC regimen six months after disease progression, and therefore disagrees with the approach taken by the company in its updated analysis.

4 SUMMARY OF THE COMPANY'S KEY RESULTS

The company's updated base case incorporated most of the ERG's original suggestions. However, it differed in two important aspects that consist on the following:

1) Using a Weibull distribution to model TTD in the economic model;

2) Assuming that vismodegib patients who progress remain on the watchful waiting period for six years before switching to a BSC regimen.

Furthermore, the company has introduced a new agreed Patient Access Scheme (PAS) of [redacted]. Results without the PAS are reported in Table 1 while results with the PAS are reported in Table 2. The combined ICERs weight the laBCC and the mBCC final ICERs by the proportion of patients in each group in STEVIE (7% in mBCC and 93% in laBCC). The company did not provide results for the probabilistic sensitivity analysis (PSA).

Table 1. Company's reported base case results using list price

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	£72,592	1.25	0.95	£76,359
Vismodegib	£163,318	10.54	8.11				

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.

Table 2. Company's reported base case results with PAS

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£90,726	9.29	7.16	[redacted]	1.25	0.95	[redacted]
Vismodegib	[redacted]	10.54	8.11				

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.

Table 3 reports the company's exploratory analysis on the different delay periods for vismodegib patients to switch to a BSC regimen. As expected, the longer it takes for patients to move to the BSC regimen after terminating treatment with vismodegib, the lower the final ICER associated with vismodegib is.

Table 3. Scenario analysis results - BSC delay – No PAS applied

Months	ICER (Log-logistic TTD extrapolation)	ICER (Weibull TTD extrapolation)
0	£109,120	£98,921
6	£106,810	£96,611
12	£104,593	£94,394
24	£100,413	£90,214
36	£96,548	£86,349
48	£92,983	£82,785
60	£89,683	£79,485
72	£86,557	**£76,359**
84	£83,691	£73,493
96	£81,004	£70,806
108	£78,484	£68,286
120	£76,121	£65,923

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.
The value in **bold** reports the company's base case ICER.

5 ADDITIONAL WORK UNDERTAKEN BY THE ERG

For inclusiveness, the ERG replicated the company's exploratory analysis for the different delay times for switching to BSC, with the ERG's choice of TTD curve and with the new PAS applied. The results are reported in Table 4.

The ERG has also replicated the results provided to the Appraisal Committee after the first ACM, which included the scenario assuming no survival benefit with vismodegib, and including the company's new PAS. Given the acknowledged uncertainty around the survival benefit associated with vismodegib for laBCC and mBCC patients, the ACD states that the ICER for vismodegib compared with BSC is likely to lie between the ICER assuming no survival benefit and the ICER assuming a gain in survival with vismodegib. The ACD reports that, "*although vismodegib was unlikely to have a direct impact on survival, it* [the committee] *could not rule out survival benefits altogether*". Results are presented in Table 5, and are for the ERG's preferred assumption of a 6-month delay in switching to BSC. From observation of the values in Table 3 and Table 4, it can be concluded that changing the assumption of when in time the switch to BSC occurs, from month 6 to year 10, leads to a drop in the final ICER by about £30,000.

When a survival benefit is assumed for treatment with vismodegib, the ICER incorporating the ERG's preferred assumptions amounts to £106,810 per QALY gained (with the PAS). When it is assumed that vismodegib has no survival benefit, the ICER incorporating the ERG's preferred assumptions amounts to £5,658,289 per QALY gained with the PAS). To note is that if the switch to BSC regimen occurred after 10 years with treatment with vismodegib, it is likely that the magnitude of the ICERs reported in Table 5 would not change considerably.

Table 4. Scenario analysis results, BSC delay – PAS applied

Months	ICER
0	
6	
12	
24	
36	
48	
60	
72	
84	
96	
108	
120	

Abbreviations: ICER, incremental cost-effectiveness ratio; TTD, Time to treatment discontinuation.
The value in **bold** reports the ERG's base case ICER.

Table 5. No survival benefit with vismodegib with PAS

Results per patient	Incremental value weighted by type of BCC in STEVIE	Incremental value weighted by type of BCC in STEVIE (PAS)	ICER	ICER (PAS)
Total costs	£93,727		£5,658,289	
QALYs	0.02	0.02		

Vismodegib for the treatment of locally advanced or metastatic basal cell carcinoma

Additional analysis requested after second Committee meeting

This report was commissioned by the NIHR HTA Programme as project number 16/51/16

BMJ Technology Assessment Group

Summary of the document

The ERG produced this document in response to NICE's requested analysis resulting from the second Committee meeting for vismodegib. The document includes the results of the following analyses:

- Combined ICER for laBCC and mBCC patients assuming no survival benefit with vismodegib, and a 3-year delay for progressed vismodegib patients to move to full BSC.

The results with vismodegib list price and with the PAS discount are presented in Table 1.

In order to derive combined ICERs, the ERG has weighted the incremental costs and QALYs for each population for each scenario analysis, by the proportion of patients in the laBCC (93%) and mBCC (7%) cohorts in STEVIE.

Table 1. No survival benefit with vismodegib list price and PAS results

Results per patient	Incremental value weighted by type of BCC in STEVIE	Incremental value weighted by type of BCC in STEVIE (PAS)	ICER	ICER (PAS)
Total costs	£113,340	[redacted]	£4,694,943	[redacted]
QALYs	0.02	0.02		