National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche	The remit should be revised to include the word advanced basal cell carcinoma	Thank you for your comment. Following the scoping workshop, it was decided not to include the word "advanced" to avoid ambiguity.
	British Association of Dermatologists (BAD)	YES-However, it does need to be recognised that this drug may be used to decrease tumour bulk to allow conventional treatments to be used. Erqi L. et al JAMA Dermatol. 2015;151(9):998-1001. doi:10.1001/jamadermatol.2015.0326	Thank you for your comment. NICE can only consider a drug within the remit of its marketing authorisation. This was discussed at the scoping workshop and the consultees agreed that

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			neoadjuvant treatment would be outside the marketing authorisation use of vismodegib.
	British Association of Skin Cancer Specialist Nurses (BA SC SN)	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording. Yes	Thank you for your comment. No changes to the scope required.
Timing Issues	Roche	Vismodegib is currently funded on the CDF. This appraisal needs to fit with the timescales for the CDF transition.	Thank you for your comment. No changes to the scope required.
	BA SC SN	Treatments in this area are limited and so a rapid appraisal would be welcome	Thank you for your comment. No changes to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	Suggested addition to the provided background information: Locally advanced BCC, in which the tumour has infiltrated a large area, account for approximately 1% of all BCC cases. Surgical management of these tumours can result in significant deformity, particularly when located on the face, and may result in loss of an ear, eye or nose, or an extensive area	Thank you for your comment. The background section provides only a general overview of the disease area.

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		of skin that requires complex and sometimes repeated surgery. Such high-risk facial tumours have typically been treated using Mohs' surgery – however the extreme deformity and associated morbidity means that this modality is not always appropriate. Recurrent tumours, especially on the face, are at high risk of further recurrence following surgical excision even with wide surgical margins. Radiation therapy is an alternative treatment but is not always appropriate and is associated with significant acute and chronic toxicity.1 Locally advanced BCC that is inappropriate for surgery is defined when the BCC recurs after ≥2 surgical procedures and curative resection is unlikely, and/or there is substantial morbidity and/or deformity expected as a result of surgery. Within the vismodegib studies, patients should have received radiotherapy to ≥1 target lesion unless medically contraindicated or inappropriate. Metastatic BCC is an incredibly rare condition, with just 0.0028–0.55% of BCCs metastasising to a non-contiguous location. , Advanced basal cell carcinoma (aBCC) is comprised of locally advanced BCC (laBCC) and metastatic BCC (mBCC). For the purpose of the vismodegib marketing authorisation, laBCC is further specified as those that are inappropriate for surgery or radiotherapy (laBCCi). Vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013. Between launch and September 2015, 225 CDF applications were made.	

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	NRI-ACP-RCP	**Page 1, 2nd paragraph 4th line** **…(BCC ….is more common in men than women[4, 5]** This information is correct as per cited referenced dated 1990 and 2007 due to mainly farming/outdoor male occupations. In recent publications there is no gender difference reported. **Page 1, 3rd paragraph 2nd line** **… However, in rare cases surgery is not an option or the cancer has metastasised, radiotherapy is commonly used.** Radiotherapy is playing more and more important role in radical treatment of BCC and is not used as rarely as the text implies. XRT has got vital role in elderly patients, patients with co-morbidities and/or when cosmesis and function preservation play an important role in anticancer management. How the sentence is structured it also implies that XRT is commonly used in metastatic cases. **Page 2, 1st paragraph** Only PDT is mentioned but there are other options in radical treatment of BCC such as topical treatment, cryotherapy or curettage. Second sentence: 'Vismodegib has been available on the Cancer Drugs Fund for locally advanced or metastatic BCC where surgery is not an option, and patients must have had radiotherapy unless it was not possible'. This would be better placed in 'The technology' section. CDF says that Vismodegib is indicated for patients with previous XRT unless contraindicated or inappropriate. **Page 2, 2nd paragraph** 'Vismodegib has a conditional marketing authorisation in the UK for treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy'.	Thank you for your comment. The scope has been amended to reflect some of the changes suggested. The background section is intended to provide only a general overview of the disease area.

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		The same wording is used in the table on p.2: Population described as people with:• symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate The document requires very clear definition and explanation in details what forms 'locally advanced BCC'. Please see the general comments further down.	
	BAD	I wouldn't narrow it down to 'back and lower legs'. Syntax in last sentence of the first paragraph is misleading. Better to use a separate sentence: 'BCCs metastasise extremely rarely' Radiotherapy is still commonly used as a treatment for extensive primary BCC. The inclusion of photodynamic therapy in this paragraph is misleading; it is almost always used for superficial BCC. If you do include it, other forms of therapy such as topical imiquimod and curettage should also be mentioned.	Thank you for your comment. The scope has been amended accordingly. The background section however provides only a general overview of the disease area.
	BA SC SN	Good	Thank you for your comment. No changes to the scope required.
The technology/ intervention	Roche	*Suggested addition to the provided information on the technology:* Molecular and genetic studies have shown that almost all basal-cell carcinomas contain genetic alterations in the hedgehog signalling pathway, resulting in aberrant pathway activation and uncontrolled proliferation of basal cells.[i]	Thank you for your comment. The technology section provides only a general brief overview of the technology.

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		Suggested amendment to text: Vismodegib has a full marketing authorisation in the UK ……. It has been studied in clinical trials in people with locally advanced or metastatic basal cell carcinoma and has mainly been studied in single arm trials.	
	BAD	Yes	Thank you for your comment. No changes to the scope required.
	BA SC SN	Yes	Thank you for your comment. No changes to the scope required.
Population	Roche	Yes, the population is defined as per the vismodegib marketing authorisation. Gorlin syndrome, or basal cell nevus syndrome (BCNS) is a rare inherited (autosomal dominant disorder) condition in which individuals develop many BCCs from a relatively early age. This patient cohort is included within the licensed indication for locally advanced BCC (laBCCi)	Thank you for your comment. The scope has been amended to incorporate patients with Gorlin syndrome in the section suggesting potential subgroups.
	BAD	No - Gorlin Syndrome patients should be included and should also be considered separately. Also patients with xeroderma pigmentosa.	Thank you for your comment. The scope has been amended to incorporate patients with Gorlin syndrome in the section suggesting potential subgroups.

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	BA SC SN	Yes	Thank you for your comment. No changes to the scope required.
Comparators	Roche	Best supportive care is the most appropriate comparator as there are no further treatment options for patients with laBCCi and mBCC, who are not appropriate or have exhausted treatment options suitable for patients with less extensive or aggressive disease.	Thank you for your comment. No changes to the scope required.
	BAD	No in the case of Gorlin Syndrome. Surgery may still be used, but the resultant morbidity from multiple surgery may be high.	Thank you for your comment. The scope has been amended to incorporate patients with Gorlin syndrome in the section suggesting potential subgroups.
	BA SC SN	***Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*** Yes	Thank you for your comment. No changes to the scope required.
Outcomes	Roche	Response rate was deemed by investigators and experts, as well as the US FDA, to be the most appropriate and feasible endpoint in the licensing study ERIVANCE. Prior to vismodegib, there had been no clinical or regulatory precedent for measuring clinical benefit in aBCC. This endpoint was reviewed with the FDA and subsequently with EU health authorities, who agreed that the endpoint as defined may adequately assess clinical benefit. Roche and the FDA believe that, in these aBCC patients, tumour shrinkage measured by	Thank you for your comment. No change to the scope required.

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		response rate and durable response is a valid and direct measure of clinical benefit. There are published data on PFS and OS, though not comparable against a control arm. PFS and OS were secondary endpoints in the ERIVANCE study. For the mBCC cohort, while it is recognised that OS is the gold-standard endpoint, a randomised comparative trial was considered not feasible because of the extreme rarity of mBCC patients. Therefore, both PFS and OS were considered suboptimal endpoints to measure clinical benefit in both control and treated patients.	
	BAD	Yes	Thank you for your comment. No changes to the scope required.
	BA SC SN	Yes	Thank you for your comment. No changes to the scope required.
Economic analysis	Roche	The time horizon used will be a patient's lifetime Incremental cost per quality adjusted life year will be calculated.	Comment noted. No changes to the scope required.
	BAD	This may be very different between non Gorlin patients and those with the syndrome.	Comment noted. No changes to the scope required.

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	BAD	This is difficult since the majority of patients with advanced un-resectable BCC are in the 8th and 9th decade of life.	Comment noted. No changes to the scope required.
Equality and Diversity		No comments received	
Innovation	Roche	We consider that vismodegib is innovative for the following reasons: Prior to the approval of vismodegib, patients with aBCC had no approved or standard therapeutic options when surgery or radiotherapy was inappropriate – vismodegib offers these patients with a significant unmet medical need a treatment option. Dosed once-daily, vismodegib offers a novel, oral, targeted, first-in-class, non-invasive, non-surgical therapeutic strategy for patients with aBCCs who had exhausted other treatment options. Long-term pivotal trial data evaluating vismodegib in patients with aBCC have shown a significant clinical benefit (in terms of response rates) that is associated with a reduction of disfigurement and preservation of structures (eyes, ears and nose) that have inherent benefits for patient wellbeing.	Comment noted. No changes to the scope required. Innovative aspects of the technology should be included in the stakeholder submissions and will be explored by the appraisal committee.
	BAD	There is little doubt that in a selected group of patients this technology can be a ‘step- change‘ in the management of this condition There is little evidence at the moment for the drug’s use in an adjuvant setting, but this may form one of its key roles in the future. Therefore this is not likely to be included in any QALY calculations at present.	Comment noted. No changes to the scope required

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		Time-trade off weighting may be skewed in view of average age of patient population.	
	BA SC SN	This is a small potential population of patients but the benefits to them could be significant.	Comment noted. No changes to the scope required
Questions for consultation	Roche	*Have all relevant comparators for vismodegib been included in the scope?* Vismodegib offers a novel treatment for locally advanced basal cell carcinoma (laBCC) patients who have exhausted their treatment options (surgery, radiation, photodynamic therapy, and topical imiquimod). Prior to vismodegib, there have been no approved treatments for metastatic basal cell carcinoma (mBCC). In the absence of approved treatments, systemic chemotherapies (e.g., cisplatin or carboplatin based regimens) have been used for advanced disease, but data are limited to case reports and case series. Additionally a diverse group of practitioners, including dermatologists, dermo-oncologists, medical oncologists, radiologists, and surgeons, diagnose and treat aBCC, which means that there is rarely a consistent treatment approach across aBCC patients. Best supportive care is the appropriate comparator for consideration in this appraisal. *Where do you consider vismodegib will fit into the existing NICE pathway, skin cancer?* Vismodegib treatment is considered after all other treatment choices have been exhausted, in patients who would derive no benefit from surgery due to	Comment noted. No changes to the scope required Comment noted. No changes to the scope required

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		the morbidity associated with the extensive surgery or incomplete clearance of the tumour; radiotherapy would have been given prior to vismodegib unless the patient was medically contraindicated. The treatment pathway is extended by the availability of vismodegib for such patients. *Would it be suitable to consider topical treatments under best supportive care?* Telfer et al.[Error! Bookmark not defined.] reviewed information available and concluded that topical imiquimod appears effective in the treatment of primary small superficial BCC and may possibly have a role in the treatment of primary nodular BCC. However, as the advanced definition in the vismodegib marketing authorisation incorporates those patients who have larger, more aggressive BCCs then topical therapy is not appropriate for consideration.	Comment noted. No changes to the scope required
	NRI-ACP-RCP	**Have all relevant comparators for vismodegib been included in the scope?** • **Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic basal cell carcinoma?** Surgery and XRT in locally advanced BCC; palliative surgery and palliative XRT in symptomatic metastatic BCC. No established chemotherapy in metastatic BCC. • **Would treatment options vary for locally advanced or metastatic basal cell carcinoma?**	Comment noted. This was discussed at the scoping workshop and the consultees agreed that curative surgery and radiotherapy are not appropriate comparators given that the marketing authorisation for vismodegib specifies

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		It depends whether they are symptomatic from their metastatic BCC. Otherwise patients may experience side effects and worsening of their Quality of Life from Vismodegib while being asymptomatic from their metastatic disease. • **How should best supportive care be defined**? A therapy that provided best possible individual supportive treatment for symptomatic patients and to improve quality of life. This aspect could link very nicely with Enhanced supportive Care initiative across the NHS England with evidence that early referral to palliative care is associated with better outcomes in terms of QoL, survival and aggressiveness of care in the end of life care. • **Would it be suitable to consider topical treatments under best supportive care?** This depends on clinical situation (size of the lesion, depth of infiltration, subtype of cancer). **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom vismodegib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Vismodegib, within its palliative remit, could be considered as 'neoadjuvant' treatment to be followed by surgery and / or XRT in case of significant clinical regression.	patients inappropriate for surgery and radiotherapy. Therefore, these treatments would not be displaced by vismodegib. Scoping workshop attendees agreed that best supportive care was the most appropriate comparator and that no changes to the scope were required Comment noted. No changes to the scope required Comment noted. No changes to the scope required

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		Where do you consider vismodegib will fit into the existing NICE pathway, Skin cancer? Yes	Comment noted. No changes to the scope required Comment noted. No changes to the scope required Comment noted. This was discussed at the scoping workshop and the consultees agreed that neoadjuvant treatment would be outside the marketing authorisation use of vismodegib Comment noted. No changes to the scope required

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	BAD	**Have all relevant comparators for vismodegib been included in the scope**? Depends on metastatic v locally advanced v Gorlin Syndrome - Comparators are not the same **Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic basal cell carcinoma?** Mohs Surgery, Conventional excisional surgery and Radiotherapy. Potentially electrochemotherapy **Would treatment options vary for locally advanced or metastatic basal cell carcinoma?** All- this is dependent on the size and site of the primary tumour **How should best supportive care be defined?** To ensure that the patient is free from pain and the potential consequences of the untreated tumour are recognised and addressed in a timely manner **Would it be suitable to consider topical treatments under best supportive care?** No **Are the outcomes listed appropriate?** Yes **Where do you consider vismodegib will fit into the existing NICE pathway, Skin cancer?** Within patient centred care **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people**	Comments noted. No changes to the scope required

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		with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: NA **Are there any subgroups of people in whom vismodegib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Gorlin Syndrome, XP, and those patients on immunosuppressive therapy	Thank you for your comment. The scope has been amended to incorporate patients with Gorlin syndrome in the section suggesting potential subgroups.
Additional comments on the draft scope	NRI-ACP-RCP	Any additional comments on the draft scope • A clear definition of locally advanced BCC is needed. As it currently states in the document Vismodegib could be potentially offered to patients who decline surgery / XRT themselves. Vismodegib is a palliative treatment with expected duration of response in the range of 12-18 months. Vismodegib could be preferred by patients (tablets) or offered to such patients while potentially curative options exist for them. • Potential benefit for patients on Vismodegib given in 'neoadjuvant' unlincesed use allowing them to proceed with XRT / surgery on clinical remission.	Comment noted. The need for a clear and precise definition of "locally advanced BCC" was discussed by consultees at the scoping workshop but it was agreed that this was much needed but required at the national level by the relevant professional bodies. The appraisal will

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			assess the technology based on the evidence available. Comment noted. This was discussed at the scoping workshop and the consultees agreed that neoadjuvant treatment is outside the marketing authorisation for vismodegib
		• Potential use of Vismodegib on intermittent basis in anticipated or experienced toxicity.	Comment noted. No change to the scope required.

[i] Sekulic A et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. N Engl J Med 2012; 366: 2171-9