NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vismodegib for treating basal cell carcinoma [ID1043]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Vismodegib for treating basal cell carcinoma [ID1043]

Contents:

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

Pre-meeting briefing
Vismodegib for treating basal cell carcinoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Key clinical issues (1)

- The key clinical effectiveness evidence for vismodegib was obtained from 2 single-arm studies: ERIVANCE and STEVIE
  - Are the populations representative of patients in UK clinical practice?
  - Given the observational nature of the evidence, is the committee satisfied that it sufficiently captures the effect on PFS and OS?
- The population of patients with mBCC was very small. What is the committee's view on the results in this population?
- No comparative data was available, and the company conducted a 6 month landmark analysis to compare vismodegib with BSC. The ERG noted several limitations around this:
  - Does the committee consider the analysis sufficiently robust for decision-making?
    - If so, which covariate adjustments does the committee consider to be most appropriate?
    - Would additional landmark analyses around the chosen landmark be useful?
  - Has the Gorlin syndrome subgroup been adequately addressed?

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Key clinical issues (2)

- What is the committee's view of the assumptions around BSC in the model?
  - Has BSC been defined appropriately?
  - What BSC would people receive following vismodegib?

- The company highlighted the unmet need and stated that vismodegib is already standard of care due to its use under the CDF, and removal of access would impact a vulnerable patient group. In the context of the limited evidence base, does the committee consider that any real world evidence from use in the CDF would support its decision-making?

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Key cost-effectiveness issues (1)

- Have OS, PFS and TTD data been extrapolated appropriately?
  - Is the adjustment of the landmark HRs undertaken by the company appropriate?
  - Is the use of a common treatment effect (laBCC and mBCC) HR appropriate
  - Have all important covariates been adjusted?
- Are the assumptions plausible?
  - Duration of treatment effect between vismodegib and BSC is set to equal after the last observation point
  - The proportional hazard assumption holds for the responders vs. non-responders
  - 67% of people who progress after receiving vismodegib are on monitoring regimen for the remainder of their lifetime and never receive BSC
  - Post-progression BSC schedule for people receiving vismodegib differs from people receiving BSC

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Key cost-effectiveness issues (2)

- Has the model captured all relevant costs and benefits associated with vismodegib?
  - Should the model use mapped QoL data from the ERIVANCE study considering its population and definition of response/progression differ from that in the STEVIE study?
- The ERG identified limitations in the company's model and provided exploratory analyses to address these
  - Are these amendments to the company's model appropriate?
  - Which of the two final ICERs does the committee consider to be most plausible?
    - the ICER assuming no survival gain with vismodegib? Or
    - the ICER assuming there is a survival benefit with vismodegib?

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Disease background

- BCC is a form of non-melanoma skin cancer (NMSC) that develops in the deep basal cell layer of the epidermis around the hair follicle
- Early treatment of BCC is curative in most cases. If left untreated for prolonged periods, it can become advanced (aBCC), either locally advanced (laBCC) or metastatic (mBCC), potentially causing extensive tissue destruction and disfigurement
- Some people with laBCC may be unsuitable for surgery or radiotherapy (laBCC*i*) due to the extent of tissue invasion, possible gross disfigurement (from extensive surgery), and the need to limit radiation damage to surrounding organs/structures
- Incidence and survival
  - BCC is the most common type of skin cancer in the UK with around 75% of NMSC being BCC
  - Approx. 53,000 new cases of BCC occur every year in the UK
  - Advanced BCC occur in up to 10% of all BCCs, with laBCC*i* occurring in up to 1% and mBCC accounting for 0.0028% to 0.55% of all BCCs
  - More common in people with Gorlin syndrome and a higher prevalence in males and people with fair skin, blond or red hair, blue, green or grey eyes, increasing age, or family history

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Note:

The true incidence and prevalence of NMSCs, and thus BCCs, are difficult to estimate because large national cancer registries do not track NMSC; additionally, NMSCs are usually treated in a primary care setting.

Vismodegib (Erivedge)

Marketing authorisation (MA): - Conditional MA: Aug 2013 - Full MA: Sep 2016	Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma (mBCC) - locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy
Mechanism of action	Hedgehog pathway inhibitor
Administration & dosage	Oral capsules, 150 mg once daily
Duration of treatment	Until disease progression or unacceptable toxicity
Cost	£6,285/cycle (28 x 150mg capsules, list price) A confidential patient access scheme has been proposed; pending approval
CDF	Available on the CDF

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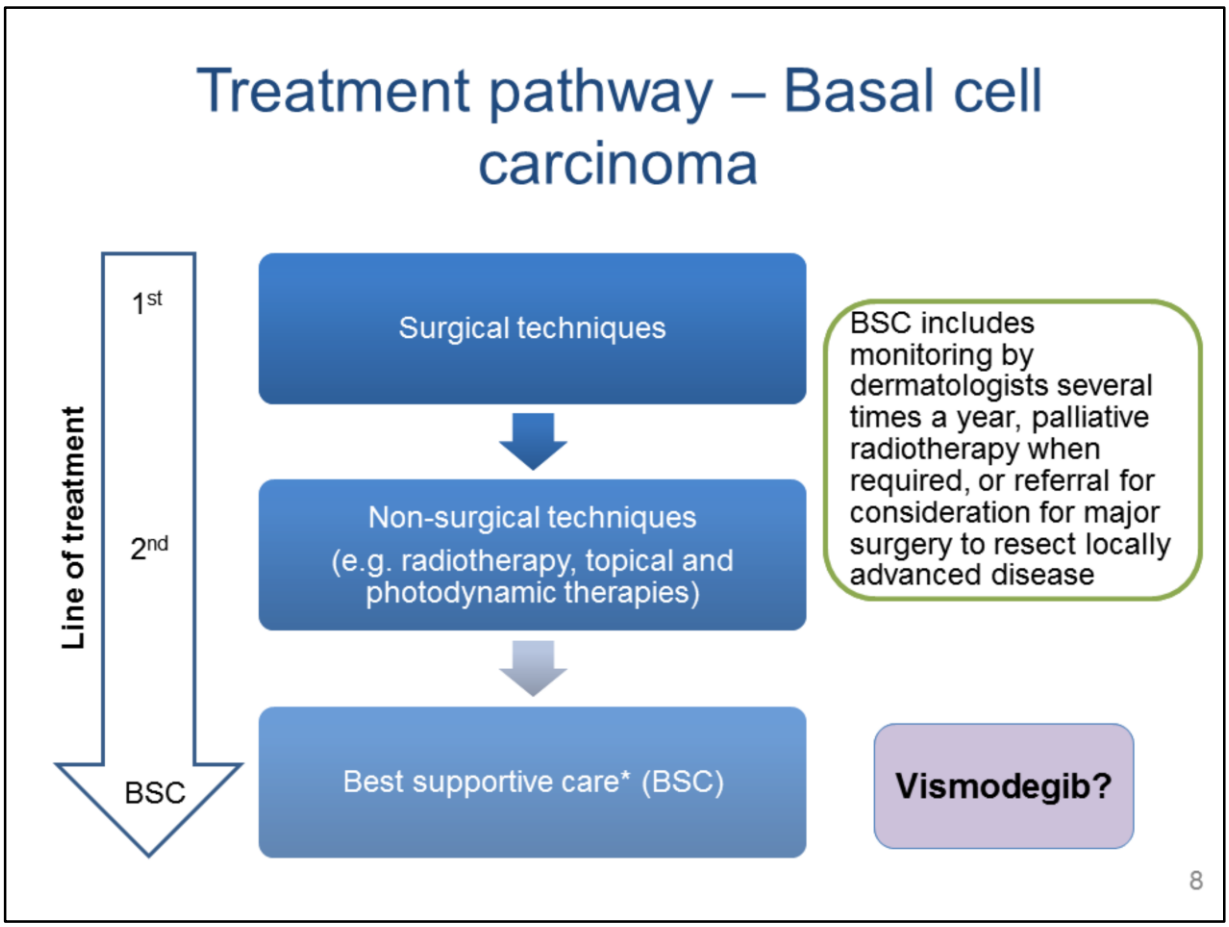
From the UK launch until the end of August 2016, 352 requests had been made for funding through the National Cancer Drugs Fund.



Proposed positioning of vismodegib

- The company propose vismodegib for patients with aBCC who have exhausted their treatment options and further surgery or radiotherapy is considered inappropriate.

	Final scope	Company submission and rationale for deviations
Pop.	People with: - symptomatic metastatic basal cell carcinoma or - locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate	
Int.	Vismodegib	
Comp.	Best supportive care (BSC)	No relevant published RCTs were identified in the company's systematic literature review
Outcomes	• PFS and OS • response rates • adverse effects of treatment • health-related quality of life	As per scope, except OS data for laBCC
Subgroups	If the evidence allows: • People with Gorlin syndrome	The company did not include people with Gorlin syndrome as a separate subgroup due to the low patient numbers in the pivotal trials

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Best supportive care:

- The company received feedback that it would not be feasible to accrue patients to a randomised study:
    - considering significant anti-tumour activity observed in patients with aBCC in the Phase I study (SHH3925g) and;
    - considering the substantial unmet medical need in aBCC.
- In addition, responses from a placebo or best supportive care arm were both (a) not expected and (b) could be addressed statistically with a significantly high response rate in the vismodegib arm.
- Lastly, there was concern that a randomised, cross-over design may inadvertently introduce bias into the results:
    - if there was no immediate clinical benefit observed in the control arm, investigators may have been biased toward prematurely assessing disease progression;
    - patients may have been biased towards withdrawing consent, before crossing over to vismodegib or enrolment into another clinical study. Such bias would impact the integrity of the study and interpretation of the true treatment effect of vismodegib.

Therefore, the single-arm study with a response rate endpoint was determined to be the most appropriate trial design for vismodegib in aBCC.

Clinical effectiveness

Studies overview

- The company identified 5 studies, and reported the methods and findings but focussed on 2 key studies, ERIVANCE and STEVIE.
- The ERG agreed and focussed their critique on ERIVANCE and STEVIE, because:

SHH3935	Phase 1; nearly 50% of patients on higher dose of vismodegib compared to the licensed dose, with no subgroup data on the licensed vismodegib dose
RegiSONIC Disease Registry study	Ongoing study; results presented only for response rate and adverse events from conference abstracts with each one focusing on different populations or analysis time-points.
Expanded Access Study (EAS)	Phase IV expanded access study to enable the compassionate use of vismodegib in the US prior to vismodegib approval by the FDA. Terminated following US marketing authorisation for vismodegib.

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ERIVANCE
(basis for conditional MA Aug 2013)

Study type	• Phase II (n=104) • International, multicentre, non-randomised, open-label, single-arm, two-cohort study
Location	31 study sites in USA, Belgium, France, Germany, UK, and Australia
Population	Adults with: • adequate organ function and ECOG PS≤ 2 • measurable mBCC or laBCC (with at least 1 lesion ≥ 10mm long in diameter) inappropriate for surgery and radiotherapy must have been previously administered unless inappropriate
Intervention	Oral vismodegib at 150 mg/day until disease progression, intolerable toxicity, or withdrawal from study (with up to 4-weeks dose interruption, if required to manage toxicity or up to 8 weeks for a planned surgical procedure)
Outcomes	• **Objective response rate (complete or partial responses)** • Duration of objective response, progression-free survival, overall survival, patient-reported symptoms and histopathologic response
Time-points (% people remaining)	• Primary analysis: 9 months after the last patients were enrolled (52.5%) • Follow-up: 12 and 30 months (27.9% and 8.7% respectively) since the primary analysis

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ERIVANCE was the key study used to gain conditional EU marketing authorisation for vismodegib.

STEVIE (led to full MA Sept 2016)

Study type	• Phase II post-approval safety study (n=1232) • International, multi-centre, open-label, non-comparative study
Location	152 sites in 36 countries including the United Kingdom
Population	Adults with: • adequate organ function and ECOG PS≤ 2 • histological confirmed diagnosis of distant mBCC or laBCC inappropriate for surgery and radiotherapy must have been previously administered unless inappropriate
Intervention	Oral vismodegib at 150 mg/day until disease progression, intolerable toxicity, or withdrawal from study (with up to 8-weeks dose interruption, if required to manage toxicity)
Outcomes	• **Incidence of treatment-emergent AEs (TEAEs)** • Objective response rate, time to response, duration of response, progression-free survival, overall survival, patient quality of life (Skindex-16), impact on treatment on disease symptoms (MDASI)
Time points	• 6 interim analyses* • 1 final analysis* • Safety follow-up: Months 1, 3, 6, 9 & 12

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Planned analyses

- The final analysis was planned to be when whichever occurred first out of the following: the last patient in the study developed progressive disease (as determined by the investigator), unacceptable toxicity, withdrew consent, died or was deemed no longer to be benefiting from treatment according to the treating physician, or the study was terminated by the sponsor; or 12 months after the last dose of vismodegib in the last enrolled patient still on study.

*The six planned interim analyses for both safety and efficacy were planned to be when:

- first 75 patients enrolled have been treated for at least 3 months;
- first 150 patients enrolled have been treated for at least 3 months;
- first 300 patients enrolled have been treated for at least 3 months;
- first 550 patients enrolled have been treated for at least 3 months;
- first 800 patients enrolled have been treated for at least 3 months; and
- 1,200 patients enrolled have been treated for at least 3 months,
    - This last interim analysis was also planned to include the analysis of 500 enrolled patients who had been followed for at least 1 year.

ERIVANCE & STEVIE – baseline characteristics

	ERIVANCE		STEVIE	
Baseline characteristic	**laBCC n=63**	**mBCC n=33**	**laBCC (n=1,119)**	**mBCC (n=96)**
Age, median (range)	62.0 (21 - 101)	62.0 (38 - 92)	72.0 (18 - 101)	67.0 (34 - 95)
Male, n (%)	35 (56)	24 (73)	634 (56.7)	60 (62.5)
Enrolled at a UK site, n (%)	2 (6)	0	NR	NR
Gorlin syndrome, n (%)	20 (32)	0	214 (19.2)	5 (5.2)
Contraindications to surgery, n (%): Inoperable tumour Surgery inappropriate	 24 (38) 39 (62)	 NA	 433 (38.7) 686 (61.3)	 NA
Prior radiotherapy, n(%): Yes Inappropriate or contraindicated	 13 (21) 50 (79)	 NA	 312 (27.9) 806 (72.0)	 59 (61.5) 37 (38.5)
Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable				

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Source: Adapted from the ERG report tables 9 and 10 (CS tables 22 and 23)

ERIVANCE:

- Substantially more patients with laBCC than mBCC enrolled (n = 63 and n = 33, respectively). The ERG's clinical experts report that these differences are likely to be a natural reflection of clinical practice where you expect to see very few cases of mBCC compared to laBCC.
- The clinical experts reported that the population in ERIVANCE is substantially younger (median age 62) than expected in clinical practice (70s).
- The ERG highlighted that 21% of patients in ERIVANCE had Gorlin syndrome, which is higher than prevalence in UK clinical practice.

STEVIE:

- The median age in STEVIE was 72 years and substantially higher proportion with laBCC, which clinical experts report is closer to UK clinical practice.
- However, the ERG note that only 3.1% of patients in STEVIE came from UK sites.
- In addition, as for ERIVANCE, the ERG's clinical experts suggest that an incidence of 18.1% for Gorlin syndrome patients eligible for vismodegib in STEVIE is higher than expected in the

UK.

- In the patients with laBCC, it was reported that 38.7% had baseline disease status that was considered inoperable, and surgery was medically contraindicated in 61.3% of patients.

The most frequent sites of disease were the head (74.9%) and trunk (21.9%) in patients with laBCC. The ERG's clinical experts report that the number of patients with truncal laBCC is possibly higher than expected in UK clinical practice. Truncal BCC would usually be suitable for surgery or radiotherapy whereas lesions on the face are less likely to be suitable for these treatments. However, they also reported that the laBCC that were extensive multifocal superficial BCC, such as those that would be seen on the trunk of Gorlin patients are also more likely to be unsuitable for radiotherapy or surgery.

ERIVANCE: efficacy results

Study arm	Primary outcomes (IRF-assessed)		Outcomes from 12-month update (IRF-assessed)		Outcomes from 30-month update (investigator-assessed)	
	laBCC n=63	mBCC n=33	laBCC n=63	mBCC n=33	laBCC n=63	mBCC n=33
Response rate						
ORR, n(%) [95% CI]	27 (43) [30 – 56]	10 (30) [16 – 48]	30 (48) [36 – 61]	11(33) [19 – 52]	38 (60.3) [47.2 - 71.7]	16 (48.5) [30.8 - 66.2]
Progression-free survival						
Median, months (95% CI)	9.5 (7.4 - 11.9)	9.5 (7.4 - NE)	9.5 (7.4 - 14.8)	9.5 (7.4 - 11.1)	12.9 (10.2 - 28.0)	9.3 (7.4 - 16.6)
Overall survival						
Median OS, months (95% CI)	Data not mature	Data not mature	NE	24.1 (14 .3 - NE)	NE (NE - NE)	33.4 (18.1 - NE)
1-year survival rate, % (95% CI)	91.6 (83.5 - 99.7)	75.5 (57.3 - 93.6)	93.1 (86.6 - 99.6)	78.7 (64.7 - 92.7)	93.2 (86.8 - 99.6)	78.7 (64.7 - 92.7)
2-year survival rate, % (95% CI)	NA	NA	85.4 (76.0 - 94.8)	60.3 (43.4 - 79.1)	85.5 (76.1 - 94.8)	62.3 (45.4 - 79.3)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; IRF, independent review committee; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; NE, not evaluable; NR, not reported; OS, overall survival

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Source: adapted from table 28 in CS

The ERG consider the 30-month data to be the most relevant to the decision problem.

ERIVANCE: HrQoL results (SF-36)

Visit	N	Baseline (laBCC + mBCC)	Value at visit (laBCC + mBCC)	Change from baseline
Mental component				
Day 1	93	49.57 (11.57)	N/A	N/A
Week 12	82	49.24 (11.79)	51.44 (12.4)	2.20 (-0.22,4.62)
Week 24	75	49.38 (11.47)	51.67 (11.62)	2.29 (0.05,4.53)
End of study	20	49.90 (12.773)	46.11 (16.44)	-3.80 (-10.55,2.96)
Physical component				
Day 1	93	47.81 (9.907)	N/A	N/A
Week 12	82	49.14 (8.85)	47.89 (9.69)	-1.25 (-2.86,0.36)
Week 24	75	49.42 (8.70)	47.52 (9.87)	-1.90 (-3.75,-0.05)
End of study	20	45.72 (11.67)	42.85 (11.14)	-2.86 (-7.39,1.66)

Abbreviations: N/A, Not applicable; SD, Standard deviation

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Source: table 13 from the ERG report. Each component is scaled from 0 to 100, with higher scores relating to higher or better HRQoL.

The summary data provided in the CS were collected at the primary analysis and comprise of combined data from the laBCC and mBCC populations. The mean change from baseline in the mental component of the SF-36 was -3.80 (95% CI: -10.55 to 2.96), and -2.86 (95% CI: -7.39 to 1.66) for the physical component of the SF-36.

The mean change from baseline in the mental component and physical components of the health-related quality of life (HRQoL) SF-36 showed no statistically significant differences at the end of the study ($p < 0.05$).

The ERG highlighted that the Canadian HTA body discussed uncertainty around the SF-36 data from ERIVANCE pointing to the lack of sensitivity of the SF-36 instrument for this indication, the ceiling effect for relatively healthy individuals at baseline and the small sample size in ERIVANCE.

STEVIE: efficacy results

Study arm	Patients with laBCC n=1103	Patients with mBCC n=89	Total N=1192
Overall survival			
Median, months (95% CI)	Data not mature	Data not mature	NE
Progression-free survival			
Median, months (95% CI)	23.2 [21.4 to 26.0]	13.1 [12.0 to 17.7]	22.1 [20.3 to 24.7]
Outcomes among patients with measurable disease at baseline			
	n=1077	**n=84**	**N=1161**
Response rate			
Objective response rate, n (%) [95% CI]	738 (68.5) [65.66 to 71.29]	31 (36.9) [26.63 to 71.29]	769 (66.2) [63.43 to 68.96]

Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not evaluable

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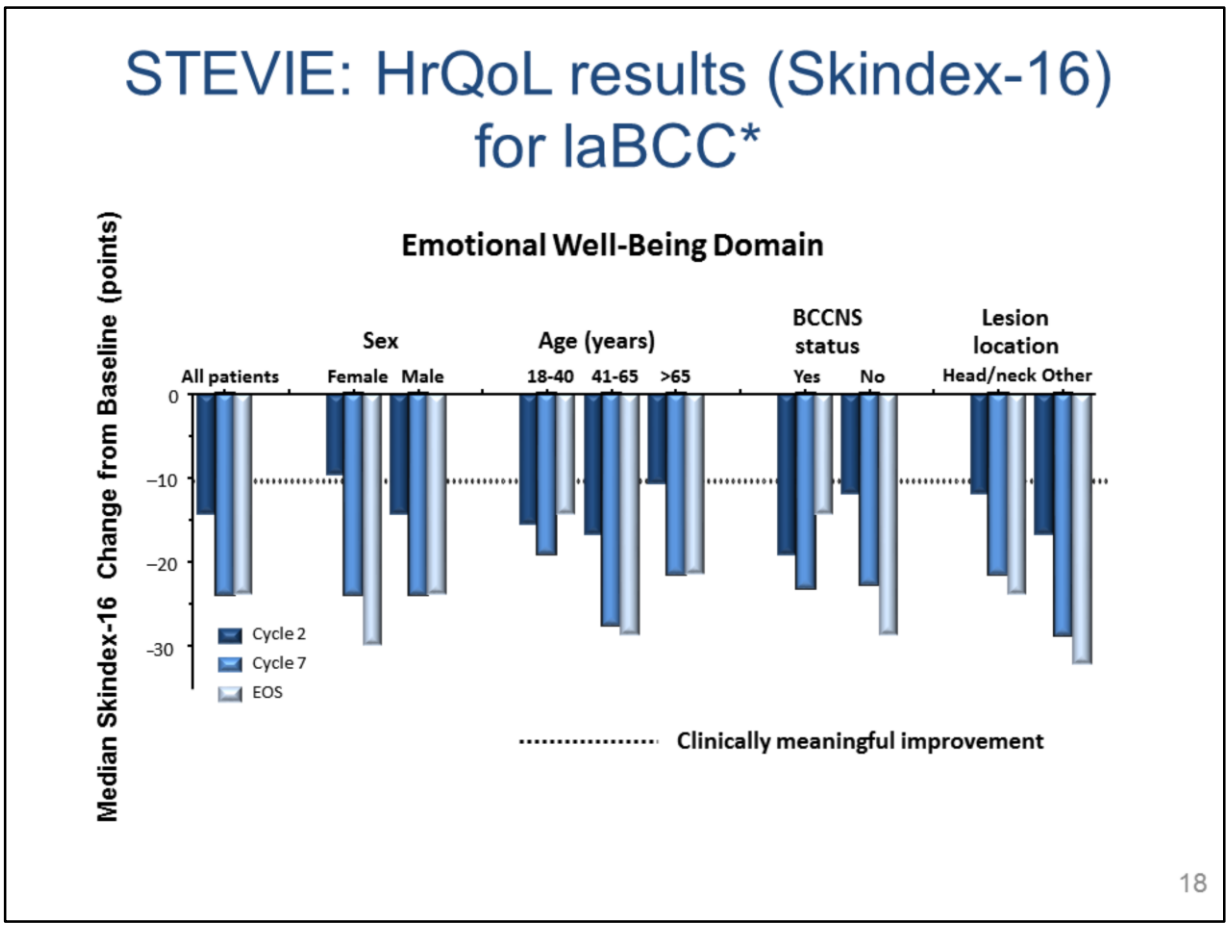
Source: adapted from table 29 in the CS

Progression-free survival

- The ERG highlighted that single-arm studies are not appropriate for capturing time-to-event data such as PFS and so the data should be interpreted with caution.
- The ERG notes that the PFS in STEVIE is substantially longer for laBCC patients compared to that seen in ERIVANCE (23.2 months vs 12.9 months, respectively). However, this is unlikely to be considered a statistically significant difference as the 95% CI for PFS in ERIVANCE includes the median PFS for STEVIE (ERIVANCE PFS 95% CI: 10.2 to 28.0 months).
- Median OS was not estimable for either the laBCC or mBCC populations in STEVIE and the data are immature as only 9.0% of patients had died by the data cut-off date of 16th March 2015.



Source: Figure 20 in CS

The Skindex-16 is a 16-item patient-completed questionnaire designed to measure QoL in patients suffering from skin disease and comprises of three domains: symptoms, emotions, and function. The 16 items are rated on a seven-point scale from zero (never bothered) to six (always bothered) and relate to the previous week.

mBCC:

no clinically meaningful improvement (defined as a decrease of ≥10 points from baseline) at any time point across all domains; the company reported that this was probably a result of the small sample size.

laBCC:

clinically meaningful improvements in emotion scores with vismodegib. The differences were irrespective of gender, Gorlin status and lesion location. There were no clinically meaningful changes seen for functional scores and there were no consistent changes seen for symptom scores. The company report that this could be a result of Skindex-16 being a dermatology focused instrument and thus does not detect other potentially important aspects of HRQoL that may be affected by vismodegib.

STEVIE: MD Anderson Symptom Inventory (MDASI) for mBCC

MDASI symptom	Baseline severity score (0 = Not Present; 10 = As Bad as You Can Imagine) Median (Range) (n = 15[a])
Pain	3.0 (0-10)
Fatigue	4.0 (0-9)
Shortness of breath	2.0 (0-6)
Loss of appetite	0.0 (0-7)
Dry mouth	1.0 (0-9)
Coughing	0.0 (0-6)

[a] Baseline MDASI data were available for 15 of 17 eligible patients.
Abbreviations: MDASI, M.D. Anderson System Inventory

People with mBCC with a baseline MDASI score ≥ 4 who achieved ≥ 30% reduction in disease-related symptoms	
No. of people	10
Yes	6 (60%)
No	4 (40%)

Notes: Baseline MDASI is defined as the last score prior to dosing within a given question.
30% reduction is at any on-treatment, post-baseline visit. A patient is considered to have had a 30% reduction if they had 4 points or more in a given question at baseline, and a 30% reduction in that question post baseline

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Source: adapted from tables 70 and 71 in CS

Patients with mBCC who were enrolled after the approval of Study Protocol Version 4.0 were asked to complete the MD Anderson Symptom Inventory (MDASI) in addition to the Skindex-16. The MDASI core instrument is a 19-item self-report questionnaire comprising of two scales, symptom severity and symptom interference. The baseline results of the MDASI revealed pain and fatigue were the worst symptoms experienced by mBCC patients

STEVIE subgroup analyses (post hoc): Gorlin syndrome

	Gorlin syndrome subgroup (n=219; of which 214 laBCC) (investigator-assessed)	Non-Gorlin syndrome subgroup (whole STEVIE population, n=1232) (investigator-assessed)
Duration of treatment		
Median, months	12.3	8.7
Response rate		
ORR n (%)	174 (81.7%)	593 (63%)
Duration of response		
Median, months (range)	28.8 (24.8 to NE)	18.5 (16.4 to 20.8)

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Results suggest that the Gorlin syndrome subgroup have a higher response rate and longer duration of response compared to non-Gorlin patients although the results are not statistically significant.

The ERG stated that these responses could however be linked to the lower age and better baseline performance score of the Gorlin subgroup:

The ERG highlighted the following:

a lower median age in people with Gorlin syndrome

- Gorlin syndrome: median 52.0 years [range 18 to 88]
- Non-Gorlin syndrome: median 72.0 years [range 20 to 101])

a greater proportion of people with Gorlin syndrome had an ECOG score of 0 (i.e. better performance status than non-Gorlin patients):

- Gorlin syndrome: 79.5%
- Non-Gorlin syndrome: 53.0%

a higher median number of target lesions in people with Gorlin syndrome:

- Gorlin syndrome median 3 [range 1 to 12]
- Non-Gorlin median 1 [range 1-10]

Overall safety profile for vismodegib

Adverse event, n (%)	ERIVANCE (n=104)	STEVIE (n=1215)*
Median duration of treatment, months	*12.9*	*9.4*
Any AE	**104 (100)**	**1192 (98)**
Any SAEs	36 (34.6)	289 (23.8)
Any grade ≥3 AE	**58 (55.8)**	**531 (43.7)**
AE resulting in treatment discontinuation	22 (21.2)	380 (31)
AE resulting in death	8 (7.7)	71 (5.8)
On-study death	33 (31.7)	110 (9.1)

Red denotes that the AEs were treatment-related
Green denotes that the AE is treatment-emergent (TEAE = an AE occurring up until 30 days after the last administration of vismodegib)

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Source: adapted from AEs tables 33-43, 45-51, 53-54 in CS

ERIVANCE:

- The most frequently occurring AEs with vismodegib were muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%), and weight loss (51.9%).
- Serious adverse effects were experienced by 34.6% of patients in ERIVANCE with a higher proportion occurring in the laBCC population compared to in the mBCC population (39.4% versus 24.2%, respectively). The most frequently occurring SAEs were pneumonia and syncope (each in 4 patients [3.8%]); death and hip fracture (each in 3 patients [2.9%]); and cardiac failure, cellulitis, gastrointestinal haemorrhage, squamous cell carcinoma, pulmonary embolism, and deep vein thrombosis (each in 2 patients [1.9%]).
- The company reported that there were in total 33 deaths in ERIVANCE (31.7%) with more deaths in the mBCC population compared to the laBCC population (51.5% versus 22.5%). The company also reported that none of the deaths were believed to be related to vismodegib (as assessed by the investigator) and that all patients who died during the study had significant pre-existing risk factors or co-morbidities at baseline.
- As of the data cut-off date 30 May 2013 (30 months since the primary analysis), 92.3% of patients had discontinued treatment. The most frequent reasons for treatment discontinuation were disease progression (27.9%), patient decision to discontinue treatment (26.0%), and AE (21.2%). A larger proportion of patients in the mBCC cohort (51.5%) had discontinued treatment because of disease progression compared with patients in the laBCC cohort

(16.9%).

STEVIE:

- The company reported that the most common TEAEs experienced in the whole trial population of STEVIE were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight loss (40.6%), and decreased appetite (24.9%). These AEs were similar to those seen in ERIVANCE.
- Grade ≥ 3 TEAEs showed there was a slightly higher proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively).
- The company reported that there were in total 110 deaths in STEVIE (9.1%) with more deaths in the mBCC population compared to the laBCC population (18.8% versus 8.2%). The ERG notes from Table 41 (in the CS) that there were four times as many deaths due to AEs compared to the number of deaths from disease progression. AEs were recorded as the primary cause of death in 71 patients although only 46 patients (3.8%) experienced a Grade 5 (fatal) TEAE (53 events). Vismodegib was considered by the investigator to be related to the deaths of 7 patients (myocardial infarction [n = 2]; pancreatitis [n = 1], pulmonary embolism [n = 1], ischemic stroke [n = 1], cardiorespiratory arrest [n = 1], and renal failure [n = 1]).
- As of the data cut-off date of 16 March 2015, almost 90% (1068 (87.9%) of patients had discontinued treatment. The most frequent reasons were adverse event (28.7%), other (23.3%; this included patients who requested withdrawal from treatment but who entered follow-up) and progressive disease (15.6%). A greater proportion of patients in the mBCC cohort (38.5%) discontinued treatment because of disease progression, compared with patients in the laBCC cohort (13.6%).

Vismodegib vs. BSC: 'Landmark' approach

- In the absence of a suitable comparator arm, a landmark analysis was conducted to compare vismodegib with BSC.
- Non-responders in STEVIE were used to derive a proxy for BSC. The definition of a non-responder varied depending on the outcome assessed:
  - **Overall survival:** people who had not died and who had either stable disease or progressive disease as their best response until the landmark
  - **Progression-free survival:** people who had not progressed or died and who had stable disease as their best response until the landmark

Non-responder data were then used to compare to responders in the STEVIE trial to estimate the relative treatment effectiveness of vismodegib vs. BSC at a 6-month landmark:

- The HRs for PFS and OS were estimated using a semi-parametric Cox proportional hazard (PH) model (assumes PH between responders and non-responders)
- To account for uncertainty in the HR:
  - a common treatment effect for both laBCC and mBCC people was used (aBCC)
  - HRs were adjusted for age and ECOG status as clinically relevant prognostic factors

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- The ERG stated that the analysis is based entirely on the use of a single arm interventional study and so constitutes observational data. The results of any analyses using the landmark approach should be considered low quality evidence.
- The ERG also highlighted that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.
- It is based on the use of responder and non-responder data from vismodegib patients in STEVIE at a fixed point in time.

Landmark method:

- STEVIE was selected over ERIVANCE to provide the clinical data used to generate the responder versus non-responders HRs, partly due to it having a much larger patient population compared to ERIVANCE, and because it was considered more reflective of UK clinical practice. The company decided not to pool the data from STEVIE and ERIVANCE because of the differences in patient characteristics between the two studies. The ERG agrees with the company's decision to use only data from STEVIE for generating the estimates of OS and PFS for responders versus non-responders in their landmark analysis.
- All analyses were carried out using data collected up until the 16th March 2015 data cut.

Non-responders

- The classification of patients as a responder or non-responder was affected by the time point

chosen as the landmark, with the landmark being the time onwards from which response was assessed with all events prior to the landmark censored.

- The company reported that to minimise the bias introduced in the analysis, all patients who experienced the event of interest before the landmark were excluded from the analysis. However, this resulted in a different definition of responders and non-responders for the analysis of PFS compared to for the analysis of OS.
- The company's rationale for this approach is provided p. 198, Section 5.3.5 in CS but relates only to mBCC, and so the ERG considers it does not provide justification for using the same approach for the laBCC population. In addition, the ERG highlighted that it results in different responder and non-responder populations for the resulting OS and PFS HRs thus limiting the comparability and extrapolation of the results within the aBCC populations of interest.

Choosing the landmark time-points: 6-month (and scenario analyses using a 3-month landmark)

- In the base case analysis, the landmark has been set according to a clear clinical rationale and the schedule of the study visits in the STEVIE study.
- The ERG considered that the choice of landmark should be done prospectively, based on a clinically meaningful time point, to prevent the results from the landmark being used to inform the landmark chosen. However, the landmark in the CS was chosen retrospectively. The company's rationale for their choice of a 6-month landmark for their primary analysis was that it, "allowed for at least two assessments of all patients regardless of treatment duration". This is because in STEVIE study visits were planned to occur every 28 days (± 5 days) with safety follow-up visits at 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib. At the 6-month landmark all patients should have received the 1 and 3-month safety follow-up, even if they have discontinued study drug prior to the first 28-day follow-up. The company further clarified it's choice in response to clarification.
- Table 68 in the CS summarises the number of responders after the landmark in the non-responders group for the 3-month landmark and 6-month landmark using the company's preferred definition of non-responders. The proportion of responders after the landmark is lower at the 6-month landmark compared with the 3-month landmark, which adds further support to the selection of the 6-month landmark.
- The ERG's clinical experts reported that they would expect to see a treatment response with vismodegib for both laBCC and mBCC patients, on average, by 3-months. The ERG thus considers the data and clinical expert opinion supports the company's choice of a 6-month landmark for their primary analysis. The ERG notes that the company also conducted a scenario analysis using a 3-month landmark with results presented in the CS for both the 3 and 6-month landmarks.

Baseline characteristics for responders and non-responders at 6-month landmark

		Responders			Non-responders		
		mBCC (N = 32)	laBCC (N = 523)	All (N = 555)	mBCC (N = 31)	laBCC (N = 213)	All (N = 244)
Number of target lesions, n(%)	1	11 (34.4)	234 (44.7)	245 (44.1)	6 (19.4)	118 (55.4)	124 (50.8)
	2	7 (21.9)	150 (28.7)	157 (28.3)	11 (35.5)	52 (24.4)	63 (25.8)
	3	7 (21.9)	36 (6.9)	43 (7.7)	7 (22.6)	11 (5.2)	18 (7.4)
	3+	6 (18.8)	99 (18.9)	105 (18.9)	4 (12.9)	17 (8.0)	21 (8.6)
ECOG status, n(%)	Grade 0	16 (50.0)	332 (63.5)	348 (62.7)	14 (45.2)	131 (61.5)	145 (59.4)
	Grade 1	14 (43.8)	131 (25.0)	145 (26.1)	11 (35.5)	62 (29.1)	73 (29.9)
	Grade 2	2 (6.3)	59 (11.3)	61 (11.0)	6 (19.4)	20 (9.4)	26 (10.7)
Gorlin syndrome, n(%)	YES	4 (12.5)	130 (24.9)	134 (24.1)	1 (3.2)	34 (16.0)	35 (14.3)
	NO	28 (87.5)	392 (75.0)	420 (75.7)	30 (96.8)	177 (83.1)	207 (84.8)
Age at baseline	Median years (range)	63 (42-88)	70 (18-100)	70 (18-100)	66 (42-90)	67 (25-95)	67 (25-95)

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Source: Table 27 in ERG report (Company clarification response Question A2)

- The baseline characteristics of the responder and non-responders at the 6-month landmark presented above suggest there is a higher proportion of patients with more than one lesion, and with Gorlin syndrome in the responder group compared to the non-responder group.
- The ERG considers this highlights the importance of also including Gorlin syndrome as a covariate in the analysis, and that number of target lesions at baseline should also ideally have been included as a covariate.

Conditional HR of non-responders vs. responders estimated using the landmark approach

	Progression-free survival		Overall survival	
	No covariates	Covariates*	No covariates	Covariates*
3-month landmark				
Common effect laBCC & mBCC (95% CI)	1.29 (1.018 to 1.636)	1.26 (0.977 to 1.626)	1.647 (1.061 to 2.556)	1.73 (1.091 to 2.744)
Separate effect laBCC (95% CI)	1.313 (1.02 to 1.691)	1.336 (1.02 to 1.75)	1.776 (1.108 to 2.844)	1.889 (1.15 to 3.103)
Separate effect mBCC (95% CI)	0.893 (0.446 to 1.788)	0.953 (0.404 to 2.247)	0.603 (0.176 to 2.062)	0.634 (0.173 to 2.321)
6-month landmark				
Common effect laBCC & mBCC (95% CI)	1.238 (0.952 to 1.61)	1.311 (0.985 to 1.746)	1.919 (1.159 to 3.177)	2.161 (1.27 to 3.676)
Separate effect laBCC (95% CI)	1.208 (0.908 to 1.608)	1.305 (0.959 to 1.776)	1.913 (1.106 to 3.309)	2.192 (1.225 to 3.922)
Separate effect mBCC (95% CI)	1.052 (0.523 to 2.113)	0.995 (0.411 to 2.408)	1.201 (0.322 to 4.478)	1.151 (0.296 to 4.473)

Red denotes statistically significant difference between non-responders and responders (>1 favour of the responders)

* Covariates included ECOG status and age at landmark

Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC.

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Source: Adapted from CS page 202, Table 67

Note: The conditional hazard ratio between non-responders and responders was estimated among patients who did not experience the event of interest before landmark.

The ERG highlighted that these results use different definitions of responders and non-responders for PFS and OS, and so the resulting hypothetical responder and non-responder populations are different depending on outcome assessed. Also of note, the covariate adjustment generally increased the HRs. This is because the non-responders group had more favourable baseline age and ECOG scores (younger age and lower ECOG score), and so the effect of "no response" was underestimated in the unadjusted analyses.

The HRs reported by the company when laBCC and mBCC were analysed as one population (aBCC) generally suggested that responders had more favourable PFS and OS HRs than non-responders, which would imply vismodegib was better than BSC. When analysed as separate populations, the HRs for the laBCC population were higher than for the combined aBCC population, whereas they were lower for the mBCC population. The HRs were <1 for mBCC patients suggesting that the non-responders with mBCC have a more favourable PFS and OS compared to mBCC responders. The company reported that this result is implausible and emphasised the considerable uncertainty in the analysis due to the small number of mBCC patients. The company highlighted that clinical opinion suggests the treatment effect with

vismodegib should be similar between laBCC and mBCC patients. The ERG stated it was difficult to draw conclusions based on the landmark analysis approach used; prefers the inclusion of additional covariates and the use of a coherent definition for non-responders for the primary analysis of PFS and OS.

Using ERG's preferred definition of non-response* and covariate adjustment on OS at 6-month landmark

	laBCC	mBCC	Combined
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-responders vs responders	1.826 (1.019 to 3.275)	1.105 (0.276 to 4.422)	1.793 (1.048 to 3.068)
Non-responders vs responders (adjusted for age and ECOG)	2.096 (1.124 to 3.908)	1.146 (0.265 to 4.956)	1.992 (1.129 to 3.515)
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**2.035 (1.085 to 3.817)**	**1.035 (0.238 to 4.491)**	1.937 (1.091 to 3.438)
Non-responders vs responders (adjusted for age)	2.176 (1.176 to 4.027)	0.959 (0.237 to 3.878)	2.091 (1.193 to 3.666)
Non-responders vs responders (adjusted for ECOG)	1.870 (1.037 to 3.373)	1.299 (0.307 to 5.503)	1.779 (1.035 to 3.059)
Non-responders vs responders (adjusted for Gorlin syndrome)	1.642 (0.913 to 2.951)	1.195 (0.285 to 5.008)	1.619 (0.944 to 2.779)

* people with stable disease where those who have progressed or died prior to the landmark were excluded (as for PFS)

Red denotes statistically significant difference between non-responders and responders (>1 favour of the responders)

Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; laBCC, locally advanced BCC; mBCC, metastatic BCC; OS, overall survival

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Source: adapted from company clarification response Question B10 d and e and ERG report table 29

This analysis:

- defined non-responders as patients with stable disease where those who have progressed or died prior to the landmark were excluded from the analysis. This results in the same patients being assessed in the same groups for both outcomes (PFS and OS).
- included a covariate adjustment for Gorlin syndrome as well as the ones applied by the company for age and ECOG status
- assumed a common effect for laBCC and mBCC

The results of the analysis for OS with covariate adjustment for age, ECOG and Gorlin syndrome applied show a statistically significant increase in mortality for non-responders compared with responders for the laBCC population (HR 2.04, 95% CI: 1.09 to 3.82). The OS in the mBCC population also suggested a trend in favour of the responders (HR 1.04; 95% CI: 0.24 to 4.49). However, there was no statistically significant difference between non-responders compared with responders in the mBCC population, and the HR was associated with more uncertainty than the laBCC HR, as demonstrated by the wider 95% CIs.

Using ERG's preferred definition of non-response* and covariate adjustment on PFS at 6-month landmark

	laBCC	mBCC	Combined
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-responders vs responders	1.208 (0.908 to 1.608)	1.052 (0.523 to 2.113)	1.238 (0.952 to 1.61)
Non-responders vs responders (adjusted for age and ECOG)	1.305 (0.959 to 1.776)	0.995 (0.411 to 2.408)	1.311 (0.985 to 1.746)
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**1.19 (0.869 to 1.629)**	**0.951 (0.388 to 2.331)**	**1.204 (0.9 to 1.611)**
Non-responders vs responders (adjusted for age)	1.314 (0.966 to 1.787)	0.91 (0.40 to 2.069)	1.329 (0.999 to 1.768)
Non-responders vs responders (adjusted for ECOG)	1.237 (0.928 to 1.647)	1.048 (0.494 to 2.223)	1.249 (0.96 to 1.625)
Non-responders vs responders (adjusted for Gorlin syndrome)	1.041 (0.778 to 1.393)	1.072 (0.523 to 2.196)	1.081 (0.828 to 1.41)

*people with stable disease where those who have progressed or died prior to the landmark were excluded (as for PFS)
Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; laBCC, locally advanced BCC; mBCC, metastatic BCC; OS, overall survival

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Source: adapted from company clarification response Question B10 d and e and ERG report table 30

The results of the analysis of PFS at the 6-month landmark with the covariate adjustments for age, ECOG and Gorlin syndrome show no statistically significant difference between the non-responder and responder groups although the HR of 1.19 suggests a trend in PFS in favour of the responder group for the laBCC population (95% CI: 0.87 to 1.63). The HR for the mBCC population was 0.95 (95% CI: 0.39 to 2.33), implying the non-responders have a longer PFS than the responders (i.e. BSC better) although it is not statistically significant and may suggest there is no difference in PFS between responders and non-responders. However, the analysis is based on a very small number of patients with a wide 95% CI.

Landmark analysis results using the ERG preferred coherent definition of non-response, covariate adjustment for baseline age, ECOG score and Gorlin status using the 6-month landmark were consistent with the company's primary analysis findings .

Landmark analysis for PFS and OS according to Gorlin syndrome status

	PFS, progression or death before landmark excluded	OS, death before landmark excluded	OS, progression or death before landmark excluded
	No covariates	No covariates	No covariates
3-month landmark			
With Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.221 (0.746 to 1.998)	4.212 (0.894 to 19.842)	4.16 (0.883 to 19.599)
Without Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.219 (1.018 to 1.46)	1.45 (1.054 to 1.997)	1.394 (0.998 to 1.946)
6-month landmark			
With Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.527 (0.852 to 2.737)	4.101 (1.023 to 16.442)	4.251 (1.062 to 17.016)
Without Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.079 (0.885 to 1.315)	1.656 (1.144 to 2.397)	1.506 (1.014 to 2.237)

Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC; OS, overall survival; PFS, progression free survival

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The company also provided an exploratory analysis for OS and PFS for the Gorlin syndrome subgroup in their response to clarification questions. The analysis assumed a common treatment effect for laBCC and mBCC as the company reported that stratifying would have resulted in extremely small sample sizes and greater uncertainty in the results. In addition, the company did not apply covariate adjustments for age and ECOG status in these analyses.

The ERG agreed that an analysis of responder versus non-responder for the mBCC population at the 6-month landmark with the Gorlin subgroup would not have been feasible as there would only have been four responders and one non-responder in the analysis according to the baseline characteristics (see table 27 in the ERG report). However, the ERG considers it would have been feasible to conduct a subgroup analysis for laBCC patients using the 6-month landmark as there were 130 responders and 34 non-responders (Table 27 in ERG report). Additionally, the ERG would have preferred to have had appropriate covariates applied to adjust for baseline differences such as age and ECOG status.

The results for the Gorlin syndrome subgroup at the 6-month landmark suggest they may have improved OS compared to the non-Gorlin subgroup (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively). However, both Gorlin and non-Gorlin responders showed a statistically significant reduction in mortality compared to non-responders. The results for PFS were not statistically significant for either the Gorlin or non-Gorlin subgroup analyses of responders versus non-responders, but the mean HR for the non-responders versus responders in the Gorlin syndrome subgroup was higher than for the non-Gorlin subgroup. These results suggest

that the Gorlin syndrome subgroup may have a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

Summary of ERG comments (1)

- ERIVANCE and STEVIE are the key studies, with STEVIE most representative of UK clinical practice (population in ERIVANCE was younger)
- Single-arm studies, thus a high risk of bias; single-arm studies are not considered appropriate to capture outcomes such as PFS and OS
- The company's search strategy was not comprehensive enough to identify studies of BSC in aBCC, the comparator of interest
- A high proportion of patients in both studies had Gorlin syndrome (not expected in the UK population)
- No data on the long-term safety and efficacy of vismodegib is available; data on OS in laBCC are immature and data on mBCC based on small patient numbers
- OS data are likely confounded by the use of subsequent treatment although no data on subsequent treatments were recorded as part of either ERIVANCE or STEVIE
- High levels of AEs in ERIVANCE and STEVIE (100% and 98% of patients, respectively)
- Compared with background mortality in the general population, there appears to be an increase in mortality in STEVIE, which has not been explained but it could be because only 3% of the STEVIE population were from UK sites

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For more information, refer to page 64 in CS.

Summary of ERG comments (2)

- **Landmark analysis is of limited value in the evaluation of comparative clinical effectiveness as the analysis is based on the use of responder and non-responder data for vismodegib people in STEVIE at a fixed time point:**
  - Non-responders have received vismodegib and therefore are not reflective of BSC population
  - Responders are not reflective of all patients treated with vismodegib and are therefore likely to overestimate PFS and OS of vismodegib
  - The results for mBCC are based on small population numbers (<100 people and therefore the evidence base is extremely limited for drawing any conclusions relating to vismodegib in mBCC

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Summary of ERG comments (3)

- **The ERG has got concerns around the validity of the methods used to carry out the landmark analysis**
  - The ERG agrees with the company that the 6 month landmark is more appropriate than the 3 month landmark but is concerned that these are only two alternatives of all possible landmarks, which have not been explored
  - The ERG notes the difficulty in choosing an appropriate landmark and suggests that it would be useful to have evidence from multiple landmark time points around the 6 month landmark to help indicate how appropriate it is
  - Important covariates may have been omitted from the landmark analysis due to the non-systematic approach taken and the limited number of covariates included
  - Different definitions of non-responders for estimation of HRs will result in different responder and non-responder populations for the resulting OS and PFS HRs thus limiting the comparability and extrapolation of the results within the aBCC populations of interest

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ERGs conclusion on the landmark analysis:

Overall, the ERG considers that results of the landmark analysis should be interpreted with caution because they are based on non-randomised data and are at a high risk of bias and the validity of the methods used to carry out the landmark analysis is questionable. In addition, conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies.

Summary of ERG comments (4)

- **The ERG does not consider the Gorlin syndrome subgroup to have been addressed adequately**
  - the ERG notes that people with Gorlin syndrome in STEVIE differed from the people with non-Gorlin syndrome in key prognostic factors, having a lower median age, a more favourable ECOG performance status and higher median number of target lesions
  - the ERG notes that the Gorlin subgroup results from the landmark analysis are not adjusted for differences in baseline characteristics. In addition, they are not presented separately for the laBCC and mBCC populations

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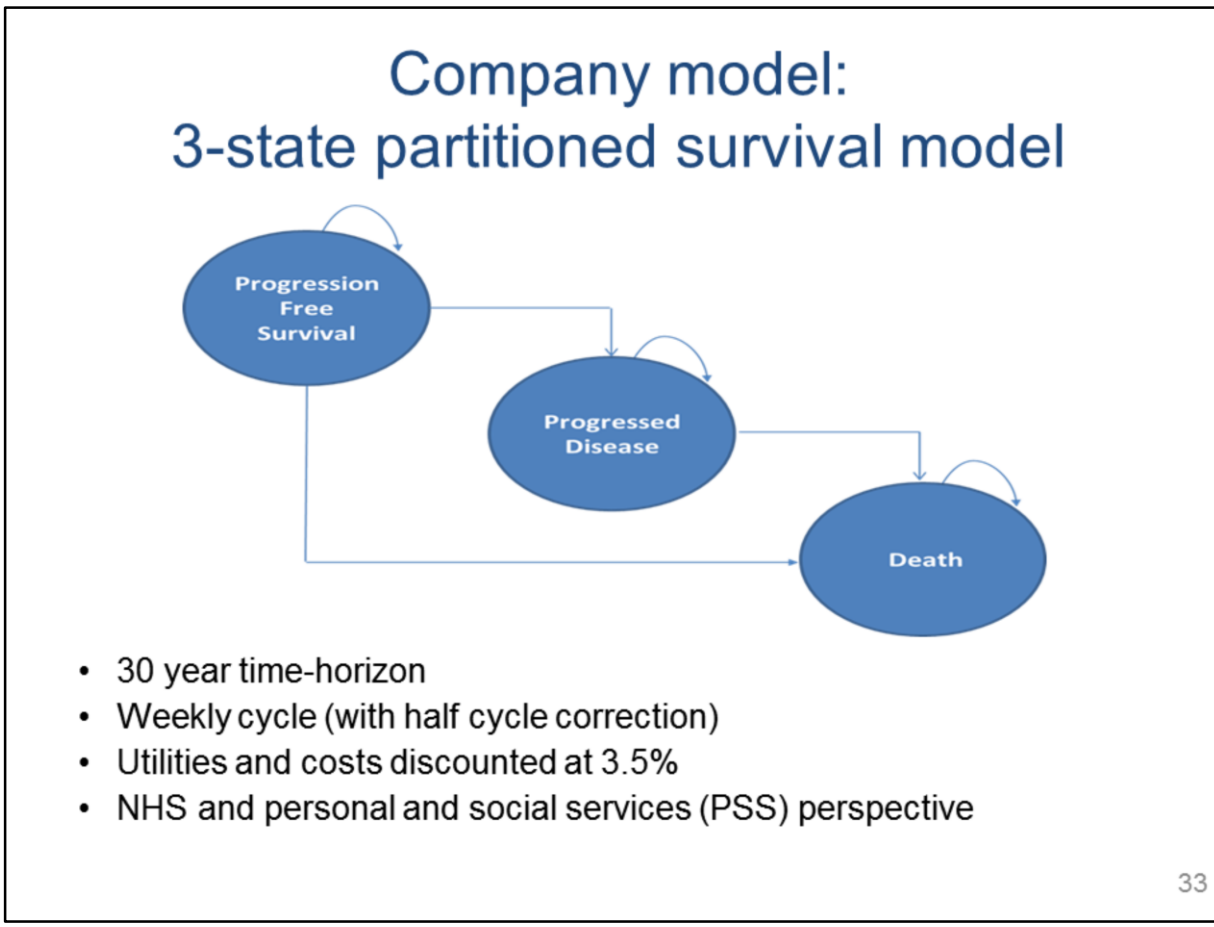
Cost effectiveness



Patients enter the model in the PFS health state and remain there until disease progression or death. While in PFS, patients receive treatment with vismodegib until disease progression or unacceptable toxicity. After transitioning to the PD state, patients remain there until they die. In this model, it is not possible for a patient to transition back from the PD state to the PFS health state. A transition to death is possible from either of the other two health states in the model. Progressed vismodegib patients are assumed to receive BSC as a subsequent treatment in the economic analysis. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome.

The company presented 2 models for la BCC and mBCC, using the same model structure and modelling approach with different data inputs. In order to estimate a single final ICER the company weighted the individual ICERs resulting from the laBCC and mBCC models by the proportion of laBCC and mBCC patients in the STEVIE trial. The ERG stated that the 2 populations should be analysed separately.

The model does not assume any subsequent lines of therapy in either treatment arm. Whilst clinical advice received by the company suggested patients would go on to receive subsequent therapies, there is a lack of data to allow robust incorporation of such a treatment pathway in the model. In spite of this, patients originally receiving vismodegib therapy are assumed to receive BSC once having progressed.

This type of model was considered appropriate for the decision problem. Both the structure and health states are in-line with the clinical pathway.

Modelling clinical outcomes

- The company base case used the 6-month landmark analysis results from the STEVIE study
- Parametric distribution used in base case for both vismodegib and BSC to extrapolate PFS, TTD & OS:
  - PFS: Weibull
  - TTD: Weibull
  - OS: Gamma (laBCC) and Weibull (mBCC)
- ITT population data was used in the vismodegib models instead of responders in STEVIE
- To estimate the relative effect of non-responders versus ITT population, the HRs derived from the landmark approach were adjusted:
- laBCC and mBCC were modelled separately but the common effect (laBCC and mBCC) HR derived from the landmark approach was used
- Duration of treatment effect between vismodegib and BSC was assumed to equal after the last observation point in STEVIE (conservative)
- The base case model assumes that the proportional hazards assumption holds for the responders vs. non-responders in STEVIE

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Survival analysis: extrapolation

- To extrapolate PFS, OS and ToT for the duration of the model, the company explored the applicability of 6 parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull). The company also explored the option of including KM curves with a parametric tail used for extrapolation in deterministic sensitive analyses. The fit of each parametric model was compared with the observed KM data and statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- Further details on the distributions selected for the company base case is provided in section 5.3 of the company submission.

Company's adjustment of HRs

- HR(t) increases over time because the proportion of responders among intent-to-treat patients who are still progression-free or alive increases over time, hence the final HR is a time-varying HR

Costs and resource use assumptions used in the economic model (base case)

1. The frequency of oncologist visits in the vismodegib arm is assumed to be once every four weeks in PFS and eight weeks in PD
2. The frequency of dermatologist visits in the BSC arm is assumed to be once every 12 weeks.
3. The frequency of GP visits are assumed to be once every 4 weeks, irrespective of health state and treatment arm.
4. The frequency of tissue viability nurse (TVN) visits is assumed to be 1,2, and 3 times per week in vismodegib PD, BSC PFS, and BSC PD respectively
5. The cost of managing a person's wound per TVN visit is assumed to be £10.00
6. 50% of people in BSC treatment receive palliative radiotherapy
7. 30% and 20% of people receiving radiotherapy are assumed to receive basic and complex treatment respectively.
8. Average treatment regimen of people receiving palliative radiotherapy in this indication is assumed to be - 20 Gray in 5 fractions, once in a lifetime
9. 67% of people receive monitoring only after progressing on vismodegib
10. 33% of people switch to BSC after progressing on vismodegib

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Source: adapted from table 89 in CS

Utility values are derived from patient level SF-36 data from ERIVANCE trial

- SF-36 data mapped to EQ-5D
- STEVIE only reports Skindex-16 and MDASI data – no mapping algorithm exist for the transformation of these data to EQ-5D
- Different utility values were applied in the model consistently over time based on progression status and type of aBCC

Health state utility values used in the model		
Health state	**laBCC (95% CI)**	**mBCC (95% CI)**
Progression-free survival	0.839 (0.81-0.87)	0.819 (0.79-0.85)
Progressive disease	0.757 (0.68-0.83)	0.639 (0.42-0.85)
Abbreviations in table: laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; SE, standard error.		

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Source: table 48 in ERG report/ table 73 in CS

- The ERG highlighted that the clinical aspects of this model have been populated using data from the STEVIE clinical trial. The ERG stated that it's main concern with applying the ERIVANCE-derived utilities to the STEVIE study population is due to the assessment of response/progression in each of the trials. In laBCC patients, disease progression in STEVIE was assessed according to the RECIST V1.1 criteria. In ERIVANCE disease progression was assessed according to a novel composite measure in the laBCC population.

Disutilities

- Utility decrements due to AEs (Grade 3 and 4) were included in the model
- The company used values reported in a study (Beusterien *et al.*) assessing the impact of treatment for advanced melanoma on quality of life for people in Australian and UK and assumed these to be applicable to laBCC and mBCC populations:

Adverse event decrements included in the model			
Adverse event	**Disutility**	**Standard error**	**Duration [days]***
Grade 3 (1 day in-/outpatient stay)	0.13	0.01	7
Grade 4 (2-5-day hospitalisation)	0.17	0.01	14
* Assumptions			

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Source: table 76 in CS

Note:

The specific AEs included in the company model did not align with those events evaluated in the Beusterien *et al.* publication. In the study, the authors reported utility decrements for generic grade three and grade four events. The values were assumed equal to a 1 day in-/outpatient stay and a 2-5 day hospitalisation, respectively.

Company base case model results (corrected)

Results were calculated separately for laBCC and mBCC, then weighted by the percentage of laBCC (92.1%) and mBCC (7.9%) patients in STEVIE to represent the aBCC population

Tx	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) incr.(QALYs)
Combined base case results using list price							
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				
La BCC base case results using list price							
BSC	£97,519	9.95	7.69	£27,345	1.16	0.90	£30,493
Vismodegib	£124,865	11.11	8.58				
mBCC base case results using list price							
BSC	£40,813	4.28	2.95	£80,651	1.20	0.80	£100,615
Vismodegib	£121,465	5.48	3.75				

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Sources: Tables 55 – 57 in ERG report

***Note:** the company corrected its base case ICER in response to clarification question B20 (using the cost of a dermatologist visit instead of a GP visit from £23,042 to £23,886) and the corrected base case ICER is presented above.

Company base case model results (including PAS – yet to be approved)

Base case results (corrected)

Tx	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) incr.(QALYs)
Combined base case results including PAS							
BSC	£93,352	9.50	7.31	[redacted]	1.16	0.89	[redacted]
Vismodegib	[redacted]	10.66	8.20				
La BCC base case results including PAS							
BSC	£97,519	9.95	7.69	[redacted]	1.16	0.90	[redacted]
Vismodegib	[redacted]	11.11	8.58				
mBCC base case results including PAS							
BSC	£40,813	4.28	2.95	[redacted]	1.20	0.802	[redacted]
Vismodegib	[redacted]	5.48	3.75				

Please note these costs and ICERs are commercial-in-confidence

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QALY breakdown according to health state

Health state	QALYs BSC	QALYs vismodegib	Incr.	QALYs BSC	QALYs vismodegib	Incr.
	laBCC			mBCC		
PFS	1.57	1.79	0.22	0.95	1.11	0.16
PD	6.12	6.79	0.67	1.99	2.63	0.64
AEs	0.00	0.00	0.00	0.00	0.00	0.00
Total	7.69	8.59	0.90	3.75	3.75	0.80

Abbreviations in table: AEs, adverse events; BSC, best supportive care; PD, progressed disease; PFS, progression-free survival; Incr, increment

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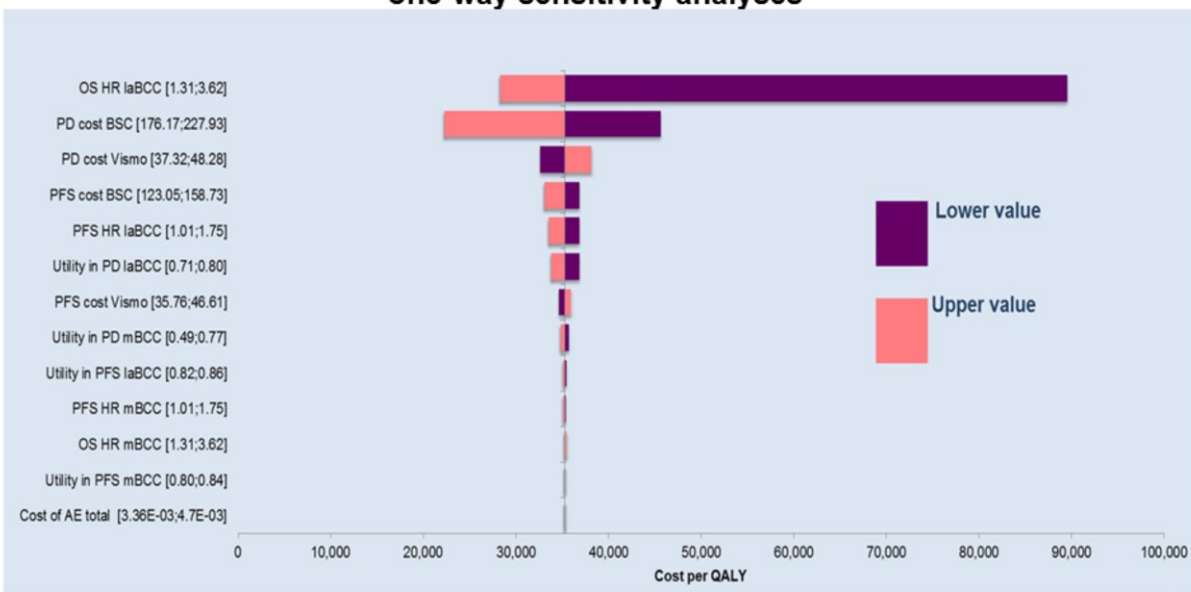
Source: table 58 in ERG report

The breakdown of QALYs accumulated in the model according to health state is presented above. Most of the incremental QALY gain for vismodegib against BSC stems from the PD health state, for both laBCC and mBCC patients. This is related with the mortality benefit seen in the company's model, as patients in the vismodegib arm live longer than in the BSC arm, therefore accruing more QALYs while in the PD state.

Deterministic sensitivity analyses showed that survival for people with laBCC is the main driver of the company base case model (vismodegib list price)

Tornado diagram of the 13 most influential parameters from the company one-way sensitivity analyses



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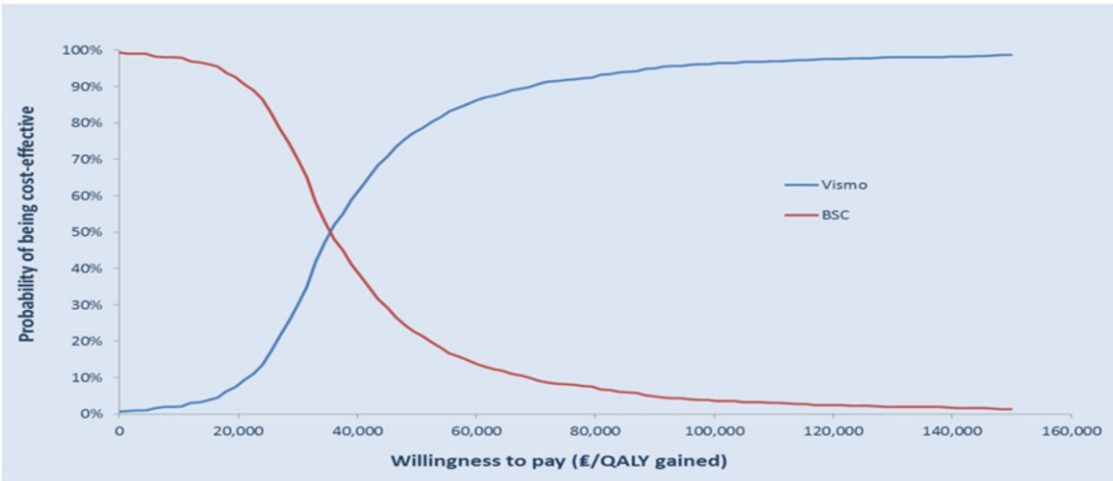
** Corrected base case model*

Source: Figure 30 in ERG report

According to the analysis the main drivers of the model are the hazard ratio for OS for patients with laBCC, and the cost for progressed disease for patients in the BSC arm of the model. Using the upper and lower limits of the OS hazard ratios for laBCC patients causes the ICER to range from £28,318 to £88,336 per QALY gained.

Probabilistic sensitivity analyses results (vismodegib list price)

Tx	Costs		QALYs		ICERs	
	Base case (deterministic)	PSA	Base case (deterministic)	PSA	Base case (deterministic)	PSA
BSC	£93,352	£93,061	7.31	7.23	£35,251	£35,798
Vismodegib	£124,699	£124,553	8.20	8.11		



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** Corrected base case model*

Source: Table 61 and figure 32 in ERG report

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results across 1,000 iterations are presented above for the corrected model. The PSA results produced a mean ICER of £35,798 per QALY gained for vismodegib compared to BSC.

Results of company scenario analyses for costs and utilities using vismodegib list price – original model (1)

Parameter	Value	Vismodegib vs. BSC
		ICER
Wound care cost per visit	£0.00	£48,409
	£20.00	£20,406
	£40.00	Dominant
	£60.00	Dominant
TVN frequency in PD for vismodegib arm	1	£34,407
	3	£54,583
TVN frequency in PFS for BSC arm	1	£40,853
	3	£27,962
	5	£15,071
TVN frequency in PD for BSC arm	1	£89,151
	3	£34,407
	5	Dominant

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Source: adapted from table 98 in CS

Note: the company corrected its base case ICER in response to clarification question B20 (using the cost of a dermatologist visit instead of a GP visit from £23,042 to £23,886). The company did not correct the results of the scenario analyses. The base case ICER in the original model was £34,407 compared with £35,251 in the corrected model per QALY gained. Even though the final results are not for the corrected model, these show the impact of changing the parameters listed above on the company's results.

Results of company scenario analyses for costs and utilities using vismodegib list price – original model (2)

Parameter	Value	Vismodegib vs. BSC
		ICER
Utilities	Shringler	£35,445
	ERIVANCE	£34,407
TTD distribution laBCC	Exponential	£36,468
	Weibull	£34,407
	Log-normal	£48,661
	Gamma	£45,296
	Log-logistic	£45,415

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Source: adapted from table 98 in CS

Note: the company corrected its base case ICER in response to clarification question B20 (using the cost of a dermatologist visit instead of a GP visit from £23,042 to £23,886). The company did not correct the results of the scenario analyses. The base case ICER in the original model was £34,407 compared with £35,251 in the corrected model per QALY gained. Even though the final results are not for the corrected model, these show the impact of changing the parameters listed above on the company's results.

Results of company scenario analyses for efficacy using vismodegib list price – original model (1)

Parameter	Value	Vismodegib vs. BSC
		ICER
PFS distribution laBCC	Exponential	£34,971
	Weibull	£34,407
	Lognormal	£34,727
	Gamma	£34,410
	Log-logistic	£34,280
	Gompertz	£32,361
OS distribution laBCC	Exponential	£65,367
	Weibull	£66,221
	Lognormal	£46,481
	Gamma	£34,407
	Log-logistic	£56,996
	Gompertz	£65,367

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Source: adapted from table 99 in CS

Note: the company corrected its base case ICER in response to clarification question B20 (using the cost of a dermatologist visit instead of a GP visit from £23,042 to £23,886). The company did not correct the results of the scenario analyses. The base case ICER in the original model was £34,407 compared with£35,251 in the corrected model per QALY gained. Even though the final results are not for the corrected model, these show the impact of changing the parameters listed above on the company's results.

Results of company scenario analyses for efficacy using vismodegib list price – original model (2)

Parameter	Value	Vismodegib vs. BSC ICER
OS treatment effect cut-off laBCC	20	£50,771
	40	£35,841
	60	£32,052
	80	£30,584
	100	£29,929
OS background mortality cut-off laBCC	0	£145,472
	75	£39,315
	150	£34,866
	225	£40,273
	300	£40,273
	375	£40,281

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Source: adapted from table 99 in CS

Note: the company corrected its base case ICER in response to clarification question B20 (using the cost of a dermatologist visit instead of a GP visit from £23,042 to £23,886). The company did not correct the results of the scenario analyses. The base case ICER in the original model was £34,407 compared with £35,251 in the corrected model per QALY gained. Even though the final results are not for the corrected model, these show the impact of changing the parameters listed above on the company's results.

ERG critique of the company's cost-effectiveness evidence

Company's adjustment of the landmark HRs & the assessment of proportional hazards

ERG disagrees with the theoretical and methodological implications of the adjustment made by the company, to try and reflect the relative treatment effectiveness of vismodegib vs. BSC (ITT)

- The final HR used in the model is a time-varying HR but there is no evidence to suggest such effects exist, and it is not methodologically-based
- But note adjusting HRs is conservative as it decreases the HRs used in the model, therefore increasing the ICERs

The ERG questions whether the assessment of PH could provide meaningful results

- Considering the landmark approach was undertaken, the extremely small number of people in the mBCC analysis and the fact that the PH assumption in the company's base case model do not seem to hold (depending on the landmark used (3- or 6- month) and on the outcome considered)
- This is likely to introduce further uncertainties in the results, particularly for OS data

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The ERG suggested the following possible alternative approaches that could have been taken, although each has their own flaws:

- The company could have explored fitting the responders and non-responders data from STEVIE independently or fitted the dataset with a time-varying model.
- However, the ERG notes that fitting responders and non-responders data independently would have raised a different issue. Using these populations as proxies for a vismodegib arm and a BSC arm, respectively, would have introduced bias in the analysis and overestimated the effectiveness of vismodegib and the effectiveness of BSC.
- Applying the "unadjusted" HR resulting from the landmark approach to the ITT population in STEVIE is also partially flawed. The HR reflects the relationship between a "perfect response" vismodegib group and a BSC group with potentially better outcomes than a real BSC group. However, assuming that the upwards bias introduced in this analysis cancels out (the overestimation of vismodegib effectiveness cancels out the overestimation of BSC effectiveness), then applying this HR to the ITT population could approximate the analysis to what would be observed in a comparative trial evaluating vismodegib vs BSC. This approach preferred by the ERG in its exploratory analysis.

Assessment of proportional hazards in clinical events:

- Although the initial tests (visual inspection of log-cumulative hazard plots) seem to indicate that PH does not hold for OS or for PFS for mBCC patients, this could be a product of the combination of the method of analysis and the extremely small numbers of mBCC patients.

- With regard 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.

For more information see section 5.4.5.2 in ERG report.

Selection of HRs to be used in the economic model

The ERG disagrees with the decision of using a common treatment effect (laBCC and mBCC) HR in the model

- ERG considers that the two patient groups should be analysed separately from a clinical point of view, as well as an economic perspective due to the clinical and prognostic differences in the two populations

The ERG is concerned that important covariates may have been omitted from the landmark analysis

- A limited number of covariates were included in the analysis
- The selection process of covariates was not systematic -> selection bias?
- ERG's clinical experts 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.)

ERG: *The HRs and the methods used to model treatment with vismodegib and BSC in the cost-effectiveness analysis (dependent fit and assumption of PH) carry a high degree of uncertainty* **->** *substantial uncertainty in the final ICERs*

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Definition of TTD and estimation of the PDS and OS HRs

The ERG noted that the definition of time to treatment discontinuation (TTD) in STEVIE may not be an accurate representation of treatment discontinuation in clinical practice

- 2 months (STEVIE) vs. 3 months (clinical practice)

The ERG has concerns regarding the methodological uncertainties associated with the estimation of the PFS and OS HRs

- OS and PFS results for mBCC from the landmark analysis are based on a small number of people (<100 people)
- In addition, the PFS HR for mBCC is <1, indicating that vismodegib is worse than BSC at delaying progression: the ERG's clinical experts do not consider this a clinically plausible scenario
- For laBCC, the OS HR for laBCC is statistically significant in favour of vismodegib but the PFS HR for laBCC is not – this is caveated by the uncertainty in the HR introduced by the methods used to estimate clinical effectiveness
- The ERG state that 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

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Time to treatment discontinuation

Considering the frequent treatment breaks required by vismodegib patients, the ERG agrees with the company's approach of using TTD data to capture treatment costs in the model. However, the definition of treatment discontinuation in STEVIE might not be an accurate representation of treatment discontinuation in clinical practice. While STEVIE patients were considered to discontinue treatment after two months off treatment, in clinical practice patients seem to have three month breaks in their treatment regimens before continuing treatment. Considering the expected vismodegib treatment regimen in the UK, both STEVIE and the economic model are unlikely to reflect clinical practice in terms of treatment costs and benefits.

Estimation of OS and TTD KM curves

The ERG questions the plateau observed in the OS and TTD KM curves

- The ERG consider it unusual that there were no death or discontinuation events for approximately 1.5 years before the end of the follow-up period (44 months for laBCC and 38 months for mBCC)
- The OS KM tails imply that no patient with mBCC would die for 18 months. The ERG finds this implausible from a clinical point of view considering by 26 months, people in STEVIE would be, on average, 74 years

The ERG has concerns regarding the estimation of OS curves

- The OS laBCC curve suggests that there is an increased mortality risk in people with laBCC but according to ERG's clinical experts, this is highly unlikely
- The mortality for people with mBCC is underestimated by the assumption that they would survive for >10 years in the model (estimated survival: 1-2 years post diagnosis)

The ERG has concerns regarding the estimation of TTD curves

- The ERG considers that there is no robust evidence to suggest using a Weibull over a log-logistic distribution to estimate TTD in the economic analysis and that the log-logistic curve provides a better fit to the KM data
- KM TTD curve crossing the KM PFS curve for mBCC population suggests that people with mBCC continued treatment after progression, which was not allowed in STEVIE. No explanation has been provided for this

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Source:

KM curves – figure 14 and 15 for laBCC and mBCC, respectively, in the ERG report

Mortality and utility estimates

The ERG agrees with the company's assessment regarding the lack of mature OS data

- The curve fitting and extrapolation exercises using these data will therefore have a high degree of uncertainty

The ERG notes that the use of ERIVANCE QoL data raises several issues:

- The baseline age of people in the ERIVANCE trial (median: 62 yrs) is not reflective of people with aBCC encountered in UK clinical practice (~70 yrs)
  -> potentially ***overestimates*** the utility values in the economic analysis when compared with those observed in clinical practice as well as the STEVIE population (median: 72 yrs)
- Progression was assessed differently in the STEVIE and ERIVANCE study
  -> potentially ***underestimates*** the average utility associated with the PD state
- Even though the mapping method employed is robust, the underlying SF-36 data is associated with uncertainty (see slide 15)

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Resource use and costs

The ERG disagrees with some of the company's assumptions for estimating disease management costs

- The company's assumption that 67% of people who progress after receiving vismodegib are on monitoring regimen for the remainder of their lifetime and never receive BSC
  - **ERG's clinical experts:** after the monitoring regimen begins, people who progressed will eventually go on to receive BSC
- The company's assumption on the frequency of wound management and TCN visits
  - **ERG's clinical experts:** uncertain; no consensus was reached amongst the ERG's clinical experts
- The company's assumption that the post-progression BSC regimen for people receiving vismodegib differs from the post-progression BSC regimen for people receiving BSC
  - **ERG's clinical experts:** the post-progression BSC schedule for the two groups are the same

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ERG exploratory analyses

ERG alternative base case: summary of changes (1)

Changes made for both the laBCC and mBBC models:

1. half-cycle correction removed;
2. PFS and OS HRs adjustment removed (ITT population vs. non-responders) and using the company's HR (responders vs. non-responders) from the landmark approach controlling for age and ECOG status;
3. Change the Weibull to a log-logistic curve to model TTD;
4. Cap the OS vismodegib curve by the background mortality curve (this is an issue mainly for laBCC OS curves);
5. Assume that people on vismodegib move to BSC six months after progression;
6. Assume that people on vismodegib moving to BSC receive the same treatment regimen as people on BSC who have progressed;

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ERG alternative base case: summary of changes (2)

Additional specific changes made for laBCC:

7. Replacing the company's PFS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 1.311) with the company's HR adjusting for age, ECOG and Gorlin syndrome for people with laBCC (HR of 1.19);

8a. Assuming that mortality for people with laBCC on vismodegib and BSC is the same as the background mortality for the UK population (i.e. no survival gain with vismodegib vs. BSC); ***or alternatively***

8b. Replacing the company's OS HR (responders vs non- responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for people with laBCC (HR of 2.035)

Additional specific changes made for mBCC:

7. Using a PFS HR of 1 in the mBCC model
8. Using a OS HR of 1 in the mBCC model

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ERG preferred results

- **For laBCC:** ERG reports two ICERs reflecting two different scenarios:
  - 8a. No survival gain with vismodegib (conservative scenario)
  - 8b. There is a survival benefit with vismodegib (less conservative scenario), incorporated using HR adjusted for age, ECOG and Gorlin syndrome

The ERG notes that some of the exploratory analyses (e.g. ones relating to using the PFS and OS HRs) are still based on flawed assumptions (e.g. assuming PH), however the ERG consider that they provide a step in the right direction compared with the company's base case approach

- **For mBCC:** ERG ran a cost minimisation analysis to reflect the level of uncertainty and the lack of robust mBCC data to draw conclusions on the relative effectiveness of vismodegib vs. BSC

The ERG also stresses its opinion that for people with mBCC, the evidence base is not roust enough to draw conclusions on the relative effectiveness of vismodegib vs. BSC

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Results of ERG alternative base case ICER for laBCC population using vismodegib list price (1)

	Results	Vismodegib	BSC	ICER
0	**Company's base case for laBCC**			
	Total costs (£)	£124,865	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER			**£30,493**
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£126,135	£97,558	£28,577
	QALYs	8.59	7.69	0.90
	ICER (compared with base case)			£31,880
	ICER with all changes incorporated			**£31,880**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£124,214	£89,170	£35,045
	QALYs	8.36	7.05	1.31
	ICER (compared with base case)			£26,820
	ICER with all changes incorporated			**£27,772**

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Source: Table 64 in ERG report

To discuss with ERG at the pre-meet:

- Which scenario is preferred or considered to be the most likely by the ERG?

Results of ERG alternative base case ICER for laBCC population using vismodegib list price (2)

	Results	Vismodegib	BSC	ICER
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£135,491	£97,519	£37,972
	QALYs	8.58	7.69	0.90
	ICER			£42,344
	ICER with all changes incorporated			**£35,888**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£124,869	£100,607	£24,262
	QALYs	8.58	7.91	0.67
	ICER (compared with base case)			£36,028
	ICER with all changes incorporated			**£39,597**
5	**Assuming that people on vismodegib move to BSC six months after progression**			
	Total costs (£)	£138,861	£97,519	£41,341
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£46,100
	ICER with all changes incorporated			**£52,356**

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Source: Table 64 in ERG report

Results of ERG alternative base case ICER for laBCC population using vismodegib list price (3)

	Results	Vismodegib	BSC	ICER
6	**Assuming that people on vismodegib moving to BSC receive the same treatment regimen as people on BSC who have progressed**			
	Total costs (£)	£142,784	£97,519	£45,264
	QALYs	8.58	7.69	0.90
	ICER			£50,474
	ICER with all changes incorporated			**£95,164**
7	**Replacing the company's PFS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 1.311) with the company's HR adjusting for age, ECOG and Gorlin syndrome for people with laBCC (HR of 1.19)**			
	Total costs (£)	£124,865	£97,214	£27,651
	QALYs	8.58	7.69	0.89
	ICER (compared with base case)			£31,107
	ICER with all changes incorporated			**£96,352**

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Source: Table 64 in ERG report

Results of ERG alternative base case ICER for laBCC population using vismodegib list price (4)

	Results	Vismodegib	BSC	ICER
8a	**Assuming that mortality for people with laBCC on vismodegib and BSC is to be the same as the background mortality for the UK population (i.e. no survival gain with vismodegib)**			
	Total costs (£)	£126,490	£117,138	£9,352
	QALYs	9.14	9.11	0.02
	ICER (compared with base case)			£435,402
	ICER with all changes incorporated			**£5,203,675**
8b	**Replacing the company's OS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for people with laBCC (HR of 2.035)**			
	Total costs (£)	£124,929	£99,278	£25,651
	QALYs	8.60	7.81	0.79
	ICER (compared with base case)			£32,442
	ICER with all changes incorporated			**£106,569**

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Source: Table 64 in ERG report

The ERG's exploratory analysis shows that both the laBCC and mBCC results are most sensitive to the assumptions made around disease-related mortality and vismodegib's survival benefit, as well as the assumptions surrounding the costs of BSC.

When the ERG assumes there is no mortality associated with laBCC, therefore assuming no survival gain with vismodegib, the final ICER for vismodegib compared with BSC is £5,203,675. The ICER for vismodegib compared with BSC when assuming the existence of laBCC-related mortality and a gain in survival with vismodegib compared with BSC is £106,569.

Results of ERG alternative base case ICER for mBCC population using vismodegib list price (1)

	Results	Vismodegib	BSC	ICER
0	**Company's base case for mBCC**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER			**£100,615**
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£122,243	£40,870	£81,373
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£101,550
	ICER with all changes incorporated			**£101,550**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£120,524	£33,729	£86,794
	QALYs	3.48	2.49	0.99
	ICER (compared with base case)			£87,939
	ICER with all changes incorporated			**£88,698**

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Source: Table 65 in ERG report

Results of ERG alternative base case ICER for mBCC population using vismodegib list price (2)

	Results	Vismodegib	BSC	ICER
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£120,573	£40,813	£79,760
	QALYs	3.75	2.95	0.80
	ICER			£99,502
	ICER with all changes incorporated			**£87,795**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£100,615
	ICER with all changes incorporated			**£87,795**
5	**Assuming that people on vismodegib move to BSC six months after progression**			
	Total costs (£)	£126,325	£40,813	£85,512
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£106,679
	ICER with all changes incorporated			**£92,161**

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Source: Table 65 in ERG report

Results of ERG alternative base case ICER for mBCC population using vismodegib list price (3)

	Results	Vismodegib	BSC	ICER
6	**Assuming that people on vismodegib moving to BSC receive the same treatment regimen as people who have progressed on BSC**			
	Total costs (£)	£129,687	£40,813	£88,874
	QALYs	3.75	2.95	0.80
	ICER			£110,873
	ICER with all changes incorporated			**£109,503**
7	**Using a PFS HR of 1 in the mBCC model**			
	Total costs (£)	£121,465	£40,187	£81,278
	QALYs	3.75	2.98	0.77
	ICER (compared with base case)			£106,092
	ICER with all changes incorporated			**£115,545**
8	**Using a OS HR of 1 in the mBCC model**			
	Total costs (£)	£125,212	£70,805	£54,407
	QALYs	4.82	4.79	0.03
	ICER (compared with base case)			£1,580,078
	ICER with all changes incorporated			**Vismodegib dominated**

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Source: Table 65 in ERG report

Due to the level of uncertainty and the lack of robust mBCC data, the ERG conducted a cost minimisation analysis for this population. When the ERG assumed a PFS and OS HR of 1, vismodegib dominated BSC (total costs for vismodegib £159,547 and £70,224 for BSC).

Company comments on innovation

The company suggests that vismodegib is innovative, with significant positive impact on people's lives because:

- Vismodegib is a first-in-class, small-molecule inhibitor of the Hedgehog signaling pathway
  - First approved treatment for mBCC
  - Offers a novel treatment for people with laBCC who have exhausted their treatment options
  - In the absence of approved treatments, systemic chemotherapies have been used for advanced disease, but data are limited to case reports and case series
  - Offers clinical benefit in terms of delay of disease progression and survival, with a manageable safety profile

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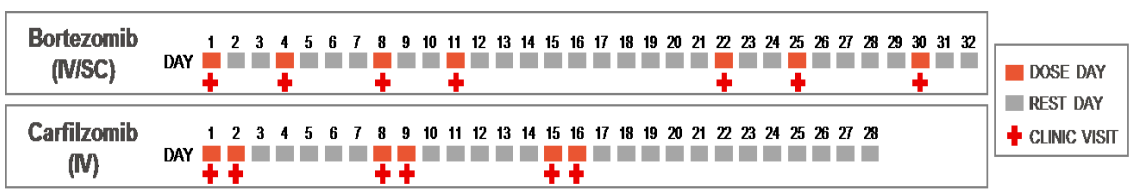

Equalities

- No issues have been raised.

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Authors

- **Aimely Lee**
  Technical Lead
- **Raisa Sidhu**
  Technical Adviser
- **Lead team** including Matt Bradley, Peter Hall, and Rebecca Harmston

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vismodegib for treating basal cell carcinoma
Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of vismodegib within its marketing authorisation for treating basal cell carcinoma.

Background

Basal cell carcinoma (BCC) is a non-melanoma form of skin cancer that develops in the deep basal cell layer of the epidermis around the hair follicle. It can occur anywhere on the body, but is most common in areas that are exposed to the sun, such as the face, head, neck and ears as well as areas where burns, scars or ulcers have damaged the skin[1, 2]. It can also develop at multiple sites simultaneously. BCC can be cured in most cases and seldom spreads to other parts of the body, although if left untreated for prolonged periods, it can become locally advanced or metastasise, that is, the tumours can grow into deeper layers and affect other tissues such as cartilage and bone.

BCC is the most common type of skin cancer in the UK with around 75% of non-melanoma skin cancers being BCC[1]. It is a slow-growing, locally invasive, malignant epidermal skin tumour predominantly affecting fair skinned adults. People with Gorlin syndrome also have an increased risk of developing BCCs with around 90% developing cancers at multiple sites. Although it is the most common malignancy worldwide, it is very difficult to estimate the incidence and prevalence of BCC because cases typically have been designated as non-melanoma skin cancers, which include both basal cell and squamous cell skin cancers, and these cases, unlike melanoma, are not required to be reported to cancer registries. Furthermore, there is no standardized staging system for BCC. As a result, the epidemiology and natural history of advanced BCC have been poorly described.

Around 98,400 cases of non-melanoma skin cancer were registered in 2011 in the UK; registration however is incomplete with an estimated 30-50% of BCC going unreported[2]. Based on published data the incidence of metastatic BCC is believed to be significantly lower than 0.1% of cases of BCC[3]. Deaths from BCC are very rare.

The main treatment for basal cell carcinoma is surgery and treatment is successful in over 90% of cases[1]. However, in cases where surgery is not an appropriate option or the cancer has metastasised, radiotherapy is commonly used. Where surgery or radiotherapy are both not considered viable options, there are no active treatments available and best supportive care remains the only option. 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.

The technology

Vismodegib (Erivedge, Roche) is an oral antagonist of the Smo protein involved in activating the Hedgehog signalling pathway that plays a critical role in the development and homeostasis of many organs and tissues. It is administered orally.

Vismodegib has a 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. It has been studied in clinical trials in people with locally advanced or metastatic basal cell carcinoma and has mainly been investigated in dose ranging studies without an active comparator.

Intervention(s)	Vismodegib
Population(s)	People with: • symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate
Comparators	• Best supportive care
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	If the evidence allows the following subgroup will be considered. • patients with Gorlin syndrome For this subgroup, an additional outcome measure of prevention of new lesions should be included. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: None Related Interventional Procedures: Interventional Procedures Guidance No. 478, 2014, 'Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma'. Interventional Procedures Guidance No. 446, 2013, 'Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma'. Related Guidelines: NICE cancer service guidance CSG8,2010,'Improving outcomes for people with skin tumours including melanoma' Related Quality Standards: Skin cancer (including melanoma). Published: September 2016 https://www.nice.org.uk/guidance/qs130/resources/skin-cancer-75545412324037 Related NICE Pathways: NICE Pathway: Skin cancer, Pathway created: 2015 https://pathways.nice.org.uk/pathways/skin-cancer
Related National Policy	Department of Health (2016) NHS outcomes framework 2016 to 2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 NHS England (2016) Manual for prescribed specialised services 16/17. Specialist cancer services (adults) 105

	(page 228) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf NHS England (2013) National cancer drug fund prioritisation scores: vismodegib for patients with advanced basal cell carcinoma (aBCC) who are no longer appropriate for any other treatment options National service framework: Cancer research and treatment, 2016 https://www.gov.uk/government/policies/cancer-research-and-treatment

References

1. NHS Choices (2014) Skin cancer (non-melanoma). Accessed July 2016.
2. Cancer Research UK, Skin cancer incidence statistics. Accessed July 2016.
3. European Medicines Agency (2013) European Public Assessment Report. Section 2, p. 6.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vismodegib for treating basal cell carcinoma [ID1043]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Manufacturers/sponsors • Roche (vismodegib, brand name erivedge) Patient/carer groups • Black Health Agency • British Skin Foundation • Cancer Black Care • Cancer Equality • Cancer 52 • Changing Faces • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Melanoma UK • Muslim Council of Britain • OcuMel UK • Rarer Cancers Foundation • Skcin - Karen Clifford Skin Cancer Charity • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Professional groups • Association of Cancer Physicians • British Association of Dermatologists • British Association of Plastic, Reconstructive and Aesthetic Surgeons • British Association of Skin Cancer Specialist Nurses	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator manufacturer(s) None Relevant research groups • British Society for Dermatological Surgery • Cochrane Skin Group • Institute of Cancer Research • MRC Clinical Trials Unit • Myfanwy Townsend Melanoma Research Fund • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Skin Cancer Research Fund • Skin Research Centre • Skin Treatment & Research Trust

Consultees	**Commentators (no right to submit or appeal)**
• British Dermatological Nursing Group • British Geriatrics Society • British Institute of Radiology • British Oculoplastic Surgery Society • British Oncology Pharmacist Association • British Psychosocial Oncology Society • British Skin Foundation • Cancer Research UK • Melanoma Focus • Primary Care Dermatology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • United Kingdom Clinical Pharmacy Association • UK Health Forum • United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS North Somerset CCG • NHS South Tees CCG • Welsh Government	<u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

(ID 1043) Vismodegib for the treatment of locally advanced or metastatic basal cell carcinoma

Company evidence submission

Roche Products Limited

March 2017

File name	Version	Contains confidential information	Date
ID1043 Vismodegib for treatment of locally advanced and metastatic BCC	V1	Yes	16/03/2017

Contents

Tables and figures

Abbreviations

Acronym	Definition
AACR	American Association for Cancer Research
AAD	American Academy of Dermatology
ACE	Angiotensin-converting enzyme
ADR	Adverse drug reactions
AE	Adverse event
AFT	Accelerated failure time
AI	Accumulation Index
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (classification system)
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BAHNO	British Association of Head and Neck Oncologists
BAPRAS	British Association of Plastic, Reconstructive and Aesthetic Surgeons
BCC	Basal cell carcinoma
BCCNS	Basal cell carcinoma naevus syndrome
BCNS	Basal cell naevus syndrome
BIC	Bayesian Information Criterion
BMI	Body mass index
BNF	British National Formulary
BOPSS	British Oculoplastic Surgery Society
BOR	Best overall response
BORR	Best overall response rate
BSC	Best supportive care
CDC	Centres for Disease Control (Prevention)
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis

Acronym	Definition
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for the Harmonisation of Medicinal Products
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRD	(York) Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DARE	Database of Abstracts of Reviews of Effectiveness
DLQI	Dermatology life quality index
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Data safety monitoring board
DSU	Decision support unit
EADO	European Association of Dermato-Oncology
EADV	European Academy of Dermatology and Venerology
EAS	Expanded Access Study
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENT	Ear, Nose, Throat
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQOL 5 Dimensions (questionnaire)
ESMO	European Society for Medical Oncology
EU	European Union
FDA	(US) Food and Drugs Administration
18-FDG	Fludeoxyglucose (^{18}F)
FSH	Follicle-stimulating hormone
GDC-0449	Development name for vismodegib
GGT	Gamma-glutamyl transferase
GLI	Glioma-Associated Oncogene
GP	General Practitioner

Acronym	Definition
HCP	Healthcare professional
HPI	Hedgehog pathway inhibitor
HR	Hazard ratio
HS	Health state
HSC	Horizon Scanning Centre
HTA	Health Technology Appraisal
HUI	Health Utilities Index Mark 3 (classification system)
IB	Investigator Brochure
ICER	Incremental cost-effectiveness ratio
IND	Investigational New Drug
IPD	Individual patient data
IQR	Interquartile range
IRF	Independent Review Facility
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
KM	Kaplan-Meier
LY	Life years
LYG	Life year gain
MAIC	Matched adjusted indirect comparison
MCS	Mental Component Summary
MDASI	M.D. Anderson Symptom Inventory
MEDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Medical Resonance Imaging
MTD	Maximum tolerated dose
MV	Megavoltage
NA	Not applicable
NB	*Nota bene*
NC	Not clear
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NE	Not evaluable
NHS	National Health Service

Acronym	Definition
NHSC	National Horizon Scanning Centre
NHS-EED	NHS Economic Evaluation Database
NICE	National Institute for health and Care Excellence
NIHR	National Institute for Health Research
NMSC	Non-melanoma skin cancers
NR	Not reported
ONS	Office of National Statistics
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PCS	Physical Component Scale
PD	Progressive disease
PDT	Photodynamic therapy
PERCIST	PET Response Criteria in Solid Tumors
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional Hazard (model)
PK	Pharmacokinetics
PPP	Pregnancy Prevention Plan
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PS	Performance Status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
PTCH	(transmembrane receptor) ‘Patched’
QALY	Quality Adjusted Life Year
QT	QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RG3616	Development name for vismodegib

Acronym	Definition
RT	Radiotherapy
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SF-36	Short Form (36) health survey
SG	Standard gamble
SLD	Single longest dimension
SLR	Systematic literature review
SMO	(transmembrane receptor) 'Smoothened'
SMR	Society for Melanoma Research
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SPM	Second primary malignancy
SSMDT	Specialist Skin Multi-Disciplinary Team
TA	(NICE) Technology Appraisal
TEAE	Treatment-emergent adverse events
TTD	Time to treatment discontinuation
TTO	Time trade-off
TTP	Time to progression
TTR	Time to response
TVN	Tissue viability nurse
UK	United Kingdom
ULN	Upper limit of normal
US(A)	United States (of America)
UV	Ultraviolet
VAS	Visual analogue scale
VAT	Value-added tax
VISMO	Vismodegib
VTE	Venous thromboembolic events
WCBP	Women of childbearing potential
WCCS	World Congress on Cancers of the Skin
WHO	World Health Organisation
WINTERCDC	Winter Clinical Dermatology Conference
YPLL	Years of potential life lost

1 Executive summary

Definition of advanced basal cell carcinoma (aBCC)

Basal cell carcinoma (BCC), a type of skin cancer, is the most common malignancy in Caucasians, typically appearing as slow-growing, translucent, elevated lesions on the sun-exposed skin of people with fair complexion – BCC is associated with good prognosis in the majority of cases. Lesions are usually indolent, with minimal soft tissue invasiveness. Limitation of growth of BCCs by microscopically controlled surgical excision gives a cure rate approaching 100%.(1)

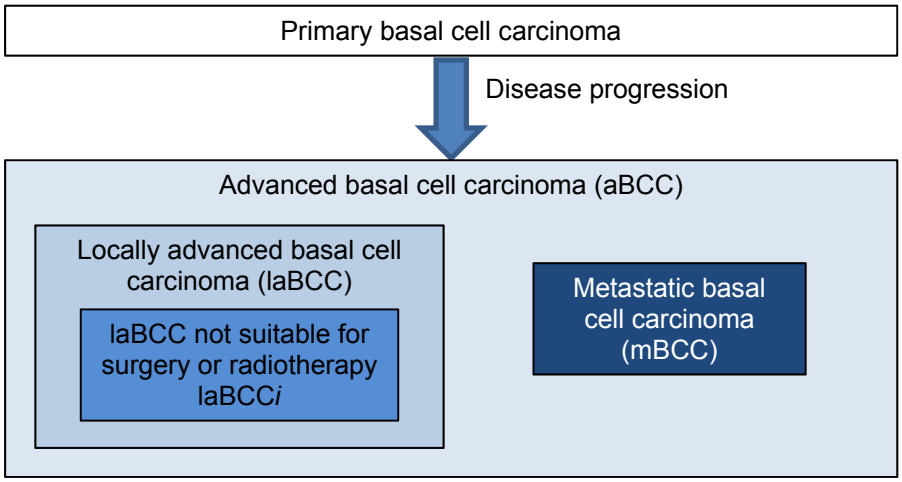
However, there is a small percentage of BCCs that develop into more advanced disease, (advanced BCC; aBCC) which is less straightforward to manage clinically. These include locally advanced, recurrent or metastatic BCC (mBCC), or tumours that occur in anatomical sites where surgical treatment would result in significant deformity.(2) Advancement of disease to affect surrounding tissues, cartilage, and bone (locally advanced basal cell carcinoma; laBCC) can potentially lead to substantial local or deep tissue destruction and disfigurement*, particularly as lesions predominantly affect the head.(3)

Some of these locally advanced lesions may progress to a state that is not appropriate for surgery, either due to the limited feasibility of the surgery obtaining complete tumour clearance, associated morbidity and mortality risks associated with the complicated and extensive surgery required, or unacceptable deformity that may result from the treatment. Radiotherapy may no longer be a treatment option for patients with BCCs that have become locally advanced, either due to recurrence of the lesion following previous radiotherapy negating the use of subsequent radiotherapy on the same site, or location of the tumour/patient factors that mean radiotherapy is inappropriate. This small cohort of patients is considered to have *locally advanced BCC inappropriate for surgery or radiotherapy* (laBCC*i*).

BCCs very rarely spread to distant regions; only 0.0028 to 0.55% of BCCs progress to mBCC.(3, 4)

* Refer to the photo appendix, Appendix 16

Figure 1: Disease progression pathway for BCC



Currently, there is no global, standardised staging system for aBCC, which presents difficulty when describing the epidemiology of this rare cancer. (2, 5) In addition, a diverse group of practitioners, including dermatologists, medical and clinical oncologists, radiologists, and surgeons, diagnose and treat aBCC, which means that there is rarely a consistent treatment approach for and unsystematic documentation of aBCC patients.

UK statistics

Non-melanoma skin cancers (NMSCs), which include BCCs and squamous cell carcinomas (SCCs), are the most common forms of cancer in humans, surpassing in incidence all other forms of cancer combined.(6),(7) BCCs occur four to five times more commonly than SCCs. It is important to note that the true incidence and prevalence of NMSCs, and thus BCCs, are difficult to estimate because large national cancer registries do not track NMSC; additionally, NMSCs are usually treated in a primary care setting (8-10). Several published reports have estimated the incidence of NMSC, and more specifically BCC.

Despite the dearth of BCC registry data, aBCC case experience data indicate that locally advanced and metastatic presentations of BCC are rare.(4),(11),(12),(13),(14, 15) Advanced BCC is thought to occur in up to 10% of all BCCs (16), with laBCC*i* occurring in up to 1% (17, 18) and mBCC accounting for 0.0028% to 0.55% of all BCCs.(4),(19) Fewer than 300 cases of mBCC have been reported in the literature.(15)

The crude incidence of BCC in the UK has been estimated to be 153.9 per 100,000 person years (95% CI: 151.1 to 156.8); incidence increases with age and there is a significantly higher rate in men than women.(20) The world age-standardised rate of BCC is 60 per 100,000 per year, and the European age-standardised rate 89 per 100,000.(20) Overall,

BCC incidence has been increasing by 3% per year between 1996 and 2003 and approximately 53,000 new cases of BCC are estimated to occur every year in the UK.(20)

Erivedge®▼ (vismodegib) has been available on the Cancer Drugs Fund in England since the UK launch in August 2013. From the UK launch until the end of August 2016, 352 requests had been made for funding for vismodegib through the Cancer Drugs Fund. (21)

Due to their size, invasiveness, or location, aBCC lesions can cause significant disfigurement or deformity, disability, and/or premature mortality. However, mortality directly attributable to laBCC is incredibly rare: laBCC would not be expected to directly cause the death of the patient. Approximately 10 years of potential life are lost per death from NMSC (22), and it could be postulated that laBCC contributes to the shorter survival in patients due to poor general health and self-care.

The prognosis is poor for patients with mBCC, and morbidity and mortality are high.(2) Published evidence has suggested overall survival from mBCC diagnosis ranges between 0 to 120+ months, varying depending on the site of metastatic disease. (11, 23)

Current UK practice

Treatment options for patients with BCC are determined by consideration of a number of factors, including: tumour size, site, and histological subtype; previous treatment history and patient comorbidities; patient preference; and access to treatment. It is also important to consider whether the intention of treatment is curative or palliative.(2) Current treatments for BCC (patients whose disease is not considered advanced) include surgical excision and/or radiotherapy, and less commonly: topical (e.g. 5-fluorouracil, imiquimod) chemotherapy or electrochemotherapy, curettage, cryotherapy, and photodynamic therapy. (24)

Patients with locally advanced disease have lesions that may not be appropriate for radiotherapy or surgery. Surgery may be considered inappropriate because it is unlikely to be curative, or disease has recurred after surgery, or due to significant deformity as a result of surgery (e.g., invasion into the skull, limb amputation, or eye removal) based on lesion location, size, and/or tumour histology. Additionally, the use of radiotherapy is not advised in tumours located near eyes (including those on eyelids) or potentially the extremities (e.g. shins), individuals who are nearing their maximum safe lifetime radiation dose, and younger patients, who are likely to suffer late cosmetic results that are inferior to those of surgery.(8, 25) For patients with disease recurrence after prior radiotherapy, subsequent radiation is contraindicated. (25),(26)

Patients whose lesions are not appropriate for surgery or radiotherapy would be either managed:

- by dermatologists who would monitor patients several times per year; more regular patient care would be carried out in the community by GPs and district nurses, potentially requiring intensive and continual wound management, or,

- with palliative (i.e. non-curative) radiotherapy, when required, for the management of bleeding and/or exudation of the wound. The dose of radiation may be given in a single fraction, or fractionated if the wound is particularly large, or,

- by referral for consideration for major surgery to resect locally advanced disease (with involvement of multiple surgical specialities e.g. ear, nose and throat (ENT) specialist / oculoplastic / maxillofacial / neurosurgical teams, with the likely requirement for complex plastic surgical reconstruction). It should be noted that this surgery would **not** be expected to be curative and is usually associated with significant morbidity (e.g. loss of an eye) and a significant risk of mortality.

Unmet need

Effective treatment options are limited for patients with aBCC. Whilst primary BCC may be managed using treatments such as surgery (including Moh's surgery), radiotherapy, curettage, topical chemotherapy, photodynamic therapy or cryotherapy, these may not be suitable for patients with advanced disease.(2)

Treatments for laBCC, such as surgery and/or radiotherapy may not be applicable for some patients, due to the extent of tissue invasion, possible gross disfigurement that extensive surgery may cause, and the need to limit radiation damage to surrounding organs/structures. Vismodegib offers a treatment option for such patients.

Prior to vismodegib, there have been no approved treatments for mBCC. In the absence of approved treatments, systemic chemotherapies (e.g., cisplatin- or carboplatin-based regimens) have been used, but data are limited to case reports and case series. A review of 47 internationally published cases of mBCC with distant metastases revealed that 36.2% of patients received chemotherapy, 42.6% received radiotherapy, and 40.4% underwent surgery. Of note, 13 patients (27.7%) received no treatment.(23)

Vismodegib

Vismodegib is an orally available small-molecule inhibitor of the Hedgehog (Hh) pathway, and acts by blocking specific genes involved in proliferation, survival, and differentiation of

cells. Key components of the Hedgehog pathway include the transmembrane receptors Patched (PTCH1) and Smoothened (SMO), the Hedgehog ligand, and the intracellular proteins responsible for stimulating the Glioma-Associated Oncogene (Gli) family of transcription factors. Approximately 90% of sporadic BCCs have identifiable mutations in at least one allele of *PTCH1*, and an additional 10% have activating mutation in the downstream SMO protein, which "presumably" render SMO resistant to inhibition of PTCH1. (1) Vismodegib binds to and inhibits the SMO protein thereby blocking Hedgehog signal transduction.

The recommended dose of vismodegib is one 150 mg capsule taken once daily.

Anticipated role of vismodegib in English and Welsh clinical practice

Due to the unmet medical need in patients with aBCC, vismodegib has become a treatment option for patients with mBCC and patients with laBCC for whom surgery and/or radiotherapy is unsuitable. Vismodegib offers clinical benefit in the majority of patients with a manageable safety profile (as shown in the pivotal ERIVANCE study and post-authorisation safety study, STEVIE; described in sections 4.11 and 4.12) and minimal impact on NHS resource use or capacity, as compared to standard of care in England and Wales without access to vismodegib. Since vismodegib is already standard of care due to its use under the CDF, removal of access would impact a vulnerable patient group who have little other option.

External expert input (clinical and economic advisory panel)

An expert advisory board was convened

- to understand the aBCC treatment pathway and how clinicians decide on different treatment strategies,
- to provide Roche with feedback on the clinical data and implication for treatment pathways,
- to advise Roche on the health economic model and inputs.

Seven expert advisors were consulted. The four clinical advisors included consultant oncologists, a dermatologist and a plastic surgeon, specialising in the management of patients with aBCC: many of whom have experience of vismodegib from clinical trials, Specialist Skin Multi-Disciplinary Team (SSMDT) involvement and private practice. The three economic advisors were experienced health economists (UK-based). The panel was selected based on their significant clinical and research experience.

At the one-day meeting, invited experts were briefed on the economic model structure and sources of key data inputs; their comments were taken into account in the subsequent development of the model.

Following the advisory board meeting, oncologists and dermatologists were consulted on an ad-hoc basis to validate clinical or economic assumptions.

1.1 Statement of decision problem

The appraisal is consistent with the reference-case and broadly in-line with the final NICE scope.

A single-arm Phase II study with a response rate primary endpoint was determined to be the most appropriate trial design for vismodegib in aBCC.

Based on the significant anti-tumour activity observed in patients with aBCC in the Phase I vismodegib study (SHH3925g; NCT00607724)(13) and considering the clinically articulated unmet need in aBCC, Roche received feedback from investigators and experts in the field that it would not be feasible to accrue patients (given the limited population) to a randomised study. In addition, responses from a placebo or best supportive care arm were both (a) not expected and (b) could be addressed statistically with a significantly high response rate in the vismodegib arm. No standardised treatment options had been identified for either laBCC or mBCC patients based on a literature review of the previous 30 years.

There was concern that, with a randomised, cross-over design, investigators may be biased toward prematurely assessing disease progression and patients biased towards withdrawing consent: enabling them to crossover to vismodegib or enrolment into another clinical study when no immediate clinical benefit was observed. Such bias would have impacted study integrity and interpretation of the true treatment effect of vismodegib. Therefore, the single-arm study with a response rate primary endpoint was determined to be the most appropriate trial design for vismodegib in aBCC.

The primary endpoint in the ERIVANCE study was objective response rate (ORR) by an independent review facility (IRF). For mBCC patients, tumour response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST). For locally advanced patients, a novel composite ORR assessment was created in consultation with the US FDA that incorporated IRF-assessed radiographic, photographic, and pathology measurements, including external tumour dimension and ulceration. This novel composite ORR was based on assessments that had been utilised in accepted response criteria for other cutaneous

malignancies and was developed because no precedent was available for laBCC objective efficacy measurement. The hypothesis tested by the primary endpoint was that the ORR was significantly greater than 20% in patients with laBCC or 10% in patients with mBCC. Secondary endpoints included ORR by investigator, duration of response, progression-free survival (PFS), overall survival (OS), and safety.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with: • symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate	People with: • symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate	No difference
Intervention	Vismodegib	Vismodegib	No difference
Comparator(s)	Best supportive care (BSC)	Best supportive care (BSC)	No difference
Outcomes	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life	No difference
Economic analysis	• The reference case stipulates that the cost effectiveness of treatment should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	• The reference case stipulates that the cost effectiveness of treatment should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	No difference

Subgroups to be considered	If the evidence allows the following subgroup will be considered • Patients with Gorlin syndrome For this subgroup, an additional outcome measure of prevention of new lesions should be included	No subgroups were addressed	Gorlin patients were not included as a separate subgroup. Low patient numbers in the pivotal trials meant that clinical data was insufficient to support a robust analysis
Special considerations including issues related to equity or equality	None	None	No difference

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Erivedge® ▼(vismodegib)
Marketing authorisation/CE mark status	• Marketing authorisation was granted on 12th July 2013
Indications and any restriction(s) as described in the summary of product characteristics	Erivedge is indicated for the treatment of adult patients with: • symptomatic metastatic basal cell carcinoma • locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy
Method of administration and dosage	• Erivedge is for oral use. The capsules must be swallowed whole with water, with or without food. The capsules must not be opened, to avoid unintended exposure to patients and health care providers • The recommended dose is one 150 mg capsule taken once daily

1.3 Summary of the clinical effectiveness analysis

The efficacy and safety of vismodegib for treating mBCC and laBCC have been demonstrated in two non-randomised clinical trials:

- ERIVANCE (NCT00833417) which led to conditional regulatory approval in the EU, and
- STEVIE (NCT01367665) results of which led to the conversion of the conditional marketing approval to full regulatory approval in September 2016

The primary endpoint of the ERIVANCE trial was overall response rate by independent review; the STEVIE study primary endpoint was the assessment of safety data obtained in a large population. The study design, patient eligibility criteria and treatment regimens were very similar between the two studies.

Eligible patients (ERIVANCE N=104; STEVIE N=1215) were treated with 150 mg vismodegib, once-daily, orally. The study populations had median ages of 62 years for ERIVANCE and 72 years for STEVIE. The majority of patients had locally advanced disease.

Supporting data from three other studies (EAS [NCT01160250], RegiSONIC [NCT01604252], and Phase I SHH3925g [NCT01367665]) are also provided.

Clinical efficacy

Overall response rates of 56.3% in ERIVANCE (laBCC and mBCC patients combined)(27) and 66.2% in STEVIE (laBCC and mBCC patients combined)(28) demonstrate that the majority of patients receive a benefit from treatment with vismodegib. Case studies from the ERIVANCE study, included in the photo appendix (Appendix 16), with pre- and post-treatment images demonstrate the impact that these responses have on patients - even some of those patients considered to have progressive disease, due to the appearance of new lesions, have demonstrated visually impactful benefits to the target lesion.

ERIVANCE: Response rate at 30 months' follow-up (as assessed by investigators at this analysis) was 60.3% in patients with laBCC, and 48.5% in patients with mBCC. The median duration of objective response was 26.2 months (95% confidence interval [CI]: 9.0 to 37.6) for patients with laBCC and 14.8 month (95% CI 5.6 to 17.0) for patients with mBCC. The median overall survival (OS) of 33.4 months in the mBCC cohort suggest that vismodegib treatment may improve OS as compared to the literature. The frequency, magnitude, and duration of objective responses observed in ERIVANCE, in addition to a generally tolerable adverse event profile, suggest that vismodegib demonstrates a positive benefit−risk profile and offers a significant clinical benefit for this patient population. (27)

STEVIE: Efficacy results in the laBCC and mBCC populations were similar to those already evident in previous reports in other vismodegib studies in the same population. Best overall response rate in laBCC group was 68.5%, and in the mBCC group was 36.9%. The median duration of objective response was 23.0 months (95% CI: 20.4 to 26.7) for patients with laBCC and 13.9 month (95% CI 9.2 to NE[*]) for patients with mBCC. For OS, the number of events was too low to estimate a stable median survival. Patients with mBCC, treatment with vismodegib demonstrated consistent benefit in terms of best overall response (BORR) and time-related parameters (time to response [TTR], duration of response [DOR], and progression-free survival [PFS]) compared with previous reported results. A clinically meaningful improvement in the score representing emotional well-being related to their skin condition (as measured by Items 5 to 11 from the self-completed Skindex-16 questionnaire) was observed among patients with laBCC after Cycle 1 (cycles being 28 days) and was maintained throughout the study. Similarly, a meaningful improvement in individual symptoms was observed in mBCC patients who were symptomatic at baseline; however, this benefit was not consistently maintained at consecutive timepoints.(28, 29)

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[*] NE not evaluable

RegiSONIC: The RegiSONIC study represents the largest planned prospective observational cohort study of patients with aBCC, and is on-going in the US. (30, 31) Patients were recruited into one of three cohorts:

- patients with aBCC who do not have Gorlin* syndrome and are Hh pathway inhibitor naïve (n=437), or,
- patients without Gorlin syndrome who were previously enroled on a vismodegib study (n=9), or,
- patients with Gorlin syndrome and were either Hh pathway inhibitor naïve or had received previous vismodegib in a clinical trial (n=57).

Treatment was determined by the clinician in line with routine practice. Preliminary data demonstrate effectiveness of vismodegib in patients newly diagnosed with non-Gorlin syndrome laBCC, with a response rate of 87.1% (95% CI 79 to 93; n=85 evaluable for efficacy). (31)

EAS: The Expanded Access Study assessed efficacy and safety of vismodegib, and provided early drug access to patients with aBCC and limited treatment options (N=119). Vismodegib demonstrated substantial clinical effect in patients with locally advanced BCC and mBCC without satisfactory treatment options. Objective responses occurred in 46.4% of laBCC and 30.8% of patients with mBCC. Efficacy outcomes were observed despite the limitations of the study: the study was halted when the US FDA granted marketing approval to vismodegib (as per study design in this expanded access program).(32)

Phase I SHH3925g: Patients (N=68) with solid tumours refractory to standard therapy were recruited into this open-label mulitcentre, two-stage phase I trial, 33 of whom had aBCC. Clinical activity was observed only in aBCC (18 of 33 [58%] patients had a response). The results from the full cohort of this Phase I trial suggested that vismodegib merited further study in aBCC. (13)

Safety of vismodegib in aBCC

Vismodegib has an identified risk of embryo-foetal death and severe birth defects, which is based on the known role of Hh signaling in embryogenesis and foetal development. Therefore, patient pregnancy status should be verified prior, during and after treatment with vismodegib. In the UK there is an MHRA-approved Pregnancy Prevention Programme,

* A brief description of Gorlin syndrome (also known as basal cell carcinoma naevus syndrome [BCCNS] is given in section 3)

allowing appropriate education of patients and documentation that counselling has been conducted. No pregnancies were reported in the five trials presented in this submission.

In the post-authorisation safety study, STEVIE, treatment-emergent adverse events (TEAEs) defined as occurring between the first administration and 30 days after the last administration of study drug, inclusive, were reported in 1192 patients (98%). The most common all-grade TEAEs were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight decreased (40.6%), and decreased appetite (24.9%). Amenorrhoea/irregular menses was also reported in 18 of 64 (28.1%) female patients who had menses at baseline. Over half of TEAEs (54%) were mild to moderate.(28)

The safety data from the five studies identified in the systematic literature review (SLR) were consistent, with no particular safety signals observed. The most common adverse events (AEs) associated with vismodegib are muscle spasm, alopecia, fatigue, dysgeusia, decreased weight and decreased appetite (see section 4.12.)

There were few AEs leading to discontinuation (which can be interpreted as those that are dangerous or intolerable to the patient). Muscle spasm is a common adverse event in vismodegib-treated patients. Although severity is typically grade 1–2 and muscle spasm usually resolves ≤6 weeks after end of treatment, it can lead to decreased quality of life (QoL) and to treatment discontinuation.(33) Treatment interruptions of up to 4 weeks were allowed in clinical trials based on individual tolerability.(34) Treatment breaks throughout a longer period of treatment exposure have been shown to aid toleration of adverse events: median duration of treatment with vismodegib has been shown to increase with increasing numbers of treatment breaks, without apparent loss in efficacy.(35)

1.4 Summary of the cost-effectiveness analysis

The cost-utility analysis was implemented in line with the NICE reference case, to determine the incremental-cost-effectiveness-ratio (ICER) for vismodegib in symptomatic mBCC and laBCC inappropriate for surgery or radiotherapy, as compared to standards of care in current clinical practice. A *de novo* model was developed to evaluate the cost-effectiveness of vismodegib. A three-state partitioned survival model was built, and included health-states for 'Progression-free survival' (PFS), 'Progressive disease', and 'Death'. A 30 year time horizon was used to capture life-time costs and benefits, with discounting applied at 3.5% for costs and effects.

Clinical inputs for the model were derived from the single arm, Phase II study, STEVIE. Utility inputs were derived from SF-36 data collected in the ERIVANCE study. The model

expressed treatment effect in quality-adjusted life years (QALYs). Costs for all therapies included drug cost, resource use, and adverse event management. All costs are taken from UK literature, and UK-based clinical experts.

Vismodegib projected a gain of 10.66 life-years, an increase of 1.16 compared to best supportive care (BSC) (see section 5.7). This result demonstrates the significant survival benefit that vismodegib provides over current treatment options. Vismodegib provides an incremental gain of 0.89 QALYs. Given the modelling approach the utility differential is derived solely by the delay in time to progression benefit seen in the vismodegib treatment arm.

The base-case ICER comparing vismodegib, at list price, to BSC is £35,251 per QALY gained (Table 3). The equivalent ICER incorporating the proposed Patient Access Scheme (PAS)* is [redacted] per QALY gained (Table 4).

* Roche has submitted a simple PAS to the Patient Access Scheme Liaison Unit (PASLU) and anticipate that at the time of ACD we should have ministerial approval.

Table 3: Incremental cost-effectiveness results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality adjusted life years

Table 4: Incremental cost-effectiveness results (PAS applied)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£101,162	9.50	7.31	[redacted]	1.16	0.89	[redacted]
Vismodegib	[redacted]	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality adjusted life years

2 The technology

2.1 Description of the technology

Brand name: Erivedge® ▼ (vismodegib)

Therapeutic class: Antineoplastic agents; ATC code: L01XX43

Erivedge (vismodegib) is an orally available small-molecule inhibitor of the Hedgehog (Hh) pathway, and acts by blocking specific genes involved in proliferation, survival, and differentiation of cells.

The Hedgehog pathway, which is largely redundant in adults, plays central roles in animal and stem cell function.(36) Key components of the Hedgehog pathway include the transmembrane receptors Patched (PTCH1) and Smoothened (SMO), the Hedgehog ligand and the intracellular proteins responsible for stimulating the Glioma-Associated Oncogene (Gli) family of transcription factors. PTCH1 is the receptor to which the Hedgehog ligand binds; this binding relieves the inhibition induced by unbound PTCH1, specifically through SMO in a non-stoichimetric manner.(1) Hedgehog pathway signalling through the SMO leads to the activation and nuclear localisation of Gli transcription factors and induction of Hedgehog target genes. Many of these genes are involved in proliferation, survival, and differentiation of cells. Approximately 90% of sporadic BCCs have identifiable mutations in at least one allele of *PTCH1* (often loss of the chromosome 9q harbouring *PTCH1*), and an additional 10% have activating mutations in the downstream SMO protein, which "presumably" render SMO resistant to inhibition of PTCH1.(1) Vismodegib binds to and inhibits the SMO protein thereby blocking Hedgehog signal transduction. (34)

Appendix 3 contains further details regarding the Hedgehog pathway and the mechanism of action of vismodegib

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 UK Marketing Authorisation status

On 12th July 2013, the European Commission granted approval for Erivedge in Europe by adopting the Committee for Medicinal Products for Human Use (CHMP) positive opinion for use in patients with basal cell carcinoma. (See Appendix 2.)

2.2.2 Indication

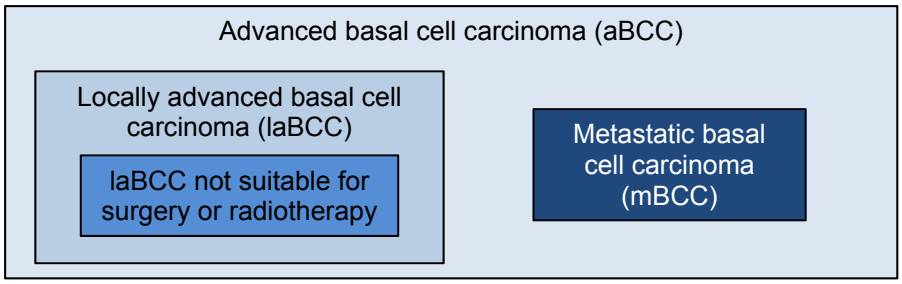
Erivedge is indicated for the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma (mBCC)
- locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy

See Section 2.2.6 for details of conditional and full Marketing Authorisation.

Together, laBCC and mBCC are collectively described as advanced basal cell carcinoma (aBCC).

Figure 2: Relationship of laBCC, mBCC and aBCC



2.2.3 Restrictions or contraindications

Erivedge should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication.

As noted in the Summary of Product Characteristics (SmPC), this medicine is contraindicated to people who demonstrate hypersensitivity to Erivedge or to any of the excipients below:

Table 5: Excipients of Erivedge capsules

Capsule contents	Capsule shell	Printing ink
Microcrystalline cellulose Lactose monohydrate Sodium lauril sulfate Povidone (K29/32) Sodium starch glycolate (Type A) Talc Magnesium stearate	Iron oxide black (E172) Iron oxide red (E172) Titanium dioxide (E171) Gelatine	Shellac glaze Iron oxide black (E172)

Additionally, Erivedge is contraindicated in the following people:

- Women who are pregnant or breast-feeding (see sections 4.4 and 4.6 of the SmPC),
- Women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme (see sections 4.4 and 4.6 of the SmPC),
- Patients receiving co-administration of St John's wort (Hypericum perforatum) (see section 4.5 of the SmPC).

The following information is also provided in the SmPC:

- The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established.
- Due to safety concerns (see sections 4.4 and 5.3 of the SmPC), this medicinal product should not be used in children and adolescents aged below 18 years.

2.2.4 Summary of Product Characteristics

The Summary of Product Characteristics is attached in Appendix 1.

2.2.5 European Public Assessment Report

The European Public Assessment Reports are attached in Appendix 2.

- EMA/CHMP/297688/2013 (conditional Marketing Authorisation)
- EMA/CHMP/641527/2016 (full Marketing Authorisation)

2.2.6 Conditions to the Marketing Authorisation

A pregnancy prevention plan and a pharmacovigilance plan for Erivedge have been implemented as part of the Marketing Authorisation. Core EU- and UK-specific Risk Management materials are available on the Electronic Medicines Compendium website at http://www.medicines.org.uk/emc/medicine/28107.

Summary of opinion: EMA/CHMP/263262/2013

In April 2013, the CHMP considered, on the basis of quality, safety and efficacy data submitted, that:

- overall, the clinical benefit of Erivedge in patients with locally advanced or symptomatic metastatic BCC had been established,
- toxicity is manageable and adequate pharmacovigilance activities and risk minimisation measures have been described,
- benefit/risk of Erivedge in the treatment of adult patients with symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy is considered favourable.

The EMA therefore recommended the granting of the Marketing Authorisation. The Marketing Authorisation was conditional requiring the completion of the following post-authorisation measures:

- provision of a safety update of the pooled safety population, a final SHH4476g[*] (pivotal study) and an interim analysis of study MO25616[†] of 500 patients with a potential one year follow up,
- provision of further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of the MO25616 study.

[*] Alternative study number for ERIVANCE (NCT00833417)
[†] Alternative study number for STEVIE (NCT01367665)

Scientific grounds for variation: EMA/CHMP/756053/2016

On 15th September 2016, the CHMP granted full Marketing Authorisation in Europe for Erivedge not subject to specific obligations, as the prior specific obligations had been fulfilled.

2.2.7 Launch in the UK

Erivedge was launched in the UK on 9th August 2013.

2.2.8 Regulatory approval outside the UK

The US Food and Drug Administration (FDA) granted a Marketing Authorisation for Erivedge on 30 January 2012.
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm289571.htm

Erivedge has received approval in approximately 40 countries outside the EU and the United States.

2.2.9 Other health technology appraisals

In October 2013, the All Wales Medicines Strategy Group (AWMSG) released a statement of advice for Erivedge, stating:

> "In the absence of a submission from the holder of the Marketing Authorisation, vismodegib (Erivedge®) cannot be endorsed for use within NHS Wales for the treatment of adult patients with symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy".
> http://www.awmsg.org/awmsgonline/app/appraisalinfo/1037

AWMSG requested a submission from Roche Products Ltd, in August 2016. Roche was not able to make a complete submission as an economic model was not available in the time allowed. AWMSG appraisal is scheduled for 26th April 2017.

The medicine has been funded in England via the Cancer Drugs Fund (CDF) at list price since 2013.

2.3 Administration and costs of the technology

Table 6: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	150 mg hard capsules	Vismodegib SmPC(34)
Acquisition cost (excluding VAT)	List price = £6,285.00 (28 x 150mg capsules)	Vismodegib BNF(37)
Method of administration	Oral	Vismodegib SmPC(34)
Doses	150 mg	Vismodegib SmPC(34)
Dosing frequency	The recommended dosing of vismodegib is 150 mg once daily	Vismodegib SmPC(34)
Average length of a course of treatment	The median treatment duration in ERIVANCE was 12.68 months (range 1.1 to 47.8) in the laBCC cohort, and13.27 months (range 0.7 to 39.1) in the mBCC cohort. The median overall treatment duration across all patients in the trial was 12.93 months (range 0.7 to 47.8). The median treatment duration in STEVIE was 256 days (range 1 to 1341) in the laBCC cohort and 319.0 days (range 2 to 1147) in the mBCC cohort. The median overall treatment duration across all patients in the trial was 263 days [8.6 months] (range 1 to 1341 days). According to the vismodegib SmPC, treatment with vismodegib should be continued until disease progression or until unacceptable toxicity.	ERIVANCE Study(38), STEVIE study (28, 39) Vismodegib SmPC(34)
Average cost of a course of treatment	**List price** Median treatment duration in days = **263** Daily treatment cost = **£224.46** Avg. cost of a course of treatment = **263 * £224.46 = £59,032.98** **With PAS** Median treatment duration in days = **263** Daily treatment cost = [redacted] Avg. cost of a course of treatment = **263** [redacted]	STEVIE Study,(38) Vismodegib BNF(37)
Anticipated average	It is anticipated that patients will only	Vismodegib SmPC

interval between courses of treatments	have one course of treatment, continued until disease progression or until unacceptable toxicity (treatment course may include one or more treatment breaks to manage adverse events; median duration of treatment break in the STEVIE study was 22 days)	(34, 35)
Anticipated number of repeat courses of treatments	The licence does not make any stipulations regarding repeat courses of treatment; however, there is very limited data available on repeat treatment (i.e. additional courses of treatment) following discontinuation after initial response: • Patients who discontinued vismodegib in the ERIVANCE study before disease progression were re-treated with vismodegib when their treatment progressed • Cohort 2 of the RegiSONIC study recruited 9 patients who have had prior vismodegib	Vismodegib SmPC(34) (40) (31)
Dose adjustments	Dose adjustments were not permitted in the ERIVANCE clinical study protocol and are not recommended in the Erivedge SmPC.	ERIVANCE Study,(38) Vismodegib SmPC(34)
Anticipated care setting	Vismodegib should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication. Treatment will therefore be initiated in the secondary care setting only and self-administered by patients at home.	Vismodegib SmPC(34)

2.4 Changes in service provision and management

2.4.1 Additional tests and investigations

Erivedge is indicated for the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma
- locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

There are no biomarker testing requirements for patients diagnosed with BCC, as almost all have a mutation present in the Hedgehog pathway.(1) Approximately 90% of sporadic BCCs have identifiable mutations in at least one allele of *PTCH1*, inactivating the inhibition

of the downstream smoothened (SMO) protein, and an additional 10% have activating mutations in this SMO protein, which render SMO resistant to inhibition by PTCH1.

Vismodegib should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication.

Due to the teratogenicity of vismodegib, a requirement of the Erivedge®▼ (vismodegib) Pregnancy Prevention Programme is that women of childbearing potential should undergo monthly medically-supervised pregnancy tests within a maximum of seven days of prescription of Erivedge®▼ (vismodegib), and that prescriptions of Erivedge®▼ (vismodegib) should be limited to 28 days' supply in these patients.

2.4.2 Resource use to the NHS

Vismodegib is currently prescribed to patients by oncologists. The chemotherapy service specification (41) mandates that the prescription of systemic anticancer therapy (including vismodegib) is initiated by an oncologist. Additionally, current reimbursement of vismodegib is obtained via an oncologists' application to the Cancer Drug Fund. Commonly, the decision to prescribe vismodegib is subsequent to the patients' case being presented at a Specialist Skin Multi-Disciplinary Team (SSMDT) meeting where dermatology, oncology and surgery specialities are represented. (However, patients may be treated privately by dermatologists, and therefore may not be subject to discussion at an SSMDT.) Vismodegib is only prescribed by consultants in secondary care. Following initiation of vismodegib, patients are usually seen in the oncology clinic monthly, when response and adverse events will be monitored and patients given advice on their management, and generally routine full blood count / biochemistry tests will be conducted. Whilst it is a stipulation of the licence that patients who are women of childbearing potential are only supplied with a 28 day prescription and have medically supervised monthly pregnancy tests (refer to the Erivedge®▼ (vismodegib) Pregnancy Prevention Programme), other groups of patients may be supplied with more than one month of vismodegib once treatment has been established. Clinical nurse specialist support is often in place for skin cancer clinics.

2.4.3 Requirements for additional infrastructure in the NHS

No additional infrastructure is required for vismodegib treatment. Vismodegib is an oral systemic anticancer therapy, dispensed from hospital pharmacies and/or on-site commercial out-patient pharmacies. Supply via homecare pharmacy is also possible if appropriate governance is in place.

2.4.4 Patient monitoring

As stated in section 2.4.2, vismodegib is almost exclusively prescribed by oncologists due to its current reimbursement through the CDF. Patients would generally be seen in clinic on a monthly basis, with routine clinical monitoring conducted as appropriate for the patients' individual circumstances. The Erivedge®▼ (vismodegib) licence does not stipulate monthly blood tests, though this would often be done for the mostly elderly demographic of patients.

Expert advice indicated that oncologists would not see patients with aBCC if vismodegib were not available; patients would be either managed:

- by dermatologists who would monitor patients several times per year; more regular patient care would be carried out in the community by GPs and district nurses, potentially requiring intensive and continual wound management,

- with palliative (i.e. non-curative) radiotherapy, when required, for the management of bleeding and/or exudation of the wound. The dose of radiation may be given in a single fraction, or fractionated if the wound is particularly large,

- by referral for consideration for major surgery to resect locally advanced disease (with involvement of multiple surgical specialities e.g. ear, nose and throat (ENT) specialist / oculoplastic / maxillofacial / neurosurgical teams, with the likely requirement for complex plastic surgical reconstruction). It should be noted that this surgery would **not** be expected to be curative and is usually associated with significant morbidity (e.g. loss of an eye) and a significant risk of mortality.

Women of childbearing potential should not be initiated on vismodegib treatment unless they have a negative pregnancy test (conducted by a healthcare professional) within a maximum of 7 days before starting vismodegib treatment; tests should be repeated monthly during treatment. Prescriptions of vismodegib should be limited to 28 days of treatment and continuation of treatment requires a new prescription.

2.4.5 Concomitant therapies

No concomitant therapies are specified as required in the Erivedge Marketing Authorisation. Adverse events, which are in the majority mild-to-moderate,(17) (42) are primarily managed by treatment breaks although some clinicians find the use of symptomatic treatment with prescription anti-emetics, quinine, or over the counter medication useful.

- The majority of treated patients (95.2%) in the ERIVANCE trial reported use of at least one concomitant medication while on study. The most frequently reported

medications included paracetamol (29.8%, 31 patients), multi-vitamin not otherwise specified (20.2%, 21 patients), aspirin and ibuprofen (each with 19.2%, 20 patients), and hydrocodone tartrate/paracetamol (13.5%, 14 patients).(43)

- The majority of treated patients (92.3%) in the STEVIE study reported use of at least one concomitant medication while on the study. The most common classes of concomitant medications were vitamins and minerals (33.2%), analgesics (27.8%), proton-pump inhibitors (25.7%), and beta-adrenoceptor blocking agents (23.2%).(39)

Due to the teratogenic nature of vismodegib, women of childbearing potential must agree and be able to comply with the terms of the Erivedge®▼ (vismodegib) Pregnancy Prevention Programme, and will use recommended contraception during vismodegib treatment and for 24 months after their final dose. Recommended contraception requires two methods, the first being a barrier method (either a male condom with spermicide, or a diaphragm with spermicide), and another highly effective method (either a hormonal depot injection, or an intrauterine device, tubular sterilisation, or their partners' vasectomy).

2.5 Innovation

Vismodegib is a first-in-class, small-molecule inhibitor of the Hedgehog signalling pathway. Prior to vismodegib, there have been no approved treatments for 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. Vismodegib offers a novel treatment for laBCC patients who have exhausted their treatment options (surgery, radiation, photodynamic therapy, and topical chemotherapy) and further surgery or radiotherapy is considered inappropriate. Refer to Appendix 16 (Photo Appendix).

The pivotal clinical study (ERIVANCE), reported a 56.3% response rate among patients with aBCC.(27) In the STEVIE study, Skindex-16 results were analysed with respect to response. Clinically meaningful improvements in emotion, functional and symptom domains were seen in those patients who achieved a complete or partial response. (29)

The mean age of patients with mBCC and laBCC in the ERIVANCE trial was 61.6 and 61.4 years old, respectively, (median 62.0 years for both patient groups).(44) This suggests that the wider patient population (outside of the clinical trial) may straddle both patients of working age (possibly an income earner for their family and responsible for the care of other family members), and those that are more elderly (with possibly more comorbidities). Vismodegib demonstrates clinical benefit, thus allowing patients to remain active and

contribute to society. The personal and wider societal benefit derived through prolonging a patient's working life and slowing disease progression is not currently captured in the QALYs calculation.

Roche consider vismodegib to be an innovative treatment, with significant positive impact on patients' lives.

3 Health condition and position of the technology in the treatment pathway

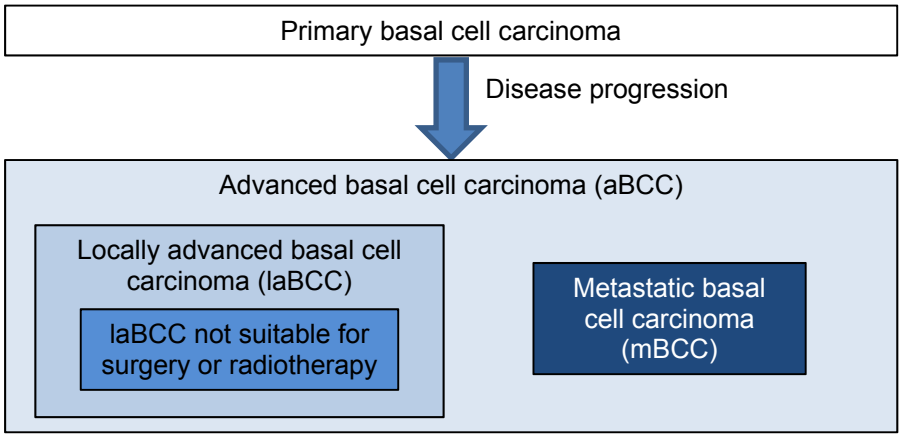
3.1 Disease overview

3.1.1 Clinical presentation

Basal cell carcinoma (BCC) is a form of non-melanoma skin cancer (NMSC). As ultraviolet (UV) radiation is a risk factor, BCCs are most often found on the head, neck, and other areas exposed to the sun in light-skinned individuals. (45) (8, 46) (8, 46) (47) (48) (49)

The common, non-advanced forms of BCC usually present as uncomplicated pearly papules with overlying telangiectases (dilated blood vessels) with a rolled border (45) (48) or as pigmented, scaly, plaque-like, or indurated lesions depending on the histologic subtype.(8) (47) (48) These lesions are usually indolent, characterised by slow growth and minimal soft tissue invasiveness (locally invasive). However, BCC can advance to affect surrounding tissues, cartilage, and bone, potentially leading to substantial local or deep tissue destruction and disfigurement (locally advanced basal cell carcinoma [laBCC]; particularly as lesions predominantly affect the head) or metastasise to regional and/or distant sites (metastatic basal cell carcinoma; mBCC). (6) These locally advanced and metastatic forms of BCC, laBCC and mBCC, are collectively described as advanced basal cell carcinoma (aBCC).

Figure 3: Advancement of basal cell carcinoma



3.1.2 BCC Clinical Subtypes

There are several distinct clinical BCC subtypes including superficial, nodular, and morpheaform (also known as sclerosing, fibrosing, or infiltrating) BCCs.(8, 48) These BCC subtypes are primarily based on their clinical appearance and vary in their malignant potential. Superficial and nodular BCC tend to be less aggressive forms of disease relative

to morpheaform.(47) Morpheaform BCC is generally more aggressive and associated with a higher risk of developing advanced disease. Furthermore, the morpheaform BCC subtype has been associated with greater subclinical depth of tissue extension and a greater rate of recurrence relative to other clinical subtypes.(47)

3.1.3 Advanced BCCs

Although surgical excision resolves most cases of non-advanced BCC described above, BCC may progress in some patients to a more serious form of cancer: aBCC.(8, 47) It has been postulated that patients presenting with aBCCs could be designated in to two categories, (1) those who present with aBCC due to delay in accessing medical attention (e.g. fears around treatment; responsibilities for caring for family member); or (2) those who have BCCs that are intrinsically aggressive and are refractory or recur after treatment.(16)

Currently, there is no global, standardised staging system for aBCC, which presents difficulty in describing the epidemiology of this rare cancer.(5) In addition, a diverse group of practitioners (including dermatologists, medical and clinical oncologists, radiologists, and surgeons) diagnose and treat aBCC, which may pose challenges to incidence assessment due to unsystematic documentation.

- Locally Advanced BCC

BCC growth is usually indolent and confined to the localised area of origin; however, some BCCs may infiltrate tissues with irregular, finger-like growth projections, which may not be obvious on visual inspection.(50) If left untreated, or inadequately treated, an infiltrating BCC can cause extensive tissue destruction, particularly on the head or neck.(50) In such cases, an infiltrating BCC may infiltrate bone and deeper structures, like the brain.(50) Advanced BCC is thought to occur in up to 10% of all BCCs (16, 18), with around 1% of BCCs developing in to advanced cases that are not appropriate for standard therapy (laBCC in appropriate for surgery or radiotherapy; laBCC*i*)(17)

- Metastatic BCC

BCCs very rarely spread to distant regions, only 0.0028 to 0.55% of BCCs progress to metastatic basal cell carcinoma (mBCC).(3, 4) Risk factors that appear to predispose patients to developing mBCC have been identified: (51)

    - long duration and persistence of the tumour for many years,

- site (in 85% of cases the primary tumour was located in the head and neck region [particularly the ears and mid-face]),
- the size of the tumour, depth of invasion and infiltrative histological pattern,
- number of lesions,
- recurrence despite optimal treatment,
- BCC refractory to conventional methods of treatment, incomplete surgical resection and previous radiation therapy either in early adulthood or for localised cancer.

Metastases most often spread to lymph nodes, lungs, and bones. Lymphatic and haematologic routes of tumour dissemination have been reported with equal frequency (11), though some case series report a dominance of lymphatic involvement.(15) Age or gender do not appear to influence survival outcomes in mBCC.(11) BCC that has metastasised locally with only regional lymph node involvement tends to be more biologically indolent, compared with those that have visceral metastases and have poor prognosis and death usually within months.(15) Once BCC has metastasised to distant structures, mean survival of between 10 to 14 months(15) and median survival of 8 months(11) is reported; it is highly malignant and currently considered incurable and life-threatening.(14) To better understand the clinical outcome for mBCC patients more recently, a retrospective analysis was undertaken by Roche.(23) Between 1981 and 2011, survival from mBCC diagnosis to death ranged from 0 to 120+ months in the 100 mBCC cases identified in the published literature. Median survival was 24 months among patients with distant metastases (just 12 months in those with bone metastases and 66 months for those without bone involvement), compared with 87 months in those patients who had local metastases.

Another notable risk factor is the inherited disorder, Gorlin syndrome (also known as basal cell naevus syndrome [BCNS], naevoid basal cell carcinoma, or Gorlin-Goltz syndrome), which is associated with a predilection for aBCC development. (47),(48), (52, 53) Gorlin syndrome is the most common of the inherited syndromes associated with BCC development.(54, 55) Gorlin syndrome is an autosomal dominant disorder characterised by the development of multiple naevoid BCCs, as well as the development of recurrent odontogenic keratocysts, skeletal anomalies, intracranial calcification, and developmental malformations.(56) The greatest health concern for patients with Gorlin syndrome is the risk of malignant tumour development, the most common of which are BCCs.(57) It is important

to note that aberrant Hh signalling is the underlying oncogenic driver for the development of aBCC in patients with or without underlying Gorlin syndrome.

3.1.4 Natural Progression of BCC

The natural progression of untreated BCC in most cases involves indolent growth with slow, progressive invasion and destruction of adjacent tissues.(50),(58) Initial tumour growth is usually localised to the area of origin; however, some BCCs may infiltrate tissues vertically, which may not be obvious on visual inspection.(50) Due to their size, invasiveness, or location, advanced BCC lesions can cause significant disfigurement or deformity, disability, and/or premature mortality. Patients with laBCC often suffer lesions that cause extensive tissue destruction through deep invasion of surrounding tissue and infiltrate into bone or deeper structures like the brain. Advanced BCC development near the eyes, ears or nose can result in loss of these organs/structures, or their function. Such lesions can be disfiguring*, particularly on the face, and potentially life-threatening. In rare cases, if left untreated or inadequately treated, BCC can metastasise to lymph nodes or distant areas such as the lung, liver, and bone.

3.1.5 Treatment

Treatment options for patients with BCC are determined by consideration of a number of factors, including: tumour size, site, and histological subtype; previous treatment history and patient comorbidities; patient preference; and access to treatment. It is also important to consider whether the intention of treatment is curative or palliative.(2) Current treatments for BCC (patients whose disease is not considered advanced) include surgical excision and/or radiotherapy, and less commonly: topical (e.g. 5-fluorouracil or imiquimod) chemotherapy or electrochemotherapy, curettage, cryotherapy, and photodynamic therapy. (24)

- **Surgery**: The majority (over 60%) of BCCs are nodular (59), and are generally treated by surgical excision, with variable margins depending on tumour characteristics and anatomy of the site A BCC with a diameter <2 cm would require a minimum margin of 4 mm to totally remove the tumour in more than 95% of cases; however, if this were a high-risk primary BCC of the same size, a margin of at least 13 mm would be required to obtain the eradication of the tumour in 95% of cases.(60) Surgery may also be used for superficial BCCs. More invasive BCC subtypes, such as infiltrative or morphoeic BCC, or large lesions and those in

* Refer to Photo Appendix for example patient cases of laBCC from the ERIVANCE study

cosmetically sensitive sites in which tissue sparing is critical, can be treated with Mohs' micrographic surgery, which results in reduced recurrence rates compared with other treatment options.(61)

- **Radiotherapy**: Radiotherapy provides an alternative treatment for some patients in whom surgery is not suitable or is not desired by the patient, or in the postoperative adjuvant setting if resection margins are positive and no further surgery is possible. (25, 62) Surgery is difficult after radiotherapy. Radiotherapy also has long-term carcinogenic potential with secondary carcinoma development associated with treatment.(60) The cosmetic result of radiotherapy can worsen over time, and this treatment method is therefore used predominantly in patients over 55 years of age.(25, 62)

- **Topical chemotherapy**: agents such as 5-fluorouracil or imiquimod may be used for primary, small, superficial BCCs, and normally yield good clearance rates.(25, 60, 62) The use of imiquimod for specific body sites (the face, and particularly the eyelids) in combination with other non-surgical modalities (e.g. photodynamic therapy), cryosurgery or Moh's surgery, and for specific clinical groups of patients such as those who are immunosuppressed, has been proposed.(60)

- **Electrochemotherapy** is a local treatment that aims to enhance the effects of chemotherapy. This is typically used to manage inaccessible or otherwise difficult-to-treat primary basal cell carcinomas.(63)

- **Curettage**: this works best on nodular or superficial BCC and involves the tumour being scraped with a curette; the wound is then treated with electrocautery to control bleeding and destroy residual tumour. Curettage and cautery are considered good treatment for low-risk BCC, with overall five-year recurrence rates for primary tumours varying from 3.3% in low-risk sites to 18.8% in high-risk sites: a recurrence rate of 60% is reported for recurrent BCCs.(60) Due to the disproportionate amount of residual tumour on head and neck wounds and higher recurrence rates, curettage and electrocautery is not considered first-line treatment for facial BCCs.(64)

- **Cryotherapy**: this involves the destruction of tissue using liquid nitrogen and tends to be useful in the treatment of low-risk BCCs. The main disadvantage of this technique is that there is no histological control to establish tumour eradication.(60) Cryotherapy is not considered first-line treatment for facial BCCs as there is a high risk of recurrence, and potentially poor cosmetic outcome.(64)

- **Photodynamic therapy (PDT)**: NICE guidance on photodynamic therapy exists for treatment of non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). Current evidence suggests that there are no major safety concerns associated with PDT with such lesions.(65) Clearance rates of up to 87% have been achieved for superficial BCCs treated with PDT, which is lower than those achieved for surgery.(64) Primary superficial and thin nodular BCCs are the most appropriate to receive topical PDT.(60)

Patients with locally advanced disease have lesions that may not be appropriate for radiotherapy or surgery. Surgery may be considered inappropriate because it is unlikely to be curative, or disease has recurred after surgery, or due to significant deformity as a result of surgery (e.g., invasion into the skull, limb amputation, or eye removal) based on lesion location, size, and/or tumour histology. Additionally, the use of radiotherapy is not advised in tumours located near eyes or on eyelids or potentially the extremities (e.g. shins), individuals who are nearing their maximum safe lifetime radiation dose, and younger patients, who are likely to suffer late adverse effects and cosmetic results that are inferior to those of surgery.(8, 25) For patients with disease recurrence after prior radiotherapy, subsequent radiation is contraindicated.(25),(26)

Vismodegib offers a novel treatment for patients with laBCC who have exhausted their treatment options and further surgery or radiotherapy is considered inappropriate.

There are particular concerns regarding the use of radiotherapy in tumour predisposing syndromes (66) - it has been generally considered that radiotherapy should be contraindicated in patients with Gorlin syndrome, due to the risk of further BCC development in the radiation field.(60) However, this has been questioned recently: there is clear evidence for BCC exacerbation in children with Gorlin syndrome treated with radiotherapy; this was not found to be the case in adults.(67) However, evidence so far is limited to small numbers of case studies with minimal follow-up, and the update of the European guidelines for BCC management still include Gorlin syndrome as a contraindication to radiotherapy.(60)

Prior to vismodegib, there have been no approved treatments for 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.

3.2 Effects of the disease on patients, carers and society

The clinical burden of disease for individuals afflicted with aBCC is significant. In aBCC, tumours have metastasised or caused extensive tissue destruction through deep invasion and deformity of surrounding tissue, particularly on the face, resulting in disfiguring and potentially life-threatening disease.(50) Patients with aBCC have expressed health-related quality of life (HRQoL) issues about fear of recurrence or metastases, pain, appearance (potentially increasing social isolation), and the inconvenience of wound care.(68) Patients with Gorlin syndrome have expressed similar HRQoL concerns in addition to anxiety regarding the future and the significant inconvenience of undergoing multiple surgeries.

Locally advanced BCC often affects visible areas of the head and neck with significant disfigurement*. For example, laBCC lesions, as a result of tumour invasion, may lead to limb amputation or surgical removal of a facial structure such as an eye, ear, or nose.(8) In addition, laBCC can be associated with significant morbidity as the result of these lesions causing chronic pain, risk of bacterial infection and sepsis, bleeding or oozing, and compromise of ear, nose, or eye function from tissue invasion.

The prognosis is poor for patients with mBCC, and morbidity and mortality are high.(2) A published retrospective case series by Von Domarus estimated median time from the first sign of metastasis to death at 8 months.(11) To gain a more recent understanding of the clinical outcome for mBCC patients, a retrospective analysis was undertaken by Roche. This retrospective review of published literature between 1981 and 2011 revealed that in the 100 mBCC cases identified, survival from mBCC diagnosis to death ranged from 0 to 120+ months.(23) Median survival was 24 months among patients with distant metastases (just 12 months in those with bone metastases and 66 months for those without bone involvement), compared with 87 months in those patients who had regional metastases. The 1-year probability of survival after mBCC diagnosis was approximately 73.2% for all cases reviewed and a lower 1-year survival probability was associated with the subset of cases reporting patients with distant metastases (58.6%) compared with those with regional disease (87.8%).(23)

The increasing trend in NMSC development, likely due to increasing UV radiation exposure, leads to concerns over losses in productivity, direct and indirect costs associated with the

* Refer to Photo Appendix for example patient cases of laBCC from the ERIVANCE study

morbidity and potential premature mortality of aBCC.(22),(69) Despite most cases of BCC being curable, deaths from aBCC are reported.

There is little published data regarding societal burden, and indirect costs including morbidity and mortality costs of BCC specifically. NMSC incorporates both BCC and the typically more aggressive SCC.(22) Mortality cost from potential lost future earnings due to premature death from NMSC have been estimated (in converted 2009 $US) to be $1 billion in the US, $8.7 million in the UK, $0.55 million to $3.6 million in Sweden, and $4.6 million in New Zealand.(22) The mortality cost per premature death from NMSC ranged from $20,550 in the UK (converted to 2009 US$) to $67,526 in Sweden.(22),(70),(71) The annual indirect morbidity costs per population, calculated from US Environmental Protection Agency and Bureau of Labor Statistics, indicated that BCC cost $1235 compared with the higher SCC cost ($4761; both 2009 $US rates).(22) A systematic literature review conducted by the US Centers for Disease Control and Prevention (CDC) found that the number of years of potential life lost (YPLL) per death attributable to NMSC was approximately 10. (22)

3.3 Clinical pathway of care

Prior to the regulatory approval of Erivedge, patients with aBCC had no approved or standard therapeutic options, when surgery or radiotherapy (with curative intent for patients with laBCC) was inappropriate.

If vismodegib were not available, patients with incurable aBCC; would be managed with best supportive care, either:

- by dermatologists who would monitor patients several times per year; more regular patient care would be carried out in the community by GPs and district nurses, potentially requiring intensive and continual wound management, or,

- with palliative (i.e. non-curative) radiotherapy, when required, for the management of bleeding and/or exudation of the wound. The dose of radiation may be given in a single fraction, or fractionated if the wound is particularly large, or,

- by referral for consideration for major surgery to resect locally advanced disease (with involvement of multiple surgical specialities e.g. ear, nose and throat (ENT) specialist / oculoplastic / maxillofacial / neurosurgical teams, with the likely requirement for complex plastic surgical reconstruction). It should be noted that this surgery would **not** be expected to be curative and is usually associated with significant morbidity (e.g. loss of an eye) and a significant risk of mortality.

3.3.1 The approach to treatment of patients with aBCC: the RONNIE study

An analysis of treatment patterns and outcomes for BCC patients (RONNIE study, NCT02100111(72, 73)) revealed that the standard approach to treatment of patients with aBCC was a succession of treatments given over a short time interval, and that the number, type, and combination of treatments varied enormously. A single treatment with a durable outcome was an exception.(73) The RONNIE study was a retrospective, multicentre, multinational chart review of real-world treatment practices to describe the usual practice for patients with aBCC before the availability of Hedgehog Pathway Inhibitors (HPI). Patients with aBCC (n=134) (eligible laBCC n=117, and eligible mBCC n=4) were identified from the files of 38 centres from France, Italy, Germany and the UK. Despite the majority of patients (n=103 of the 117 laBCC cases) being considered inoperable (46 of 117 patients with laBCC, 39.3%), or surgery being contraindicated (26/117 (22.2%) because recurrent BCC unlikely to be curatively resected, and 31/117 (26.5%) because of anticipated substantial morbidity or deformity), almost half of patients with laBCC received surgery at some point (12/106 [11.5%] of patients for whom treatment was recorded underwent Moh's surgery, and 38/106 [35.8%] received excisional surgery).(73)

Vismodegib provides adult patients with laBCC or mBCC the first approved treatment for aBCC. Surgery and radiotherapy are often not suitable for aBCC patients due to risks associated with surgical disfigurement and significant deformity or highly-invasive tumour locations, large tumour sizes, and tumours associated with recurrent lesions, or metastatic disease. (6, 50),(25),(9) Vismodegib represents an important treatment modality for these patients and those with Gorlin syndrome, who are predisposed to develop aBCCs over their lifetime.(74)

Sonidegib (trade name Odomzo®, Novartis Europharm Ltd.) received Marketing Authorisation throughout the EU on 14th August 2015 for the treatment of adults with locally advanced basal cell carcinoma (BCC).* However, this is not commercially available in the UK.

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* http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002839/human_med_001897.jsp&mid=WC0b01ac058001d124

3.4 Life expectancy of people with the disease in England

3.4.1 Background incidence and prevalence of BCC and limitations for aBCC epidemiology data

NMSCs, which include BCCs and squamous cell carcinomas (SCCs), are the most common forms of cancer in humans, surpassing in incidence all other forms of cancer combined.(6) Approximately 2 to 3 million cases of NMSC are estimated to occur every year worldwide.(75) Although BCCs and SCCs are usually reported collectively as NMSCs, the majority of NMSCs are BCCs with BCCs accounting for 80% to 90% of NMSCs.(9) It is important to note that the true incidence and prevalence of NMSCs, and thus BCCs, are difficult to estimate because large national cancer registries do not track NMSC; additionally, NMSCs are usually treated in a primary care setting.(8-10) Despite these limitations, several published reports have estimated the incidence of NMSC, or more specifically for BCC. Epidemiology data for BCC and aBCC are limited(76): very little epidemiologic data are currently available that differentiate epidemiology trends more specifically within BCC for the laBCC and mBCC populations.

3.4.2 Incidence of locally advanced and metastatic BCC

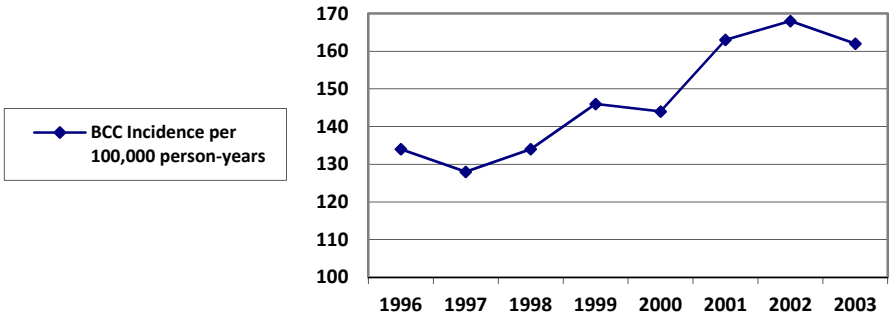
As in all NMSCs, the true incidence of laBCC or mBCCs is difficult to estimate because these cases are not captured in national cancer registries.(45) (10) Case experience data indicate that locally advanced and metastatic presentations of BCC are rare. The estimation of aBCC incidence also faces additional challenges, due to the lack of a global, standardised staging system for aBCC, and the diverse group of practitioners diagnosing and treating aBCC (as described in section 3.1).

Despite these limitations, rare cases in which invasion of BCC into subcutaneous structures and beyond leading to unresectable, locally advanced disease and metastatic disease have been reported.(4),(11),(12),(13) ,(14) Advanced BCC is thought to occur in up to 10% of all BCCs(16), with laBCCi occurring in up to 1% (17, 18) and metastatic BCCs accounting for 0.0028% to 0.55% of all BCCs. (4),(19) Fewer than 300 cases of mBCC have been reported in the literature (15). For the model, the incidence of laBCC that is not suitable for surgery or radiotherapy and of mBCC in the UK have been estimated from the UK primary care database (20) with the proportions of laBCC and mBCC reported in the US retrospective analysis of an insurance database applied.(18)

United Kingdom

As with other countries around the world, the incidence of BCC is increasing in the UK (Figure 4).(77),(78) Over a 10 year period, the incidence rate of BCC increased 66% between 1988 and 1998.(78) The crude incidence of BCC in the UK has been estimated to be 153.9 per 100,000 person years (95% CI: 151.1 to 156.8) with a slightly higher rate in men than women.(20) The world age-standardised rate of BCC is 60 per 100,000 per year, and the European age-standardised rate is 89 per 100,000.(20) Overall, BCC incidence has been increasing by 3% per year between 1996 and 2003 and approximately 53,000 new cases of BCC are estimated to occur every year in the UK.(20)

Figure 4: Crude annual incidence rates by year in the UK(20)



An estimation of the numbers of laBCC and mBCC in England and Wales has been made, based on the following:

- The population of England and Wales was obtained from ONS, 2014-based National Population Projections (published 29-Oct-2015), Table 7.
- Trends in incidence of skin basal cell carcinoma obtained from a UK primary care database study(20) and extrapolated using linear regression, Table 8.
- Incidence and prevalence of BCC and laBCC was obtained from a retrospective cohort study of a large commercially insured population in the United States (18), Table 9.

Applying the proportions obtained in the retrospective US insurance claims publication enabled the estimation of the numbers of laBCC and mBCC in England and Wales, Table 10.

Vismodegib has been available on the CDF in England since the UK launch of Erivedge in August 2013. From the UK launch until the end of August 2016, 352 requests had been made for funding for Erivedge through the National Cancer Drugs Fund.(21)

Table 7: Population of England and Wales (Office of National Statistics population projections)(79)

	2014	2015	2016	2017	2018	2019	2020	2021
Female population of England & Wales	29,114,000	29,324,000	29,526,000	29,723,000	29,919,000	30,110,000	30,298,000	30,481,000
Male population of England & Wales	28,295,000	28,557,000	28,803,000	29,038,000	29,272,000	29,495,000	29,713,000	29,925,000

Table 8: Trends in incidence of BCC obtained from UK primary care database – extrapolated (20)

	2014	2015	2016	2017	2018	2019	2020	2021
Female BCC incidence per 100,000	223	229	235	241	247	252	258	264
Male BCC incidence per 100,000	237	243	248	253	259	264	269	275

Table 9: Incidence and prevalence of BCC and laBCC in the US (18)

	Female	Male
BCC	17,942	21,093
laBCC	122	139
mBCC	1	6
% laBCC of BCC	0.68	0.66
% mBCC of BCC	0.01	0.03

Table 10: Estimation of the numbers of laBCC and mBCC in England and Wales

	2014	2015	2016	2017	2018	2019	2020	2021
Female laBCC	441	456	471	486	502	517	532	548
Male laBCC	442	456	471	485	499	513	527	542
Female mBCC	4	4	4	4	4	4	4	4
Male mBCC	19	20	20	21	22	22	23	23
laBCC incidence	883	912	942	971	1,000	1,030	1,060	1,090
laBCC inappropriate for surgery or radiotherapy (assumption: 40% of laBCC are inappropriate)	353	365	377	388	400	412	424	436
mBCC incidence	23	23	24	25	26	26	27	28

3.4.3 Prognosis

Due to their size, invasiveness, or location, aBCC lesions can cause significant disfigurement or deformity, disability, and/or premature mortality. However, mortality directly attributable to laBCC is incredibly rare, with elderly patients often dying from other co-morbidities associated with old age. Locally advanced disease is considered a chronic condition and unless present near a vital blood vessel, perineural, or at a very advanced stage involving the skull; laBCC would not be expected to directly cause the death of the patient. However, approximately 10 years of potential life are lost per death from NMSC (22), and it could be postulated that laBCC contributes to the shorter survival in patients due to poor general health and self-care.

The prognosis is poor for patients with mBCC, and morbidity and mortality are high.(2) A published retrospective case series by von Domarus estimated median time from the first sign of metastasis to death at 8 months.(11) To gain a more recent understanding of the clinical outcome for mBCC patients since then, a retrospective analysis was undertaken by Roche.(23) This retrospective review of published literature between 1981 and 2011 revealed that in the 100 mBCC cases identified, survival from mBCC diagnosis to death ranged from 0 to 120+ months.(23) Median survival was 24 months among patients with distant metastases (just 12 months in those with bone metastases and 66 months for those without bone involvement), compared with 87 months in those patients who had local metastases. The 1-year probability of survival after mBCC diagnosis was approximately 73.2% (95% CI 64.4 to 82.0) for all cases reviewed and a lower 1-year survival probability was associated with the subset of cases reporting patients with distant metastases (58.6%; 95% CI 44.6 to 72.6) compared with patients with regional metastases (87.8%; 95% CI 78.6 to 97.0).(23)

3.5 Guidance related to the condition

NICE have published guidelines on improving outcomes for people with skin tumours including melanoma [CSG8] in 2006, with a partial update in 2010.(80)

3.6 Other clinical guidelines

Basal cell carcinoma guidelines are available from the British Association of Dermatologists. (25)

An update of the European guidelines for basal cell carcinoma management was developed by the Guideline Subcommittee of the European Dermatology Forum in 2014. The guideline endorsed the use of targeted therapy inhibiting the SMO receptor in the Hedgehog pathway

as effective management against laBCC or mBCC, with strength of recommendation ‘A’ and quality of evidence ‘II-I’.(60)

3.7 Issues relating to current clinical practice

Across all available BCC treatment guidelines, recommendations are focused on primary BCCs and prospective evidence-based guidance for aBCC is lacking.

In general, BCC guidelines emphasise the need to stratify patients by level of BCC recurrence risk to manage the likelihood of recurrence and, consequently, tailor treatment selection based on the size, site, histological subtype, presence of perineural invasion, evidence of previous recurrence, and immunosuppression status.(6, 25, 60) Although there are anecdotal reports of chemotherapeutic regimens for mBCC mentioned in some BCC guidelines, there is no prospective evidence-based guidance for the chemotherapeutic treatment of laBCC and mBCC.

Prior to the development of vismodegib, there were no systemic therapies indicated for use in aBCC. Limited case report and retrospective case series data have suggested that platinum-based combination chemotherapy may provide some response in some aBCC patients; however, given the retrospective nature of the reports, bias may exist and no prospective data are available for aBCC.(6, 81)(6)

Patients with aBCC who are not candidates for surgery or radiation have historically been limited to unapproved treatment options.(81) Prior to the availability of vismodegib, aBCC treatment data has been limited to case reports and small case series for unapproved therapies (e.g., platinum-based chemotherapy).(4) (6) (11, 12, 14),(82)

Recurrent BCC can prove a significant problem to manage, requiring multiple and/or repeated treatments. However, after a time, repeated surgical intervention (excision) may be prohibitive, and repeated radiotherapy for further BCCs may be contraindicated.(2)

The use of targeted therapy inhibiting the SMO receptor in the Hedgehog pathway has been endorsed in the European Guidelines for BCC Management as effective against laBCC or mBCC, with strength of recommendation ‘A’ and quality of evidence ‘II-I’.(60)

3.8 Equality issues

We do not believe that there are any subgroups of patients who would be at a disadvantage following the introduction of any recommendations regarding this medicine.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search overview

A systematic literature review (SLR) was conducted in November 2016 to investigate the clinical outcomes associated with the use of vismodegib for the treatment of locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC) in randomised controlled trials (RCTs) or non-RCTs.

4.1.2 Search strategy

The SLR was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care, and is reported here in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.(83, 84)

The following electronic databases were all searched on 17th November 2016 from their inception dates to the date of the search:

- MEDLINE, MEDLINE In-Process and MEDLINE Daily and Epub Ahead of Print; 1946 to present
- Embase; 1974 to 16 November 2016
- The Cochrane Library, specifically the following:
    - The Cochrane Central Register of Controlled Trials (CENTRAL); Issue 10 of 12, October 2016
    - The Cochrane Database of Systematic Reviews (CDSR); Issue 11 of 12, November 2016
    - Database of Abstracts of Reviews of Effectiveness (DARE); Issue 2 of 4, April 2015

MEDLINE and Embase were searched separately via the Ovid SP platform and the Cochrane Library databases were searched simultaneously via the Wiley Online platform.

As well as the electronic database searches, abstract books from major oncology and dermatology conferences were searched. Full details are presented in Appendix 4.

Manual searches for conference abstracts were limited to those published a maximum of two years ago (i.e. conferences held in 2015 and 2016), as it is assumed that high-quality studies reported in abstract form before this time would have since been published in a peer-reviewed journal.

Reference lists of any systematic reviews or meta-analyses identified as relevant at the title and abstract screening stage were hand-searched to identify any further relevant publications for inclusion in the SLR.

Finally, a search of ClinicalTrials.gov was conducted, using the Advanced Search function, for trials of vismodegib in laBCC or mBCC patients. Relevant studies were cross-checked against the results obtained from the electronic database searches and the manual congress abstract searches, to ensure that no relevant studies with published results were missed.

Full details of the search strategies employed are presented in Appendix 4.

4.1.3 Study selection

Following the database search, duplicate results were excluded. The titles and abstracts of identified sources were assessed against the eligibility criteria presented in Table 11. No language restrictions were used.

Table 11: Eligibility criteria for systematic review of vismodegib for advanced or metastatic basal cell carcinoma

Domain	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years) with: • symptomatic mBCC • laBCC, for whom surgery or radiotherapy is not appropriate Studies were included if patients with advanced or metastatic BCC were at least 50% of the study population, or if results were presented separately for patients with advanced or metastatic BCC.	Any of the following: • patients without BCC • patients with early BCC (not advanced or metastatic) • studies only including patients <18 years old • studies with mixed patient populations where outcomes were not presented separately for the specific population of interest • studies of adjuvant or neoadjuvant therapy
Intervention	Vismodegib (Erivedge®) monotherapy	Studies not investigating vismodegib (Erivedge®) as monotherapy, or studies where outcomes for the relevant intervention were not presented separately to those for interventions not of interest
Comparator	Any therapies, including: • placebo or best supportive care • no comparator (if the study is a non-RCT or observational study)	NA
Outcomes (considered at full-text review only)	Any efficacy or safety outcomes including: • Response rate (complete, partial, stable disease) • Duration of response • Tumour shrinkage • Progression-free survival (PFS) • Overall survival (OS) • Time to progression (TTP) • Clinical benefit rate • Treatment-emergent and treatment-related adverse events (safety and tolerability) • Health-related quality of life (HRQoL) • Time-to-treatment discontinuation	Studies not presenting relevant outcomes
Study design	• RCTs • Interventional non-RCTs, including single-arm clinical trials • Observational studies SLRs and (network) meta-analyses were included at the title/abstract review stage, then excluded at the full-	Any other study designs, including: • Economic evaluations • Case studies and case reports • Editorials, notes, comments or letters • Narrative or non-systematic literature reviews

	text review stage following hand-searching of their reference lists	
Other considerations	English language and non-English language full-texts Human subjects	Articles not on human subjects

Abbreviations: BCC, basal cell carcinoma; HRQoL, Health Related Quality of Life; NA, not applicable; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SLR, systematic literature review; TTP, time to progression

Data from included studies were extracted by one reviewer, and reviewed for accuracy and completeness by a second independent reviewer.

Review strategy

Following the database search, duplicate results were excluded. For those sources considered potentially relevant, or for which the relevance was unclear based on the title or abstract, full texts were obtained and screened for relevance. The screening was performed by two independent reviewers at both stages, and disputes relating to eligibility were resolved through discussion between reviewers until consensus or consultation of a third reviewer.

4.1.4 Included and excluded studies

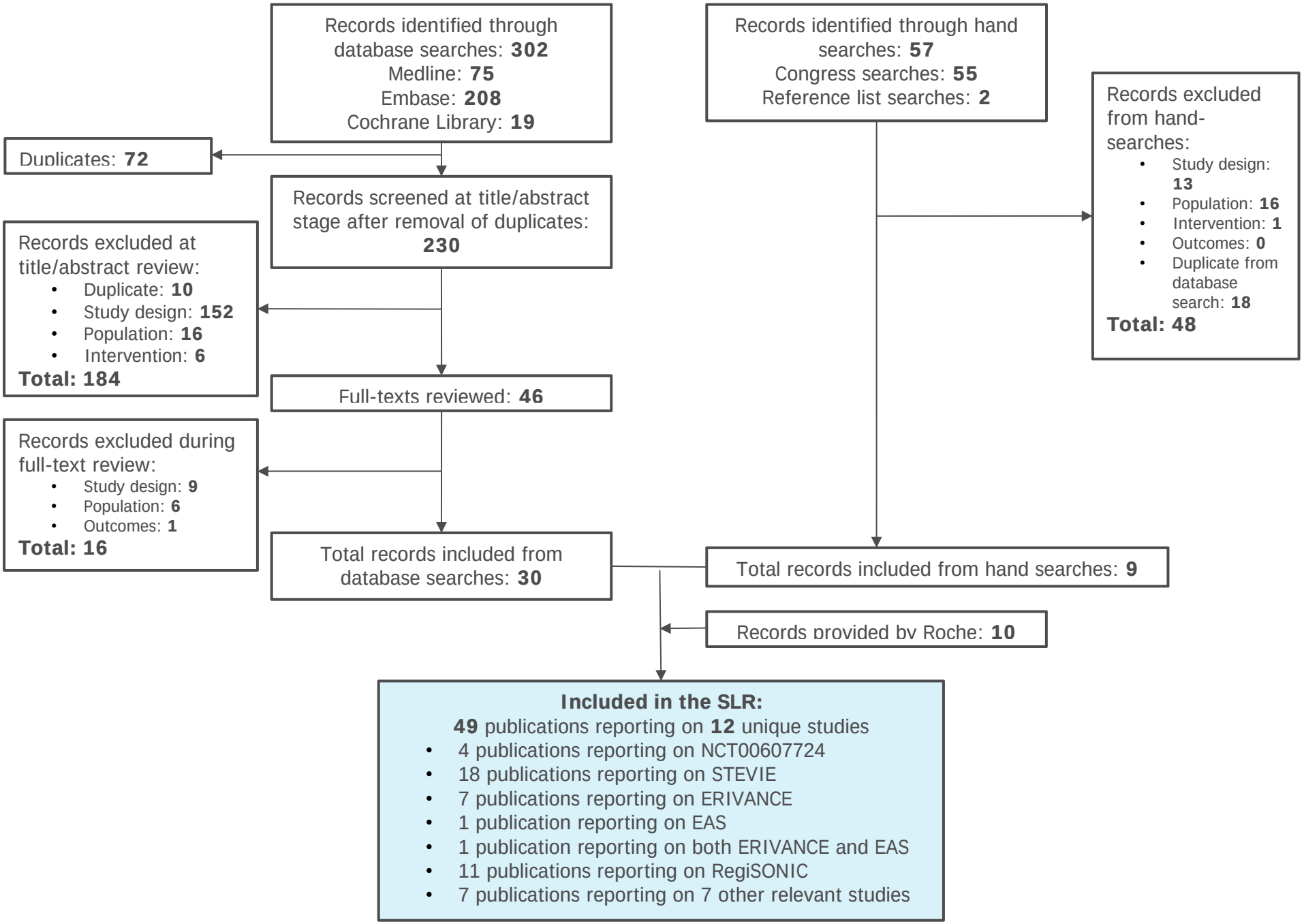
Database searches identified 230 unique records, of which 46 were selected for full-text review and 27 were ultimately found to be relevant. Congress searches and reference list searches identified a further 43 records, of which 6 were found to be relevant. A total of 33 publications were therefore included in the review.

These publications reported on 12 unique studies, which were all non-randomised. Details of these 12 studies are provided in Section 4.11.

A PRISMA flow diagram of the evidence identified is presented in Figure 5.

Please refer to Appendix 5 for a full list of vismodegib publications and studies included in the systematic review. Records identified from ClinicalTrials.gov are detailed in Appendix 6. A complete list of publications excluded after the full-text review stage is provided in Appendix 7.

Figure 5: PRISMA flow diagram for the clinical systematic review



4.2 List of relevant randomised controlled trials

No relevant published RCTs were identified. The search of ClinicalTrials.gov did not identify any ongoing or completed RCTs of vismodegib in patients with laBCC or mBCC.

4.3 Summary of methodology of the relevant randomised controlled trials

No relevant RCTs were identified.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

No relevant RCTs were identified.

4.5 Participant flow in the relevant randomised controlled trials

No relevant RCTs were identified.

4.6 Quality assessment of the relevant randomised controlled trials

No relevant RCTs were identified.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

No relevant RCTs were identified.

4.8 Subgroup analysis

No relevant RCTs were identified.

4.9 Meta-analysis

As no relevant RCTs were identified, it was not possible to perform a meta-analysis.

4.10 Indirect and mixed treatment comparisons

As no relevant RCTs were identified, it was not possible to perform an indirect or mixed treatment comparison.

4.11 Non-randomised and non-controlled evidence

4.11.1 List of studies

Search Strategy

As reported in Section 4.1, a systematic literature review was conducted to identify publications investigating the efficacy and safety of vismodegib for the treatment of laBCC or mBCC. Please see Section 4.1.1 for details of the search strategy.

Study selection

The eligibility criteria for the systematic review are presented in Section 4.1.3 above, while a PRISMA flowchart of publications included and excluded at each stage of the review is presented in section 4.1.

Please refer to Appendix 5 for a full list of vismodegib publications and studies identified in the systematic review. A complete list of vismodegib publications excluded after the full-text review stage is provided in Appendix 7.

The database searches and grey literature searches identified 33 publications on 12 unique studies.

Five studies are presented in detail in this submission. Four publications reported the NCT00607724 study, 18 publications reported the STEVIE study (NCT01367665), seven publications reported the ERIVANCE study (NCT00833417), one publication reported the Expanded Access Study (EAS, NCT01160250), one study reported both ERIVANCE and EAS, and 11 publications reported the RegiSONIC Disease Registry study (NCT01604252). A summary of these five studies is presented in Table 12. Further details of these five studies, including the methodology, statistical analyses, participant flow, quality assessments and results are detailed below.

Table 12: Details of relevant non-randomised studies identified in the systematic review

Trial number (acronym)	NCT00833417 (ERIVANCE)(44)	NCT01367665 (STEVIE)(28)	NCT00607724(13)	NCT01604252 (RegiSONIC)(31)	NCT01160250 (EAS)(32)
Phase	II	II	I		IV
Sponsor	Genentech Inc.	Hoffmann-La Roche	Genentech Inc.	Genentech Inc.	Genentech Inc.
Objective	To estimate the clinical benefit of vismodegib given as therapy for patients with locally advanced or metastatic BCC, as measured by objective response rate (ORR)(43)	To assess safety and efficacy of vismodegib in patients with aBCC in a real-world setting.	To assess the safety and pharmacokinetics of GDC-0449, a small-molecule inhibitor of SMO, and responses of laBCC or mBCC to the drug.	To evaluate the effectiveness, safety and utilisation of treatments in patients with aBCC and BCCNS.(85)	To assess efficacy and safety of vismodegib, while providing early drug access to patients with aBCC and limited treatment options.
Population	104 patients; 33 with mBCC and 71 with laBCC. (Eight patients with laBCC were excluded from the efficacy analysis) (44)	1232 patients with laBCC or mBCC. (17 patients were excluded from the safety and efficacy analysis due to no documented exposure based on return of drug dispensed)	Full study included 68 patients with solid tumours refractory to current therapies or for which no standard therapy existed. This publication reports on 33 patients with mBCC or laBCC.	Patients treated for aBCC and BCCNS. 3 cohorts of patients with BCC: Cohort 1: Patients with a new aBCC who do not have BCCNS and are HPI naïve. Cohort 2: Patients with aBCC who do not have BCCNS and who were previously enroled in Phase 2 SHH4437g (NCT00959647), ERIVANCE SHH4476g or EAS SHH4811g. Cohort 3: Patients with BCCNS who have aBCC as defined for cohort 1 (HPI naïve) or cohort 2	120 patients; 58 with mBCC and 62 with laBCC.

				(vismodegib exposed) or who have multiple non-advanced, HPI-naïve BCCs. As of 11th September 2015, 503 patients with laBCC were enroled across all cohorts.	
Intervention	Oral vismodegib at 150 mg/day(44)	Oral vismodegib at 150 mg/day	Oral vismodegib at 150 mg/day, 270 mg/day or 540 mg/day	Patients are treated according to clinician's standard or care	Vismodegib at 150 mg/day
(For details of all references for studies included in the clinical systematic review, please refer to in Appendix 5)	Sekulic 2012(44) The primary analysis (data cut-off: 26 November 2010; 9 months after the last patients were enroled in the study)(44). Analysis (data cut-off 28 November 2011) provided efficacy and safety data at 12 months since the primary analysis (38) Analysis (data cut-off 30 May 2013) provided efficacy and safety data at 30 months since the primary analysis. (27)	Hansson 2016(28)	Von Hoff 2009(13)	Lacouture 2015(86) 12 September 2014 (87) 13 February 2015 (86, 88, 89) 11 September 2015(30, 31)	Chang 2014(32)

Abbreviations: BCCNS, basal cell naevus syndrome (Gorlin syndrome); HPI, Hedgehog pathway inhibitors; SMO, smoothened

4.11.2 Justification of exclusion of trials from further discussion

Seven studies identified in the systematic review were eligible for inclusion but are not presented here. Details of these studies, including reasons why they were not selected for extraction, are presented in Appendix 7.

4.11.3 Summary of methodology of the relevant non-randomised and non-controlled evidence

A summary of the methodology employed in the studies identified in the systematic review is presented in Table 13.

Table 13: Methodology of the relevant non-randomised trials identified in the systematic review

Trial number (acronym)	ERIVANCE (NCT00833417)(44)	STEVIE (NCT01367665)(28)	Phase I Shh3925g (NCT00607724)(13)	RegiSONIC (NCT01604252)(31)	EAS (NCT01160250)(32)
Location	USA, Belgium, France, Germany, UK, Australia(90)	36 countries	USA	USA and Puerto Rico(85)	USA
Study design	International, multicentre, non-randomised, two-cohort study(44)	Single-arm, open-label, international study	Open-label, multicentre, two-stage phase 1 trial	Prospective, multicentre, observational study(85)	Open-label, two-cohort, multicentre study
Duration of study	22 months (10th February 2009 to 26th November 2010)(44)	~45 months (30th June 2011 to 16th March 2015)	26 months (January 2007 to February 2009)	Total duration anticipated to be 6.25 years (including 3.25 years for patient recruitment and 3 years' follow-up)(89)	22 months (July 2010 to April 2012)(91)
Trial drugs **Permitted and disallowed concomitant medication**	Eligible patients with laBCC or mBCC received oral vismodegib 150 mg/day continuously until disease progression, unacceptable toxicity, or discontinuation of the study. Dose interruption for up to 4 weeks was allowed in order for patients to recover from toxic effects. Concurrent anti-tumour therapy was not permitted. (44)	Eligible patients with laBCC or mBCC received oral vismodegib 150 mg/day continuously until disease progression, unacceptable toxicity, patient consent withdrawal, death, or other reasons. No dose reductions were allowed, but treatment interruption of up to 8 weeks was permitted for managing toxicity or temporary inability to swallow capsules	<u>Stage 1</u> In stage 1, the dose-escalation stage, the investigators wanted to estimate the maximum tolerated dose of GDC-0449. Patients received a single oral dose of GDC-0449 on day 1, followed by daily administration at the same dose beginning on day 8. Seven patients were assigned to receive 150 mg per day, nine patients 270 mg per day, and four patients 540 mg per day; each dose cohort included one patient with aBCC. GDC-0449 was to be discontinued in patients who had dose-limiting toxic effects or other intolerable side effects or disease progression or in patients who did not benefit from treatment, as decided by the investigator. No dose-limiting toxic effects were	Patients were treated according to clinician's standard of care.	All patients received 150 mg oral vismodegib once daily, with treatment cycles defined as every 28 days. Clinic visits occurred every 1 to 2 treatment cycles. The clinic visits included medical history; adverse event (AE) recording; ascertainment of concomitant medications; ECOG performance status; vital signs including weight; physical examination; complete blood cell count and metabolic panel; and urinalysis. Screening electrocardiography was also performed. Treatment was administered until investigator-assessed disease progression, unmanageable toxicities, patient or physician request to discontinue, or study termination by sponsor. Dose reduction was not permitted.

			observed. The recommended phase 2 dose was 150 mg per day because pharmacokinetic analyses indicated that doses greater than this did not result in higher plasma concentrations of the drug. <u>Stage 2</u> In stage 2, an expansion cohort was included that received the recommended phase 2 dose, with the goal of obtaining additional information on pharmacokinetics, pharmacodynamics, and safety; 12 patients (none with aBCC) enroled in this cohort, and all received 150 mg per day. The study was amended to include two further cohorts in stage 2. One of these cohorts was added because of evidence of clinical benefit in two patients with aBCC during stage 1; this cohort consisted of 20 patients with aBCC, who were treated with 150 mg per day or 270 mg per day (with the dose chosen on the basis of drug availability) to evaluate the activity and safety of GDC-0449 in this population. The second cohort, which consisted of 16 patients with solid tumours (including 10 with aBCC), was added to investigate the pharmacokinetic properties of a new formulation of GDC-0449 at 150 mg per day. In stage 2, all patients received continuous		Dose interruption up to 8 weeks was permitted to manage toxicity. Concurrent anti-tumour therapy was not permitted.

			daily administration of the drug, beginning on day 1, and were treated until disease progression, the occurrence of intolerable toxic effects, or withdrawal from the study.		
Inclusion criteria	Men and women ≥18 years of age who had adequate organ function and ECOG PS≤2. Patients with mBCC had measurable disease (including nodal metastases), according to the RECIST guidelines, as assessed with CT or MRI. Patients with laBCC had at least one lesion that was 10 mm or more in the longest diameter and was considered inoperable or for which surgery was considered inappropriate, in the opinion of a specialist in Mohs dermatologic, head and neck, or plastic surgery. Acceptable reasons for surgery to be considered inappropriate were one or both of the following: the recurrence of BCC after two or more surgical procedures and an expectation that curative resection would be unlikely, or substantial morbidity or deformity anticipated from surgery. For patients with laBCC, radiotherapy must have been previously administered for their laBCC, unless radiotherapy is contraindicated	Patients aged ≥18 years with a histologically confirmed diagnosis of laBCC or mBCC, ECOG PS ≤2, and adequate organ function. For patients with laBCC, ≥1 histologically confirmed lesion deemed inoperable or surgery deemed inappropriate, and radiotherapy must have been previously administered, unless inappropriate. For patients with mBCC, histologic confirmation of distant metastasis. Patients with Gorlin syndrome had to meet criteria for laBCC or mBCC. Patients eligible for enrolment with measurable and/or nonmeasurable disease, as defined by RECIST v1.1.	Patients were at least 18 years of age and had histologically confirmed laBCC or mBCC that had been documented on pathological analysis and that were considered by the investigator to be refractory to standard therapy. All patients had tumours that could be evaluated on physical examination or radiographic imaging and had an ECOG PS ≤2. Documentation of a negative pregnancy test was required for women of childbearing potential. GDC-0449 treatment did not begin until more than 3 weeks after the patient's last therapy or major surgical procedure.	Adult patients with BCC, ≥18 years of age, who meet any of the following definitions:(85) Patients who were determined with aBCC within 90 days prior to study enrolment, have not been diagnosed with BCCNS and have not been treated with an investigational or approved Hedgehog pathway inhibitor Patients with aBCC who have not been diagnosed with BCCNS and who were previously treated with vismodegib as part of Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS) Patients with BCCNS who either have aBCC or multiple BCCs of any stage as defined by protocol (may include patients previously enroled in Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS))	Eligible patients were 18 years or older; had adequate organ function; had an ECOG PS≤2; and had measurable, evaluable disease as defined by RECIST v1.0 criteria. BCC metastatic to the bone, termed ''non-measurable'' disease by RECIST v1.0 was included. Patients with laBCC had at least 1 histologically confirmed lesion 10 mm or larger in diameter with written confirmation from a surgical specialist that the tumour was inoperable, or that surgery was contraindicated. Surgery was considered inappropriate if BCC recurred in the same location after 2 or more surgical procedures and curative resection was deemed unlikely, or when there was substantial morbidity and/or deformity anticipated. Patients with laBCC were required to have had prior radiation therapy to greater than or equal to 1 target lesion unless contraindicated or inappropriate. Histologic confirmation of laBCC and mBCC lesion(s) was required in all cases. Patients with BCCNS could enrol if they met

	or inappropriate.(90) For patients whose laBCC has been irradiated, disease must have progressed after radiation.(90) Women of childbearing potential and men with female partners of childbearing potential were required to use two methods of contraception, owing to the teratogenic potential of vismodegib.				inclusion criteria. Women of childbearing potential and men with female partners of childbearing potential were required to use medically reliable contraception because of vismodegib teratogenicity.
Exclusion criteria	Major organ dysfunction. Pregnancy or lactation.(92) Recent, current, or planned participation in an experimental drug study.(92) Life expectancy of <12 weeks.(92) Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics, or other conditions that would contraindicate the use of an investigational drug.(92) Inability to swallow capsules. Prior treatment with vismodegib or other Hedgehog pathway inhibitors.(92) Patients with superficial multifocal BCC who may be considered unresectable due to breadth of involvement.(92) History of other malignancies within 3 years of the first day of treatment with vismodegib in this study (Day 1), except for tumours with a negligible risk	Concurrent non-protocol-specified anti-tumour therapy. Completion of most recent anti-tumour therapy <21 days before initiation of treatment. Uncontrolled medical illness. History of other disease that contraindicates the use of an investigational drug or that may affect interpretation of the study results.	Exclusion criteria included major organ dysfunction, a long QT interval or any medication known to prolong the QT interval (because preliminary evaluation of the potential of GDC-0449 to prolong the QT interval was an ancillary objective of the study), active infection requiring intravenous antibiotics, pregnancy, other conditions that in the opinion of the investigator would contraindicate investigational drug use, and an inability to swallow pills.	Participation in a clinical trial within 90 days prior to study enrolment that has either involved treatment of aBCC or involved treatment with an investigational or approved Hedgehog pathway inhibitor, except for patients treated with vismodegib as part of Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS)(85)	Patients were ineligible to participate if they had major organ dysfunction; were pregnant, lactating, or unwilling to practice birth control; had completed anti-tumour therapy less than 21 days before treatment initiation; had a history of other diseases or uncontrolled medical illnesses that would contraindicate vismodegib; were on concurrent anti-tumour therapy; or had a less than 12-week life expectancy.

	for metastasis or death, such as adequately treated squamous-cell carcinoma of the skin, ductal carcinoma in situ of the breast, or carcinoma in situ of the cervix.(92)				
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome measure was ORR (complete and partial responses) assessed by independent review facility. For patients with mBCC, RECIST was used.(92) For patients with laBCC, a composite response endpoint was used that incorporated externally visible tumour dimension and tumour ulceration, as well as RECIST for lesions with a RECIST-measurable component.(92) In patients achieving a clinical response, tumour biopsies were used in the final determination of CR vs PR.(92) Patients were followed until disease progression, death, or withdrawal of consent. Tumour assessment was performed at screening, every 8 weeks, and at the end of the study.(92)	The primary end point was safety (incidence of adverse events until disease progression or unacceptable toxic effects), with assessments on day 1 of each treatment cycle (28 days) by the principal investigator and co-investigators at the site.(93) Percentage of participants who experienced (according to the NCI CTCAE, v4.03): Any AEs(94) AEs grade 3 or 4, AEs leading to drug interruptions or discontinuations(94) Any SAEs(94)	Percentage of participants with dose-limiting toxicities, defined as any grade 3 or 4 hematologic or major organ toxicity according to NCI CTCAE v3.0 that occurred during the first 35 days after the initiation of study drug and was attributable to GDC-0449(95) Maximum observed plasma concentration (C_{max}) after a single dose of GDC-0449(95) C_{max} after multiple doses of GDC-0449(95) Time to maximum plasma concentration (T_{max}) after a single dose of GDC-0449(95) T_{max} after multiple doses of GDC-0449(95) Average plasma concentration at steady state (Css, Avg) after multiple doses of GDC-0449(95) Area under the plasma concentration-time curve from time 0 to 24 Hours (AUC_{0-24}) after a single dose of GDC-0449(95) AUC0-24 after multiple doses of GDC-0449, accumulation index (AI) after multiple doses of GDC-0449(95)	Primary outcome measures are response rate, duration of response, recurrence rate, progression-free survival, overall survival and safety (incidence of adverse events)(85) Data collection occurred approximately every 3 months via an electronic data capture system, coinciding with the expected schedule of routine care for this patient population. Each patient was observed for up to 3 years. Patient enrolment period: 3.25 years (89) A steering committee composed of participating study clinicians and a patient advocate provide guidance regarding study conduct and data analysis and interpretation throughout the course of the study.(89)	Primary outcomes were to measure ORR and overall response rate (efficacy) and safety. Tumour responses were investigator-assessed according to RECIST v1.0 criteria. Physical examinations were performed to assess measurable tumours within 7 days of treatment initiation, then every 4 to 8 weeks. Patients with radiographically measurable disease underwent CT or MRI assessment within 30 days before treatment initiation, then every 8 to 16 weeks thereafter. Patients with non-measurable disease, eg. bone metastases, were evaluated for disease progression by the clinical judgment of the treating physician. Objective tumour responses, defined as the best overall complete response or partial response, were confirmed by investigators using 2 consecutive tumour assessments performed at least 4 weeks apart according to RECIST v1.0. For instance, if a tumour had a partial response followed by complete

					response but no second assessment of complete response, the tumour was labelled as partial response. For this study, appearance of a new cutaneous BCC was considered progressive disease if the lesion was larger than 5 mm and clearly documented as not previously present. Safety was assessed by AE collection including incidence, type, severity, vismodegib discontinuation/ interruption because of AEs, and on-study deaths (drug and nondrug related). Descriptions of all collected AEs were mapped to MedDRA terms (v15.0) and graded using the NCI CTCAE (v4.0)
Secondary outcomes (including scoring methods and timings of assessments)	Duration of OR determined by the independent review facility(92) PFS determined by the independent review facility(92) OS(92) Change from baseline in SF-36 health survey scores(92) Percentage of patients with absence of residual BCC in patients with laBCC. (92)	Secondary end points included: Overall response rate (investigator-assessed according to RECIST v1.1) in those patients with measurable disease o CR defined as the disappearance of all target lesions, any pathological lymph nodes (target or non-target) needed to have a reduction in short axis to less than 10 mm.[93] o PR defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference	Percentage of participants with a >2-fold down-modulation of GLI1 expression in skin biopsy-derived or hair follicle-derived messenger ribonucleic acid (mRNA) (95) Percentage of participants with a BOR of CR or PR: all participants; participants with BCC[95] o BOR was defined as the best objective response CR or PR determined by two consecutive investigator assessments which were at least 28 days apart) observed during the	NR	NR

		the baseline sum diameters.[93] Time to response Duration of response PFS and OS Quality of life (assessed by Skindex-16 and impact of treatment on disease symptoms in patients with mBCC assessed using the MD Anderson Symptom Inventory) Measurable tumours accessible by physical examination were assessed every 4 to 8 weeks. If necessary, CT and MRI scans were done every 8 to 16 weeks. RECIST assessments from the investigators were reviewed by Roche against the tumour measurements reported; there was no central review.[93]	treatment period according to RECIST v1.0.[95] o CR = disappearance of all target lesions, with any pathological lymph nodes (whether target or non-target) having a reduction in short axis to less than 10 mm.(95) o PR = at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters(95) o Assessments at screening, week 8, and every 8 weeks thereafter up to week 116.[95] Duration of objective response: all participants; participants with BCC[95] o Duration of response during first line therapy is defined as the time from when response (CR or PR) was first documented to first documented disease progression or death (whichever occurs first) during first line therapy. This was only calculated for patients who achieved a BOR of CR or PR. Participants who did not progress or die after they had a confirmed response were censored at the date of their last tumour measurement or last follow-up for progression of disease during first line therapy.[95] o Assessments at		

			screening, week 8, and every 8 weeks thereafter up to week 116.[95] PFS: all participants; participants with BCC[95] o PFS was defined as the time from first dose of GDC-0449 to documented disease progression (deterioration of evaluable lesions and/or tumour-related symptoms defined using RECIST v1.0) or death from any cause within 30 days of the last dose of GDC-0449, whichever occurred first. [95] Assessments at screening, week 8, and every 8 weeks thereafter up to week 116[95]		
Other outcomes (eg. exploratory; including scoring methods and timings of assessments)	The exploratory objectives of this study were the following: To evaluate the effect of GDC-0449 treatment on the Hedgehog signalling pathway using qRT-PCR and/or other approaches in tissue obtained at baseline and/or following GDC-0449 treatment.[92] To evaluate the relationship between the effects of GDC-0449 treatment on the Hedgehog signalling pathway and efficacy.[92]	NA	Preliminary evaluation of the potential of GDC-0449 to prolong the QT interval was an ancillary objective of the study	NA	NA
Pre-planned subgroups	Patients with laBCC and patients with mBCC	Patients with laBCC and patients with mBCC	<u>Stage 1</u> 3 patients; 1 received 150 mg/day, 1 received 270 mg/day and 1 received 540 mg/day	3 cohorts as previously described	Safety evaluable (119/120 patients) and efficacy evaluable (95/120 patients)

			Stage 2 30 patients; 16 received 150 mg/day and 14 received 270 mg/day		

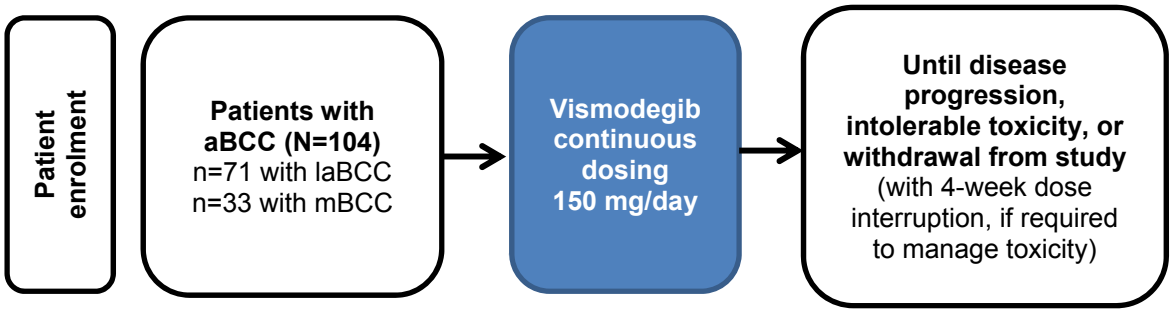
Abbreviations: AE, adverse event; CNS, central nervous system; CT, computed tomographic; DLT, dose-limiting toxicities; ER, oestrogen receptor; HER2, human epidermal growth factor receptor; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; PFS, progression free survival; RECIST, response evaluation criteria in solid tumours; RP2D, recommended phase II dose

ERIVANCE

Trial design

ERIVANCE (NCT00833417) was an international, multicentre, open-label, single-arm, two-cohort clinical study. A total of 104 patients (33 patients with metastatic BCC and 71 patients with locally advanced BCC) were enroled at 31 study sites in the United States, England, France, Germany, Belgium, and Australia.(90)

Figure 6: ERIVANCE study design(44)



The population of patients with laBCC and mBCC was chosen based on scientific rationale, evidence of drug activity in these populations in the Phase I study, and the lack of other therapeutic alternatives for these patients.(44)

The study was not randomised. Patients were enrolled into either the locally advanced or metastatic cohort. A control group was not used, given that there was no accepted standard of care and no data suggesting spontaneous responses in advanced BCC. The 150 mg daily continuous dosing schedule of vismodegib was chosen on the basis of the pharmacokinetic (PK) properties of vismodegib characterised in the Phase I study of this agent, and to maximise plasma exposure and potential therapeutic effect.(44)

A single-arm study with a response rate endpoint was deemed by investigators and experts in the field, as well as the US FDA, to be the most appropriate and feasible design in this rare advanced basal cell carcinoma (aBCC) population with unmet medical need.

Duration of study

The primary analysis (data cut-off: 26 November 2010; 9 months after the last patients were enroled in the study)(44) led to approval of vismodegib globally. Additional patient follow-up provided efficacy and safety data at 12 and 30 months since the primary analysis (data cut-offs 28 November 2011 and 30 May 2013, respectively).(27, 38)

Eligibility criteria

Key eligibility criteria in the study are listed in Table 14.

Table 14: Key eligibility criteria in the ERIVANCE study(43)

Inclusion criteria	Exclusion criteria
• Men and women aged ≥ 18 years • Eastern Cooperative Oncology Group performance status of 0, 1, or 2 • mBCC patients: o Histologic confirmation of distant BCC metastasis (e.g., lung, liver, lymph nodes, bone), with metastatic disease that was RECIST measurable using CT or MRI. Patients with metastatic disease confined to bone were not considered eligible because of the lack of RECIST measurability • laBCC patients: o At least one histologically confirmed lesion ≥ 10 mm in the longest diameter that was considered to be inoperable or who had a medical contraindication to surgery, in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon. Acceptable medical contraindications to surgery included: • BCC that recurred in the same location after two or more surgical procedures, and curative resection was deemed unlikely • Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, or eye; or requirement for limb amputation) • Other conditions considered to be medically contraindicated were discussed with the Medical Monitor before the patient was enroled o Radiotherapy was previously administered for their locally advanced BCC, unless radiotherapy was contraindicated or inappropriate (e.g., hypersensitivity to radiation because of a genetic syndrome such as Gorlin syndrome, limitations because of location of tumour, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC was irradiated, disease had progressed after radiation o If a patient with locally advanced BCC also had a tumour that was not contiguous with cutaneous BCC, e.g., regional lymph nodes (if confirmed on biopsy as BCC and RECIST measurable), the patient was considered as having metastatic BCC and was enroled in the metastatic cohort • Patients with Gorlin syndrome could have been enroled in this study, but had to have met the criteria for locally advanced or metastatic disease listed above • Adequate haematopoietic capacity, defined by the following: o Haemoglobin >8.5 g/dL and not transfusion dependent; o Granulocyte count ≥1000/μL; and o Platelet count ≥75,000/μL	• Inability or unwillingness to swallow capsules • Prior treatment with vismodegib or other antagonists of the Hh pathway • Pregnancy or lactation • Life expectancy of < 12 weeks • Patients with superficial multifocal BCC considered unresectable because of breadth of involvement • Concurrent non–protocol-specified anti-tumour therapy • Recent (within 4 weeks of Day 1), current, or planned participation in an experimental drug study • History of other malignancies within 3 years of Day 1, except for tumours with a negligible risk for metastasis or death • Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gave reasonable suspicion of a disease or condition that contraindicated use of an investigational drug

• Adequate hepatic function, defined by the following:
  o Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3 × the upper limit of normal (ULN); and
  o Total bilirubin ≤1.5 × the ULN or within 3 × the ULN for patients with Gilbert disease
• Women of childbearing potential, agreement to use two acceptable methods of contraception, including one barrier method, during the study and for 7 months after discontinuation of vismodegib
• Men with female partners of childbearing potential, agreement to use a latex condom and to advise their female partner to use an additional method of contraception during the study and for 7 months after discontinuation of vismodegib
• Agreement not to donate blood or blood products during the study and for at least 7 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 2 months after discontinuation of vismodegib	

Trial drugs and concomitant medication

Patients received 150 mg vismodegib daily orally, beginning on Day 1 and continued as specified, unless one of the following occurred:

- disease progression;
- intolerable toxicity; and/or
- withdrawal from the study

No dose modifications or reductions were allowed in this study. Treatment with vismodegib could be interrupted for up to 4 weeks for evaluation of an intolerable toxicity(44) finding or up to 8 weeks for a planned surgical procedure. In addition, treatment with vismodegib could be interrupted for up to 4 weeks if a patient became temporarily unable to swallow capsules.(43)

This was an open-label study; no blinding procedures were required.(43)

No specific concomitant medications were prohibited during this study (other than concomitant anti-tumour therapies).(43)

Primary and secondary outcomes

Primary outcome

The primary efficacy endpoint in this study was objective response rate (ORR) as determined by independent review facility (IRF).* Objective response was defined as a complete response (CR) or partial response (PR) determined on two consecutive assessments ≥4 weeks apart. Patients with these responses were referred to as responders: ORR was defined as the proportion of responders. Patients without a baseline or post-baseline tumour assessment were considered non-responders.(43, 44)

- In the metastatic BCC cohort, tumour response was assessed by the IRF according to RECIST(96) v1.0 criteria
- There was no clinical or regulatory precedent for objective measurement of efficacy in patients with laBCC. Therefore, based on the key evidence of clinical benefit reported by patients and Investigators in the Phase I study (SHH3925g) of vismodegib and in consultation with the U.S. FDA, a composite endpoint was created

* At the 30-month analysis, results were presented for efficacy as assessed by investigators only

for ERIVANCE and was determined as a function of a photographic IRF (visual assessment of external tumour and ulceration), radiographic IRF (tumour imaging, if appropriate), and pathology IRF (tumour biopsy)

- Patients who did not meet criteria for response or progressive disease (PD) were considered as having stable disease (SD)

Secondary outcomes

Secondary efficacy endpoints included duration of objective response, progression-free survival (PFS), overall survival (OS), change from Day 1 in patient-reported symptoms, and absence of residual BCC in patients with locally advanced BCC (histopathologic response).(43, 44)

Duration of objective response: defined for patients with objective response as the time from the initial CR or PR, i.e., from the time that measurement criteria were met for CR or PR (whichever status was recorded first) to the earliest documented disease progression or death within 30 days of last exposure to study treatment

Duration of PFS: defined as the time from the initial dose of vismodegib to the earliest documented disease progression or death within 30 days of last exposure to study treatment.

Duration of OS: defined as the time from the initial dose of vismodegib until death from any cause.

Patient-reported symptoms: characterised through the use of the SF-36 Health Survey (Version 2), which consists of eight subscales: Physical Functioning, Role−Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role−Emotional, and Mental Health. In addition to the eight subscale scores, two summary scores were derived from the eight subscales: the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Histopathologic response: In patients with laBCC, the histopathologic effect of vismodegib was to be determined in tissue biopsies obtained at baseline and following vismodegib treatment. Histopathologic responses were defined as post-baseline samples that were found to be absent of residual BCC assessed by the independent pathologist. The absence of residual BCC was to be used in the determination of response (complete or partial) for patients in the locally advanced BCC cohort who met the remaining response criteria. The

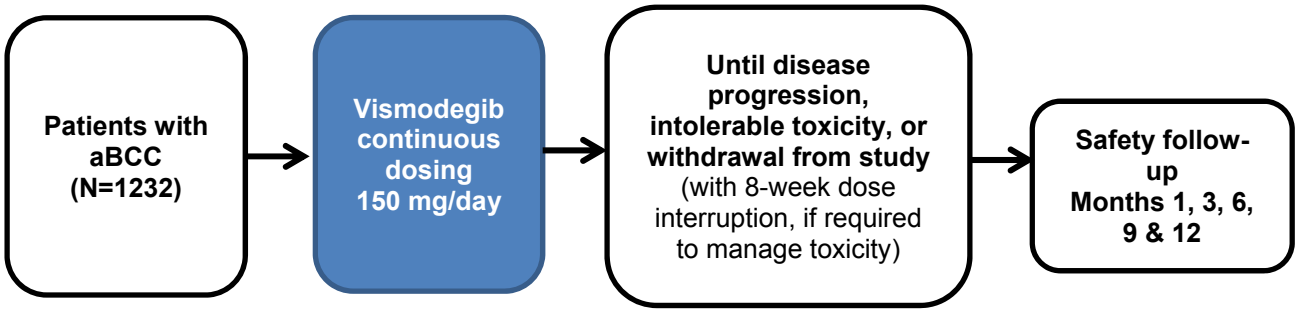
absence of residual BCC was tabulated for all patients whose lesions were assessed by the independent pathological review.

STEVIE

Study design

STEVIE was an international, multi-centre, open-label, non-comparative, Phase II study. The study enroled 1232 patients at 152 sites in 36 countries; countries with more than 1 site included Australia, Austria, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Finland, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Poland, Romania, Russian Federation, Serbia, Spain, Sweden, Turkey, and the United Kingdom.

Figure 7: STEVIE study design



The trial consists of a Treatment Phase, an End-of-Treatment Visit (when the patient receives the last dose of vismodegib and thereafter discontinues vismodegib), and five safety follow-up visits.

The STEVIE study was a post-approval safety study, fulfilling one of the specific obligations required to convert the initial conditional Marketing Authorisation in the EU: namely, to gather further data on safety and data on efficacy in patients with symptomatic mBCC from the primary analysis of STEVIE. In addition, STEVIE provided further evidence of tolerability and efficacy in laBCC patients.

Trial duration

Enrolment for Study MO25616 began on 30 June 2011, and enrolment was complete as of 2 September 2014.

As of 6 November 2013, 499 patients had received study drug and had the potential to be followed up for 12 months or longer. 99 (20%) patients were receiving ongoing treatment with vismodegib.

As of 16 March 2015, 517/1215 patients (42.6%) had completed the study, and 375/1215 patients (30.9%) were still on study (147 [12.1%] on treatment and 228 [18.8%] in follow-up).

Eligibility criteria

Key eligibility criteria are listed in Table 15.

Table 15: Key eligibility criteria in the STEVIE

Inclusion criteria	Exclusion criteria

• Men and women aged ≥18 years
• Eastern Cooperative Oncology Group performance status of 0, 1, or 2
• mBCC patients:
  o Histologic confirmation of distant BCC
• laBCC patients:
  o At least one histologically confirmed lesion ≥10 mm in the longest diameter that was considered to be inoperable or who had a contraindication to surgery, Acceptable medical contraindications to surgery included:
  • BCC that recurred in the same location after two or more surgical procedures, and curative resection was deemed unlikely
  • Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, or eye; or requirement for limb amputation)
  o Radiotherapy was previously administered for their locally advanced BCC, unless radiotherapy was contraindicated or inappropriate (e.g., hypersensitivity to radiation because of a genetic syndrome such as Gorlin syndrome, limitations because of location of tumour, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC was irradiated, disease had progressed after radiation
• Patients with Gorlin syndrome could have been enroled in this study, but had to have met the criteria for locally advanced or metastatic disease listed above
• Adequate haematopoietic capacity, defined by the following:
  o Haemoglobin >8.5 g/dL and not transfusion dependent;
  o Granulocyte count ≥1000/μL; and
  o Platelet count ≥75,000/μL
• Adequate hepatic function, defined by the following:
  o Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3 × the upper limit of normal (ULN); and
  o Total bilirubin ≤1.5 × the ULN or within 3 × the ULN for patients with Gilbert disease
	• Inability or unwillingness to swallow capsules
	• Pregnancy or lactation
	• Concurrent non–protocol-specified anti-tumour therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy, including participation in an experimental drug study; note that treatment breaks up to 8 weeks for radiation therapy were allowed
	• Recent (within 21 days of Day 1) completion of anti-tumour therapy
	• Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics
	• History of other malignancies within 3 years of Day 1, except for tumours with a negligible risk for metastasis or death
	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gave reasonable suspicion of a disease or condition that contraindicated use of an investigational drug

• Women of childbearing potential, agreement to use two acceptable methods of contraception, including one highly effective method and one barrier method, during the study and for at least 24 months after discontinuation of vismodegib o Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential could be included if they were either surgically sterile or had been postmenopausal for ≥1 year • Men with female partners of childbearing potential, agreement to use a condom with spermicide, even after vasectomy, during the study and for 2 months after discontinuation of vismodegib • Agreement not to donate blood or blood products during the study and for at least 7 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 2 months after discontinuation of vismodegib • Life expectancy ≥12 weeks	• Patients with one of the following rare hereditary conditions: galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption

Trial drugs and concomitant medications

Patients received 150 mg vismodegib daily orally, on a continuous basis in 28-day cycles, unless one of the following occurred:

- disease progression,
- intolerable toxicity, and/or,
- withdrawal from the study.

No dose modifications or reductions were allowed in this study. Treatment with vismodegib could be interrupted for up to 8 weeks for evaluation of an intolerable toxicity finding or if a patient became temporarily unable to swallow capsules.

This was an open-label study; no blinding procedures were required.

Co-administration of St John's wort (Hypericum perforatum) and other concomitant anti-tumour therapies was prohibited during this study. Patients who used oral contraceptives, hormone-replacement therapy, or other maintenance therapy could continue their use where appropriate.

Primary and secondary outcomes

Primary outcome

The primary endpoint in this study was safety (incidence of adverse events until disease progression or unacceptable toxic effects), as assessed by the investigator on day 1 of each treatment cycle (28 days).

Secondary outcomes

Secondary efficacy endpoints included overall response rate (ORR; according to RECIST, v1.1) in those patients with measurable disease, as permitted by local regulatory requirement; time to response, duration of response, progression-free survival (PFS), and overall survival (OS); patient quality of life (QoL) (Skindex-16); impact of vismodegib treatment on disease symptoms in patients with metastatic BCC using the M.D. Anderson Symptom Inventory (MDASI).

Objective response rate was assessed by the investigator according to RECIST, v1.1. The best overall response rate (BORR) is reported. BORR was defined as the number of patients whose best response was complete response (CR) or partial response (PR) divided by the total number of treated patients in the group for which BORR was estimated.

Time to response was assessed by the investigator and was defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occurred first).

Duration of response was defined only for the patients whose confirmed best response was CR or PR as the time interval between the date of the earliest qualifying response and the date of PD or death from any cause.

Progression-free survival was assessed by the investigator and was defined as the time interval between the date of the first therapy and date of progression or death from any cause, whichever occurred first

Overall survival was defined as the time from the date of first treatment to the date of death, regardless of the cause of death

Patient quality of life: Skindex-16 was used to assess the effects of skin disease on patients' HRQoL in both laBCC and mBCC patients. Patients completed a 16-item questionnaire whose items compose three domains: symptoms, emotional well-being and functioning. Items are rated on a 7-point scale measuring the level of bother over the previous week, ranging from 0 (never bothered) to 6 (always bothered).

The M.D. Anderson Symptom Inventory (MDASI) instrument was used to assess the impact of treatment on symptoms in patients with mBCC who were enroled after the approval of Study Protocol Version 4.0.

Phase I SHH3935g (NCT00607724)

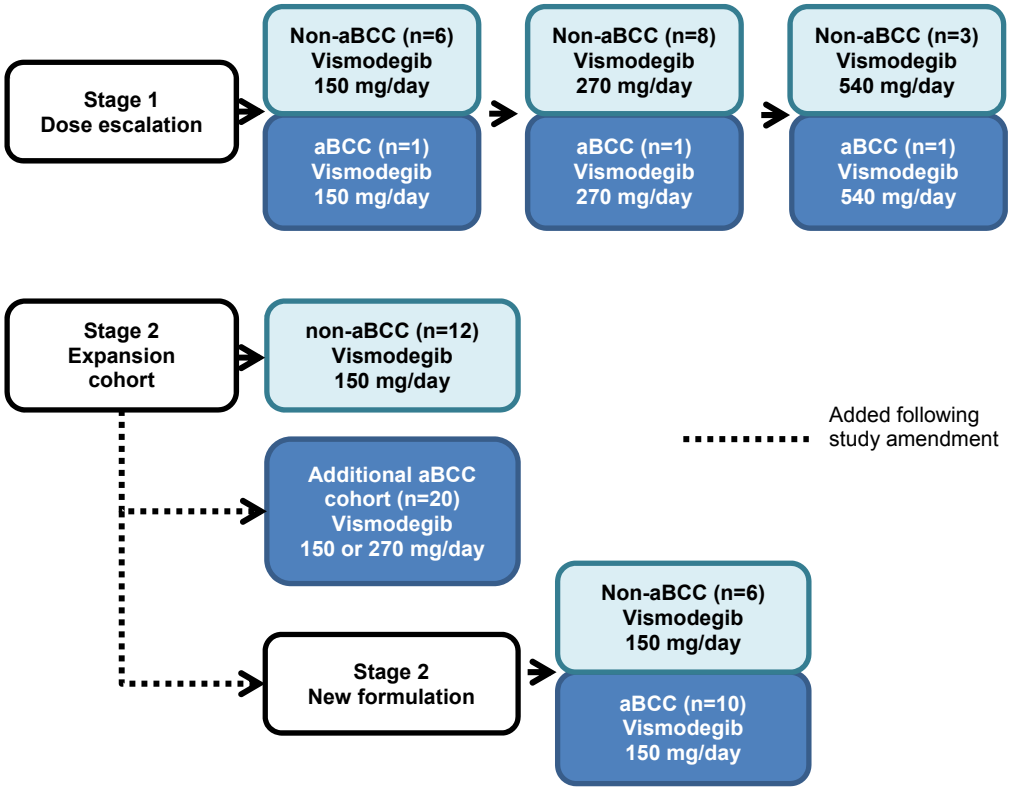
Trial design

This was an open-label, multicentre, Phase I study using a 3 + 3 design to evaluate the safety and tolerability of escalating doses of vismodegib administered orally on a once-daily or twice-daily schedule for 28 days, to patients with advanced solid malignancies that were refractory to standard therapy or for which no standard therapy existed. (It should be noted that the patient population was not exclusively those with basal cell carcinoma.) The study was a first-in-human study of a first-in-class agent.

Enrolment into the trial occurred in two stages, a dose-escalation stage with the goal of estimating the maximum tolerated dose (MTD; Stage 1), and an expanded cohort to collect additional safety, pharmacokinetics, and pharmacodynamic data at the proposed Phase II

dose. An additional cohort of patients with locally advanced or metastatic basal cell carcinoma was enroled concurrently with Stage 1 (three patients) and Stage 2 (total of 30 patients), following the same treatment guidelines as Stage 2.

Figure 8: Study design for Phase I SHH3925g



Duration of study

The patients with aBCC in this study were enroled between January 2007 and December 2008. As of the data cut-off date (28 February 2009), all 33 patients had undergone at least one follow-up tumour assessment and could be evaluated for a response to treatment.

Eligibility criteria

Key eligibility criteria are provided in Table 16.

Table 16: Key eligibility criteria in Phase I SHH3925g

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • ECOG performance status of 0, 1 or 2 • Histologically documented, incurable, locally advanced or metastatic solid malignancy that had progressed after first-line and second-line therapy (if there was a second-line therapy that had been shown to provide clinical benefit) • For inclusion in the Basal Cell Carcinoma Cohort, histopathologic documentation of basal cell carcinoma from a metastatic or locally advanced lesion was required. • Granulocyte count of ≥1000/μL, platelet count of ≥100,000/μL, and haemoglobin of ≥9 g/dL • Serum bilirubin ≤1.5 × the upper limit of normal (ULN) and AST and ALT ≤2.5 × the ULN, with the following exceptions: o Patients with liver metastases who had ALT and AST up to 5 × the ULN and patients with known Gilbert's disease who had serum bilirubin ≤3 × ULN may have been enroled • Serum creatinine ≤1.5 × ULN • At least 3 weeks since last chemotherapy, investigational agent, radiation therapy, or major surgical procedure and recovery pre-treatment baseline or stabilisation of all treatment-related toxicities	• Inability or unwillingness to swallow pills • Active infection requiring intravenous (IV) antibiotics • Clinically important history of liver disease significantly impairing hepatic function, including active viral or other hepatitis, current alcohol abuse, or cirrhosis • Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

Trial drugs and concomitant medications

This was an open-label study. All patients were treated on a daily basis until disease progression or intolerable toxicity or withdrawal from study.

The three patients with aBCC in stage 1 (dose escalation) of the study received a single oral dose on day 1, followed by daily administration from day 8. Three doses levels were explored; there was one aBCC patient per dose level. The doses administered were 150 mg, 270 mg and 540 mg.

The dose for the aBCC expansion cohort of stage 2 of the study (n=20) was 150 mg or 270 mg vismodegib (the dose chosen on the basis of drug availability).

Ten patients with aBCC who were treated in the stage 2 cohort with the new formulation of vismodegib were given doses of 150 mg per day.

Concomitant medications

Patients who used oral contraceptives, hormone-replacement therapy, or other maintenance therapy were allowed to continue their use.

Treatment of hypercholesterolaemia: A key objective of this study was to characterise the effect of GDC-0449 on cholesterol levels over time. Therefore, patients who exhibited total fasting serum cholesterol levels up to 500 mg/dL (the upper limit of Grade 3) prior to Day 36 would continue taking vismodegib without cholesterol-lowering therapy. Patients who developed Grade 4 cholesterol elevations prior to Day 36 and patients with Grade 3 cholesterol who continued taking vismodegib beyond Day 35 were treated according to the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (http://www.nhlbi.nih.gov/guidelines/cholesterol/). Treatment of these patients was initiated with 40 mg pravastatin sodium daily, with weekly monitoring of cholesterol levels until values returned to baseline. Pravastatin was to be taken at least 3 hours apart from vismodegib administration. If a patient's cholesterol levels did not return to at least Grade 3 within 1 week of starting treatment with 40 mg pravastatin, the dose of pravastatin was to be increased to 80 mg and cholesterol levels were to be assessed 1 week later.

Anti-seizure medications: Vismodegib was suspected to be a potential inhibitor of the hepatic cytochrome P450 enzymes, and administration could interfere with the metabolism of anti-seizure drugs that are substrates for cytochrome P450. Therefore, patients treated with these medications had the serum levels of their medication monitored prior to the first dose of study drug, then weekly during the first 6 weeks of taking vismodegib, and then at least monthly while taking vismodegib.

Electrolyte supplements: The pro-arrhythmic potential of vismodegib was not known prior to the study. Therefore, electrolyte disturbances that may contribute to arrhythmias, particularly hypokalaemia and hypomagnesaemia, and that arise during treatment with vismodegib were to be treated aggressively. If electrolyte deficiencies were noted from the weekly safety evaluations, treatment with oral electrolyte supplements was to be initiated or the doses of current supplements increased appropriately.

Prohibited medications: Medications with narrow therapeutic indices (e.g., phenytoin, digoxin, warfarin) were to be avoided if possible. If these medications were necessary, careful and frequent monitoring of blood levels (weekly for at least the first 6 weeks of vismodegib treatment) occurred.

Primary and secondary outcomes

Primary outcome

Safety (the frequency, nature, and severity of adverse events and their relation to study drug) was the primary endpoint of this study. The primary outcome measures were the following:

- Occurrence of dose limiting toxicities (DLTs) and the associated NCI CTCAE grade
- Occurrence of adverse events and the associated NCI CTCAE grade
- Occurrence of Grade 3 or 4 abnormalities in safety-related laboratory parameters
- Occurrence of Grade 3 or 4 changes in vital signs
- Single- and multiple-dose PK parameters (not reported in this submission)

Secondary outcomes

Secondary outcomes in this study included best overall response, duration of objective response, and PFS in all enroled patients and patients with advanced or metastatic basal cell carcinoma. Objective response and disease progression were determined using RECIST, Version 1.0. (Other secondary and exploratory outcomes included biomarker related endpoints, which are not reported here.)

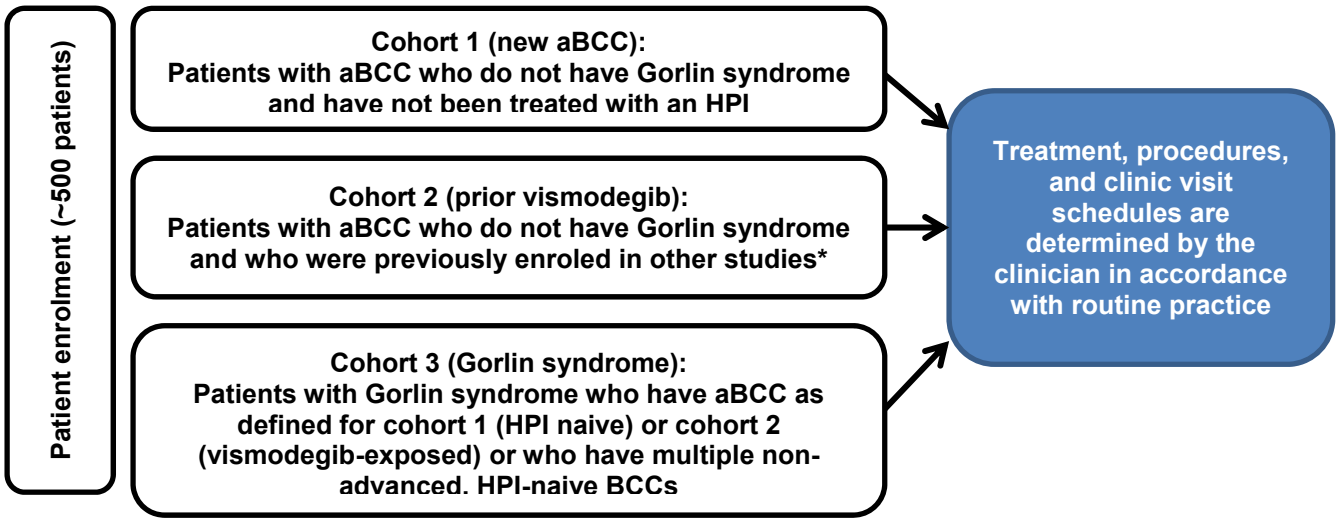
Objective response was defined as a CR or PR as determined on two consecutive occasions 4 or more weeks apart.

Progression-free survival was defined as the time from first dose of vismodegib to documented disease progression or death from any cause within 30 days of the last dose of vismodegib, whichever occurred first.

RegiSONIC (NCT01604252)

Trial design

Figure 9: RegiSONIC / NCT01604252 study design(31)



* Phase 2 SHH4437g (phase 1 rollover; NCT00959647); ERIVANCE SHH4476g (NCT00833417); EAS SHH4811g (NCT01160250)

Abbreviations: aBCC, advanced basal cell carcinoma; HPI, Hedgehog pathway inhibitor

Duration of study

Enrolment was completed on August 17, 2015. As of the September 11, 2015, data cut-off date, 101 newly diagnosed patients with laBCC without Gorlin syndrome had been enroled in cohort 1 and treated with vismodegib (31)

Eligibility criteria

Table 17: Key eligibility criteria in the RegiSONIC (85)

Inclusion criteria	Exclusion criteria
Adult patients with BCC, ≥18 years of age, who meet any of the following definitions: • Patients who were determined with aBCC within 90 days prior to study enrolment, have not been diagnosed with BCCNS and have not been treated with an investigational or approved Hedgehog pathway inhibitor • Patients with aBCC who have not been diagnosed with BCCNS and who were previously treated with vismodegib as part of Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS) • Patients with BCCNS who either have aBCC or multiple BCCs of any stage as defined by protocol (may include patients previously enroled in Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS))	• Participation in a clinical trial within 90 days prior to study enrolment that has either involved treatment of aBCC or involved treatment with an investigational or approved Hedgehog pathway inhibitor, except for patients treated with vismodegib as part of Genentech study SHH4476g, SHH4437g, or SHH4811g (EAS)(Genentech)

Trial drugs and concomitant medications

Treatment, procedures and clinic visit schedules are determined by the clinician in accordance with routine practice.(31)

Primary and secondary outcomes (85)

- Response rate
- Duration of response
- Recurrence rate
- Progression-free survival
- Overall survival
- Safety: Incidence of adverse events

Data collection occurred approximately every 3 months via an electronic data capture system, coinciding with the expected schedule of routine care for this patient population. Each patient was observed for up to 3 years. Patient enrolment period: 3.25 years.(89)

A steering committee composed of participating study clinicians and a patient advocate provide guidance regarding study conduct and data analysis and interpretation throughout the course of the study.(89)

EAS SHH4811g (NCT01160250)

Study rationale and design

The encouraging results from the vismodegib clinical development program generated significant interest and demand for access to vismodegib because of the unmet medical need in this patient population. However, after enrolment of the phase II study ERIVANCE had been fulfilled, no clinical studies were open to patients with advanced BCC and such patients did not have satisfactory therapeutic options. The potential use of vismodegib for the treatment of advanced BCC had been established at the time this trial was initiated in the phase I Study SHH3925g, which demonstrated significant anti-tumour activity of vismodegib in this patient population, with an acceptable benefit-risk profile. Thus, an expanded access program for compassionate use was initiated in the United States to provide vismodegib to patients with locally advanced BCC or mBCC who qualified as having no satisfactory treatment options.

This was an open-label, non-comparative, multicentre, expanded access study of vismodegib in patients with locally advanced BCC or mBCC who were otherwise without satisfactory treatment options.

The trial consisted of a screening period, a treatment phase, and one post-study follow up visit occurring 30 days after the last dose of vismodegib as provided by the expanded access protocol. Day 1 of the study was defined as the first day a patient received vismodegib. During the treatment phase, all study assessments were conducted on Day 1 (± 3 days) of each cycle, with the exception of CT and/or MRI imaging, which occurred every 8 to 16 weeks.

Duration of study

The study was expected to enrol approximately 100 patients over an approximately 2-year period and was to continue until vismodegib was approved by the U.S. Food and Drug

Administration (FDA) and became commercially available, which occurred in the United States on 30 January 2012.

Study enrolment ended on the day that vismodegib became commercially available following its approval by the FDA for use in patients with locally advanced BCC or mBCC. Patients already enroled by that date were allowed to receive up to one additional cycle of therapy through this expanded access protocol up to 30 days after vismodegib became commercially available.

Eligibility criteria

Key eligibility criteria in the study are listed in Table 18.

Table 18: Key eligibility criteria in EAS

Inclusion criteria	Exclusion criteria

• Age ≥ 18 years
• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
• Patients with laBCC
  o at least one histologically confirmed lesion 10 mm or more in diameter and written confirmation from a surgical specialist that the tumour was considered inoperable or that surgery was contraindicated. Examples of medical contraindications to surgery included but were not limited to the following:
  ▪ BCC that had recurred in the same location after two or more surgical procedures and curative resection was deemed unlikely
  ▪ Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation)
• Adequate haematopoietic capacity, defined by the following:
  o Haemoglobin >8.5 g/dL and not transfusion dependent;
  o Granulocyte count ≥1000/μL; and
  o Platelet count ≥75,000/μL
• Adequate hepatic function, defined by the following:
  o Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3 × the upper limit of normal (ULN); and
  o Total bilirubin ≤1.5 × the ULN or within 3 × the ULN for patients with Gilbert disease
  o Serum creatinine ≤ 2.0 mg/dL or measured or calculated creatinine clearance > 50 mL/min
• For women of childbearing potential, agreement to the use of two acceptable methods of contraception, including one barrier method, during the study and for 12 months after discontinuation of vismodegib
• For men with female partners of childbearing potential, agreement to use a latex condom and to advise their female partner to use an additional method of contraception during the study and for 3 months after discontinuation of vismodegib
• Agreement not to donate blood or blood products during the study and for at least 12 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 3 months after discontinuation of vismodegib
	• Inability or unwillingness to swallow capsules
	• Pregnancy or lactation
	• Life expectancy ≤ 12 weeks
	• Concurrent non-protocol-specified anti-tumour therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy) including participation in an experimental drug study; note that treatment breaks up to 8 weeks for radiation therapy are allowed
	• Completion of most recent anti-tumour therapy less than 21 days prior to initiation of treatment
	• Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics
	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk from treatment complications
	• Unwillingness to practice effective birth control

Trial drugs and concomitant medication

Patients received 150 mg of vismodegib daily, orally, beginning on Day 1, and once daily until one of the following occurred:

- Disease progression
- Intolerable toxicity most probably attributable to vismodegib
- Patient request for discontinuation
- Study termination by the Sponsor

If there was objective evidence of progressive disease, but the investigator believed that the patient was still deriving benefit from treatment, the investigator could continue vismodegib therapy after consultation with the medical monitor. However, if there was evidence of further disease progression at the next tumour assessment, the investigator had to discontinue vismodegib.

Dose reduction of vismodegib was not permitted, as there was only a 150 mg capsule strength available. Temporary discontinuation of drug was allowed for up to 8 weeks. Temporary discontinuation of vismodegib could occur for a period longer than 8 weeks, but only after discussion with the medical monitor. If a treatment interruption occurred, and it was determined to re-start vismodegib, the original dose was maintained.

This was an open-label study; no blinding procedures were required.

There were no specific restrictions on concomitant medications in this study.

Primary and secondary objectives / outcomes

Primary objective

The primary objective of the expanded access study was to provide vismodegib to patients with locally advanced BCC or mBCC who were otherwise without satisfactory treatment options.

Secondary outcomes

The secondary outcomes in this study included safety and objective response.

Safety: Incidence, type, and severity of AEs; incidence and nature of serious adverse events (SAEs); incidence of AEs leading to vismodegib discontinuation or interruption; cause of death on study.

Objective response: defined as a complete response (CR) or partial response (PR), as assessed by the investigator (according to RECIST, v1.0) on two consecutive assessments at least 4 weeks apart. For those with measurable disease, tumours could have been evaluated by physical examination and/or imaging (CT and/or MRI scans) at the investigator's discretion. Other imaging techniques could have been performed as clinically indicated, but could not have been used for determining tumour response.

Patients with non-measurable disease were assessed for disease progression when clinically indicated and in accordance with standard clinical practice.

For both metastatic and locally advanced BCC cohorts, a new cutaneous BCC was considered as progressive disease (PD) if the lesion was >5 mm and could be clearly documented as not being previously present, unless it was confirmed on biopsy not to be consistent with BCC.

4.11.4 Statistical analysis of the non-randomised and non-controlled evidence

Details of any statistical analyses performed in the relevant non-RCTs identified in the systematic review are presented in Table 19.

Table 19: Statistical analyses employed in the relevant non-randomised trials identified in the systematic review

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ERIVANCE(44) (92)	The primary hypotheses were that the response rate would be greater than 20% for patients with laBCC and greater than 10% for those with mBCC.	Duration of objective response was defined and analysed only for patients who achieved an objective response. Ninety-five percent Blyth–Still–Casella exact confidence intervals for ORR were calculated in each patient cohort. For these patients, duration of objective response was defined as the time from the initial confirmed compete response or partial response to the earlier of documented disease progression or death within 30 days of last exposure to study treatment. The Kaplan–Meier method was used to estimate the median duration of objective response and 95% confidence intervals for the median were computed in each cohort using the Brookmeyer and Crowley method (1982).[92] Duration of PFS was defined as the time from the initial dose of GDC-0449 until the earlier of documented disease progression or death within 30 days of last exposure to study treatment. Duration of OS was defined as the time from the initial dose of GDC-0449 until death from any cause. The Kaplan–Meier method was used to estimate median duration in each cohort for both PFS and OS.(92)	The sample size was chosen to allow adequate characterisation of the safety and efficacy of GDC-0449 in this patient population. With respect to efficacy, this study had approximately 80% probability of rejecting the null hypothesis given a true ORR of 37% in the mBCC cohort (with 20 treated patients) and 34% in the laBCC cohort (with 80 treated patients).(92)	Patients who received at least one dose of GDC-0449 and who discontinued for any reason prior to undergoing one post-baseline response evaluation were considered non-responders in the primary analysis, and disease progression was censored at the date of baseline tumour assessment + 1 day. For patients who were alive at the last contact date, duration of survival was censored at the last contact date. Duration of objective response and PFS were censored at the last tumour assessment date for patients without disease progression who had not died within 30 days of last exposure to study treatment.(92)
STEVIE(28)	No hypothesis tests were planned for either the basal cell	NR	A sample size of approximately 1200 patients allows the true AE incidence rate to be	NR

	carcinoma or basal cell carcinoma subpopulations.[93]		estimated within 1.6% and 1.8% if an observed incidence of 10% is assumed (i.e., within a 95% Clopper-Pearson CI of 8.4 to 11.8) and with a precision to estimate an AE of 1% frequency to within 0.5% to 1% of the true AE rate.	
Phase I SHH3925g(13)	NR	NR	NR	NR
RegiSONIC(31, 85)	NR	NR	NR	NR
EAS(32)	NR	Efficacy and safety data were summarised by descriptive statistics. The association between tumour response and selected baseline characteristics of age, prior radiotherapy exposure, prior systemic cancer therapy, and number of involved sites was evaluated using Fisher exact test.	NR	NR

Abbreviations: AE, adverse event; CI, confidence interval; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

ERIVANCE(43)

Primary hypothesis

The magnitude of ORR was formally tested in two parallel analyses using one-sided exact binomial tests in the metastatic and locally advanced BCC cohorts. Specifically, the following hypothesis was tested at the one-sided α = 0.025 level in the metastatic BCC cohort:

H_0: ORR ≤ 0.10; vs H_a: ORR > 0.10

Similarly, the following hypothesis was tested at the one-sided α = 0.025 level in the locally advanced BCC cohort:

H_0: ORR ≤ 0.20; vs H_a: ORR > 0.20

The null hypotheses were that ORR was at or below 10% for the metastatic BCC arm and at or below 20% for the advanced BCC arm. Response rates of >10% for metastatic disease and > 20% for locally advanced disease were deemed to represent clinically meaningful benefits for patients with advanced BCC, given that no therapeutic options existed for these patients and spontaneous responses had not been reported in this disease.(92)

Sample size and power calculation:

The sample size was chosen to allow adequate characterisation of the safety and efficacy of vismodegib in patients with advanced BCC. With 100 patients, this study had adequate sensitivity to detect safety signals with a relatively low incidence. The probabilities of a particular AE occurring in a study size of 100, with a "signal" expressed as one or more, or two or more particular AEs, is presented in Table 20

Table 20: Probability of a particular AE occurring in a study size of 100 patients

Incidence of Adverse Event	Probability of One or More Adverse Events Occurring	Probability of Two or More Adverse Events Occurring
2%	87%	60%
3%	95%	81%
4%	98%	91%
5%	99%	96%

With respect to efficacy, this study had approximately 80% probability of rejecting the null hypothesis given a true ORR of 37% in the metastatic BCC cohort (with 20 treated patients) and 34% in the locally advanced BCC cohort (with 80 treated patients).(92)

Interim analyses and stopping guidelines

No interim analyses were planned.

Statistical methods

Efficacy analyses(43)

OR: Objective response was defined as a CR or PR determined on two consecutive assessments ≥ 4 weeks apart. Patients with these responses were referred to as responders. The magnitude of ORR was formally tested in two parallel analyses using one-sided exact binomial tests in the metastatic and locally advanced BCC cohorts. Response rates of > 10% for metastatic disease and > 20% for locally advanced disease represent clinically meaningful benefits for patients with advanced BCC defined in the study protocol because no therapeutic options existed for these patients and spontaneous responses had not been reported in this disease. 95% Blyth–Still–Casella exact confidence intervals for the ORR were calculated for each patient cohort.

Duration of objective response was analysed only for responders in each cohort. For such patients, duration of objective response was defined as the time from the initial confirmed CR or PR to the earlier of documented disease progression or death within 30 days of last exposure to study treatment. The Kaplan–Meier method was used to estimate the median duration of objective response, and 95% confidence intervals for the median will be computed for each cohort using the Brookmeyer and Crowley method. Data for responders without disease progression who had not died within 30 days of last exposure to study treatment were censored at the time of the last tumour assessment.

PFS and OS: Methods for handling censoring were the same as described for duration of response.

Safety analyses

The incidence in patients of the following events were summarised by system organ class and preferred term. For each patient's adverse events, the maximum severity recorded was used in the summary.

Methods for additional analyses:

Quality of life(43)

Patient-reported symptoms were characterised through the use of the SF-36 Health Survey (Version 2) and its associated subscales. The instrument was administered at Day 1, Week 12, Week 24, and End of Study or Early Termination. The change in SF-36 was formally analysed by calculating the 95% confidence intervals for the mean change from Day 1 at Weeks 12 and 24 and End of Study or Early Termination.

Trial population included in analyses:

All safety analyses were performed using the all-treated patient population, defined as all enroled patients who received any amount of study drug.

The primary analysis population for efficacy consisted of all treated patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with BCC (the efficacy-evaluable population). In locally advanced BCC cases, when there was a conflicting interpretation of archival tissue versus a baseline biopsy by the independent pathologist, the baseline biopsy was used to determine inclusion in the efficacy analyses. Efficacy analyses were performed on the efficacy-evaluable patient population.

Analyses of primary and key secondary efficacy parameters were repeated for all enroled patients (ORR assessed by the IRF, ORR assessed by the investigator, and duration of response assessed by the IRF).

Patients without interpretable baseline or archival tissue were to be excluded from the efficacy analyses. Patients who received at least one dose of vismodegib and who discontinued for any reason prior to undergoing one post-baseline response evaluation were considered non-responders in the primary analysis, and disease progression was censored at the date of baseline tumour assessment + 1 day. For patients who were alive at the last contact date, duration of survival was censored at the last contact date. Duration of objective response and PFS was censored at the last tumour assessment date for patients without disease progression who had not died within 30 days of last exposure to study treatment.(43)

STEVIE(39)

Primary hypothesis

The primary objective of this trial is to assess the safety of vismodegib in patients with laBCC or mBCC. There were no formal statistical hypothesis tests to be performed.

Sample size and power calculation

It was originally planned that 150 patients would be enroled in the study. The planned sample size was increased to approximately 1200 patients to provide an adequate safety database and allow the AE incidence rate to be estimated within 1.6 to 1.8% of the true adverse event rate, assuming an observed incidence of 10% (i.e., within a 95% Clopper-

Pearson CI of 8.4 to 11.8) and with a precision to estimate an AE of 1% frequency to within a frequency of 0.5 to 1% of the true adverse event rate.

Interim analyses and stopping guidelines

The final analysis for safety and efficacy was planned to be performed when the last patient on treatment developed progressive disease (as determined by the Investigator) or unacceptable toxicity, withdrew consent, or died or the treating physician deemed the patient no longer benefited from treatment; the study was terminated by the Sponsor; or 12 months after the last dose of vismodegib in the last enroled patient still on study, whichever occurred first.

In addition to final analysis, there were six interim analyses for publication of safety and efficacy results and DSMB reviews when the:

- First 75 patients enroled have been treated for at least 3 months,
- First 150 patients enroled have been treated for at least 3 months,
- First 300 patients enroled have been treated for at least 3 months,
- First 550 patients enroled have been treated for at least 3 months,
- First 800 patients enroled have been treated for at least 3 months, and
- 1200 patients enroled have been treated for at least 3 months
    - This last interim analysis will also include analysis of 500 enroled patients who have been followed for at least 1 year

Statistical methods

Safety analyses

Treatment-emergent AEs (TEAEs) were defined as AEs occurring between the first administration of study vismodegib and 30 days after the last administration of vismodegib, inclusive.

All AEs were listed by patient, and TEAEs were summarised for all patients and by disease cohort (laBCC and mBCC). Serious TEAEs were summarised by system organ class (SOC) and preferred term (PT). TEAEs leading to death were summarised by SOC and PT. Selected AEs (including potential risks identified in the Risk Management Plan for additional pharmacovigilance) were summarised separately.

Efficacy analyses

ORR: BORRs together with the corresponding 95% Clopper-Pearson confidence intervals were calculated

Duration of response: For patients who were alive without progression following the qualifying response, DOR was censored on the date of last evaluable tumour assessment or last follow-up for progression of disease.

Time to response: For patients who did not respond, TTR was censored at the date of the last tumour assessment (or the treatment start date if no tumour assessments had yet been performed at the time of the data cut-off date).

Progression-free survival: A patient who died without a reported progression was considered as a PFS event on the date of death. Patients who neither progressed nor died were censored on the date of last evaluable tumour assessment.

Overall survival: For patients alive at the time of analysis, OS time was censored at the last date the patient was known to be alive. Patients with no post-baseline information were censored at the time of first treatment with vismodegib.

Estimates for the survivor function for the time-to-event endpoints, including PFS, OS, time to response, and DOR, were created graphically using Kaplan-Meier (KM) curves. Estimates for the median time to event and the corresponding two-sided 95% confidence interval were calculated with the estimates for the other quartiles and the associated ranges (minimum, maximum).

Methods for additional analysis

The Skindex-16 questionnaire was completed by patients with laBCC and patients with mBCC at selected sites at four timepoints: baseline, after Cycle 1, after Cycle 6, and at the end-of-treatment visit. A decrease in score represents clinical improvement; clinically meaningful improvement is defined as decrease of ≥10 points from baseline.(97) Descriptive tables were created for each domain and summarised scores at baseline and over time through measures of central tendency (mean, median) and dispersion (standard deviation, minimum, maximum, 25th, and 75th percentile).

A clinically meaningful difference on the MDASI was estimated to be a 30% reduction in symptom severity, based on evidence suggesting that a 3-point change on an 11-point numerical rating scale is meaningful.(98) For patients with mBCC who enrolled in the study after Protocol Version 4 was implemented, MDASI was collected at baseline and all

subsequent visits including safety follow-up visits for up to 1 year. For these patients, the frequency and type of symptoms at baseline were summarised. In addition, the number of patients with mBCC who were symptomatic at baseline and who achieved a 30% reduction in symptom severity at any post-baseline visit were summarised. This was analysed in two groups of symptomatic patients: (1) patients with a baseline score of ≥ 4 points on the composite score of 6 symptoms (i.e., pain, fatigue, shortness of breath, lack of appetite, dry mouth, and coughing) and (2) patients with a baseline score of ≥ 4 points on any of the 6 individual symptoms.

Trial population included in the analyses

All-enrolled population: The all-enrolled population includes all patients enrolled on study.

Safety-evaluable population: The safety-evaluable population includes all patients with documented exposure to vismodegib based on return of drug dispensed.

Efficacy-evaluable population: The efficacy-evaluable population includes all patients with documented exposure to vismodegib based on return of drug dispensed. This population includes the same patients as the safety-evaluable population

Phase I SHH3925g(99)

Primary hypothesis

This trial was designed to make a preliminary assessment of the safety, tolerability, pharmacokinetics, and anti-tumour activity of vismodegib in patients with locally advanced or metastatic tumours. The final analysis was based on patient data collected through study termination.

Sample size and power calculation

The sample size for this study was based on common Phase I study designs and not with regard to explicit power and type I error considerations. The planned enrolment for this study was 42−80 patients. (Further details regarding sample size are given in the Clinical Study Report.)(99)

Interim analysis and stopping guidelines

Dose escalation was to continue until the MTD was exceeded, excessive pill burden was declared, or analysis of available PK data indicated that exposure would not increase with further increases in the dose of vismodegib.

Dose escalation in Stage 1 was to proceed according to a modified doubling scheme (100% or less increase between cohorts) until the first Grade 2 or greater study drug–related adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 3.0) occurred during the DLT assessment window.

Subsequent dose escalation was to proceed according to a modified Fibonacci scheme. Toxicities were reported as attributed to vismodegib unless they were clearly related to tumour progression or could be clearly attributed to a cause other than vismodegib administration by the investigator and Medical Monitor. The maximum dose would be reached when one of the following occurred:

- The MTD was exceeded: incidence of DLT was 33% or greater (2 of 6 patients)
- Excessive pill burden: 2 or more patients in a cohort were unable to take ≥90% of their doses at a dose level that required a minimum of seven 270 mg capsules to be taken per dose (in consultation with the Medical Monitor)
- PK futility was encountered:
- In Stage 2, the expansion phase of the study, an additional 12 patients were enroled in a Safety Expansion Cohort to better characterise the safety profile and the PK and PD properties of vismodegib at the proposed Phase II dose.

In addition, up to 20 patients with metastatic or locally advanced basal cell carcinoma were enroled into a separate Basal Cell Carcinoma Cohort to provide a preliminary estimate of efficacy of vismodegib in this population. Enrolment to this cohort began while Stage 1 was ongoing. Patients enroled in the Basal Cell Carcinoma Cohort received either the highest daily dose of vismodegib that did not result in DLTs in the dose-escalation portion of the study (i.e., the highest “cleared” dose) or received the same dose as the Safety Expansion cohort once this cohort had been initiated. There were no planned dose cessation periods, and patients received vismodegib daily until disease progression, maximum benefit, or intolerability.

Statistical methods

Safety was assessed through summaries of adverse events, deaths, changes in laboratory test results, and changes in vital signs. Safety follow up included adverse events reported until 30 days after study drug discontinuation or study termination, whichever was earlier, in order to capture any acute drug-related toxicities and to evaluate adverse event reversibility.

An estimate of the objective response rate and 95% exact confidence intervals (Blyth−Still−Casella) were calculated. For patients with an objective response, duration of objective response was defined as the time from the initial response to disease progression or death from any cause within 30 days after receiving the last dose of vismodegib.

Methods for additional analyses

Methods for analysis of pharmacokinetic, pharmacodynamics and biomarker data are not relevant to this submission and are therefore not included here.

Trial populations included in analyses

Safety-evaluable population consisted of patients who received at least one dose of vismodegib.

Efficacy-evaluable population: patients with measurable disease at baseline who received at least one dose of GDC-0449 and either had a post-baseline tumour assessment or progressed before any tumour assessment.

(NB: PK-evaluable, PD-evaluable and DLT-evaluable populations are not relevant to this submission and are therefore not described here.)

RegiSONIC

No data regarding the statistical methods for this study have been reported so far in the congress proceedings.

A steering committee composed of participating study clinicians and a patient advocate provide guidance regarding study conduct and data analysis and interpretation throughout the course of the study. (89)

EAS(100)

Primary hypothesis

This study was not designed to evaluate a specific hypothesis: thus, there were no formal hypothesis tests to be performed. The primary analysis was performed based on patient data collected through 30 days after the last vismodegib dose for the last patient enroled into the study.

Sample size and power calculation

Approximately 100 patients were anticipated to be enroled. The total number of patients enroled was based on drug availability and duration of the study.

Data from a previous study ((99)) showed that the incidence rate of Grade ≥ 3 AEs and SAEs were approximately 40% and 20%, respectively, in patients treated with vismodegib. Based on this assumption, the estimated 95% confidence intervals for the event rates are described below.(100)

Table 21: Estimated 95% Confidence Intervals for Event Rates in EAS

Sample size	Incidence (%) [95% CI]
100 100	20 [12.2 to 27.8] 40 [30.4 to 49.6]

Interim analyses and stopping guidelines

No interim analyses were planned. Interim data (~12 months after the first patient was enroled) for the laBCC cohort were described in a presentation at the American Academy of Dermatology Summer Meeting 2012.

Statistical methods

Continuous data were summarised using mean, standard deviation, median, minimum, and maximum. Discrete data were summarised using frequencies and percentages. The number of enroled patients was tabulated. Eligibility exceptions and protocol deviations were listed. Patient disposition and reasons for premature discontinuation were tabulated.

Safety analyses

Safety was assessed through summaries of AEs (including deaths).

Exposure was described by a summary of number of doses received, weeks of therapy, number of patients requiring a dose interruption, and discontinuation for reasons other than disease progression.

All AEs occurring on or after the first treatment until 30 days after the last oral administration of vismodegib were summarised by mapped term, appropriate MedDRA, v15.0 levels, and National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) grade.

All SAEs were listed separately and summarised.

Laboratory data were summarised by grade using the NCI CTCAE, v4.0 toxicity grade.

Deaths reported during the study treatment period and those reported during the 30-day follow-up after patients discontinued treatment were summarised.

The number of patients who discontinued from the study was summarised. Descriptive statistics were also presented for cumulative vismodegib doses, the number of cycles, the number of patients requiring discontinuation of vismodegib for reasons other than progressive disease, and weeks of exposure.

Efficacy analyses

Objective response rates were estimated for the efficacy-evaluable population. An estimate of the objective response rate was computed, as well as the corresponding 95% confidence interval.

Methods for additional analyses

Not applicable.

Trial population included in analyses

The efficacy-evaluable population was defined as patients who had received at least one dose of vismodegib, had measurable disease at baseline, and had at least one follow-up tumour assessment or died within 30 days from the last dose of study drug.

The safety population was defined as all patients who had received at least one dose of vismodegib.

4.11.5 Participant flow in the studies

The numbers of patients screened, selected, treated and included in analyses for each study are presented below in **Figure 10** to **Figure 15**.

Figure 10: Participant flow in ERIVANCE at primary analysis (44)

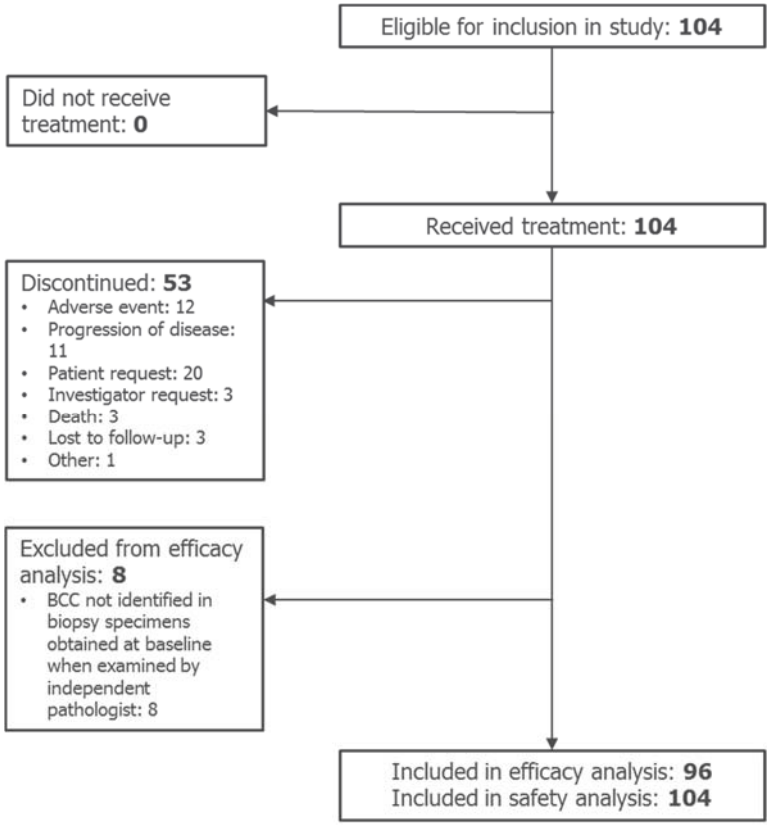


Figure 11: Participant flow in ERIVANCE (as of 30-month follow-up)(27)

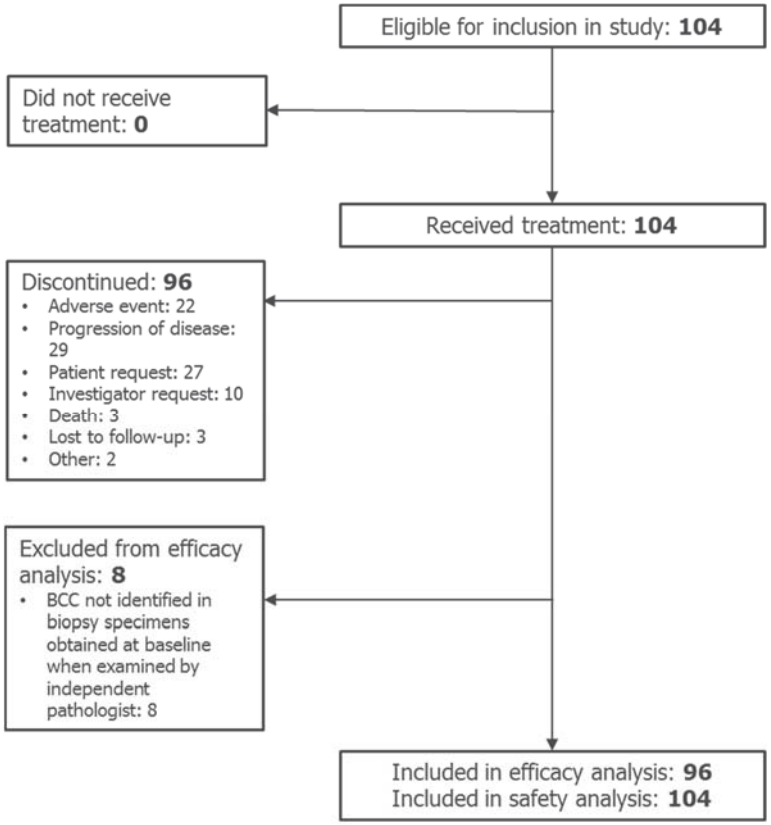


Figure 12: Participant flow in STEVIE(28)

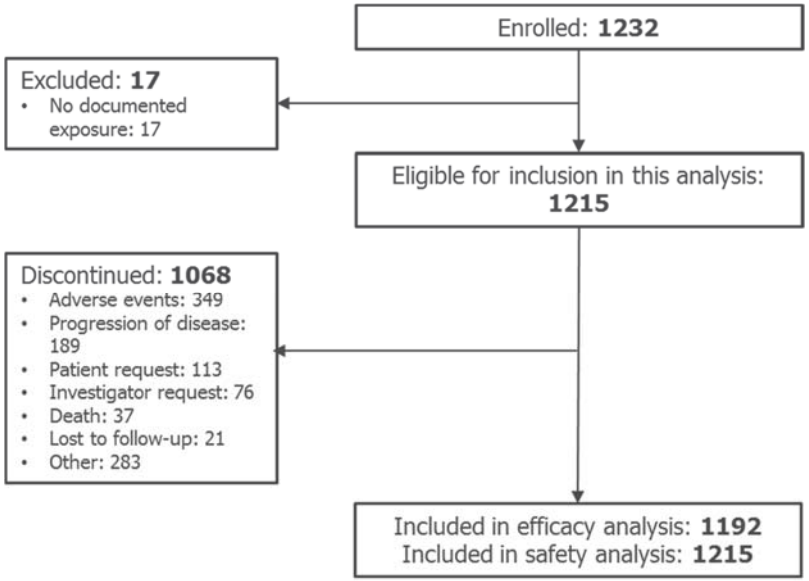


Figure 13: Participant flow in Phase I SHH3925g(13)

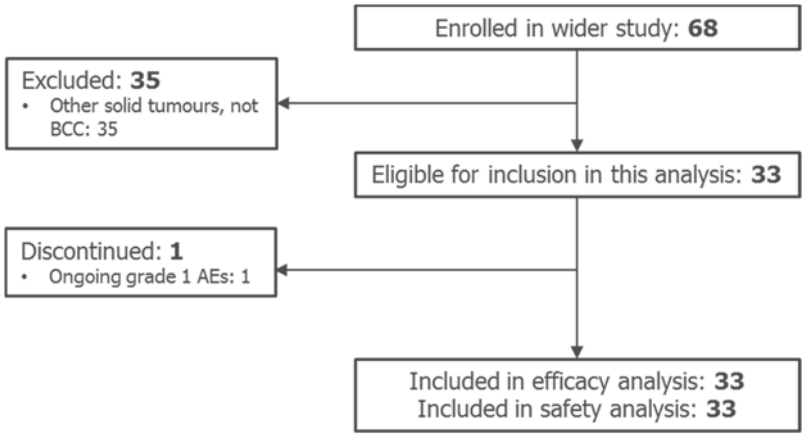
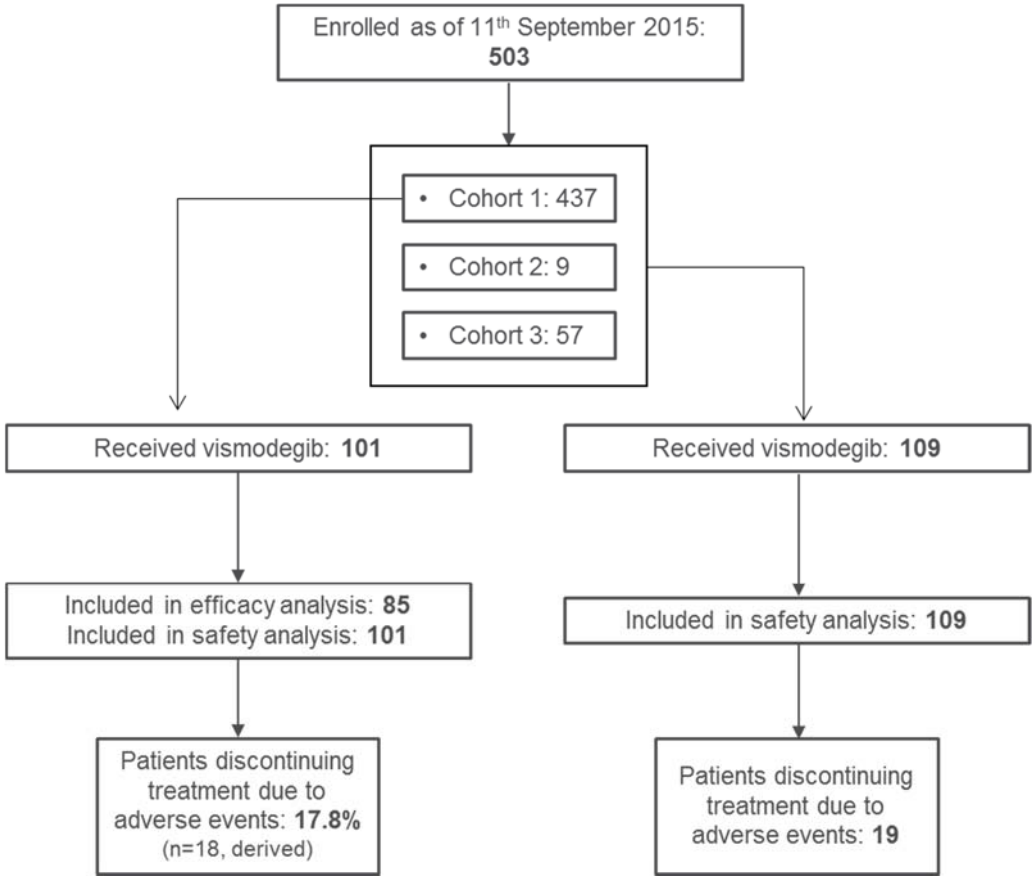
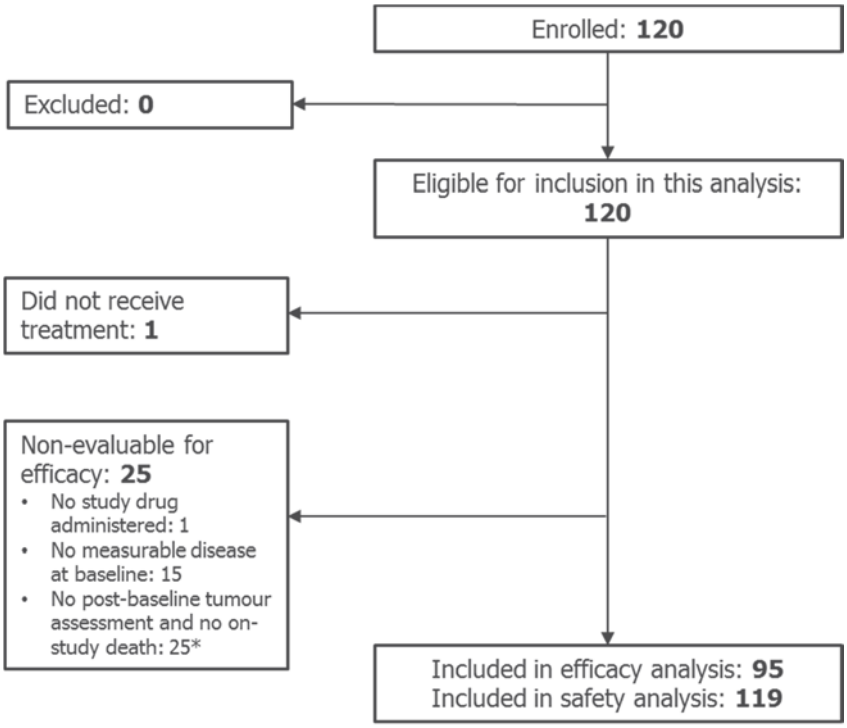


Figure 14: Participant flow in RegiSONIC (31)*



* RegiSONIC is an on-going registry study, so the numbers presented here represent patients available for analysis at the latest data-cut (11 September 2015).

Figure 15: Participant flow in EAS (32)



The baseline characteristics of patients across treatment groups in the identified non-RCTs are presented below for ERIVANCE (Table 22), STEVIE (Table 23), Phase I SHH3925g,(Table 25), and EAS (Table 26).

Table 22: Baseline characteristics of patients in ERIVANCE (44)

Baseline characteristic	laBCC n=63	mBCC n=33
Age, mean (SD); median (range)	61.4 (16.9); 62.0 (21 to 101)	61.6 (11.4); 62.0 (38 to 92)
Gender, n (%)		
Male	35 (56)	24 (73)
Female	28 (44)	9 (27)
Race or ethnic background, n (%)		
White	63 (100)	33 (100)
Contraindications to surgery, n (%)		
Inoperable tumour	24 (38)	NA
Surgery inappropriate	39 (62)	
Prior radiotherapy, n (%)		
Yes	13 (21)	NA
Inappropriate or contraindicated	50 (79)	

Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NA, not applicable

Table 23: Baseline characteristics of patients in STEVIE (28)

Baseline characteristic	laBCC (n=1,119)	mBCC (n=96)	Total (N=1,2135)
Age, median (range)	72.0 (18 to 101)	67.0 (34 to 95)	72.0 (18 to 101)
Gender, n (%)			
Male	634 (56.7)	60 (62.5)	694 (57.1)
ECOG score, n (%)			
0	662 (59.2)	39 (40.6)	701 (57.7)
1	316 (28.3)	42 (43.8)	358 (29.5)
2	138 (12.3)	15 (15.6)	153 (12.6)
Gorlin syndrome, n (%)			
Yes	214 (19.2)	5 (5.2)	219 (18.1)
No	899 (80.8)[a]	91 (94.8)	990 (81.9)[a]
Contraindications to surgery, n (%)	433 (38.7)	NA	433 (35.6)
Inoperable			
Surgery contraindicated	686 (61.3)		686 (56.5)
Prior radiotherapy, n (%)			
Yes	312 (27.9)	59 (61.5)	371 (30.5)
No	806 (72.0)	37 (38.5)	843 (69.4)

a Gorlin status not recorded for 6 patients
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not applicable

In total, 98.8% of patients had histologically confirmed disease at baseline (99.3% in the laBCC cohort and 92.7% in the mBCC cohort), and 96.8% of patients had measurable disease (97.0% in the laBCC cohort and 94.8% in the mBCC cohort). In addition, among patients with laBCC, 38.7% had baseline disease status that was considered inoperable, and for 61.3% of patients with laBCC, surgery was medically contraindicated.

Among patients with laBCC, the most frequent site of disease was the head (74.9%; 838 patients), followed by trunk (21.9%; 245 patients), other skin location (17.3%; 194 patients), extremity (12.6%; 141 patients), and neck (11.2%; 125 patients). Five patients (0.4%) had disease in “lymph nodes local regional.”

Among patients with mBCC, the most frequent sites of disease were lung (65.6%; 63 patients), bone (32.3%; 31 patients), lymph nodes (31.3%; 30 patients), “other site” (13.5%; 13 patients), head (12.5%; 12 patients), and trunk (10.4%; 10 patients).

Among the 96 patients with mBCC, 87 patients (90.6%) had prior surgery or procedures related to mBCC; 6 (6.3%) had received prior systemic cancer therapy for mBCC at baseline; and 59 (61.5%) had received prior radiotherapy for mBCC.

Table 24: Baseline characteristics of patients in Phase I SHH3925g (13)

Baseline characteristic	Patients with BCC treated with vismodegib
N	33
Median age, years (range)	53 (38 to 84)
Gender, n (%) Male	 25 (76)
Race or ethnic background, n (%) White Latino	 32 (97) 1 (3)
Type of disease, n (%) laBCC mBCC	 15 (45) 18 (55)
ECOG score, n (%) 0 1	 14 (42) 19 (58)
Previous therapies, n (%) Surgery Radiotherapy Systemic therapy	 28 (85) 19 (58) 15 (45)

Abbreviations: ECOG, Eastern Cooperative Oncology Group;

Table 25: Baseline characteristics of vismodegib-treated patients RegiSONIC

Baseline characteristic	Patients in Cohort 1 (newly-diagnosed laBCC without Gorlin syndrome) treated with vismodegib (31)	Patients in Cohort 1 (newly-diagnosed laBCC without Gorlin syndrome) treated with vismodegib(88)
N	**n=101**	**n=77**
Median age, (range) years	67 (34 to 99)	67 (34 to 99)
Gender, (%) Male	68%	69%
Follow-up duration, median (range) months	17.6 (0.2 to 36.0)	NR
ECOG PS at enrolment, %[a] 0 1 ⩾2 Unknown	NR	(n=55) 42 27 15 16
Multiple laBCC lesions, % **Median number of lesions, n (range)**	NR	31 3 (1 to 50)[b]
Median target lesion size n, (range) mm		(n=71) 32 (0 to 250)
Definition of laBCC based on, %[c] Location Curative resection unlikely Medical contraindication to radiation Medical contraindication to surgery	NR	 66 53 30 25
Target lesion location, % **Head** Scalp Forehead Eye Nose Cheek Ear Neck	NR	(n=76) 61 7 12 5 16 8 9 4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported
a Denominator for percentage is n for particular characteristic
b N for median number of lesions is 26
c Patients may be counted in more than one category; not all categories shown

Minimal patient demographic and disease characteristic data for cohort 1 was presented in the latest congress proceedings for RegiSONIC (American Academy of Dermatology, 2016; data cut-off 11 September 2015).(31) Therefore, we have also included more comprehensive information for cohort 1 from an earlier data cut-off (13 February 2015; presented at EADO 2015) in slightly fewer patients. (88)

In addition, data from the same cut (13 February 2015; ESMO 2015) have been presented in an analysis of all vismodegib-treated patients in cohorts 1, 2 and 3 combined (n=96). Median age (67 years) and proportion of male patients (67%) were reported.(86)

Table 26: Baseline characteristics of patients in EAS (32)

Baseline characteristic	Patients with laBCC	Patients with mBCC	Total
N	n=62	n=57	n=119
Age, median (range)	61.0 (26 to 92)	63.0 (24 to 100)	62.0 (24 to 100)
Gender, n (%) Male	 43 (69.4)	 45 (78.9)	 88 (73.9)
Race or ethnic background, n (%) White	 60 (96.8)	 56 (98.2)	 116 (97.5)
ECOG performance status, n (%) 0 1 2	 39 (62.9) 19 (30.6) 4 (6.5)	 30 (52.6) 22 (38.6) 5 (8.8)	 69 (58.0) 41 (34.5) 9 (7.6)
Current disease status, n (%) Metastatic Locally advanced Inoperable Surgery medically contraindicated Recurrent BCC unlikely to be curatively resected Anticipated substantial morbidity and/or deformity from surgery Other contraindications to surgery	 - 62 (100) 27 (43.5) 35 (56.5) 10 (16.1) 28 (45.2) 2 (3.2)	 57 (100) - - - - - -	 57 (47.9) 62 (52.1)
Measurable disease at baseline, n (%)	56 (90.3)	48 (84.2)	104 (87.4)
Patients with BCCNS, n (%)	12 (19.4)	7 (12.3)	19 (16.0)
Contraindications to surgery or radiation therapy, n (%) Inoperable tumour Surgery inappropriate	 27 (43.5) 35 (56.5)	NA	NR
Prior treatments, n (%) Surgery Radiotherapy	 57 (91.9) 20 (32.3)	 54 (94.7) 35 (61.4)	 111 (93.3) 55 (46.2)
Prior systemic therapy, n (%) Mean (SD) Median Range	11 (17.7) 1.7 (1.8) 1.0 1 to 7	20 (35.1) 3.7 (3.1) 3.5 1 to14	31 (26.1) 3.0 (2.8) 2.0 1 to14

Abbreviations: BCCNS, basal cell carcinoma naevus syndrome (Gorlin syndrome); ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NR, not reported; SD, standard deviation

119 patients (99.2% of enroled) comprised the Safety Evaluable Population (one enroled patient did not receive study drug). In the Safety Evaluable Population, 62 patients (52.1%) had laBCC and 57 (47.9%) had mBCC.

The Efficacy Evaluable Population, defined as patients who had received at least one dose of vismodegib, had measurable disease at baseline, and had at least one follow-up tumour assessment or died within 30 days from the last dose of study drug, comprised 95 patients (79.2% of enroled). Among these, 56 (58.9%) had laBCC and 39 (41.1%) had mBCC.

4.11.6 Quality assessment of the relevant non-randomised and non-controlled evidence

The non-randomised studies identified as relevant for inclusion were assessed using the checklist from Downs and Black (1998).(101) Full quality appraisals for each study identified in the systematic review are presented in Appendix 9.

4.11.7 Describe the methods used for assessing risk of bias of individual studies

Full quality appraisals for each study identified in the systematic review are presented in Appendix 9.

4.11.8 Tabulated summary of the quality assessment criteria.

Full quality appraisals for each study identified in the systematic review are presented in Appendix 9.

4.11.9 Quality assessment for each study

Full quality appraisals for each study identified in the systematic review are presented in Appendix 9.

4.11.10 Clinical effectiveness of the non-randomised and non-controlled evidence

ERIVANCE(44)*

Table 27: Summary of analyses and data cuts for ERIVANCE(43)

Data cut-off date	26 November 2010(44)	28 November 2011(38)	30 May 2013(27)
Analysis timepoint	Primary analysis; 9 months after last patient enroled	12-month follow-up	30-month follow up
% patients remaining on study	52.5%	27.9%	8.7%
Analyses performed		Non-specified efficacy analyses: • IRF- and investigator-assessed response rate and duration of response • Investigator-assessed PFS • OS • 1-year survival rates	Non-specified efficacy analyses: • Investigator-assessed response rate and duration of response • Investigator-assessed PFS • OS • 1- and 2-year survival rates

12-month efficacy update(38, 43)

Independently-assessed response rate was 47.6% (95% CI, 35.5 to 60.6; p<0.001), with complete responses in 14 patients (21%) in 63 patients with laBCC. In 33 patients with mBCC, the response rate was 33.3% (95% CI, 19.2 to 51.8; p=0.002). The median duration of response was 9.5 months and 7.6 months in the laBCC and mBCC cohorts respectively.

30-month efficacy update (27)

Investigator-assessed response rate at 30-months follow-up was 60.3% in patients with laBCC, and 48.5% in patients with mBCC. The median duration of objective response improved dramatically between the 12-month and 30-month follow-ups for laBCC: from 7.6 months to 26.2 months (95% CI: 9.0 to 37.6). The metastatic cohort improved slightly from 12.9 months to 14.8 months (95% CI: 5.6 to 17.0).

* Primary outcomes in ERIVANCE were from independent review; results from site investigators are also reported. 12-month follow-up outcomes were from independent review. 30-month follow-up outcomes in ERIVANCE were from investigator review.

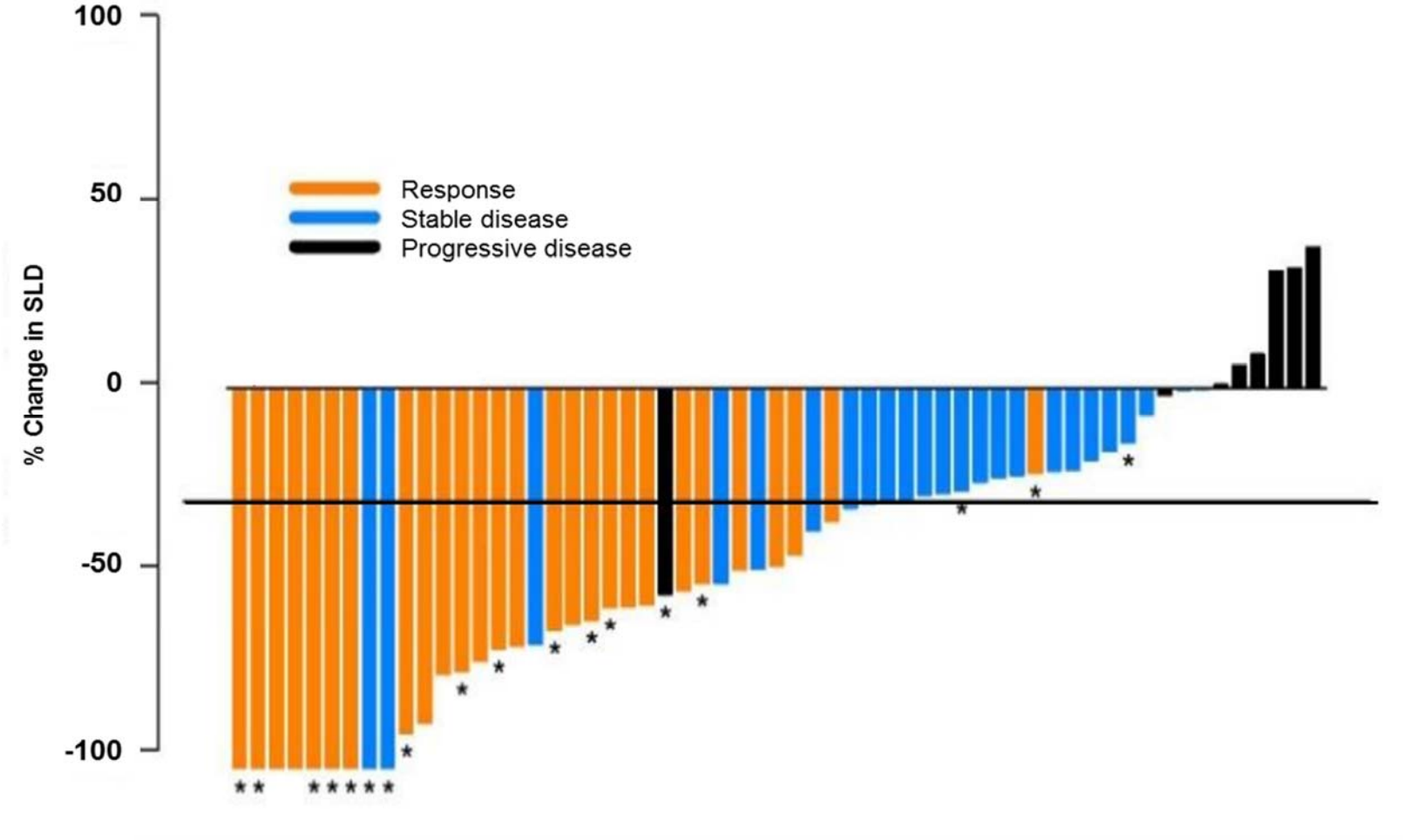
A summary of the efficacy data is presented in Table 28.

Assessment of clinical benefit for locally advanced BCC

In the ERIVANCE study, a novel composite endpoint for laBCC incorporated radiographic, photographic, and pathology measurements, including external tumour dimension and ulceration. Tumour dimension was measured by sum of single longest dimension [SLD]. Responses of patients with laBCC have been presented graphically. Overall confirmed response is the composite response for the patient, and the waterfall plot bar (see Figure 16) represents the maximum change in target lesion SLD. Both overall confirmed response and the maximum change in target lesion SLD were determined by IRF assessment.

Additionally, cases are illustrated in Appendix 16. This photo appendix presents the images of the target, laBCC lesions evaluated in the study. The de-identified data, showing laBCC evaluable patients with photos and case synopses, provide a view of the clinical effect of vismodegib for patients who responded, were stable, and did not respond in the laBCC cohort over time. The appendix does not include four laBCC patients who did not have target lesion measures; nor does it include metastatic BCC cohort patients.

Figure 16: Waterfall plot of maximum tumour shrinkage in laBCC patients in ERIVANCE



Abbreviations: SLD, Sum of single longest dimension
* asterisks indicate patients with complete resolution of ulceration. Adapted from Sekulic et al (44)

Table 28: Summary of clinical effectiveness data presented in ERIVANCE[a]

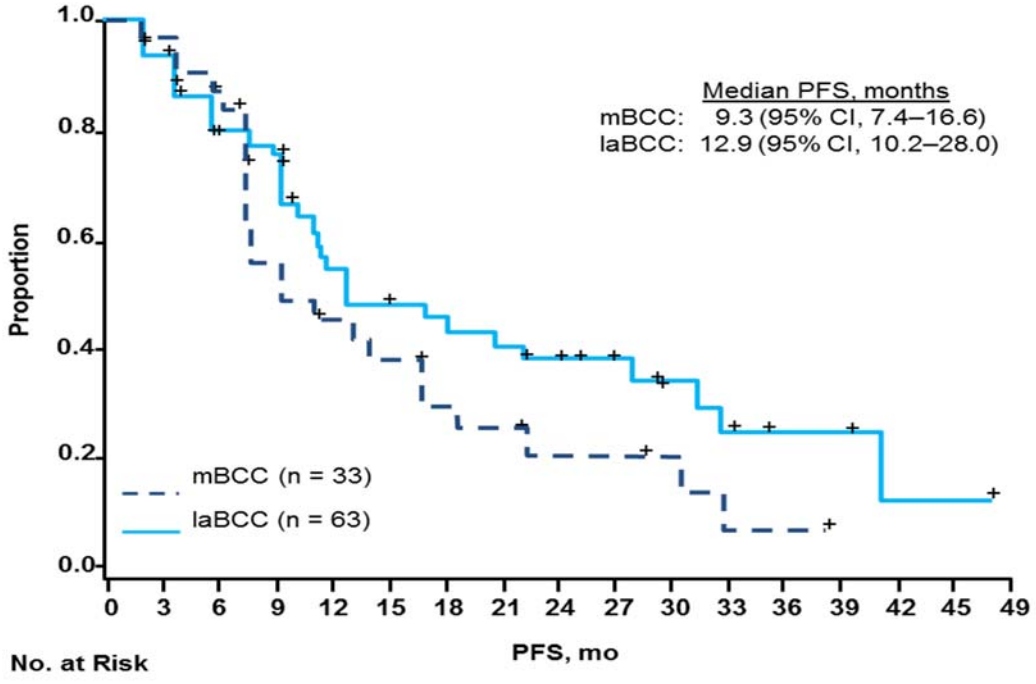
Study arm	Primary outcomes (IRF-assessed) (data cut-off 26 November 2010)(44)			Outcomes from 12-month update (IRF-assessed) (data cut-off 28 November 2011)(38)			Further outcomes from 30-month update (investigator-assessed) (data cut-off 30th May 2013)(27, 43)		
	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	laBCC n=63	mBCC n=33	Total N=96
Response rate									
Objective response rate, n (%) [95% CI]	27 (43) [30 to 56]	10 (30) [16 to 48]	NR	30 (48) [36 to 61]	11(33) [19 to 52]	NR	38 (60.3) [47.2 to 71.7]	16 (48.5) [30.8 to 66.2]	54 (56.3) [45.7 to 66.4]
Complete response, n (%)	13 (21)	0	NR	14 (22)	0	NR	20 (NR)	0 (0)	20 (NR)
Partial response, n (%)	14	10 (30)	NR	16 (25)	11 (33)	NR	18 (NR)	16 (NR)	34 (NR)
Stable disease, n (%)	24 (38)	21 (64)	NR	22 (35)	20 (60)	NR	15 (NR)	14 (NR)	29 (NR)
Progressive disease, n (%)	8 (13)	1 (3)	NR	8 (13)	1 (3)	NR	6 (NR)	2 (NR)	8 (NR)
Missing or NE, n (%)	4 (6)	1 (3)	NR	3 (5)	1 (3)	NR	4	1	5
Duration of response									
Median, months (range)	7.6 (1.0 to 12.9)	7.6 (2.1 to 11.1)	NR	9.5 (7.4 to 21.4)	7.6 (5.5 to 9.4)	NR	26.2 [9.0 to 37.6)	14.8 [5.6 to 17.0]	16.1 [9.5 to 26.2]
Tumour shrinkage									
n (%)	57 (NR)	24 (73)	NR			NR			
Progression-free survival									
Median, months [95% CI]	9.5 [7.4 to 11.9]	9.5 [7.4 to NE]	NR	9.5 [7.4 to 14.8]	9.5 [7.4 to 11.1]	NR	12.9 [10.2 to 28.0]	9.3 [7.4 to 16.6]	12.8 [9.5 to 26.2]
Overall survival									
Median OS, months [95% CI]	Data not mature	Data not mature	Data not mature	NE	24.1 [14 .3 to NE]	NR	NE [NE to NE]	33.4 [18.1 to NE)	NE [41.2 to NE]
1-year survival rate, % [95% CI]	91.6 [83.5-99.7]	75.5 [57.3-93.6]	NA	93.1 [86.6 to 99.6]	78.7 [64.7 to 92.7]	NR	78.7 [64.7 to 92.7)	93.2 [86.8 to 99.6)	NA

Study arm	Primary outcomes (IRF-assessed) (data cut-off 26 November 2010)(44)			Outcomes from 12-month update (IRF-assessed) (data cut-off 28 November 2011)(38)			Further outcomes from 30-month update (investigator-assessed) (data cut-off 30th May 2013)(27, 43)		
	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	laBCC n=63	mBCC n=33	Total N=96
2-year survival rate, % [95% CI]	Not applicable	Not applicable	Not applicable	85.4 [76.0 to 94.8]	60.3 [43.4 to 79.1]	NR	85.5 [76.1-94.8)	62.3 [45.4-79.3)	NA
Time to treatment discontinuation (reported as 'duration of treatment')									
Median, months (range)	9.7 (1.1 to 18.7)	10.0 (0.7 to 16.4)	NR	12.7 (1.1 to 30.6)	13.3 (0.7 to 24.8)	NR			NR
Duration of follow up									
Median, months (range) [95% CI]				21.7	22.4		39.1 (2.4 to 49.2) [37.8 to 40.3]	39.1 (6.7 to 43.4) [31.4 to 40.2]	39.1 (2.4 to 49.2) [37.8 to 39.6]
SF-36									
Mental component score, mean [95% CI] change from baseline at end of study, n=20	NR	NR	-3.80 [-10.55 to 2.96]	NR	NR	NR	NR	NR	NR
Physical component score, mean [95% CI] change from baseline at end of study, n=20	NR	NR	- 2.86 [-7.39 to 1.66]	NR	NR	NR	NR	NR	NR

[a] Primary outcomes in ERIVANCE were from independent review; results from site investigators are also reported

Abbreviations: CI, confidence interval; IRF, independent review committee; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NA, not available; NE, not evaluable; NR, not reported; OS, overall survival

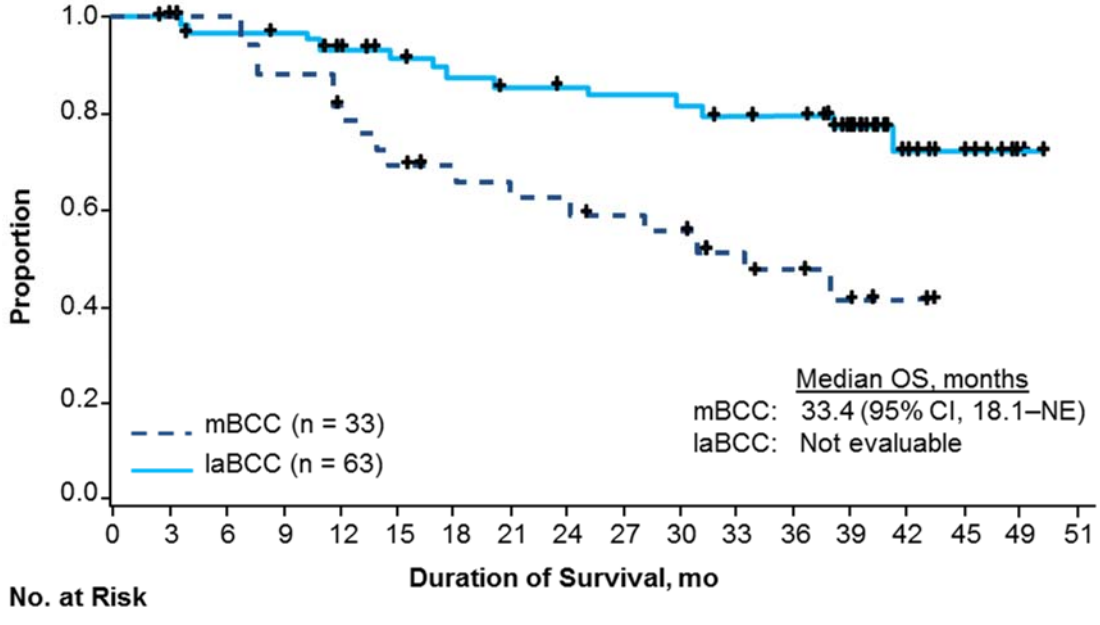
Figure 17: Kaplan-Meier plot of PFS by investigator assessment in ERIVANCE (adapted from Sekulic et al, ASCO 2014(27))



No. at Risk

mBCC	33	31	26	16	12	10	7	6	4	4	3	1	1	0	0	0	0
laBCC	63	55	42	38	24	19	17	16	13	10	7	5	3	3	1	1	0

Figure 18:Kaplan-Meier plot of OS by investigator assessment in ERIVANCE(adapted from Sekulic et al, ASCO 2014(27))



No. at Risk

mBCC	33	33	33	29	25	22	20	18	18	16	15	12	10	7	2	0	0	0
laBCC	63	61	58	56	52	48	45	43	42	41	40	38	37	25	13	8	2	0

STEVIE(28)

NCT01367665 evaluated the safety of vismodegib, with efficacy and quality of life as secondary objectives. The best overall confirmed responses (as assessed by investigator according to RECIST v1.1) were noted in 769 patients (66.2%): 738 of 1103 patients with laBCC (68.5%) and 31 of 89 patients with mBCC (36.9%). Tumour or disease control was assumed from the number of complete and partial responses and number of stable disease combined, meaning from these results, disease control was estimated to be 92.9%.

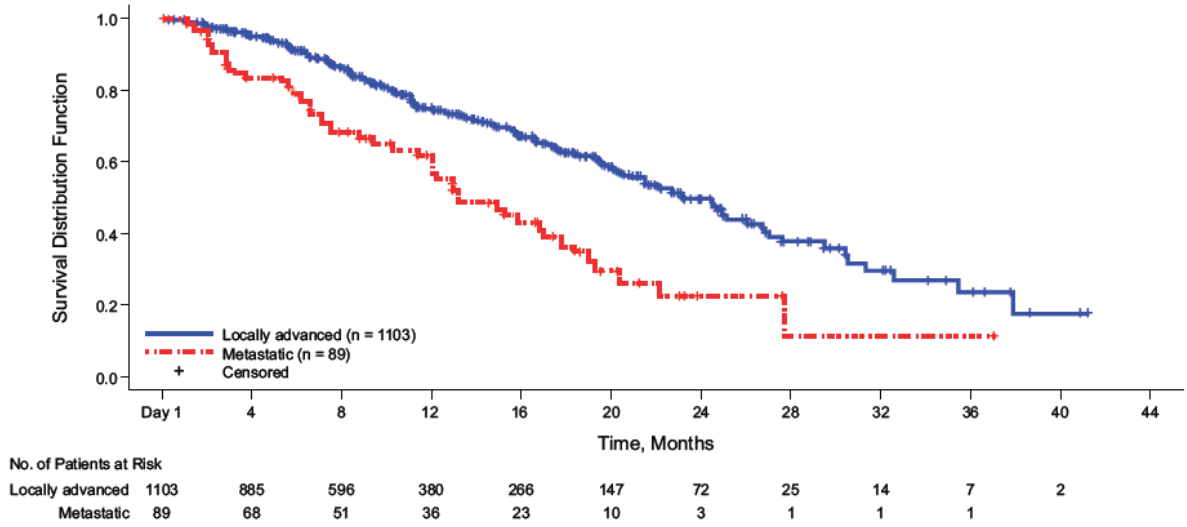
A summary of the efficacy data reported is presented in Table 29.

Table 29: Summary of clinical effectiveness data presented in STEVIE(28)

Study arm	Patients with laBCC n=1103	Patients with mBCC n=89	Total N=1192
Progression-free survival			
Median, months (95% CI)	23.2 [21.4 to 26.0]	13.1 [12.0 to 17.7]	22.1 [20.3 to 24.7]
	Outcomes among patients with measurable disease at baseline		
	n=1077	**n=84**	**N=1161**
Response rate			
Objective response rate, n (%) [95% CI]	738 (68.5) [65.66 to 71.29]	31 (36.9) [26.63 to 71.29]	769 (66.2) [63.43 to 68.96]
Complete response, n (%)	360 (33.4)	4 (4.8)	364 (31.4)
Partial response, n (%)	378 (35.1)	27 (32.1)	405 (34.9)
Stable disease, n (%)	270 (25.1)	39 (46.4)	309 (26.6)
Progressive disease, n (%)	21 (1.9)	9 (10.7)	30 (2.6)
Missing or NE, n (%)	48 (4.5)	5 (6.0)	53 (4.6)
Duration of response			
Median, months [95% CI]	23.0 [20.4 to 26.7]	13.9 [9.2 to NE]	22.7 [20.3 to 24.8]
Time to response			
Median, months [95% CI]	3.7 [2.9 to 3.7]	NE [5.5 to NE]	3.7 [3.5 to 3.7]

Median (95% CI) progression-free survival in the 1192 patients with histologically confirmed disease and measurable or non-measurable disease at baseline was 23.2 months (95% CI 21.4-26.0) in the laBCC cohort and 13.1 months (95% CI 12.0-17.7) in the mBCC cohort (see Figure 19). In the overall study population, PFS was 22.1 (95% CI 20.3-24.7).

Figure 19: PFS in patients with histologically confirmed disease in STEVIE



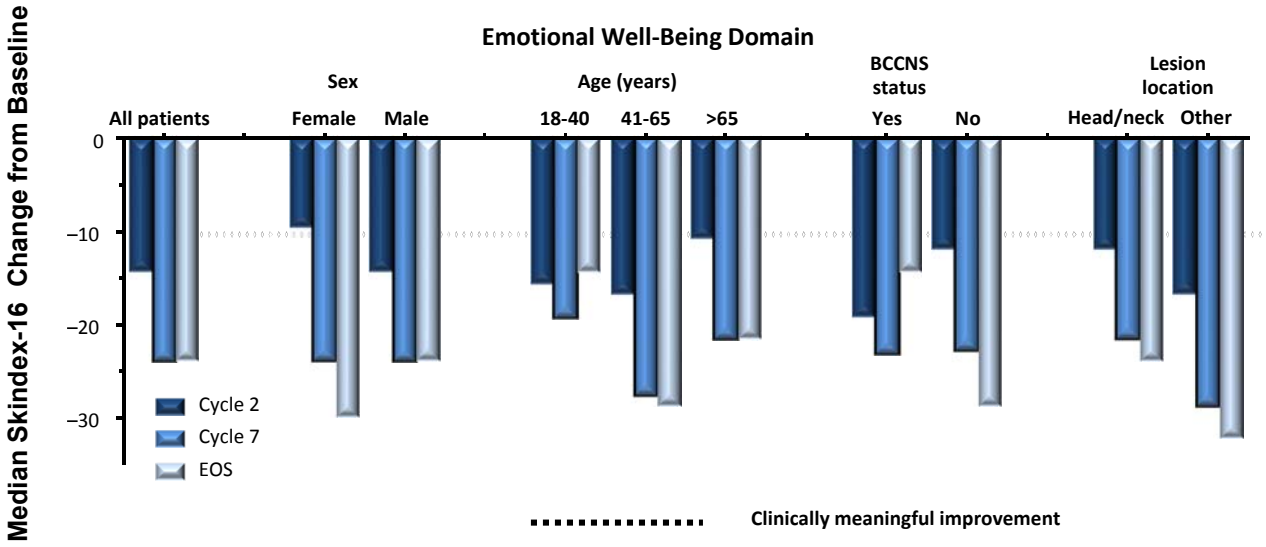
The OS data are still immature as only 9.0% of patients had died as of the data cut-off date. Among the 1192 efficacy-evaluable patients with histologically confirmed disease and available measurable disease status at baseline, the median OS was not estimable, nor was it estimable for either the laBCC cohort or mBCC cohort.

Assessment of quality of life using Skindex-16(29)

The sample size of patients with mBCC was limited; no meaningful improvement was seen at any timepoint across all domains.

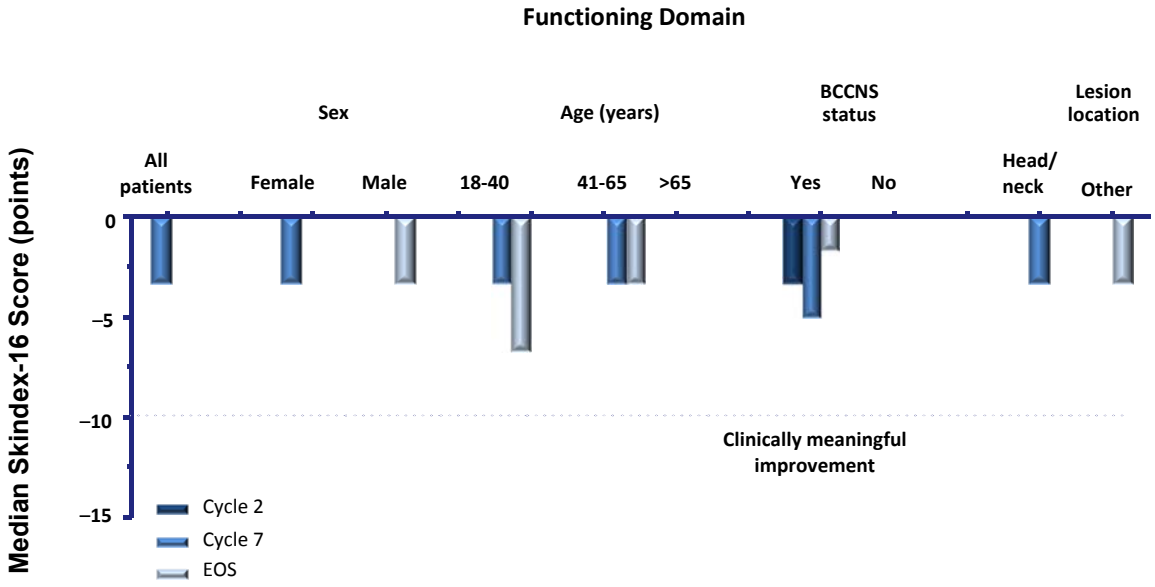
Treatment with vismodegib was consistently associated with clinically meaningful improvements in emotion scores in patients with laBCC, which the Skindex-16 is designed to capture, across subgroups and timepoints. No consistent differences were seen by gender and Gorlin status. Improvements from baseline were consistently larger for patients with primary lesions in a location other than head/face or neck, and for patients aged 41 to 65 years. See Figure 20.

Figure 20: Change in emotional domain of Skindex-16 by subgroup in STEVIE



No clinically meaningful changes (either improvement or deterioration) were seen for functional scores. See Figure 21.

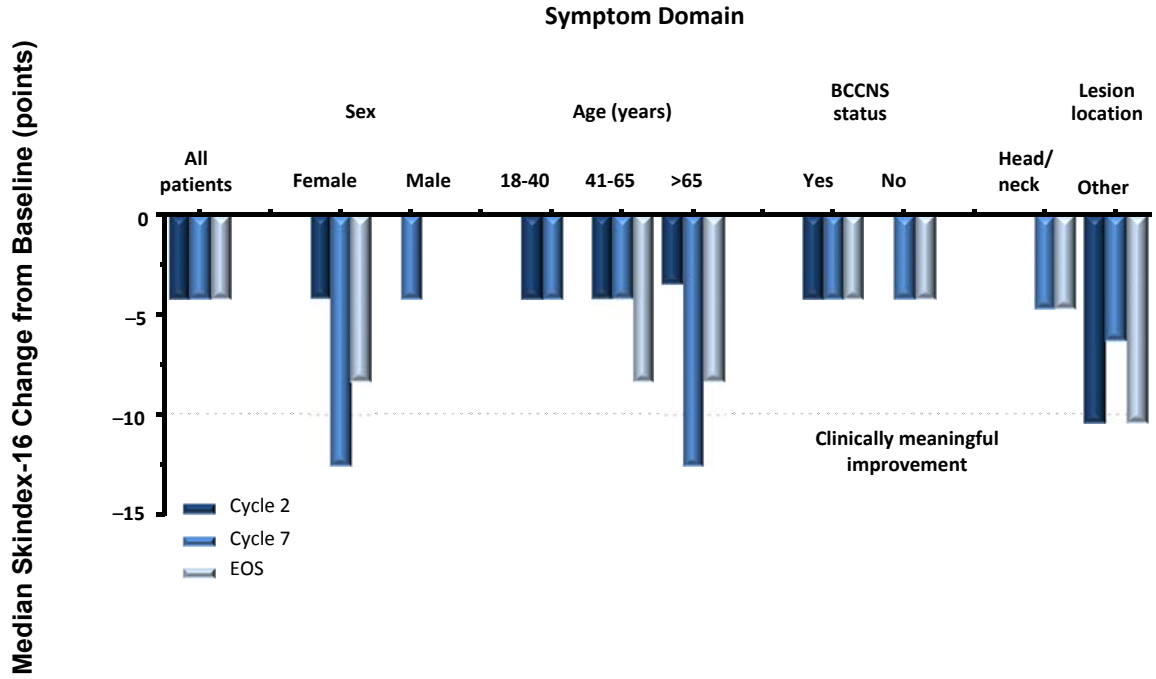
Figure 21: Change in function domain of Skindex-16 by subgroup in STEVIE



No consistent differences were seen in symptom scores by subgroup or cycles. A limitation to this study includes the Skindex-16's limited applicability to non-skin-related symptoms: as a dermatology-focused instrument, it does not comprehensively capture all relevant aspects of HRQoL (e.g., treatment burden). However, some clinically meaningful improvements in

symptom scores were seen in limited subgroups of patients categorised by age, sex, and lesion location. See Figure 22.

Figure 22: Change in symptom domain of Skindex-16 by subgroup in STEVIE



Phase I SHH3925g(13)

In the Phase I study SHH3925g, patients received daily vismodegib at one of three doses; 17 patients received 150 mg per day, 15 patients received 270 mg per day, and one patient received 540 mg per day. The median duration of the study treatment was 9.8 months. Of the 33 patients, 18 had an objective response to vismodegib, according to assessment on imaging (seven patients), physical examination (10 patients), or both (one patient). Of the patients who had a response, two had a complete response and 16 had a partial response. The other 15 patients had either stable disease (11 patients) or progressive disease (four patients).

A summary of the efficacy data reported is presented in Table 30.

Table 30: Summary of clinical effectiveness data for Phase I SHH3925g(13)

Study arm	Patients with laBCC n=15	Patients with mBCC n=18	Total N=33
Response rate			
Objective response rate, n (%) [95% CI]	NR (60) [33 to 83]	NR (50) [29 to 71]	18 (55)[(102)] [NR]
Complete response, n (%)	2 (13)	0 (0)	2 (6)
Partial response, n (%)	7 (47)	9 (50)	16 (48)
Stable disease, n (%)	4 (27)	7 (39)	11 (33)
Progressive disease, n (%)	2 (13)	2 (11)	4 (12)
Duration of response			
Median, months	NR	NR	8.8
Time to treatment discontinuation			
Median, months	NR	NR	9.8

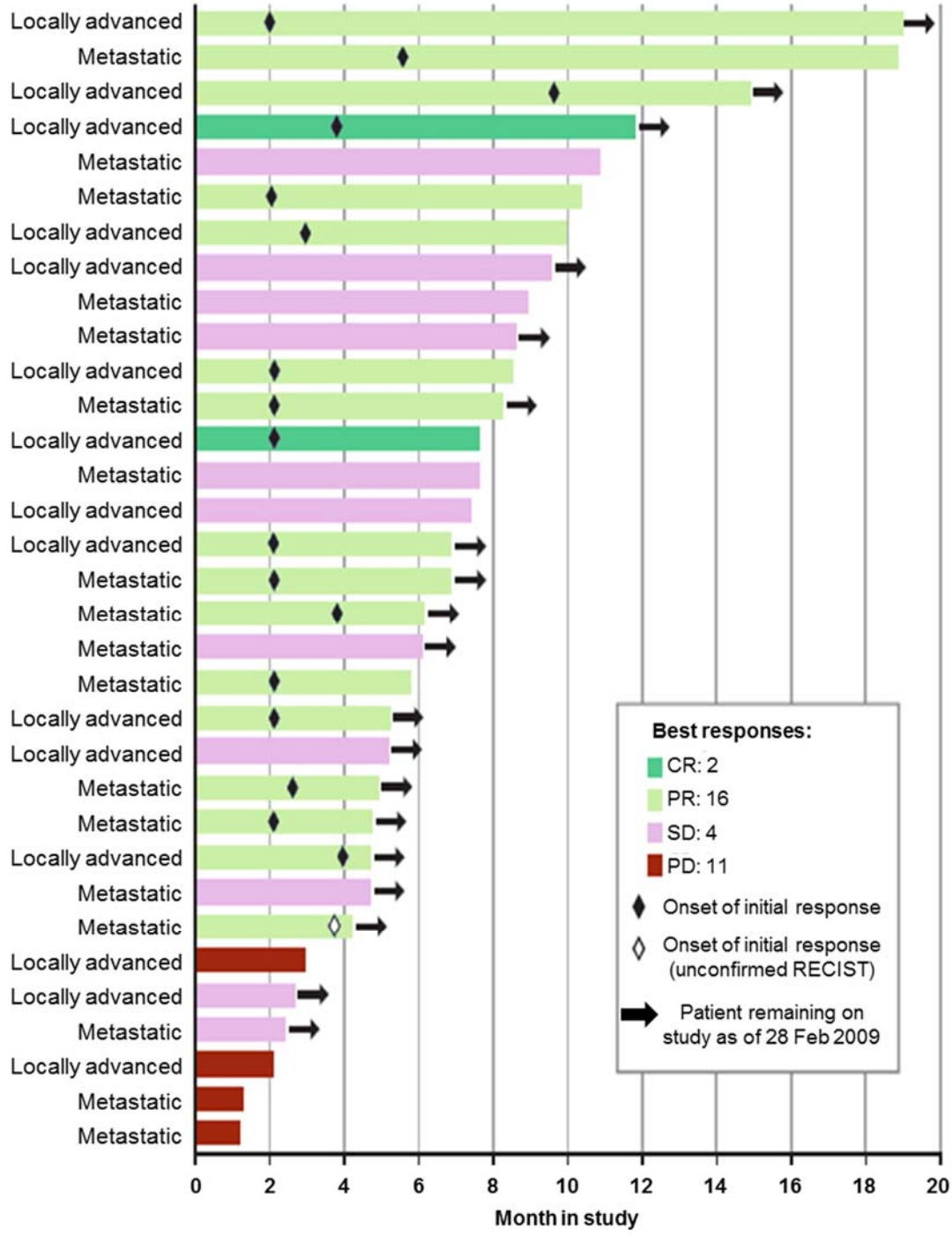
Abbreviations: CI, confidence interval; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NR, not reported

Of the 18 patients with mBCC, 15 had radiologically measurable disease, and 7 of these patients had a partial response, as assessed on imaging only (with 6 responses confirmed and 1 unconfirmed at the time of the data cut-off). Two other patients with metastatic tumours had partial responses, one assessed on both imaging and physical examination and the other on physical examination only. Seven patients with metastatic tumours had stable disease (with six patients assessed with the use of RECIST and one on physical examination), and two had progressive disease as the best response. The overall response rate among the 18 patients with metastatic tumours was 50% (95% CI 29 to 71).

Of the 15 patients with locally advanced tumours, 13 were assessed on physical examination (clinical response), and 2 with measurable disease were assessed on imaging, according to RECIST. Of these 15 patients, 2 had a complete clinical response, and 7 had a partial clinical response; 4 patients had stable disease as the best response, with a duration of participation in the study ranging from 2.1 to 19.0 months; 2 of the patients had progressive disease. Overall, the response rate in patients with locally advanced tumours was 60% (95% CI, 33 to 83).

Responses to treatment are shown graphically in Figure 23.

Figure 23: Response to treatment in patients with aBCC in Phase I SHH3925g



RegiSONIC

This multicentre, prospective observational study is on-going. The efficacy results reported here (data cut-off 11 September 2015) are from 101* newly diagnosed laBCC patients without BCCNS enroled in cohort 1 and treated with vismodegib. The response was 87.1% (95% CI, 79 to 93), with complete response in 58.8% and partial response in 28.2%. Median duration of response was 9.6 months.(31)

Median progression-free and overall survival were not estimable by the Kaplan-Meier method at the time of data cut-off.(31)

The efficacy data reported for NCT01604252 are presented in Table 31.

Table 31: Summary of clinical effectiveness data presented in RegiSONIC(31)

Study arm	Patients with laBCC n=101
Effectiveness evaluable	**n=85**
Response rate	
Best overall response (CR + PR), % [95% CI]	87.1 [79 to 93]
Complete response, n (%)	58.8
Partial response, n (%)	28.2
Stable disease, n (%)	11.8
Disease control rate (CR + PR + SD), % [95% CI]	98.8 [94 to 100]
Progressive disease, %	0
Recurrence, %	1.2
Duration of response	
Median, months[a,b] (range)	9.6 (0.03 to 30.1)

Abbreviations: CI, confidence interval; CR, complete response; laBCC, locally advanced basal cell carcinoma; PR, partial response; SD, stable disease
[a]n=74; [b]Univariate analysis

* Abstract presents results from 88 patients; congress presentation presents results from 101 patients (more data available since the submission of the abstract)

EAS(32)

In this open-label, multicentre study, a total of 119 patients with advanced basal cell carcinoma (aBCC) took vismodegib for a median of 5.5 months. Objective responses occurred in 46.4% of laBCC and 30.8% of patients with mBCC. Response was negatively associated with prior systemic therapy in patients with laBCC (p=0.002).

The efficacy data reported for EAS are presented in Table 32.

Table 32: Summary of clinical effectiveness data presented in EAS(32)

Study arm	Patients with laBCC n=56	Patients with mBCC n=39	Total N=95
Response rate			
Objective response rate, n (%) [95% CI]	26 (46.4) [33.0 to 60.3]	12 (30.8) [17.0 to 47.6]	NR
Complete response, n (%)	6 (10.7)	2 (5.1)	8 (8.4)
Partial response, n (%)	20 (35.7)	10 (25.6)	30 (31.6)
Stable disease, n (%)	27 (48.2)	20 (51.3)	47 (49.5)
Progressive disease, n (%)	0	3 (7.7)	NR
Missing or NE, n (%)	3 (5.4)	4 (10.3)	NR
Time to response in Patients who Exhibited Complete Response or Partial Response			
Median, months Mean (SD), months Range, months	2.6 3.5 (2.4) 1.0 to 11.0	2.6 3.8 (3.3) 1.4 to 12.6	NR

Abbreviations: CI, confidence interval; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NE, not evaluable; NR, not reported

Waterfall plots of response (tumour shrinkage) are shown in Figure 24 and Figure 25.

Figure 24: Waterfall plot of maximum tumour shrinkage in laBCC patients in EAS(32)

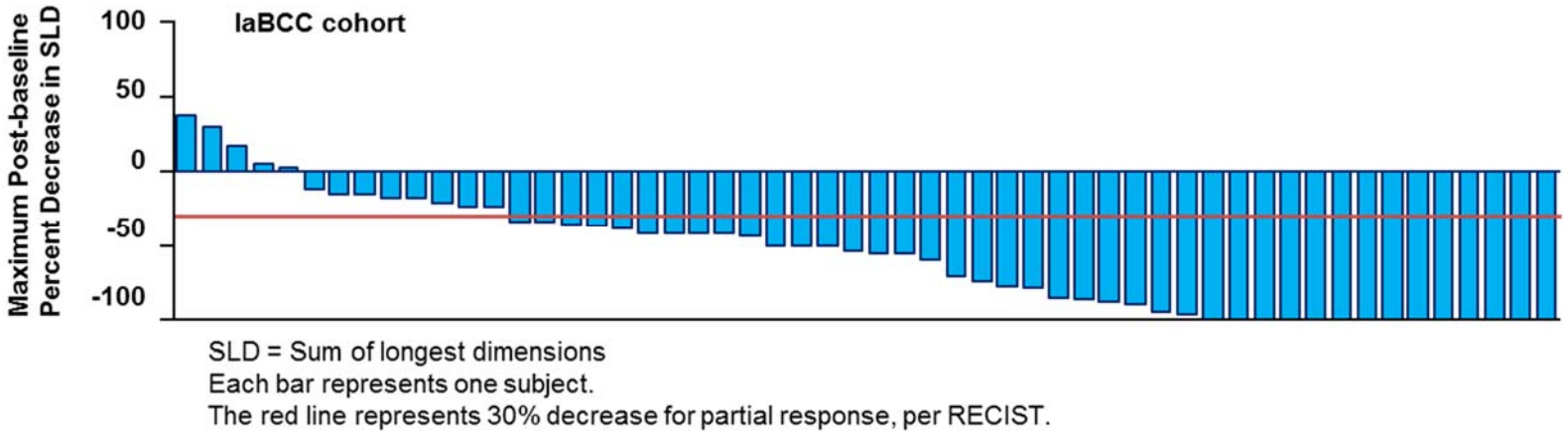
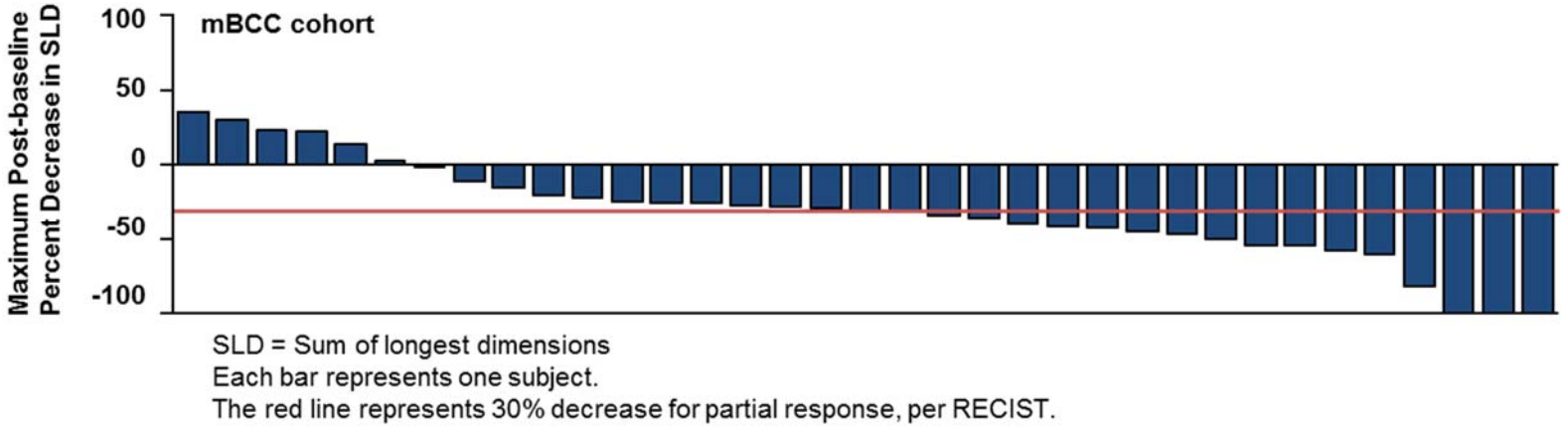


Figure 25: Waterfall plot of maximum tumour shrinkage in mBCC patients in EAS(32)



4.12 Adverse reactions

4.12.1 Adverse events from RCTs

There were no RCTs identified. The data in the following section are from the non-randomised studies described in section 4.11.

4.12.2 Adverse reactions reported in the relevant non-randomised and non-controlled evidence

ERIVANCE(44)

In this multi-centre, international, two-cohort, non-randomised study, adverse events occurring in more than 30% of patients were muscle spasms, alopecia, dysgeusia, weight loss, fatigue and nausea. Serious adverse events were reported in 25% of patients at the primary analysis and 35% of patients at the 30-month analysis; eight deaths due to adverse events were noted.

A summary of treatment-related adverse events reported in ERIVANCE is presented in Table 33.

Table 33: Treatment-emergent AEs (total and by grade) occurring in ≥10% of all treated patients in ERIVANCE(27)

AE, n (%)	NCI CTCAE Grade (N = 104)					
	Total	1	2	3	4	5
Any AE	104 (100.0)	8 (7.7)	37 (35.6)	37 (35.6)	13 (12.5)	8 (7.7)
Muscle spasms	74 (71.2)	45 (43.3)	23 (22.1)	6 (5.8)	0	0
Alopecia	69 (66.3)	49 (47.1)	20 (19.2)	NA	NA	NA
Dysgeusia	58 (55.8)	32 (30.8)	26 (25.0)	NA	NA	NA
Weight decreased	54 (51.9)	29 (27.9)	16 (15.4)	9 (8.7)	NA	NA
Fatigue	45 (43.3)	33 (31.7)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	29 (27.9)	19 (18.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	NA	NA
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	(3.8) 1	4 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	NA	NA
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	NA	NA	NA
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	NA	NA	NA
Pruritus	11 (10.6)	8 (7.7)	2 (1.9)	1 (1.0)	NA	NA
Dyspepsia	11 (10.6)	8 (7.7)	3 (2.9)	0	NA	NA

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Serious adverse events

In total, 36 of 104 patients (34.6%) experienced an SAE. A higher proportion of patients in the locally advanced BCC cohort (28 of 71 subjects [39.4%]) experienced an SAE compared with patients in the metastatic BCC cohort (8 of 33 patients [24.2%]).

The SAEs experienced by ≥ 2 patients overall included pneumonia and syncope (each in 4 patients [3.8%]); death and hip fracture (each in 3 patients [2.9%]); and cardiac failure, cellulitis, gastrointestinal haemorrhage, squamous cell carcinoma, pulmonary embolism, and deep vein thrombosis (each in 2 patients [1.9%]).

Medical review did not identify any pattern of association between SAE occurrence and duration of vismodegib treatment. Further, there were factors that confounded the association between the AEs and vismodegib treatment.(43) A summary of SAEs in ERIVANCE is provided in Table 34.

Table 34: Serious adverse events by system organ class in ERIVANCE(43)

MedDRA System Organ Class	laBCC (n=71)	mBCC (n=33)	All patients (N=104)
All SAEs	28 (39.4)	8 (24.2)	36 (34.6)
Blood and lymphatic system disorders	1 (1.4)	0	1 (1.0)
Cardiac disorders	5 (7.0)	0	5 (4.8)
Eye disorders	1 (1.4)	1 (3.0)	2 (1.9)
Gastrointestinal disorders	4 (5.6)	0	4 (3.8)
General disorders and administration site conditions	5 (7.0)	2 (6.1)	7 (6.7)
Hepatobiliary disorders	1 (1.4)	0	1 (1.0)
Infections and infestations	8 (11.3)	1 (3.0)	9 (8.7)
Injury, poisoning and procedural complications	4 (5.6)	2 (6.1)	6 (5.8)
Metabolism and nutrition disorders	1 (1.4)	1 (3.0)	2 (1.9)
Musculoskeletal and connective tissue disorders	1 (1.4)	0	1 (1.0)
Neoplasms	6 (8.5)	1 (3.0)	7 (6.7)
Nervous system disorders	6 (8.5)	3 (9.1)	9 (8.7)
Psychiatric disorders	2 (2.8)	0	2 (1.9)
Renal and urinary disorders	1 (1.4)	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	3 (4.2)	1 (3.0)	4 (3.8)
Vascular disorders	4 (5.6)	1 (3.0)	5 (4.8)

Abbreviations: MEDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event

Deaths

A review of all Grade 5 AEs suggests that there was no definite pattern of events and that all patients had significant pre-existing risk factors or co-morbidities at baseline. No patient deaths were assessed by the investigator as related to vismodegib. (43) A summary of the deaths in ERIVANCE is provided in Table 35.

Table 35: Deaths (all treated patients) in ERIVANCE

	laBCC (n=71)	mBCC (n=33)	All patients (N=104)
All deaths, n (%)	16 (22.5)	17 (51.5)	33 (31.7)
Time of death, n (%) Death on study drug Death during survival follow up	 6 (8.5) 10 (14.1)	 1 (3.0) 16 (48.5)	 7 (6.7) 26 (25.0)
Cause of death, n (%) Progressive disease Adverse event Other	 4 (5.6) 7 (9.9) 5	 13 (39.4) 1 (3.0) 3	 17 (16.3) 8 (7.7) 8

Extent of exposure to treatment

The median duration of exposure to vismodegib was 13.27 months for the metastatic BCC cohort and 12.68 months for the locally advanced BCC cohort respectively. Median dose intensity was 98.89% and 96.93%, for the two cohorts respectively.(43) A summary of exposure to treatment in ERIVANCE is provided in Table 36.

Table 36: Exposure to treatment in ERIVANCE

	laBCC (n=71)	mBCC (n=33)	Total (N=104)
Median duration of treatment, months (range)	12.7 (1.1 to 47.8)	13.3 (0.7 to 39.1)	12.9 (0.7 to 47.8)
Dose intensity % Medan (range)	96.9 (58.5 to 107.5)	98.9 (77.4 to 102.5)	97.4 (58.5 to 107.5)
Median Total number of 150 mg capsules taken n (range)	347 (25 to 1380)	403 (19 to 1189)	384 (19 to 1380)

Treatment discontinuation

As of the data cut-off date 30 May 2013, >90% of patients had discontinued treatment. The most frequent reasons for treatment discontinuation were disease progression (27.9%), patient decision to discontinue treatment (26.0%), and AE (21.2%). A larger proportion of

patients in the metastatic BCC cohort (51.5%) had discontinued treatment because of disease progression compared with patients in the locally advanced BCC cohort (16.9%)(43) A summary of treatment discontinuations in ERIVANCE is provided in Table 37.

Table 37: Patient disposition in ERIVANCE - all treated patients

	laBCC (n=71)	mBCC (n=33)	Total (N=104)
Patients still on treatment	7 (9.9)	1 (3.0)	8 (7.7)
Discontinued treatment			
Total	64 (90.1)	32 (97.0)	96 (92.3)
Adverse event	17 (23.9)	5 (15.2)	22 (21.2)
Death	2 (2.8)	1 (3.0)	3 (2.9)
Lost to follow-up	2 (2.8)	1 (3.0)	3 (2.9)
Physician decision	7 (9.9)	3 (9.1)	10 (9.6)
Patient decision	23 (32.4)	4 (12.1)	27 (26.0)
Disease progression	12 (16.9)	17 (51.5)	29 (27.9)
Other	1 (1.4)	1 (3.0)	2 (1.9)

Adverse events of special interest

The teratogenic potential of vismodegib has not been investigated in humans. However, given the key role of the Hh pathway in embryogenesis, and the embryotoxic and teratogenic effects of vismodegib observed in other animals, pregnancies, abortions, congenital anomalies, and birth defects were defined as events of special interest; as of the data cut-off date, none of these events had been reported in this study.(43)

Concomitant medications

The majority of treated patients (95.2%) reported use of at least one concomitant medication while on study. The most frequently reported medications included paracetamol (29.8%, 31 patients), multivitamin not otherwise specified (20.2%, 21 patients), aspirin and ibuprofen (each with 19.2%, 20 patients), and hydrocodone tartrate/paracetamol (13.5%, 14 patients).(43)

STEVIE(28)

In this single-arm, open-label international study TEAEs defined as occurring between the first administration and 30 days after the last administration of study drug, inclusive, were reported in 1192 patients (98%). The most common all-grade TEAEs were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight decreased (40.6%), and decreased appetite (24.9%). Amenorrhoea/irregular menses was also reported in 18 of 64 (28.1%)

female patients who had menses at baseline. The majority of TEAEs (54%) were mild-to-moderate.

A summary of adverse events reported in this trial is presented in Table 38.

Table 38: Summary of adverse events reported in >10% of patients in STEVIE(28)

Study arm	TEAEs, all patients N=1215	TEAEs leading to discontinuation		
		laBCC n=1119	mBCC n=96	Total N=1215
Any TEAE, n (%)				
All	1192 (98)	-	-	380 (31)
Grade 5 (fatal)	46 (3.8)			-
Ageusia, n (%)				
All	213 (17.5)	23 (2.1)	0	23 (1.9)
Grade 3	15 (1.2)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Alopecia, n (%)				
All	747 (61.5)	39 (3.5)	0	39 (3.2)
Grade 3	15 (1.2)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Arthralgia, n (%)				
All	124 (10.2)	NR	NR	NR
Grade 3	4 (0.3)	-	-	-
Grade 4	0	-	-	-
Asthenia, n (%)				
All	291 (24.0)	35 (3.1)	0	35 (2.9)
Grade 3	22 (1.8)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Decreased appetite, n (%)				
All	303 (24.9)	37 (3.3)	0	37 (3.0)
Grade 3	20 (1.6)	-	-	-
Grade 4	0	-	-	-
Diarrhoea, n (%)				
All	197 (16.2)	NR	NR	NR
Grade 3	8 (0.7)	-	-	-
Grade 4	0	-	-	-
Dysgeusia, n (%)				
All	663 (54.6)	55 (4.9)	0	55 (4.5)
Grade 3	25 (2.1)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Fatigue, n (%)				
All	201 (16.5)	25 (2.2)	2 (2.1)	27 (2.2)
Grade 3	19 (1.6)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Muscle spasm, n (%)				
All	807 (66.4)	84 (7.5)	1 (1.0)	85 (7.0)
Grade 3	94 (7.7)	-	-	-
Grade 4	1 (<0.1)	-	-	-
Nausea, n (%)				
All	218 (17.9)	12 (1.1)	1 (1.0)	13 (1.1)
Grade 3	4 (0.3)	-	-	-
Grade 4	0	-	-	-
Weight decreased, n (%)				
All	493 (40.6)	46 (4.1)	1 (1.0)	47 (3.9)
Grade 3	47 (3.9)	-	-	-
Grade 4	1 (<0.1)	-	-	-

Abbreviations: NR, not reported; TEAE, treatment-emergent adverse event

Grade ≥ 3

Grade ≥ 3 TEAEs were reported in 43.7% of patients.

Table 39: Grade ≥ 3 Adverse events occurring in >2% patients in STEVIE(39)

	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Total number of patients with ≥1 AE, n (%) Overall total number of events, n	484 (43.3) 949	47 (49.0) 85	531 (43.7) 1034
Muscle spasms	90 (8.0)	5 (5.2)	95 (7.8)
Weight decreased	44 (3.9)	4 (4.2)	48 (4.0)
Gamma-glutamyltransferase increased	28 (2.5)	2 (2.1)	30 (2.5)
Hypertension	23 (2.1)	4 (4.2)	27 (2.2)
Dysgeusia	25 (2.2)	1 (1.0)	26 (2.1)
Asthenia	23 (2.1)	1 (1.0)	24 (2.0)

Except for hypertension, all of these Grade ≥ 3 TEAEs are known to be associated with vismodegib treatment. Twenty-seven patients developed Grade ≥ 3 hypertension during study. Detailed medical review of patients with hypertension revealed that the majority of these patients (70%) had hypertension at baseline. Six of the 27 patients had events that were considered related to treatment by the investigator; all 6 patients had confounding factors based on medical review including age, hypocholesterolaemia, and/or obesity.(39)

Serious TEAEs

Serious TEAEs were reported in 289 patients (23.8%); 260 with laBCC and 29 with mBCC. SAEs reported in ≥ 0.5% of patients were pneumonia (18 patients; 1.5%); SCC of skin and general physical health deterioration (12 patients each; 1.0%); fall and myocardial infarction (MI) (9 patients each; 0.7%); and gastroenteritis, hip fracture, and syncope (6 patients each; 0.5%). SAEs that were considered by the investigator to be related to vismodegib were experienced by 83 patients (6.8%). Medical review of the 5 patients with general physical health deterioration showed that all patients had factors that confounded the association between SAEs and vismodegib treatment including advanced age (4/5 patients are older than 75 years old) and/or significant pre-existing risk factors or comorbidities at baseline (3/5 patients).

A summary of SAEs in STEVIE is provided in Table 40.

Table 40: SAEs occurring in ≥ 0.5% patients in STEVIE (safety population)

MedDRA Preferred Term	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Total number of patients with ≥1 AE, n (%) Overall total number of events	260 (23.2) 401	29 (30.2) 40	289 (23.8) 441
Pneumonia	17 (1.5)	1 (1.0)	18 (1.5)
Squamous cell carcinoma of skin	11 (1.0)	1 (1.0)	12 (1.0)
General physical health deterioration	11 (1.0)	1 (1.0)	12 (1.0)
Fall	9 (0.8)	0	9 (0.7)
Myocardial infarction	8 (0.7)	1 (1.0)	9 (0.7)
Gastroenteritis	5 (0.4)	1 (1.0)	6 (0.5)
Hip fracture	6 (0.5)	0	6 (0.5)
Syncope	6 (0.5)	0	6 (0.5)

Deaths

A total of 110 patients (9.1%) died while on study or in follow-up (92 patients [8.2%] with laBCC and 18 patients [18.8%] with mBCC).

A total of 53 Grade 5 TEAEs occurred in 46 patients (3.8% of all patients; a number of patients experienced more than one Grade 5 TEAE). 44 of the 53 grade 5 TEAEs events were considered by the investigator to be unrelated to vismodegib; 7 patients had events that were considered to be related to vismodegib (myocardial infarction [n = 2]; pancreatitis [n = 1], pulmonary embolism [n = 1], ischemic stroke [n = 1], cardiorespiratory arrest [n = 1], and renal failure [n = 1]).

A summary of the deaths in STEVIE is provided in Table 41.

Table 41: Summary of deaths in STEVIE (safety population)

Status	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Number of patients who died, n (%)	92 (8.2)	18 (18.8)	110 (9.1)
Primary reason for death, n (%) Adverse event Disease progression Other[a]	 65 (5.8) 15 (1.3) 12 (1.1)	 6 (6.3) 12 (12.5) 0	 71 (5.8) 27 (2.2) 12 (1.0)

[a] Reasons for "other" included "unknown," "natural causes," "cardiac decompensation," "general state alteration," "deterioration of general state," "clinical deterioration taking into consideration patient's age," "old age," and "disease progression of mediastinal SCC

Extent of exposure to treatment

The median duration on treatment was 263 days (256 days in the laBCC cohort and 319 days in the mBCC cohort). The median dose intensity was 97.7% (97.6% in the laBCC cohort and 98.9% in the mBCC cohort).

A summary of exposure to treatment in STEVIE is provided in Table 42.

Table 42: Exposure to treatment in STEVIE

	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Median duration of treatment, days (range)	256.0 (1 to 1341)	319.0 (2 to 1147)	263.0 (1 to 1341)
Dose intensity Median % (range)	97.59 (38.4 to 100.0)	98.92 (72.3 to 100.0)	97.74 (38.4 to 100.0)
Median total number of 150 mg capsules taken, n (range)	243.0 (1 to 1284)	298.0 (2 to 993)	244.0 (1 to 1284)

Treatment discontinuation

As of the data cut-off date of 16 March 2015, almost 90% of patients had discontinued treatment. The most frequent reasons for treatment discontinuation were adverse event (28.7%), other (23.3%; see table footnote) and progressive disease (15.6%). A greater proportion of patients in the mBCC cohort (38.5%) discontinued treatment because of disease progression, compared with patients in the laBCC cohort (13.6%). A summary of treatment discontinuations is provided in Table 43.

Table 43: Reasons for discontinuation from treatment in STEVIE (safety population)

Patients, n (%)	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Discontinued treatment	988 (88.3)	80 (83.3)	1068 (87.9)
Adverse event	340 (30.4[a]	9 (9.4)[a]	349 (28.7)[a]
Death	32 (2.9)	5 (5.2)	37 (3.0)
Lost to follow-up	19 (1.7)	2 (2.1)	21 (1.7)
Other	269 (24.0)	14 (14.6)	283 (23.3)
Physician decision	72 (6.4)	4 (4.2)	76 (6.3)
Progressive disease	152 (13.6)	37 (38.5)	189 (15.6)
Patient decision[b]	104 (9.3)	9 (9.4)	113 (9.3)

[a] The number of discontinuations from treatment due to AE is lower from that reported in Section 5.8 of the CSR (i.e., 31.3%) because this summary only shows the primary reason for treatment discontinuation. Therefore, a patient could have an AE leading to withdrawal of treatment, but the AE may not have been recorded as the primary reason for withdrawal; such AEs are not included in this summary.

[b] Only includes patients who have requested withdrawal from the study overall. Patients who requested withdrawal from treatment but who entered follow-up are included in the "other" category (n = 124).

Muscle spasm (103)

Of the 1215 treated patients with advanced BCC in the STEVIE study, 66.4% reported muscle spasm and 7% withdrew from the study treatment because of this AE. An exploratory analysis of the STEVIE study assessed baseline factors that might affect muscle spasm development and the effects of treatment interruption on muscle spasm in vismodegib-treated patients.

Sixteen clinicopathologic baseline prognostic factors were selected, and their influence on muscle spasm development was assessed by logistic regression using univariate and multivariate analyses.

Table 44: Clinicopathologic Prognostic Factors for muscle spasm in STEVIE (103)

Demographic factors	Age Sex
Physical findings at baseline	BMI: grouped according to WHO guidelines ECOG PS
Tumour-related factors	Type of BCC (la BCC, mBCC) Gorlin syndrome
Biochemical and metabolic factors at baseline	Hyponatraemia Hypokalaemia Hypercreatinaemia Hyperbilirubinaemia Anaemia
Medical history at baseline	Diabetes Hypothyroidism
Concomitant medications at baseline	Statins Fibrates Diuretics

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; WHO, World Health Organization

In the univariate analysis, obese body mass index (BMI) category and Gorlin syndrome were potentially associated with increased odds of muscle spasm; baseline patient age ≥70 years, ECOG PS ≥1, grade ≥1 hyponatraemia, grade ≥1 anaemia, and diuretic use were all potentially associated with decreased odds of muscle spasm.

In the multivariate analysis, three parameters were found to be associated with development of muscle spasm:

- Patients ≥70 years had lower odds of muscle spasm than those <50 years,

- Patients with ECOG PS grade ≥2 had lower odds of muscle spasm than those with ECOG PS grade 0,

- Patients with BMI in the obese category had higher odds of muscle spasm than those with BMI in the normal range.

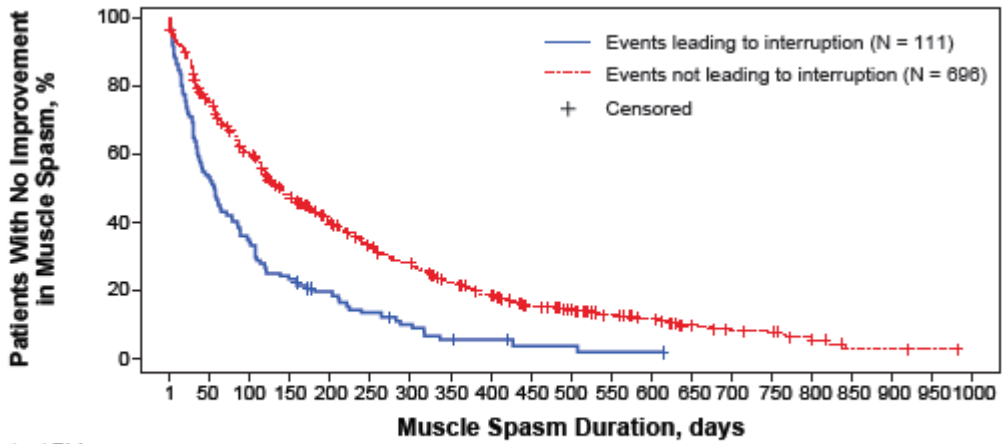
In this exploratory analysis, the largest decrease in odds of muscle spasm while receiving vismodegib treatment was for older patients (≥70 years) and those with ECOG PS ≥2. The largest increase in odds occurred in patients with increased BMI.

Another analysis explored the effect of vismodegib treatment interruption (because of muscle spasm) on time from onset of the patient's most severe muscle spasm* to date of reduction in severity. Patients whose most severe muscle spasm led to treatment interruption were compared with those whose most severe muscle spasm did not lead to treatment interruption.

Patients whose most severe muscle spasm led to interruption of vismodegib treatment had a shorter median duration of most severe muscle spasm (56 days [95% CI, 37 to 78]) than patients whose most severe muscle spasm did not lead to treatment interruption (139 days [95% CI, 120 to 158]): Figure 26.

* per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] grade

Figure 26: Kaplan-Meier plot of time from worst TEAE of muscle spasm to any improvement or resolution, by treatment interruption status, in STEVIE (103)



No. of Patients at Risk																			
Events leading to interruption	111	59	38	26	19	13	9	5	4	2	2	1	1						
Events without interruption	696	516	403	308	251	198	166	126	100	72	60	45	35	23	16	13	7	2	2	1

Investigators text for AEs encoded using MedDRA version 18.0; time to improvement is defined as the interval between the start date for the worst TEAE and the end date (if resolved) or the start date of next decreased grade, or last visit date if neither was available; patients without an AE end date were censored at the end of last visit.

Adverse events of special interest(39)

The selected AEs of irregular menses/amenorrhoea, second primary malignancies (SPMs), skin squamous cell carcinoma (SCC), sudden death, keratitis, fractures, and venous thromboembolic events (VTEs) were identified as potential risks associated with vismodegib treatment, and were specifically analysed in STEVIE as additional pharmacovigilance per the Risk Management Plan.

Irregular menses or amenorrhoea: In this study, at baseline, 64 female patients had menses. These included 62 females of childbearing potential and 2 females with no childbearing potential due to medical reasons including bilateral oophorectomy and bilateral tubal ligation. Of the 64 patients who had menses at baseline, 18 experienced 26 events of irregular menses/amenorrhea, including one patient with an AE reported as intermittent menses but coded erroneously under the PT term “metrorrhagia”. Because of the limited information available on these patients (prior and current menstrual history, follicle-stimulating hormone [FSH] level), internal medical review by a clinical expert was unable to determine the causality (ovarian vs. pituitary/hypothalamus) of the 26 events.

Second primary malignancies (SPMs): The incidence of SPM excluding squamous cell carcinoma (SCC) was 2.6%. A total of 37 events of SPM occurred in 31 patients. There was

no discernable pattern in the type of SPMs reported on study. Two events of SPM were assessed as related to vismodegib by the investigator.

Skin squamous cell carcinoma (skin SCC): 60 TEAEs of skin SCC were reported in 51 patients with advanced BCC (4.2%). A medical review of patients with skin SCC indicates that the majority were older than 75 years with lesions located in sun-exposed areas. In addition, 18/51 patients with SCC had a history of skin SCC, 3/51 patients had a history of Bowen's disease, and 2/51 patients had history of actinic keratosis (a premalignant neoplasia for SCC). A total of 35 patients had events that recovered/resolved; 4 patients had events that recovered/resolved with sequelae; and 12 patients had events that were not resolved. Sixteen patients had SCC of the skin events that were Grade 3 in severity, one patient had a Grade 4 event, and three patients had Grade 5 (fatal) events. All three events of Grade 5 SCC had concurrent medical histories or other confounding factors and were considered unrelated to vismodegib by the investigator.

Sudden death: there were 2 reported cases using the PT term "sudden death (0.2% patients). Neither case was considered related to study drug by the investigator.

Keratitis / ulcerative keratitis: 10 TEAEs of keratitis/ulcerative keratitis had been reported in 10 patients (0.8%). All patients with keratitis had Grade 1 or 2 events except for 2 patients with Grade 3 AEs; none of the events was reported as serious. Seven of the 10 patients with keratitis had events that resolved; 1 patient had an event that resolved with sequelae; and 2 patients had events that were not resolved. Investigator assessment considered 7 events of keratitis to be unrelated to study drug and 3 events to be related. Medical review by the Sponsor of all cases of keratitis indicated that corneal-related AEs were associated with pre-existing BCC tumours involving the orbit or adjacent anatomical structures and appeared to be related either to mechanical abnormalities due to an existing tumour or to tumour-related surgical procedures.

Fracture: 36 patients (3.0%) had reported 39 TEAEs of fracture. 23 of the 36 patients with fractures were females, and 26/36 were older than age 50, when the risk of age-related fractures increases. 29 of the 36 patients had medical history that confounded the assessment and attribution of the TEAEs to vismodegib treatment. A relevant medical history associated with the development of fractures could include, for example, osteoporosis, cerebrovascular disease, alzheimer's/dementia, or alcohol abuse.

Venous thromboembolic events: 10 patients (0.8%) reported 12 TEAEs of VTE, which included deep vein thrombosis (n = 4), thrombosis (n = 2), venous thrombosis (n = 1), and

pulmonary embolism (n = 3). Seven events were assessed as serious, and the remaining were non-serious. Four patients had Grade 3 AEs, two patients had Grade 4 AEs, and one patient had a Grade 5 (fatal) AE. Of the VTEs, five patients had events that resolved, two patients had events that resolved with sequelae, and three patients had events that were ongoing at the data cutoff date. Investigator assessment considered two of the 12 events (one event of Grade 4 pulmonary embolism and one event of Grade 5 [fatal] pulmonary embolism) to be related to study treatment. All (except one) patients with TEAEs of VTE had medical history or risk factors that confounded the assessment and attribution of the events to vismodegib.

Concomitant medications

The majority of treated patients (1121; 92.3%) reported the use of at least one concomitant medication while on study. The most common classes of concomitant medications were vitamins and minerals (33.2%), analgesics (27.8%), proton-pump Inhibitors (25.7%), and beta-adrenoceptor blocking agents (23.2%).

Phase I SHH3925g(99)

Summary of adverse events in patients with aBCC

All patients with aBCC in this study experienced an adverse event. Adverse events experienced by > 25% of study patients with BCC included muscle spasms (85%), dysgeusia (64%), alopecia (64%), fatigue (49%), diarrhoea (39%), weight decreased (36%), nausea (33%), decreased appetite (30%), and cough (27%).

A summary is provided in Table 45.

Table 45: Summary of adverse events for patients with aBCC in Phase I SHH3925g

Event, n (%)	Vismodegib 150 mg (n=17)	Vismodegib 270 mg (n=15)	Vismodegib 540 mg (n=1)	Total (n=33)
All adverse events	17 (100)	15 (100)	1 (100)	33 (100)
Grade 3 to 4 adverse events	6 (35.3)	7 (46.7)	0	13 (39)
Grade 5 adverse events	0	0	1 (100)	1 (3)
Serious adverse events	3 (17.6)	4 (26.7)	1 (100)	8 (24)
Adverse events leading to discontinuation	1 (5.9)	0	0	1 (3)

Four patients with aBCC experienced Grade 4 events: one experienced Grade 4 hyponatraemia, one experienced Grade 4 pre-syncope, and one experienced Grade 4 pancreatic adenocarcinoma. The fourth patient with BCC experienced both Grade 4 paranoia and Grade 4 hyperglycaemia. One patient withdrew from the study because of adverse events.

In the patients with aBCC in this trial, eight grade 3 adverse events that were deemed to be possibly related to the study drug were reported in six patients, including four with fatigue, two with hyponatraemia, one with muscle spasm, and one with atrial fibrillation. One grade 4 event, asymptomatic hyponatraemia, was judged to be unrelated to vismodegib.

Serious adverse events

Eight (24.2%) patients with BCC experienced 11 serious adverse events including (in 1 patient each): atrial fibrillation, duodenal ulcer, impaired gastric emptying, pneumonia, hyponatraemia, adenocarcinoma pancreas, basal cell carcinoma (disease progression), presyncope, paranoia, dyspnoea, and haemorrhage.

Three SAEs in 3 patients were reported by investigators to be related to study drug.

- One patient (150 mg group) experienced a serious Grade 3 atrial fibrillation,
- One patient (270 mg group) experienced serious Grade 4 paranoia thought to be related to study drug,
- One patient with metastatic BCC (new formulation cohort 150 mg) was newly diagnosed with a Grade 4 resectable pancreatic adenocarcinoma (patient had a prior history of testicular cancer, papillary thyroid carcinoma, and mucoepidermoid carcinoma). The patient was taken off study for the management of pancreatic cancer.

Deaths

One patient with aBCC experienced grade 5 (fatal) adverse events of pneumonia and disease progression; these were not thought to be treatment-related.

Extent of treatment exposure

Table 46: Extent of exposure to study drug in patients with aBCC in Phase I SHH3925g

	Patients with aBCC n=33
Total cumulative dose, g Mean (SD) Median (range)	 64.2 (42.5) 52.9 (5 to 204)
Days on study Mean (SD) Median (range)	 320.1 (170.6) 314.0 (36 to 810)
Number of non-missing doses Mean (SD) Median (range)	 326.9 (168.8) 320 (32 to 805)

Treatment discontinuation

Over half of the patients with BCC discontinued the study; the main reasons were progression of disease (clinical or radiographic). One patient discontinued treatment due to an adverse event: impaired gastric emptying. A summary of reasons for discontinuation are provided in Table 47.

Table 47: Patient disposition in Phase I SHH3925g

Disposition	Patients with aBCC n=33
Study completion	12 (36.4)
Study discontinuation Adverse event Disease progression (clinical) Disease progression (radiographic) Physician's decision Patient's decision	21 (63.6) 1 (3.0) 8 (24.2) 10 (30.3) 1 (3.0) 1 (3.0)

Concomitant medications

All patients with aBCC treated in the study reported the use of at least one concomitant medication during the study. The most common classes of concomitant medications (i.e. those used in ≥20% patients) were: angiotensin-converting enzyme (ACE) inhibitors, (24.2%), antacids (30.3%), anti-anaemic agents (24.2%), antianxiety agents (36.4%), anticonvulsants (29.3%), antidepressants (24.2%), anti-rheumatic and anti-inflammatory agents (45.5%), calcium regulators and replenishers (21.2%), cephalosporins (24.2%), dermatologic agents (24.2%), fluoroquinolines (24.2%), herbal / homeopathic and dietary

supplements (42.4%), laxatives (24.2%), local anaesthetics (30.3%), macrolides (33.3%), mild analgesics (66.7%), antimicrobials (36.4%), muscle relaxants (30.3%), proton pump inhibitors (42.4%), steroids (27.3%), strong analgesics (48.5%), supplements (36.4%).

RegiSONIC

In this on-going, multicentre, prospective observational study the most common adverse events (AEs) observed with vismodegib treatment were ageusia/dysgeusia, muscle spasms, alopecia, weight loss, and fatigue.

Cohort 1

Adverse events taken from the latest data cut (11 September 2015) are provided for 101 patients with laBCC receiving vismodegib in cohort 1.(31)

Table 48: Summary adverse events (as of 11 September 2015) reported in cohort 1 of RegiSONIC(31, 86)(31, 86)(31, 86)(31, 86) (31, 85)

	Patients with newly-diagnosed laBCC treated with vismo (n=101)
Any AE, n (%)	**88.1**
Ageusia/dysgeusia	59.4
Muscle spasms	56.4
Alopecia	47.5
Weight loss	20.8
SCC	11.9
Fatigue	8.9
Arthralgia	5.0
Nausea	5.0

Abbreviations: AE, adverse event; SCC, squamous cell carcinoma; vismo, vismodegib

In vismodegib-treated patients in cohort 1,SAEs were reported in 17.8% of patients. AEs leading to treatment discontinuation were reported in 17.8% of patients.(31)

All vismodegib-treated patients

A summary of adverse events taken from the latest data cut (11 September 2015) is provided for all patients receiving vismodegib across the three cohorts.(30)

Table 49: Summary of adverse events in all vismodegib-treated patients (as of 11 September 2015) of RegiSONIC(30)

	Patients with laBCC (all cohorts) treated with vismodegib n=109
Any protocol-specified AE/SAE while on study, %	88
Any SAE on study, %	18
Any vismodegib-related AE on study, (%)	82
Total number of vismodegib-related AEs, events	301
Action taken for vismodegib-related AEs/SAEs, % Permanent vismodegib discontinuation Vismodegib temporarily held Vismodegib dosing alteration	 19 27 9
Time between start of vismodegib and earliest vismodegib-related AE/SAE, median (IQR), days	36 (22-67)

Abbreviations: AE, adverse even; IQR, interquartile range; SAE, serious adverse event

AE management strategies for AEs such as muscle spasm, ageusia/dysgeusia and alopecia included vismodegib interruption or discontinuation. (30)

A total of 76 muscle spasm events were reported in 58 patients (53%). (Patients may have had multiple events, and may have had multiple treatments for an event.) For 28% of events, vismodegib treatment was stopped or withheld; for 59% of events no treatment of AE was indicated. The median time between start of vismodegib treatment and the earliest vismodegib-related muscle spasm was 36 days (interquartile range 23 to 64).(30)

EAS(32)

Mean follow-up for safety in this open-label, multicentre study was 6.5 months, with muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhoea (25.2%) as the most common adverse events.

A summary of adverse events is presented in Table 50.

Table 50: Treatment-Emergent Adverse Events by NCI CTCAE Grade in EAS (Incidence Rates ≥ 5%)(100)

Event, n (%)	All Subjects (N = 119)	NCI CTCAE Grade				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dysgeusia	84 (70.6)	68 (57.1)	16 (13.4)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasms	84 (70.6)	63 (52.9)	19 (16.0)	2 (1.7)	0 (0.0)	0 (0.0)
Alopecia	69 (58.0)	57 (47.9)	12 (10.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	30 (25.2)	23 (19.3)	5 (4.2)	1 (0.8)	1 (0.8)	0 (0.0)
Fatigue	23 (19.3)	14 (11.8)	8 (6.7)	1 (0.8)	0 (0.0)	0 (0.0)
Nausea	23 (19.3)	19 (16.0)	4 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	19 (16.0)	12 (10.1)	7 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	16 (13.4)	12 (10.1)	4 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	14 (11.8)	11 (9.2)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	13 (10.9)	10 (8.4)	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)
Vomiting	13 (10.9)	12 (10.1)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	11 (9.2)	10 (8.4)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	10 (8.4)	5 (4.2)	5 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	10 (8.4)	8 (6.7)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	10 (8.4)	5 (4.2)	3 (2.5)	2 (1.7)	0 (0.0)	0 (0.0)
Acne	10 (8.4)	10 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	8 (6.7)	8 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry mouth	8 (6.7)	8 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	8 (6.7)	3 (2.5)	4 (3.4)	1 (0.8)	0 (0.0)	0 (0.0)
Dry Skin	8 (6.7)	8 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	7 (5.9)	5 (4.2)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	7 (5.9)	1 (0.8)	6 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma [a]	7 (5.9)	1 (0.8)	3 (2.5)	1 (0.8)	2 (1.7)	0 (0.0)
Dyspepsia	6 (5.0)	6 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	6 (5.0)	3 (2.5)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)

Urinary tract infection	6 (5.0)	1 (0.8)	4 (3.4)	1 (0.8)	0 (0.0)	0 (0.0)
Pain in extremity	6 (5.0)	3 (2.5)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Includes all adverse events occurring on or after the first treatment until 30 days after the last oral administration of vismodegib.
Multiple occurrences of a specific adverse event for a subject were counted once at the highest NCI CTCAE grade of these occurrences.
Percentages are based on N . Incidence rate of ≥ 5% is based on all safety evaluable patients.
[a] AE term includes "Squamous cell carcinoma of the skin".

Grade ≥ 3 AEs and SAEs

The overall rates of AEs and SAEs in the locally advanced and metastatic disease cohorts were similar.

A summary of grade 3+ AEs and SAEs is provided in Table 51 and Table 52.

Table 51: Summary of Adverse Events by Grade in EAS

	laBCC (n=62)	mBCC (n=57)	All subjects (N=119)
Any adverse event, n (%)	61 (98.4)	55 (96.5)	116 (97.5)
Grade 3 adverse event Grade 4 adverse event Grade 5 adverse event	11 (17.7) 6 (9.7) 1 (1.6)	13 (22.8) 3 (5.3) 1 (1.8)	24 (20.2) 9 (7.6) 2 (1.7)
SAEs, n (%)	9 (14.5)	9 (15.8)	18 (15.1)
Grade 3 SAE Grade 4 SAE Grade 5 SAE	6 (9.7) 4 (6.5) 1 (1.6)	6 (10.5) 2 (3.5) 1 (1.8)	12 (10.1) 6 (5.0) 2 (1.7)

Table 52: Summary of SAEs in EAS

NCI CTCAE Grade			
Grade 2	Grade 3	Grade 4	Grade 5
Deep vein thrombosis Dyspnea	Syncope Spinal compression fracture Gastric ulcer Hypercalcaemia Small intestinal obstruction Anaemia Osteomyelitis Pneumonia Ankle fracture Muscle spasms[a] Pancreatitis Sinusitis and epistaxis	Embolism Squamous cell carcinoma Hypercalcemia B-cell lymphoma Wound infection bacterial Ruptured cerebral aneurysm	Wound complication Clostridial infection

Events occurred in one patient each. Multiple occurrences of a specific adverse event for a subject were counted once at the highest NCI CTCAE grade of these occurrences.
[a] Judged by the investigator to be possibly related to vismodegib administration

Deaths

Three patients died on study:

- A 93-year-old male in the locally advanced cohort who died from worsening chronic complications of gunshot wounds on the same date as his last dose of vismodegib
- An 86-year-old male in the metastatic cohort who died due to Clostridium difficile infection 9 days after his last dose of vismodegib
- A 56-year-old male in the metastatic cohort who died due to mBCC disease progression on the same date as his last dose of vismodegib

Extent of exposure to study drug

The relatively short exposure time was attributable to the timeframe when patients were enroled and approval of vismodegib by the US FDA, at which time patients were switched to commercial product and the trial ended. The mean dose intensity (± SD), i.e., the total dose actually received divided by the total dose that should have been taken on study, was approximately 96%, indicating that patients, on average, took nearly all prescribed vismodegib capsules per treatment cycle.

A summary of exposure to treatment in EAS is provided in Table 53.

Table 53: Exposure to treatment in EAS

	Locally Advanced (n=62)	Metastatic (n=57)	All Subjects (N=119)
Median duration of treatment (range) Mean duration of treatment (SD)	5.6 (1.1 to 19.6) 7.2 (4.6)	5.4 (0.4 to 19.3) 6.6 (4.7)	5.5 (0.4 to 19.6) 6.9 (4.6)
Dose intensity Mean (SD) Median % (range)	 94.9 (9.6) 98.2 (55 to 110)	 96.6 (6.6) 98.8 (65 to 117)	 95.7 (8.3) 98.2 (55 to 117)
Median total number of 150 mg capsules taken, n (range)	164.5 (32 to 553)	162.0 (13 to 585)	162.0 (13 to 585)

Treatment discontinuation

All 120 patients enroled in the EAS discontinued from the trial. The most common reason for discontinuation was Sponsor decision (n=79 [65.8%]), which reflected the decision to switch patients to commercial drug after US FDA approval of vismodegib. The three next most common reasons for discontinuation included disease progression (n=16 [13.3%]); subject decision (n=7 [5.8%]); and lost to follow-up (n=6 [5.0%]). Five patients (4.2%) withdrew because of AEs. A summary of reasons for discontinuation is provided in Table 54.

Table 54: Reasons for study discontinuation in EAS

	laBCC (n=62)	mBCC (n=58)	All Subjects (N=120)
Safety evaluable	62 (100.0)	57 (98.3)	119 (99.2)
Discontinued study	62 (100)	58 (100)	120 (100)
Disease progression	6 (9.7)	10 (17.2)	16 (13.3)
Adverse event	4 (6.5)	1 (1.7)	5 (4.2)
Death	1 (1.6)	2 (3.4)	3 (2.5)
Lost to follow-up	2 (3.2)	4 (6.9)	6 (5.0)
Physician decision	1 (1.6)	1 (1.7)	2 (1.7)
Subject decision	4 (6.5)	3 (5.2)	7 (5.8)
Sponsor decision	44 (71.0)	35 (60.3)	79 (65.8)
Other	0 (0.0)	2 (3.4)	2 (1.7)
Not safety evaluable	0 (0.0)	1 (1.7)	1 (0.8)

Concomitant medications

Concomitant medications initiated on or after the first day of study drug administration in ≥ 10% of the safety population were: analgesics (25.2%), vitamins and minerals (21.8%), supplements (19.3%), laxatives and stool softeners (16.8%), quinolone antibiotics 11.8%), calcium compounds and regulators (10.9%).

Adverse events of special interest

Squamous Cell Carcinoma: Seven patients (5.9%) in this study, all in the locally advanced BCC cohort, developed treatment-emergent squamous cell carcinoma:

- Following a diagnosis of inoperable locally advanced BCC of the skin and neck at baseline, worsening SCC, right nasal cavity (Grade 4, Non-Serious, Unrelated) was reported on Day 24. Patient discontinued vismodegib due to SCC and died from SCC 39 days after the last dose

- Invasive SCC of the scalp (Grade 3, Non-Serious, Unrelated). Reported on Day 175 and continued until Day 203. On Day 204, the event was upgraded to worsening of invasive SCC (Grade 4, Serious [Life-Threatening], Unrelated) and the vismodegib dose was held. The event was ongoing at the time the patient was lost to follow-up (Day 206). The patient was re-enroled approximately 5 months later without consulting the medical monitor and was inadvertently assigned a new patient number, at which point no additional data on the SCC were reported

- SCC, right leg (Grade 2, Non-Serious, Unrelated). Reported on Day 198 and resolved on Day 225. A second SCC on the right forehead (Grade 2, Non-Serious, Unrelated) was reported on Day 227 and was ongoing at the time of study discontinuation

- SCC, bilateral upper extremity (Grade 2, Non-Serious, Unrelated). Reported on Day 141. Ongoing at the time of study discontinuation

- Worsening of SCC of the face (Grade 1, Non-Serious, Unrelated). Reported on Day 170 and resolved on Day 268.

- SCC, triceps and left cheek (Grade 2, Non-Serious, Unrelated). Reported on Day 202. Ongoing at the time of study discontinuation

- SCC, left forehead (Grade 3, Non-Serious, Unrelated). Reported on Day 62. Ongoing at the time of study discontinuation.

Amenorrhoea / Irregular menstruation: Among eight women of childbearing potential in the trial, four in the locally advanced cohort developed amenorrhea or irregular menstruation:

- A 38-year-old subject with Gorlin syndrome reported amenorrhoea (Grade 1; non-serious) on Day 75, which continued until Day 187. Upgraded to Grade 2 amenorrhoea (non-serious) on Day 187 and continued until Day 243. Upgraded to

Grade 3 amenorrhoea (non-serious) on Day 244 and was ongoing at the time of study discontinuation. The investigator assessed the Grade 1 and Grade 3 amenorrhoea events as related to vismodegib. The investigator assessed the Grade 2 amenorrhoea as unrelated to vismodegib; no other suspected cause(s) of the event was noted. There was no vismodegib dose interruption for the AE amenorrhoea

- A 33-year-old subject with Gorlin syndrome reported amenorrhoea (Grade 2, Non-Serious) on Day 60. On-going at the time of study discontinuation. The investigator assessed the event as related to vismodegib. There was no vismodegib dose interruption for the AE amenorrhoea

- A 48-year-old subject with locally advanced BCC reported irregular menstruation (Grade 1; Non-Serious) on Day 77. On-going at the time of study discontinuation. The investigator assessed the event as related to vismodegib therapy. There was no vismodegib dose interruption for the AE irregular menstruation.

- A 48-year-old subject with locally advanced BCC reported irregular menstruation (Grade 1; Non-Serious) on Day 61. On-going at the time of study discontinuation. The investigator assessed the event as related to vismodegib therapy. There was no vismodegib dose interruption for the AE irregular menstruation

4.12.3 Additional adverse reactions

Studies identified in the SLR

The clinical systematic review identified 12 studies meeting the pre-specified eligibility criteria, of which five have been presented in full in section 4.11.The remaining seven studies were not extracted in full – reasons for not extracting these studies is provided in Appendix 8. In all seven studies, AEs were consistent with those reported in the larger studies. Common AEs reported in at least 20% of patients in at least one study included muscle spasms, alopecia, dysgeusia, muscle cramps, weight loss, decreased appetite, fatigue and gastrointestinal disturbance.

Report of cutaneous squamous cell carcinoma (cSCC)

We are aware of an article published in JAMA Dermatology in 2015 by Mohan et al. (104) This was excluded at the full text review stage of the Systematic Literature Review, since the authors had classed their study as a case control series. Upon reading the article and the associated responses by Gjersvik (105) and Puig et al (106), the study is determined to be a retrospective cohort study (one cohort of patients exposed to vismodegib; another cohort not exposed to vismodegib) which were followed longitudinally.

The authors purported to have identified an increased risk of cutaneous squamous cell carcinoma (cSCC) in patients with aBCC who had been treated with vismodegib.

However, in addition to the discrepancy regarding the classification of this study, there are several questions/limitations to the reported conclusions to this study. First, patients in the vismodegib-exposed cohort were only required to have at least 7 days' exposure to vismodegib. Secondly, non-BCC malignancies reported in the study as associated to vismodegib were defined from a minimum of 2 weeks after the first exposure to vismodegib. Furthermore, differences in follow-up periods for the two cohorts and latency period (for development of non-BCC malignancy after BCC malignancy) were not adequately addressed.

Thus, we conclude that this report is does not present a valid description of increased risk of cSCC following exposure to vismodegib.

4.12.4 Overview of the safety of the technology in relation to the decision problem.

ERIVANCE

Viewed in totality, these long-term safety follow-up data continue to suggest that vismodegib has an acceptable safety profile for patients with advanced BCC. Overall, the safety profile of vismodegib is characterised predominantly by commonly occurring adverse events of muscle spasms, dysgeusia, alopecia, fatigue, and weight loss; these were largely Grade 1 or 2 in severity.(43)

STEVIE

Safety results from STEVIE as of the 16 March 2015 data cut-off date indicate that the safety profile of vismodegib was generally consistent with that seen in other studies of vismodegib in patients with advanced BCC.

Phase I SHH3925g

An acceptable safety profile was determined in this Phase I study: no dose-limiting toxicities (DLTs) observed. The most frequently reported adverse events were muscle spasms, dysgeusia, alopecia, fatigue, diarrhoea, weight decreased, nausea, decreased appetite and cough. Ten (of 33) patients had 13 Grade 3 or 4 events. Eight patients experienced 11 serious adverse events. One patient with aBCC experienced grade 5 (fatal) adverse events of pneumonia and disease progression; these were not thought to be treatment-related.

RegiSONIC

The RegiSONIC study is still on-going. Preliminary data showed that the most common AEs leading to treatment discontinuation were muscle spasms, alopecia, and ageusia/dysgeusia (consistent with the results of previous studies). Common AE management strategies included vismodegib interruption or discontinuation

EAS

Safety findings for vismodegib 150 mg once daily in patients with locally advanced BCC or mBCC were similar in this expanded access trial to those reported in the pivotal study in patients with advanced BCC. Common AEs associated with vismodegib treatment were predominantly mild to moderate. Among women of childbearing potential (n=8), four patients experienced treatment-related amenorrhoea.

Muscle spasm and treatment breaks

The most common adverse events associated with vismodegib are muscle spasm, alopecia, dysgeusia and decreased weight and appetite.

Severity of muscle spasm is in vismodegib-treated patients is typically grade 1-2. Muscle spasm usually resolves ≤6 weeks after end of treatment, it can lead to decreased quality of life (QoL) and to treatment discontinuation.(33)

Treatment breaks throughout a longer period of treatment exposure aid tolerability of adverse events: median duration of treatment with vismodegib increases with more frequent treatment breaks, without apparent loss in efficacy.[*](30, 35)

Pregnancy

Vismodegib has an identified risk of embryo-foetal death and severe birth defects, which is based on the known role of Hh signaling in embryogenesis and foetal development. Therefore, patient pregnancy status should be verified prior, during and after treatment with vismodegib. No pregnancies were reported in the five trials presented in this submission. Due to the teratogenic nature of vismodegib, the Medicines and Healthcare products Regulatory Agency (MHRA) approved the Erivedge®▼ Pregnancy Prevention Programme in the UK which has additional steps to that of the EU-approved Risk Management Plan. To date, there has been one reported pregnancy in a UK patient taking vismodegib; however

[*] As stated in the licence, treatment interruptions of up to 4 weeks were allowed in clinical trials based on individual tolerability.34. (EMC) EMC. Erivedge 150 mg hard capsules SPC 2016 [cited 2017 10th January]. Available from: http://www.medicines.org.uk/emc/medicine/28107.

the credibility of this case cannot be confirmed as it was reported during market research and no follow-up was available – the case was reported to have involved a pregnant woman being treated with vismodegib ceasing treatment due to undisclosed adverse events – a healthy baby was reported to have been delivered with no adverse outcome. There have been no reports of pregnancy in female partners exposed to vismodegib by male patients [MHRA Erivedge PPP annual report 2016].

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Principal (interim) findings from the clinical evidence

ERIVANCE

This is the first time any therapy has demonstrated a clinically meaningful benefit in a clinical trial in this population with a high unmet medical need, as measured by substantial and durable tumour responses. The median OS of 33.4 months in the metastatic BCC cohort suggest that vismodegib treatment may improve OS as compared with alternative approaches in the literature. The frequency, magnitude, and duration of objective responses observed in ERIVANCE, in addition to a manageable adverse event profile, suggest that vismodegib demonstrates a positive benefit−risk profile and offers a significant clinical benefit for this patient population.

STEVIE

Efficacy results in the laBCC and mBCC populations were similar to those already evident in previous reports from other vismodegib studies in the same population. For OS, the number of events was too low to estimate a stable median survival. Among patients with mBCC, treatment with vismodegib demonstrated consistent benefit in terms of BORR and time-related parameters (TTR, DOR, and PFS) compared with previous reported results. A clinically meaningful improvement in the score representing emotional well-being related to their skin condition (as measured by Items 5 to 11 from the self-completed Skindex-16) was observed among patients with laBCC after Cycle 1 and was maintained throughout the study. Similarly, a meaningful improvement in individual symptoms was observed in mBCC patients who were symptomatic at baseline; however, this benefit was not consistently maintained at consecutive timepoints.

Phase I SHH3925g

Vismodegib was generally well tolerated in this Phase I trial, with an acceptable safety profile. Clinical activity was observed only in aBCC (18 of 33 patients had a response). The

results from the full cohort of this Phase I trial suggested that vismodegib merited further study in aBCC.

RegiSONIC (31)

The RegiSONIC study, which represents the largest planned prospective observational study of patients with aBCC, is still on-going. Preliminary data from the RegiSONIC study demonstrate effectiveness of vismodegib in patients newly diagnosed with non-BCCNS laBCC, with a response rate of 87.1%. Future data-cuts and analyses are expected to provide real-world data that will inform the medical community and potentially improve the treatment of patients with aBCC.

EAS

Targeted inhibition of Hedgehog signaling with vismodegib demonstrated substantial clinical effect in patients with locally advanced BCC and mBCC without satisfactory treatment options. Efficacy outcomes were observed despite the limitations of the study: the study was halted when the US FDA granted Marketing Authorisation to vismodegib (as per study design in this expanded access program), CT/MRIs were performed every 8 to 16 weeks apart, and physical examinations were performed every 4 to 8 weeks.

Overall findings from the clinical evidence

Clinical trial results demonstrate a clear benefit for treatment of vismodegib in patients with advanced BCC.

Overall response rates of 56.3% (ERIVANCE (44)) and 66.2% (STEVIE (28), both combined laBCC and mBCC cases) demonstrate that the majority of patients receive a benefit from treatment with vismodegib, based on complete or partial response. Case studies included in the photo appendix (Appendix 16), with pre- and post-treatment images demonstrate the impact that these responses have on patients - even some of those patients considered to have progressive disease, due to the appearance of new lesions, have demonstrated visually impactful benefits to the target lesion.

BCC may sometimes be known as rodent ulcer, due to the chronic, relentless ‘nibbling away’ progression of the tumour. The benefit of vismodegib may be extended to all patients not experiencing disease progression, i.e. including those with stable disease, as well as those with complete or partial response. Tumour or disease control is assumed from the combined number of complete or partial responses and stable disease, and has been estimated to be 92.9% in the ERIVANCE study.(107)

Treatment emergent adverse events (TEAEs) occurred in 98% of patients; over half (54%) were mild to moderate. The most common adverse events were muscle spasm, alopecia, dysgeusia and decreased weight and appetite. Adverse events were the main reason for treatment discontinuation in 28.7% of patients (30.4% in the laBCC cohort, and 9.4% in the mBCC cohort). Serious TEAEs occurred in 289 patients in the STEVIE study, and 46 patients died following adverse events. Seven of these were considered by the investigator to be related to study drug, but causality was confounded by comorbidities or risk factors.

Management strategies for the most common adverse events, such as (but not limited to) muscle spasms, included interruption (and/or discontinuation) of vismodegib.(30, 103)

As patients eligible for treatment with vismodegib for advanced BCC are inappropriate for surgery or radiotherapy, there is no alternative/existing therapy other than best supportive care.

Impact of treatment duration and treatment breaks

In the STEVIE trial, 97.9%, (769/788) patients who had received vismodegib for <12 months experienced treatment emergent adverse events (TEAEs) compared with 99.1% (423/427) patients who received >12 months treatment. To address the impact of longer exposure, rate of occurrence of TEAEs (number of events per 100 patient years) was calculated, comparing the rates of new TEAEs that occurred within the first 12 months and after 12 months of exposure:

- A total of 1060.5 events per 100 patient-years occurred during the first 12 months and 391.6 events per 100 patient-years occurred after the first 12 months(28)
- Grade ≥3 TEAEs also showed numerically higher rates per 100 patient-years in the first 12 months of treatment (93.6 events) than with exposure after 12 months of treatment (58.3 events)(28).

The licensed dose of vismodegib is 150 mg, once-daily until disease progression or unacceptable toxicity. The licence also makes reference to the treatment breaks that were permitted in the pivotal clinical trial.(37) The ERIVANCE clinical trial allowed dose interruption for up to 4 weeks to allow patients to recover from adverse events (44); this was increased to up to 8 weeks in the STEVIE protocol (28). An exploratory analysis of the STEVIE study investigated the impact of treatment breaks for patients with aBCC. The most common reasons for treatment breaks included intolerable toxicity (53%), AEs which did not meet the definition of intolerable toxicity (23%), patient decision (9%), and inability to swallow capsules (5%). The data, (although exploratory in nature, from a planned interim

analysis), showed that an increased number of treatment breaks was associated with longer median duration of vismodegib treatment. The data also showed that increased number of treatment breaks did not appear to compromise efficacy: though the number of patients in groups with more treatment breaks was small, the best overall response rate remained similar or improved with more treatment breaks. A summary of treatment duration and efficacy by treatment breaks in STEVIE is provided in Table 55. (35)

Table 55: Treatment duration and efficacy by number of treatment breaks in STEVIE(35)

Number of treatment breaks	0 (n=368)	1 (n=76)	2 (n=41)	≥3 (n=14)
Total population, %	74	15	8	3
Treatment duration, median (range), days[a]	223.5 (1–841)	299 (29–820)	399 (82–846)	454 (183–658)
Best overall response rate, n (%) [95% CI]	(n=358) 218 (61) [56 to 66]	(n=72) 47 (65) [53 to 76]	(n=39) 37 (95) [83 to 99]	(n=13) 11 (85) [55 to 98]

Anecdotally, we are aware that clinicians may be using intermittent dosing regimens to optimise patient outcomes.

Intermittent treatment regimens are of particular interest in patients with multiple BCCs (including those with Gorlin syndrome) where there is unmet need for long-term effective treatments. The MIKIE study (NCT01815840: a randomised, double-blind, regimen-controlled, phase II, multicentre study) was conducted to assess the efficacy and safety of two long-term intermittent dosing regimens (108); however, as the eligibility criteria for this study excluded patients with mBCC or inoperable laBCC, this study is outside the scope of this appraisal (see Appendix 6).

Physical and psychological impact of disfiguration from aBCC

The lesions and scarring associated with aBCC can be extremely disfiguring; in many cases, the head and neck are the anatomical areas most greatly affected, with facial structures including the eyes and nose commonly involved. As such, aBCC will almost certainly affect patients' psychological state and general quality of life (109).

- Surgical procedures that are particularly psychologically intrusive include orbital exenteration, and midface resection that extirpates the nose (110)

- Basal cell carcinoma is the most common periocular skin cancer and represents 90% of malignant eyelid tumours (111)

- Orbital invasion is reported in 2 to 4% of cases with an increased risk associated with large lesion size, recurrences, medial canthal location, perineural spread, aggressive histologic subtype and older patients (112)

- Around 40-50% of exenterations performed by ophthalmologists are for eyelid or periocular skin tumours (113) (114) (115)

- There is a growing body of evidence that orbital exenteration may be avoided by treatment with vismodegib of advanced BCCs in the periocular region (116) (117)

4.13.2 Strengths and limitations of the clinical evidence base

Internal validity of the studies included in the evidence base

The pivotal trial (ERIVANCE) and post-authorisation commitment safety study (STEVIE) for vismodegib were single-arm trials and hence inherently no internal validity can be proposed. For the design of the pivotal trial (44), a single-arm study with a response rate endpoint was deemed by investigators and experts in the field, as well as the US FDA, to be the most appropriate and feasible design in this rare aBCC population with unmet medical need. 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: both 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 response rate and durable response is a valid and direct measure of clinical benefit.(43)

The primary endpoint in ERIVANCE was objective response rate (ORR) as assessed by an independent review facility (IRF). For patients with mBCC, tumour response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST). For patients with laBCC, tumour response was evaluated based on visual assessment of external tumour and ulceration, tumour imaging (if appropriate) and tumour biopsy. Secondary endpoints included investigator-assessed ORR, duration of response, progression-free survival (PFS), overall survival (OS), and safety.

A randomised study was considered not feasible because no standard treatment options were identified for either laBCC or mBCC patients based on a literature review of the previous 30 years. Anecdotal therapeutic responses to chemotherapies have been noted in the literature as well as chemotherapy-related toxicities; however, practice guidelines

provided limited to no guidance or consensus on the management of aBCC. Furthermore, Roche received feedback from investigators and experts in the field that it would not be feasible to accrue patients to a randomised study: considering the significant anti-tumour activity observed in patients with aBCC in the Phase I study (SHH3925g) (13) and considering the substantial unmet medical need in aBCC. In addition, responses from a placebo or best supportive care arm were both (a) not expected and (b) could be addressed statistically with a significantly high response rate in the vismodegib arm. Lastly, there was concern that a randomised, cross-over design may inadvertently introduce bias into the results: if there was no immediate clinical benefit observed in the control arm, investigators may have been biased toward prematurely assessing disease progression; patients may have been biased towards withdrawing consent, before crossing over to vismodegib or enrolment into another clinical study. Such bias would impact the integrity of the study and interpretation of the true treatment effect of vismodegib. Therefore, the single-arm study with a response rate endpoint was determined to be the most appropriate trial design for vismodegib in aBCC.

External validity of the studies in the clinical evidence base

STEVIE and ERIVANCE were international studies with UK centres included; study results should therefore be applicable to routine clinical practice in England.

The pivotal trial of vismodegib (ERIVANCE) resulted in the licence for patients with laBCC that is inappropriate for surgery or radiotherapy, and symptomatic mBCC, thus endorsing the external validity of the trials. Interpretation and consideration of 'appropriateness' for surgery or radiotherapy may be variable depending on the clinical circumstances of the patient, and indeed therapeutic options available locally. In the ERIVANCE(44) and STEVIE studies, acceptable justification of inappropriateness for surgery for patients with laBCC was defined as:(39, 43)

- having at least one lesion ≥10 mm in the longest diameter that was considered inoperable, or for which surgery was considered inappropriate in the opinion of a Moh's dermatologic, head and neck or plastic surgeon,
- recurrence of BCC after two or more surgical procedures and an expectation that curative resection would be unlikely, or ,
- substantial morbidity or deformity would be anticipated from surgery.

In the group of patients with laBCC in ERIVANCE and STEVIE, prior radiotherapy to one or more target lesions was required, unless it was inappropriate or contraindicated.

The response endpoint in STEVIE was assessed by investigator, rather than independent review committee. In this respect, this would parallel response assessment by a clinician in practice.

The Phase I study, was a proof of concept study, with stage 1 of the study investigating vismodegib in a variety of solid tumours (n=33 with aBCC) at a range of doses. Three of the patients with aBCC were enroled in stage 1 of the study; each of the three received a different daily dose of vismodegib: 150 mg, 270 mg, or 540 mg. When clinical efficacy was demonstrated in the patients with aBCC, this cohort was expanded. The 30 other patients were enroled in stage 2; 16 received vismodegib at 150 mg per day, and 14 received 270 mg per day. Of the 33 patients, 8 (24%) were women. A total of 18 patients (55%) had metastatic disease, and 15 (45%) had locally advanced disease. The overall response rate among the 18 patients with metastatic tumours was 50% (95% CI, 29 to 71). The response rate in patients with locally advanced disease was 60% (95% CI, 33 to 83).(13)

The Expanded Access Study (EAS) sought to assess efficacy and safety of vismodegib in the US, prior to the commercial availability of the drug. A limitation of this study was the abbreviated follow-up (mean 6.5 months) resulting from study termination once FDA approval of vismodegib had been received and commercially available. Patients (N=119) received vismodegib for a median of 5.5 months; objective responses occurred in 46.4% of laBCC and 30.8% of patients with mBCC. There were several differences in response assessment between the Phase I and EAS studies. EAS used RECIST criteria for both cohorts and did not use independent review to assess the tumour responses to vismodegib. Secondly, a small number of patients (6 of 119) in this study had been exposed to an SMO inhibitor before enrolment, which was not the case in the Phase-II study.(32)

RegiSONIC is a prospective, observational, US disease registry designed to collect real-world data on the diagnosis and treatment of patients with advanced BCC (laBCC and mBCC) and/or Gorlin syndrome.(31) The relevance to typical patient care is complicit in this study as clinicians could choose treatment modality dependent on the patient's clinical situation; however, as only US centres were involved this may limit the validity of the results somewhat to the situation in the UK.

Lear *et al* (2) commented on the challenges of provision of a standardised definition for locally advanced tumours (particularly those that develop in facial sites that are difficult to treat, aggressively recurrent tumours, and large tumours that may have developed over a significant period of time before treatment was sought). In the manuscript, a UK-based group of multidisciplinary experts (including clinicians experienced in dermatology,

dermatologic surgery, plastic surgery and medical and clinical oncology) proposed the definition of advanced BCC being “basal cell carcinoma of American Joint Committee on Cancer (AJCC) stage II or above, in which current treatment modalities are considered potentially contraindicated by clinical or patient-driven factors.”

Disease factors guiding a diagnosis of aBCC include:

- tumour size: giant tumours, defined as those >5 cm in diameter;
- tumour location: particularly those in the high-risk ‘mask’ or H-zone area including the eyelids, nose, ear, chin, lips, mandible, temple, periorbital, periauricular and postauricular skin; also those with perineural or perivascular involvement are associated with increased risks of recurrence;
- the number of tumours: particularly including the genodermatosis Gorlin syndrome;
- tumour subtype: particularly the aggressive histological subtypes such as infiltrative or morphoeic tumours;
- likelihood of successful treatment: cure rates of recurrent BCC being lower than those for primary disease.

Patient factors that might influence whether or not the tumour is considered ‘advanced’ include:

- patient age and performance status: elderly or frail patients may not be suitable candidates for invasive surgery; radiotherapy is generally not considered to be appropriate for younger patients due to the long-term adverse events and worsening cosmetic results over time;
- effects of treatment on quality of life: consideration of the level of deformity resulting from surgery, particularly in lesions affecting the face; morbidity associated with radical surgery involving loss of structures (such as orbital exenteration) which is associated with significant post-surgical complications and may result in subsequent functional deterioration;
- patient opinions regarding treatment: patients with tumours that have been neglected may be averse to invasive treatment; poor experiences associated with previous treatment may discourage patients from seeking treatment;

- presence of genodermatoses;

- presence of co-morbidities (contraindicating surgery or radiotherapy; or a medical condition resulting in a pre-disposition to developing multiple BCCs e.g. immunosuppression therapy).

As listed in Appendix 6, there is a randomised, double-blind, placebo-controlled trial of vismodegib in patients with Gorlin syndrome, in which vismodegib was demonstrated to reduce BCC tumour burden in patients with Gorlin syndrome (NCT00957229).(118) As patients were required to have at least ten BCCs that were eligible for surgical resection this study was outside of the scope of the Marketing Authorisation for Erivedge, and hence is outside the scope of this NICE appraisal. However, as raised by the clinical experts present at the NICE scoping meeting for this appraisal, it was compelling to note that the number of surgeries per patient per year reduced from a mean of 28.0 (SD 19.6) before vismodegib treatment to 0.5 (0.5) surgeries per patient per year during vismodegib treatment, given the surgical burden for this subset of patients with multiple BCCs. This reduction in surgical burden was maintained while patients were off treatment; patients required a mean of 4.9 surgeries per year (SD 6.3) after a mean of 14 months (SD 7 months) since discontinuing vismodegib.

Results from a subgroup analysis of patients with and without Gorlin syndrome enroled in the STEVIE study was presented at ESMO.(107) Of the 1232 patients enroled in STEVIE, 219 patients had Gorlin syndrome and met the eligibility criteria of either laBCC (n=214) or mBCC (n=5). Baseline characteristics of the cohort of patients with Gorlin syndrome versus those without differed in:

- median age of patients (those with Gorlin syndrome were a median of 52.0 years of age [range 18 to 88] compared with those without Gorlin syndrome who were median of 72.0 years old [range 20 to 101])

- a greater proportion of patients with Gorlin syndrome had a better performance status than patients in the non-Gorlin cohort (ECOG PS grade 0 79.5% versus 53.0%, respectively)

Best overall confirmed responses (investigator-assessed according to RECIST v1.1) were identified in 174 (81.7%) of patients with Gorlin syndrome and 593 (63%) in patients without Gorlin syndrome. Disease control rate (complete and partial response, and stable disease) was 96.7% and 92.0% in patients with and without Gorlin syndrome respectively. The median duration of treatment was longer in patients with Gorlin syndrome compared with in

those patients without Gorlin syndrome (12.3 months vs.8.1 months, respectively). Median duration of response was longer in patients with Gorlin syndrome compared with patients without Gorlin syndrome (28.8 months, range 24.8 to NE, vs. 18.5 months, range 16.4 to 20.8, respectively).

Authors concluded that the patients with Gorlin syndrome showed numerically (though not statistically) higher responses and duration of response compared with the overall STEVIE patient population; it was postulated that this was due to the younger age and better performance status at baseline of the patients with Gorlin syndrome compared with those in the overall population.

Life expectancy

Mortality directly attributable to laBCC is incredibly rare, with elderly patients often dying from other co-morbidities associated with old age. Locally advanced disease is considered a chronic condition and unless perivascular, perineural, or at a very advanced stage involving the skull, laBCC would not be expected to directly cause the death of the patient. However, approximately 10 years of potential life are lost per death from NMSC (22) and it could be postulated that laBCC contributes to the shorter survival in patients due to poor general health and self-care.

Although mBCC is rare, the prognosis for these patients is poor, with high morbidity and mortality (2, 4) Large primary tumours or those with aggressive histological phenotypes (morphoeic, infiltrating and basosquamous) are the most likely to metastasise, with metastases commonly developing in the lymph nodes, skin, bones and lungs. (4, 119) The 1-year probability of survival after mBCC diagnosis was approximately 73.2% (95% CI 64.4 to 82.0) for all cases reviewed and a lower 1-year survival probability was associated with the subset of cases reporting patients with distant metastases (58.6%; 95%CI 44.6 to 72.6) compared with patients with regional metastases (87.8%; 95% CI 78.6 to 97.0).(120)

Vismodegib is reimbursed through the Cancer Drug Fund. From the UK launch of Erivedge in August 2013 until the end of August 2016 (21), 352 requests had been made for funding for vismodegib through the Cancer Drug Fund - suggesting that treatment rates are significantly lower than prevalence rates in the UK.

Table 56: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	No
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No – clinical study data included in this submission relate to single-arm, non-randomised, non-comparator studies. There are no studies assessing vismodegib vs current NHS treatment (best supportive care)
The treatment is licensed or otherwise indicated for small patient populations	Yes, advanced BCC is very rare with fewer than 500 patients estimated to have received treatment in England since launch in August 2013

4.14 Ongoing studies

Study data available in the next 12 months

The global safety study (STEVIE)(39) continues after (conditional approval in the EU) to further evaluate safety and efficacy of vismodegib in aBCC.

The observational study of treatment patterns, effectiveness, and safety outcomes in advanced BCC and BCCNS patients (RegiSONIC; NCT01604252) is on-going. Several abstracts are planned for submission to conferences in 2017.

Vismodegib is also being studied under a Collaborative Research and Development Agreement Letter of Intent with the National Cancer Institute (NCI) Division of Cancer Treatment and Diagnosis and under agreements for Investigator-Sponsored Trials (ISTs), which comprise multiple Phase I and Phase II studies

Table 57: On-going investigator-initiated studies with vismodegib

Study name / number / identifier	ML28580 / NCT01835626	ML28485 / NCT01700049	ML28244/IND 113813 / NCT01556009
Chief Investigator	Sue Yom	Scott Fosko	Ervin Epstein
Institution	University of California San Francisco	St. Louis University School of Medicine	Children's Hospital Oakland Research Institute
Title	An open-label phase II study to assess the safety and tolerability of an induction and concurrent regimen of GDC-0449 plus radiation therapy for locally advanced basal cell carcinoma	Phase 2b single-site, open-label, nonrandomized study evaluating the efficacy of oral Vismodegib in various histologic subtypes (infiltrative/morpheaform, nodular and superficial) of high-risk and/or locally advanced basal cell carcinoma	A Phase II Randomized, Open Label Trial Comparing the Effects of Intermittent Vismodegib vs. Photodynamic Therapy on the Maintenance of Benefit Following 7 Months of Continuous Vismodegib Treatment in Patients With Multiple Basal Cell Carcinomas
Status	Active	Active	Closed to accrual
Limitations on applicability to decision problem	Includes radiation	Not clear how many had laBCC or whether they were otherwise eligible for surgery	Gorlin syndrome, not laBCC or mBCC

5 Cost-effectiveness

- A cost-utility analysis was conducted to compare vismodegib to best supportive care
- A three-state partitioned survival model was built and included the health-states "Progression-free survival", "progressive disease" and death. The time horizon is 30 years, which captures all relevant costs and benefits
- Clinical benefits were derived from the STEVIE study and extrapolated to the 30 year time horizon
- The following parametric extrapolations were used for both vismodegib and best supportive care (BSC):
    - Time to treatment discontinuation = Weibull
    - PFS = Weibull
    - OS = Gamma (locally advanced basal cell carcinoma; laBCC) and Weibull (metastatic basal cell carcinoma; mBCC)
- Costs and resource use were taken from the NHS reference schedule (2015-2016), Personal Social Services Research Unit (PSSRU) health and social care unit costs (2016), the British National Formulary, expert opinion and assumptions
- Benefits are expressed in quality adjusted life years (QALYs). Utility values were derived from SF-36 data collected in the ERIVANCE trial
- Vismodegib provided a life-year and QALY gain over BSC
- The resulting incremental cost-effectiveness ratio (ICER) without patient access scheme (PAS) is:
    - £35,251 versus BSC
- The resulting ICERs (with PAS) is:
    - [redacted] versus BSC

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

Objective

A systematic literature review (SLR) was conducted to identify economic evidence in the basal cell carcinoma (BCC) indications. The aim of the SLR was to identify all literature published since database inception on any of the following topics:

- Economic evaluations of pharmacological interventions for the treatment of locally advanced BCC (laBCC) or metastatic BCC (mBCC)
- Health state utility values for advanced or mBCC patients
- Cost and resource use data for advanced or mBCC patients

Search strategy

The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care".(84)

The following electronic databases were searched:

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print; 1946 to present
- Embase; 1974 to 2016 November 23
- The Cochrane Library, specifically the following:
    - Health Technology Assessment (HTA) Database; Issue 4 of 4, October 2016
    - NHS Economic Evaluation Database (NHS-EED); Issue 2 of 4, April 2015
    - EconLit; 1886 to October 2016

MEDLINE and Embase were searched separately via the Ovid SP platform on 25th November 2016. The Cochrane Library databases were searched simultaneously via the Wiley Online platform on 25th November 2016 and EconLit was searched via the EBSCO platform on 10th November 2016. Database search strategies are presented in Appendix 10.

As well as the electronic database searches, abstract books from major oncology, dermatology and pharmacoeconomics conferences were searched. Full details are presented in Appendix 10.

Manual searches for conference abstracts were limited to those published a maximum of two years ago (i.e. conferences held in 2015 and 2016), as it is assumed that high-quality studies reported in abstract form before this time would have since been published in a peer-reviewed journal.

Finally, a search of ClinicalTrials.gov was conducted, using the Advanced Search function, for trials in advanced or metastatic BCC patients that reported health state utility values or cost and resource use data. Full details are presented in Appendix 11.

The bibliographies of included articles (including systematic reviews and meta-analyses identified during the abstract review stage) were hand-searched for references to other potentially relevant studies for inclusion in the systematic review.

Study selection

To be included in the review, articles had to meet pre-defined eligibility criteria which are detailed in Table 58.

The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail by the two independent reviewers. At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second individual.

Table 58: Eligibility criteria for the economic systematic review

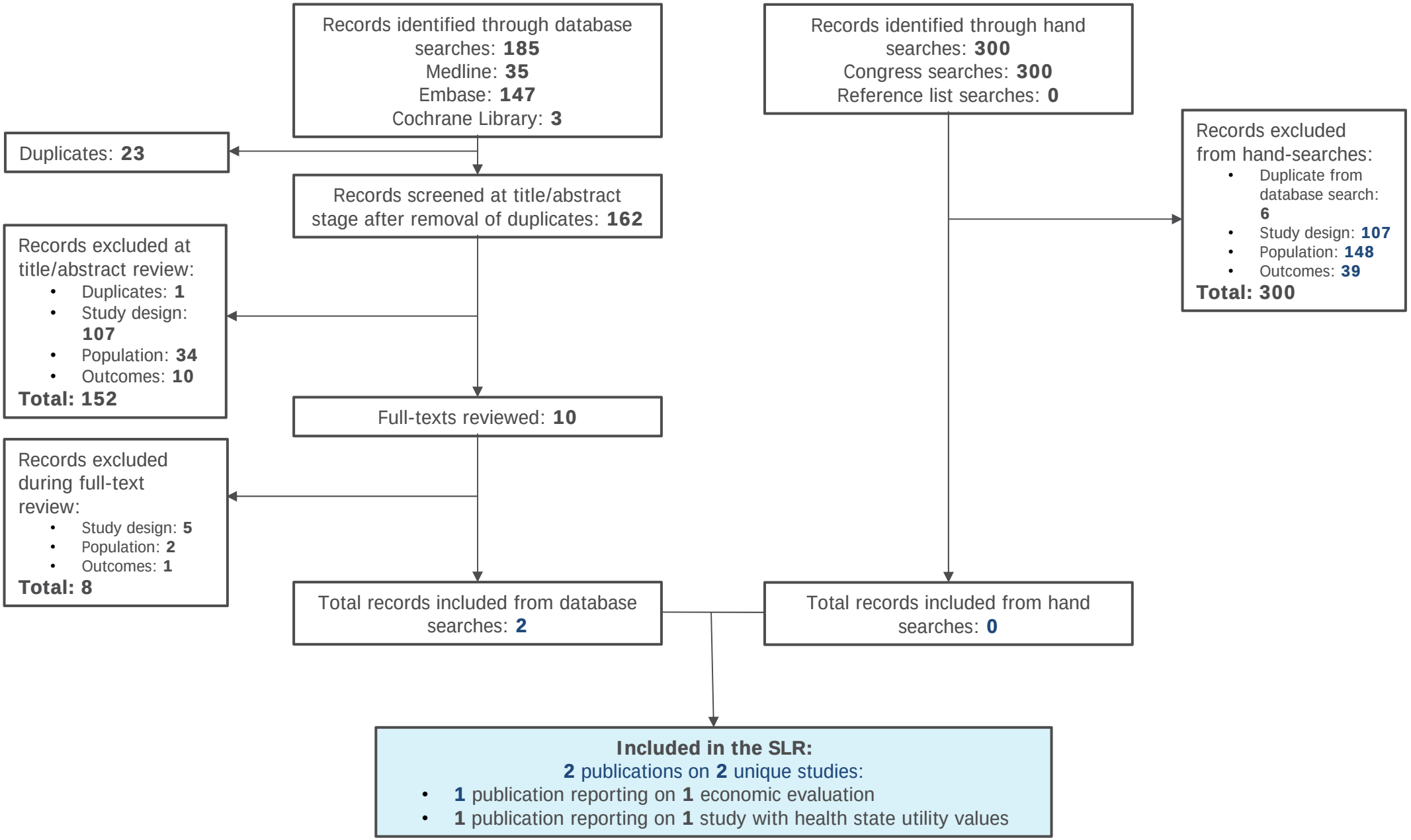
Domain	Inclusion	Exclusion
Population	Adult patients (≥18 years) with: • symptomatic metastatic BCC • locally advanced BCC, for whom surgery or radiotherapy is not appropriate	Any of the following: • Patients without BCC • Patients with early BCC (not advanced or metastatic) • Studies only including patients <18 years old • Studies with mixed patient populations where outcomes were not presented separately for the specific population of interest • Studies of adjuvant or neoadjuvant therapy
Intervention	Economic evaluations: any pharmacologic intervention Utilities: any or none Cost and resource use: any or none	Economic evaluations of non-pharmacologic interventions
Comparator	Any or none	N/A
Outcomes	Economic evaluations: • Costs • Life years • Quality-adjusted life years (QALYs) • Incremental costs and QALYs • Incremental cost-effectiveness ratios (ICERs) Utilities: • EQ-5D • SF-6D • HUI3 • Time trade-off • Standard gamble • Health state utility values measured using any other tool, or mapped from generic quality of life (QoL) questionnaires Cost and resource use:	Studies not presenting relevant outcomes

	• Costs relevant to the UK National Health Service (NHS) and Personal Social Services (PSS) • Resource use relevant to the UK NHS and PSS	
Study design	Economic evaluations: Original economic evaluations considering both the costs and benefits of alternative interventions, specifically: • Cost-effectiveness • Cost-utility • Cost-benefit • Cost-minimisation • Cost-consequence Utilities, and cost and resource use: Any primary research, such as: • RCTs • Interventional non-RCTs, including single-arm clinical trials • Observational studies SLRs, meta-analyses and HTAs were included at the title/abstract review stage, then excluded following hand-searching of their reference lists at the full-text review stage. The exception to this was HTAs presenting original economic evaluations or original cost or resource use data, which were eligible for inclusion in their own right	Any other study design
Other considerations	• English language and Non-English language full-texts • Human subjects Cost and resource use: If sufficient costs from the last 5 years (2011-2016) were identified, costs from before 2011 would have been excluded	Articles not on human subjects

Abbreviations: EQ-5D, EuroQoL-5 Dimension; HTA, health technology assessment**;** HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; N/A, Not applicable; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomised controlled trial; SF-6D, Short Form-6 Dimension; SLR, systematic literature review;

A total of 162 articles were identified from the electronic database searches, all of which were reviewed at the title/abstract review stage. After title/abstract review, 10 articles were reviewed at the full-text stage with two articles ultimately meeting the inclusion criteria. No additional articles to those captured through the database searches were identified through congress searching and through hand searching of bibliographies. The flow of studies through the systematic review process is presented in Figure 27.

Figure 27. PRISMA flow diagram of identified studies in economic systematic review



5.1.2 Description of identified studies

The study by Purser 2016 was the only study identified in the economic evaluations review.(121) The authors used a partitioned survival-model to estimate annual treatment costs to be £146,362 for sonidegib and £167,423 for vismodegib, representing a £21,061 difference. Undiscounted life years were estimated to be equal across the two treatment arms (9.43 LYs), while discounted quality adjusted life years (QALYs) were 5.10 and 4.98 respectively.

The results reported in the Purser *et al.* publication sizably differ from those reported in section 5.7 of this submission. The disparity in results can be ascribed to fundamental differences in methodology and data sources. These differences are outlined in the following passage. First, and perhaps most importantly, Purser and colleagues populated the vismodegib arm of their economic analysis using data collected in the ERIVANCE study. As explained in section 5.3, the *de novo* analysis used STEVIE data to populate the clinical parameters of the model. The STEVIE study had a much greater study population, (1,215 versus 104) and was therefore deemed to be more appropriate of the two studies. The higher number of patients meant that more events (progression and death) were observed, leading to more accurate parametric extrapolations. This difference in data sources has implications on the estimation of life years as well as treatment duration and costs.

In addition, Purser *et al.* also assumed that there was no excess disease mortality due to laBCC; i.e. they used mortality rates of the general UK population to estimate overall survival for both treatment arms. According to clinical opinion (see section 5.10.1) this assumption is questionable. In the *de novo* model, the overall survival (OS) and its extrapolation was based on actual data from the STEVIE study in combination with background mortality rather than just background mortality.

Other differences include the length of time horizon. Purser assumed a time horizon of only 10 years compared to the lifetime time horizon observed in this analysis.

Details and results of the relevant study identified in the economic review are presented below in Table 59.

Table 59: Details of the relevant economic evaluation identified in the economic systematic review

Author, Year [Cost year]	Summary of model: Analysis or model type; analysis time frame; and rationale for design and time frame	Patient population, including average age	Interventions and comparators	Costs and outcomes	ICER
Purser 2016 [NR](121)	A partitioned-survival model with a 10-year time horizon was developed in Microsoft Excel to conduct the CEA. The partitioned-survival model included three health states: • PFS (which was further partitioned into three response levels: CR, PR and SD) • PD • Death The model estimated expected costs, LYs, QALYs, and ICERs. A discount rate of 3.5% was applied to costs and QALYs. An OSA and a PSA were performed. For sonidegib, PFS was estimated from the single-arm BOLT trial using the MAIC IPD*. For vismodegib, a published KM plot from the single-arm ERIVANCE trial was digitised to create approximated IPD. General UK mortality data were used to estimate OS, assuming no difference between the comparators. The model included AEs that occurred in ≥20% of patients and were reported at Grade 3 or 4 in ≥3% in either BOLT or ERIVANCE.	The model patient population was adults with laBCC not amenable to surgery or radiotherapy. A mean model cohort age of 63 years was assumed (based on a mean age of 64.6 years in the BOLT(122) trial and a mean age of 61.4 years in the ERIVANCE(27) trial).	Vismodegib and sonidegib	<u>Sonidegib</u> *Total cost:* £146,362 *LYs (undiscounted):*9.43 *QALYs (discounted):* 5.10 <u>Vismodegib</u> *Total cost:* 167,423 *LYs (undiscounted):* 9.43 *QALYs (discounted):* 4.98 <u>Difference (Absolute [%])</u> *Total cost:* £21,061 (14.4) *LYs (undiscounted):* 0.00 *QALYs (discounted):*0.12 (2.4)	The CEA found that sonidegib results in lower costs and better health outcomes than vismodegib. The OSA revealed that dose intensity and drug price had the largest effects on the ICER (detailed results not provided). The PSA found that approximately 71% of the simulated ICERs fell below a threshold of £30,000/QALY gained.

Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; CR, complete response; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; laBCC, locally advanced basal cell carcinoma; LY, life year; MAIC, matched adjusted indirect comparison; OS, overall survival; OSA, one-way sensitivity analysis; PD, progressive disease; PFS, progression-free survival; PR, partial response; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SD, stable disease; UK, United Kingdom
*It is unclear how the MAIC was conducted across the two studies and which baseline characteristics and assumptions were used, no source was given for the MAIC

5.1.3 Quality assessment of identified studies

The study identified as relevant for inclusion was assessed using the Drummond et al. checklist. (123) A quality appraisal for this study is presented in Appendix 13.

5.2 De novo analysis

5.2.1 Patient population

The *de novo* analysis assessed the use of vismodegib as a treatment option for adult patients with symptomatic mBCC or laBCC inappropriate for surgery or radiotherapy. This population is consistent with both the appraisal scope and Marketing Authorisation.(34)

Clinical parameters of the model were primarily populated using data from the STEVIE trial. STEVIE was preferred over ERIVANCE due to the larger patient population recruited (i.e. 1,215(28) and 104(27) patients, respectively) thus enabling a more reliable parametric extrapolation over the time horizon. In addition, as STEVIE was a single arm study, a landmark approach was used to derive a proxy for the BSC comparator in the economic analyses, which would have been difficult to assess with the small sample size of ERIVANCE.

Both sets of study characteristics are discussed in detail in section 4 of this submission. Some key baseline characteristics of this cohort are presented in Table 60. Full details regarding patient characteristics are presented in section 4.11.4.

Table 60: Key baseline characteristics of ITT population of STEVIE (28, 39)

	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Mean age in years (SD)	69.7 (16.1)	66.6 (13.0)	69.5 (15.9)
Female (%)	485 (43.3)	36 (37.5)	521 (42.9)
Gorlin syndrome patients (%) Yes No	 214 (19.2) 899* (80.8%)	 5 (5.2) 91 (94.8%)	 NR NR

Abbreviations: kg, kilograms; NR, not reported; SD, standard deviation.
*The Gorlin syndrome status of 6 patients was not recorded

Patients diagnosed with a locally advanced form of the disease are clinically different to those diagnosed with mBCC. Despite an observed difference in response between these populations, distinct subgroup analyses were not performed. Results are presented across the entire aBCC cohort as a whole as per the license indication.

Gorlin syndrome (also known as basal cell carcinoma naevus syndrome [BCCNS], Gorlin-Goltz syndrome), is a rare genetic condition characterised by the development of multiple BCCs. Patients suffering from this condition can be clinically differentiated from non-Gorlin patients. Gorlin patients will tend to present with BCCs at an earlier age, and in much greater numbers, compared with non-Gorlin patients. The underlying pathology of Gorlin patients also means that their treatment pathway may be atypical.(2) For these reasons, it is widely documented among clinicians that these patients should be treated as a separate subgroup.(2, 124, 125) Roche agrees with this assessment; however, a subgroup analysis of Gorlin patients has not been included in this submission. This decision was primarily based on significant limitations in the clinical data. Ultimately, it was decided that the number of Gorlin patients enroled in the STEVIE clinical trial was insufficient to support a robust subgroup analysis. See Table 60.

The population evaluated in the model is reflective of this disease population within UK clinical practice and also consistent with the scope of the appraisal. The decision to conduct the analysis as stated was affirmed through consultation with clinical experts.

5.2.2 Model structure

A partitioned survival model has been developed to assess the cost-effectiveness of vismodegib versus best supportive care (BSC) over the course of a 30-year (lifetime) time horizon. The model is comprised of three health states: 'Progression-free survival' (PFS), 'Progressive disease' (PD), and 'Death', see Figure 28.

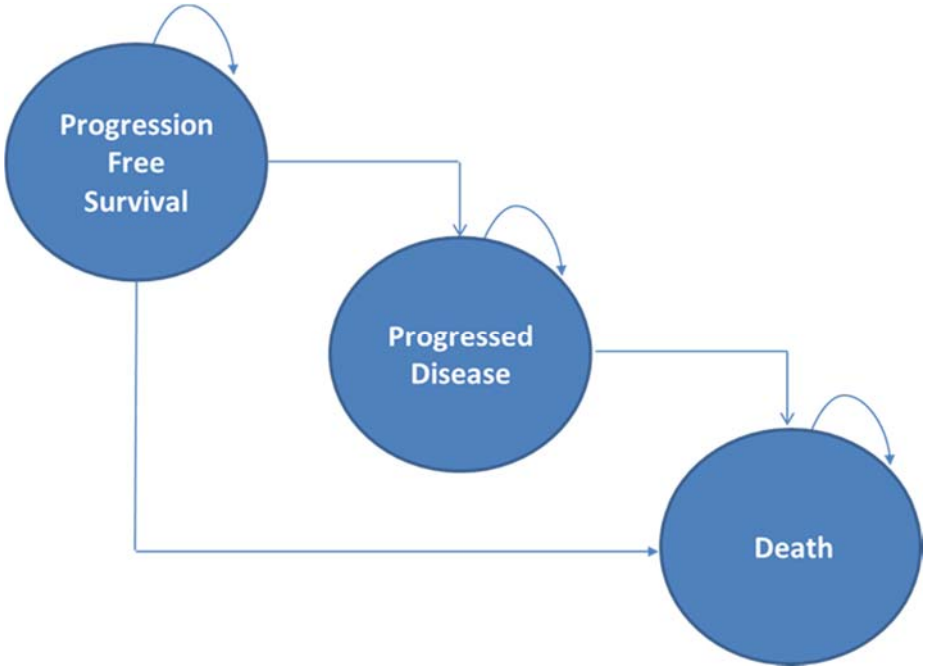
Patients enter the model in the PFS health state and remain there until disease progression or death. While in PFS, patients receive treatment with vismodegib until disease progression or unacceptable toxicity. After transitioning to the PD state, patients remain there until they die. In this model, it is not possible for a patient to transition back from the PD state to the PFS health state. A transition to death is possible from either of the other two health states in the model. Death is the absorbing state in this model, once there it is impossible for patients to leave.

Throughout the clinical trials, patients are categorised into their respective health states according to the investigators assessment of progression, which is performed according to the RECIST criteria.(126)

The model does not assume any subsequent lines of therapy in either treatment arm. Whilst clinical advice received by Roche suggested patients would go on to receive subsequent therapies, there is a lack of data to allow robust incorporation of such a treatment pathway in

the model. In spite of this, patients originally receiving vismodegib therapy are assumed to receive BSC once having progressed.

Figure 28: Cost-effectiveness model scheme



This type of model was considered appropriate for the decision problem. Both the structure and health states are in-line with the clinical pathway outlined in section 3. The chosen approach is consistent with previous NICE technology appraisals in similar disease areas (TA 414,(127) TA 357,(128) and TA 396(129)) as well as the economic study identified in the SLR (section 5.1).(121)

The cycle length of the model is one week, with the proportion of patients in each health state calculated every 7 days. A half cycle correction has been applied in the model.

5.2.3 Features of the de novo analysis

The table below outlines some of the key features of the economic analysis. All of the features in Table 61 are in-line with the guidelines stipulated in the NICE reference case.(130)

Table 61: Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	30 years (lifetime)	Thirty years is believed to be long enough to reflect all important differences in costs or outcomes between the technologies being compared.(130)
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case.(130)
Discount of 3.5% for utilities and costs	Yes	NICE reference case.(130)
Perspective (NHS/PSS)	Yes	NICE references case.(130)

Abbreviations: NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life years; PSS, personal social services; QALYs, quality-adjusted life years

5.2.4 Intervention technology and comparators

In the economic model, vismodegib is administered orally at a daily dose of 150 mg. The intervention is assessed in-line with both the decision problem (see section 1.1) and the Marketing Authorisation.(34)

For the patient population in question, vismodegib represents the only available treatment option. When considering this, and the fact that both pivotal trials were single arm, it makes selecting a comparator for the economic analysis problematic. For this reason, clinical experts were consulted during an advisory board.

The clinical experts suggested a range of treatment options for these patients if vismodegib were unavailable. The primary options suggested were:

- **Wound management**: dermatologists would monitor patients several times per year; more regular patient care would be carried out in the community by GPs and nurses, potentially requiring intensive and continual wound management

- **Palliative radiotherapy**: non-curative radiotherapy, considered when required, for the management of bleeding and/or exudation of the wound. The dose of radiation may be given in a single fraction, or fractionated if the wound is particularly large

- **Surgery**: referral for consideration for major surgery to resect locally advanced disease (with involvement of multiple surgical specialities e.g. ear, nose and throat (ENT) specialist / oculoplastic / maxillofacial / neurosurgical teams, with the likely requirement for complex plastic surgical reconstruction). It should be noted that this

surgery would not be expected to be curative and is usually associated with significant morbidity (e.g. loss of an eye) and a significant risk of mortality

The primary option resulting from the advisory board was an intensive wound management regimen. This regimen comprises regular visits by a tissue viability nurse, a dermatologist, a GP, and, in certain patients, a course of palliative radiotherapy. This treatment combination was deemed to be BSC and was therefore selected as the most appropriate comparator in our economic analysis. More information on the resource use associated with this treatment arm is given in section 5.5.2.3.

Vismodegib is indicated in adult patients with symptomatic mBCC or laBCC inappropriate for surgery or radiotherapy. Including surgery or radical radiotherapy as a comparator in the economic analysis would not be consistent with the marketing authorisation. In addition, during the advisory board, Roche received advice which informed our decision: (i) given the advanced state of disease in these patients, surgical intervention would be difficult, extensive and would only be attempted as a last resort; (ii) surgery may result in the loss of an ear, an eye, or part of the nose; (iii) such a procedure is unlikely to achieve an acceptable result due to likely extent of disease and difficulty in obtaining clear margins; (iv) the detriment to a patient's HRQoL could be considerable; (v) frailty and comorbidities are likely in elderly patients, reducing operability (mean age of laBCC patients in STEVIE was 69.7 years) and the possibility of radical radiotherapy.

The SLR described in section 5.1 captured an economic evaluation by Purser et al. in which the authors compared vismodegib to sonidegib. Sonidegib is a Hedgehog pathway inhibitor indicated for the treatment of BCC. Sonidegib (trade name Odomzo®, Novartis Europharm Ltd.) received Marketing Authorisation throughout the European Union on 14th August 2015 for the treatment of adults with locally advanced basal cell carcinoma (BCC)* However, given that sonidegib is not commercially available in the UK, it was not considered to be a relevant comparator in this economic analysis.

5.2.5 Treatment continuation

According to the Erivedge licence, patients receive treatment until disease progression or unacceptable toxicity.(34) This is consistent with clinical practice and both the ERIVANCE and STEVIE study protocols.(38, 131) Assessment of disease progression, and therefore

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* http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002839/human_med_001897.jsp&mid=WC0b01ac058001d124

treatment discontinuation, will be carried out during a routine visit to an oncologist. It is reasonable to assume that implementation of this treatment discontinuation rule will not require additional resource use, or changes to current routine clinical practice.

BSC treatment is not curative, and is believed to continue until the patient dies. No treatment discontinuation rule will be observed in the analysis.

Section 5.3 includes further details of time on treatment assumptions.

5.3 Clinical parameters and variables

5.3.1 Incorporation of clinical data into the economic model

The primary data source used to populate the clinical elements of this analysis was the single-arm, open-label, Phase II multicentre STEVIE (NCT01367665) study. STEVIE was preferred over the pivotal ERIVANCE study (NCT00833417) because of its clear advantages in patient numbers, and therefore extrapolation accuracy. It is believed that the cohort evaluated in this study is representative of patients receiving vismodegib in the UK (see section 4.13). As a result, responses and outcomes seen in this study are assumed to be reflective of UK clinical practice. Both key studies are discussed in detail in section 4 of this submission.

The pooling of these two trial populations may have served to further strengthen this analysis. Pooling the populations would have resulted in an increase in sample size of 96 patients; however it would have also introduced a great deal of uncertainty. Ultimately, it was decided that the ~8% gain in sample size did not justify the additional uncertainty.

All analyses were carried out using data collected up until the 16th March 2015 data cut. As STEVIE was a single-arm study, a landmark approach was used to derive a proxy for the BSC comparator in the economic analyses (described later in section 5.3.5).

The survival curves and parametric extrapolations in the vismodegib arm were modelled using time to event data reported in STEVIE. A criterion-based guide, based on the NICE DSU Technical Report, was used to facilitate accurate extrapolation and to justify survival estimates when needed. (132)

5.3.2 Progression free survival – vismodegib arm

Patients remain in the PFS health state as long as they remain progression free or have not died. The probability of remaining in the PFS health state is determined by the PFS probabilities obtained from the STEVIE study.

Several parametric distributions were fitted to the existing PFS data in order to extrapolate it beyond the observation period: Exponential, Log Weibull, Log-logistic, Log-normal, Gamma and Gompertz. These parametric extrapolations can be used directly for the entire time horizon of the model (30 years). Alternatively, Kaplan-Meier (KM) estimates with a parametric tail can be used for the extrapolation. The approach to use KM with a parametric tail is possible, but it should be noted that the KM part of the extrapolation will remain fixed without random variation, when probabilistic sensitivity analysis is run. Thus, the option of using the KM and a parametric tail is only explored in the deterministic sensitivity analyses. In addition, sensitivity analyses were conducted on all other plausible extrapolation methods.

Akaike information criterion (AIC) Goodness of fit

Parametric distributions were assessed for their goodness of fit to the observed data using the Akaike Information Criterion (AIC). Lower values for AIC indicate a better mathematical assessment of the fit to the actual data. Bayesian Information Criterion (BIC) values have also been calculated and reported in this submission. As the approach taken here is Frequentist, as opposed to Bayesian, the BIC values do not factor into the decision-making process when selecting a distribution. This is also the case in the selection of the time to treatment discontinuation (TTD) and OS functions. BIC values have simply been included for completeness.

Table 62 presents the AIC values for the extrapolation of PFS data, the rank of the goodness of fit is shown with one indicating the best fit and six the worst, i.e. lowest and highest AIC values.

Table 62: AIC ranking for progression-free survival

	AIC		BIC	
	Locally advanced	**Metastatic**	**Locally advanced**	**Metastatic**
Exponential	1'503.05 (5)	203.97 (6)	1'508.06 (6)	206.45 (1)
Weibull	1'444.66 (1)	201.94 (1)	1'454.67 (1)	206.91 (2)
Log-logistic	1'448.69 (4)	203.22 (3)	1'458.71 (2)	208.20 (4)
Log-normal	1'475.24 (3)	203.07 (2)	1'485.25 (5)	208.05 (3)
Gamma	1'446.63 (2)	203.67 (5)	1'461.65 (3)	211.14 (6)
Gompertz	1459.73 (6)	203.53 (4)	1'469.74 (4)	208.50 (5)

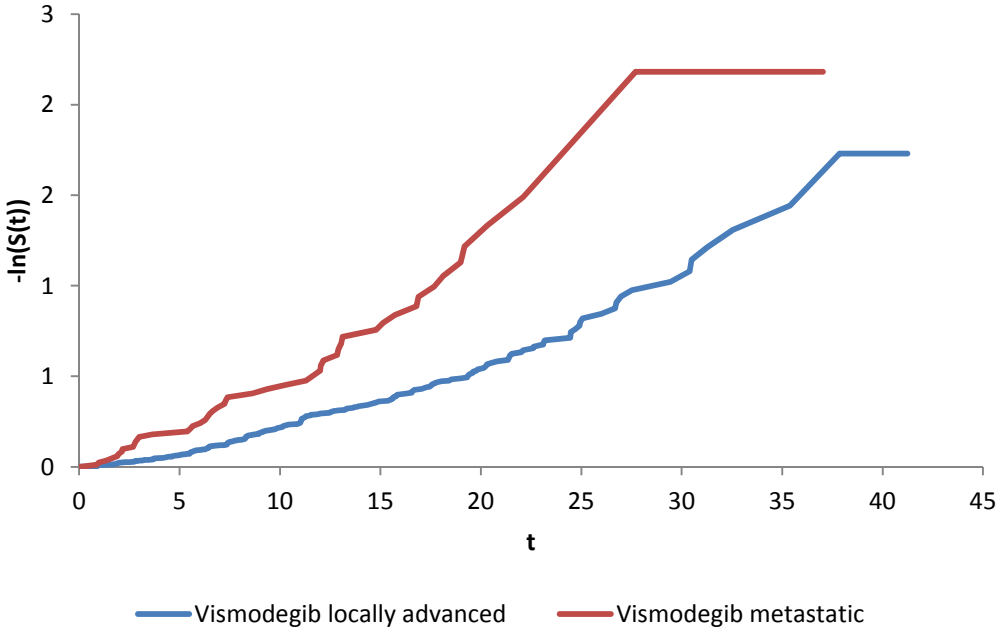
Abbreviations: AIC, Akaike information criterion.

Based on the AIC statistics, the best fit overall would be obtained with a Weibull function in both locally advanced and metastatic patients. In the metastatic group, the AIC values are similar, indicating that the choice of model will not greatly impact the extrapolation. The rest of the distributions are explored in sensitivity analyses.

Log-Cumulative Hazard Plot

A key property of the Weibull model is that the log cumulative hazard is linear in log time. The log-cumulative hazard plot Figure 29 shows a relatively linear pattern over the intervals and thus confirms that this assumption is fulfilled with our data.

Figure 29: Log-Cumulative hazard plot - PFS STEVIE

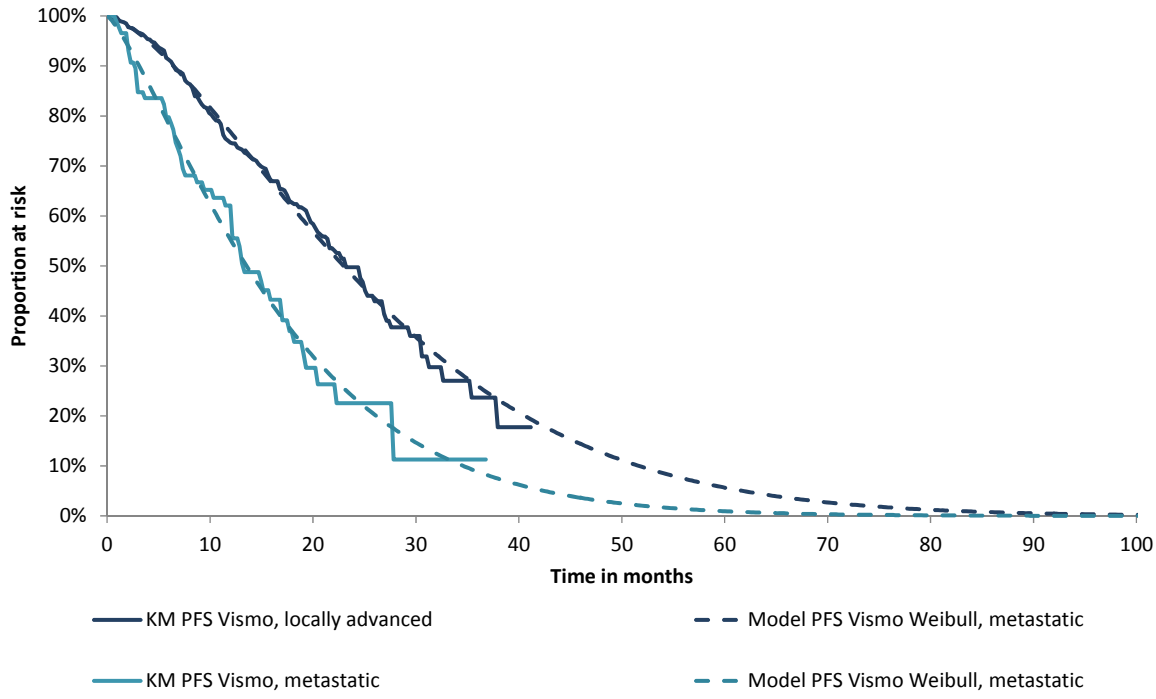


Visual Inspection

Visual inspection checks how closely the parametric curve fits the KM. It is often used as another way of assessing goodness of fit. Visual inspection of the curve should also consider the tail of the fitted model, as it might provide the closest fit to the KM but may have an implausible tail. Although there is a lot of censoring in STEVIE PFS analyses, the Weibull function seemed to fit the KM best and provided a reasonable tail. Figure 30 shows the PFS KM and the best fitted Weibull parametric curve for the vismodegib arm.

Please note that visual fits for all other extrapolations can be found in Appendix 14.

Figure 30: PFS KM and extrapolation - Weibull distribution - vismodegib arm



Based on the assessment described above, the Weibull distribution has been used for the PFS extrapolations for both laBCC and mBCC populations in the base case.

5.3.3 Time to treatment discontinuation – vismodegib arm

In STEVIE, patients received treatment until disease progression or unacceptable toxicity. Treatment duration in the model was derived from the time to treatment discontinuation (TTD) data from the STEVIE trial. As with the PFS data, the TTD data is not complete and thus parametric distributions were fitted to the data for extrapolation.

Similar to the steps followed for the PFS extrapolation, the choice of the most appropriate distribution was based on the AIC and visual assessment of both the fit and hazard shape. Kaplan-Meier estimates with a parametric tail can be used for the extrapolation. For the same reason described above, the approach to use KM with a parametric tail is possible and is only explored in the deterministic sensitivity analyses.

Akaike information criterion (AIC) Goodness of fit

Table 63 provides the AIC and BIC goodness of fit values for the extrapolation of the TTD data.

Table 63: AIC ranking for time to treatment discontinuation

	laBCC	mBCC	Locally advanced	Metastatic
Exponential	3'112.46 (5)	239.94 (2)	3'117.46 (4)	242.43 (1)
Weibull	3'112.02 (4)	241.92 (3)	3'122.03 (5)	246.90 (3)
Log-logistic	3'043.02 (1)	239.66 (1)	3'053.03 (1)	244.64 (2)
Log-normal	3'061.75 (3)	242.74 (5)	3'071.76 (2)	247.71 (5)
Gamma	3'058.96 (2)	N/A	3'073.98 (3)	250.10 (6)
Gompertz	3'114.46 (6)	241.94 (4)	3'124.47 (6)	246.92 (4)

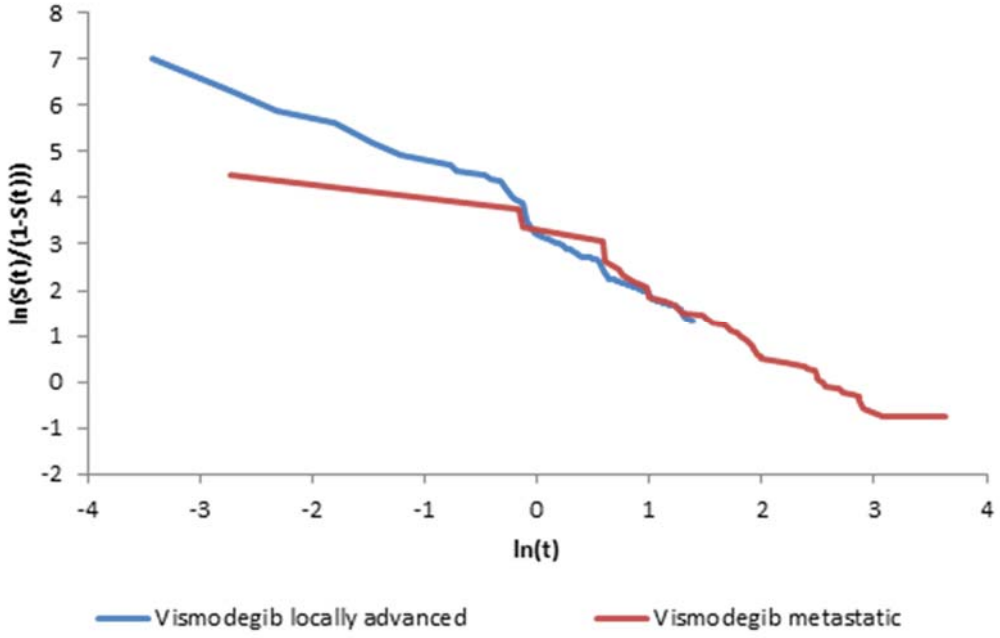
Abbreviations :NA, not applicable

Based on the AIC statistics, the best statistical fit overall would be obtained with a Log-logistic function in both locally advanced and metastatic patients. Similarly to the PFS, in the metastatic group, the AIC values are clustered, indicating that the choice of model will not have a great impact upon the extrapolation.

Log survival odds plot

The log-logistic is an accelerated failure time proportional odds model. The log-logistic model implies that the log odds of the event of interest are linear in log time. This assumption seems to be fulfilled for both locally advanced and metastatic patients as shown in Figure 31.

Figure 31 Log survival odds over log time - TTD STEVIE



Visual Inspection

Figure 32 shows the TTD KM curve and extrapolation for both locally advanced and mBCC. Although the KM of the mBCC group is always on top of the laBCC, the extrapolated tail of the metastatic group crosses and eventually drops below the locally advanced curve. This might be an artefact of the data, given the low number of metastatic patients, especially at the tail.

Figure 32: TTD KM and extrapolation - Log-logistic distribution - vismodegib arm

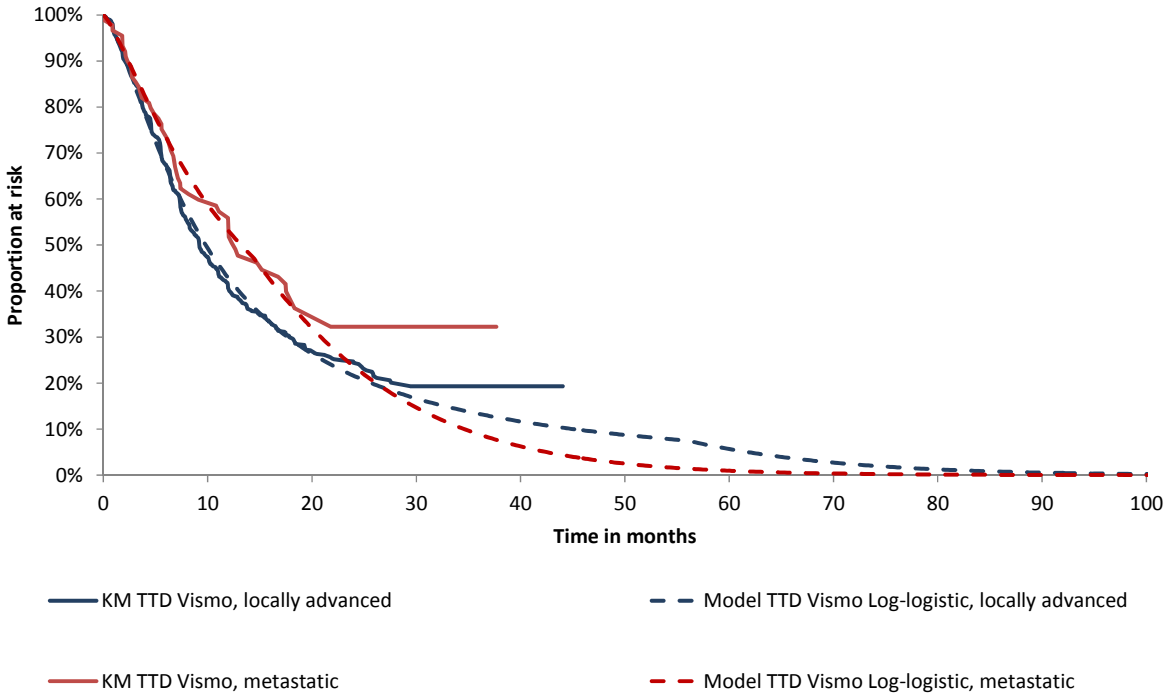
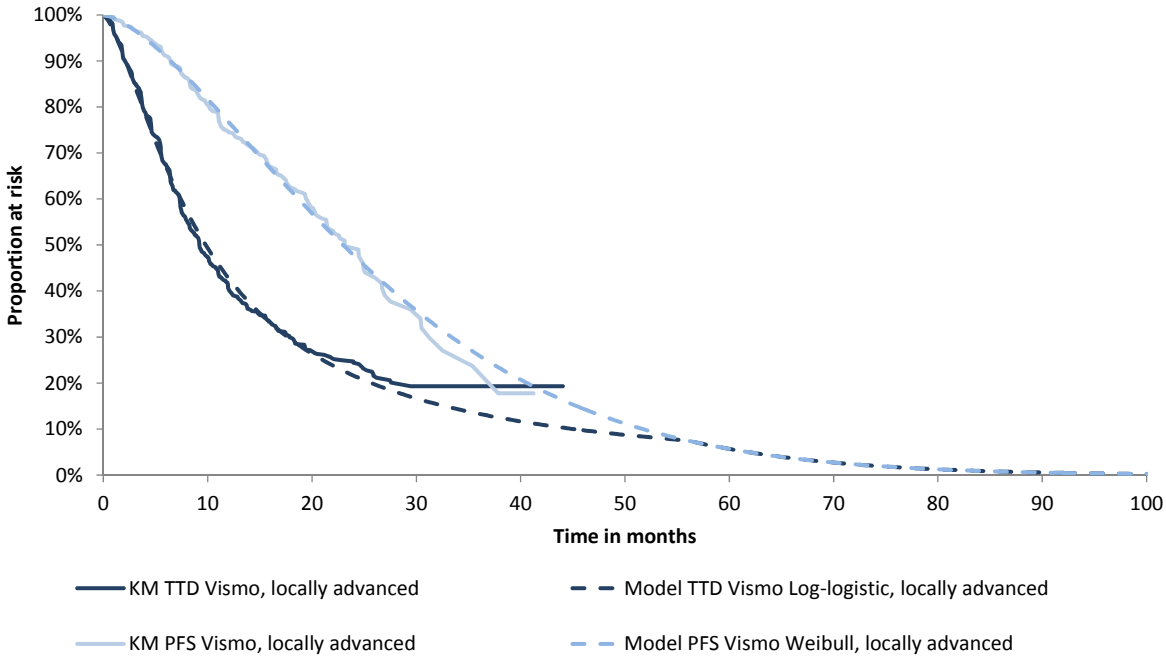


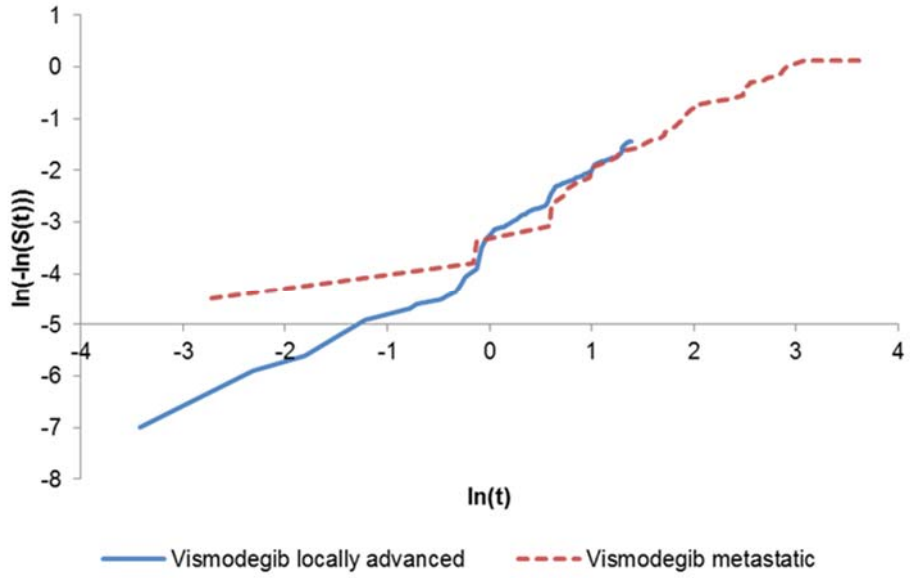
Figure 33 depicts the KM TTD and KM PFS for the laBCC group as well as their respective extrapolated curves. The KM TTD is always substantially lower than the PFS curve, this is because patients discontinue treatment for reasons other than progression and death. In addition, the laBCC TTD KM curve seems to cross the PFS KM curve at approximately 38 months whereas their respective extrapolated curves cross at 55 months. As previously reported, the flat tail of the TTD KM curve is highly uncertain given the low number of patients at risk (2.4% of patients at risk), and thus the fact that the TTD reaches PFS is more likely an artefact of the data. If TTD was to be equal to the PFS, it would imply that patients discontinue treatment because of progression or death only. However, from what we have observed in the previous 30 months of follow-up, where the PFS KM is a lot higher than the TTD KM, it does not seem plausible that the TTD would reach PFS.

Figure 33: TTD and PFS KM and extrapolation (laBCC) – Log-logistic (TTD) and Weibull (PFS) distributions – vismodegib arm



For these reasons, a different extrapolation for the laBCC group was used to correct for this. As shown in Appendix 14, the Log-normal and Gamma models do not deal with this issue as they all have a tail similar to Log-logistic. The Weibull, Exponential and Gompertz have very similar tails and dealt with this issue of TTD exceeding PFS. The Weibull model was the best fit of the three candidates and as shown in Figure 34, the log cumulative hazard is linear in log time (Weibull property). Therefore, the Weibull model was selected in the base case analysis.

Figure 34: Log cumulative hazard over log time – TTD – Weibull distribution



5.3.4 Overall survival – Vismodegib arm

Similar to the approach taken to incorporate PFS and TTD into the economic model, the alternative parametric functions used for OS extrapolation were assessed using AIC goodness of fit, visual inspection and observing the hazard shape.

Overall survival was modelled using overall survival times (time from randomisation to death) observed during the STEVIE trial and resulting parametric extrapolations.

Akaike information criterion (AIC) Goodness of fit

Table 64 shows the AIC and BIC goodness of fit across all distributions.

Table 64: AIC ranking for overall survival

	AIC		BIC	
	Locally advanced	**Metastatic**	**Locally advanced**	**Metastatic**
Exponential	783.93 (3)	128.77 (3)	788.93 (2)	131.25 (1)
Weibull	785.92 (5)	129.93 (5)	795.93 (5)	134.91 (4)
Log-logistic	784.87 (4)	129.49 (4)	794.88 (4)	134.46 (3)
Log-normal	778.48 (2)	128.19 (1)	788.49 (1)	133.17 (2)
Gamma	775.49 (1)	128.52 (2)	790.51 (3)	135.98 (6)
Gompertz	785.93 (6)	130.77 (6)	795.94 (6)	135.74 (5)

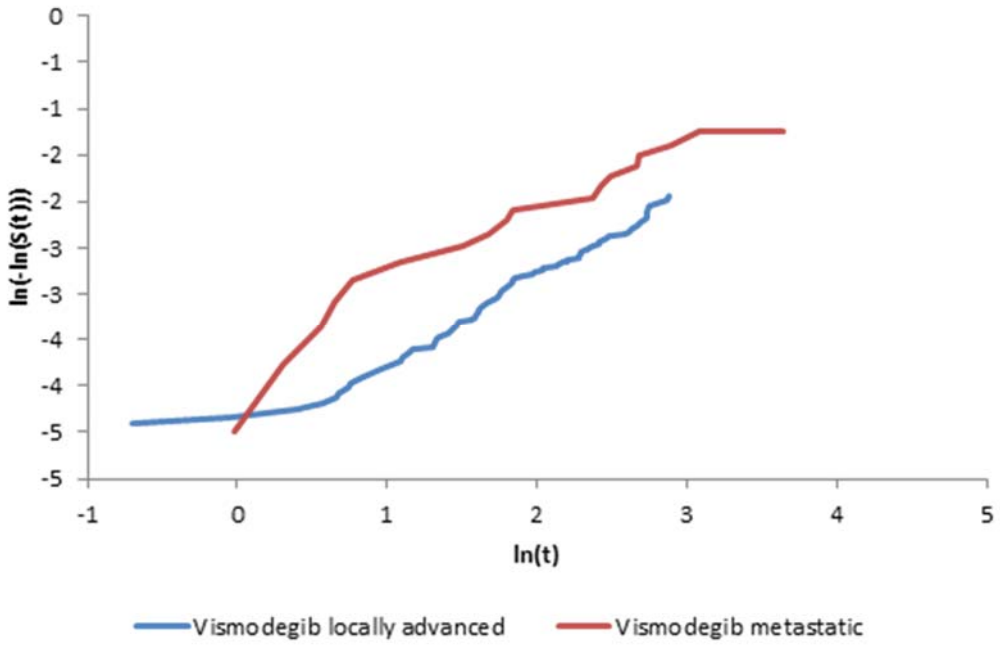
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian Information Criterion.

The Gamma function yielded the lowest AIC value for locally advanced patients and the second lowest for metastatic patients. Similar to the observation made for PFS, the AIC values for the metastatic group are close to each other. However, for OS, the choice of the distribution has a larger impact on the tail of the curve, and subsequent estimates of life years in the vismodegib arm. This is because of the large amount of censoring in the evaluation of OS in STEVIE, with only 9.0% of patients having died as of the data cut-off date. Among the 1192 efficacy-evaluable patients with histologically confirmed disease and available measurable disease status at baseline, the median OS was not estimable for the full study cohort, nor was it estimable for either the laBCC cohort or mBCC cohort.

Log-Cumulative Hazard Plot

The Weibull and log-normal functions are special cases of the gamma function. A plot of the log cumulative hazard over log time showed that the Weibull assumption of a linear relationship was not rejected by the data (Figure 35).

Figure 35: Log-Cumulative hazard plot – OS STEVIE

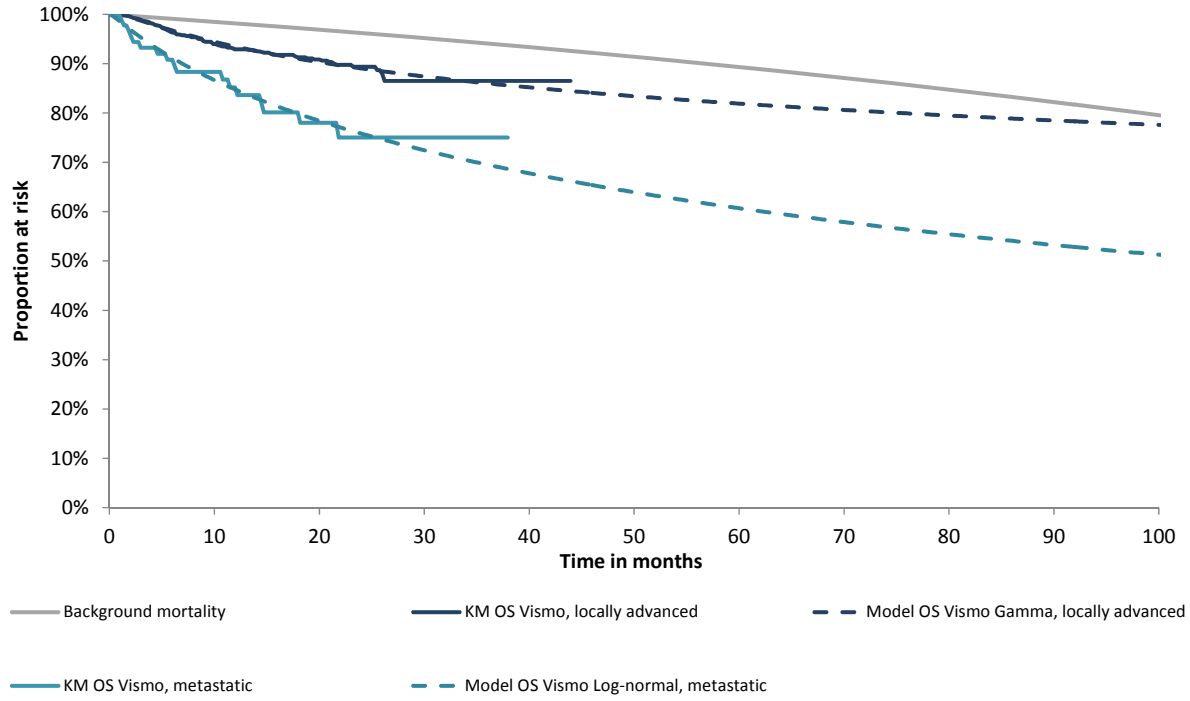


In light of the data immaturity and the amount of extrapolation required in this case, the AIC and hazard plots should have limited impact on the choice of extrapolation. Visual inspection of the tail as well as external validity of the tail should play a more important role in this instance.

Visual Inspection

Figure 36 shows a comparison of the Kaplan-Meier curves and the corresponding best fitting (according to the AIC) parametric extrapolations to the OS data. The x-axis has been limited to the point where the fit of the best fitted parametric curve against the KM can be assessed visually.

Figure 36: OS KM and extrapolation – Log-Logistic distribution – vismodegib arm

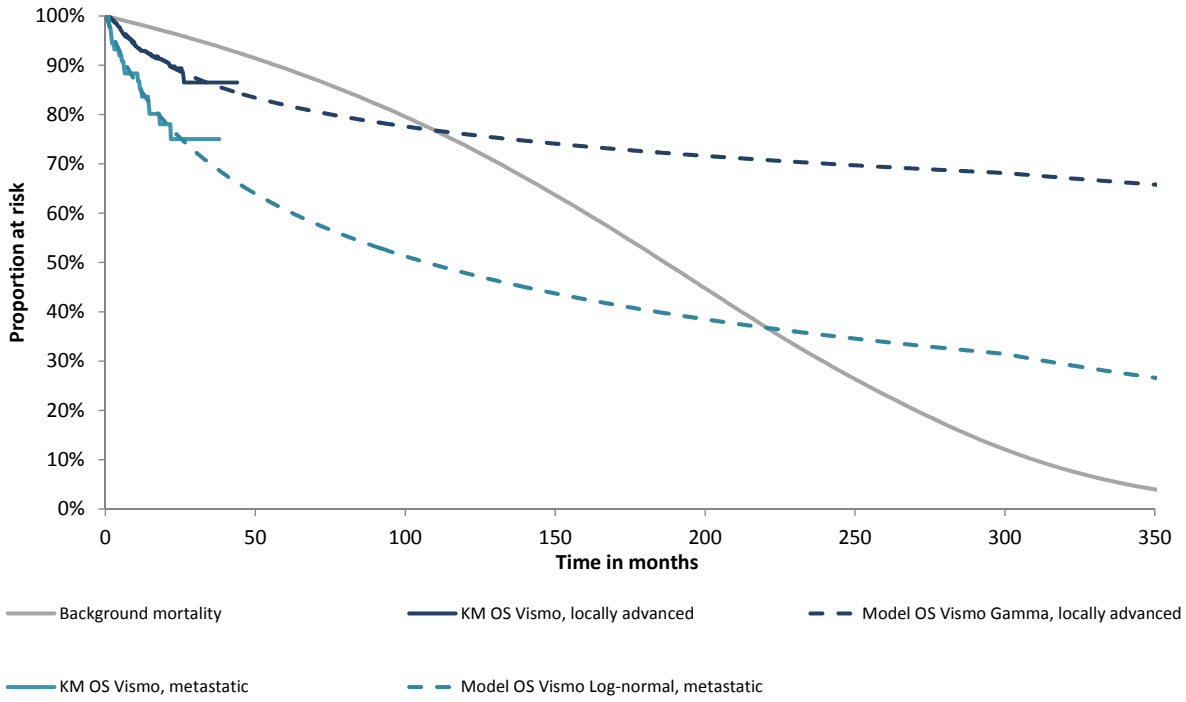


Overestimation of long-term survival based on parametric extrapolations

As mentioned previously, few death events were observed within the observation period of STEVIE. The mortality rates observed in the STEVIE trial do not reflect the increase in mortality rates at older ages; therefore the data does not accurately represent the evolution of mortality rates over a long-term horizon. In addition, the more flexible parametric models, i.e. Gamma, Log-normal, Log-logistic, usually result in quite heavy tails, which are leading to an overestimation of the underlying survival rate.

As a consequence, when the Gamma (locally advanced) and Log-normal (metastatic) distributions are used for the overall survival data in STEVIE, the survival rates were overestimated compared to the U.K general population (Figure 37).

Figure 37: Comparison of parametric extrapolations of overall survival time to the UK general population survival curve



As described in the clinical section of this submission, mortality directly attributed to laBCC is incredibly rare. Patients are usually elderly and are often suffering from other co-morbidities; however, patients diagnosed with non-melanoma skin cancer have a 10 year lower life expectancy than background. The prognosis for patients with mBCC is poor, both morbidity and mortality are high.(2, 22)

Taking this into account, for mBCC patients, an extrapolated tail that does not exceed background mortality should be considered. Clinical opinion was also sought to validate this assumption. During this consultation, it was stated that patients with mBCC have excess disease mortality and would not reach background at any point in the extrapolation. In this case, the use of parametric models with a "lighter" tail, such as the Weibull, Exponential, or Gompertz might be more appropriate. The exponential distribution incorporates a hazard function that is constant over time. As shown in Figure 35 the cumulative hazard was increasing over time, thus indicating that the exponential might not be the most appropriate choice. The Gompertz converged almost to an Exponential model (theta parameter = 0.00000001), thus the same rationale of not using it in the base case applies. For the aforementioned reasons, the Weibull model was used as the base case for the mBCC group. Clinical opinion also agreed that this is a reasonable extrapolation for OS in mBCC patients.

For the laBCC group, the OS picture is different. Clinical opinion suggested that patients at lower ages are more likely to have a slight excess mortality directly attributable to laBCC. However, as patients get older, it is more likely that they die from other comorbidities and not from laBCC. In this case, the Gamma function adjusted for background mortality was considered for the base case.

Two methods were evaluated in order to prevent OS extrapolations exceeding background mortality rates in the model. These methods have implications on the evaluation of treatment effect when the BSC arm is incorporated; therefore these approaches are discussed later in section 5.3.6. Survival curves that are used for the base case in the model are also shown in the clinical effectiveness section 4.11.

5.3.5 Incorporation of the comparator into the economic model

Both the STEVIE and ERIVANCE studies were phase II single arm studies. These design limitations meant that there were sizable methodological issues in terms of modelling approach: the principle issue being the lack of comparator arm data and the subsequent need to artificially create it. For this reason, both economic and clinical experts were consulted at an independent advisory board (see section 5.10 for further details). During this meeting, several possible approaches were suggested. The following section describes both the rationale behind the exclusion of some of these options and the decision to proceed with our chosen method.

Matched adjusted indirect comparison

The first option suggested at the advisory board was a matched adjusted indirect comparison (MAIC). This approach would involve sourcing and using data on patients in the same population of interest who have received BSC as opposed to vismodegib therapy. The aim would then 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 was advantageous in the fact that it addressed the lack of comparator data issue by allowing the assessment of relative efficacy across comparable patient groups. Unfortunately, this approach was deemed unfeasible, simply because of data limitations.

To inform this analysis, OS and PFS data of aBCC patients treated with BSC was required. Typically, this data may come from published observational literature, disease registries, or clinical studies. Roche is aware of a single study that evaluated BSC treatment in the aBCC

setting (RONNIE; NCT02100111)(72, 73), the study included patients receiving supportive or palliative care.

RONNIE (72) was a multi-centre retrospective chart review study to describe patient characteristics, treatment patterns and outcomes among patients with aBCC. The study included eight patients who received supportive or palliative care. In the RONNIE study, time to progression and death were measured from diagnosis of aBCC, not since date of first treatment. In addition, study visits were not planned but only recorded when a patient visited the study centre. The RONNIE study was deemed an unsuitable source upon which to base a MAIC for the following reasons.

- Only eight of the 121 eligible patients received palliative/supportive care as their first therapy option. This sample size of the study is not large enough to power such an analysis

- The mean age at the time of aBCC diagnosis in RONNIE was 74.6 years; it is therefore assumed that 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

- The definition of time to progression and death was different from the definition in the STEVIE study. STEVIE investigators used the RECIST V1.1 criteria to assess progression, whereas RONNIE investigators used the following definition “Disease progression will be defined as any increase in the sum of the sizes (longest diameters) or number of existing target lesions; recurrence of the primary lesion; and/or increase in the extent of the disease as noted by a physician in the medical record”. This disparity in the assessment of disease progression questions the validity of a MAIC

- The process and timings associated with data collection in the RONNIE study were not as strictly regimented. This point is illustrated by the fact that, target lesions were assessed at a frequency according to the standard of care at each study site. A lack of uniformity on data collection makes the statistical analysis of time-to-event data and thus, an indirect comparison of this data, difficult

- The inclusion criteria in the RONNIE study were less restrictive than in the STEVIE study, see Table 65. This translates into considerable differences in the eligible patient populations of the two studies, which questions the validity of a matching adjustment based on observed patient characteristics

Table 65: Comparison of eligibility criteria in the STEVIE and RONNIE studies

STEVIE(94)
• Patients aged ≥18 years with a histologically confirmed diagnosis of laBCC or mBCC, ECOG PS ≤2, and adequate organ function • Patients with laBCC, ≥1 histologically confirmed lesion deemed inoperable or surgery deemed inappropriate, and radiotherapy must have been previously administered, unless inappropriate • Patients with mBCC, histologic confirmation of distant metastasis • Patients with Gorlin syndrome had to meet criteria for laBCC or mBCC • Patients eligible for enrolment with measurable and/or non-measurable disease, as defined by RECIST v1.1.
RONNIE(72)
• Patients aged ≥18 years • New diagnosis of advanced BCC, defined as (1) locally advanced BCC (inoperable as determined by the site investigator or surgery contraindicated) with receipt of radiation therapy (unless radiation was contraindicated), or (2) metastatic BCC, from 01 January 2005 through 31 December 2010

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status

Use of relative treatment effect from a published vismodegib RCT

In 2012, a study was published by Tang *et al*. that reported on vismodegib therapy in patients diagnosed with Gorlin syndrome. (118) From September 2009 through January 2011, a total of 42 patients with a diagnosis of Gorlin syndrome were enroled at three clinical centres. Patients were randomly assigned to receive either oral vismodegib at a dose of 150 mg daily or placebo for a planned duration of 18 months.

The original notion was to analyse the relative efficacy in the Tang *et al*. RCT and apply it to the clinical data collected in the STEVIE study. The strength of this approach is apparent in the fact that it uses RCT data, the gold standard in evidence-based medicine. However, this modelling strategy was not adopted as Roche was unable to gain access to the complete dataset; therefore, it was uncertain if the outcomes collected in this study were suitable for our purposes. Another prominent issue was the fact that it may not be appropriate to apply conclusions drawn from a Gorlin population to a cohort of laBCC patients.

Selected approach - Landmark method

In light of the issues in the aforementioned approaches, survival curves in the vismodegib arm of the model were adapted using hazard ratios (HRs) to model the survival curves in the BSC arm.

<u>General approach</u>

Non-responders in the STEVIE study were used as a proxy group for patients receiving BSC. To estimate the relative effect of non-responders versus intent-to-treat patients, first, the hazard ratio (hr) of non-responders versus responders for PFS and OS were estimated using a cox regression model. This hazard ratio was then used in the economic model to

calculate the hazard ratio of non-responders versus intent-to-treat patients as $HR(t) = hr^{p(t)}$, where p denotes the proportion of responders in the intent-to-treat population. In the economic model, $HR(t)$ increases over time because the proportion of responders among intent-to-treat patients who are still progression-free or alive increases over time.

Definition of non-responders

The classification of patients according to best response required the definition of a time window. Evaluating patient response over the entire observation period would have led to a biased estimate of the effect of response. Patients who exhibited shorter progression-free and OS times for unobserved reasons were more likely to be classified as non-responders. A comparison between non-responders and responders would thus overestimate the positive effect of response, and consequently the relative effects of vismodegib versus BSC.

To circumvent this issue, a landmark point was defined. The landmark was the point after which response was assessed. To avoid the mentioned bias due to grouping based on expected outcomes we removed all patients who experienced the event of interest (death or progression) before the landmark from the analysis. As a consequence of this definition, non-responders included different patients in the estimation of progression-free survival and overall survival.

In the estimation of PFS, non-responders included patients with stable disease as best response until landmark that have not progressed or died yet. In the estimation of OS, non-responders included patients with stable disease or progressive disease as best response until landmark that had not yet died. The exclusion of patients who progressed or died for both outcomes was deemed inappropriate because it would have left only patients with stable disease in the group of non-responders for both outcomes, and stable disease can be considered a sign of response in metastatic patients. The inclusion of metastatic patients who actually show signs of response would lead to an underestimation of the effect of response, and consequentially of the relative effects of vismodegib versus BSC. This underestimation is particularly pronounced in the estimation of OS hazard rates, which are much higher in metastatic patients.

Table 66: Definition of non-responders for the estimation of hazard ratios

	Overall survival	Progression-free survival
Locally advanced	SD, PD (death until landmark excluded)	SD (PD & death until landmark excluded)
Metastatic	SD, PD (death until landmark excluded)	SD (PD & death until landmark excluded)

Abbreviations: SD, Stable disease; PD, Progressed disease.

Landmark

The STEVIE study protocol stipulated a study visit every 28 days (± 5 days) and safety follow-up visits at 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib. A 6-month landmark point was chosen as a base case value because this period allowed for at least two assessments of all patients regardless of treatment duration. The median time until response of 3.6 months (95% CI: 2.8 to 3.7) in the locally advanced cohort and 9.2 months (95% CI: 2.7, NE) in the metastatic cohort suggested that the time until landmark must be sufficient to observe the required number of responses needed to power the estimation of the hazard ratios. This statistical power is compromised by the fact that the longer the time until landmark, the more patients had to be excluded because they had progressed or died beforehand. For this reason, an option of a 3-month landmark was also built into the model as a scenario analysis. A 3-month period still includes at least two scheduled follow-up study visits for patients who used the treatment for more than 28 days, but not for patients who discontinued treatment early.

Cox proportional hazard regression model

The hazard ratio (hr) was estimated using a semi-parametric cox proportional hazard model. The semi-parametric cox proportional hazard model does not make any assumption about the shape of the hazard over time but assumes that the shape of the hazard function is the same for everyone. In addition, it assumes that differences between individuals are only the consequence of a proportional shift in this hazard function.

Equation 1

$$\boldsymbol{h(t|x) = h_0(t) exp(x\beta_x)}$$

Equation 2

$$\frac{\boldsymbol{h(t|x_j)}}{\boldsymbol{h(t|x_k)}} = \frac{\boldsymbol{exp(x_j\beta_x)}}{\boldsymbol{exp(x_k\beta_k)}}$$

Patient grouping was not based on randomisation therefore imbalances in prognostic factors were expected. To counteract this, ECOG status and age at landmark were controlled for to adjust for differences in prognostic factors of progression-free and overall survival. ECOG status and age were selected because they are known predictors of progression-free and overall survival in skin cancer.(133, 134) The regression was run separately for locally advanced patients, metastatic patients and the combined cohort using either a 3-month or a 6-month landmark. Two candidate specifications, including indicators of being a non-responder(n), ECOG status at baseline(e), as well as age at baseline(a), were assessed. The first specification only included n as a predictor (Equation 3). The second specification included e and a as control variables to adjust for differences in patient characteristics between responders and non-responders at baseline (Equation 5).

Equation 3

$$\boldsymbol{xb = n\beta_n}$$

Equation 4

$$\boldsymbol{xb = n\beta_n + e\beta_e + a\beta_a}$$

The Cox proportional hazard model relies on the proportional hazard assumption. This assumption can be assessed using a plot of the log cumulative hazard over log time for different values of independent variables, in this case an indicator of non-response.

Equation 5

$$\boldsymbol{-ln[-ln\{S(t|x)\}] = -ln[-ln\{S_0(t)\}] - x\beta_x)}$$

The proportionality assumption is deemed to hold if the log cumulative hazard curves for two values of an explanatory variable x are parallel. For PFS, the curves for responders and non-responders are generally parallel or overlap regardless of the landmark. For OS, the log cumulative hazard curves exhibit deviations from a parallel trend. The OS estimates are more uncertain than the PFS estimates because few events were observed. In addition, the diagnostic plots underline the low number of events observed in the group of metastatic

patients. This low number of events leads to considerable uncertainty in the hazard ratio derivation and questions the use of an interaction term for the estimation of heterogeneous effects of response in laBCC and mBCC patients. To account for this, Equation 5 was used with a common effect for locally advanced and metastatic patients and covariate adjustment as a base case scenario in the model.

Results

The hazard ratios calculated from the methodology above generally suggest that non-responders exhibit higher PFS and OS hazard rates than responders. Despite this, results changed considerably when the effect of non-response was estimated separately for laBCC and mBCC patients using an interaction term and when covariates were used in the regression model. When the hazard ratios were estimated separately for laBCC and mBCC patients, the hazard ratios were higher than the common effect among laBCC patients and lower among mBCC patients. Surprisingly, the hazard ratios for mBCC patients were <1. These values suggest that metastatic non-responders exhibited lower PFS and OS rates than metastatic responders. This result is implausible and is also subject to considerable uncertainty because it was only informed by a small number of patients, see Table 67. In addition, clinical opinion suggested that the treatment effect seen with vismodegib is very similar across locally advanced and metastatic group.

Covariate adjustment generally increased the hazard ratios. The effects of covariates suggested that non-responders who did not experience the event of interest until the landmark exhibited more favourable prognostic factors, and thus the effect of non-response was underestimated in an unadjusted estimation. In light of these results, covariate adjusted common hazard ratios for both laBCC and mBCC patients were used in the base case. Sensitivity analyses were performed for the rest of the hazard ratios, except from the not plausible hazard ratios, i.e. those with a value below one.

Table 67: Conditional hazard ratios of non-responders versus responders estimated using the landmark approach

	Progression-free survival		Overall survival	
	No covariates	Covariates*	No covariates	Covariates*
3-month landmark				
Common effect laBCC & mBCC (95% CI)	1.29 (1.018 to 1.636)	1.26 (0.977 to 1.626)	1.647 (1.061 to 2.556)	1.73 (1.091 to 2.744)
Separate effect laBCC (95% CI)	1.313 (1.02 to 1.691)	1.336 (1.02 to 1.75)	1.776 (1.108 to 2.844)	1.889 (1.15 to 3.103)
Separate effect mBCC (95% CI)	0.893 (0.446 to 1.788)	0.953 (0.404 to 2.247)	0.603 (0.176 to 2.062)	0.634 (0.173 to 2.321)
6-month landmark				
Common effect laBCC & mBCC (95% CI)	1.238 (0.952 to 1.61)	1.311 (0.985 to 1.746)	1.919 (1.159 to 3.177)	2.161 (1.27 to 3.676)
Separate effect laBCC (95% CI)	1.208 (0.908 to 1.608)	1.305 (0.959 to 1.776)	1.913 (1.106 to 3.309)	2.192 (1.225 to 3.922)
Separate effect mBCC (95% CI)	1.052 (0.523 to 2.113)	0.995 (0.411 to 2.408)	1.201 (0.322 to 4.478)	1.151 (0.296 to 4.473)

* Covariates included ECOG status and age at landmark

Discussion of methodology and results

In the absence of any suitable data for a MAIC, the landmark method was used to assess outcomes in patients who did not respond to vismodegib as a proxy for patients receiving BSC. The landmark method removes the bias that would occur in a comparison of ever-responders to never-responders over the entire observation period. The conditional hazard ratio between non-responders and responders was estimated among patients who did not experience the event of interest before landmark. This approach hinges on the assumption that the hazard ratio of non-responders versus responders conditional on progression-free and overall survival until the landmark is an unbiased estimated for the hazard ratio over the entire observation time of the STEVIE study. This assumption is impossible to test, and the choice of the landmark is rather arbitrary, therefore two different landmarks were analysed in the model, i.e. 3-months and 6-months.

The use of the landmark methodology is a conservative approach because non-responders until the landmark point can still respond at a later time, thus achieving better outcomes than patients in the BSC arm. An analysis of the clinical assessments of non-responders showed that a large proportion of non-responders subsequently responded after the landmark, regardless of the timepoint chosen, (Table 68).

Table 68: Number of responders/non-responders at landmark, who respond thereafter

	3-month landmark		6-month landmark	
	Non-responders	**Response after landmark**	**Non-responders**	**Response after landmark**
Progression-free survival				
Locally advanced	493	294	213	102
Metastatic	50	14	31	6
Overall survival				
Locally advanced	545	295	274	102
Metastatic	61	14	39	6

The landmark estimated conditional hazard ratio approach has several advantages over alternative approaches. First, the relative comparison between patients treated with vismodegib and BSC is made within the same controlled environment and in the same patient population. Secondly, the classification of patients according to response until landmark and the subsequent removal of patients who experienced the event of interest before the landmark, correct the bias from an endogenous grouping based on expected outcomes. Furthermore, the covariate adjustment corrects the bias from differences in differences between non-responders and responders that originates from differences in patients' baseline risk of progression and death.

The landmark approach also has limitations. The validity of the estimated conditional hazard ratios hinges on the assumption that the conditional hazard ratios estimated after the landmark also apply to the time before the landmark, and to those patients who were excluded because they experienced the event of interest before the landmark. However, this assumption does not seem overly restrictive because it is always fulfilled when the vital proportional hazard assumption is fulfilled. In addition, the choice of the landmark is an

arbitrary decision that cannot be guided by empirical evidence. The lack of a clear decision rule for the choice of the landmark is problematic because the hazard ratios are sensitive to this parameter (Table 68). In the base case analysis, the landmark has been set according to a clear clinical rationale and the schedule of the study visits in the STEVIE study. Two different landmarks were also assessed to illustrate the importance of this choice. Finally, the landmark is too conservative because approximately 50% of non-responders until landmark still respond afterwards (regardless of the choice of landmark). The inclusion of patients who respond after the landmark in the comparison group leads to an overestimation of progression-free and overall survival in patients receiving BSC, and thus to an underestimation of the incremental effect of vismodegib.

5.3.6 Treatment effect duration in OS

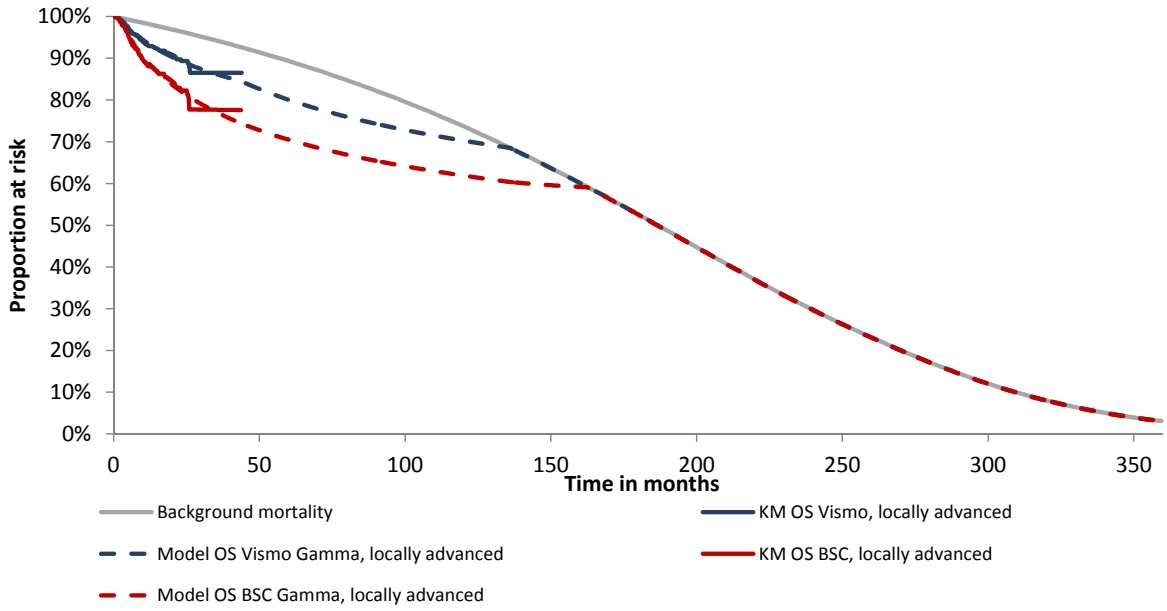
The hazard ratios derived from the analyses described above, were applied to the vismodegib arm to derive the BSC comparator. As briefly mentioned above, it is unrealistic to assume that the treatment effect in OS would last for the entire time horizon. A conservative assumption has been used in the base case to limit the treatment effect to the maximum follow up time in the mBCC and laBCC cohorts. Specifically, the hazard ratio is applied until 44 months in the laBCC cohort and until 38 months in the mBCC cohort. After this timepoint, the vismodegib arm takes the hazard rate of the BSC arm.

5.3.7 Background mortality adjustment

As described in section 5.3.4, the background mortality adjustment can be considered an issue only in the laBCC patients, as the mBCC patients are expected to die from the aBCC.

Option 1: OS curves as the minimum of extrapolations and background mortality
OS rates can be limited to the background mortality rates. This option implies that the OS rates in patients with laBCC are calculated as the minimum of the parametric extrapolations and the background mortality survival rates. When this option is used the difference in survival probabilities between vismodegib and BSC diminishes once the vismodegib curve crosses the background mortality curve and disappears entirely when the BSC survival curve crosses the background mortality survival curve (Figure 38). According to clinical opinion patients who receive just BSC are not expected to show any health improvement with their disease worsening over the years, i.e. the BSC curve is expected to lie always below the vismodegib curve and the UK general population curve. Therefore, this approach seems to be unrealistic.

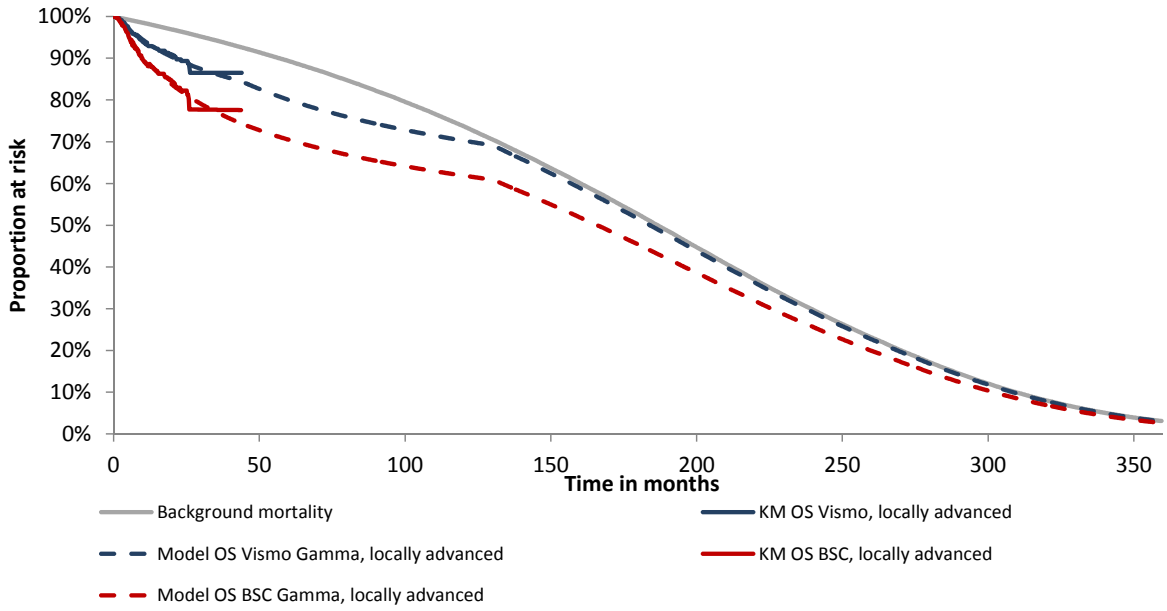
Figure 38: Modelling of overall survival curves as the minimum of parametric extrapolations and background mortality survival



Option 2: Uniform background mortality rates

The second option allows the model to apply uniform background mortality rates to the OS curves in both model arms after a user-defined point in time. This option still assumes that the treatment effect will cease at the end of the STEVIE follow up period and after a particular cut-off point, the background mortality would apply in both arms. The cut-off point, at which background mortality will apply, was selected at the point where the extrapolated curve crosses the background mortality curve, which is approximately 147 months (12.25 years).

Figure 39: Modelling of overall survival curves using uniform background mortality rates after a user-defined timepoint



This approach assumes that after a certain point patients on the BSC arm would have the same risk of dying according to general UK mortality data (background mortality). However, in contrast to the previous approach, the BSC curve lies below the general UK population, as shown Figure 39, i.e. patients who would get BSC have a reduced life expectancy compared to general UK population over the entire time horizon.

The second approach was used in the base case, while the first approach is used as a scenario analysis.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

STEVIE trial

Patients in the STEVIE trial reported HRQoL data using the Skindex-16, a disease-specific questionnaire designed to measure QoL in patients suffering from skin disease. The Skindex-16 is a 16-item patient-completed questionnaire whose items comprise three domains: symptoms, emotions, and function. The items are rated on a seven-point scale measuring the level of bother over the previous week, ranging from zero (never bothered) to six (always bothered). For ease of interpretation of scores, responses to each item were transformed to a linear scale of 100 varying from zero (never bothered) to 100 (always bothered).

The Skindex-16 questionnaire was completed by laBCC and mBCC patients at four timepoints: baseline, 28 days, 168 days, and at the end-of-treatment visit. Descriptive statistics associated with this data are presented below in Table 69.(29, 39)

No mapping function exists for the transformation of Skindex-16 data to EQ-5D, therefore these HRQoL data were not used in the cost-effectiveness analysis.

Table 69: Skindex-16 results reported in STEVIE(39)

		laBCC (N=1,111)	mBCC (N=89)	Total (N=1,200)
Domain: Emotion				
Baseline	n	724	49	773
	Mean (SD)	48.11 (31.23)	37.37 (32.70)	47.43 (31.41)
Cycle 2	n	603	39	642
	Mean (SD)	-17.99 (26.13)	-8.68 (23.50)	-17.42 (26.05)
Cycle 7	n	379	25	404
	Mean (SD)	-25.99 (30.65)	-13.14 (33.25)	-25.20 (30.93)
End of study	n	293	15	308
	Mean (SD)	-22.92 (32.31)	12.49 (26.74)	-21.19 (32.93)
Domain: Function				
Baseline	n	723	49	772
	Mean (SD)	27.29 (30.12)	28.30 (30.42)	27.35 (30.12)
Cycle 2	n	602	39	641
	Mean (SD)	-7.42 (22.19)	-1.71 (16.31)	-7.07 (21.91)
Cycle 7	n	379	25	404
	Mean (SD)	-11.20 (26.51)	-10.00 (24.74)	-11.13 (26.37)
End of study	n	292	15	307
	Mean (SD)	-8.24 (26.29)	7.78 (31.64)	-7.46 (26.74)
Domain: Symptom				
Baseline	n	723	50	773
	Mean (SD)	25.06 (24.69)	23.94 (26.99)	24.99 (24.83)
Cycle 2	n	603	39	642
	Mean (SD)	-9.95 (22.02)	-5.06 (23.10)	-9.66 (22.10)
Cycle 7	n	378	26	404
	Mean (SD)	-12.00 (24.95)	-6.73 (28.92)	-11.66 (25.21)
End of study	n	293	15	308
	Mean (SD)	-11.12 (26.15)	3.61 (22.04)	-10.40 (26.12)

In addition to the Skindex-16 survey, patients with mBCC who were enroled after the approval of Study Protocol Version 4.0 were also asked to complete the MD Anderson Symptom Inventory (MDASI). The MDASI core instrument is a 19-item self-report questionnaire whose items comprise two scales, symptom severity and symptom interference. MDASI was collected at baseline and all subsequent visits including safety follow-up visits for up to 1 year. Baseline results of the MDASI are presented below in Table 70.(39)

Table 70: Baseline MDASI Results for Individual Symptoms in Patients with mBCC Who Originally Signed Protocol Version ≥ 4 (n = 17)(39)

MDASI symptom	Baseline severity score (0 = Not Present; 10 = As Bad as You Can Imagine) Median (Range) (n = 15[a])
Pain	3.0 (0-10)
Fatigue	4.0 (0-9)
Shortness of breath	2.0 (0-6)
Loss of appetite	0.0 (0-7)
Dry mouth	1.0 (0-9)
Coughing	0.0 (0-6)

Abbreviations: MDASI, M.D. Anderson System Inventory.
[a] Baseline MDASI data were available for 15 of 17 eligible patients.

Table 71 shows the number of patients with a greater than or equal to 30% reduction in disease-related symptoms according to the MDASI scale.

Table 71: Patients with a ≥ 30% Reduction in Disease-Related Symptoms According to the MDASI Scale in Patients with Baseline Score ≥ 4(39)

	mBCC	Total
n	10	10
Yes	6 (60%)	6 (60%)
No	4 (40%)	4 (40%)

Baseline MDASI is defined as the last score prior to dosing within a given question.
30% reduction is at any on-treatment, post-baseline visit.
A patient is considered to have had a 30% reduction if they had 4 points or more in a given question at baseline, and a 30% reduction in that question post baseline.

Similarly to Skindex-16, no mapping function exists for the transformation of MDASI data to EQ-5D. This HRQoL data was therefore deemed unsuitable for use in the cost-effectiveness analysis.

ERIVANCE trial

Patients provided data on both BCC symptoms and functioning using the 36-item short form health survey (SF-36; Version 2). The survey consists of the following eight subscales: Physical Functioning, Role−Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role−Emotional, and Mental Health. In addition, two summary scores are derived from these eight subscales: the physical component summary (PCS) and mental component summary (MCS). Each score is scaled from 0 to 100, with higher scores relating to higher or better HRQoL.

The instrument was administered on Day 1, at Week 12, Week 24, and at the end of study or early termination visit. Each of the eight subscale scores, two summary scores, and total score were calculated for each patient at each timepoint. Only patients who completed the SF-36 on Day 1 in accordance with the predefined missing data rules were included in the final data analysis.

All HRQoL data reported in the clinical trials were collected directly from the patients themselves. As EQ-5D is the preferred option for the measurement of HRQoL, SF-36 data was mapped onto EQ-5D using a mapping algorithm developed by Rowen et al. This algorithm allows generic non-preference based data (SF-36), which cannot be used in the QALYs calculation, to be converted into generic preference-based measures (EQ-5D index). It is then possible to derive utilities and subsequently calculate QALYs. This methodology adheres to the guidelines stipulated in the NICE Reference Case and is more fully explored in section 5.4.2 of this submission. (130)

The mental and physical component summary scores are presented in Table 72.

Table 72: Mental and physical component summary scores from SF-36 data - ERIVANCE(39)

Visit	N	Baseline	Value at visit	Change from baseline
Mental component				
Day 1	93	49.57 (11.57)	N/A	N/A
Week 12	82	49.24 (11.79)	51.44 (12.4)	2.20 (-0.22,4.62)
Week 24	75	49.38 (11.47)	51.67 (11.62)	2.29 (0.05,4.53)
End of study	20	49.90 (12.773)	46.11 (16.44)	-3.80 (-10.55,2.96)
Physical component				
Day 1	93	47.81 (9.907)	N/A	N/A
Week 12	82	49.14 (8.85)	47.89 (9.69)	-1.25 (-2.86,0.36)
Week 24	75	49.42 (8.70)	47.52 (9.87)	-1.90 (-3.75,-0.05)
End of study	20	45.72 (11.67)	42.85 (11.14)	-2.86 (-7.39,1.66)

Abbreviations: N/A, Not applicable; SD, Standard deviation.

5.4.2 Mapping

As stated above in section 5.4.1, SF-36 data was collected during the ERIVANCE clinical trial. A mapping algorithm was used to transform this data into EQ-5D indices. As EQ-5D is the preferred measure of adult HRQoL, this methodology is in-line with the guidelines stipulated in the NICE reference case.(130)

The algorithm used in the mapping was originally developed by Rowen *et al.* in 2009.(135) SF-36 assessments were converted into EQ-5D tariff scores using the coefficients from a regression. The regression analysis used all dimensions of the SF-36, along with quadratic terms and interactions. A total of three models were presented in the original publication, model (3) was deemed most appropriate for our purposes. The general model reported in the paper is given below in Equation 6

Equation 6

$$\gamma_i = \alpha + \beta x_{ij} + \theta r_{ij} + \delta z_{ij} + \varepsilon_{ij}$$

where i = 1,2,..., n represents individual respondents and j = 1,2,..., m represents the eight different dimensions. The dependent variable, γ, represents the EQ-5D utility score, x

represents the vector of SF-36 dimensions, r represents the vector of squared terms, z represents the vector of interaction terms and ε_{ij} represents the error term.(135)

Roche is not aware of any appraisals in a similar disease area that have utilised this mapping algorithm.

Mapping was carried out on data collected in ERIVANCE up until the 28th November 2011. To be included in this analysis, patients must have completed the SF-36 at least twice - at baseline and one other follow-up assessment. Patients must also have complied with the missing data rules of the SF-36, as defined in the SF-36, Version 2, scoring manual .(136) Instances where these two criteria were not fulfilled were classified as "missing data". No missing data was imputed in this analysis.

The average EQ-5D utilities in the progression-free and post progression states were calculated as the raw means of the data collected from patients in these health states. The analysis was conducted separately for locally advanced and metastatic patients. Results of the mapping are presented below in Table 73.

Table 73: Results of mapping SF-36 data to EQ-5D utilities

	laBCC (SE)	mBCC (SE)
Progression-free survival	0.839 (0.014)	0.819 (0.017)
Progressive disease*	0.757 (0.037)	0.639 (0.110)

Abbreviations: SE, Standard error.
* Independent Review Facility assessed

5.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL evidence in aBCC patients. This included health state utility values for advanced or metastatic BCC patients that would be suitable for use in a cost-utility analysis. The methodology of this review has been described in section 5.1. As reported in section 5.1.1, to be included in the review, articles had to meet the pre-defined eligibility criteria detailed in Table 58.

Summary of identified studies and results

The systematic literature review identified one publication meeting the pre-specified eligibility criteria, Shingler *et al.*(109)

Five experienced field interviewers based in different locations around the UK undertook the time trade-off (TTO) interviewing, collecting data from 100 patients. Two expert dermatologists with experience of working with patients with BCC and aBCC were interviewed in the development of the health states. Information on how patient functioning was affected in each of the EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) was sought, as well as any other information thought to be relevant to patients with aBCC.

The main study consisted of two parts: the visual analogue scale (VAS) and the TTO exercise. The VAS allowed participants to familiarise themselves with the health states and to collect information on how the states were valued. The states were presented to participants in a random order. The TTO exercise followed completion of the VAS. The aim of the TTO exercise was to elicit utility values for each of the nine included health states.

A summary of the included study, and the utility data reported, is presented in Table 74. The health state considered to give the highest health state utility value was Complete response (0.94 [95% CI 0.92 to 0.95]), whereas the health state with the lowest utility was Progressive disease with a 6 cm lesion (0.67 [95% CI 0.62 to 0.71]).

Differences between the utilities derived from SF-36 mapping and those reported in the Shingler et al. publication can be attributed to methodology. The Shingler et al. utilities have been derived from 100 members of the general UK population, whereas those values mapped from SF-36 data were derived directly from patients in the population of interest. In addition, different health states are evaluated in the Shingler paper and ERIVANCE. This difference in health state definitions makes a direct comparison of utilities difficult.

Table 74: Study summary and reported utility data of the relevant study identified in the systematic review

Study [Country]	Description of population (including sample size, response rate and baseline characteristics)	Description of health states	Results (including uncertainty)	Quality and relevance assessment
Shingler 2013 [UK](109)	A broadly representative sample of 100 members of the UK general public was recruited (100% response rate). All participants had to be 18 years of age or older, reside in the UK, and be able to provide written informed consent. Participant characteristics *Gender (female, %)* 57 *Mean age, years (SD)* 39.1 (15.6) *Ethnicity, %* White: 96.0 Black: 0.0 Asian: 3.0 Other (includes mixed): 1.0	The nine health state vignettes developed and used in the valuation exercise were: • CR • Post-surgical state • PR with small growth (2 cm) • PR with large growth (6 cm) • SD with small growth (2 cm) • SD with multiple growths (at 2 cm) • SD with large growth (6 cm) • PD with small growth (2 cm) • PD with large growth (6 cm)	Health states for aBCC, mean utility (standard deviation) [95% CI] • CR, 0.94 (0.08) [0.92 to 0.95] • Post-surgical state, 0.72 (0.24) [0.67 to 0.76] • PR with small growth, 0.88 (0.12) [0.86 to 0.90] • PR with large growth, 0.82 (0.16) [0.79 to 0.85] • SD with small growth, 0.82 (0.16) [0.79 to 0.86] • SD with multiple growths, 0.80 (0.20) [0.76 to 0.84] • SD with large growth, 0.76 (0.20) [0.72 to 0.80] • PD with small growth, 0.74 (0.21) [0.70 to 0.78] • PD with large growth, 0.67 (0.25) [0.62 to 0.71] VAS rating scores were also reported but not extracted.	Consistency with NICE reference case: × Not EQ-5D × Responses not elicited from patients ✓ Health states valued by members of UK general population Other comments on quality: × Study does not include any description of adverse events × Small sample size × Definitions of the health states are not given ✓ 100% response rate

Abbreviations: CR, complete response; EQ-5D, EuroQol five dimensions questionnaire; NICE, National Institute for Health and Care Excellence; NR, not reported; ONS, Office for National Statistics; PD, progressive disease; PR, partial response; SD, stable disease; TTO, time trade off; UK, United Kingdom; VAS, visual analogue scale

5.4.4 Adverse reactions

There are two approaches that could be taken regarding the inclusion of AE impacts on HRQoL:

- Any disutility resulting from AEs will have been captured in the trial collected HRQoL data. This data was used to derive the health state utilities in the base case economic analysis. It can therefore be assumed that incorporating an additional disutility can be considered double counting
- It can be assumed that trial derived utilities typically underestimate disutility associated with AEs. It is therefore reasonable to apply an additional disutility in the model

For the sake of completeness in this analysis, additional utility decrements are applied in the base case settings.

Adverse events were considered in the base case analysis for the vismodegib therapy arm only. The data used to populate this aspect of the model were taken from the STEVIE clinical study. Following the guidance received in recent technology appraisals, the criteria used for the inclusion/exclusion of an AE are outlined below:

- **Only AEs of Grade ≥ 3:** Typically clinicians will only intervene and treat an AE if it is severe enough to be classified as grade three or above. The costs and HRQoL effects associated with grade one and two events are therefore assumed to be negligible and hence omitted from this analysis
- **Occur in ≥ 2% of patients:** A reasonable assumption was made that an AE must have occurred in at least 2% of the study population in order to be considered included in the model

A summary of the AEs included in the economic analysis are presented below in Table 75. Occurrence rates have been taken from the STEVIE clinical trial. For full details of the adverse events reported in the relevant vismodegib studies, please refer to section 4.12 of this submission.

Hypertension fulfilled the pre-specified criteria for inclusion yet is not known to be associated with vismodegib. Grade ≥ 3 hypertension occurred in 27 (2.2%) of patients during STEVIE. Detailed medical review of these patients revealed that the majority (70%) had hypertension at baseline. Six of the 27 patients had events that were considered related to treatment by

the investigator; all 6 patients had confounding factors based on medical review including age, hypocholesterolaemia, and/or obesity. For these reasons hypertension has been excluded as a relevant AE in this economic analysis.

Table 75: Adverse events included in the model (Grade ≥ 3 Adverse Events Occurring in >2% Patients in STEVIE)(39)

	laBCC (n=1,119)		mBCC (n=96)		Entire STEVIE population (N=1,215)	
Adverse Event	Occurrence of AE	N patients with AE	Occurrence of AE	N patients with AE	Occurrence of AE	N patients with AE
Dysgeusia	29	26	1	1	30	27
Gamma-glutamyltransferase increased	29	29	3	2	32	31
Hypertension	29	23	4	4	33	27
Muscle spasms	115	90	5	5	120	95
Weight decrease	52	45	4	4	56	49

Abbreviations: AE, Adverse event; SCC, Squamous cell carcinoma

Disutilities were taken from a study by Beusterien *et al.* In the study, the authors attempted to derive preference-based utilities in advanced melanoma that capture both the intended clinical response and unintended toxicities associated with treatment. Standard gamble methodology was used and utilities were subsequently elicited from 140 respondents in the UK and Australia for 13 health states.(137) The focus in the Beusterien *et al.* study is advanced melanoma and therefore different from the condition being evaluated in this submission. Despite this difference, the disease areas are very similar and the lack of other suitable sources meant that this study was the best available evidence.

The specific AEs included in our model did not align with those events evaluated in the Beusterien *et al.* publication. In the study, the authors reported utility decrements for generic grade three and grade four events. The values were assumed equal to a 1 day in-/outpatient stay and a 2-5 day hospitalisation, respectively.(137) These values were employed in our analysis.

The loss of QALYs per adverse event was calculated as the product of the utility decrement and the duration of the AE. The AE decrements applied in our model are presented in Table 76, along with their assumed durations.

Table 76: Adverse event decrements included in the model

Adverse event	Disutility	Standard error	Duration [days]*
Grade 3 (1 day in-/outpatient stay)	0.13	0.01	7
Grade 4 (2-5-day hospitalisation)	0.17	0.01	14

* Assumptions

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

Utility is applied to the model consistently over time based on the health state a patient is in. Due to the differing levels of utility, HRQoL is not assumed constant over time, rather overall utility decreases over time as patients transition to both the post-progression health state and death.

Base case analysis: ERIVANCE utilities

Health state utilities in the base case analysis were derived through mapping SF-36 data, collected during ERIVANCE, to EQ-5D. Full details of this methodology are presented in section 5.4.2.

The clinical aspects of this model have been populated using data from the STEVIE clinical trial. The major reservation with applying the ERIVANCE-derived utilities to the STEVIE study population is due to the assessment of response/progression in each of the trials. In laBCC patients, disease progression in STEVIE was assessed according to the RECIST V1.1 criteria. In ERIVANCE disease progression was assessed according to a novel composite measure in the laBCC population. This composite measure was a function of a photographic IRF (visual assessment of external tumour and ulceration), radiographic IRF (tumour imaging, if appropriate), and pathology IRF (tumour biopsy). It is worth noting that the composite measure was based on the RECIST criteria. In addition to the progression assessment discrepancy, the study populations exhibited slight differences in baseline characteristics, some of which are highlighted in Table 77.

Despite these differences, these utilities were both derived from and subsequently applied to a patient population identical to the Erivedge licence, using methodology that is in-line with the NICE Reference case.(130)

Table 77: Baseline characteristics comparison - ERIVANCE vs. STEVIE

	STEVIE (n= 1,215)(39)	ERIVANCE (n= 96)(43)
Age (mean ± SD)	69.5 (15.9)	61.5 (N/A)
Male (%)	694 (57.1%)	59 (61.5%)
White race (%)	879 (72.4%)	96 (100%)
laBCC (%)	1,119 (92.1%)	63 (65.6%)
mBCC (%)	96 (7.9%)	33 (34.4%)

Abbreviations: SD, Standard deviation

The utilities used in the base case economic analysis are presented in Table 81 below.

Scenario analysis: Shingler et al.(109)

In order to present a more complete analysis, a second set of health-state utilities have been included in the model. These health-state utilities were populated using data found in published literature. Values were taken from Shingler *et al.,* a UK vignette study designed to measure societal preferences in nine aBCC disease states.(109) A comprehensive description of this study has been provided in section 5.4.3 of this submission. Reservations over the vignette study design are well documented; nevertheless this study has proven to be the best available evidence in utility literature relevant to this decision problem.

Utilities were firstly calculated for the complete response (CR), partial response (PR), stable disease (SD), and progressed disease (PD) states. This was done by taking an average of the relevant values reported in the Shingler *et al.* publication. Components of these calculations are reported below in Table 78.

Table 78: Response state utilities from Shingler et al. and the adjusted values used in *de novo* economic analysis

Health state in *de novo* analysis	Health states in Shingler *et al.*	Utility reported in Shingler *et al.*	Mean utility used applied in the *de novo* analysis
Complete response	Complete response	0.94	0.94
Partial response	Partial response with small growth (2 cm)	0.88	0.85
	Partial response with large growth (6 cm)	0.82	
Stable disease	Stable disease with small growth (2 cm)	0.82	0.79
	Stable disease with multiple growths (2 cm)	0.80	
	Stable disease with large growth (6 cm)	0.76	
Progressed disease	Progressed disease with small growth (2 cm)	0.74	0.70
	Progressed disease with large growth (6 cm)	0.67	

Progressive disease utility was simply calculated by weighting the proportion of patients in PD by the adjusted utility value from Shingler *et al*.

To calculate the utility associated with the progression free health state per cycle, a weighted average was taken. Utilities for the progression-free states (i.e. CR, PR, and SD) were summed and then each utility was weighted by the proportion of patients in the respective health state in that cycle. These proportions were modelled using descriptive statistics of the number of patients in these states over time since study baseline. The distribution of patients across these response states changed over time, therefore the average utility of patients in the progression-free state of the model also changed. To extrapolate the distribution of patients over these progression-free health states beyond the observation period of STEVIE, the model allows the user to define a timepoint after which the proportions are held constant at the average of the subsequent measurements. While the proportions follow a smooth pattern and a convergence towards a stable proportion for locally advanced patients (Figure 40), the proportion of metastatic patients exhibit some discontinuities which become more pronounced over time (Figure 41). The reason for these variations is the low number of metastatic patients and the higher rate of progression in this population. The proportion of

patients in CR, PR, and SD is probabilistic in the model. This is in order to account for the low absolute number of patients.

Figure 40: Distribution of progression-free locally advanced patients over complete response, partial response and stable disease over time

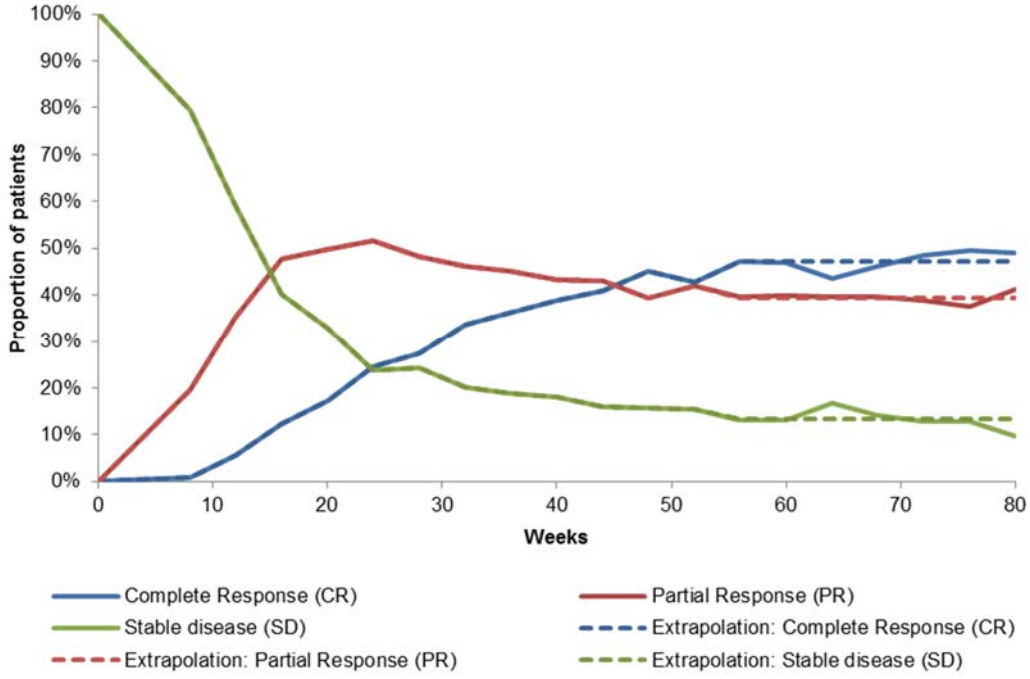
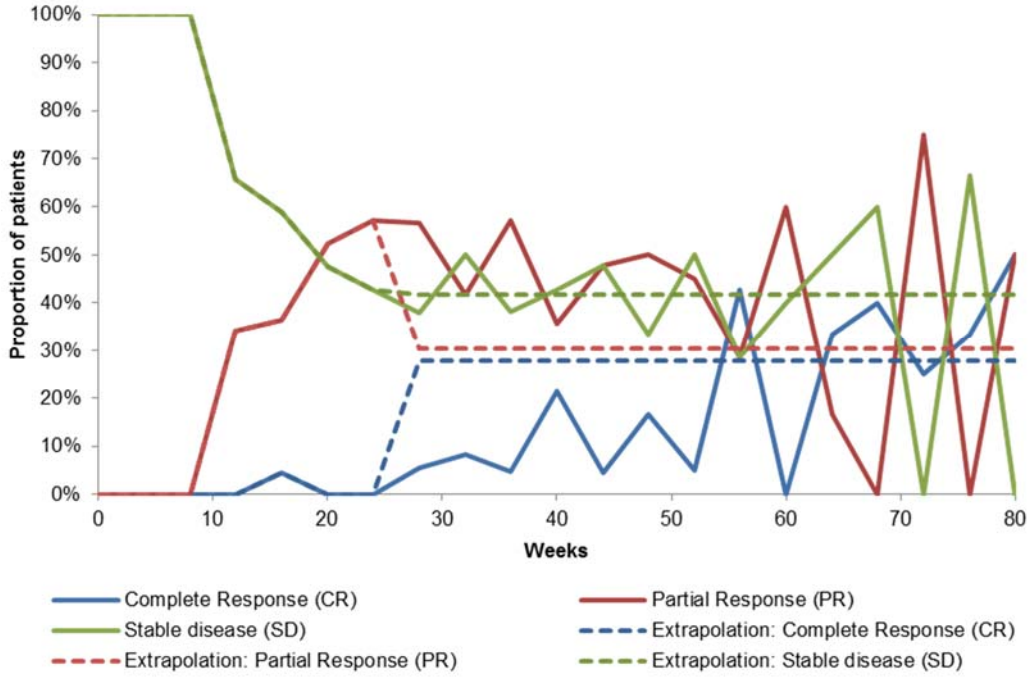


Figure 41 Distribution of progression-free metastatic patients over complete response, partial response and stable disease over time



As an alternative to the observed proportions of patients in the CR, PR and SD states the economic model offers the use of transition probabilities. The transition probabilities were estimated using the R statistics msm package.(138) These transition probabilities for laBCC and mBCC patients are presented below in Table 79 and Table 80, respectively.

Table 79: Transition probabilities across response states, locally advanced patients

		t + 1				
		SD	**PR**	**CR**	**PD**	**Death**
t	SD	0.953	0.035	0.007	0.004	0.001
	PR	0.000	0.979	0.015	0.006	0.000
	CR	0.000	0.000	0.996	0.004	0.000
	PD	0.000	0.000	0.000	0.992	0.008
	Death	0.000	0.000	0.000	0.000	1.000

Table 80: Transition probabilities across response states, metastatic patients

		t + 1				
		SD	**PR**	**CR**	**PD**	**Death**
t	SD	0.974	0.016	0.001	0.009	0.000
	PR	0.000	0.980	0.003	0.009	0.008
	CR	0.000	0.000	0.997	0.003	0.000
	PD	0.000	0.000	0.000	1.000	0.000
	Death	0.000	0.000	0.000	0.000	1.000

In summary, Table 81 displays utilities used in the base case of the economic model. The CR, PR, and SD values derived from Shingler et al. must be interpreted with caution. Values for PR and SD are superior to those reported in the general population for this age. The UK male general population mean utility at this age is 0.79, and female 0.77, giving an average of 0.78. These values are calculated from the regression equations shown below(139)

Utility males = $0.9508566 - 0.0002587 \times age - 0.0000332 \times age^2 + 0.0212126$

Utility females = $0.9508566 - 0.0002587 \times age - 0.0000332 \times age^2$

Table 81: Summary of utility values used in the cost-effectiveness analysis

State	Disease status	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
HS utilities – base case					
Progression-free state	laBCC	0.839 (0.014)	0.811-0.867*	Section 5.4.2	SF-36 data from ERIVANCE mapped to EQ-5D Methodology in-line with NICE reference case(130)
	mBCC	0.819 (0.017)	0.785-0.852*		
Progressed disease state	laBCC	0.757 (0.037)	0.684-0.830*		
	mBCC	0.639 (0.109)	0.424-0.855*		
HS utilities – Scenario analysis					
Progression-free state	Complete response	0.940 (0.080)	0.752-1.00	Section 5.4.5	Health state utilities derived using TTO methodology in aBCC
	Partial response	0.850 (0.020)	0.680-1.00		
	Stable disease	0.793 (0.032)	0.634-0.951		
Progressed disease state		0.705 (0.033)	0.564-0.846		
AE-related disutilities					
Grade 3		- 0.13 (0.01)	N/R	Section 5.4.4	Generic AE disutilities derived using standard gamble methodology in a similar disease area
Grade 4		- 0.17 (0.01)	N/R		

***** No 95% confidence intervals were readily available. Values presented here are ± 20% of the mean
Abbreviations: aBCC, Advanced basal cell carcinoma; AE, Adverse event; HS, Health state; NICE, National Institute for Health and Care Excellence; N/R, Not reported; TTO, Time trade-off.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

Search strategy

Please refer to Section 5.1.1.

Study selection

Please refer to Section 5.1.1.

Summary of identified studies and results

The economic evaluation conducted by Purser et al. reported some data on costs and resource use in this population. This study is described in detail in section 5.1.2 and relevant cost and resource use findings are discussed in section 5.5.2.

5.5.2 Intervention and comparators' costs and resource use

The model uses a price year of 2015/2016. Where available, costs were taken from the following three sources: 2015-2016 NHS national schedule of reference costs,(140) Personal Social Service Research Unit (PSSRU) Unit Costs of Health & Social Care 2016,(141) and the British National Formulary (BNF).(142) Where costs were not available from these sources, other available evidence was used such as expert advice and assumptions.

5.5.2.1 Technology costs

Vismodegib is available in 150 mg capsules to be administered orally. The recommended dose is one 150 mg capsule daily.(34)

According to the BNF, vismodegib has a UK list price of £6,285.00 for 28 capsules, each containing 150 mg. Drug dosing is fixed in the model, as per the SmPC, and therefore the cost of vismodegib per patient per model cycle is calculated as follows.(143)

Table 82: Vismodegib treatment cost per patient per model cycle

Contents per pack	List price	Cost per mg	Frequency per cycle	Mg per cycle	Treatment cost per cycle
28 * 150 mg **=4200.00 mg**	**£6,285.00**(37)	£6,285.00 / 4200.00 mg = **£1.50**	7	150 * 7 = **1050 mg**	£1.50 * 1050 mg = **£1,571.25**

Patients assigned to the BSC treatment arm in the model will not receive any active pharmaceutical intervention. The costs associated with this treatment arm are outlined in the resource use subsection below.

5.5.2.2 Administration costs

Administration for vismodegib is oral and no additional clinical visits are needed for administration. As previously stated, those on BSC receive no active pharmaceutical intervention, therefore administration costs are also zero.

5.5.2.3 Resource use costs

Vismodegib arm

Progression free survival

Resource use associated with vismodegib therapy, for patients in PFS, is minimal. Oncologists are the only physicians permitted to prescribe vismodegib to patients. In the model it is assumed that patients will be required to regularly visit their oncologist for the purposes of treatment monitoring, AE management, and the re-issuing of prescriptions. As part of this treatment monitoring, patients have also been assumed to undergo a blood test. These assumptions have been discussed with clinical experts and are believed to mirror current clinical practice. Patients classified as being in PFS are assumed to visit the oncologist every four weeks (once every four model cycles). The national average unit cost of an oncologist visit was sourced from the NHS reference schedule 2015-2016 and, is reported to be £163.00. The cost of a blood test evaluating "clinical biochemistry" was also taken from the same schedule and is assumed to cost £1.18.(140) Table 83 shows the resource use cost per cycle for this health state in the model.

Table 83: Resource use cost per cycle in PFS in the vismodegib therapy arm

Resource	Unit cost	Reference	Frequency per cycle	Cost per cycle in vismodegib PFS
Oncologist visit	£163.00	NHS Ref. schedule (140) - WF01A-370	0.25	£40.75
Blood test	£1.18	NHS Reference schedule (140) - DAPS04	0.25	£0.30
Total base case cost per cycle in vismodegib PFS = **£41.05**				

Abbreviations: PFS, Progression free survival.

Progressed disease

Once patients have progressed, vismodegib therapy ceases and they are assumed to receive one of two treatment options:

- Monitoring only
- Switch to BSC

In the base case analysis, 67% of patients are believed to receive monitoring only. It is thought that the wounds of these patients will no longer be ulcerative and frequently bleeding, and therefore extensive wound management is unnecessary. The remaining 33% are assumed to receive BSC therapy. The proportion of patients assigned to these options once having progressed was based on consultation with clinical experts (see section 5.10). These proportions are essentially informed assumptions and so will be subject to extensive sensitivity analysis. Both treatment options are outlined in more detail below:

i) Monitoring only

In this regimen patients are assumed to visit their GP once every four weeks to monitor overall health and comorbidities. A GP visit is assumed to constitute 9.22 minutes of patient contact, the average unit cost of such a visit is £36.00. This cost was taken from page 145 of the PSSRU 2016.(141) In addition to a frequent GP visit, patients would also visit the oncologist every 12 weeks to monitor disease status. Details of the resource use associated with this regimen are displayed in Table 84.

Table 84: Resource use associated with "Monitoring only"

Resource	Unit cost	Reference	Frequency per cycle	Cost per cycle
GP visit	£36.00	PSSRU – 2016 (141)	0.25	£24.75
Oncologist visit	£163.00	NHS Ref. schedule (140) - WF01A-370	0.08	£13.58
Total base case cost per cycle (un-weighted) = **£24.75 + £13.58 = £38.33**				
Total base case cost per cycle in MO (with patient proportion applied) = **£25.68**				

Abbreviations: GP, General practitioner; MO, Monitoring only.

ii) "Switch to BSC"

The remaining patients who have progressed on vismodegib therapy are assumed to transfer to the BSC therapy arm. The full extent of the resource use associated with this

regimen is given below. It is assumed that patients would have benefitted from exposure to vismodegib and therefore receive a less demanding schedule of BSC. Full details of this adapted regimen are given below in Table 86.

Best supportive care

Best supportive care is predominantly comprised of wound management. No active, curative treatment is administered; the main treatment aims of this regimen are to manage acute health issues, and make patients as comfortable as possible.

Wound management

Wound management is expected to be administered by a tissue viability nurse (TVN). Given the age and level of frailty in this patient population, these visits are assumed to occur in the community, with the TVN travelling to patients. Frequency of these visits varies widely in clinical practice. We have assumed a base case estimate of two and three times per week in patients with aBCC and no active treatment; as wound management requirements in these patients will only increase over time, for modelling purposes they have been designated 'PFS' and 'PD', respectively. The level of uncertainty around this estimate means that extensive sensitivity analysis will be carried out. As a patient moves from PFS to PD it is assumed that disease worsens and a patient requires a more aggressive treatment regimen, hence the increase in weekly TVN visits. The assumptions around the frequency of the TVN visits are based on clinical opinion as described in 5.10.1. The average unit cost of a TVN visit is £50.65, according to the NHS reference schedule 2016-2016.(140) This figure is assumed to include the cost of the nurse's time and travel only.

Any additional resources used by the TVN, such as bandages and dressings, must also be accounted for. It is assumed that the cost per visit per patient for these resources is £10.00. This estimate is believed to be conservative. The value chosen in the base case analysis assumes the use of basic dressings only. In reality, some patients may receive far more complex forms of wound management, such as silver impregnated dressings. This form of bandage is far more expensive and would therefore increase this parameter dramatically in the model. An ad-hoc literature search was undertaken in attempt to find definitive information pertaining to wound management costs in aBCC. No relevant data was found, however some publications evaluating wound management in similar disease areas were captured. In 2004, Bennett *et al.* estimated the daily cost of treating pressure ulcers in the UK health and social care setting. They reported an estimate of £38.00 to £196.00, depending on severity and complications.(144) Furthermore, the work by Bennett *et al.* was built upon by NICE when they released a costing statement on pressure ulcers in 2014.(145) The costing statement reports that the daily cost of treating a pressure ulcer can expect to

range from £43 to £374, for treating an ulcer without complications the daily cost is assumed to range from £43-£57. The figures quoted here are assumed to include nurse time, dressings, antibiotics, diagnostic tests, and pressure redistributing devices.(145) As these figures encompass some factors not relevant to this patient population, it is difficult to extract an exact figure suitable for use in the model. Given the uncertainty around this assumption, scenario analysis has been undertaken in which this cost is increased over a sizable range.

The Purser publication (see section 5.1.2) also included a wound management/care regimen. Purser reported that wound care would cost £672.90 per month across PFS and PD, this value is an estimate based on a review of vismodegib conducted by the Pan-Canadian Oncology Drug Review, however no specific reference was given on the poster. The four weekly cost of wound care in this submission is £617.20 and £859.80 in PFS and PD respectively (see section 5.5.2.3). The value reported in Purser et al. proved to be a rudimentary form of validation for the assumptions made in the vismodegib model, despite costs and resource use coming from different sources.

Assumptions surrounding the frequency and resource use associated with TVN visits were ascertained through consultation with a practising TVN. The nurse has first-hand experience of treating this patient population, and is therefore believed to be well placed to comment (see section 5.10).

Locally advanced BCC can be associated with significant morbidity as the result of these lesions causing chronic pain, risk of bacterial infection, and sepsis. It should be noted that costs for analgesia and antibiotic therapy have not been factored in to the costs of this model. Justification for this decision is provided in section 5.5.5.

Palliative radiotherapy

Based on consultation with clinical experts, a proportion of patients receiving BSC would undergo a course of palliative radiotherapy. This radiotherapy is not curative and is intended as a tool in wound management only. Clinicians would typically decide to irradiate in situations where a BCC is bleeding both heavily and frequently. According to physicians with first-hand experience, approximately 50% of patients on BSC would receive radiotherapy. The radiotherapy regimen used in the model is laid out as follows: Patients receive 20 Gray in five fractions on a megavoltage machine. It has been assumed that 20% of patients on BSC would undergo “complex” radiotherapy treatment. Complex treatment would be required in situations where the patient needs to be immobilised, the remainder receive basic treatment. Radiotherapy would only be administered once over the course of a patient’s lifetime and is therefore applied as a one-off cost in the model. A summary of the

assumptions, costs, and references involved in a course of palliative radiotherapy are given below in Table 85.

Table 85: Costs and assumptions related to palliative radiotherapy

Item	% of patients in BSC arm	Description	Unit cost	Reference	Regimen	One-off model cost
Palliative RT	30%	A fraction of treatment on a MV machine	£107.00	NHS reference schedule(140) - SC22Z	20 Gray in 5 fractions	£107.00 * 5 = £535 £535 * 0.30 = **£160.50**
Complex palliative RT	20%	A fraction of complex treatment on a MV machine	£153.00	NHS reference schedule(140) - SC23Z	20 Gray in 5 fractions	£153.00 * 5 = £765 £765 * 0.2 = **£153.00**

Abbreviations: MV, Mega voltage; RT, Radiotherapy.

All patient proportions and assumptions stated above are also assumed to apply to those who have progressed on vismodegib and have subsequently received BSC treatment (with the exception of TVN visits; see below).

Monitoring visits

In addition to wound management and palliative radiotherapy, patients will also be expected to visit a dermatologist every 24 weeks in order to monitor their disease. The unit cost of a face-to-face dermatologist visit is £99.00. This value was taken from the NHS reference schedule 2016-2016.(140) Patients will also visit a GP once every four weeks for a check-up and comorbidity management. Assumptions surrounding the frequency of monitoring visits in this arm are assumed to remain constant irrespective of progression.

Table 86 presents a summary of resource use for both the intervention (vismodegib) and comparator (BSC) per cycle in the economic model.

Table 86: List of health states and associated cycle costs in the economic model

Model arm	Health state	Item	Unit cost	Reference	Schedule	Frequency per cycle	Cycle cost
Vismodegib	Progression-free survival	Technology	£6,285.00	BNF	150 mg daily	7	£1,571.25
		Oncologist visit	£163.00	NHS Ref. schedule (140) - WF01A-370	Every 4 weeks*	0.25	£40.75
		Total per model cycle	£1,612.00				
	Progressed disease (Monitoring only)	Oncologist visit	£163.00	NHS Ref. schedule (140) - WF01A-370	Every 12 weeks*	0.083	£13.58
		GP visit	£36.00	PSSRU 2016(141) - page 145	Every 4 weeks	0.250	£24.75
		Total per model cycle	£25.68¥				
	Progressed disease (Switch to BSC)	Oncologist visit	£163.00	NHS Ref. schedule (140) - WF01A-370	Every 12 weeks*	0.083	£13.58
		GP visit	£36.00	PSSRU 2016(141) - page 145	Every 4 weeks	0.250	£24.75
		Tissue viability nurse visit	£50.65	NHS Ref. schedule (140) - N25AF	Once per week*	1	£50.65
		Wound management	£10.00	Consultation with TVN	Once per week*	1	£10.00

		Total per model cycle	£32.66¥				
BSC	Progression-free survival	Dermatologist visit	£99.00	NHS Ref. schedule (140) - WF01A-330	Every 12 weeks*	0.083	£8.25
		GP visit	£36.00	PSSRU 2016(141) - page 145	Every 4 weeks	0.250	£24.75
		Tissue viability nurse visit	£50.65	NHS Ref. schedule (140) - N25AF	Twice per week*	2	£101.30
		Wound management	£10.00	Consultation with TVN	Twice per week*	2	£20.00
		Total per model cycle	£154.30				
	Progressed disease	Dermatologist visit	£99.00	NHS Ref. schedule (140) - WF01A-330	Every 12 weeks*	0.083	£8.25
		GP visit	£36.00	PSSRU 2016(141) - page 145	Every 4 weeks	0.250	£24.75
		Tissue viability nurse visit	£50.65	NHS Ref. schedule (140) - N25AF	Three times per week*	3	£151.95
		Wound management	£10.00	Consultation with TVN	Three times per week*	3	£30.00
		Total per model cycle	£214.95				

Please note: This table does not include any one-off costs applied in the model. Only cyclical resource use is presented. One-off costs are presented in section 5.5.2.3
*** =** Assumption
¥ = Base case patient weightings have been applied. i.e. it has been assumed that 33% of patients switch to BSC, 67% monitoring only.
Abbreviations: BNF, British national formulary; NHS, National health service; TVN, Tissue viability nurse

5.5.3 Health-state unit costs and resource use

The costs and resource use included in each health state for both treatment arms are outlined above in Table 86.

5.5.4 Adverse reaction unit costs and resource use

Adverse events were identified for inclusion in the model according to criteria outlined in section 5.4.4 of this submission. The data used to inform this aspect of the analysis was taken directly from the STEVIE clinical trial. The daily costs of treating these AEs are reported in Table 87. The principle source of cost information was the BNF.(142) and NHS Reference Schedule 2015-2016.(140)

Table 87: List of adverse reactions(39) and summary of costs in the economic model

Adverse reactions	Treatment	Unit cost	Treatment regimen	Weekly cost
Dysgeusia	No treatment available	N/A	N/A	£0.00
GGT increased	No treatment available	N/A	N/A	£0.00
Muscle spasms	Quinine sulphate	£2.17	200mg, once daily	£0.54
Weight decreased	Dietician (Band 3)	£30.00	Monthly visit	£7.50

Abbreviations: N/A, not applicable; GGT, Gamma glutamyltransferase; mg, milligram; mL, millilitre;

5.5.5 Miscellaneous unit costs and resource use

According to the SmPC, patients receiving vismodegib should also be taking contraceptive measures. Given that the average age of patients in the STEVIE trial was 69.50 years, Roche have assumed that the costs associated with pregnancy prevention would be negligible.

Patients in this population have been known to suffer from chronic pain as a result of their BCCs becoming infected. To counteract this, very often a patient's GP may prescribe a form of analgesia along with a course of antibiotics. The cost and resource use associated with this pathway have not been incorporated into this economic analysis. This omission was principally due to a lack of available data. Clinical experts were not able to give informed estimates surrounding frequency of infection, severity, and treatment. Despite this, generic pain relief and antibiotics are thought to be relatively inexpensive; therefore their exclusion from the model is thought to be negligible.

All other costs and resource use included in the analysis have been described and justified in the preceding sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 88 summarises all key variables applied in the base case of the economic model.

Table 88: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	30 years	Fixed	5.2.3
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			
Age	69.5 years	Fixed	5.2.1
% of mBCC patients	7.90%	Fixed	
Clinical inputs			
Treatment duration - laBCC	Actual treatment duration	N/A	5.3
Treatment duration - mBCC	Actual treatment duration	N/A	
Hazard ratio - OS	2.161	1.27 - 3.68 - Lognormal	
Hazard ratio - PFS	1.311	0.99 - 1.75 - Lognormal	
Parametric curves			
TTD – laBCC	Weibull	Multivariate normal	5.3
TTD – mBCC	Weibull	Multivariate normal	
PFS – laBCC	Weibull	Multivariate normal	
PFS – mBCC	Weibull	Multivariate normal	
OS – laBCC	Gamma	Multivariate normal	
OS – mBCC	Weibull	Multivariate normal	
Utilities – base case			
Progression free – laBCC	0.839 (0.014)	0.811-0.867 - Beta	5.4.2
Progressed free – mBCC	0.819 (0.017)	0.785-0.852 - Beta	
Progressed – laBCC	0.757 (0.037)	0.684-0.830 - Beta	
Progressed – mBCC	0.639 (0.109)	0.424-0.855 - Beta	
Utilities – Adverse events			
Grade 3 AE	- 0.13	0.11-0.15 – Normal	5.4.4
Grade 4 AE	- 0.17	0.15-0.19 – Normal	
Technology acquisition costs			
Vismodegib	£6,285.00	Fixed	5.5.2.1
BSC	£0.00	Fixed	
Resource use (patient weightings)			
Vismodegib PD - % to MO	67%	Fixed	5.5.2.3
Vismodegib PD - % to BSC	33%	Fixed	
% of patients on basic RT	30%	Fixed	
% of patients on complex RT	20%	Fixed	
Health state costs (cyclical costs only)			
Vismodegib – PFS	£41.05	£32.84 - £49.25 - Normal	5.5.2.3
Vismodegib – PD	£58.35	£46.68 - £70.02 - Normal	
BSC - PFS	£154.30	£123.44 - £185.16 - Normal	
BSC - PD	£214.95	£171.96 - £257.94 - Normal	
Adverse event management costs (cycle			
Muscle spasms	£0.54	Fixed	5.5.4
Weight decrease	£7.50	Fixed	

* 95% limits calculated using ±30% of mean value

Abbreviations: AE, Adverse event; BSC, Best supportive care; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; OS, Overall survival; PD, Progressive disease; PFS, Progression free survival; RT, Radiotherapy; TTD; Time to treatment discontinuation; TVN; Tissue viability nurse visit.

5.6.2 Assumptions

The key assumptions applied in the base case of the economic model are specified in Table 89.

Table 89: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	30 years (lifetime)	Thirty years is believed to be long enough to reflect all important differences in costs or outcomes between the technologies being compared.
Comparator	Wound management, monitoring visits, and a single course of palliative radiotherapy	Vismodegib represents the only treatment option for this population of patients. Further justification of the choice of comparator is provided in section 5.2.4.
Clinical inputs	Common treatment effect in laBCC and mBCC patients	Clinical experts confirmed that they would expect a similar treatment effect across the locally advanced and metastatic populationsEBSCO
	Six- month landmark point in the hazard ratios calculation	The 6-month landmark incorporates more follow-up visits, therefore more data was available. In addition, the mean treatment duration in STEVIE was 3.6 months; a lower landmark point would not have accurately reflected the true treatment effect in the resulting hazard ratios.
	Hazard ratios were adjusted for age and ECOG status	Patient grouping into responders vs non-responders was not based on randomisation therefore imbalances in prognostic factors were expected. Age and ECOG status at landmark were used to adjust for differences in prognostic factors. ECOG status and age were selected because they are known predictors of survival in skin cancer.(133, 134)
	Duration of treatment effect	Assumed that the treatment effect between vismodegib and BSC is set to equal after the last observation point in STEVIE (conservative)
	Application of HR to accelerated failure time (AFT) models as well as proportional hazard (PH) models	The HR should only be applicable to proportional hazards models, such as Weibull, Exponential and Gompertz. Practically, very few options are left when this is assumed, thus all distributions are used with cautious interpretation. Please note that only OS in laBCC using a HR applied to an AFT model.
HRQoL	Utility decrements were measured in an advanced melanoma population and assumed to be applicable to la/mBCC patients.	Similar disease area and currently the best available evidence.
	Grade 3 and grade 4 AEs were assumed to produce the same decrement in HRQoL as 1 day	

	in-/outpatient stay and 2-5 day hospitalisation, respectively.	
Costs and resource use	The frequency of oncologist visits in the vismodegib arm is assumed to be once every four weeks in PFS and eight weeks in PD	Assumptions surrounding monitoring visits were validated during teleconference calls with several clinical experts.
	The frequency of dermatologist visits in the BSC arm is assumed to be once every 12 weeks.	
	The frequency of GP visits are assumed to be once every 4 weeks, irrespective of health state and treatment arm.	
	The frequency of TVN visits is assumed to be 1,2, and 3 times per week in vismodegib PD, BSC PFS, and BSC PD respectively	Assumptions regarding TVN visits were validated with a practicing TVN with first-hand experience of treating this patient population.
	The cost of managing a patients wound per TVN visit is assumed to be £10.00	
	50% of patients in BSC treatment receive palliative radiotherapy	Assumptions on radiotherapy were developed through indirect consultation with a practising radiologist before being validated amongst clinical experts.
	30% and 20% of patients receiving radiotherapy are assumed to receive basic and complex treatment respectively.	
	Average treatment regimen of patients receiving palliative radiotherapy in this indication is assumed to be - 20 Gray in 5 fractions, once in a lifetime	
	50% of patients receive BSC after progressing on vismodegib therapy	Validated during teleconference calls with several clinical experts.

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Base case results of the economic model are presented below. Results were calculated separately for the laBCC and mBCC cohorts, before being weighted by the percentage of laBCC (92.1%) and mBCC (7.9%) patients in STEVIE to produce economic results for the entire aBCC population.

Vismodegib provided a QALY gain of 8.20, and a life-year gain of 10.66, at a total drug cost of £101,065, and total overall cost of £124,699 when evaluated at list price. In contrast, BSC provides a QALY gain of 7.31, and a life-year gain of 9.50, at a total cost of £93,352.

The resulting base case ICER when comparing vismodegib versus BSC is £35,251 per QALY gained. The equivalent ICER when incorporating the proposed PAS for vismodegib is [redacted] per QALY gained.

See Table 90 for a summary of the base case results at list price and Table 91 for a summary of the base case results with the confidential PAS applied.

Table 90: Base case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years

Table 91: Base case results (PAS applied)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£101,162	9.50	7.31	[redacted]	1.16	0.89	[redacted]
Vismodegib	[redacted]	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years

5.7.2 Clinical outcomes from the model

As described in section 5.3, the primary data source for the economic model was the data derived from the STEVIE study. The follow-up period in STEVIE was shorter than the time horizon of the economic model (30 years to represent a lifetime time horizon); therefore extrapolation of OS, PFS and TTD from STEVIE was required for the area-under-the-curve (AUC) partitioned survival approach.

Median OS and PFS values projected by the model are presented, along with the values reported in ERIVANCE and STEVIE, in Table 92. In both pivotal trials, investigators described the overall survival data as immature, which meant median OS values were not able to be estimated.

Table 92: Summary of model results compared with clinical data

Outcome	ERIVANCE	STEVIE	CE Model
Median PFS (months)	12.8	22.1	22.25
Median OS (years)	N/E	N/E	15.27

Abbreviations: CE, cost-effectiveness; N/E, Not estimable; OS, Overall survival; PFS, Progression free survival

During an ad-hoc teleconference, a clinical expert stated that they would expect an approximate difference of 10%, in terms of the proportion of patients still alive, between the two treatment arms across the time horizon of the model. As a result of this discussion, the difference between treatment arms at various different timepoints was compared. Results of this comparison are displayed in Table 93

Table 93: Proportion of patients still alive at various timepoints in the model

Months	Vismodegib	BSC	Incremental
36	84.62%	74.80%	9.82%
72	74.50%	65.15%	9.35%
120	66.35%	58.23%	8.12%
180	51.99%	45.69%	6.30%

Abbreviations: BSC, Best supportive care

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregating the overall cost and QALY values allows for clarification on which health state is driving the totals in the model. Table 94 shows the disaggregated QALY results for the comparison of vismodegib to BSC.

Table 94: Summary of QALY gain by health state

Health state	QALYs - BSC	QALYs - vismodegib	Increment	Absolute increment	% absolute increment
PFS	1.52	1.74	0.22	0.22	25%
PD	5.79	6.46	0.67	0.67	75%
AEs	0.00	0.00	0.00	0.00	0%
Total	7.31	8.20	0.89	0.89	100%

Abbreviations: AEs, Adverse events; BSC, Best supportive care; PD, Progressive disease; PFS, Progression free survival; QALYs, Quality-adjusted life years

A breakdown of the total costs can be found in Table 95, below. Costs are disaggregated by health state and resource use for both treatment arms. For the with-PAS cost breakdown, please see the confidential PAS appendix.

Table 95: Summary of costs by health state (vismodegib list price)

	BSC	Vismodegib	Increment
Mean costs in PFS			
Treatment cost	£0	£101,065	£101,065
Adverse events	£0	£0	£0
Supportive care	£13,407	£4,438	-£8,969
Total mean cost in PFS	£13,407	£105,503	£92,095
Mean costs in PD			
Supportive care	£79,945	£19,197	-£60,748
Total mean cost in PD	£79,945	£19,197	-£60,748
Total costs	£124,699	£93,352	£31,347

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The

mean values, distributions around the means, and sources used to estimate the parameters are detailed in section 5.6.1.

The PSA results produced a mean ICER of £35,798 per QALY gained when vismodegib was compared with BSC. Results of the PSA compared to the base case analysis are presented in Table 96. Figure 42 and Figure 43 show the cost-effectiveness plane and acceptability curve, respectively.

The analyses below are based on the established list price of vismodegib. Please see the confidential Patient Access Scheme appendix for PSA results incorporating the vismodegib Patient Access Scheme.

Table 96: PSA results compared to base-case (vismodegib list price)

	Costs		QALYs		ICERs	
	Base case (deterministic)	PSA	Base case (deterministic)	PSA	Base case (deterministic)	PSA
BSC	£93,352	£93,061	7.31	7.22	£35,251	£35,798
Vismodegib	£124,699	£124,553	8.20	8.10		

Abbreviations: BSC, best supportive care; ICERs, Incremental cost-effectiveness ratios; PSA, Probabilistic sensitivity analysis; QALYs, Quality-adjusted life-years

Figure 42: Cost-effectiveness plane (vismodegib list price):

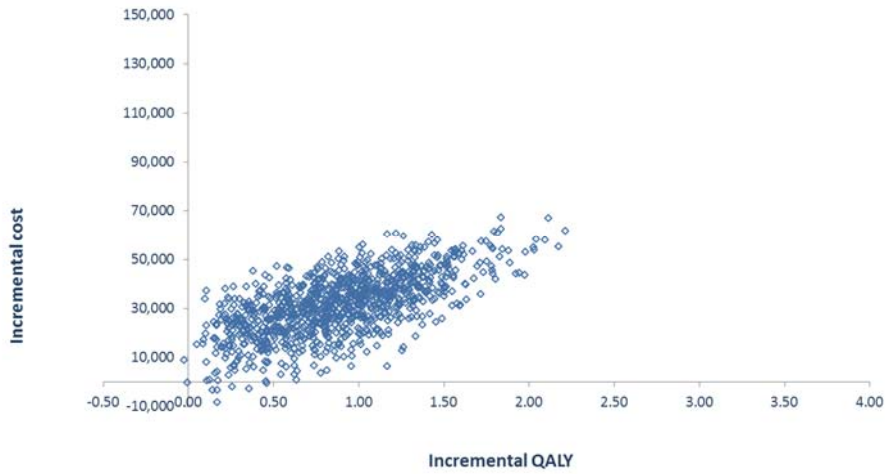
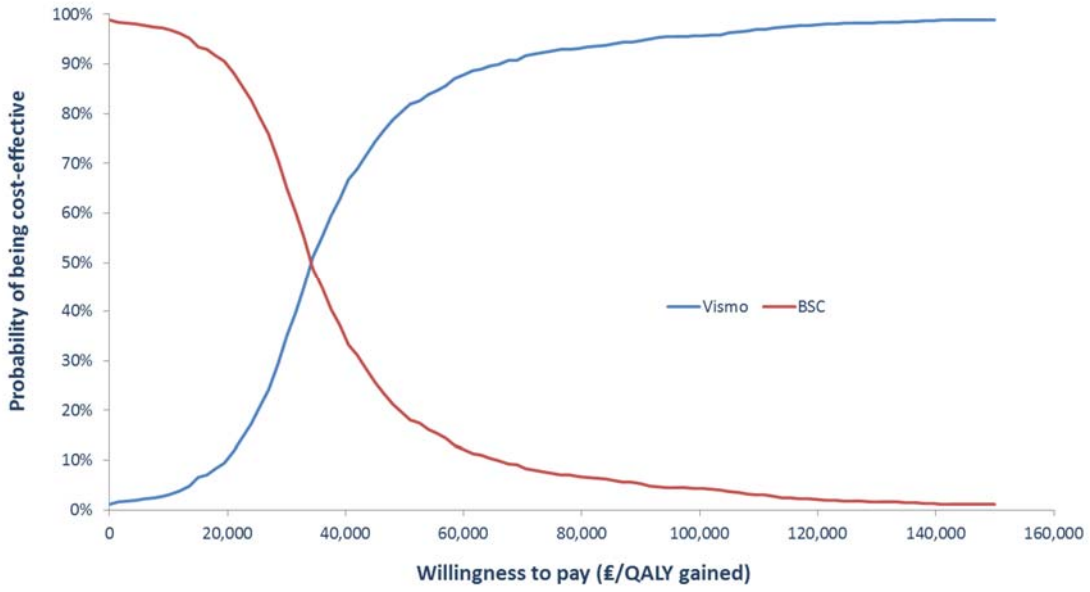


Figure 43: Cost-effectiveness acceptability curve (vismodegib list price)



5.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered *a-priori*, and further informed by the results in section 5.7. For each parameter, the lower and upper values used in the univariate analysis were the 10th and 90th percentiles of the values used in the simulations of the PSA.

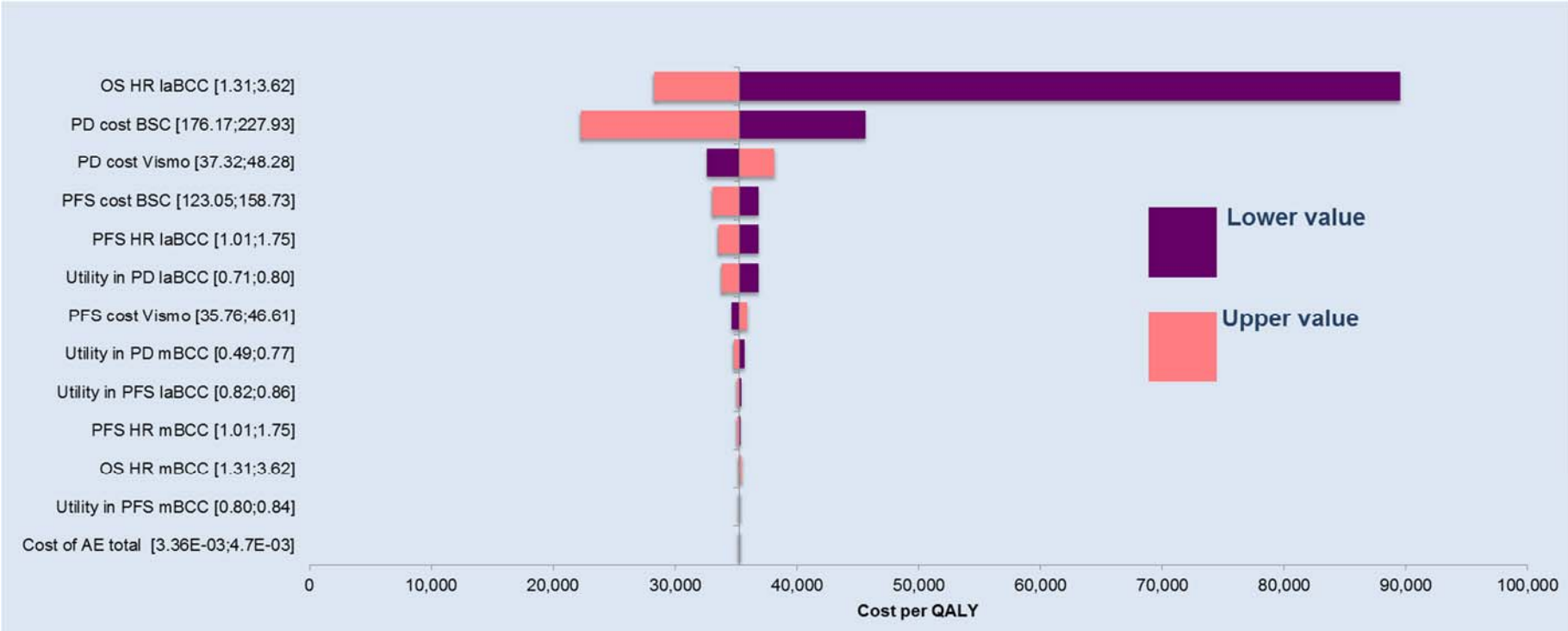
The parameters, distributions used in the PSA, and the values featured in the univariate analysis are given below in Table 97. For the results of the deterministic sensitivity analysis with-PAS, please see the confidential PAS appendix.

Table 97: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Distribution	10th– 90th percentile
PFS cycle cost BSC	£138.55	Log normal distribution	£123.06 – £158.73
PFS cycle cost Vismo	£41.05	Log normal distribution	£35.76 – £46.61
PD cycle cost BSC	£199.20	Log normal distribution	£176.17 – £227.93
PD cycle cost Vismo	£42.60	Log normal distribution	£37.32 – £48.28
Cost of AE total	£0.00	Log normal distribution	£0.00 – £0.00
OS HR laBCC	2.16	Log normal distribution	1.31 – 3.62
OS HR mBCC	2.16	Log normal distribution	1.31 – 3.62
PFS HR laBCC	1.31	Log normal distribution	1.01 – 1.75
PFS HR mBCC	1.31	Log normal distribution	1.01 – 1.75
Utility in PFS laBCC	0.84	Beta distribution	0.82 – 0.86
Utility in PFS mBCC	0.82	Beta distribution	0.80 – 0.84
Utility in PD laBCC	0.76	Beta distribution	0.71 – 0.80
Utility in PD mBCC	0.64	Beta distribution	0.49 – 0.77

Abbreviations: AE, Adverse events; BSC, Best supportive care, HR, Hazard ratio; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; OS, Overall survival; PD, Progressive disease; PFS, Progression free survival; Vismo, Vismodegib.

Figure 44: Univariate sensitivity analysis - Tornado diagram



5.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. The list below outlines the areas of the model that were evaluated. Key without-PAS results are shown in Table 98 and Table 99; entire results of the scenario analysis are reported in Appendix 15.

- Model settings:
    - Time horizon

- Clinical inputs:
    - Alternative parametric distributions for: TTD, PFS, and OS
    - Landmark
    - HR estimation procedure
    - Covariate adjustment
    - Duration of treatment effect cut-off point
    - Starting point to apply background mortality

- Health state utilities:
    - Shingler *et al.* values

- Costs and resource use:
    - Frequency of TVN nurse visit in the vismodegib PD, BSC PFS, and BSC PD health states
    - Cost of wound care per TVN visit

Table 98: Results from scenario analyses – costs and utilities (vismodegib list price)

Parameter	Value	Vismodegib			BSC			Vismodegib vs. BSC			
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Life Years	QALYS	Costs	ICER
Wound care cost per visit	£0.00	10.66	8.20	£123,220	9.50	7.31	£79,422	1.16	0.89	£43,798	£49,252
	£20.00	10.66	8.20	£126,178	9.50	7.31	£107,282	1.16	0.89	£18,896	£21,249
	£40.00	10.66	8.20	£129,137	9.50	7.31	£135,142	1.16	0.89	-£6,006	Dominant
	£60.00	10.66	8.20	£132,095	9.50	7.31	£163,002	1.16	0.89	-£30,907	Dominant
TVN frequency – Vismo - PD	1	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
	3	10.66	8.20	£142,641	9.50	7.31	£93,352	1.16	0.89	£49,289	£55,427
TVN frequency – BSC PFS	1	10.66	8.20	£124,699	9.50	7.31	£87,620	1.16	0.89	£37,079	£41,696
	3	10.66	8.20	£124,699	9.50	7.31	£99,084	1.16	0.89	£25,615	£28,805
	5	10.66	8.20	£124,699	9.50	7.31	£110,548	1.16	0.89	£14,152	£15,914
TVN frequency – BSC PD	1	10.66	8.20	£124,699	9.50	7.31	£44,671	1.16	0.89	£80,028	£89,994
	3	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
	5	10.66	8.20	£124,699	9.50	7.31	£142,034	1.16	0.89	-£17,334	Dominant
Utilities	Shingler	10.66	7.85	£124,699	9.50	6.99	£93,352	1.16	0.86	£31,347	£36,314
	ERIVANCE	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
TTD - laBCC	Exponential	10.66	8.20	£126,531	9.50	7.31	£93,352	1.16	0.89	£33,179	£37,311
	Weibull	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
	Log-normal	10.66	8.20	£137,372	9.50	7.31	£93,352	1.16	0.89	£44,020	£49,504
	Gamma	10.66	8.20	£134,381	9.50	7.31	£93,352	1.16	0.89	£41,029	£46,139
	Log-logistic	10.66	8.20	£134,487	9.50	7.31	£93,352	1.16	0.89	£41,134	£46,258
	Gompertz	10.66	8.20	£126,531	9.50	7.31	£93,352	1.16	0.89	£33,179	£37,311

Abbreviations: HR, Hazard ratio; laBCC, locally advanced basal cell carcinoma; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survival; TTD, Time to treatment discontinuation; TVN, Tissue viability nurse.

Table 99: Results from scenario analyses – efficacy (vismodegib list price)

Parameter	Value	Vismodegib			BSC			Vismodegib vs. BSC			
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Life Years	QALYS	Costs	ICER
PFS - laBCC	Exponential	10.66	8.27	£124,628	9.50	7.36	£91,336	1.16	0.91	£33,292	£36,597
	Weibull	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
	Log-normal	10.66	8.30	£124,601	9.50	7.38	£90,781	1.16	0.92	£33,820	£36,632
	Gamma	10.66	8.20	£124,698	9.50	7.31	£93,315	1.16	0.89	£31,384	£35,270
	Log-logistic	10.66	8.26	£124,637	9.50	7.35	£91,894	1.16	0.91	£32,743	£35,794
	Gompertz	10.66	8.19	£122,894	9.50	7.30	£93,701	1.16	0.88	£29,193	£33,042
OS - laBCC	Exponential	7.95	6.15	£118,670	6.93	5.36	£66,617	1.02	0.78	£52,053	£66,471
	Weibull	7.89	6.10	£118,528	6.87	5.32	£65,992	1.02	0.78	£52,537	£67,334
	Log-normal	9.39	7.24	£121,877	8.25	6.36	£80,311	1.14	0.88	£41,566	£47,350
	Gamma	10.66	8.20	£124,699	9.50	7.31	£93,352	1.16	0.89	£31,347	£35,251
	Log-logistic	8.48	6.55	£119,859	7.40	5.72	£71,465	1.09	0.83	£48,394	£57,965
	Gompertz	7.95	6.15	£118,670	6.93	5.36	£66,617	1.02	0.78	£52,053	£66,471
OS – tx effect cut-off - laBCC	20	10.28	7.91	£123,847	9.54	7.34	£93,728	0.74	0.57	£30,120	£52,686
	40	10.61	8.16	£124,589	9.51	7.31	£93,401	1.11	0.85	£31,188	£36,778
	60	10.76	8.27	£124,908	9.49	7.30	£93,268	1.26	0.97	£31,639	£32,741
	80	10.82	8.32	£125,057	9.49	7.30	£93,209	1.33	1.02	£31,848	£31,178
	100	10.86	8.35	£125,129	9.49	7.30	£93,180	1.37	1.05	£31,949	£30,480
OS BG mort – cut-off - laBCC	0	11.34	8.71	£126,196	11.23	8.62	£111,310	0.11	0.09	£14,887	£163,190
	75	10.24	7.88	£123,754	9.13	7.03	£89,433	1.11	0.85	£34,322	£40,240
	150	10.66	8.20	£124,703	9.53	7.33	£93,661	1.13	0.87	£31,042	£35,756
	225	10.66	8.20	£124,703	9.78	7.52	£96,193	0.89	0.68	£28,511	£41,696
	300	10.66	8.20	£124,703	9.78	7.52	£96,193	0.89	0.68	£28,511	£41,696
	375	10.66	8.20	£124,703	9.78	7.52	£96,196	0.89	0.68	£28,508	£41,705

Abbreviations: BG, Background; HR, Hazard ratio; laBCC, locally advanced basal cell carcinoma; mort., Mortality; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survival.

5.8.4 Summary of sensitivity analyses results

The results of the univariate sensitivity analysis show that the model drivers were the OS hazard ratio in the laBCC population, and the cyclical supportive care costs in PD on both treatment arms. The lowest ICER produced was £22,286/ QALY gained, this result was generated using the lower value (£190.11) for the supportive care cost whilst in PD in the BSC treatment arm. When using the lower value for the OS hazard ratio in the laBCC population the highest ICER was generated (£89,525/ QALY gained). The hazard ratio in OS for the laBCC population also had the largest range in ICERs (£28,311 - £89,525), showing this parameter to be the main driver in the model with a large degree of uncertainty associated.

PSA results are compared to the base case in Table 96. The PSA simulations produced a mean ICER of £35,798/ QALY gained. This value is in close proximity to the base case value of £35,251/ QALY gained. Furthermore, the cost-effectiveness acceptability curve showed that vismodegib had a 30% probability of being the most cost-effective treatment at the £30,000 willingness-to pay-threshold.

A large number of scenario analyses were conducted as part of this submission. The parameters varied included those pertaining to the model settings, clinical parameters, health state utilities, and cost and resource use. ICERs produced by the scenario analysis ranged from vismodegib dominating BSC (cost of wound care per visit = £40, and £60 and TVN visits set to five times per week in PD BSC) to £163,190 (when the starting point at which to apply background mortality is set to zero in the laBCC cohort).

The results included above have been conducted on the list price of vismodegib. However, a PAS has been submitted to the Patient Access Scheme Liaison Unit (PASLU), hence the above results do not accurately reflect the true cost-benefit of vismodegib versus BSC. For the with-PAS results, please see the confidential PAS appendix.

This analysis was limited by the availability of relevant data. To compensate for the shortfall in data, assumptions and expert opinion was relied upon heavily. Along with the chosen modelling approach, these factors introduced a relatively high degree of uncertainty into the analysis. The company is aware of this uncertainty, hence the extensive sensitivity analysis that has been documented in this section.

5.9 Subgroup analysis

Gorlin patients were not included as a separate subgroup in this analysis. Low patient numbers in the pivotal trials meant that clinical data was insufficient to support a robust analysis (see section 5.2.1).

Locally advanced and metastatic disease behaves differently. Despite an observed difference in response between these populations, distinct subgroup analyses were not performed. Results are presented across the entire aBCC cohort as a whole as per the licence indication.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The economic model was constructed specifically from the UK-NHS perspective. The structure is consistent with various other oncology models and previous submissions to NICE in similar disease areas. The methodology described above has broadly adhered to the guidelines stipulated in the NICE reference case. Instances in which Roche has deviated from this guide have been highlighted and justified.

The general model approach and inputs were validated by external health economists and UK clinical experts on two separate occasions. The purpose of this validation was to ensure the model was both theoretically sound and reflective of clinical practice (see section 5.10). Issues discussed with experts included, but were not limited to, resource use; health state utilities; OS projections and extrapolation techniques.

External advisory board

In the first instance, an external advisory board was scheduled. Four practising clinicians were invited to this meeting, all of whom had intimate exposure to both vismodegib therapy and this patient population. In addition to the clinical experts, three external health economists were also present. A range of topics were discussed at this meeting, the most prominent of which are outlined as follows.

i) Health state utilities

The Company presented two possible methodologies for the inclusion of health state utilities in the model (see section 5.4.5):

- Use SF-36 data collected in ERIVANCE and map to EQ-5D indices
- Employ adjusted values originally taken from Shingler *et al.*

The health economists in attendance unanimously agreed that the first approach was the more appropriate option. It was conceded that mapping is not ideal and should only be used where primary EQ-5D data is not available. Ultimately it was decided to use the mapped SF-36 data as the base case utilities and include values taken from Shingler *et al.* as a scenario analysis.

ii) Choice of comparator

As STEVIE and ERIVANCE were single arm and vismodegib is the only established treatment option in this indication, the choice of comparator to include in the model was difficult. Clinical experts suggested a range of treatment options they may consider if vismodegib was unavailable. The options suggested were heroic surgery, palliative radiotherapy, radical radiotherapy, and wound management. Clinical experts agreed that heroic surgery and radical radiotherapy was both detrimental to patient HRQoL and outside of licence in this context. It was therefore decided that BSC in the model would be comprised of wound management and palliative radiotherapy. A more complete description of this discussion is described in section 5.2.4.

iii) Modelling approach

The key studies evaluating vismodegib are both Phase II and single arm. These limitations in the clinical data and lack of relevant published literature meant there were sizable difficulties in the inclusion of a comparator arm in the model. The most promising suggestions offered by the attendees are discussed in detail in section 5.10.

iv) Gorlin subgroup

The inclusion of Gorlin patients as a separate subgroup analysis was also debated at this meeting. Clinical experts agreed that Gorlin patients were indeed atypical aBCC patients and should therefore be considered as such. Roche argued that the clinical data pertaining to this population in STEVIE was insufficient to power a robust analysis. A consensus was reached that nothing could be done to circumvent this issue.

Ad-hoc teleconferences

The treatment pathway that constitutes BSC in this model is not well established: published literature in this area is also very limited. These factors made it necessary for Roche to make certain assumptions in the analysis. Validation of these assumptions was recognised to be crucial, hence the organisation of teleconferences with the clinical experts present at the advisory board. The discussions in these teleconferences were comprised of two main components; clinical aspects, and costs and resource use issues.

Clinical issues

i) Excess disease mortality

A study conducted by Purser and colleagues is discussed in section 5.1.2 of this submission. In this study a partitioned survival model was developed to assess the cost-effectiveness of sonidegib compared to vismodegib. As part of this analysis, authors assumed overall survival rates to be equal to the UK general population mortality data. We therefore wanted to assess the validity of the assumption that there was no excess mortality associated with aBCC in this population.

Those diagnosed with mBCC experience an increased risk of mortality, according to clinicians. The mortality risk associated with laBCC patients is not as clear. Patients with laBCC have a higher risk of death than the general population, however, whether or not the laBCC is always the primary cause of death is unclear.

Ultimately, clinicians thought it is entirely reasonable to assume that this population of aBCC patients would have a greater mortality risk than the general population.

ii) Observed treatment effect difference in laBCC and mBCC

Clinicians were asked to evaluate the assumption that the treatment effect observed with vismodegib therapy is the same, regardless of whether the patient is classified as locally advanced or metastatic. Experts generally thought this was a reasonable assumption to make, thus validating Roche's decision to apply equal hazard ratios to the laBCC and mBCC populations in the base case analysis. As part of scenario analyses, the application of a different effect for laBCC and mBCC was explored.

iii) Difference in the proportion of patients still alive between the vismodegib and BSC arms

The difference in the proportion of patients still alive between the two treatment arms was discussed. One expert expected there to be approximately 10% difference in the proportion of patients still alive between the treatment arms at any point throughout the time horizon.

Projections resulting from the economic model have been compared to this estimate in section 5.7.2.

iv) Overall survival curves – visual inspection

A range of parametric functions can be selected in the model. Due to artefacts in the data, certain assumptions had to be made. Clinicians were asked to examine the curves and offer an opinion as to how realistic they were. Sense checks were also conducted, clinicians were asked to comment on how accurately model projections reflected clinical practice.

Details of these assumptions are specified in their entirety in section 5.3.

Cost and resource use

i) TVN visits

One of the main drivers in the CEM is the frequency with which a TVN visits a patient. Clinicians suggested that a TVN may visit the average patient approximately 2-3 times per week. It is worth noting here that one of the experts stated that depending on severity, some patients may require dressings changed twice per day.

Clinicians also acknowledged that there may be a difference in visit frequency between patients who have progressed on vismodegib and are subsequently receiving BSC and those who have received BSC from the beginning. Furthermore, it was also agreed that there would be an intensifying of visit frequency as a patient moves from PFS to PD.

In Table 100 below, the weekly TVN visit frequencies for each health state are presented. According to the clinicians, these assumptions are thought to be perfectly plausible and perhaps even conservative.

Table 100: Weekly tissue viability nurse visit frequencies by health state

Health state	TVN visit frequency (per week)
Vismodegib – PD	1
BSC – PFS	2
BSC – PD	3

Abbreviations: BSC, Best supportive care; PD, Progressive disease; PFS, Progression free survival; TVN, Tissue viability nurse

ii) Cost of bandages and dressings

There are numerous different dressings and wound management materials available in clinical practice. A nurse may base their choice of dressing on the location of the BCC,

severity of the wound, and general patient preference. This makes the costing of such a resource difficult. Published literature in this area has been highlighted in section 5.5.2.3 but is ultimately insufficient to base a model parameter on.

A practising TVN nurse was consulted and they provided an estimate of £10.00 per visit. Roche appreciates that there is a large degree of variation in wound management costs however this estimate has been calculated under the provision that only basic wound dressings were used. Clinicians warned that a lot of patients would require more advanced and expensive bandages/dressing and therefore agreed that the £10.00 figure was conservative.

iii) Resource use in vismodegib PFS

Clinicians agreed unanimously that a visit to an oncologist every 4 weeks accurately reflected the resource use typically seen in clinical practice in this health state. One clinician did report that a blood test every four weeks is fairly common practice. For the sake of completeness, this suggestion was also incorporated into the model.

iv) Vismodegib PD

The regimen followed by patients who had progressed whilst on vismodegib was discussed. Clinicians agreed that it was reasonable to assume that a proportion of patients would receive BSC once having progressed. When asked to propose an exact proportion of who would receive BSC versus monitoring only, there was some variation. The proportions of patients who progress and subsequently receive BSC put forward by clinicians ranged from 25-33%. The upper value of this range has been used in the base case analysis.

v) BSC Monitoring visits

Patients in BSC are assumed to visit a GP and a dermatologist once every 4 weeks and once every 12 weeks respectively. This was deemed plausible by the clinicians. Interestingly, they maintained that despite progression, it would be impractical to increase the frequency of these visits.

vi) Radiotherapy

The inclusion of palliative radiotherapy as part of BSC was discussed. Despite being technically outside of licence, the clinicians stated that patients in this population are irradiated. This radiotherapy regimen is intended as being purely palliative and has no curative intent; patients are only irradiated to help manage wounds.

A palliative radiotherapy regimen was included in the model. A course of 20 Gray over five fractions administered using a megavoltage machine was deemed to be representative of

the radiotherapy typically given in this population. Palliative radiotherapy is only expected to be given once. Clinicians did however state that not all patients could expect to receive radiotherapy, estimating only 50% of patients receiving BSC would be irradiated.

BCC typically present around sensitive areas, such as the head and neck. Given the severity of disease in this patient population and their unsuitability for surgery, clinicians warned that many of these patients would require special precautions when undergoing radiotherapy. Twenty percent of patients receiving radiotherapy have been assumed to receive “complex” radiotherapy.

Unit costs and references related to the resource use of this treatment are detailed above in section 5.5.2.3.

Technical validation of CEM

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of ‘pressure tests’ were conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

5.11 Interpretation and conclusions of economic evidence

This economic evaluation focused on assessing the cost-effectiveness of vismodegib for the treatment of patients with aBCC from a UK health care perspective.

The economic evaluation utilises clinical data from STEVIE: a single-arm, Phase II study conducted in 152 centres in 36 countries, including the UK. The baseline characteristics of patients with the STEVIE trial have been validated by clinical experts and can be considered broadly representative of the UK vismodegib-eligible population. This evaluation can therefore be considered relevant to clinical practice in England and Wales. A second vismodegib clinical study was used as the source of HRQoL data in the model. ERIVANCE collected SF-36 data throughout the trial period this data was then mapped to produce EQ-5D utilities, as per the NICE reference case. A UK-NHS perspective was taken throughout in terms of cost and resource use. All costs were either taken from published UK sources or health care professionals practising in the UK.

Vismodegib projected a gain of 10.66 life-years, an increase of 1.16 compared to BSC. This result demonstrates the significant survival benefit that vismodegib provides over current treatment options.

Vismodegib provides an incremental gain of 0.89 QALYs. Given the modelling approach the utility differential is derived solely by the time to progression benefit seen in the vismodegib treatment arm.

The base-case ICER comparing vismodegib at list price to BSC is £34,407 (Table 90). The equivalent ICER incorporating the proposed PAS is [redacted] per QALY gained ([redacted]).

Extensive sensitivity analyses were conducted to test how robust the model results were to change in parameter values, and to consider alternative approaches or sources related to the estimation of QALYs, costs, and clinical inputs.

The main drivers of the cost effectiveness results include the hazard ratio for OS and supportive care costs in the PD state.

Purser *et al.* developed an academic poster to report the results and conclusions of an economic evaluation involving vismodegib. The results reported in this submission greatly differ from those reported by Purser and colleagues. The difference in results stems from the difference in comparator (i.e. sonidegib) and the difference in various aspects of the modelling approach. These reasons are specified in greater detail in section 5.1.2.

Roche is aware of certain economic evaluations including vismodegib that were not captured in the economic SLRs. These other evaluations including vismodegib are encompassed in HTA submissions to other countries (e.g. Republic of Ireland and Canada). The company is aware of these submissions and the results reported. Once again these results greatly differ between submissions and once again the differences can be ascribed to modelling approach and choice of comparators.

The key strengths associated with the cost-effectiveness analysis surround its use of the best available evidence to inform the model:

- HRQoL taken directly from pivotal trial population
- Treatment effect data taken from a large (N=1,215) multi-centre clinical trial. Study population were in accordance with the Erivedge licence and the decision problem of this submission

- Costs and resource use data was taken from published UK sources were possible and formally validated by clinical experts

- Extensive sensitivity and scenario analyses were conducted to understand what key variables could potentially have a major impact on the cost-effectiveness results.

Limitations associated with this analysis were primarily due to data. Both vismodegib pivotal trials are single-arm Phase II. The absence of any randomised data made informing the comparator arm of the model very difficult. Various solutions to this problem were explored; unfortunately data availability limited our options again (see 5.3.1). The comparator selected in the economic analysis is not particularly well established. A lack of available published literature meant that the company had to rely on expert opinion and assumptions to inform the cost and resource use parameters.

This economic evaluation could be strengthened in two respects. First, a robust source of comparator data is required. This would greatly reduce the uncertainty surrounding the hazard ratios, which is a main driver of results in this model. A second weakness in this analysis is the lack of data surrounding cost and resource use, especially in the BSC treatment arm. A possible solution to this would be either a longitudinal observational study or the establishment of a registry.

6 Assessment of factors relevant to the NHS and other parties

6.1 Patients eligible for treatment in England and Wales

The incidence of BCC is increasing in the UK. Currently, the crude incidence of BCC in the UK has been estimated to be 153.9 per 100,000 person years (95% confidence interval 151.1 to 156.8). Overall, BCC incidence has been increasing by 3% per year between 1996 and 2003 and approximately 53,000 new cases of BCC are estimated to occur every year in the UK. (20)

The true incidence of symptomatic mBCC, and laBCC that is inappropriate for surgery or radiotherapy (i.e. vismodegib-eligible population) in the UK has been estimated from the UK primary care database. Proportions of laBCC and mBCC reported in the US retrospective analysis of an insurance database have then been applied to the UK specific figures. Further details of this methodology have been presented in section 3.4.

It is estimated that 426 patients will be eligible to receive vismodegib in England and Wales in 2018 (Table 101).

Vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013. Between launch and the end of August 2016, 352 requests had been made for funding for vismodegib through the National Cancer Drugs Fund.

6.2 Market share assumptions

Vismodegib is the only available treatment in this population therefore market share assumptions have not been applied.

6.3 Resource impact

Technology costs and other significant costs associated with vismodegib therapy are identical to those assumed in the cost-effectiveness model and are described in section 5.5.

Vismodegib has been available in England since the Marketing Authorisation was granted in 2013: resource impact is well established and not expected to differ to that which is detailed in section 5.5 of this submission.

6.4 Estimated budget impact

Unit costs for the budget impact were derived from the total year one costs generated in the economic analysis. This accounts for drug acquisition costs, supportive care costs and AE management.

The estimated budget impact on the NHS in England for the first five years is presented in **Table 102**. For with-PAS budget impact, please see the confidential appendix.

Roche estimate 150 patients are currently being treated per year based on an extrapolation of CDF patient applications from January 2016 to August 2016. This estimate gives a market uptake of 35% for 2018, and then this rate has been applied to incidence numbers (calculated as described in section 6.1 above) for the years 2018-2023.

The budget impact analysis utilises year one costs only, and applies this costs for each subsequent year. This does not account for the reducing proportional cost of treating patients after year one, and assumes 100% of patients are new each year in the analysis. The figures presented here are therefore thought to be excessive. In addition, a number of assumptions were made in terms of proportion of patients eligible for treatment, which introduced further uncertainty into the estimates.

Table 101: Vismodegib eligible population in England and Wales: 2018-2023(18)

Population	2018	2019	2020	2021	2022	2023	Comments
Female laBCC	502	517	532	548	564	579	
Male laBCC	499	513	527	542	556	571	
Female mBCC	4	4	4	4	5	5	
Male mBCC	22	22	23	23	24	25	
laBCC incidence	1,000	1,030	1,060	1,090	1,120	1,150	
laBCC inappropriate for surgery or RT	400	412	424	436	448	460	40% of laBCC are inappropriate
mBCC incidence	26	26	27	28	29	29	
aBCC incidence (vismodegib eligible)	426	438	451	464	477	489	

Table 102: Estimated budget impact of vismodegib over 5 years

	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*	£9,399,648	£9,677,143	£9,956,226	£10,236,311	£10,519,254	£10,804,555

* Assumption (as per section 6.4)

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8 List of Appendices

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NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Vismodegib for treating basal cell carcinoma [ID1043]

Dear Company

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 16 March 2017 from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Tuesday 25 April 2017.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Raisa Sidhu, Technical Adviser (raisa.sidhu@nice.org.uk). Any procedural questions should be addressed to Jenna Dilkes, Project Manager (jenna.dilkes@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

A1. Priority question: Please provide the primary SHH4476g (ERIVANCE) clinical study report (CSR) document (data cutoff date: 26 November 2010), referred to in the interim SHH4476g (ERIVANCE) CSR submitted.

A2. Priority question: Please provide the baseline characteristics (including the number of patients with Gorlin syndrome) for the responder and non-responder patient groups at the following landmarks:

a. 3 months;

b. 6 months.

A3. Priority question: Please provide details of the subsequent anti-cancer therapies (including surgery, radiotherapy and those classified as BSC) received by patients following vismodegib treatment discontinuation in:

a. STEVIE;

b. ERIVANCE;

c. Responders and non-responders from STEVIE at the 3 month landmark;

d. Responders and non-responders from STEVIE at the 6 month landmark.

A4. Priority Question: Please provide the rationale for using different definitions of non-responders for the estimation of hazard ratio's for overall survival and progression-free survival (Table 66 in the company's submission (CS)).

A5. Priority Question: Please provide landmark analyses as in Table 67 of the CS for overall survival (OS) using the definition of non-responder for both locally advanced and metastatic BCC of stable disease (i.e. progressed disease and death until landmark excluded) for:

a. 3 months;

b. 6 months.

A6. Priority question: Please provide a landmark analysis at 6 months for all outcomes and the corresponding baseline characteristics for the responders/non-responders for:

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Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

a. the subgroup of patients in STEVIE with Gorlin syndrome at baseline;

b. the subgroup of patients without Gorlin syndrome at baseline.

A7. Priority question: Please provide the following time to response data:

a. mean time to response in STEVIE;

b. median time to response in ERIVANCE;

c. mean time to response in ERIVANCE;

d. median time to response in the responders in the 3 month landmark analysis of STEVIE.

e. median time to response in the responders in the 6 month landmark analysis of STEVIE.

A8. Priority question: Please provide the results of the SF-36 data collection in ERIVANCE.

A9. Priority question: Please clarify where the time to treatment discontinuation (TTD) data from STEVIE was obtained as this is not a specified outcome in the STEVIE CSR.

A10. Priority question: Please provide the number of patients at baseline with:

a. Regional mBCC in STEVIE;

b. Distant mBCC in STEVIE;

c. Regional mBCC in ERIVANCE;

d. Distant mBCC in ERIVANCE.

A11. Priority question: Please provide the number (and percentage) of patients with Gorlin syndrome at baseline in ERIVANCE.

A12. Priority question: Please provide details of the number of patients who had a treatment break and the mean and median duration of treatment breaks in:

a. STEVIE;

b. ERIVANCE;

c. Responders and non-responders from STEVIE at the 3 month landmark;

d. Responders and non-responders from STEVIE at the 6 month landmark.

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Manchester
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United Kingdom

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A13. Please provide the number (and percentage) of patients at baseline in the ERIVANCE and STEVIE studies who are from the UK.

A14. Please provide the definition of progression-free survival (PFS) used in STEVIE for patients with multiple target lesions.

A15. Please clarify if the percentages reported in Table 6 of the CSR for STEVIE for 'substantial morbidity and/or deformity', 'unlikely to be curatively resected' and 'other' all refer to reasons why surgery was medically contraindicated, and clarify if patients could have more than one contraindication to surgery.

A16. Please provide further details of the reasons why the 21% of BCCs located on the trunk in patients in STEVIE were deemed to be unsuitable for surgery (Table 6 of the CSR).

A17. Please provide an explanation for why the median treatment duration in ERIVANCE (17 months) was 6 months longer than in STEVIE (11 months).

A18. Please clarify the number of people for each duration of treatment break in STEVIE and the total number of people in the analyses presented in Table 55 of the CS as the total number (n=499) does not match the number of patients in STEVIE (n=1,215).

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** For the STEVIE study, please provide the following data:

a. Kaplan-Meier (KM) curve for OS for the entire study population, for the entire follow-up period, with numbers-at-risk included;
b. Estimated OS, PFS and TTD curves using the entire STEVIE cohort dataset for the entire observed period (i.e. all patients, no separation into responders/no responder, no landmark), for the different distributions considered in the economic analysis (exponential, Weibull, log-logistic, lognormal, gamma and Gompertz) together with assessment of best fit, separately for laBCC and mBCC.;
c. The KM curves for OS and PFS data for responders and non-responders (defined at landmark), with numbers-at-risk included, for laBCC and mBCC, considered separately. Please provide the KM curves when a 3-month and a 6-month landmark is used, respectively;

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d. Please provide the number of deaths and disease progression events censored before landmark. Please provide these values when a 3-month and a 6-month landmark is used, respectively.

B2. **Priority question:** Please include an option in the economic model (through a scenario analysis to be selected in a drop-down menu) to use the entire STEVIE cohort survival curves (requested in Question B1.b) as the baseline curves for vismodegib. This entails adding an option in the model to replace the baseline vismodegib survival curves used at the moment, based on the responders group in STEVIE, with the survival curves based on all STEVIE patients, to then apply the HRs from the landmark approach in order to derive the BSC curves. Please note that this scenario does not require changing the implementation (or the data) of the HRs used to estimate BSC curves, but only replacing the baseline survival curves used for vismodegib. This should include the OS, PFS and TTD outcomes in the economic analysis, for laBCC and mBCC.

B3. **Priority question:** Please provide an explanation for the difference between the OS extrapolated curves in the CS (for example Figure 37, page 194) and the statistical appendix (Figure 22, gamma distribution for laBCC and Figure 21, lognormal distribution, mBCC) in terms of where the curves cross the background mortality rate.

B4. **Priority question:** Please provide Figure 19 to Figure 24 in the Appendix (pages 234-239) with all the OS unadjusted extrapolated curves (instead of the adjusted OS curves). Please include the background mortality curve in the graphs.

B5. **Priority question:** Please provide the theoretical and the methodological rationale for raising the hazard ratio (HR) estimated for OS, PFS and TTD (used to derive best supportive care (BSC) curves) to the power of one minus the proportion of non-responders in the population (as shown for example in sheet “BSC locally advanced”, column F12:F1577) in the economic model.

B6. **Priority question:** Figure 1 and Figure 2 below show the fitted curves selected to model laBCC and mBCC mortality, together with the adjusted curves used in the vismodegib model. Please provide the clinical and the methodological rationale for the adjustments made to the vismodegib curves in both graphs. In particular, please provide an explanation for why the vismodegib curves depart from the fitted distributions before the latter cross the background mortality curves (i.e. the adjustment made to the fitted vismodegib curves which is not related to these curves crossing the background mortality rate curves). Please also explain why the BSC OS curves are not equally adjusted.

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Figure 1. Overall survival laBCC

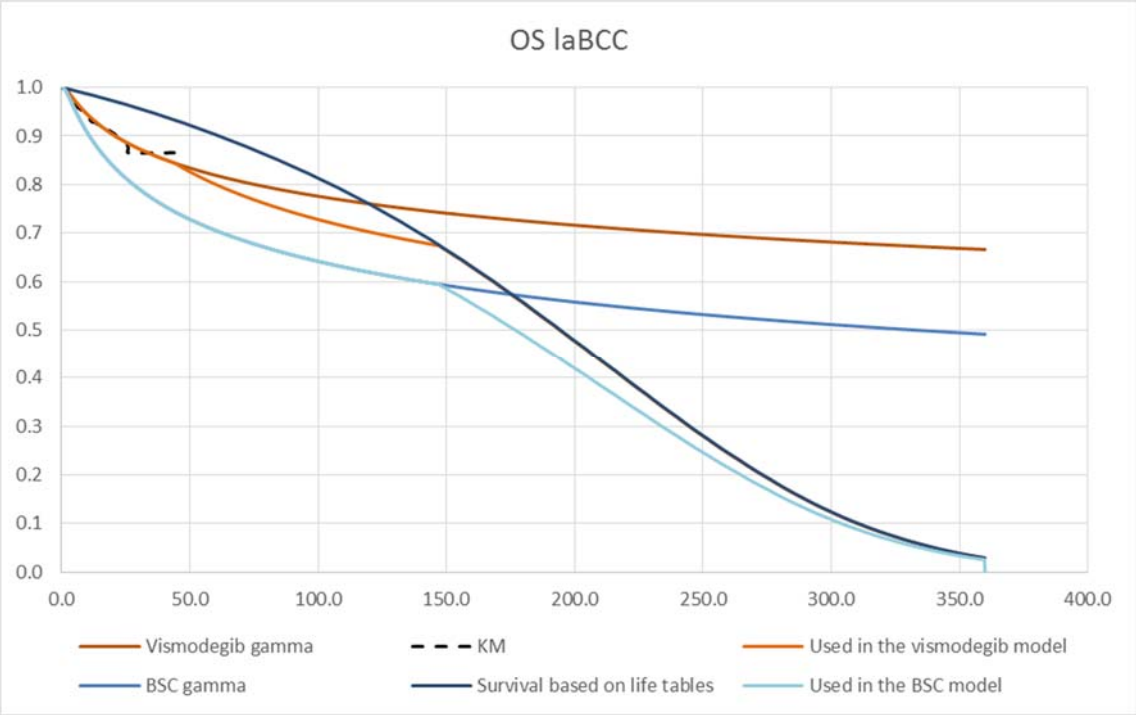

Figure 2. Overall survival mBCC

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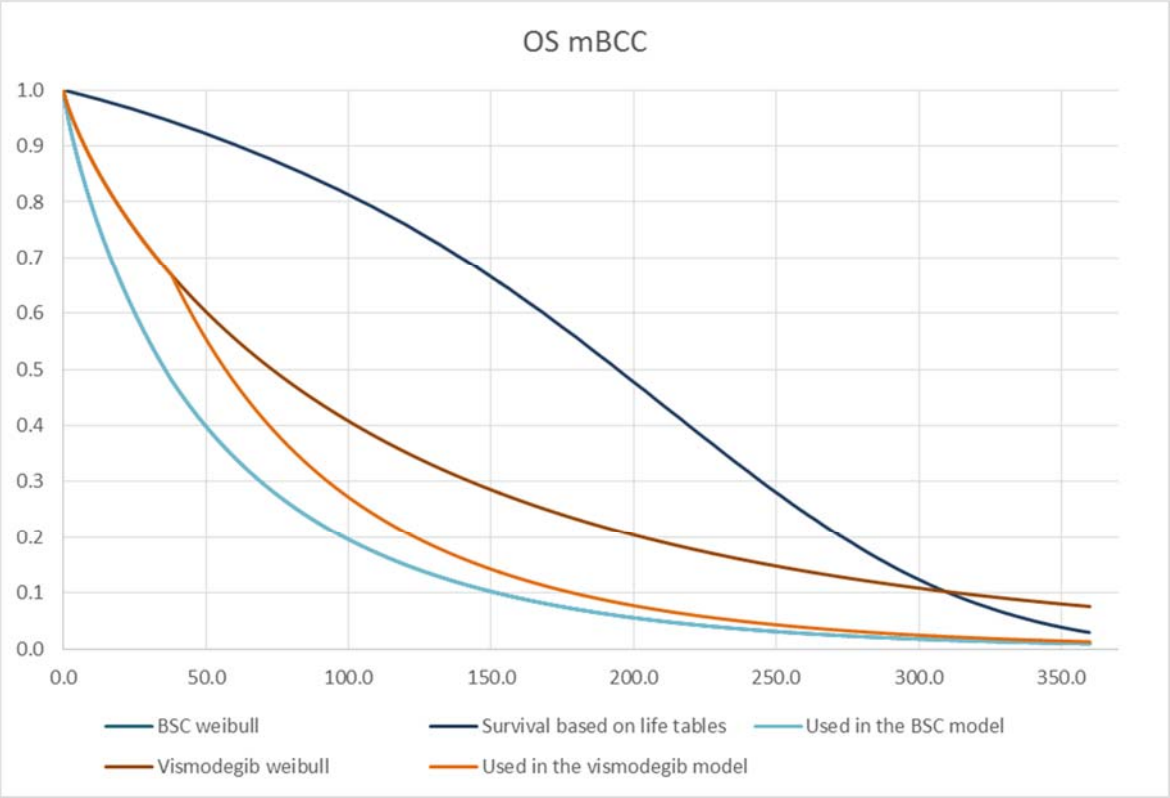

B7. **Priority question:** Please provide the methodological and clinical justification for using the background mortality rate to model the first six cycles of the vismodegib laBCC arm of the model, instead of using the estimated survival curves. Please also explain why the same approach was taken for the first seven cycles of the vismodegib mBCC model.

B8. **Priority question:** The ERG would like to explore the modelled BSC arm for mBCC. If feasible, please use the McCusker *et al.* paper (reference 23 in the CS) to conduct a validation exercise on the modelled BSC arm for mBCC. More specifically please compare, and explain the differences (if any) between the distant mBCC (worst case scenario), regional mBCC (best case scenario) and overall mBCC for BSC in the economic model for:

a. One-year survival probability;
b. Median survival probability;
c. Mean survival;
d. Please estimate an average KM curve (i.e. averaging the distant and regional metastatic KM curves in the McCusker *et al.* paper) as a validation tool for

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comparison with the estimated KM curve for non-responders in mBCC for the BSC arm, using the 3-month and the 6-month landmark, separately;

e. Please use the average KM curve mentioned in Question B8d from the McCusker *et al.* paper to fit a survival curve to these data;

f. Please apply the inverse HR obtained through the landmark approach to the fitted survival curve mentioned in Question B8e as a means to obtain the survival curve for vismodegib and present both estimates curves for BSC and vismodegib;

g. Please include the vismodegib and BSC curves mentioned in Question B8f as a scenario analysis to be selected through a drop-down menu in the economic model.

B9. **Priority question:** Please provide details on the responders and non-responders groups created through the landmark approach using STEVIE data. In particular, please provide:

a. The number of patients in the responders and in the non-responders group for laBCC used to estimate OS and PFS, separately at landmark;

b. The number of patients in the responders and in the non-responders group for mBCC used to estimate OS and PFS, separately at landmark;

c. The mean and median OS for the groups specified in a) and b);

d. The mean and median PFS for the groups specified in a) and b);

e. The mean and median time to response for the groups specified in a) and b).

B10. **Priority question:** Please provide a list demonstrating that a systematic approach was taken to select the prognostic factors included in the estimation of OS and PFS HRs. In particular, please provide:

a. All the prognostic factors considered for their prognostic value in survival outcomes for mBCC and laBCC;

b. The clinical rationale for inclusion/exclusion of these factors;

c. The models with the initial set of covariates considered for inclusion (before the backwards and forwards stepwise selection) together with the results of the stepwise selection process for mBCC and laBCC separately;

d. The results for the covariate analysis using Gorlin syndrome as a covariate.

e. The results with each covariate applied independently and the combined covariate analysis.

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B11. **Priority question:** Please provide the log-cumulative hazard plots for OS and PFS for responders and non-responders mentioned in Page 200 of the CS (first paragraph after Equation 5).

B12. **Priority question:** Please provide the 95% confidence intervals for the mean change in the skindex-16 domains reported in Table 69 (page 208) of the CS.

B13. **Priority question:** Please provide descriptive statistics for the SF-36 dimensions scores data captured in ERIVANCE. More specifically, for each one of the **eight dimensions** of SF-36 please provide:

a. Mean (SD), median and inter-quartile range at baseline and at end of study;
b. Mean change from baseline to end of study, with respective 95% CI;
c. Number of observations obtained at baseline and at end of study;
d. Mean age of responders.

B14. **Priority question:** Please provide the results of the regression analyses using dimensions, squared terms and interaction terms for the ERIVANCE SF-36 dataset. Please provide between and overall R-squared, root mean squared error, rho and Wald chi-square statistics (please see Table 2 in Rowen *et al*. 2009).

B15. **Priority question:** Please clarify why the third GLS model reported in the Rowen *et al*. 2009 publication was deemed the most appropriate model for mapping the SF-36 values from the ERIVANCE trial to obtain mean EQ-5D values for the model.

B16. **Priority question:** Please provide the estimated mean EQ-5D utility values from alternative statistical models that may be accurate predictors of EQ-5D data.

B17. **Priority question:** Please provide a list of the potential implications of using ERIVANCE QoL data to predict utility values for STEVIE, considering these are two different studies, deemed unsuitable for pooling data, and with different baseline prognostic factors, such as age.

B18. **Priority question:** Please include a scenario analysis in the model assuming that vismodegib patients who progress and switch to BSC (assumed to be 33% of patients in the model) receive the same treatment regimen (in terms of resource use) as patients in the BSC treatment arm who have progressed.

B19. Please clarify why the utility values selected for adverse events from the Beusterien *et al*. paper is based on the mean of UK and Australian patients, instead of the values reported for UK patients?

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B20. The cost of a GP visit estimated in cells H52, H73, H107 and H129 in the Excel sheet "Background costs" uses the cost of a dermatologist visit instead of a GP visit. Please correct this in the model.

B21. In Section 5.11 on page 255 of the CS it is stated that "Roche is aware of certain economic evaluations including vismodegib that were not captured in the economic SLRs. These other evaluations including vismodegib are encompassed in HTA submissions to other countries (e.g. Republic of Ireland and Canada)." Please summarise the content of these evaluations similarly to Table 59 of the CS, and provide the full text files of the publications of these economic evaluations.

Section C: Textual clarifications and additional points

C1. Please confirm that Figure 36 (page 193) is not reporting the log-logistic distribution but instead the log-normal (for mBCC) and the gamma (for laBCC) distributions?

C2. Please confirm that the sentence on page 193 of the CS mentioning that the lognormal distribution was used to model mBCC OS in the model is a typo? Please can you confirm that a Weibull distribution was intended to be used for this purpose?

C3. Please report Table 68 (page 203) as percentage values (i.e. please report the values in Table 68 as percentages of the total number of patients included in the laBCC and mBCC responders and non-responders groups, respectively).

C4. Please specify the source of the background mortality data used in the model.

C5. Please clarify whether the following sentence on page 228 of the CS should say 12 weeks instead of 24 weeks: "In addition to wound management and palliative radiotherapy, patients will also be expected to visit a dermatologist every 24 weeks in order to monitor their disease."

ID 1043 – vismodegib in advanced basal cell carcinoma

Response to the Clarification Questions

25th April, 2017

A Clarification on effectiveness data

A.1 **Priority question:** Please provide the primary SHH4476g (ERIVANCE) clinical study report (CSR) document (data cutoff date: 26 November 2010), referred to in the interim SHH4476g (ERIVANCE) CSR submitted.

This report will be provided as part of the response to the ERG's clarification letter.

A.2 **Priority question:** Please provide the baseline characteristics (including the number of patients with Gorlin syndrome) for the responder and non-responder patient groups at the following landmarks:

A.2.a 3 months

A.2.b 6 months

Patients' gender, number of target lesions, race, ECOG performance status, diagnosis of Gorlin syndrome, time from diagnosis, and age by responder status and landmark are included in the Excel file "NICE clarification questions supplementary data", sheet "A2". The descriptive statistics are presented for patients who did not progress or die before the landmark and for patients who did not die before the landmark separately.

A.3 Priority question: Please provide details of the subsequent anti-cancer therapies (including surgery, radiotherapy and those classified as BSC) received by patients following vismodegib treatment discontinuation in:

A.3.a STEVIE

A.3.b ERIVANCE

A.3.c Responders and non-responders from STEVIE at the 3 month landmark

A.3.d Responders and non-responders from STEVIE at the 6 month landmark

No information on subsequent treatments following vismodegib discontinuation was captured during ERIVANCE and STEVIE. It is not possible to provide this information.

A.4 **Priority Question:** Please provide the rationale for using different definitions of non-responders for the estimation of hazard ratios for overall survival and progression-free survival (Table 66 in the company's submission (CS)).

Evaluating patient response over the entire observation period would have led to a biased estimate of the effect of response. Patients who exhibited shorter progression-free and overall survival (OS) times for unobserved reasons were more likely to be classified as non-responders. A comparison between non-responders and responders would thus overestimate the positive effect of response, and consequently the relative effects of vismodegib versus best supportive care (BSC).
To avoid introducing bias due to grouping based on expected outcomes we removed all patients who experienced the event of interest (death or progression) before the landmark from the analysis. As a consequence of this definition, non-responders included different patients in the estimation of progression-free survival (PFS) and OS.

A.5 **Priority Question:** Please provide landmark analyses as in Table 67 of the CS for overall survival (OS) using the definition of non-responder for both locally advanced and metastatic BCC of stable disease (i.e. progressed disease and death until landmark excluded) for:

A.5.a 3 months

A.5.b 6 months

The hazard ratios (HRs) for PFS and OS estimated at 3 and 6 months from baseline using the same definition of non-responders (did not respond and did not progress nor die before the landmark) are included in the Excel file "NICE clarification questions supplementary data", sheet "A5".

Please note that the HRs for PFS did not change compared to the original submission because the same exclusion criterion (patients who died or progressed before the landmark) was already used in the analysis of PFS in the original submission.

A.6 **Priority question:** Please provide a landmark analysis at 6 months for all outcomes and the corresponding baseline characteristics for the responders/non-responders for:

A.6.a The subgroup in STEVIE with Gorlin syndrome at baseline;

A.6.b The subgroup in STEVIE without Gorlin syndrome at baseline;

The HRs of non-responders versus responders by diagnosis of Gorlin syndrome at baseline are included in the Excel file "NICE clarification questions supplementary data", sheet "A6".

Please note that HRs were estimated for the total trial population without stratification by locally advanced and metastatic disease and without covariate adjustment. The stratification by locally advanced and metastatic disease would have led to very small sample sizes and increased uncertainty even further.

A.7 Priority question: Please provide the following time to response data

A.7.a Mean time to response in STEVIE

A.7.b Median time to response in ERIVANCE

A.7.c Mean time to response in ERIVANCE

Answers to part a, b, and c of this question are given in the Excel file "NICE clarification questions supplementary data", sheet "A7".

We calculated the arithmetic mean and median for time to first confirmed response for complete response (CR) / partial response (PR) in STEVIE. These values therefore do not match with the CSR outputs (time to best overall response BOR).
For parts b, and c, estimated means and medians were calculated based on the grouped frequency data in Table 25 of the ERIVANCE CSR.

A.7.d Median time to response in the responders in the 3 month landmark analysis of STEVIE

A.7.e Median time to response in the responders in the 6 month landmark analysis of STEVIE

The mean and median times to first confirmed complete or partial response among patients who showed confirmed response before the 3 and 6-month landmarks are included in the Excel file "NICE clarification questions supplementary data", sheet "A7". The analysis was done separately for patients who did not progress or die before the landmark and for patients who did not die before the landmark, by diagnosis of locally advanced and metastatic disease at baseline.

A.8 Priority question: Please provide the results of the SF-36 data collection in ERIVANCE

Of the 96 efficacy-evaluable patients at baseline, 99% (95 patients) completed at least one question of the SF-36; 96.6% (85 of 88 patients) completed at least one question at 12 weeks, 96.3% (77 of 80 patients) at 24 weeks, and 59.5% (22 of 37 patients) at the end of the study. The change from baseline is presented over time for the SF-36 summary scores (i.e., MCS and PCS) in Figure 1 and Figure 2, respectively.[1]

Figure 1 Change from baseline in SF-36 MCS scores by visit[1]:

		Baseline (Day 1)				Value at Visit				Change from Baseline at Visit					
Visit	n	Mean (SD)	Median	Min	Max	Mean (SD)	Median	Min	Max	Mean (95% CI)	(SD)	SE	Med	Min	Max
Day 1	93	49.57 (11.574)	52.68	11.32	68.01	—	—	—	—	—	—	—	—	—	—
Week 12	82	49.24 (11.787)	52.55	11.32	63.87	51.44 (12.405)	56.14	−2.31	70.05	2.20 (−0.22, 4.62)	(11.007)	1.216	1.61	−37.58	35.58
Week 24	75	49.38 (11.473)	52.41	11.32	63.87	51.67 (11.623)	54.48	4.82	72.29	2.29 (0.05, 4.53)	(9.740)	1.125	0.81	−30.45	34.70
End of study[3]	20	49.90 (12.773)	54.40	17.20	62.39	46.11 (16.438)	51.77	12.49	63.05	−3.80 (−10.55, 2.96)	(14.435)	3.228	0.21	−41.64	13.83

Max=maximum; MCS=Mental Component Summary; Med=median; Min=minimum; SD=standard deviation; SE=standard error of the mean; SF-36=Short Form 36.

Notes: Only patients who had completed the SF-36 Health Survey on Day 1 in accordance with the missing data rules defined in the SF-36, v2, scoring manual were included in this analysis.

Missing data were not imputed. Only observed data were used in this summary.

The n reflects number of patients with both baseline and visit data for this visit available.

[3] Or early termination.

Figure 2 Change from baseline in SF-36 PCS scores by visit[1]:

		Baseline (Day 1)				Value at Visit				Change from Baseline at Visit					
Visit	n	Mean (SD)	Median	Min	Max	Mean (SD)	Median	Min	Max	Mean (95% CI)	(SD)	SE	Median	Min	Max
Day 1	93	47.81 (9.907)	49.05	13.27	62.72	—	—	—	—	—	—	—	—	—	—
Week 12	82	49.14 (8.846)	50.83	19.49	62.72	47.89 (9.687)	48.74	18.38	67.05	−1.25 (−2.86, 0.36)	(7.325)	0.809	−1.22	−25.80	17.89
Week 24	75	49.42 (8.702)	51.08	19.49	62.72	47.52 (9.868)	47.74	14.00	66.82	−1.90 (−3.75, −0.05)	(8.045)	0.929	−2.20	−24.81	23.91
End of study[3]	20	45.72 (11.665)	46.83	13.27	60.50	42.85 (11.135)	41.91	22.73	59.09	−2.86 (−7.39, 1.66)	(9.668)	2.162	−4.29	−18.29	16.79

Max=maximum; Med=median; Min=minimum; PCS=Physical Component Summary; SD=standard deviation; SE=standard error of the mean; SF-36=Short Form 36.

Notes: Only patients who had completed the SF-36 Health Survey on Day 1 in accordance with the missing data rules defined in the SF-36,v2, scoring manual were included in this analysis.

Missing data were not imputed. Only observed data were used in this summary.

The n reflects the number of patients with both baseline and visit data for this visit available.

[3] Or early termination.

In the efficacy-evaluable population, changes from baseline in the SF-36 results varied by subscale and component scores. The mean increase in MCS scores and decrease in PCS scores from baseline to week 24 were 2.3 points (95% CI: 0.05, 4.53) and 1.9 points (95% CI: − 3.75, − 0.05), respectively. The mean changes from baseline in MCS and PCS scores suggest that patient quality of life on treatment was maintained through Week 24.

The changes from baseline over time for the eight SF-36 subscale scores are provided in a separate file to these responses. The supplementary file is entitled "ERIVANCE – SF-36 results".[1]

A.9 Priority question: Please clarify where the time to treatment discontinuation (TTD) data from STEVIE was obtained as this is not a specified outcome in the STEVIE CSR.

Time to treatment discontinuation is calculated as the number of days from first dose to last known dose plus one day, divided by 30.4375. According to a standard internal process used for all of Roche's submissions, treatment was deemed to be discontinued if a patient had a completed treatment discontinuation page and/or study discontinuation page. Otherwise the patient's treatment duration is considered as censored.

The censoring of treatment durations is also the main difference between time to treatment discontinuation used in the model and exposure times reported in the CSRs. The method used, accounts for the fact that patients whose discontinuation date is not observed may continue to take the medication beyond a data cut. Therefore median exposure (~8.6m in STEVIE) is smaller than the median time to treatment discontinuation (~9.2m in STEVIE).

A.10 Priority question: Please provide the number of patients at baseline with:

A.10.a Regional mBCC in STEVIE;

A.10.b Distant mBCC in STEVIE;

Patients with mBCC in STEVIE were not classified as regional (RM, spread to regional lymph nodes, soft tissue (including subcutaneous tissue or skin), salivary glands or ipsilateral muscle in the same anatomic region (e.g. head and neck primary and metastasis) or distant (DM, spread to distant lymph nodes, viscera, bone, brain or meninges).

In STEVIE, patients with mBCC required histologic confirmation of distant BCC metastasis. Of the 96 patients with mBCC, 89 had histologically-confirmed disease (Table 6 in the CSR). The other seven patients had histologically unconfirmed distant metastasis (these patients were excluded from the efficacy-evaluable population).

30 patients in mBCC cohort (31.3%) had lymph node involvement, and 0 had lymph node local regional involvement

A.10.c Regional mBCC in ERIVANCE;

A.10.d Distant mBCC in ERIVANCE.

Patients with mBCC in ERIVANCE were not classified as regional (RM, spread to regional lymph nodes, soft tissue (including subcutaneous tissue or skin), salivary glands or ipsilateral muscle in the same anatomic region (e.g. head and neck primary and metastasis) or distant (DM, spread to distant lymph nodes, viscera, bone, brain or meninges).

In ERIVANCE patients with metastatic BCC required histologic confirmation of distant BCC metastasis (e.g., lung, liver, lymph nodes, or bone) with metastatic disease that was RECIST measurable using CT or MRI. Patients with metastatic disease confined to bone were not considered eligible because of the lack of RECIST measurability. If a patient with locally advanced BCC also had a tumor that

was notcontiguous with cutaneous BCC, e.g., regional lymph nodes (if confirmed on biopsy as BCC and RECIST measurable), the patient was considered as having metastatic BCC and was enrolled in the metastatic cohort.

33 patients in ERIVANCE were considered to have mBCC, of these 7 had lymph node involvement.

A.11 Priority question: Please provide the number (and percentage) of patients with Gorlin syndrome at baseline in ERIVANCE

Twenty patients in the laBCC cohort and zero patients in the mBCC cohort had been diagnosed with Gorlin syndrome.[1]

A.12 Priority question: Please provide details of the number of patients who had a treatment break and the mean and median duration of treatment breaks in:

A.12.a STEVIE;

In an exploratory analysis of the STEVIE study, Dummer et al (Journal of Clinical Oncology 33, no. 15_suppl (May 2015) 9024-9024) analysed 499 patients according to number of treatment breaks received. Median treatment break duration for these 499 patients was 22 days (standard deviation: 13.92). A breakdown of the number and median duration of treatment breaks are reported below in Table 1:

Table 1 Number and duration of treatment breaks reported in STEVIE

No of treatment breaks	Patients	Median treatment duration (days)
0	368	0
1	76	25
2	41	27
3 or more	14	11
Any	499	22

The mean treatment break duration was not reported.

A.12.b ERIVANCE;

No specific analysis has been performed to identify numbers of patients in the ERIVANCE study who had treatment breaks. However, table 10.3.14 of the CSR identifies adverse events leading to interruption of study drug. This shows that, of 104 patients in the study, 29 patients [27.9%] had an adverse event (any grade) which lead to interruption of study drug (7/33 [21.2%] in the metastatic group; 22/71 [31.0%] in the laBCC group). Duration of treatment interruption is not reported in the CSR.

A.12.c Responders and non-responders from STEVIE at the 3 month landmark;

A.12.d Responders and non-responders from STEVIE at the 6 month landmark.

According to the exploratory analysis mentioned in (a), the number of patients per response category who had a treatment break were as follows:

Figure 3 Treatment breaks by response

	Number of treatment breaks			
	0 (n = 358)	1 (n = 72)	2 (n = 39)	≥3 (n = 13)
Best overall response rate, n (%)	218 (61)	47 (65)	37 (95)	11 (85)
Complete response	106 (30)	24 (33)	20 (51)	5 (39)
Partial response	112 (31)	23 (32)	17 (44)	6 (46)
Stable disease	101 (28)	23 (32)	2 (5)	2 (15)
Progressive disease	14 (4)	1 (1)	0	0
Missing/not evaluable	25 (7)	1 (1)	0	0

Results above are as reported in the presentation: it is acknowledged that the numbers of patients do not match those reported in (a). No comment/reason is made in the presentation.

The exploratory analysis was carried out using data from a planned interim analysis that included 499 patients (data cut off: November 6, 2013)

Data on treatment breaks in responders and non-responders are not available at the 3- and 6-month landmarks.

A.13 Please provide the number (and percentage) of patients at baseline in the ERIVANCE and STEVIE studies who are from the UK.

A.13.a ERIVANCE

Please see Table 2 below:

Table 2 UK patients in ERIVANCE[1]

Country / site name	mBCC (n = 33)	laBCC (n = 71)	All patients (n = 104)
United Kingdom	2 (6.1%)	0 (0.0%)	2 (1.9%)
Poole	1 (3.0%)	0 (0.0%)	1 (1.0%)
Royal Marsden	1 (3.0%)	0 (0.0%)	1 (1.0%)

Abbreviations: laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.

A.13.b STEVIE

At total of 1,237 patients were screened in STEVIE, of which 41 were screened in the UK. A total of 1215 patients were in the ITT population, of which 38 were enroled in the UK, please see Table 3 below:

.

Table 3 UK patients in ITT population of STEVIE[2]

Country / centre number	All patients (n = 1215)
United Kingdom	38 (3.13%)
Addenbrooke's	18 (1.48%)
Royal Marsden	1 (0.08%)
St. Thomas'	5 (0.40%)
Western Infirmary	6 (0.49%)
Salford Royal	4 (0.33%)

Freeman	4 (0.33%)

A.14 Please provide the definition of progression-free survival (PFS) used in STEVIE for patients with multiple target lesions.

Patients with measurable or non-measurable disease (per Response Evaluation Criteria in Solid Tumors [RECIST]; version 1.1) were allowed. Objective response was a secondary endpoint, investigator-assessed based on clinical assessments.

As per RECIST when more than one measurable lesion was present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs were identified as target lesions and were recorded and measured at baseline (this means in instances where patients had only one or two organ sites involved a maximum of two and four lesions respectively were recorded).

Progressive disease (clinically assessed as per RECIST v1.1): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.[2,3]

A.15 Please clarify if the percentages reported in Table 6 of the CSR for STEVIE for 'substantial morbidity and/or deformity', 'unlikely to be curatively resected' and 'other' all refer to reasons why surgery was medically contraindicated, and clarify if patients could have more than one contraindication to surgery.

The percentages reported in Table 6 of the CSR for STEVIE for 'substantial morbidity and/or deformity', 'unlikely to be curatively resected' and 'other' all refer to reasons why surgery was medically contraindicated. Patients could have more than one contraindication to surgery. The Case Report Form collected disease history and status (see page 9623 of the CSR). The investigator could record 'metastatic' or

'locally advanced' disease. If 'locally advanced' was selected, there was a further option of selecting either 'inoperable' or 'surgery medically contraindicated'. If 'surgery medically contraindicated' was selected, the investigator could tick any/all of the following that applied:

- recurrent BCC unlikely to be curatively resected
- anticipated substantial morbidity and /or deformity from surgery
- other condition (specify)

This accounts for why the numbers of patients for each reason do not add up to the number of patients contraindicated for surgery: there could be overlap between categories.

A.16 Please provide further details of the reasons why the 21% of BCCs located on the trunk in patients in STEVIE were deemed to be unsuitable for surgery (Table 6 of the CSR).

The CSR only provides details of the reasons for unsuitability for surgery for the two main patient groups (i.e. metastatic or locally advanced). There is no data listing (either in the primary data listings or in the supporting presentations) that breaks down the reasons for unsuitability for surgery by site of disease.

A.17 Please provide an explanation for why the median treatment duration in ERIVANCE (17 months) was 6 months longer than in STEVIE (11 months).

The ERIVANCE trial data has a longer follow-up period as it comes from a follow up analysis, whereas the STEVIE data are from the primary analysis thus resulting in shorter average follow up for PFS. Despite this, >80% of patients in STEVIE had discontinued treatment at the primary analysis cutoff, so duration of treatment estimates can therefore be considered mature.

In both trials, treatment was scheduled to be given until PD, unmanageable toxicity, or patient decision. The majority of patients discontinued treatment for the non-PD

reasons; in STEVIE a higher percentage of patients are censored in the PFS analysis at the time of cutoff. In spite of this, after taking into account the large sample size of STEVIE and the expectation for additional PD events to be reported during safety follow up, it is considered unlikely that PFS estimates will change substantially with further follow up.

Overall, the differing extent of censoring (higher proportion in STEVIE) and the different sample sizes are likely to be contributing reasons for the observed differences in PFS estimates between ERIVANCE and STEVIE. Given the large sample size and substantial amount of PFS information collected at the time of the primary analysis, the PFS results of STEVIE are considered to be representative of the benefit of treatment with vismodegib and supportive of the efficacy previously established in ERIVANCE.

It is also worth noting that the median treatment durations are arithmetic estimates whereas median PFS is from Kaplan Meier estimates and so this should be taken into account when comparing duration of treatment and PFS.

A.18 Please clarify the number of people for each duration of treatment break in STEVIE and the total number of people in the analyses presented in Table 55 of the CS as the total number (n=499) does not match the number of patients in STEVIE (n=1,215).

Please see Table 4 below:

Table 4 Breakdown of treatment breaks by patient number

Number of treatment breaks	Number of patients
0	368
1	76
2	41
3	14

This information is taken from an exploratory analysis, presented by Dummer *et al*. at EADV 2015 (oral presentation) and ASCO 2015 (poster). In the oral presentation, Dummer *et al*. state: "We evaluated outcomes according to number of treatment breaks in an exploratory analysis using data from a planned interim analysis that included 499 patients (data cutoff: November 6, 2013)[1]".[4]

The reference number [1] that Dummer refers to is: Basset-Seguin N et al. Lancet Oncol. 2015;16:729-736.[5]

B Clarification on cost-effectiveness data

B.1 Priority question: For the STEVIE study, please provide the following data:

B.1.a Kaplan-Meier (KM) curve for OS for the entire study population, for the entire follow-up period, with numbers-at-risk included;

The OS Kaplan-Meier data for the combined (locally advanced and metastatic) STEVIE trial population is included in the attached Excel file "NICE clarification questions supplementary data", sheet "B1 – a)".

B.1.b Estimated OS, PFS and TTD curves using the entire STEVIE cohort dataset for the entire observed period (i.e. all patients, no separation into responders/no responder, no landmark), for the different distributions considered in the economic analysis (exponential, Weibull, log-logistic, lognormal, gamma and Gompertz) together with assessment of best fit, separately for laBCC and mBCC.;

The OS, PFS and time-to-treatment discontinuation (TTD) curves in the vismodegib arm of the model were estimated using data on all intent-to-treat (ITT) patients in the STEVIE trial, separately for locally advanced and metastatic basal cell carcinoma. The likelihood-based information criteria can be found on the "Parameters - SAS outputs" sheet, and the diagnostic plots on the "Diagnostic plots" sheet of the submitted Excel model.

B.1.c The KM curves for OS and PFS data for responders and non-responders (defined at landmark), with numbers-at-risk included, for laBCC and mBCC, considered separately. Please provide the KM curves when a 3-month and a 6-month landmark is used, respectively;

The Kaplan-Meier data for OS and PFS for responders and non-responders (defined at 3 and 6 months), separately for locally advanced and metastatic patients, are

included in the Excel file “NICE clarification questions supplementary data”, sheet “B1 – c)”. The overall survival data is provided for both definitions of non-responders, i.e. either exclusion of patients who did not progress or die before the landmark or exclusion of patients who died before the landmark.

B.1.d Please provide the number of deaths and disease progression events censored before landmark. Please provide these values when a 3-month and a 6-month landmark is used, respectively.

The number of patients who were removed from the estimation of the HR of non-responders versus responders because they experienced the event of interest (progression or death for progression-free survival and death for overall survival) is included in the Excel file “NICE clarification questions supplementary data”, sheet “B1 – d)”. The tables include the number of patients who died, progressed or were censored.

B.2 Priority question: Please include an option in the economic model (through a scenario analysis to be selected in a drop-down menu) to use the entire STEVIE cohort survival curves (requested in Question B1.b) as the baseline curves for vismodegib. This entails adding an option in the model to replace the baseline vismodegib survival curves used at the moment, based on the responders group in STEVIE, with the survival curves based on all STEVIE patients, to then apply the HRs from the landmark approach in order to derive the BSC curves. Please note that this scenario does not require changing the implementation (or the data) of the HRs used to estimate BSC curves, but only replacing the baseline survival curves used for vismodegib. This should include the OS, PFS and TTD outcomes in the economic analysis, for laBCC and mBCC.

In the submitted model, the survival curves used to model OS, PFS, and TTD in the vismodegib arm were estimated using the entire ITT population of the STEVIE trial, separately for patients with locally advanced and metastatic disease. The survival curves for the vismodegib arm do not represent the times to event of responders. The central idea of the model was to calculate the HR of non-responders versus ITT

patients from the HR of non-responders versus responders and then apply the HR of non-responders versus ITT patients to the curves estimated based on data of the ITT population.

B.3 **Priority question:** Please provide an explanation for the difference between the OS extrapolated curves in the CS (for example Figure 37, page 194) and the statistical appendix (Figure 22, gamma distribution for laBCC and Figure 21, lognormal distribution, mBCC) in terms of where the curves cross the background mortality rate.

The OS graph presented in Figure 37 of the CS differs from those presented in the appendices due to the option selected in the "duration of treatment effect" field. Figure 37 of the CS presents the OS curves when treatment effect has been maintained for the entire time horizon, whereas the graphs in the appendices present OS results where there is no more effect after the user-defined cut-off point (laBCC cohort = 44.06 months and mBCC cohort = 38.01 months).

This difference is thought to be the reason behind the curves intersecting background mortality at different time points despite the same parametric function being used.

B.4 Priority question: Please provide Figure 19 to Figure 24 in the Appendix (pages 234-239) with all the OS unadjusted extrapolated curves (instead of the adjusted OS curves). Please include the background mortality curve in the graphs.

Unadjusted figures have been provided in the Excel file "NICE clarification questions supplementary data", sheet "B4".

B.5 Priority question: Please provide the theoretical and the methodological rationale for raising the hazard ratio (HR) estimated for OS, PFS and TTD (used to derive best supportive care (BSC) curves) to the power of one minus the proportion of non-responders in the population (as shown for example in sheet "BSC locally advanced", column F12:F1577) in the economic model.

The survival curves in the vismodegib group were modelled using the Kaplan-Meier curves and parametric functions estimated in the entire ITT population of the STEVIE trial. The survival curves in the BSC group were modelled using the survival curves in the vismodegib group of the model and HRs of non-responders versus ITT patients. The HRs of non-responders versus ITT patients were derived from the HRs of non-responders versus responders that were estimated in semi-parametric Cox regressions.

To obtain the HRs of non-responders versus ITT patients from the HRs of non-responders versus responders we first define the log hazard rate in the ITT population as a weighted average of the log hazard rate among responders and non-responders. Let h_{itt} be the hazard rate in the ITT population, h_r the hazard rate in the responder group, h_{nr} the hazard rate in the non-responder group, and p_r the proportion of responders in the ITT population.

$$\log(h_{itt}) = p_r \times \log(h_r) + (1 - p_r) \times \log(h_{nr})$$

To obtain the HR of non-responders versus ITT patients as a function of the HR of non-responders versus responders we first subtract the log hazard rate in the non-responder group from both sides of the above equation and multiply the entire equation by minus 1.

$$\log(h_{nr}) - \log(h_{itt}) = p_r \times [\log(h_{nr}) - \log(h_r)]$$

The differences in the log hazard rates can then be re-written as log HRs.

$$\log\left(\frac{h_{nr}}{h_{itt}}\right) = p_r \times \log\left(\frac{h_{nr}}{h_r}\right)$$

This relationship indicates that the log HR of non-responders versus ITT patients is the log hazard ratio of non-responders versus responders multiplied by the

proportion of responders in the ITT population, or equivalently, that the HR of non-responders versus ITT patients equals the HR of non-responders versus responders in the power of the proportion of responders in the ITT population.

$$\frac{h_{nr}}{h_{itt}} = \left(\frac{h_{nr}}{h_r}\right)^{p_r}$$

Because non-responders die at higher rates than responders the proportion of responders in the ITT population increases over time. The HR between non-responders and ITT patients $HR_{nr-itt}(t)$ is thus modelled to vary over time dependent on the time-invariant average HR of responders versus non-responders HR_{nr-r} and the time-varying proportion of responders in the ITT population $p_r(t)$.

$$HR_{nr-itt}(t) = HR_{nr-r}^{p_r(t)}$$

B.6 **Priority question:** Figure 1 and Figure 2 below show the fitted curves selected to model laBCC and mBCC mortality, together with the adjusted curves used in the vismodegib model. Please provide the clinical and the methodological rationale for the adjustments made to the vismodegib curves in both graphs. In particular, please provide an explanation for why the vismodegib curves depart from the fitted distributions before the latter cross the background mortality curves (i.e. the adjustment made to the fitted vismodegib curves which is not related to these curves crossing the background mortality rate curves). Please also explain why the BSC OS curves are not equally adjusted.

The adjustment made independent of the background mortality is related to the treatment duration assumption. In the model, we have assumed that patients will only experience a treatment effect for the duration of the STEVIE observation period. Once this period has elapsed, patients are no longer expected to derive any further benefit from treatment. In other words, the HR between the vismodegib and BSC arm is set to one.

The rationale for this assumption was that it would have been unrealistic to assume that the HR remains constant for the entirety of a patient's life. It is worth noting however, that setting the treatment benefit to cease after the STEVIE observation

period (44.06 months for laBCC and 38.01 months in mBCC) is conservative. In clinical practice, patients can expect to see a treatment benefit after these time points.

B.7 **Priority question:** Please provide the methodological and clinical justification for using the background mortality rate to model the first six cycles of the vismodegib laBCC arm of the model, instead of using the estimated survival curves. Please also explain why the same approach was taken for the first seven cycles of the vismodegib mBCC model.

Overall survival was modelled using parametric extrapolation functions modelled on the Kaplan-Meier curves ("Model Inputs" sheet, cells G99 (km_os_new_l) & G100 (km_os_new_m)). Background mortality rates were applied to the OS curves after 147 months in the locally advanced group and 360 months in the metastatic group to prevent the overall survival curves crossing the background mortality survival curve.

B.8 **Priority question:** The ERG would like to explore the modelled BSC arm for mBCC. If feasible, please use the McCusker et al. paper (reference 23 in the CS) to conduct a validation exercise on the modelled BSC arm for mBCC. More specifically please compare, and explain the differences (if any) between the distant mBCC (worst case scenario), regional mBCC (best case scenario) and overall mBCC for BSC in the economic model for:

B.8.a One year survival probability

One year survival probabilities have been calculated using digitised Kaplan-Meier curves. In some instances exactly 12 month probabilities were unavailable due to the nature of this technique. In these cases, survival probability has been reported over two time points either side of 12 months.

In the metastatic BSC population 12-month survival probabilities were derived through the application of HRs to vismodegib ITT Kaplan-Meier curves. At 11.30

months = 76.2% of patients were alive and at 12.15 months = 73.8% of patients were alive.

In the regional metastases and distant metastases groups of the McCusker *et al.*, 2014 study, 12 month survival probabilities were as follows: in the regional metastases cohort, at 10.63 months = 88.36% of patients were alive and at 14.45 months = 85.9% of patients were alive. In the distant metastases cohort, at 10.46 months = 66.11% of patients were alive and at 12.41 months = 59.45% of patients were alive (Excel file "NICE clarification questions supplementary data", sheet "B8".).[6]

B.8.b Median survival probability;

Using the modelled Kaplan-Meier curves in the metastatic BSC population (application of HRs to vismodegib ITT Kaplan-Meier curves) the median survival time is not reached.
In the regional metastases and distant metastases groups of the McCusker et al., 2014 study the median survival probabilities were as follows: In the regional metastases cohort, at 63.03 months = 55.9% of patients were alive and at 86.71 months = 29.1% of patients were alive. In the distant metastases cohort, at 15.42 months = 57% of patients were alive and at 24.31 months = 45.3% of patients were alive (Excel file "NICE clarification questions supplementary data", sheet "B8".).[6]

B.8.c Mean survival;

It is worth noting that the (McCusker et al., 2014) review reported survival since time of diagnosis and not time since trial baseline which, for some patients, was a long time since their initial diagnosis A comparison of restricted mean survival times would not be meaningful because the observation time was different in the STEVIE trial and the (McCusker et al., 2014) review.[6]

B.8.d Please estimate an average KM curve (i.e. averaging the distant and regional metastatic KM curves in the McCusker et al. paper) as a validation tool for comparison with the estimated KM curve for non-responders in mBCC for the BSC arm, using the 3-month and the 6-month landmark, separately;

The Kaplan-Meier data of the digitized curves for patients with regional and distant metastases and the average Kaplan-Meier data is included in the Excel file "NICE clarification questions supplementary data", sheet "B8". The average Kaplan-Meier data was then used to estimate extrapolation parameters using the Algorithm published by Guyot et al. (2012).[7] These parameters were implemented in the submitted economic model and can be compared to the modeled OS curves in the metastatic BSC arm for all estimated HRs.

B.8.e Please use the average KM curve mentioned in Question B8d from the McCusker et al. paper to fit a survival curve to these data;

See above.

B.8.f Please apply the inverse HR obtained through the landmark approach to the fitted survival curve mentioned in Question B8e as a means to obtain the survival curve for vismodegib and present both estimates curves for BSC and vismodegib;

The reversely modeled Kaplan-Meier curve using the average Kaplan-Meier curve from McCusker et al. (2014) and the inverse HRs are included in the Excel file "NICE clarification questions supplementary data", sheet "B8". The updated Excel model also allows using the reversely modeled OS curves based on the McCusker et al. (2014) BSC curve and the inverse HRs of non-responders versus ITT patients.[6]

B.8.g Please include the vismodegib and BSC curves mentioned in Question B8f as a scenario analysis to be selected through a drop-down menu in the economic model.

The drop down menu to use the average McCusker et al. (2014) et al OS data for modelling OS in the metastatic BSC and the vismodegib group can be found on the "Model Inputs" sheet, cells E142 and E144.[6]

B.9 Priority question: Please provide details on the responders and non-responders groups created through the landmark approach using STEVIE data. In particular, please provide:

B.9.a The number of patients in the responders and in the non-responders group for laBCC used to estimate OS and PFS, separately at landmark;

B.9.b The number of patients in the responders and in the non-responders group for mBCC used to estimate OS and PFS, separately at landmark;

The number of patients with locally advanced and metastatic disease in the responder and non-responder groups at 3 and 6 months after baseline can be found in the Excel file "NICE clarification questions supplementary data", sheet "B1 – d)".

B.9.c The mean and median OS for the groups specified in a) and b);

B.9.d The mean and median PFS for the groups specified in a) and b);

B.9.e The mean and median time to response for the groups specified in a) and b).

The restricted mean and median progression-free and overall survival times among responders and non-responders (defined at 3-month and 6-month landmarks) with locally advanced and metastatic disease are included in the Excel file "NICE clarification questions supplementary data", sheet "B9 – c-e)". Please note that responders and non-responders in this analysis were defined in the same manner as in the original submission, i.e. patients who progressed or died before the landmark

were excluded from the analysis of PFS and patients who died before the landmark were excluded from the analysis of OS.

B.10 Priority question: Please provide a list demonstrating that a systematic approach was taken to select the prognostic factors included in the estimation of OS and PFS HRs. In particular, please provide:

B.10.a All the prognostic factors considered for their prognostic value in survival outcomes for mBCC and laBCC;

B.10.b The clinical rationale for inclusion/exclusion of these factors;

B.10.c The models with the initial set of covariates considered for inclusion (before the backwards and forwards stepwise selection) together with the results of the stepwise selection process for mBCC and laBCC separately;

No systematic approach was taken in the selection of the covariates. We included two clinically relevant prognostic factors (age and ECOG).[8,9]
No exclusion of covariates based on significance was performed in order to have a single consistent model across the different analysis (two endpoints, PFS and OS; two landmarks, 3 and 6 months and two cohorts, laBCC and mBCC).

B.10.d The results of the covariate analysis using Gorlin syndrome as a covariate.

B.10.e The results with each covariate applied independently and the combined covariate analysis.

The results of part d and e have been provided in a separate supplementary Excel booklet entitled “NICE clarification questions – supplementary data – B10 d e”.

B.11 Priority question: Please provide the log-cumulative hazard plots for OS and PFS for responders and non-responders mentioned in Page 200 of the CS (first paragraph after Equation 5).

The requested plots are provided in sheet “B1 – c” of the workbook entitled “NICE clarification questions supplementary data”.

B.12 Priority question: Please provide the 95% confidence intervals for the mean change in the skindex-16 domains reported in Table 69 (page 208) of the CS.

Please see Table 5 below.

Table 5 Skindex 16 results reported in STEVIE[2]

		laBCC (N=1,111)	mBCC (N=89)	Total (N=1,200)
Domain: Emotion				
Baseline	n	724	49	773
	Mean (SD)	48.11 (31.23)	37.37 (32.70)	47.43 (31.41)
	95% CI	(45.84, 50.38)	(28.21, 46.53)	(45.22, 49.64)
Cycle 2	n	603	39	642
	Mean (SD)	-17.99 (26.13)	-8.68 (23.50)	-17.42 (26.05)
	95% CI	(-20.08, -15.9)	(-16.06, -1.3)	(-19.44, -15.4)
Cycle 7	n	379	25	404
	Mean (SD)	-25.99 (30.65)	-13.14 (33.25)	-25.20 (30.93)
	95% CI	(-29.08, -22.9)	(-26.17, -0.11)	(-28.22, -22.18)
End of study	n	293	15	308
	Mean (SD)	-22.92 (32.31)	12.49 (26.74)	-21.19 (32.93)
	95% CI	(-26.62, -19.22)	(-1.04, 26.02)	(-24.87, -17.51)
Domain: Function				
Baseline	n	723	49	772
	Mean (SD)	27.29 (30.12)	28.30 (30.42)	27.35 (30.12)
	95% CI	(25.09, 29.49)	(19.78, 36.82)	(25.23, 29.47)
Cycle 2	n	602	39	641
	Mean (SD)	-7.42 (22.19)	-1.71 (16.31)	-7.07 (21.91)
	95% CI	(-9.19, -5.65)	(-6.83, 3.41)	(-8.77, -5.37)
Cycle 7	n	379	25	404
	Mean (SD)	-11.20 (26.51)	-10.00 (24.74)	-11.13 (26.37)

	95% CI	(-13.87, -8.53)	(-19.7, -0.3)	(-13.7, -8.56)
End of study	n	292	15	307
	Mean (SD)	-8.24 (26.29)	7.78 (31.64)	-7.46 (26.74)
	95% CI	(-11.26, -5.22)	(-8.23, 23.79)	(-10.45, -4.47)
Domain: Symptom				
Baseline	n	723	50	773
	Mean (SD)	25.06 (24.69)	23.94 (26.99)	24.99 (24.83)
	95% CI	(23.26, 26.86)	(16.46, 31.42)	(23.24, 26.74)
Cycle 2	n	603	39	642
	Mean (SD)	-9.95 (22.02)	-5.06 (23.10)	-9.66 (22.10)
	95% CI	(-11.71, -8.19)	(-12.31, 2.19)	(-11.37, -7.95)
Cycle 7	n	378	26	404
	Mean (SD)	-12.00 (24.95)	-6.73 (28.92)	-11.66 (25.21)
	95% CI	(-14.52, -9.48)	(-17.85, 4.39)	(-14.12, -9.2)
End of study	n	293	15	308
	Mean (SD)	-11.12 (26.15)	3.61 (22.04)	-10.40 (26.12)
	95% CI	(-14.11, -8.13)	(-7.54, 14.76)	(-13.32, -7.48)

Abbreviations: CI, Confidence interval; laBCC, Locally advanced basal cell carcinoma; mBCC, Metastatic basal cell carcinoma; SD, Standard deviation.

B.13 Priority question: Please provide descriptive statistics for the SF-36 dimensions scores data captured in ERIVANCE. More specifically, for each one of the eight dimensions of SF-36 please provide:

B.13.a Mean (SD), median and inter-quartile range at baseline and at end of study;

B.13.b Mean change from baseline to end of study, with respective 95% CI;

B.13.c Number of observations obtained at baseline and at end of study;

B.13.d Mean age of responders.

The requested descriptive statistics for all eight dimensions of SF-36 collected in the ERIVANCE study by study visit are included in the Excel file "NICE clarification questions supplementary data", sheet "B13". The data is presented for the November 26, 2010 and for the November 28, 2011 data cuts.

B.14 Priority question: Please provide the results of the regression analyses using dimensions, squared terms and interaction terms for the ERIVANCE SF-36 dataset. Please provide between and overall R-squared, root mean squared error, rho and Wald chi-square statistics (please see Table 2 in Rowen et al. 2009).

Regression coefficients reported in Rowen et al. (2009) were used to obtain EQ-5D utilities from the SF-36 data collected in the ERIVANCE trial.[10] Rowen et al. (2009) used regression analysis to examine the relationship between EQ-5D and the eight dimension scores of the SF-36. They assessed the predictive performance of 5 different models using within R-squared, between R-squared, overall R-squared, Root mean squared error, rho, and Wald Chi-squared statistics. These statistics were derived from a comparison of the observed and predicted EQ-5D utilities. In ERIVANCE, no EQ-5D data was collected, only SF-36. Therefore, a comparison of observed and predicted EQ-5D utilities and a re-estimation of the models was not possible.

B.15 Priority question: Please clarify why the third GLS model reported in the Rowen et al. 2009 publication was deemed the most appropriate model for mapping the SF-36 values from the ERIVANCE trial to obtain mean EQ-5D values for the model.

Rowen et al. (2009)[10] assessed the predictive performance of alternative regression models using measures of the predictive error and a graphical comparison of predicted versus observed EQ-5D utilities. Based on these criteria, the authors concluded that the random effects generalized least squares model using higher order and interactions terms of the eight SF-36 dimensions (model 3) performed best. Because EQ-5D was not collected in the ERIVANCE study a re-assessment of the predictive performance of the proposed regression models using ERIVANCE data was not possible. We therefore used model 3 which was deemed most accurate by Rowen et al. Results produced by the other models quoted in Rowen *et al.* have also been provided in the answer to question B.16 of this document.

B.16 Priority question: Please provide the estimated mean EQ-5D utility values from alternative statistical models that may be accurate predictors of EQ-5D data.

The predicted utilities in progression-free and post progression health states using models 1 to 5 from Rowen et al. (2009) are included in the Excel file "NICE clarification questions supplementary data", sheet "B16".[10] The utilities were estimated separately for locally advanced and metastatic patients and the combined trial population using both the November 26, 2010 and the November 28, 2011 data cuts.

B.17 Priority question: Please provide a list of the potential implications of using ERIVANCE QoL data to predict utility values for STEVIE, considering these are two different studies, deemed unsuitable for pooling data, and with different baseline prognostic factors, such as age.

In the absence of direct EQ-5D data, Roche would have ideally chosen to use HRQoL data collected in STEVIE and mapped this data in order to derive health

state utilities. Unfortunately, algorithms to map Skindex-16 or MDASI data to EQ-5D do not exist. The only way to incorporate EQ-5D data (NICE's preferred measurement of HRQoL) in our analysis was to use the SF-36 data collected in ERIVANCE.

Given the difference in patient populations, the validity of applying utilities derived from one cohort and applying to another can be questioned. Despite the differences in patient population, ultimately both STEVIE and ERIVANCE evaluated patients in the same disease population. The SF-36 data from ERIVANCE has proven to be the best available evidence in relation to this decision problem. For the sake of completeness, utilities from Shingler *et al.* were also included in the model as part of a scenario analysis.[11] However, the use of these values also has its limitations (see section 5.4.5 of the CS).

B.18 Priority question: Please include a scenario analysis in the model assuming that vismodegib patients who progress and switch to BSC (assumed to be 33% of patients in the model) receive the same treatment regimen (in terms of resource use) as patients in the BSC treatment arm who have progressed.

The scenario analysis macro in the submitted model is designed in such a way that adding the requested scenario would involve also having to alter some of the base case parameter values.

Roche has manually explored the scenario outlined above and the results are presented below in Table 7.

Table 6 Base case results - with corrections made (B.19 & B.20) - PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	XXXX	1.16	0.89	XXXX
Vismodegib	XXXX	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years

Table 7 B.18 scenario analysis results - with corrections made (B.19 & B.20) - PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	XXXX	1.16	0.89	XXXX
Vismodegib	XXXX	10.66	8.20				

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years

This scenario is extremely conservative and Roche feels it is unrealistic to assume patients would experience no benefit (in terms of resource use) after receiving vismodegib therapy compared to patients who are vismodegib-naïve. This view is also in alignment with the clinical experts who were consulted throughout the development of the submission (please see section 5.11 of the CS).

B.19 Please clarify why the utility values selected for adverse events from the Beusterien et al. paper is based on the mean of UK and Australian patients, instead of the values reported for UK patients?

Roche has no justification for this selection and acknowledges that the use of the UK values would be most applicable. Both sets of values are presented below in Table 8.

Table 8 Mean disutilities reported in Beusterien *et al.*[12]

Health state	UK patients (s.e.)	Australian patients (s.e.)	All patients (s.e.)
1-day in-/outpatient stay for severe toxicity (grade III/IV)	-0.11 (0.02)	-0.14 (0.01)	-0.13 (0.01)
2 – 5-day hospitalisation for severe toxicity (grade III/IV)	-0.13 (0.02)	-0.20 (0.02)	-0.17 (0.01)

Abbreviations: s.e.; Standard error.

There is minimal difference in the sets of values reported in UK patients versus the values reported in all the patients (values used in the model). In addition, the total effect on both cost and health-related quality of life of adverse events can be seen to

be negligible in the model. Roche believes that this change will have almost no effect on overall results.

B.20 The cost of a GP visit estimated in cells H52, H73, H107 and H129 in the Excel sheet "Background costs" uses the cost of a dermatologist visit instead of a GP visit. Please correct this in the model.

This error has been corrected. Upon correction, the base case ICER (with PAS applied) increased from XXXX to XXXX (~X.X% change).

B.21 In Section 5.11 on page 255 of the CS it is stated that "Roche is aware of certain economic evaluations including vismodegib that were not captured in the economic SLRs. These other evaluations including vismodegib are encompassed in HTA submissions to other countries (e.g. Republic of Ireland and Canada)." Please summarise the content of these evaluations similarly to Table 59 of the CS, and provide the full text files of the publications of these economic evaluations.

Summaries of both the Irish and Canadian submissions have been provided below in Table 9. Full text summaries of these analyses have been provided as supplementary materials in this response.

Table 9 Summary of previous HTA economic analyses

Author, Year [Cost year]	Summary of model: Analysis or model type; analysis time frame; and rationale for design and time frame	Patient population, including average age	Interventions and comparators	Costs and outcomes	ICER
Roche (Canada), 2013 (NR)[13]	Two separate models were developed. One for the laBCC and one for mBCC cohort. Both models were 3-state Markov models: 1) PFS 2) Progression 3) Death Both models used a time horizon of 40 years (equivalent to lifetime) in the base case analysis Both models had weekly cycles One-way and multi-way sensitivity analysis was conducted	The patients included in both the laBCC and mBCC analysis were representative of the patient population enrolled in the ERIVANCE clinical trial Average patient age (years) was: - laBCC = 61.4 - mBCC = 61.6	Vismodegib (150mg) and Best supportive care (BSC)	**Analysis 1 = laBCC** Vismodegib Costs = $476,852 QALYs(MM utilities) = 7.562 QALYs = (TTO utilities) = 9.553 BSC Costs = $298,160 QALYs(MM utilities) = 6.883 QALYs = (TTO utilities) = 9.150 **Analysis 2 = mBCC** Vismodegib Costs = $182,339 QALYs(MM utilities) = 2.380 QALYs = (TTO utilities) = 2.907 BSC Costs = $56,597 QALYs(MM utilities) = 1.607 QALYs = (TTO utilities) = 2.178	**Analysis 1 = laBCC** ICER (MM utilities) = **$263,141** ICER (TTO utilities) = **$443,613** **Analysis 2 = mBCC** ICER (MM utilities) = **$162,646** ICER (TTO utilities) = **$172,464**

Roche (Ireland), 2014 (NR)[14]	3 state Markov model 1) PFS 2) Progressive disease 3) Death All patients receiving vismodegib were assumed to start in the PFS health state and were at risk of moving to progressive disease or death in each model cycle. All patients in the BSC arm were assumed to start in the progressive-disease health state and can only progress to the dead state in each model cycle. Lifetime time horizon was used Cycle length not reported One-way and probabilistic sensitivity analysis was conducted	Patient population evaluated in the model are assumed to be in-line with the ERIVANCE trial population Average patient age not reported	Vismodegib (150mg) and Best supportive care (BSC)	NR	laBCC = **€556,657** mBCC = **€240,902**

C Textual clarification and additional points

C.1 Please confirm that Figure 36 (page 193) is not reporting the log-logistic distribution but instead the log-normal (for mBCC) and the gamma (for laBCC) distributions?

The caption for Figure 36 has been erroneously stated as “OS KM and extrapolation – **Log-Logistic distribution** – vismodegib arm”. It should be altered to say “OS KM and extrapolation – vismodegib arm”.

C.2 Please confirm that the sentence on page 193 of the CS mentioning that the lognormal distribution was used to model mBCC OS in the model is a typo? Please can you confirm that a Weibull distribution was intended to be used for this purpose?

This is in fact a typographical error. Indeed, a Weibull distribution was used to model OS in the mBCC population.

C.3 Please report Table 68 (page 203) as percentage values (i.e. please report the values in Table 68 as percentages of the total number of patients included in the laBCC and mBCC responders and non-responders groups, respectively).

Please see Table 10 below:

Table 10 Number of non-responders at landmark, who respond thereafter

	3-month landmark		6-month landmark	
	Non-responders (% of NR out of entire la/mBCC cohorts)	Response after landmark (% of NR who responded after landmark)	Non-responders (% of NR out of entire la/mBCC cohorts)	Response after landmark (% of NR who responded after landmark)
Progression-free survival				
Locally advanced	493 (44%)	294 (60%)	213 (19%)	102 (48%)
Metastatic	50 (52%)	14 (28%)	31 (32%)	6 (19%)
Overall survival				
Locally advanced	545 (49%)	295 (54%)	274 (24%)	102 (37%)
Metastatic	61 (64%)	14 (23%)	39 (41%)	6 (15%)

Abbreviations: NR, Non-responders.

C.4 Please specify the source of the background mortality data used in the model.

Background mortality data was derived from national lifetables of the UK population (2013-2015) as reported on the Office of National Statistics website (https://www.ons.gov.uk/).[15]

C.5 Please clarify whether the following sentence on page 228 of the CS should say 12 weeks instead of 24 weeks: "In addition to wound management and palliative radiotherapy, patients will also be expected to visit a dermatologist every 24 weeks in order to monitor their disease."

Yes, this sentence should be corrected in order to align with the calculations in the cost-effectiveness model. The sentence should read: "In addition to wound management and palliative radiotherapy, patients will also be expected to visit a dermatologist every **12 weeks** in order to monitor their disease."

References

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14. (NCPE), T.N.C.f.P., *Cost effectiveness of vismodegib (Erivedge®) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy*. 2014.
15. (ONS), O.f.N.S. *National Life Tables: United Kingdom*. 2016 [cited 2017 12th February]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

ID 1043 – vismodegib in advanced basal cell carcinoma

Additional clarification

4th May, 2017

1 Updated cost-effectiveness results

In response to question B.20 of the evidence review group's clarification questions document, Roche has corrected the cost-effectiveness models with and without the confidential patient access scheme (PAS) applied. Updated base case results without and with PAS applied are presented below in Table 1 and Table 2, respectively.

Table 1. Corrected base case results - No PAS

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				

Abbreviations: LY, Life years; Inc, incremental; ICER, Incremental cost-effectiveness ratio; QALYs, Quality adjusted life years.

Table 2. Corrected base case results - PAS applied

	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Inc LY	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	[redacted]	1.16	0.89	[redacted]
Vismodegib	[redacted]	10.66	8.20				

Abbreviations: LY, Life years; Inc, incremental; ICER, Incremental cost-effectiveness ratio; QALYs, Quality adjusted life years.

Following the correction of the models, both deterministic (DSA) and probabilistic sensitivity analyses (PSA) were re-run. Figure 1 and Figure 2 present the updated DSA results as Tornado diagrams.

Figure 1. Corrected Tornado diagram - No PAS applied

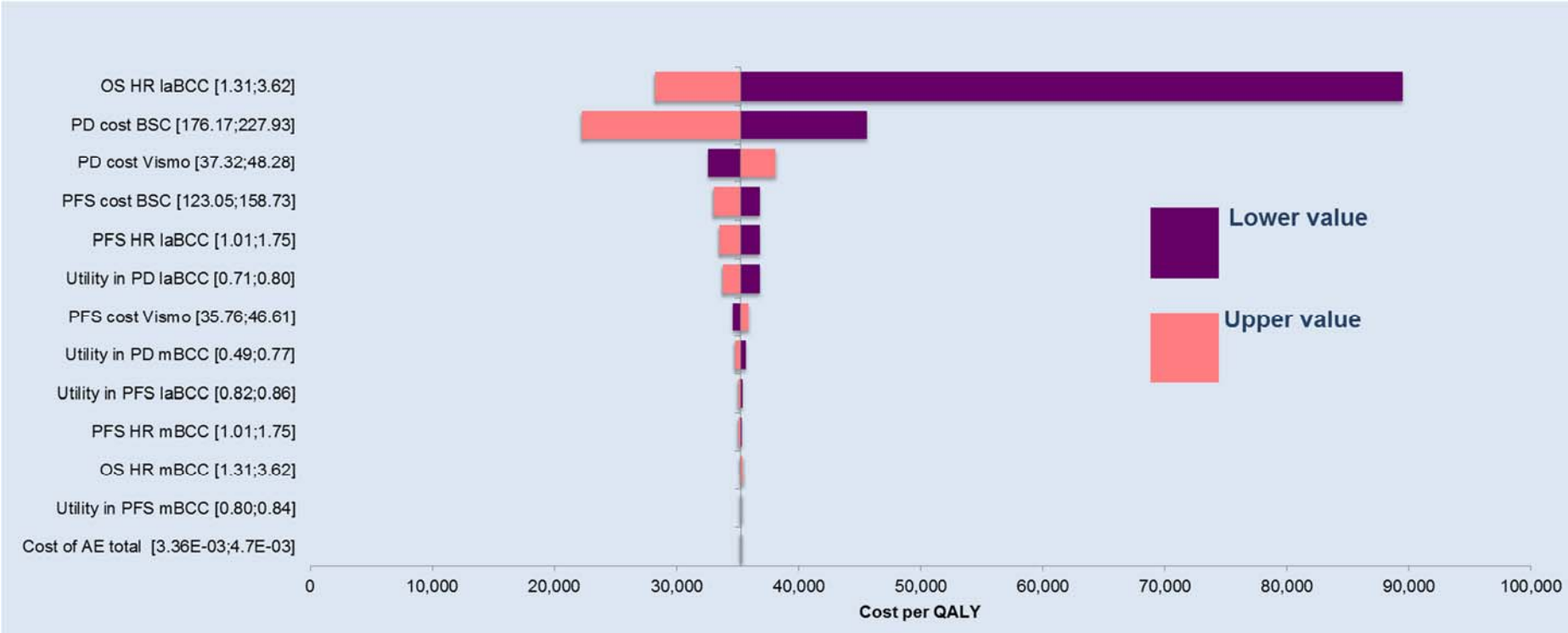

Figure 2. Corrected Tornado diagram - PAS applied

REDACTED

Results from the updated PSAs are presented without and with PAS applied in Table 3 and Table 4, respectively.

Table 3. Corrected base case vs. PSA results - No PAS applied

	Total Costs		Total QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA
BSC	£93,352	£93,061	7.31	7.22	£35,251	£35,798
Vismodegib	£124,699	£124,553	8.20	8.10		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALYs, Quality adjusted life years.

Table 4. Corrected base case vs. PSA results - PAS applied

	Total Costs		Total QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA
BSC	£93,352	£92,540	7.31	7.22	[redacted]	[redacted]
Vismodegib	[redacted]	[redacted]	8.20	8.11		

Abbreviations: ICER, Incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALYs, Quality adjusted life years.

Cost-effectiveness planes presenting the results from the PSAs are reported in Figure 3 and Figure 4.

Figure 3. Corrected cost-effectiveness plane - No PAS applied

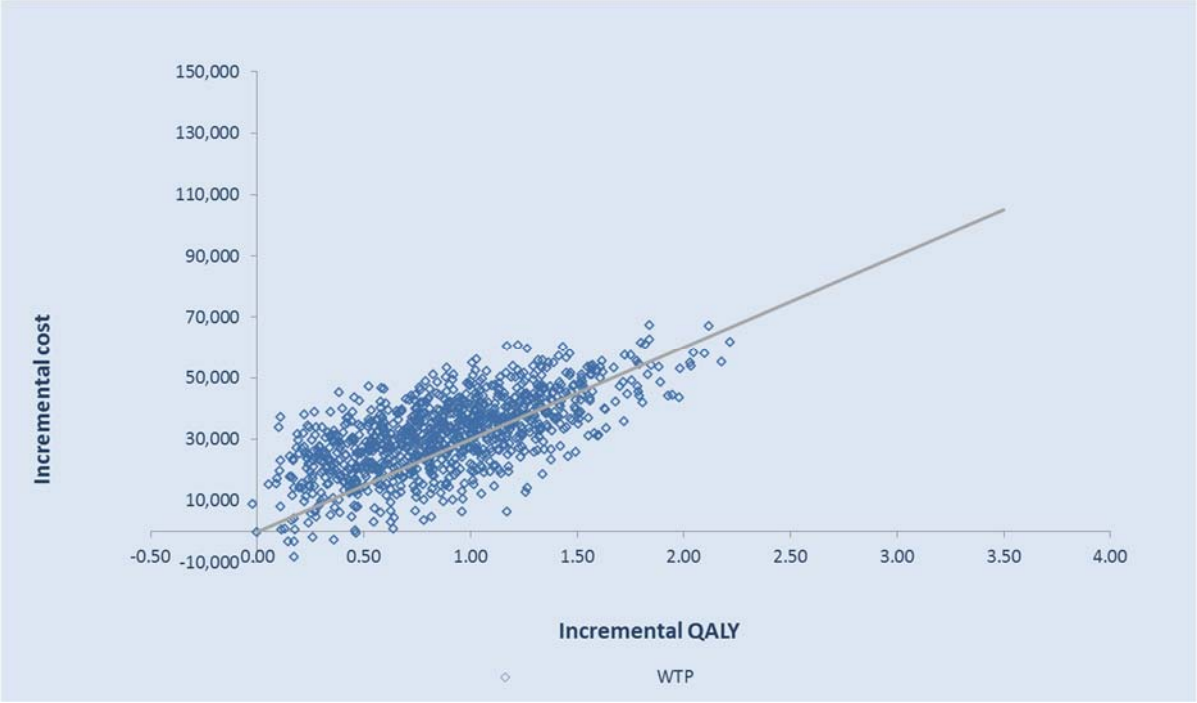

Figure 4. Corrected cost-effectiveness plane - PAS applied

REDACTED

Finally, the cost-effectiveness acceptability curves of both corrected models are presented below in Figure 5 and Figure 6.

Figure 5. Corrected cost-effectiveness acceptability curve – No PAS applied

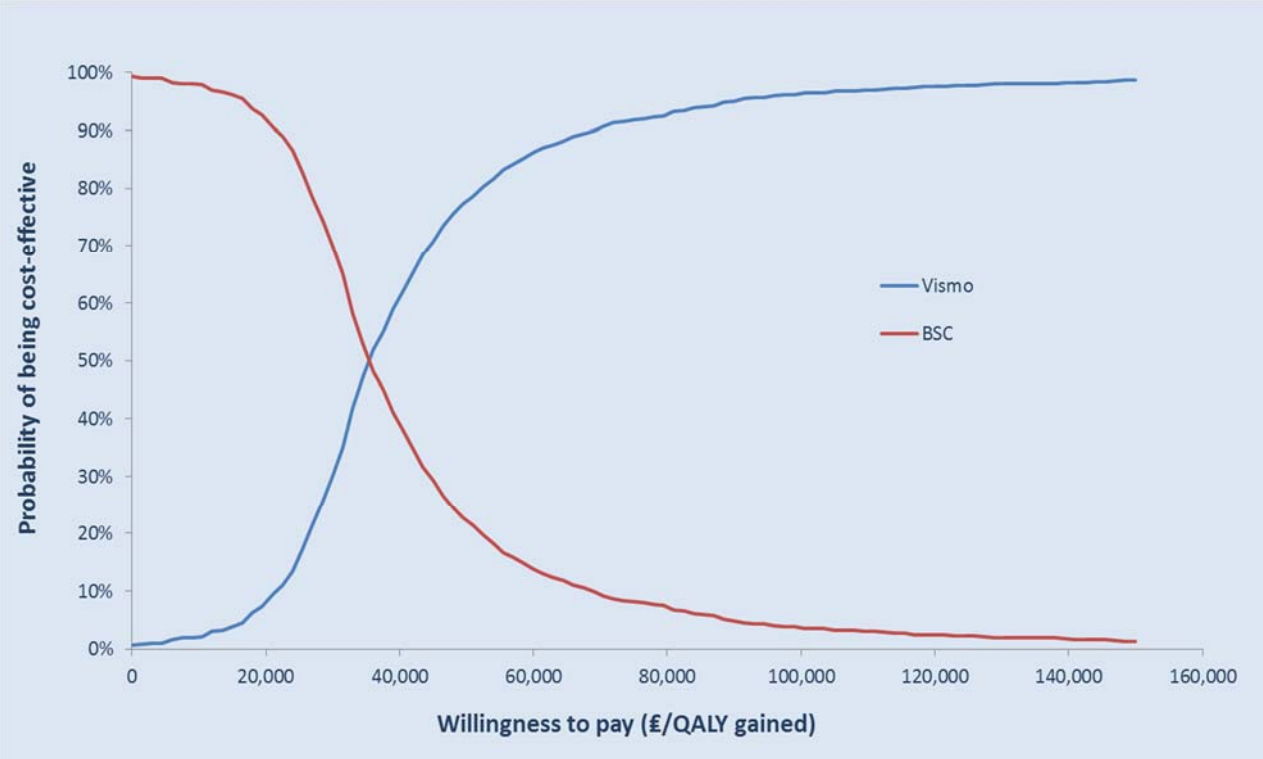

Figure 6. Corrected cost-effectiveness acceptability curve - PAS applied

REDACTED

2 Vismodegib Kaplan-Meier data from STEVIE

2.1 Please could you provide details of when the last follow-up time point was for collecting effectiveness outcomes on OS, PFS and TTD

As per the STEVIE study protocol, patients were followed for up 12 months after the last dose of vismodegib. Efficacy results (Overall survival (OS), Progression free survival (PFS), and Time-to-treatment discontinuation (TTD)) included all information up to the clinical data cut-off on the 16th March 2015, i.e. the same follow-up period for all three endpoints.

The first patient was enroled on the 30 June 2011 and the clinical data cut-off was on the 16th March 2015. This leaves a total of 44 months and 17 days of potential follow-up time.

For specific last follow-up time points, please see the “KM OS”, “KM PFS”, and “KM TTD” worksheets of the cost-effectiveness model.

2.2 Please could you also provide an explanation for why the follow-up time for collecting PFS events was approximately 1 year longer than OS and TTD events (38 months vs. 26 and 29 months, respectively, as can be seen from the KM curves)

The time-points quoted in the question above are not the last follow-up times. Instead they are the points at which the last event was observed. The time of the last event and the time of the last follow-up are reported in Table 5 below.

Table 5. Time of last event vs. final follow-up time for OS, PFS, and TTD

	laBCC (months)	mBCC (months)

	Time of last event (months)	Last follow-up time (months)	Time of last event (months)	Last follow-up time (months)
OS	26.15	44.06	21.65	38.01
PFS	37.85	41.23	37.03	37.03
TTD	29.40	44.06	21.82	37.68

Abbreviations: laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; OS, Overall survival; PFS, Progression free survival; TTD, Time to treatment discontinuation.

Time of the last event is not expected to be the same across OS, PFS, and TTD as these are ultimately different endpoints. In addition, the last follow-up time for each endpoint is very similar but not identical as these are different endpoints and time to last follow up time can vary slightly across endpoints.

3 Status of confidential PAS

I can confirm that the confidential PAS has been referred by the Department of Health (DoH) to PAS Liaison Unit (PASLU). However, due to the triggering of the UK general election and subsequent enforcement of PURDAH we have been advised the following by the DoH.

"As you will be aware we are now in purdah and do not expect to be in a position to seek a Ministerial view on PAS proposals until after the election and formation of the next Government. This is in line with Cabinet Office guidance on the restrictions on government activity during this pre-election period. Unfortunately we cannot give a specific timescale on this as it will depend on the time taken to form a Government and Ministerial priorities and workload. Therefore, PAS proposals at this stage of the process, where we need to seek a Ministerial view, are likely to be subject to delays."

We plan to update NICE accordingly should there be any progress.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Association of Skin Cancer Specialist Nurses

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? Chair of BASCSN
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Waiting times for patients to be seen and treated can be long, as other skin cancers take priority. Often pts who present are elderly and frail with a number of comorbidities, and on a number of medications, making both surgery and radiotherapy challenging. Particular problems we encounter when considering surgery are when patients are on anticoagulants and patients then are referred to radiotherapy. Problems we may encounter when considering radiotherapy include poor mobility, dementia and travelling particularly when living far away. Elderly patients tend to present with larger more symptomatic lesions and because of the issues outlined above, surgery or radiotherapy may be challenging.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients who present with morpheic lesions, particularly in areas where obtaining a good cosmetic outcome or good clearance may be difficult eg around the eye. In the rare case where patients have metastatic BCC, prognosis is worse. In those patients where both surgery or radiotherapy cannot be delivered, due to the size or site of the lesion, prognosis may be worse. Also patients with Gorlins syndrome, radiotherapy is contraindicated and prognosis may be worse

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Vismodegib should be used in specialist clinics – patients seen in either dermatology or oncology clinics where all treatment options can be carefully considered

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There may be some variation, particularly in parts of the country where there is a large elderly population, who as mentioned above may have a number of comorbidities and present at a later stage. Also depends on clinicians exposure and experience of using vismodegib. We think mostly it is used within licensed indications.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The technology will be easier to use for certain groups of patients who will not be able to tolerate surgery or radiotherapy, but need

treatment for a large symptomatic lesion. This would include patients with dementia, where treatment can prove challenging. If started on vismodegib, patients need to attend clinic on a more regular basis. It seems to be well tolerated with minimal toxicities and minimal monitoring of blood tests.

Advantages:- once daily tablet, minimal toxicities, minimal monitoring of blood tests. There has been some anxiety around hair loss and body image. Overall in our experiences response to treatment has been very good and well tolerated.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Adverse effects we have seen include asthenia, mild hair loss, muscle cramps and taste change. The side effects tend to occur after about 3 months and resolve soon after stopping. In patients who have continued with the treatment despite having some of these effects, they seem to be very manageable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We don't think any extra training would be needed as this drug is well tolerated overall with manageable side effects.

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

There are several ways of treating basal cell carcinoma (BCC) of the skin available under NHS. The majority of these options are radical and offer long-term cure.

Patients with locally advanced BCC (LABCC) and /or metastatic BCC (mBCC) represent a challenging subgroup of BCC. mBCC is very rare, treatment is always palliative in intent. There is no established systemic management in patients with LABCC or mBCC.

BCC patients who not eligible for radical anti-cancer treatment are usually offered best supportive care. Their management is symptom-driven and intended to improve quality of life but not cure.

Patients who have had previous radiotherapy in the BCC area unlikely will be offered skin radiotherapy due to significant risk of late toxicity and secondary carcinogenesis. Patients with Gorlin's syndrome are likely to develop multiple BCC, often advanced and / or simultaneously. Gorlin's syndrome is well known contraindication to radiotherapy.

Surgery may not be offered in some BCC patients due to significant risk of the procedure itself due to e.g. co-morbidities or significant surgery-related disfigurement e.g. in fascial locations.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Vismodegib constitutes a new option of palliative treatment for patients with BCC for whom there are no radical treatment options available. Expected duration of response to vismodegib is in the range of 12 to 18 months. It can cause also significant side effects with toxicity prompting interruption or discontinuation of the treatment in some patients. For these reasons vismodegib treatment should be delivered in secondary or tertiary care centres with specialist MDT and nursing input available. Such set up also ensures that vismodegib is used within its licensed indications and patients are closely monitored by experienced staff.

At present vismodegib is available under NHS. It must be prescribed by a clinical oncologist following successful CDF application. There is a significant geographical difference in access to vismodegib e.g. the drug is not funded by Welsh NHS.

There are no available clinical guidelines for vismodegib. Its usage in clinical practice follows licensing instructions.

All cases considered for vismodegib should be discussed within Skin MDT and the MDT should be in equipoise that there is no active radical treatment option(s) available for the patient. Such equipoise can be challenging and differs between skin SMDT, pending local expertise in surgery and radiotherapy.

It is generally accepted that patient's refusal to proposed active radical anticancer treatment should not constitute indication for vismodegib itself.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There is currently no alternative treatment available to vismodegib. NICE approval will add a treatment option to the palliative management of BCC patients that would be otherwise referred for best supportive care.

Vismodegib is a relatively new drug. Evidence base data come mainly from observational or phase II studies. There are no phase III studies.

NICE approval should not change a practice in centres already treating patients with vismodegib under CDF.

There is a definite need for a more structured approach to clinical use of vismodegib and a clinical trial would be the right way to go.

As indicated in the above paragraph vismodegib has also significant side effects with toxicity prompting interruption or discontinuation of the treatment in some patients. Most common side effects are fatigue, muscle spasms, alopecia, pruritis, lack of appetite and weight loss, dysgeusia, nausea and vomiting. Toxicity profile should be taken into consideration particularly in patients who may be otherwise asymptomatic from their LABCC or mBCC. Such approach could be in direct confrontation with the general principle of palliative management.

Expected duration of response to vismodegib is in the range of 12 to 18 months. There is no established management for patients who progressed after vismodegib.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None available

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

It is not expected that NICE approval will dramatically increase number of patients eligible for vismodegib.

Vismodegib should be provided in centres already experienced in management of patients with complex BCC, including treatment of vismodegib-related toxicity. Vismodegib should be delivered in secondary or tertiary care centres with specialist skin MDT and nursing input available. In view of limited number of patients it is advised that treatment with vismodegib should remain centralised in highly specialist centres. Centres which currently do not provide vismodegib should undertake some form of extra training and work in close co-operation with centres already experienced in treating patients with vismodegib.

It is pivotal that NICE provide clear information on palliative intent of treatment with vismodegib and stated indications should cover patients for whom there are no radical treatment options available. It should be also clearly stressed that patient's choice, if radical treatment option(s) is available, should not be regarded as indication for vismodegib.

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. I am not aware on any such issues.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation Salford royal nhs foundation trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? NO
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
NONE

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

This is the only treatment for patients with advanced bcc that is unsuitable for surgery or radiotherapy. There are no other options to help these patients with highly disfiguring disease. They are a rare group of patients but suffer significant psychological distress due to the visible nature and extent of the disease. This should be set in secondary care and managed through he specialist skin cancer mdt. The trial results help guide who is prescribed the drug and for how long.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Given that this is the only available treatment option for these patients, it is important to have access to this therapy in England. The use in clinical practice does reflect that in the trials. There are a number of side effects which can be difficult to manage, often a treatment break before restarting is the most effective option. It improves patients quality of life.

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Single Technology Appraisal (STA)

Equality and Diversity

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

None applicable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Single Technology Appraisal (STA)

Information is there in the trials

Implementation issues

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Given this is being prescribed through mdt's, no additional training should be needed

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Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation Northern Cancer for Cancer Care

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? ✓ Consultant Medical Oncologist specialising in skin cancer treatment
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Basal cell carcinomas which are not complex or recurrent are treated curatively with surgery, and this represents the vast majority of cases. Radiotherapy is also a good option for these patients, with an estimated ~95% chance of cure without local recurrence. The disadvantage of radiotherapy is that surgical margins are not assessed, but given that most BCCs, if they recur, grow slowly the majority of recurrent cases are also managed surgically.

It is very rare for this disease to metastasise an estimated less than 1% of cases

Locally advanced basal cell carcinoma, and the rare cases of metastatic disease are treated by the multidisciplinary skin cancer teams, and all cases discussed through SSMDTs.

If the case is considered surgically unresectable, either due to complexity, associated comorbidity, cosmetic challenges or local invasion the patient's case is discussed at the SSMDT and radiotherapy as a treatment option considered.

If neither radiotherapy nor surgery is considered appropriate the patients is referred to the systemic therapy team to discuss treatment with vismodegib. This agent is available under the Cancer Drugs Fund.

Current guidelines recommend that vismodegib is prescribed by an oncologist as it is licensed as an anti-cancer agent and drug is given within secondary care. Some

services are led by dermatology colleagues. Patients are supported in clinics by the Skin Cancer Clinical Nurse Specialists, but do not require additional specialised input from this team. Some patients require referral for dietary advice as the loss of taste associated with treatment can lead to weight loss in some elderly patients.

Generally the local practice is that the prescribing is supervised within secondary care, with monitoring for side effects and safety by physicians but continuing discussion and input from the SSMDT with surgical colleagues. Our local practice is for 12 weekly scans, if appropriate due to local invasion, and also 3 monthly review by the surgical team. If response is such that the lesion is more deemed resectable patients will be offered surgery.

The rare subgroup of patients where this agent is a significant advantage are those with Multiple Basal Cell Naevus Syndrome or Gorlin's Syndromes. These patients can get BCCs very early in life, with a life long impact of multiple surgeries. Vismodegib offers a treatment option for them when there are multiple BCCs (can be many 10s of lesions) or when surgery is becoming challenging due to other scars/skin grafts. In these patients consideration needs to be given to allowing intermittent courses of vismodigib over their life time. For them the potential teratogenic effects of the class of agents is a significant risk and needs counselling and monitoring.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The use of vismodegib via the Cancer Drugs Fund has been a significant advantage to a vulnerable patients group. Patients with advanced BCCs are often elderly, have neglected the condition such that it is not resectable in the majority of cases and can become socially isolated as BCCs most frequently affect head and neck areas so there is a significant impact on appearance. This agent offers a valuable treatment option, improving appearance, reducing pain and bleeding risk, and also allowing better social integration for these patients.

The clinical trials with vismodegib and the other agent in the class Sonidegib were carried out in accordance with UK practice, with many UK centres putting a significant number of patients on these studies. Regression of the BCC lesions was the primary outcome of the studies, and this was carefully monitored with independently assessed clinical photographs. Response rates are high, ~60%, so there is a good chance patients will benefit from the agents.

The agent can be given within routine outpatient care, routine blood monitoring is required, but once established on treatment clinic visits can be at 8 week intervals.

The major side effects are loss of taste, muscle cramps and gradual hair loss. Muscle cramps can be managed with exercise regimens and quinine, the most challenging side effect is the loss of taste as this impacts significantly on a patient's quality of life. There is some evidence that treatment "holidays" can help with this and the muscle cramps, but these need to be of several weeks as side effects are slow to resolve. Re-introduction of the agent after a treatment break can lead to a recurrence of side effects but they seem to be less intense. Flexibility in any guidelines of the length of a treatment break would be helpful.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

None of these apply

Any additional sources of evidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No other evidence sources identified

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

In my opinion there would not be a significant impact in implementing this treatment. In the majority of large skin cancer practices, where most of these complex cases are seen, use of vismodegib in appropriate cases is already standard practice as this agent has been available under guidance from the Cancer Drugs Fund

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vismodegib for treating basal cell carcinoma [ID1043] – Additional Committee Paper

Questions posed to and responses from Clinical Expert [redacted] who is unable to attend Appraisal Committee Meeting on 28 June 2017

Q1. What is the prevalence of aBCC with Gorlin syndrome in the UK?

Patients with Gorlin's rarely get advanced BCCs, these patients start getting BCC in childhood, and can develop an average of 20-30 per year. As they have a recognised inherited syndrome the lesions rarely become advanced, but the patients face repeated surgeries throughout their life. They respond well to vismodegib, and in the pivotal trial in this disease the average number of BCCs forming in a year went down from 29 to less than 3. We have treated a number of these patients on various access programmes/trials. For example a lady who had had nearly 300 BCCs surgically removed in her lifetime, to the point where it was difficult to excise with a skin graft due to previous scars.

Vismodegib gives them a break from surgical procedures, although most only wish to stay on for a period because of the low grade side effects of loss of taste and muscle cramps.

I am not sure of the prevalence of Gorlins, but all of these patients get multiple BCCs. The key thing is that this is a younger age group, and with the teratogenic risk we only treat the older patients generally, once they have completed their families.

Q2. Do people with BCC generally experience more comorbidities than the average UK population?

Yes, but only as the typical patient is elderly. And often referred to us as either they have neglected a BCC such that surgery is impossible or very disfiguring, or they are not fit for surgery. So we see really quite frail patients in the clinic, but they tolerate the drug and respond really well – with great benefit in terms of quality of life as their aBCC often are requiring regular dressings, or bleeding. These lesions are usually on face or head so very obvious and socially isolating for some patients, which to me has been the huge benefit of treating with vismodegib. I have a couple of ladies who felt unable to leave the house as they were so conscious of their appearance who have got back to normal social events – highlighting in clinic how much simple pleasure they got from going shopping.

Vismodegib for treating basal cell carcinoma

STA REPORT

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

BMJ Technology Assessment Group

Vismodegib for treating basal cell carcinoma

Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Head of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Senior Health Technology Assessment Analyst, BMJ-TAG, London Mariana Bacelar, Senior Health Economist, BMJ-TAG, London Fatima Salih, Health Economist, BMJ-TAG, London Natalie Masento, Associate Health Technology Assessment Analyst, BMJ-TAG, London Charlotta Karner, Health Technology Assessment Analysis Manager, BMJ-TAG, London
Correspondence to:	Steven J. Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JP.
Date completed:	31/05/2017

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Declared competing interests of the authors:
None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Wakefield V, Bacelar M, Salih F, Masento N, Karner C. Vismodegib for treating basal cell carcinoma: A Single Technology Appraisal. BMJ-TAG, 2017.

Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and provided feedback on the clinical sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AAD	American Academy of Dermatology
aBCC	Advanced BCC
anti-SMO	'Smoothened' antagonists
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALT	Alanine transaminase
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BCC	Basal cell carcinoma
BCNS	Basal cell naevus syndrome
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSC	Best supportive care
CDC	Centers for Disease Control and Prevention
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLAD	Censored least absolute deviation
CR	Complete response
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
ECOG	Eastern Cooperative Oncology Group
EGP	Economic Guidance Panel
EMA	European Medicines Agency
ENT	Ear, nose and throat
EQ-5D	EuroQoL 5-Dimension
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Association
GGT	Gamma-glutamyltransferase
GLS	Generalized least squares
Gli	Glioma-associated oncogene
GP	General practitioner
Hh	Hedgehog
HPI	Hedgehog pathway inhibitors
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio

IRF	Independent review committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
laBCC	Locally advanced BCC
laBCC*i*	laBCC inappropriate for surgery or radiotherapy
LCL	Lower confidence limit
LY	Life-year
MAIC	Matched-adjusted indirect comparison
mBCC	Metastatic BCC
MDASI	M.D. Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NICE	National Institute for Health and Care Excellence
NMSC	Non-melanoma skin cancer
NR	Not reported
ONS	Office of National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PDT	Photodynamic therapy
PE	Pulmonary embolism
PFS	Progression free survival
PH	Proportional hazards
PO	Proportional odds
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PTCH	Patched
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SMO	(transmembrane receptor) ‘Smoothened’
SmPC, SPC	The Summary of Product Characteristics

SPM	Second primary malignancies
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTO	Time trade-off
TTP	Time to progression
TTR	Time to response
TVN	Tissue viability nurse
UCL	Upper confidence limit
ULN	Upper limit of normal
UV	Ultraviolet
VAT	Value added tax
VTE	Venous thromboembolic events
WCCS	World Congress on Cancers of the Skin
YPLL	Years of potential life lost

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of vismodegib (Erivedge®; Roche Products Ltd) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of vismodegib in the treatment of adult patients with symptomatic metastatic basal cell carcinoma (mBCC); or locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy.

Vismodegib received conditional marketing authorisation from the European Medicines Agency (EMA) on the 12th July 2013 subject to additional follow-up data from STEVIE, a single-arm study from which evidence in the company's submission (CS) is derived, and further analyses of the data. The additional data requested by the EMA were:

- a safety update comprising the pooled safety population using the final data from ERIVANCE (a second single-arm study contributing to the evidence base relevant to the decision problem) and an interim analysis of STEVIE of 500 patients with a potential one-year follow up; and
- data on safety and on efficacy in patients with symptomatic mBCC from the final analysis of STEVIE.

The Committee for Medicinal Products for Human Use (CHMP) issued a positive recommendation on 15th September 2016 following the review of the additional data and vismodegib was granted full approval by the EMA on 14th November 2016. Vismodegib is approved in the EU for use in the treatment of adult patients with:

- symptomatic mBCC; or
- laBCC inappropriate for surgery or radiotherapy.

Both ERIVANCE and STEVIE enrolled adults with an Eastern Cooperative Oncology Group (ECOG) status of ≤ 2 who had either mBCC or laBCC meeting the trial entry criteria. The final scope issued by NICE specified the population of interest to be patients with symptomatic mBCC; or laBCC inappropriate for surgery or radiotherapy. The Evidence Review Group (ERG) considers the population in ERIVANCE and STEVIE to be relevant to the decision problem. All clinically relevant outcomes were reported in the CS, with the exception of overall survival (OS) data for laBCC.

In the final scope issued by NICE, the comparator of interest was identified as best supportive care (BSC). The ERG notes that no trial level data were presented in the CS for BSC. The company presented the results of a landmark analysis using responders and non-responders to vismodegib from the STEVIE

study. The hazard ratios (HRs) estimated in the landmark analysis were used, along with the survival curves for the whole vismodegib population, to estimate survival curves for BSC in the economic model. However, the non-responder patients in the landmark analysis had also received vismodegib, and so the landmark analysis results are not a true representation of vismodegib versus BSC. No clinical data were presented in the CS that directly address the comparison of vismodegib versus BSC.

A subgroup analysis for patients with Gorlin syndrome was specified in the final scope issued by NICE 'if evidence allows'. The ERG note that data from a *post hoc* analysis are reported in the CS for STEVIE but no subgroup data are reported from ERIVANCE.

1.2 Summary of clinical effectiveness evidence submitted by the company

ERIVANCE was the key study used to gain conditional EU marketing authorisation for vismodegib. It was a multicentre international, open-label, single-arm, two-cohort clinical study comprising patients with laBCC and mBCC. There were 104 patients (33 patients with mBCC and 71 patients with laBCC) enrolled in ERIVANCE across 31 study sites in the USA, England, France, Germany, Belgium, and Australia. Vismodegib was given orally at the EU licensed dose of 150 mg/day in ERIVANCE until disease progression or study withdrawal for any reason including intolerable toxicity. The median duration of exposure to vismodegib in ERIVANCE was 13.3 months (range: 0.7 to 39.1) for patients with mBCC and 12.7 months (range: 1.1 to 47.1) for the laBCC group of patients. At the 30-month follow-up all 96 patients suitable for the efficacy analysis had discontinued treatment. The most common reasons for discontinuation were disease progression (30%), patient request (28%) and adverse events (AEs; 23%). The primary efficacy endpoint in ERIVANCE was objective response rate (ORR) as determined by the independent review facility (IRF) for the primary analysis with the 30-month efficacy results based on investigator only assessment.

STEVIE was a post-approval safety study designed to fulfil one of the specific obligations required by the initial conditional marketing authorisation for vismodegib in the EU by providing further data on safety and data on efficacy in patients with symptomatic mBCC. STEVIE also included laBCC patients and thus also provided further evidence of vismodegib safety and efficacy in laBCC patients. STEVIE, like ERIVANCE, was a multicentre international, open-label, single-arm, phase II clinical study comprising patients with laBCC and mBCC but contained a larger number of patients. The inclusion criteria in STEVIE were broader than those of ERIVANCE, as in STEVIE there were no restrictions on entry based on co-morbidities, other cancers and superficial multifocal BCC considered unresectable because of breadth of involvement. In total 1,232 patients were enrolled in STEVIE across 152 sites in 36 countries that included the UK. Treatment in STEVIE comprised the EU licensed dose of oral vismodegib, 150 mg daily, and was continued until disease progression, intolerable toxicity, or withdrawal from the study for any reason. The median duration of vismodegib treatment in STEVIE

was 263 days (256 days for laBCC and 319 days for mBCC). The primary outcome in STEVIE was safety, defined as the incidence of adverse events until disease progression or unacceptable toxic effects as assessed by the investigator on day 1 of each 28-day treatment cycle. The most common reason for discontinuation in STEVIE was AEs (28.7%). A higher proportion of patients discontinued due to AEs in STEVIE compared with ERIVANCE (29% versus [vs] 23%, respectively) and a smaller proportion discontinued in STEVIE due to disease progression compared with ERIVANCE (16% vs 30%, respectively). The results presented from STEVIE relate to an interim analysis and the final results are yet to be reported as the study is still ongoing.

The median age in STEVIE was 72 years, which clinical experts report is closer to what would be expected in UK clinical practice than the median age of 62 years in ERIVANCE. In addition, there were substantially fewer patients with mBCC compared with laBCC in both STEVIE and ERIVANCE (mBCC 96 and laBCC 1,119; mBCC 33 and laBCC 63; respectively) as would be expected in clinical practice based on the incidence rates of laBCC and mBCC and clinical expert opinion. In total, only 3.1% of patients in STEVIE and 2% in ERIVANCE came from UK sites. Thus, the contribution from UK sites is low and, as ERIVANCE and STEVIE were international studies, it is difficult for the ERG to comment on the potential impact of this on the generalisability of the whole trial results to the UK population. The ERG also considers it important to highlight that 21% of patients in ERIVANCE and 18.1% of patients in STEVIE had Gorlin syndrome, which experts report is quite high compared with the prevalence in UK clinical practices.

Investigator assessed ORR in ERIVANCE was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. Median investigator assessed progression-free survival (PFS) with vismodegib in the laBCC population was 12.9 months (95% CI: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months). Median OS for laBCC was not estimable (NE) but for the mBCC patients it was 33.4 months (95% CI: 18.1 months to NE). The mean change from baseline in the mental component and physical components of the health-related quality of life (HRQoL) SF-36 showed no statistically significant differences at the end of the study for the ERIVANCE combined (laBCC and mBCC) aBCC population ($p < 0.05$).

The ORR in STEVIE was 68.5% (95% CI: 65.7% to 71.3%) in the laBCC population and 36.9% (95% CI: 26.6% to 71.2%) in the mBCC population, and the median PFS for laBCC patients was 23.2 months (95% CI: 21.4 to 26.0) and 13.1 months (95% CI: 12.0 to 17.7) for mBCC patients. Median OS wasn't reached for either laBCC or mBCC patients. The only Skindex-16 HRQoL score for either mBCC or laBCC that showed a clinically meaningful change from baseline was the emotion score, which suggested an improvement with vismodegib. Efficacy results of STEVIE were thus in keeping with those of ERIVANCE, although PFS was longer for laBCC patients and shorter for mBCC patients.

The rate of AEs in both STEVIE and ERIVANCE was high, with 100% of patients in ERIVANCE and 98% in STEVIE experiencing an AE. Moreover, 55.8% of patients in ERIVANCE and 43.7% in STEVIE experienced a Grade 3 or higher treatment-emergent AE (TEAE). A total of 7.7% of the AEs in ERIVANCE and 3.8% in STEVIE resulted in death. The most frequently occurring AEs with vismodegib in both studies were muscle spasms (71.2% and 66.4%, ERIVANCE and STEVIE, respectively), alopecia (66.3% and 61.5%, respectively), dysgeusia (55.8% and 54.6%, respectively), and weight loss (51.9% and 40.6%, respectively).

The baseline characteristics of the Gorlin syndrome subgroup in STEVIE compared with the non-Gorlin subgroup differed substantially, with the Gorlin subgroup having:

- a lower median age (Gorlin syndrome: median 52.0 years [range 18 to 88]; non-Gorlin syndrome median 72.0 years [range 20 to 101]);
- a greater proportion of patients with an ECOG score of 0 (i.e. better performance status than non-Gorlin patients; ECOG Grade 0: 79.5% versus 53.0%, respectively); and
- a higher median number of target lesions (Gorlin syndrome median 3 [range 1 to 12], non-Gorlin median 1 [range 1-10]).

The *post hoc* Gorlin syndrome subgroup results from STEVIE also suggested that the Gorlin syndrome subgroup have a higher response rate (81.7% versus 63%) and longer duration of response (12.3 months versus 8.1 months) than non-Gorlin syndrome patients, although the results are not statistically significant ($p < 0.05$).

A landmark analysis was conducted by the company to inform the comparison of vismodegib with BSC, which the ERG considers to be of limited value in the evaluation of comparative clinical effectiveness as the analysis is based on the use of responder and non-responder data from vismodegib patients in STEVIE at a fixed point in time. Non-responders have received vismodegib and thus are not reflective of BSC patients. However, the absence of any comparative data on vismodegib makes meta-analysis unfeasible and thus alternative approaches, such as a landmark analysis or matched-adjusted indirect comparison (MAIC), are likely to be the only options to enable any comparison of vismodegib with BSC. The ERG notes that the company used a different definition to define responders in their analysis of PFS compared with the definition used for the analysis of OS. In this specific example, the landmark needs to be late enough that most patients will have responded, but not so late that most patients in the non-responder group have already had the event of interest (i.e. progressed or died). Similarly, the landmark should be early enough so that most patients have not had the event of interest, but not so early that a high proportion of late responders are misclassified (and so analysed) as non-responders after the landmark. The ERG agrees with the company's choice of a 6-month landmark for their primary analysis as it exceeds the mean and median time to first confirmed response in STEVIE. The company conducted sensitivity analyses using a 3-month landmark. However, the choice of a 3-month landmark

is likely to be too early as it is close to the median time to first response of 2.76 months and is less than the mean of 3.40 months for the combined aBCC population (laBCC and mBCC). The company also included covariate adjustment for age and ECOG status at baseline. However, the ERG considers the company not to have fully explored other important covariates such as Gorlin syndrome status that may have impacted the results.

The landmark analysis results from the company's primary analysis at the 6-month landmark for PFS showed no statistically significant difference between non-responders and responders with laBCC (HR 1.31; 95% CI: 0.96 to 1.78) or with mBCC (HR 0.99; 95% CI: 0.41 to 2.41). There was a significantly higher risk of death in the non-responders compared with the responders who had laBCC (HR 2.19; 95% CI: 1.23 to 3.92), but no significant difference for those with mBCC (HR 1.15; 95% CI: 0.30 to 4.47).

Landmark analysis results using the ERG preferred coherent definition of non-response, covariate adjustment for baseline age, ECOG score and Gorlin status using the 6-month landmark were consistent with the company's primary analysis findings (PFS: HR 1.19, 95% CI: 0.87 to 1.63 for laBCC and HR 0.95, 95% CI: 0.39 to 2.33 for mBCC; OS: HR 2.04, 95% CI: 1.09 to 3.82 for laBCC and HR 1.04; 95% CI: 0.24 to 4.49 for mBCC).

The results provided by the company following a clarification question on the Gorlin syndrome subgroup at the 6-month landmark suggest people with Gorlin syndrome may have improved OS (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively) and a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

The ERG considers it important to highlight that the results of ERIVANCE, STEVIE and the landmark analysis all comprise evidence on vismodegib from single arm studies that is at high risk of bias and thus should be interpreted with caution. In addition, the results for the mBCC subgroup are based on small subgroups and so are subject to large amounts of uncertainty.

The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or chemotherapy and so are left with no other treatments options at this point in the clinical pathway. The company adds that vismodegib offers clinical benefit in terms of delay of disease progression and survival, with a manageable safety profile.

1.3 Summary of cost effectiveness evidence submitted by the company

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS, PFS and time-to-treatment discontinuation (TTD) data from STEVIE to determine mortality, disease progression and time on treatment for each cycle of the economic model,

respectively. The company built two separate models, one each for laBCC and mBCC. Data from STEVIE were therefore used according to the type of aBCC, in each model, separately.

In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to STEVIE Kaplan-Meier (KM) data. The company also explored the option of including KM curves with a parametric tail used for extrapolation in their sensitivity analyses. Once the best-fitting model was selected, survival curves for vismodegib were derived through the use of survival functions, and were then used to estimate the proportion of patients in each health state for every cycle of the vismodegib laBCC and mBCC models.

To obtain OS and PFS curves for BSC, the HRs derived from the landmark approach were applied to the estimated vismodegib PFS and OS survival curves. Even though the company built two separate models, using separate data for laBCC and mBCC, the common effect (laBCC and mBCC) HR derived through the landmark approach was applied to the laBCC and the mBCC curves. Patients on BSC were assumed to be on a specific BSC treatment regimen until progression, and on a different BSC regimen after disease progression.

The company's base case model assumes that the proportional hazards (PH) assumption holds for the responders compared with non-responders in STEVIE. The company provided log-cumulative hazard plots for OS and PFS data for responders and non-responders in the STEVIE study. The company did not undertake an assessment of the proportional odds (PO) or accelerated failure time (AFT) assumptions.

Patients in STEVIE received treatment until progression or unacceptable toxicity. Treatment duration with vismodegib in the model was defined through the use of TTD data from STEVIE. The company decided to model TTD curves with a Weibull model. The company also used a Weibull model to estimate PFS for laBCC and mBCC patients.

The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the lognormal was best fitting model for the OS mBCC data. The CS notes the lack of maturity in OS data, and the fact that the extrapolated tails of the OS curves carry a high level of uncertainty in the economic analysis, regardless of the distribution used.

The CS reports that the mortality rates observed in the STEVIE trial do not reflect the increase in mortality rates at older ages and, therefore, the OS fitted curves are likely to overestimate long-term survival in the laBCC and the mBCC populations, when compared with the survival of the general population. The company reinforces the view that mortality directly attributed to laBCC is incredibly rare and that laBCC patients are usually elderly and are often suffering from other co-morbidities. Nonetheless, the company adds that patients diagnosed with non-melanoma skin cancer (including BCC

and squamous cell carcinoma [SCC]) have a 10-year lower life expectancy than the general population. With regards to mBCC patients, the CS states that these patients' prognosis is poor, with mortality being higher than that for the general population. Two methods were evaluated in order to prevent OS extrapolations exceeding background mortality rates in the model.

The company considered that it would be unrealistic to assume a life-long treatment effect with vismodegib and so applied the relevant HRs for 44 months in the laBCC model and until month 38 in the mBCC population. These time points correspond to the maximum follow-up times in STEVIE. After these time points, the company used the hazard rate from the BSC arm to model OS for vismodegib patients.

Utility data in STEVIE were captured with the Skindex-16 instrument. Given the lack of a published algorithm to map Skindex-16 into EQ-5D data, the company could not use the utility data captured in STEVIE. The HSUVs used in the model are based on SF-36 data collected in the ERIVANCE trial. The SF-36 data were mapped to EQ-5D tariff scores, using a mapping algorithm published by Rowen *et al*.

The costs included in the economic analysis fall within three cost categories: pharmacological, disease management, and adverse event costs.

The company presented a weighted aggregated ICER for the laBCC and mBCC populations of £35,251 per QALY gained. The disaggregated results amount to an ICER of £30,493 for laBCC patients and £100,615 for mBCC patients.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The CS contained a systematic review that addressed the population and intervention specified in the decision problem outlined in the final scope issued by NICE. The company's search strategies were well designed for identifying studies of vismodegib.

Economic

The formulae within the economic model are generally sound and the economic model is well constructed. The company provided all the additional analyses requested by the ERG at the clarification stage.

1.4.2 Weaknesses and areas of uncertainty

Clinical

A key limitation of the submission is the lack of direct randomised evidence comparing vismodegib versus BSC. In addition, the ERG is concerned that the company's search strategy omitted search terms for BSC, the key comparator of interest in the final scope issued by NICE. The ERG is not qualified to comment on the feasibility of an RCT of vismodegib in the population of interest in this decision problem, although the ERG does consider a comparative study design to be preferable. The ERG considers a potential comparator of physician's choice could have been used in an RCT to represent BSC. In addition, the ERG considers the company's rationale that it would be difficult to recruit sufficient patients due to the limited aBCC population to be unjustified given the size of the STEVIE study.

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).

Overall, the ERG considers that the available evidence on the clinical efficacy of vismodegib for the treatment of symptomatic mBCC and laBCC inappropriate for surgery or radiotherapy is of limited quality due to the single-arm non-randomised study design of ERIVANCE and STEVIE. However, the ERG also acknowledges that ERIVANCE and STEVIE at this time, represent the best available evidence on the clinical effectiveness of vismodegib.

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. In addition, it is considered that 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 based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies. 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 adjusted for differences in baseline characteristics. In addition, they are not presented separately for the laBCC and mBCC populations.

Economic

The ERG is concerned with the extremely high degree of uncertainty embedded in the analysis of relative treatment effectiveness of vismodegib compared with BSC. The landmark method used to derive the HRs for OS and PFS introduces uncertainty in the analysis, which is only exacerbated by the small number of patients in the mBCC group. In addition, the non-systematic selection of prognostic factors in the HR estimations potentially introduces further uncertainty and bias in the analysis. The company's assumption that PH holds in the analysis is also likely to introduce further uncertainty in the results, particularly for OS data.

It is the ERG's view that, in particular for mBCC patients, the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib compared with BSC in terms of OS and PFS outcomes. With regards to 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.

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.

The ERG discusses below, the particularities of the STA and its issues in more detail:

- The landmark approach undertaken by the company produced a HR for responders vs non-responders in the STEVIE study. Therefore, the company adjusted the HR obtained in the landmark approach to reflect the HR of non-responders vs intention-to-treat (ITT) patients, as a proxy of the measure of relative effectiveness for vismodegib compared with BSC. The ERG disagrees with the theoretical and methodological implications of the adjustment made by the company. The final HR used in the model is a time-varying HR, which resulted from the company imposing a time-varying component in the landmark HR that was derived as a time-invariant HR, with a Cox PH model. If the company had reasons to believe that there is evidence of a time-varying treatment effect, then a different modelling approach should have been explored. The company could have explored fitting the responders and non-responders data from STEVIE independently or fitted the dataset with a time-varying model. If, on the contrary, the evidence does not substantiate the existence of a time-varying HR, then this time dependency should not be forced into the HR, which is what the company's approach implies. Even though the ERG does not agree with the company's adjustment made to the HRs, it notes that adjusting the HRs is in detriment of the company's analysis as this decreases the HRs used in the model, therefore increasing the final ICER. It is also worth noting that fitting responders and non-responders data independently would have raised a different issue. Using these populations as proxies for a vismodegib arm and a BSC arm, respectively, would have introduced bias in the analysis and overestimated the effectiveness of vismodegib and the effectiveness of BSC.

  Applying the "unadjusted" HR resulting from the landmark approach to the ITT population in STEVIE is also partially flawed. The HR reflects the relationship between a "perfect response" vismodegib group and a BSC group with potentially better outcomes than a real BSC group. However, if one hypothesises that the upwards bias introduced in this analysis cancels out (meaning that the overestimation of vismodegib effectiveness cancels out the overestimation of BSC effectiveness), then applying this HR to the ITT population, could approximate the

analysis to what would be observed in a comparative trial, evaluating vismodegib vs BSC. This was the approach followed by the ERG in its exploratory analysis.

- Related to this issue is the assessment of PH in the clinical events observed in the responders and non-responders groups of STEVIE. 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. Although the initial tests (visual inspection of log-cumulative hazard plots) seem to indicate that PH does not hold for OS or for PFS for mBCC patients, this could be a product of the combination of the method of analysis and the extremely small numbers of mBCC patients. 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. The HRs and the methods used to model treatment with vismodegib and BSC in the cost-effectiveness analysis (dependant fit and assumption of PH) carry a high degree of uncertainty. This, in turn, adds substantial uncertainty in the final ICERs.

- The ERG disagrees with the company's approach of using a common treatment effect (laBCC and mBCC) HR in the model. The company built two separate models, using separate data for laBCC and mBCC patients but decided to use a common treatment effect HR in both models. Due to the clinical and prognostic differences in the populations (discussed in Section 5.4.2), the ERG considers that the two patient groups should be analysed separately, as should the effectiveness of vismodegib in these populations. For example, while it is plausible to assume that vismodegib has a mortality benefit for mBCC patients (who eventually die from their disease), it is less likely that vismodegib has a mortality benefit on laBCC (who are unlikely to die from their disease).

- 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 characteristic are likely to be relevant prognostic factors, such as Gorlin syndrome, nerve infiltration and BCC location (i.e. head, neck, etc.).

- The mBCC HRs are not statistically significant for OS or PFS outcomes. This is not surprising considering the limited number of patients observed in the group. Interestingly the PFS HR for laBCC is also not statistically significant, despite the considerably larger sample size in this population (736 patients overall). The only HR that is statistically significant in the company's analysis is the OS HR for laBCC patients.

- There is an unusual plateau at the end of the OS and TTD KM curves for laBCC and mBCC patients. The KM curves and the data suggest that, for laBCC patients, there were no death or discontinuation events for approximately 1.5 years before the end of the follow-up period. The same is true for mBCC patients where for approximately 16 months before the end of the follow-up period there were no deaths or discontinuation events. The ERG asked the company to confirm if this had been the case in STEVIE and the company confirmed that the 44 months for laBCC and 38 months for mBCC data points correspond to the entire follow-up period in STEVIE and added that no events were observed from the previous date point in the KM curves till the end of the follow-up. By 26 months patients in STEVIE would be, on average, 74 years. The OS KM tails imply that no patient with mBCC would die for 18 months, which the ERG finds implausible from a clinical point of view. The long tails of the TTD curves suggest that patients continued treatment after progression in the mBCC population. This is difficult to explain as STEVIE patients could not continue treatment after progression.

- The ERG has some concerns regarding the estimation of TTD curves in the laBCC and mBCC vismodegib models:

    - The company's decision to use a Weibull instead of a log-logistic model to estimate TTD: the ERG considers that there is no robust evidence to suggest using a Weibull over a log-logistic distribution to estimate TTD in the economic analysis 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;

    - The KM TTD curve crossing the KM PFS curve for mBCC patients: 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. The company has dealt with the issue of TTD and PFS crossing curves by capping the 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.

With regards to laBCC patients, the fact that the KM TTD and the PFS curves cross at around month 38 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 7%. Considering the small percentage of patients, the ERG's preferred approach would still be to use a better fitting curve 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. 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. 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, it 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 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.

- 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. Due to this, clinical expert opinion might be of more value than the traditional curve fitting validation exercises. This is only caveated by the fact that out of the three clinical experts contacted by the ERG (two dermatologists and one oncologist), only one had had contact with a mBCC patient. As mentioned in Section 4, the incidence of mBCC is extremely low, and therefore clinical expert opinion given for mBCC data also carries considerable 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 (Figure A). Clinical experts stated that patients are highly unlikely to die from laBCC, as acknowledged by the company several times in the CS. One clinical expert added that the advantage of vismodegib in laBCC patients is in preventing progression, but that once that point is reached, then the journey of the patient is the same irrespective of treatment.

The CS does 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 also interesting to note that for the first five cycles in the economic model, the company used the background survival curve to model OS for vismodegib (instead of the Gamma model), as the survival predicted by the Gamma model was higher than the background survival for the matched UK population. It is therefore difficult to understand the extent to which the company's analysis is generalizable to laBCC patients in the UK. For example, the fact that laBCC patients have a higher mortality rate than the average age and gender-matched population in the UK might be related to the fact that only 3% of patients in the STEVIE trial came from the UK. Given these patients age, and the possibility that patients' co-morbidities are the main cause of death, it could be hypothesised that the other 97% of the STEVIE population had higher mortality rates due to different co-morbidities from the ones observed in the UK for the gender and age-matched average population This could also be related to differences in management/treatment options for these conditions in other health care systems.

With regards to mBCC-related mortality, the clinical experts advising the ERG presented different views. Even though the three experts agreed that (unlike for laBCC) patients will die from mBCC, there was not a consistent view on which curve was a better representation of the vismodegib OS curve for mBCC. One clinical expert's opinion was that none of the curves were accurate representations of mortality for mBCC patients. The expert indicated that most mBCC patients would be expected to die between 12 and 24 months and so it was unrealistic

to assume that patients would survive for more than 10 years (Figure B). This is consistent with the view of the Economic Guidance Panel (EGP) in Canadian Health Technology Assessment (HTA) body, who considered that mBCC patients were expected to survive for less than 10 years.

Figure A. Survival curves and KM curve for OS laBCC

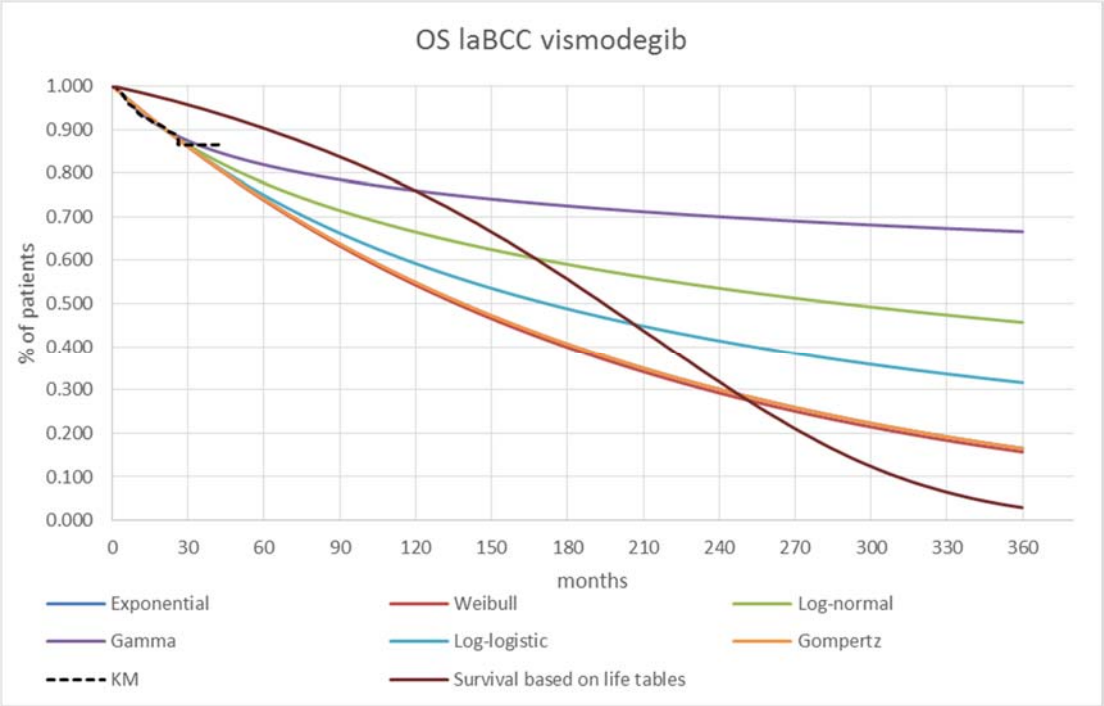
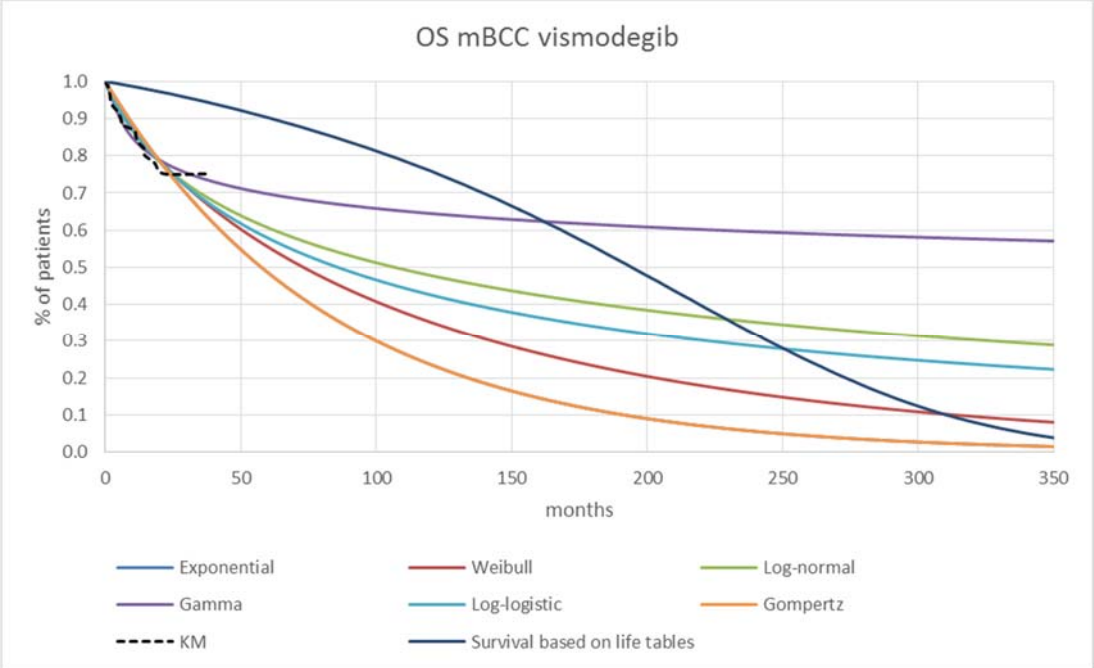


Figure B. Survival curves and KM curve for OS mBCC



The ERG asked the company to use the McCusker *et al.* paper to conduct a validation exercise on the modelled BSC arm for mBCC as this study appears to be the only available evidence for BSC-related mortality in aBCC patients. The company aggregated the distant and regional metastatic KM OS curves from McCusker *et al.* as requested by the ERG and used it to fit BSC OS curves in the economic model for mBCC patients. The company then applied the inverse HR obtained through the landmark approach to derive an mBCC vismodegib curve. The modelled survival curves from STEVIE (i.e. ITT population curve for vismodegib patients and BSC curve estimated by applying the landmark HR to the ITT vismodegib curve) and the McCusker *et al.* curves (i.e. the observed BSC curve for mBCC patients and the vismodegib curve estimated by applying the landmark HR to the McCusker *et al.* curve) are similar, which is not unexpected, considering that the same HR was used to derive the comparator curve in each case (i.e. the BSC curve in STEVIE data and the vismodegib curve in the McCusker *et al.* data). As the observed curves (i.e. ITT curve in STEVIE and BSC curve in McCusker *et al.*) are not comparable, the difference in these curves cannot be validated by any other data source. Figure C also shows the difference between the non-responders in STEVIE and the BSC patients in the McCusker *et al.* source (dark green and pink curves). This shows that the non-responders group in STEVIE and the BSC patients in McCusker *et al.* have very different survival prognosis. This analysis is caveated by the fact that the number of patients in the non-responders group in STEVIE is incredibly small (31 patients) and that only four patients died. It should also be noted that patients in McCusker *et al.* are younger than in STEVIE, which suggests patients would have a better survival prognosis instead of worse survival outcomes, when compared with STEVIE.

Figure C. Survival in mBCC patients

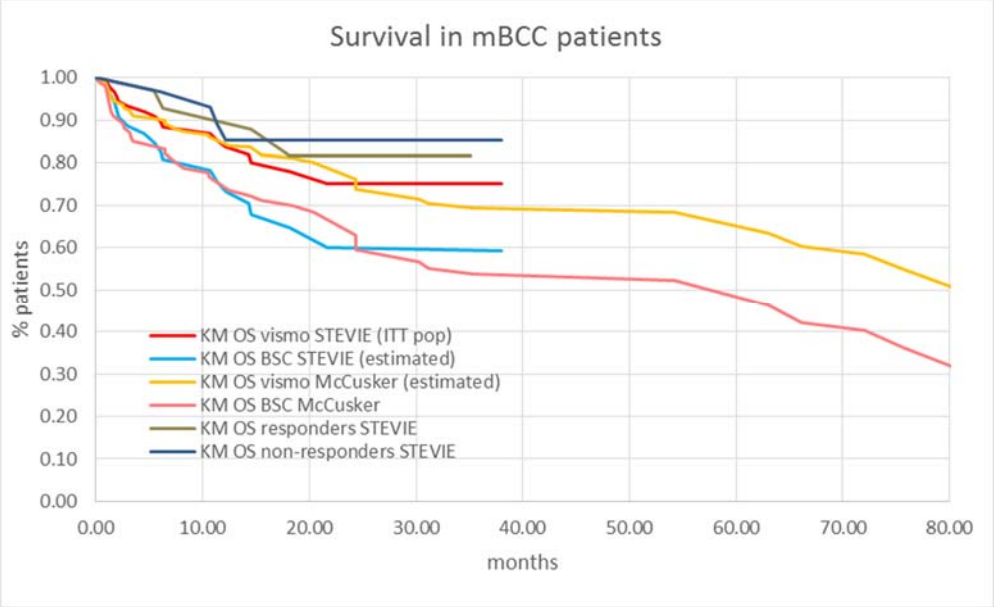
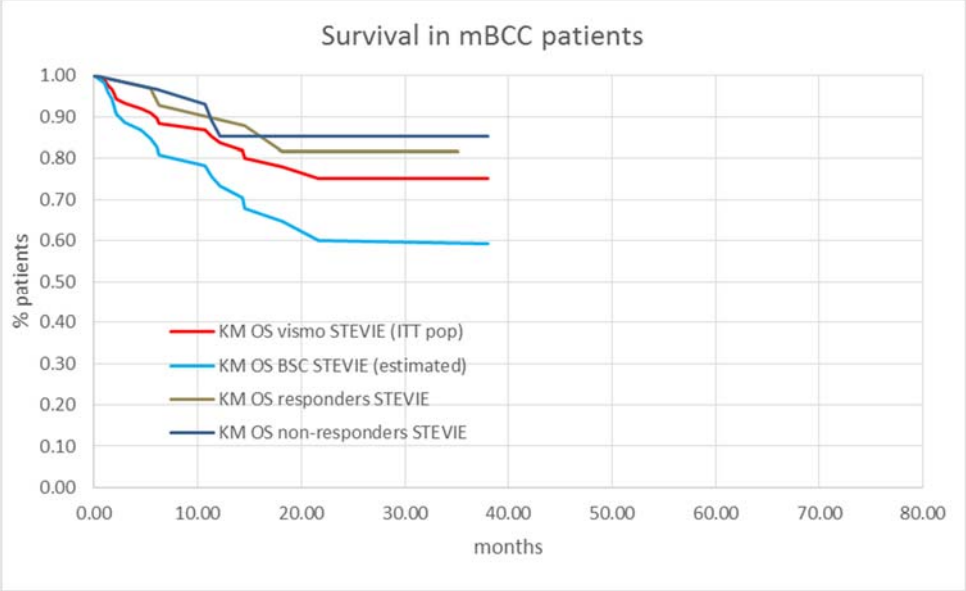


Figure D shows how the responders and non-responders groups from STEVIE compare with the modelled vismodegib and BSC curves for mBCC. The difference in these curves is overwhelming. While the responders and non-responders KM curves clearly reflect the lack of statistical significance encountered in the landmark HR for OS in mBCC patients (as they cross and overlap a few times), the ITT and estimated BSC curves do not, and show a clear separation of the curves throughout the entire time horizon of the model. This is worrying as it reveals the lack of robust evidence substantiating the vismodegib and BSC estimated curves and the contradiction between observed and estimated outcomes. The ERG does not consider that the evidence provided by STEVIE or clinical experts (due to the very low incidence of mBCC cases) is robust enough to make conclusions on the effectiveness of vismodegib in the mBCC population.

Figure D. Survival in STEVIE for mBCC patients



- The quality of life data incorporated in the model are from the ERIVANCE study, while the clinical effectiveness data used in the model are based on the STEVIE study. The ERG acknowledges that there are no published algorithms for mapping quality of life data captured through the Skindex-16 instrument into EQ-5D values, therefore using data from STEVIE was not an option. Nonetheless using ERIVANCE quality of life data raises several issues:

    - 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 on average 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, who was on average 10 years older than the population in ERIVANCE;

- Progression was assessed differently in the two studies. In STEVIE, progression was assessed using the RECIST v1.1 criteria, while in ERIVANCE a novel composite method was used to determine progression in the laBCC population. It is difficult to anticipate the impact that the difference in progression criteria could have on the cost-effectiveness results;

- The Canadian HTA body also raised some valid points on the uncertainty of the SF-36 data from ERIVANCE. They point to the lack of sensitivity of the SF-36 instrument for this indication, the ceiling effect for relatively healthy individuals at baseline and the small sample size in ERIVANCE.

According to the descriptive statistics provided by the company at clarification stage, the mean change from baseline in SF-36 values for all the dimensions does not seem to be 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) for the physical functioning and vitality components seems to be statistically significant. All the other dimensions do not seem to show statically significant reductions at the end of the study. The lack of statistical significance in the results might be related with the points raised by the Canadian HTA body, which noted 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 is robust, the underlying SF-36 data seems to carry a lot of uncertainty. The company used SF-36 values who mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values who suggest a decrease in patients' quality of life upon progression.

- Resource use estimates applied in the model are based on feedback from the company's clinical experts as there are no known sources for resource use in the study population. The ERG's clinical experts confirmed that the assumptions made in the model surrounding pharmacological costs are reasonable. However, there are some concerns surrounding the company's assumptions for estimating disease management costs. More specifically these are related with:

    - The company's assumption that 67% of patients who progress after receiving vismodegib are on a monitoring regimen for the remainder of their lifetime and never receive BSC. The ERG's clinical experts explained that even if these patients require a

less intensive regimen for managing disease progression after vismodegib, they will eventually go on to receive BSC as their disease progresses. Clinical experts' input indicates that the duration of the watchful waiting period is highly volatile and depends on the location 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, progressed patients will eventually move to BSC;

- The company's assumption on the frequency of wound management and TVN visits. There was no consensus amongst the clinical experts advising the ERG with regards to the frequency of wound management in the PD and in the PFS states for BSC patients. While one clinical expert agreed with three visits for the PD state and two visits for the PFS state, the other two clinical experts suggested that a less intense regimen would be more plausible (two visits for the PD state and one visit for the PFS state);

- The company's assumption that the post-progression BSC regimen for vismodegib patients differs from the post-progression BSC regimen for BSC patients. Clinical expert opinion provided to the ERG was consensual that once vismodegib patients progress and require BSC, the treatment schedule for these patients is the same as the one required by patients on the BSC treatment arm who have progressed.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

Some of the exploratory analyses undertaken by the ERG (such as the ones relating to using the PFS and OS HRs) are still based on flawed assumptions or methods (for example assuming PH), but do provide a step in the right direction compared with the company's base case approach. The ERG notes that all exploratory analyses conducted for mBCC patients are an academic exercise to explore the possible direction of the change in the final ICER and the overall impact of changes when considered together. Nonetheless the ERG stresses its opinion that for mBCC patients, the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib compared with BSC.

The ERG's exploratory analysis has shown that both the laBCC and mBCC results are most sensitive to the assumptions made around disease-related mortality and vismodegib's survival benefit, as well as the assumptions surrounding the costs of BSC. Removing the AE-related disutilities and the cost of a dietician from the model had a negligible impact on the model results for both laBCC and mBCC patients.

When the ERG assumed that there is no mortality associated with laBCC, therefore assuming no survival gain with vismodegib, the final ICER for vismodegib compared with BSC is £5,203,675. The ICER for vismodegib compared with BSC when assuming the existence of laBCC-related mortality and a gain in survival with vismodegib compared with BSC is £106,569 (Table A).

As previously explained, due to the level of uncertainty and the lack of robust mBCC data, the ERG conducted a cost minimisation analysis for this population. When the ERG assumed a PFS and OS HR of 1, the final ICER for vismodegib vs BSC became dominated, with a zero QALY gain and an additional cost of £89,323 (total costs for vismodegib £159,547 and £70,224 for BSC – Table B).

Table A. ERG base case ICER for laBCC patients

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's base case for laBCC patients**			
	Total costs (£)	£124,865	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER			**£30,493**
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£126,135	£97,558	£28,577
	QALYs	8.59	7.69	0.90
	ICER (compared with base case)			£31,880
	ICER with all changes incorporated			**£31,880**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£124,214	£89,170	£35,045
	QALYs	8.36	7.05	1.31
	ICER (compared with base case)			£26,820
	ICER with all changes incorporated			**£27,772**
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£135,491	£97,519	£37,972
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£42,344
	ICER with all changes incorporated			**£35,888**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£124,869	£100,607	£24,262
	QALYs	8.58	7.91	0.67
	ICER (compared with base case)			£36,028
	ICER with all changes incorporated			**£39,597**
5a	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£138,861	£97,519	£41,341

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£46,100
	ICER with all changes incorporated			**£52,356**
5b	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			
	Total costs (£)	£142,784	£97,519	£45,264
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£50,474
	ICER with all changes incorporated			**£95,164**
6	**Replacing the company's PFS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 1.311) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 1.19)**			
	Total costs (£)	£124,865	£97,214	£27,651
	QALYs	8.58	7.69	0.89
	ICER (compared with base case)			£31,107
	ICER with all changes incorporated			**£96,352**
7	**Assuming that mortality for laBCC patients with vismodegib and BSC is to be the same as the background mortality for the UK population (i.e. no survival gain with vismodegib)**			
	Total costs (£)	£126,490	£117,138	£9,352
	QALYs	9.14	9.11	0.02
	ICER (compared with base case)			£435,402
	ICER with all changes incorporated			**£5,203,675**
8	**Replacing the company's OS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 2.035)**			
	Total costs (£)	£124,929	£99,278	£25,651
	QALYs	8.60	7.81	0.79
	ICER (compared with base case)			£32,442
	ICER with all changes incorporated			**£106,569**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table B. ERG base case ICER for mBCC patients

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's base case for mBCC patients**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER			£100,615
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£122,243	£40,870	£81,373

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£101,550
	ICER with all changes incorporated			**£101,550**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£120,524	£33,729	£86,794
	QALYs	3.48	2.49	0.99
	ICER (compared with base case)			£87,939
	ICER with all changes incorporated			**£88,698**
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£120,573	£40,813	£79,760
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£99,502
	ICER with all changes incorporated			**£87,795**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£100,615
	ICER with all changes incorporated			**£87,795**
5a	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£126,325	£40,813	£85,512
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£106,679
	ICER with all changes incorporated			**£92,161**
5b	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			
	Total costs (£)	£129,687	£40,813	£88,874
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£110,873
	ICER with all changes incorporated			**£109,503**
6	**Using a PFS HR of 1 in the mBCC model**			
	Total costs (£)	£121,465	£40,187	£81,278
	QALYs	3.75	2.98	0.77
	ICER (compared with base case)			£106,092
	ICER with all changes incorporated			**£115,545**
7	**Using a OS HR of 1 in the mBCC model**			
	Total costs (£)	£125,212	£70,805	£54,407
	QALYs	4.82	4.79	0.03
	ICER (compared with base case)			£1,580,078

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	ICER with all changes incorporated			**Vismodegib dominated**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

2 BACKGROUND

Section 3 of the company submission (CS) provides an overview of the key aspects of locally advanced (laBCC) and metastatic basal cell carcinoma (mBCC). The Evidence Review Group (ERG) notes the population outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) is people who have symptomatic mBCC or people with laBCC for whom surgery or radiotherapy is not appropriate.[1]

The ERG considers the information in the CS to provide a reasonable overview of laBCC and mBCC and to be relevant to the NICE final scope.[1]

All information that appears in boxes in the ERG report is taken directly from the CS, unless otherwise stated, and the references have been renumbered.

The company's overview of BCC, laBCC and mBCC are presented in the Boxes below (Box 1, Box 2 and Box 3). The major cause of BCC is sun exposure.[2] Risk factors associated with increased incidence of BCC include fair skin, blond or red hair, blue, green and grey eyes, increasing age and family history.[2] Males are also more likely to have BCC than females.[2]

Box 1. BCC disease overview (Adapted from CS, page 39, Section 3.1.1)

BCC is a form of NMSC. As ultraviolet (UV) radiation is a risk factor, BCCs are most often found on the head, neck, and other areas exposed to the sun in light-skinned individuals. [3-8]

The common, non-advanced forms of BCC usually present as uncomplicated pearly papules with overlying telangiectases (dilated blood vessels) with a rolled border [3, 7] or as pigmented, scaly, plaque-like, or indurated lesions depending on the histologic subtype.[4, 6, 7] These lesions are usually indolent, characterised by slow growth and minimal soft tissue invasiveness (locally invasive). However, BCC can advance to affect surrounding tissues, cartilage, and bone, potentially leading to substantial local or deep tissue destruction and disfigurement (laBCC; particularly as lesions predominantly affect the head) or metastasise to regional and/or distant sites (mBCC).[9] These locally advanced and metastatic forms of BCC, laBCC and mBCC, are collectively described as aBCC.

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NMSC, non-melanoma skin cancer; UV, ultraviolet.

Advanced BCCs are split into laBCCs and mBCCs. A subset of laBCCs are not suitable for surgery or radiotherapy and these are the focus of this STA along with the whole population of patients with mBCC. Mohan *et al.* report from their clinical experience that, "patients presenting with aBCCs appear to fall into two categories: (1) those who present with aBCC due to delay in accessing medical attention; or (2) those who have BCCs that are intrinsically aggressive and are refractory or recur after treatment."[10]

Box 2. Overview of locally advanced BCC (Adapted from CS, page 40, Section 3.1.3)

BCC growth is usually indolent and confined to the localised area of origin; however, some BCCs may infiltrate tissues with irregular, finger-like growth projections, which may not be obvious on visual inspection.[11] If left untreated, or inadequately treated, an infiltrating BCC can cause extensive tissue destruction, particularly on the head or neck.[11] In such cases, an infiltrating BCC may infiltrate bone and deeper structures, like the brain.[11] Advanced BCC is thought to occur in up to 10% of all BCCs[10, 12], with around 1% of BCCs developing in to advanced cases that are not appropriate for standard therapy (laBCC inappropriate for surgery or radiotherapy; laBCC*i*).[13]

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; laBCC*i*, laBCC inappropriate for surgery or radiotherapy.

Box 3. Overview of metastatic BCC (Adapted from CS, pages 40-41, Section 3.1.3)

BCCs very rarely spread to distant regions, only 0.0028 to 0.55% of BCCs progress to metastatic basal cell carcinoma (mBCC).[14, 15] Risk factors that appear to predispose patients to developing mBCC have been identified:[16]

- long duration and persistence of the tumour for many years,
- site (in 85% of cases the primary tumour was located in the head and neck region [particularly the ears and mid-face]),
- the size of the tumour, depth of invasion and infiltrative histological pattern,
- number of lesions,
- recurrence despite optimal treatment,
- BCC refractory to conventional methods of treatment, incomplete surgical resection and previous radiation therapy either in early adulthood or for localised cancer.

Metastases most often spread to lymph nodes, lungs, and bones. Lymphatic and haematologic routes of tumour dissemination have been reported with equal frequency [17], though some case series report a dominance of lymphatic involvement.[18] Age or gender do not appear to influence survival outcomes in mBCC.[17] BCC that has metastasised locally with only regional lymph node involvement tends to be more biologically indolent, compared with those that have visceral metastases and have poor prognosis and death usually within months.[18]

Once BCC has metastasised to distant structures, mean survival of between 10 to 14 months[18] and median survival of 8 months[17] is reported; it is highly malignant and currently considered incurable and life-threatening.[19]

Abbreviations: BCC, basal cell carcinoma; CS, company submission; mBCC, metastatic BCC.

A further important risk factor for developing both laBCC and mBCC is the inherited disorder, Gorlin syndrome (Box 4).

Box 4. Overview of Gorlin syndrome (Adapted from CS, page 41, Section 3.1.3)

The inherited disorder, Gorlin syndrome (also known as basal cell naevus syndrome [BCNS], naevoid basal cell carcinoma, or Gorlin-Goltz syndrome), is associated with a predilection for aBCC development.[6,7,20, 21] Gorlin syndrome is the most common of the inherited syndromes associated

with BCC development.[22, 23] Gorlin syndrome is an autosomal dominant disorder characterised by the development of multiple naevoid BCCs, as well as the development of recurrent odontogenic keratocysts, skeletal anomalies, intracranial calcification, and developmental malformations.[24] The greatest health concern for patients with Gorlin syndrome is the risk of malignant tumour development, the most common of which are BCCs.[25] It is important to note that aberrant Hh signalling is the underlying oncogenic driver for the development of aBCC in patients with or without underlying Gorlin syndrome.

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; BCNS, basal cell naevus syndrome; CS, company submission.

BCCs can be split into different subtypes and these can further help guide prognosis (Box 5 and Box 6).

Box 5. BCC clinical subtypes (Adapted from CS, pages 39-40, Section 3.1.2)

There are several distinct clinical BCC subtypes including superficial, nodular, and morpheaform (also known as sclerosing, fibrosing, or infiltrating) BCCs.[4, 7] These BCC subtypes are primarily based on their clinical appearance and vary in their malignant potential. Superficial and nodular BCC tend to be less aggressive forms of disease relative to morpheaform.[6] Morpheaform BCC is generally more aggressive and associated with a higher risk of developing advanced disease. Furthermore, the morpheaform BCC subtype has been associated with greater subclinical depth of tissue extension and a greater rate of recurrence relative to other clinical subtypes.[6]

Abbreviations: BCC, basal cell carcinoma; CS, company submission.

The ERG notes that the company refer to a paper by von Domarus[17] that was published in 1984 for details on the prognosis of mBCC as well as providing provide more recent evidence from their own study published in 2014 (McCusker 2014)[26] (Box 6). The von Domarus study included patients spanning 1894 to 1980 and the McCusker study covered cases between 1981 and 2011. The ERG considers the McCusker study to be more representative of the current prognosis for mBCC as along with changes in management of mBCC in terms of BSC, other general differences in lifestyle, health and social factors are likely to confound the results of the von Domarus study and make its findings less applicable today.

Box 6. Prognosis of aBCC, laBCC and mBCC (Adapted from CS, page 53, Section 3.4.3)

Due to their size, invasiveness, or location, aBCC lesions can cause significant disfigurement or deformity, disability, and/or premature mortality. However, mortality directly attributable to laBCC is incredibly rare, with elderly patients often dying from other co-morbidities associated with old age. Locally advanced disease is considered a chronic condition and unless present near a vital blood vessel, perineural, or at a very advanced stage involving the skull; laBCC would not be expected to directly cause the death of the patient. However, approximately 10 years of potential life are lost per death from NMSC [27], and it could be postulated that laBCC contributes to the shorter survival in patients due to poor general health and self-care.

The prognosis is poor for patients with mBCC, and morbidity and mortality are high.[28] A published retrospective case series by von Domarus estimated median time from the first sign of metastasis to death at 8 months.[17] To gain a more recent understanding of the clinical outcome for mBCC patients since then, a retrospective analysis was undertaken by Roche.[26] This retrospective review of published literature between 1981 and 2011 revealed that in the 100 mBCC cases identified, survival from mBCC diagnosis to death ranged from 0 to 120+ months.[26] Median survival was 24 months among patients with distant metastases (just 12 months in those with bone metastases and 66 months for those without bone involvement), compared with 87 months in those patients who had local metastases. The 1-year probability of survival after mBCC diagnosis was approximately 73.2% (95% CI 64.4 to 82.0) for all cases reviewed and a lower 1-year survival probability was associated with the subset of cases reporting patients with distant metastases (58.6%; 95% CI 44.6 to 72.6) compared with patients with regional metastases (87.8%; 95% CI 78.6 to 97.0).[26]

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NMSC, non-melanoma skin cancer.

The company provides information on the patient impact of aBCC along with details of the estimated economic costs associated with non-melanoma skin cancers (NMSC; Box 7). The ERG considers it important to highlight that while NMSC includes BCC, it also comprises of squamous cell carcinoma (SCC), which is known to be faster growing than BCC.[29] The prognosis and economic impact for BCC are thus unclear and the information presented in Box 7 should be interpreted with caution.

Box 7. Impact of aBCC on patients and the economic effects of NMSC (Adapted from CS, pages 45-46, Section 3.2)

The clinical burden of disease for individuals afflicted with aBCC is significant. In aBCC, tumours have metastasised or caused extensive tissue destruction through deep invasion and deformity of surrounding tissue, particularly on the face, resulting in disfiguring and potentially life-threatening disease.[11] Patients with aBCC have expressed HRQoL issues about fear of recurrence or metastases, pain, appearance (potentially increasing social isolation), and the inconvenience of wound care.[30] Patients with Gorlin syndrome have expressed similar HRQoL concerns in addition to anxiety regarding the future and the significant inconvenience of undergoing multiple surgeries.

Locally advanced BCC often affects visible areas of the head and neck with significant disfigurement. For example, laBCC lesions, as a result of tumour invasion, may lead to limb amputation or surgical removal of a facial structure such as an eye, ear, or nose.[4] In addition, laBCC can be associated with significant morbidity as the result of these lesions causing chronic pain, risk of bacterial infection and sepsis, bleeding or oozing, and compromise of ear, nose, or eye function from tissue invasion.

The increasing trend in NMSC development, likely due to increasing UV radiation exposure, leads to concerns over losses in productivity, direct and indirect costs associated with the morbidity and potential premature mortality of aBCC.[27,31] Despite most cases of BCC being curable, deaths from aBCC are reported.

There is little published data regarding societal burden, and indirect costs including morbidity and mortality costs of BCC specifically. NMSC incorporates both BCC and the typically more aggressive

SCC.[27] Mortality cost from potential lost future earnings due to premature death from NMSC have been estimated (in converted 2009 $US) to be $1 billion in the US, $8.7 million in the UK, $0.55 million to $3.6 million in Sweden, and $4.6 million in New Zealand.[27] The mortality cost per premature death from NMSC ranged from $20,550 in the UK (converted to 2009 US$) to $67,526 in Sweden.[27,32,33] The annual indirect morbidity costs per population, calculated from US Environmental Protection Agency and Bureau of Labor Statistics, indicated that BCC cost $1235 compared with the higher SCC cost ($4761; both 2009 $US rates).[27] A systematic literature review conducted by the US Centers for Disease Control and Prevention (CDC) found that the number of years of potential life lost (YPLL) per death attributable to NMSC was approximately 10.[27]

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; CDC, Centers for Disease Control and Prevention; CS, company submission; HRQoL, health-related quality of life; laBCC, locally advanced BCC; mBCC, metastatic BCC; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; UV, ultraviolet; YPLL, years of potential life lost.

2.1 Epidemiology

The company provided a comprehensive overview of the challenges in providing relevant estimates of the incidence and prevalence of laBCC and mBCC along with estimates of the general incidence of BCC in the UK (Box 8). The ERG agrees with the company's findings of limited UK specific data and the ERG's clinical experts were unable to provide any additional UK specific data for aBCC, laBCC or mBCC incidence in the UK.

Box 8. Incidence of BCC, laBCC and mBCC (Adapted from CS, pages 48-49, Section 3.4.1 and 3.4.2)

Background incidence and prevalence of BCC and limitations for aBCC epidemiology data

NMSCs, which include BCCs and squamous cell carcinomas (SCCs), are the most common forms of cancer in humans, surpassing in incidence all other forms of cancer combined.[9] Approximately 2 to 3 million cases of NMSC are estimated to occur every year worldwide.[34] Although BCCs and SCCs are usually reported collectively as NMSCs, the majority of NMSCs are BCCs with BCCs accounting for 80% to 90% of NMSCs.[35] It is important to note that the true incidence and prevalence of NMSCs, and thus BCCs, are difficult to estimate because large national cancer registries do not track NMSC; additionally, NMSCs are usually treated in a primary care setting.[4, 35, 36] Despite these limitations, several published reports have estimated the incidence of NMSC, or more specifically for BCC. Epidemiology data for BCC and aBCC are limited[37]: very little epidemiologic data are currently available that differentiate epidemiology trends more specifically within BCC for the laBCC and mBCC populations.

Incidence of locally advanced and metastatic BCC

As in all NMSCs, the true incidence of laBCC or mBCCs is difficult to estimate because these cases are not captured in national cancer registries.[3,36] Case experience data indicate that locally advanced and metastatic presentations of BCC are rare. The estimation of aBCC incidence also faces additional challenges, due to the lack of a global, standardised staging system for aBCC, and the diverse group of practitioners diagnosing and treating aBCC.

Despite these limitations, rare cases in which invasion of BCC into subcutaneous structures and beyond leading to unresectable, locally advanced disease and metastatic disease have been reported.[14,17,38,39,19] Advanced BCC is thought to occur in up to 10% of all BCCs[10], with laBCC*i* occurring in up to 1%[12, 13] and metastatic BCCs accounting for 0.0028% to 0.55% of all BCCs.[14,40] Fewer than 300 cases of mBCC have been reported in the literature[18]. For the model, the incidence of laBCC that is not suitable for surgery or radiotherapy and of mBCC in the UK have been estimated from the UK primary care database[41] with the proportions of laBCC and mBCC reported in the US retrospective analysis of an insurance database applied.[12]

United Kingdom

As with other countries around the world, the incidence of BCC is increasing in the UK (CS page 49, Figure 4).[42,43] Over a 10 year period, the incidence rate of BCC increased 66% between 1988 and 1998.[43] The crude incidence of BCC in the UK has been estimated to be 153.9 per 100,000 person years (95% CI: 151.1 to 156.8) with a slightly higher rate in men than women.[41] The world age-standardised rate of BCC is 60 per 100,000 per year, and the European age-standardised rate is 89 per 100,000.[41] Overall, BCC incidence has been increasing by 3% per year between 1996 and 2003 and approximately 53,000 new cases of BCC are estimated to occur every year in the UK.[41]

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; laBCC*i*, laBCC inappropriate for surgery or radiotherapy; mBCC, metastatic BCC; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma.

2.2 Critique of company's overview of current service provision

The company provides an overview of the current UK and European guidelines that are relevant to BCC. These include:

- NICE guideline CSG8 on improving outcomes for people with skin tumours including melanoma that was published in 2006 and partially updated in 2010;[37]
- The British Association of Dermatologists guidelines for the management of BCC published in 2008;[44] and
- The European guidelines for BCC management developed by the Guideline Subcommittee of the European Dermatology Forum in 2014.[45]

The ERG notes that neither the NICE guideline CSG8 nor the British Association of Dermatologists BCC guideline provide any guidance specific to the treatment of laBCC or mBCC. The European guidelines for BCC management are the only one of these three guidelines to provide any guidance related to vismodegib. The guideline reports generally on (transmembrane receptor) 'Smoothened' antagonists (anti-SMO) and vismodegib is classified as one. It reports that anti-SMO agents are effective against locally advanced or metastatic BCC and that the strength of recommendation is Grade A with the quality of evidence graded as II-i. This strength and quality of recommendation means that there is good evidence to support the use of anti-SMO agents, and that the recommendation is based on

evidence obtained from well-designed non-randomised controlled trials.[44] The ERG does, however, note that the data are limited and that there is an absence of data from high quality randomised-controlled trials.

The company provides a detailed general overview of the treatment pathway for BCC (Box 9) and further details of the treatments for laBCC and mBCC (Box 10).

Box 9. Current treatment options for BCC (Adapted from CS, pages 42-44, Section 3.1.5)

Treatment options for patients with BCC are determined by consideration of a number of factors, including: tumour size, site, and histological subtype; previous treatment history and patient comorbidities; patient preference; and access to treatment. It is also important to consider whether the intention of treatment is curative or palliative.[28] Current treatments for BCC (patients whose disease is not considered advanced) include surgical excision and/or radiotherapy, and less commonly: topical (e.g. 5-fluorouracil or imiquimod) chemotherapy or electrochemotherapy, curettage, cryotherapy, and photodynamic therapy.[37]

Surgery: The majority (over 60%) of BCCs are nodular[46], and are generally treated by surgical excision, with variable margins depending on tumour characteristics and anatomy of the site A BCC with a diameter <2 cm would require a minimum margin of 4 mm to totally remove the tumour in more than 95% of cases; however, if this were a high-risk primary BCC of the same size, a margin of at least 13 mm would be required to obtain the eradication of the tumour in 95% of cases.[45] Surgery may also be used for superficial BCCs. More invasive BCC subtypes, such as infiltrative or morphoeic BCC, or large lesions and those in cosmetically sensitive sites in which tissue sparing is critical, can be treated with Mohs' micrographic surgery, which results in reduced recurrence rates compared with other treatment options.[47]

Radiotherapy: Radiotherapy provides an alternative treatment for some patients in whom surgery is not suitable or is not desired by the patient, or in the postoperative adjuvant setting if resection margins are positive and no further surgery is possible.[44, 48] Surgery is difficult after radiotherapy. Radiotherapy also has long-term carcinogenic potential with secondary carcinoma development associated with treatment.[45] The cosmetic result of radiotherapy can worsen over time, and this treatment method is therefore used predominantly in patients over 55 years of age.[44, 48]

Topical chemotherapy: agents such as 5-fluorouracil or imiquimod may be used for primary, small, superficial BCCs, and normally yield good clearance rates.[44, 45, 48] The use of imiquimod for specific body sites (the face, and particularly the eyelids) in combination with other non-surgical modalities (e.g. photodynamic therapy), cryosurgery or Moh's surgery, and for specific clinical groups of patients such as those who are immunosuppressed, has been proposed.[45]

Electrochemotherapy is a local treatment that aims to enhance the effects of chemotherapy. This is typically used to manage inaccessible or otherwise difficult-to-treat primary basal cell carcinomas.[49]

Curettage: this works best on nodular or superficial BCC and involves the tumour being scraped with a curette; the wound is then treated with electrocautery to control bleeding and destroy residual

tumour. Curettage and cautery are considered good treatment for low-risk BCC, with overall five-year recurrence rates for primary tumours varying from 3.3% in low-risk sites to 18.8% in high-risk sites: a recurrence rate of 60% is reported for recurrent BCCs.[45] Due to the disproportionate amount of residual tumour on head and neck wounds and higher recurrence rates, curettage and electrocautery is not considered first-line treatment for facial BCCs.[50]

Cryotherapy: this involves the destruction of tissue using liquid nitrogen and tends to be useful in the treatment of low-risk BCCs. The main disadvantage of this technique is that there is no histological control to establish tumour eradication.[45] Cryotherapy is not considered first-line treatment for facial BCCs as there is a high risk of recurrence, and potentially poor cosmetic outcome.[50]

Photodynamic therapy (PDT): NICE guidance on photodynamic therapy exists for treatment of non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). Current evidence suggests that there are no major safety concerns associated with PDT with such lesions.[51] Clearance rates of up to 87% have been achieved for superficial BCCs treated with PDT, which is lower than those achieved for surgery.[50] Primary superficial and thin nodular BCCs are the most appropriate to receive topical PDT.[45]

Patients with locally advanced disease have lesions that may not be appropriate for radiotherapy or surgery. Surgery may be considered inappropriate because it is unlikely to be curative, or disease has recurred after surgery, or due to significant deformity as a result of surgery (e.g., invasion into the skull, limb amputation, or eye removal) based on lesion location, size, and/or tumour histology. Additionally, the use of radiotherapy is not advised in tumours located near eyes or on eyelids or potentially the extremities (e.g. shins), individuals who are nearing their maximum safe lifetime radiation dose, and younger patients, who are likely to suffer late adverse effects and cosmetic results that are inferior to those of surgery.[4, 44] For patients with disease recurrence after prior radiotherapy, subsequent radiation is contraindicated.[44, 52]

Prior to vismodegib, there have been no approved treatments for 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.

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NICE, National Institute for Health and Care Excellence; PDT, photodynamic therapy.

As part of the overview of the current treatment pathway for aBCC, the company presented details and results of the RONNIE study (Box 10). RONNIE was funded by Roche and aimed to provide information on the treatment pathway for aBCC, including what best supportive care comprised, prior to the uptake of hedgehog pathway inhibitors (HPIs) such as vismodegib.

Box 10. Treatment pathway for aBCC and results of RONNIE (Adapted from CS, pages 46-47, Section 3.3)

Prior to the regulatory approval of Erivedge [vismodegib], patients with aBCC had no approved or standard therapeutic options, when surgery or radiotherapy (with curative intent for patients with laBCC) was inappropriate.

If vismodegib were not available, patients with incurable aBCC; would be managed with best supportive care, either:

- by dermatologists who would monitor patients several times per year; more regular patient care would be carried out in the community by GPs and district nurses, potentially requiring intensive and continual wound management, or,
- with palliative (i.e. non-curative) radiotherapy, when required, for the management of bleeding and/or exudation of the wound. The dose of radiation may be given in a single fraction, or fractionated if the wound is particularly large, or,
- by referral for consideration for major surgery to resect locally advanced disease (with involvement of multiple surgical specialities e.g. ear, nose and throat (ENT) specialist / oculoplastic / maxillofacial / neurosurgical teams, with the likely requirement for complex plastic surgical reconstruction). It should be noted that this surgery would not be expected to be curative and is usually associated with significant morbidity (e.g. loss of an eye) and a significant risk of mortality.

The approach to treatment of patients with aBCC: the RONNIE study

An analysis of treatment patterns and outcomes for BCC patients (RONNIE study, NCT02100111[53, 54]) revealed that the standard approach to treatment of patients with aBCC was a succession of treatments given over a short time interval, and that the number, type, and combination of treatments varied enormously. A single treatment with a durable outcome was an exception.[54] The RONNIE study was a retrospective, multicentre, multinational chart review of real-world treatment practices to describe the usual practice for patients with aBCC before the availability of Hedgehog Pathway Inhibitors (HPI). Patients with aBCC (n=134) (eligible laBCC n=117, and eligible mBCC n=4) were identified from the files of 38 centres from France, Italy, Germany and the UK. Despite the majority of patients (n=103 of the 117 laBCC cases) being considered inoperable (46 of 117 patients with laBCC, 39.3%), or surgery being contraindicated (26/117 (22.2%) because recurrent BCC unlikely to be curatively resected, and 31/117 (26.5%) because of anticipated substantial morbidity or deformity), almost half of patients with laBCC received surgery at some point (12/106 [11.5%] of patients for whom treatment was recorded underwent Moh's surgery, and 38/106 [35.8%] received excisional surgery).[54]

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; CS, company submission; ENT, ear, nose and throat; GP, general practitioner; laBCC, locally advanced BCC; mBCC, metastatic BCC.

The company's proposed positioning of vismodegib in the treatment pathway for aBCC is as a treatment option for patients who would otherwise receive best supportive care (BSC) as they are unsuitable or unresponsive to curative therapies. BSC is defined by the company as on-going follow-up by dermatologists as well as possible palliative radiotherapy and/or palliative surgery to help with symptom control.

Vismodegib is currently available via the Cancer Drugs Fund (CDF) and like other systemic anticancer therapies, it must be prescribed by an oncologist. The company reported that the decision to prescribe

vismodegib at the moment is generally a joint decision made by a multi-disciplinary team (MDT) comprising of dermatologists, oncologists and surgeons.

In terms of resource use, the company reported that vismodegib would not require any change to the existing infrastructure for BCC management as it is a capsule taken orally as an outpatient. It is anticipated that vismodegib would be initiated by a consultant oncologist in the secondary care outpatient setting with monthly follow-up for response and adverse events. Women of childbearing potential are required to have medically supervised pregnancy tests conducted every 28-days and prescriptions limited to 28-days. No specific concomitant medications are routinely required alongside vismodegib and the management of most adverse effects is a break from treatment. The company reported that all patients on vismodegib are likely to have routine monthly blood tests although this is not a specific requirement in the vismodegib marketing authorisation. The ERG's clinical experts agree with the company's proposed resource use for vismodegib although they consider that follow-up may actually be two weekly for the first six weeks of treatment with a blood test for liver function at two weeks. Clinical experts reported that routinely patients would then be seen monthly while on the drug, with monthly blood tests (full blood count, urea and electrolytes, and liver function tests).

The company provided a breakdown of the drug acquisition costs associated with vismodegib use and estimates of treatment duration based on the STEVIE study (Table 1).

Table 1. Costs associated with vismodegib (Adapted from CS, pages 33-34, Table 6)

	Cost	**Source**
Pharmaceutical formulation	150 mg hard capsules	Vismodegib SmPC[55]
Acquisition cost (excluding VAT)	List price = £6,285.00 (28 x 150mg capsules)	Vismodegib BNF[56]
Method of administration	Oral	Vismodegib SmPC[55]
Doses	150 mg	Vismodegib SmPC[55]
Dosing frequency	The recommended dosing of vismodegib is 150 mg once daily	Vismodegib SmPC[55]
Average length of a course of treatment	The median treatment duration in ERIVANCE was 12.68 months (range 1.1 to 47.8) in the laBCC cohort, and13.27 months (range 0.7 to 39.1) in the mBCC cohort. The median overall treatment duration across all patients in the trial was 12.93 months (range 0.7 to 47.8). The median treatment duration in STEVIE was 256 days (range 1 to 1341) in the laBCC cohort and 319.0 days (range 2 to 1147) in the mBCC cohort. The median overall treatment duration across all patients in the trial was 263 days [8.6 months] (range 1 to 1341 days). According to the vismodegib SmPC, treatment with vismodegib should be continued until disease progression or until unacceptable toxicity.	ERIVANCE Study[57], STEVIE study [58, 59] Vismodegib SmPC[55]

Average cost of a course of treatment	**List price** Median treatment duration in days = **263** Daily treatment cost = **£224.46** Avg. cost of a course of treatment = **263 * £224.46 = £59,032.98** **With PAS** Median treatment duration in days = **263** Daily treatment cost = [redacted] Avg. cost of a course of treatment = **263** [redacted]	STEVIE Study,[57] Vismodegib BNF[56]
Anticipated average interval between courses of treatments	It is anticipated that patients will only have one course of treatment, continued until disease progression or until unacceptable toxicity (treatment course may include one or more treatment breaks to manage adverse events; median duration of treatment break in the STEVIE study was 22 days)	Vismodegib SmPC [55, 60]
Anticipated number of repeat courses of treatments	The licence does not make any stipulations regarding repeat courses of treatment; however, there is very limited data available on repeat treatment (i.e. additional courses of treatment) following discontinuation after initial response: Patients who discontinued vismodegib in the ERIVANCE study before disease progression were re-treated with vismodegib when their treatment progressed Cohort 2 of the RegiSONIC study recruited 9 patients who have had prior vismodegib	Vismodegib SmPC[55] [61] [62]
Dose adjustments	Dose adjustments were not permitted in the ERIVANCE clinical study protocol and are not recommended in the Erivedge SmPC.	ERIVANCE Study,[57] Vismodegib SmPC[55]
Anticipated care setting	Vismodegib should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication. Treatment will therefore be initiated in the secondary care setting only and self-administered by patients at home.	Vismodegib SmPC[55]

Abbreviations: BCC, basal cell carcinoma; BNF, British National Formulary; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; PAS, patient access scheme; SmPC, summary of product characteristics; VAT, value added tax.

The company has attempted to provide an estimate of the number of patients in England and Wales eligible for vismodegib treatment although as discussed earlier in Section 2.1.1, the number of patients in England and Wales with laBCC and mBCC is unknown and so the company has made several assumptions (Box 11).

Box 11. Assumptions and data used in the company's estimate of the number of patients eligible for vismodegib in England and Wales (Adapted from CS, page 49, Section 3.4.2)

An estimation of the numbers of laBCC and mBCC in England and Wales has been made, based on the following:

- The population of England and Wales was obtained from ONS, 2014-based National Population Projections (published 29-Oct-2015);
- Trends in incidence of skin basal cell carcinoma obtained from a UK primary care database study[41] and extrapolated using linear regression;
- Incidence and prevalence of BCC and laBCC was obtained from a retrospective cohort study of a large commercially insured population in the United States[12].

Applying the proportions obtained in the retrospective US insurance claims publication enabled the estimation of the numbers of laBCC and mBCC in England and Wales.

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; ONS, Office of National Statistics.

The company's resulting estimate for the number of patients potentially eligible for vismodegib in England and Wales is presented in Table 2 and assumes everyone with mBCC and those with laBCC inappropriate for curative surgery or radiotherapy would be eligible for vismodegib. The company's estimate is thus that 426 patients would be eligible for vismodegib in 2018. However, the ERG notes that the company also report that vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013 and up until the end of August 2016 only 352 requests had been made for CDF funding for vismodegib. The company is thus suggesting that more patients would receive vismodegib in a one-year period compared to in a 3-year period while it has been available via the CDF. The ERG and its clinical experts are unclear why more patients would be expected to be treated with vismodegib if it were approved by NICE as the indication would remain the same.

Table 2. Company's estimate of the number of patients with laBCC and mBCC in England and Wales (Adapted from CS, page 52, Table 10)

	2014	2015	2016	2017	2018	2019	2020	2021
Female laBCC	441	456	471	486	502	517	532	548
Male laBCC	442	456	471	485	499	513	527	542
Female mBCC	4	4	4	4	4	4	4	4
Male mBCC	19	20	20	21	22	22	23	23
laBCC incidence	883	912	942	971	1,000	1,030	1,060	1,090
laBCC inappropriate for surgery or radiotherapy (assumption: 40% of laBCC are inappropriate)	353	365	377	388	400	412	424	436
mBCC incidence	23	23	24	25	26	26	27	28

Abbreviations BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.

The ERG agrees with the company's findings of no data on the current incidence of laBCC or mBCC in England and Wales and agrees with the approach taken by the company to source suitable data from other countries. The ERG notes that both the incidence of laBCC and mBCC have been based on US incidence data and the ERG are unsure of exactly how much these would differ to those in England and Wales. The ERG's clinical experts report that the incidence of BCC may be higher in the US than in

the UK due to the difference in sun exposure. However, the clinical experts also reported that there are difficulties in using the reported incidence of BCC in the US to calculate the UK incidence. This is because under reporting in both countries is prevalent, and sun exposure and access to healthcare (which affects disease stage at diagnosis) is different. The ERG thus considers the company's estimates of the number of patients potentially eligible for vismodegib is associated with a large amount of uncertainty although the ERG considers it is likely to be an over-estimate rather than under-estimate.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company submission (CS) provides a summary of the decision problem and tabulates a comparison with the National Institute for Health and Care Excellence (NICE) final scope[1] together with the rationale for any deviation from the NICE final scope (Table 3Table 3. Summary of decision problem as outlined in the company's submission (Adapted from CS, pages 20-21, Table 1).).

Table 3. Summary of decision problem as outlined in the company's submission (Adapted from CS, pages 20-21, Table 1).

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the NICE final scope**
Population	People with: • symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate	People with: • symptomatic metastatic basal cell carcinoma or • locally advanced basal cell carcinoma for whom surgery or radiotherapy is not appropriate	No difference
Intervention	Vismodegib	Vismodegib	No difference
Comparator(s)	Best supportive care (BSC)	Best supportive care (BSC)	No difference
Outcomes	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life	No difference
Economic analysis	• The reference case stipulates that the cost effectiveness of treatment should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	• The reference case stipulates that the cost effectiveness of treatment should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	No difference
Subgroups to be considered	If the evidence allows the following subgroup will be considered • Patients with Gorlin syndrome	No subgroups were addressed	Gorlin patients were not included as a separate subgroup. Low patient numbers in the pivotal trials meant that clinical data was

	For this subgroup, an additional outcome measure of prevention of new lesions should be included		insufficient to support a robust analysis
Special considerations including issues related to equity or equality	None	None	No difference
Abbreviations: BSC, best supportive care; CS, company submission; NICE, National Institute for Health and Care Excellence.			

3.1 Population

Clinical effectiveness data in the submission are derived mainly from the two key trials designed to evaluate the efficacy and safety of vismodegib: ERIVANCE and STEVIE. Patients eligible for inclusion in these trials were adults with an ECOG status of ≤ 2 who had either mBCC or laBCC meeting the trial entry criteria.

The criteria for mBCC in ERIVANCE were that there was histological confirmation of distant BCC metastasis (e.g. lung, liver, lymph nodes, and bone) and metastatic disease that was RECIST measurable using CT or MRI. Patients with metastatic disease confined to bone were not eligible because of the lack of RECIST measurability of bone disease. LaBCC patients in ERIVANCE were required to have at least one histologically confirmed lesion ≥ 10 mm in the longest diameter that was considered to be inoperable (or they had a medical contraindication to surgery) and had progressed since prior treatment with radiotherapy unless radiotherapy was contraindicated or inappropriate (e.g. limitations because of location of tumour). Patients with Gorlin syndrome who met the criteria for laBCC or mBCC were eligible for inclusion although the ERG notes that patients with superficial multifocal BCC considered unresectable because of breadth of involvement were excluded according to the inclusion/exclusion criteria for ERIVANCE presented in the CS. The ERG's clinical experts report that this exclusion criterion may have restricted the entry to ERIVANCE of some Gorlin syndrome patients who may be eligible for vismodegib in clinical practice.

The inclusion criteria for mBCC in STEVIE was only that there was histological confirmation of distant BCC metastases. The inclusion criteria for patients with laBCC in STEVIE were the same as for ERIVANCE although patients with superficial multifocal BCC considered unresectable because of breadth of involvement were not excluded from STEVIE. The ERG notes that there was a similar proportion of patients with Gorlin syndrome in ERIVANCE compared to STEVIE (21%, and 18%, respectively), although the median age of patients in ERIVANCE was substantially lower than in STEVIE (62 years and 72 years, respectively). The ERG's clinical experts report that the population likely to be treated with vismodegib in the UK are likely to be closer to 72 years in age and that the population in STEVIE is more applicable to clinical practice. The clinical experts also reported that a younger population in a clinical trial such as ERIVANCE is not unusual due to restrictions in trial inclusion criteria and that patients with Gorlin syndrome are likely to have a lower median age than

non-Gorlin syndrome aBCC patients. The ERG considers STEVIE is a closer match to the UK population who are likely to receive vismodegib.

The final scope issued by NICE[1] specifies the population of interest to be either people with symptomatic mBCC or people with laBCC for whom surgery or radiotherapy is not appropriate. In summary, the ERG considers the data presented within the submission to be representative of UK patients with laBCC and mBCC, and to be relevant to the decision problem that is the focus of this STA.

3.2 Intervention

The intervention specified in the final scope issued by NICE[1], and that was the focus of the CS for this STA, was vismodegib. Vismodegib, brand name Erivedge®, is an antineoplastic drug that works as a small-molecule inhibitor of the Hedgehog signalling pathway thus blocking specific genes involved in cell growth and survival. The company reported that it is a first-in-class drug, and the only one from its class currently available in England and Wales.

Box 12. Biomarkers and the Hedgehog pathway (Adapted from CS, page 28, Section 2.1)

The Hedgehog pathway, which is largely redundant in adults, plays central roles in animal and stem cell function.[63] Key components of the Hedgehog pathway include the transmembrane receptors Patched (PTCH1) and Smoothened (SMO), the Hedgehog ligand and the intracellular proteins responsible for stimulating the Glioma-Associated Oncogene (Gli) family of transcription factors. PTCH1 is the receptor to which the Hedgehog ligand binds; this binding relieves the inhibition induced by unbound PTCH1, specifically through SMO in a non-stoichimetric manner.[64] Hedgehog pathway signalling through the SMO leads to the activation and nuclear localisation of Gli transcription factors and induction of Hedgehog target genes. Many of these genes are involved in proliferation, survival, and differentiation of cells. Approximately 90% of sporadic BCCs have identifiable mutations in at least one allele of *PTCH1* (often loss of the chromosome 9q harbouring *PTCH1*), and an additional 10% have activating mutations in the downstream SMO protein, which "presumably" render SMO resistant to inhibition of PTCH1.[64] Vismodegib binds to and inhibits the SMO protein thereby blocking Hedgehog signal transduction. [55]
There are no biomarker testing requirements for patients diagnosed with BCC, as almost all have a mutation present in the Hedgehog pathway.[64]
Abbreviations: BCC, basal cell carcinoma; CS, company submission; Gli, Glioma-associated oncogene; PTCH, patched; SMO, smoothened.

Vismodegib received conditional marketing authorisation from the European Medicines Agency (EMA) on the 12th July 2013 subject to additional follow-up data from STEVIE and further analyses of the data. The additional data requested by the EMA were:

- a safety update comprising of the pooled safety population using the final data from ERIVANCE and an interim analysis of STEVIE of 500 patients with a potential one year follow up; and

- data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of STEVIE.

The Committee for Medicinal Products for Human Use (CHMP) issued a positive recommendation on 15th September 2016 following the review of the additional data and vismodegib was granted full approval by the EMA on 14th November 2016. Vismodegib is approved in the EU for use in the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma (mBCC); or

- locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy.

The recommended dose in the summary of product characteristics (SPC) is one 150 mg capsule once daily. Vismodegib treatment should only be prescribed by or under the supervision of a specialist physician experienced in the management of aBCC. There are no specific monitoring requirements for vismodegib other than regular pregnancy testing for women of childbearing potential and routine monitoring for adverse events. Vismodegib is contraindicated to people who demonstrate hypersensitivity to it or to any of its excipients. In addition, vismodegib is contraindicated in women who are pregnant or breast-feeding, women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme, and patients receiving co-administration of St John's wort (Hypericum perforatum). The Pregnancy Prevention Programme was implemented as part of a requirement of the vismodegib marketing authorisation due to the teratogenicity of vismodegib. It requires women of childbearing potential to undergo monthly medically-supervised pregnancy tests within a maximum of seven days of prescription of vismodegib with prescriptions of vismodegib limited to 28 days' supply in these patients.

Vismodegib has been available via the Cancer Drugs Fund (CDF) in England since August 2013. The company reported in the CS that since the UK launch, up until the end of August 2016 there had been 352 requests for funding of vismodegib via the National Cancer Drugs Fund.[65]

The company reports in the CS that vismodegib has marketing authorisation in approximately 40 countries outside the EU and the United States (US), and that authorisation in the US was granted on 30th January 2012. The All Wales Medicines Strategy Group (AWMSG) are due to re-appraise vismodegib on 26th April 2017 as Roche were unable to provide a complete submission in time for the previously scheduled appraisal in August 2016.

The ERG notes that there is a second Hedgehog pathway inhibitor approved for use in the EU, sonidegib (trade name Odomzo®, Novartis Europharm Ltd). However, sonidegib is not commercially available in the UK at present despite sonidegib having been granted EU marketing authorisation on 14th August 2015 for the treatment of adults with laBCC.

The ERG notes that in ERIVANCE and STEVIE (the two key trials informing the clinical effectiveness of vismodegib in the CS), the dose and use of vismodegib are generally in keeping with that of the EU marketing authorisation and the anticipated use of vismodegib. The ERG's clinical experts reported that the restrictions on the use of vismodegib in the clinical trials and the current CDF prevented continuation of treatment following a treatment break of more than 8 weeks whereas treatment could potentially have been continued for longer following resolution of adverse events had it been allowed.

In summary, the ERG considers the intervention in the key vismodegib trials presented in the CS to be consistent with that specified in the final scope issued by NICE[1], and in keeping with the EU marketing authorisation for vismodegib.

3.3 Comparators

The ERG notes that the only comparator specified in the final scope issued by NICE[1] was best supportive care (BSC). However, all trial level data provided in the CS are from single arm studies of vismodegib and thus is observational in nature, not having a randomised component. In addition, the ERG notes that the trials used to gain the EU marketing authorisation were two single arm studies of vismodegib, STEVIE and ERIVANCE. The company reported in the CS that, "A randomised study was considered not feasible because no standard treatment options were identified for either laBCC or mBCC patients based on a literature review of the previous 30 years." Further justification from the company on the rationale behind not using a comparative study design to assess the safety and efficacy of vismodegib was also provided (Box 13).

Box 13. Company rationale for single arm design of vismodegib studies (CS, page 18, Section 1.1)

> Based on the significant anti-tumour activity observed in patients with aBCC in the Phase I vismodegib study (SHH3925g; NCT00607724)[39] and considering the clinically articulated unmet need in aBCC, Roche received feedback from investigators and experts in the field that it would not be feasible to accrue patients (given the limited population) to a randomised study. In addition, responses from a placebo or best supportive care arm were both (a) not expected and (b) could be addressed statistically with a significantly high response rate in the vismodegib arm.
>
> There was concern that, with a randomised, cross-over design, investigators may be biased toward prematurely assessing disease progression and patients biased towards withdrawing consent: enabling them to crossover to vismodegib or enrolment into another clinical study when no immediate clinical benefit was observed. Such bias would have impacted study integrity and interpretation of

the true treatment effect of vismodegib. Therefore, the single-arm study with a response rate primary endpoint was determined to be the most appropriate trial design for vismodegib in aBCC.
Abbreviations: aBCC, advanced basal cell carcinoma; BCC, basal cell carcinoma; CS, company submission.

The ERG is not qualified to comment on the feasibility of an RCT of vismodegib in the population of interest in this decision problem although the ERG does consider a comparative study design to be preferable. The ERG considers a potential comparator of physician's choice could have been used in an RCT to represent BSC. In addition, the ERG considers the company's rationale that it would be difficult to recruit sufficient patients due to the limited aBCC population to be unjustified given the size of the STEVIE study. The company have, however, managed to provide a comparison of vismodegib with BSC in the CS through the use of a landmark analysis approach where the relative treatment effect of responders compared to non-responders is used as a surrogate for the relative difference between vismodegib and BSC in the economic model (Section 5). The company also reported that they had an advisory board to help them identify what BSC would be in aBCC patients given the lack of a standardised definition for BSC. The results of the advisory board and the resulting definition of BSC was an intensive wound management regimen comprising of regular appointments with a tissue viability nurse, a dermatologist, a GP, and, in certain patients, a course of palliative radiotherapy. The ERG's clinical experts are in agreement with the company's definition of BSC and that there is no standard treatment pathway for aBCC patients at present. The non-responder patients in the landmark analysis had still received vismodegib though and so the landmark analysis results are thus not a true representation of vismodegib versus BSC. However, the landmark analysis provides the only data in the CS informing the comparison of vismodegib with BSC requested in the final scope issued by NICE[1].

The details and limitations of the landmark analysis will be discussed further in Section 4.

3.4 Outcomes

The outcomes requested in the NICE final scope[1] were:

- progression-free survival (PFS);
- overall survival (OS);
- response rate;
- adverse effects of treatment; and
- health-related quality of life (HRQoL).

The company provided evidence from ERIVANCE and STEVIE for all of these outcomes in the CS apart from median OS in people with laBCC. OS data were not available from STEVIE as the trial data are still immature and so median OS was not estimable and median OS was not estimable for the laBCC population in ERIVANCE. The only median OS data reported in the CS are thus data for mBCC patients in ERIVANCE. Data on the one-year and two-year survival rates in ERIVANCE were also reported

and thus provide limited information on the impact of vismodegib on OS in laBCC. It is noted that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS although they provide an accurate assessment of ORR.[66] The ERG thus recommends that the PFS and OS estimates from ERIVANCE and STEVIE are interpreted with caution.

Response rate data were reported as objective response rate (ORR) in ERIVANCE and STEVIE and comprised of complete response and partial response. In addition, response by category (e.g. number of patients with complete response, partial response, and stable disease), time to response and duration of response were presented. HRQoL data in the CS for vismodegib were limited, however, the company supplied additional HRQoL data from ERIVANCE following the ERG request during the clarification stage. The HRQoL data from ERIVANCE were based on the SF-36 Health Survey (Version 2) which consists of eight subscales: Physical Functioning, Role−Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role−Emotional, and Mental Health. The HRQoL data from STEVIE were limited to data gathered from the Skindex-16 questionnaire which assessed the effects of skin disease on patients' HRQoL and the M.D. Anderson Symptom Inventory (MDASI) instrument which assessed the impact of treatment on symptoms in patients with mBCC who were enrolled after a study protocol amendment. However, based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to the decision problem and address those specified in the final scope issued by NICE[1] with the exception of OS in the laBCC population.

3.5 Timeframe

The median length of follow-up in ERIVANCE was 39.1 months. Median length of follow-up for STEVIE was not reported in the CS although the ERG notes that the study is still ongoing. At the time of the data cut-off for the analyses presented in the CS (16th March 2015) 30.9% of patients remained in the study (147 [12.1%] on treatment and 228 [18.8%] in follow-up). The ERG also note from the CSR that only 21.9% of patients had completed 12 months of follow-up at the 16th March 2015 analysis. In addition, mature and final OS data are yet to be collected from STEVIE.

In summary, the ERG considers the duration of follow-up in both ERIVANCE and STEVIE to be suitable for assessing the short-term safety and efficacy outcomes of treatment with vismodegib. However, the ERG considers further trial data are required to assess the long term effects of vismodegib both in terms of efficacy and safety.

3.6 Other relevant factors

The ERG notes that the final scope issued by NICE[1] specified that evidence permitting, consideration should be given to the subgroup of patients with Gorlin syndrome and that for this subgroup, an additional outcome measure of prevention of new lesions should be included. The company provided

the results for the subgroup of patients with Gorlin syndrome from STEVIE for both the mBCC and laBCC populations although it appears to have been a *post hoc* subgroup analysis as it was not mentioned in the original study protocol. The company did not, however, include an analysis of Gorlin patients as a separate subgroup in the CS for the comparison of vismodegib versus BSC and so the ERG requested analyses during the clarification stage. The company reported in the CS that the low patient numbers in the pivotal trials meant that clinical data was insufficient to support a robust analysis for this subgroup. The ERG agrees that there are small numbers of patients with Gorlin syndrome in STEVIE and ERIVANCE but still considers the subgroup to be an important subgroup of interest based on feedback from clinical experts. In addition, the ERG notes that the Gorlin subgroup was a bigger subgroup in STEVIE than the mBCC subgroup and so even if it had been analysed only for the combined aBCC population, the ERG considers it reasonable evaluation of the important subgroup. In ERIVANCE, there were only Gorlin patients in the laBCC cohort, but even so they represented nearly a third of the laBCC patients (n=20 [32%]). The data from the Gorlin subgroups are discussed in detail in Section 4.

There are no known issues relating to equality in this technology appraisal according to the CS and the ERG's clinical experts.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company carried out a systematic literature review to identify studies investigating clinical outcomes associated with the use of vismodegib for the treatment of locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC).

Electronic databases (MEDLINE, Embase, Cochrane library [CENTRAL, CDSR and DARE]) were searched from inception to 17th November 2016. The search was not limited by language. Study design was inclusive of randomised control trials (RCTs), systematic reviews (SRs), observational studies and single arm studies. Animal studies, comments, letters and case studies were determined to be unsuitable study designs and excluded from the searches.

The search strategy outlined by the company used key search terms for the disease area including 'basal cell carcinoma' combined with additional search terms for disease severity 'metastatic' or 'advanced' which related to the population of interest specified in the NICE final scope[1]. The ERG notes that the inclusion of search terms relating to disease severity could have resulted in missed evidence where studies investigating BCC may not have indexed the stage of the disease. Search terms relating to the drug intervention, vismodegib, were combined with the search terms for the population. The ERG notes that no search terms were used to identify the comparator treatment outlined in the decision problem, best supportive care (BSC). The ERG considers the company's search strategy to be appropriate for identifying studies of vismodegib but does not consider it suitable for identifying studies for the comparator, BSC. The ERG finds it particularly unusual that the company didn't search for studies of BSC given that their key studies for vismodegib were single arm studies and so they knew that data for BSC would be required to enable a comparison to address the decision problem in the final scope issued by NICE[1].

The company also assessed conference abstracts, identifying key oncology and dermatology conferences and manually searching the conference proceedings for the last two years (2015 and 2016) to identify any relevant studies. The ERG might agree with the conferences identified by the company if they were justified as the most relevant conferences to include. However, the company provided no rationale as to how these particular conferences were identified and chosen over others. The ERG's clinical experts do however support the company's choice of conferences. The conferences searched by the company are listed below:

- World Congress on Cancers of the Skin (WCCS);

- American Academy of Dermatology (AAD);
- European Society for Medical Oncology (ESMO);
- American Society for Clinical Oncology (ASCO);
- Society for Melanoma Research;
- European Academy of Dermato-oncology;
- American College of Mohs Surgeons;
- British Association of Dermatologists;
- British Association of Plastic, Reconstructive and Aesthetic Surgeons.

The company outline that despite identifying conferences that were relevant and should be searched, not all titles were included in the manual search process. The company justify the exclusion of these conferences due to the proceedings not being freely available. The conferences not searched include the following: European Academy of Dermatology and Venereology; British Oculoplastic Surgery Society; Winter Clinical Dermatology Conference; Fall Clinical Dermatology Conference; World Cutaneous Malignancies Conference. The ERG notes that identifying these conference as relevant for the disease area and then subsequently not searching them for relevant evidence is a limitation to the company's search. The ERG is unable to comment on the likely impact this selective searching has on the results of the literature review.

The company carried out additional searches which included searching the ClinicalTrials.gov website using the advanced search function to employ relevant search terms relating to the disease and intervention. The reference lists of systematic reviews and meta-analyses included as relevant from title and abstract stages were also hand searched to identify any further relevant studies.

The ERG considers the search strategy designed by the company for the review of clinical effectiveness to be comprehensive and appropriate. The ERG agrees that the lack of search terms for comparators in the search strategy is appropriate given that the comparator of interest in the final scope issued by NICE[1] is BSC, which can consist of a multitude of different treatments. The ERG considers the methods used to search for relevant conference proceedings to lack transparency by the company and the selective searching procedures of these conferences to be problematic.

4.1.2 Inclusion criteria

The eligibility criteria for the review of clinical effectiveness of vismodegib is summarised in Table 4.

Table 4. Eligibility criteria for the review of clinical effectiveness (Adapted from CS, page 57-58, Table 11)

Domain	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years) with: •symptomatic mBCC; •laBCC, for whom surgery or radiotherapy is not appropriate; Studies were included if patients with advanced or metastatic BCC were at least 50% of the study population, or if results were presented separately for patients with advanced or metastatic BCC.	Any of the following: •patients without BCC •patients with early BCC (not advanced or metastatic) •studies only including patients <18 years old •studies with mixed patient populations where outcomes were not presented separately for the specific population of interest •studies of adjuvant or neoadjuvant therapy
Intervention	Vismodegib (Erivedge®) monotherapy	Studies not investigating vismodegib (Erivedge®) as monotherapy, or studies where outcomes for the relevant intervention were not presented separately to those for interventions not of interest
Comparator	Any therapies, including: •placebo or best supportive care •no comparator (if the study is a non-RCT or observational study)	NA
Outcomes (considered at full-text review only)	Any efficacy or safety outcomes including: •Response rate (complete, partial, stable disease) •Duration of response •Tumour shrinkage •Progression-free survival (PFS) •Overall survival (OS) •Time to progression (TTP) •Clinical benefit rate •Treatment-emergent and treatment-related adverse events (safety and tolerability) •Health-related quality of life (HRQoL) •Time-to-treatment discontinuation	Studies not presenting relevant outcomes
Study design	RCTs Interventional non-RCTs, including single-arm clinical trials Observational studies SLRs and (network) meta-analyses were included at the title/abstract review stage, then excluded at the full-text review stage following hand-searching of their reference lists	Any other study designs, including: •Economic evaluations •Case studies and case reports •Editorials, notes, comments or letters •Narrative or non-systematic literature reviews
Other considerations	English language and non-English language full-texts Human subjects	Articles not on human subjects

Abbreviations: BCC, basal cell carcinoma; CS, company submission; HRQoL, health-related quality of life; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; OS, overall survival; PFS, progression free survival; RCT, randomised control trial; SLR, systematic literature review; TTP, time to progression.

The eligibility criteria outlined by the company shows an inclusive approach. The population is described as all patients with mBCC or laBCC. No restrictions were discussed by the company with regards to anatomical site of BCC or whether patients were eligible who had Gorlin syndrome. The comparator of interest was outlined as 'best supportive care' however no definition of BSC was

specified. The outcomes of interest are relevant to those listed in the NICE final scope[1]. The study design was not limited to RCT studies which the ERG considers to be appropriate due to the limited available evidence in this disease area, with the available evidence known to consist mostly of single arm studies. There was no language restriction applied which ensured no relevant evidence was excluded. Therefore the ERG considers the eligibility criteria outlined by the company to be appropriate for identifying relevant evidence aligned with the NICE final scope for vismodegib[1] but not for identifying studies of BSC.

4.1.3 Critique of screening process

The company outlines the methods implemented to screen the studies retrieved by the systematic search of the literature and the methods are in line with those recommended by the Centre for Reviews and Dissemination.[67] The record screening at title and abstract stage as well as full text were carried out by two independent reviewers. Any disputes relating to eligibility of records were resolved between the reviewers or under the consultation of a third reviewer. Data extraction was carried out by one reviewer and reviewed by a second reviewer for accuracy.

The database search in November 2016 retrieved 230 unique study records, 46 of which were selected for full text review and 30 were deemed as relevant. Conference searches and reference list searches resulted in identification of 57 records of which 9 were included as relevant. An additional 10 unpublished records were supplied by the company for inclusion. The company provide no details of how these records were identified. A total of 49 records which reported results from 12 unique studies were included in the review. The ERG notes that the company report a disparity in the number of included studies from their database searches in the CS: in Section 4.1.4 of the CS the company suggest a total of 33 records were identified however these numbers do not correlate with those presented in the company's PRISMA diagram, shown in Figure 1 of the ERG report.

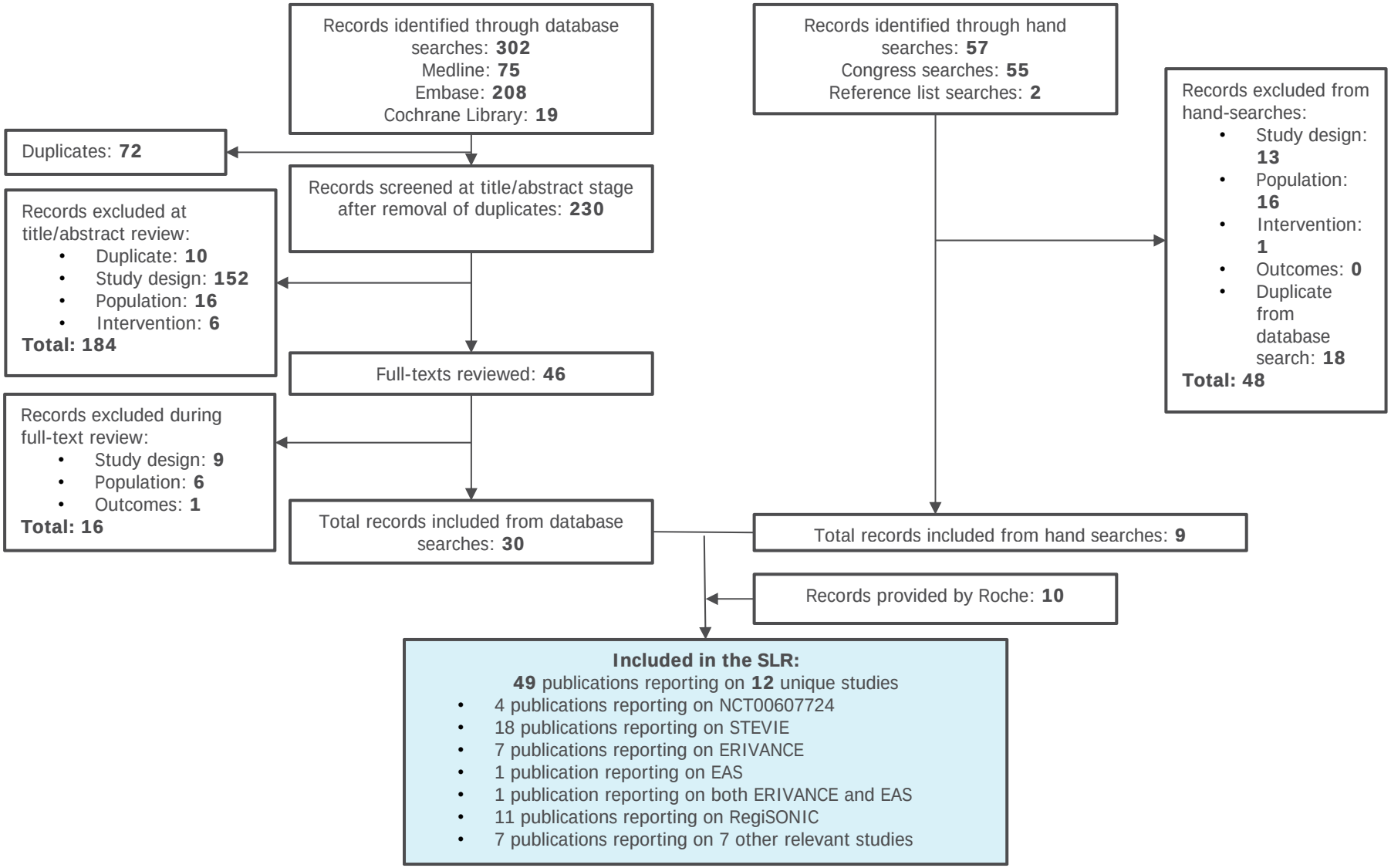
The company report the study methods and results of five unique studies investigating vismodegib (NCT00607724 [Phase 1 SHH3935g],[39] NCT01367665 [STEVIE],[59] NCT00833417 [ERIVANCE],[68] NCT01160250 [EAS],[69] NCT01604252 [RegiSONIC][70]). Therefore, seven studies identified in the search were not included as supporting evidence in the CS by the company. The details of these seven studies are outlined in the CS, Appendix 8. The company's reasoning for not including six of the studies in the review was due to small sample sizes. The sample size of these six studies[71,72,73,74,75,76] was between 7 and 24 patients. The ERG notes that the company does not provide an *a priori* sample size requirement as an inclusion/exclusion criterion for the review. The remaining study, Alkeraye 2015[77], was not included due to a lack of relevant outcome measures other than the incidence of a specific adverse events, alopecia. The ERG considers this to be a relevant reason for exclusion, however based

on the systematic screening process it would be expected that this study Alkeraye 2015[77] would have been excluded at an earlier stage of the process such as full text stage due to insufficient outcome data.

Although the company report the methods and findings of five unique studies[39,59,68,69,70] the conclusions presented by the company for the clinical efficacy of vismodegib are largely attributed to the two studies ERIVANCE and STEVIE. For the EU and FDA market authorisation applications ERIVANCE and STEVIE were the main studies used as supporting evidence of vismodegib in advanced BCC. The ERG agrees with the decision taken by the company to focus on these two studies in the CS to provide evidence addressing the decision problem outlined in the NICE final scope[1].

In summary, the ERG finds the methods undertaken by the company in screening relevant evidence to address the decision problem in the NICE final scope[1] to be appropriate. However, the ERG notes there is a lack of clarity with regards to the number of records retrieved from the search and screening process with inconsistent reporting between the text and the PRISMA diagram presented in the CS. The company's decision to present five studies of the 12 identified is justified.

Figure 1. PRISMA flow diagram for the company's clinical systematic review search (Adapted from CS, page 59, Figure 5)



4.1.4 Quality assessment

The company provided quality assessments for five studies (NCT00607724, STEVIE, ERIVANCE, EAS and RegiSONIC), using the Downs and Black checklist.[78] This checklist consists of 26 questions under four domains: 'Reporting', 'External validity', 'Internal validity- bias', 'Internal validity-confounding' and 'Power'. Each question is answered with 'Yes', 'No', 'Unable to determine' or 'NA' (not applicable). Additional qualitative details are also provided if necessary. Summaries of the company's assessment together with those of the ERG review are shown in Table 5. The company draw their main conclusions on the safety and efficacy of vismodegib based on the ERIVANCE and STEVIE studies and therefore only the quality assessment of these two studies will be discussed.

The company assessment of ERIVANCE and STEVIE using the Downs and Black checklist[78] identified areas where both studies were at risk of bias. Firstly, for both ERIVANCE and STEVIE, there was a lack of consistency in reporting a measure of variability for all outcomes such as 95% confidence intervals. There was also limited reporting on whether patients were compliant to the received intervention and little detail on the sites where these studies took place when considering whether they were representative of clinical practice. The single arm study design of both ERIVANCE and STEVIE means there is a lack of comparative data for the efficacy of vismodegib as well as the potential for confounding as they are observational studies rather randomised double-blind controlled trials. In addition, the lack of blinding and thus awareness of the study drug received also provides the potential for reporting bias to have occurred in ERIVANCE and STEVIE. It is also noted that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.[66]

The ERG's quality assessment of ERIVANCE and STEVIE was in keeping with that of the company. However, one element overlooked in the company assessment was the consideration of confounding factors when analysing results for key outcomes. The ERG considers the inclusion of approximately 20% of patients with Gorlin syndrome in both the ERIVANCE and STEVIE study's to be an over-representation of Gorlin patients compared to UK clinical practice. In addition, the ERG's clinical experts report that these patients are likely to have differential characteristics to non-Gorlin aBCC patients, such as a younger average age and better ECOG performance status thus resulting in a better prognosis. Therefore, the lack of consideration for this population as an important prognostic indicator is an oversight by the company and a potential source of bias for the ERIVANCE and STEVIE study's that may lead to an overestimation of the efficacy of vismodegib.

Overall, the ERG considers ERIVANCE and STEVIE to be studies that are of low quality to inform the comparative efficacy of vismodegib with BSC due to the single-arm observational nature of their study design. They are at a high risk of bias due to the inherent bias associated with their study design, which

relates to the internal validity of the studies. The population in STEVIE is the most representative of those in UK clinical practice as the population in ERIVANCE was much younger, however, both STEVIE and ERIVANCE have a higher proportion of Gorlin patients than would be expected in the UK population and so their external validity is also open to question.

Table 5. Quality assessment of STEVIE and ERIVANCE using the Downs and Black checklist[78]

Trial Number	ERIVANCE Company Review	ERIVANCE ERG Review	STEVIE Company Review	STEVIE ERG Review
Reporting				
1. Is the hypothesis/ aim/ objective of the study clearly described?	Yes	Yes – objective presented in Table 12 of CS: To look at clinical benefit of vismodegib for patients with laBCC or mBCC measured by ORR.	Yes	Yes – objective presented in Table 12 of CS: To assess safety and efficacy of vismodegib in patients with aBCC in a real-world setting.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section	Yes	Yes – outcomes listed in Table 13 CS. Primary outcome ORR assessed differently for laBCC and mBCC. Secondary outcome included duration of OR (independent assessed), PFS, OS and HRQoL.	Yes	Yes – outcomes listed in Table 13 CS. Primary endpoint was safety looking at incidence of AE. Secondary outcome included ORR, PFS and OS (all investigator assessed).
3. Are the characteristics of the patients included in the study clearly described	Yes	Yes – baseline characteristics in Table 22 of CS: Limited details of patients' disease state, anatomical site of BCC.	Yes	Yes – baseline characteristics in Table 23 of CS: Limited details are reported in CS. A full set of data are provided in the CSR.
4. Are the intervention(s) of interest clearly described	Yes	Yes – vismodegib is outlined as the intervention of interest.	Yes	Yes – vismodegib is outlined as the intervention of interest.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described	NA – not comparative	NA – this study is not comparative.	NA – not comparative	NA – this study is not comparative.
6. Are the main findings of the study clearly described?	Yes	Yes – summary of efficacy results presented in Table 28 of CS, adverse events in Table 33 of CS. Outcomes reported include ORR, DoR, PFS, OS, and treated emergent adverse events.	Yes	Yes – summary of efficacy results presented in Table 29 of CS. Safety results presented in Table 38 of CS. Efficacy data presented includes PFS, ORR, DoR, TTR and treatment emergent events.

7. Does the study provide estimates of the random variability in the data for the main outcomes	No – 95% CIs given for some outcomes but not all.	No - 95% CI only reported for the following outcomes: ORR, PFS, OS.	No – 95% CIs given for some outcomes but not all.	No – 95% CI only reported for the following outcomes: PFS, ORR, DoR and TTR.
8. Have all important adverse events that may be a consequence of the intervention been reported	Yes	Yes – all AE were reported for Total AE and Grade 1-5 in all patients.	Yes	No – only reported for total AE and Grade 3 and 4 reported in >10% of patients in the study.
9. Have the characteristics of patients lost to follow-up been described?	Yes	Yes – treatment discontinuation details of patients were summarised in Table 37 of CS. Patients lost to follow up totals to 2.9%.	Yes	Yes – treatment discontinuation details of patients were summarised in Table 43 of CS. Patients lost to follow up totals to 1.7%.
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability values is less than 0.001?	Yes	Yes, main outcome of ORR was reported as p<0.001.	NA	NA – no probability values were reported.
External Validity				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	No – Limited demographic data is provided for the study. The average age of patients, 61 years was lower than typically found in UK clinical practice, around 70 years. 21% of patients in ERIVANCE had Gorlin syndrome, which clinical experts report is quite high compared to the prevalence in UK clinical practices.	Yes	No – Patients in the study had a similar demographic profile (age, gender, and race) to those seen in UK clinical practice. The proportion of patients in the study with Gorlin syndrome (~20%) which clinical experts report is higher than typically seen in the UK clinical practices.
12. Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	Unable to determine – limited data concerning site location and facilities where study treatment took place.	Unable to determine	Unable to determine - limited data concerning site location and facilities where study treatment took place.
Internal validity – Bias				
13. Was an attempt made to blind study subjects to the intervention they have received?	No	No – due to single arm study design blinding was not attempted.	No	No – due to single arm study design blinding was not attempted.
14. Was an attempt made to blind those measuring the main outcomes of the intervention	No	No blinding occurred. Outcomes were independently assessed.	No	No blinding occurred.

15. If any of the results of the study were based on 'data dredging' was this made clear?	NA	Unable to determine.	NA	Unable to determine.
16. In trials and cohort studies, do the analyses adjust for different lengths of follow up patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	NA	NA	NA	NA
17. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes – the Kaplan Meier method was used for median duration of ORR, PFS and OS.	Yes	Yes – primary outcome for study was AE which did not require statistical testing. However secondary outcome PFS used Kaplan-Meier method.
18. Was compliance with the intervention/s reliable?	Unable to determine	Unable to determine.	Unable to determine.	Unable to determine.
19. Were the main outcome measures used accurate (valid and reliable)	Yes	Yes- Primary outcome ORR was assessed differently for laBCC and mBCC. For mBCC standard reliable RECIST criteria was used. For laBCC a composite measure was used.	Yes	Yes – ORR was assessed using RECIST for both cohorts (laBCC and mBCC).
Internal Validity – Confounding (selection bias)				
20. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA	NA	NA
21. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	NA	NA	NA
22. Were study subjects randomised to intervention groups?	No	No – due to the ERIVANCE being a single arm study, no randomisation occurred.	No	No – due to STEVIE being a single arm study, no randomisation occurred.

23. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable	NA	NA	NA	NA
24. Was there adequate adjustment for the confounding in the analyses from which the main findings were drawn?	NA	NA	NA	No – the proportion of Gorlin syndrome patients were not considered as a subgroup in the results.
25. Were losses of patients to follow-up taken into account?	Yes	Yes – all patients who were enrolled were used in primary and secondary efficacy outcomes.	Yes	Yes – all enrolled patients were considered for safety and efficacy analyses based on return of drug dispensed.
Power				
26. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to change is less than 5%?	Yes	Yes – sample size of the study was calculated to have 80% probability of rejecting the null hypothesis.	Yes	Yes – the sample size was sufficient to observe AE incidence rate.

Abbreviations: aBCC, advanced BCC; AE, adverse events; BCC, basal cell carcinoma; CI, confidence interval; CS, company submission; CSR, clinical study report; DoR, duration of response; ERG, evidence review group; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to response.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

As discussed in Section 4.1.3, the company included 12 studies in their review of clinical efficacy but reported data for only the five studies that they deemed to be most relevant to the decision problem. The key features of these five studies are presented in Table 6 with the studies discussed further below.

Table 6. Summary of five included studies (Adapted from CS, page 62, Table 12)

Study ID	ERIVANCE[68]	STEVIE[59]	NCT00607724[39]	RegiSONIC[62]	EAS[69]
Phase	II	II	I	Not applicable	IV
Objective	To estimate the clinical benefit of vismodegib given as therapy for patients with locally advanced or metastatic BCC, as measured by objective response rate (ORR)[79]	To assess safety and efficacy of vismodegib in patients with aBCC in a real-world setting.	To assess the safety and pharmacokinetics of GDC-0449, a small-molecule inhibitor of SMO, and responses of laBCC or mBCC to the drug.	To evaluate the effectiveness, safety and utilisation of treatments in patients with aBCC and BCNS.[70]	To assess efficacy and safety of vismodegib, while providing early drug access to patients with aBCC and limited treatment options.
Intervention	Oral vismodegib at 150 mg/day	Oral vismodegib at 150 mg/day	Oral vismodegib at 150 mg/day, 270 mg/day or 540 mg/day	Patients are treated according to clinician's standard or care	Vismodegib at 150 mg/day
Population	104 patients; 33 with mBCC and 71 with laBCC. (Eight patients with laBCC were excluded from the efficacy analysis) [68]	1232 patients with laBCC or mBCC. (17 patients were excluded from the safety and efficacy analysis due to no documented exposure based on return of drug dispensed)	Full study included 68 patients with solid tumours refractory to current therapies or for which no standard therapy existed. This publication reports on 33 patients with mBCC or laBCC.	3 cohorts of patients treated for aBCC +/- BCNS: Cohort 1: Patients with a new aBCC who do not have BCNS and are HPI naïve. Cohort 2: Patients with aBCC who do not have BCNS and who were previously enrolled in Phase 2 SHH4437g (NCT00959647), ERIVANCE or EAS. Cohort 3: Patients with BCNS who have aBCC as defined for cohort 1 (HPI naïve) or cohort 2 (vismodegib exposed) or who have multiple non-advanced, HPI-naïve BCCs. As of 11th September 2015, 503 patients with laBCC were enrolled across all cohorts.	120 patients; 58 with mBCC and 62 with laBCC.

Abbreviations: aBCC, advanced BCC; BCC, basal cell carcinoma; BCNS, basal cell naevus syndrome (Gorlin syndrome); CS, company submission; HPI, Hedgehog pathway inhibitors; laBCC, locally advanced BCC; mBCC, metastatic BCC; SMO, smoothened.

The ERG notes that ERIVANCE and STEVIE are the two studies that were used to gain the EU marketing authorisation for vismodegib and that they are also the studies on which the company have

based the economic model (discussed in Section 5). The Phase I study SHH3925g included nearly 50% of patients on a higher dose of vismodegib compared to the licensed dose for aBCC, with no subgroup data presented in the CS based on the licensed vismodegib dose. As such, the ERG does not consider study SHH3925g to be relevant to the decision problem specified in the final scope issued by NICE[1]. RegiSONIC is an ongoing study which has had results presented only for response rate and adverse events in the CS and they are reported to be from conference abstracts with each one focusing on different populations or analysis time-points. The efficacy results presented in the CS were from a cohort of newly diagnosed laBCC patients without BCC-naevus syndrome (i.e. non-Gorlin syndrome patients) and so they represent a subgroup of the laBCC patients eligible for vismodegib. EAS SHH4811g was a phase IV expanded access study to enable the compassionate use of vismodegib in the US prior to vismodegib approval by the FDA. It included both laBCC and mBCC patients but the study was terminated following the granting of the US marketing authorisation for vismodegib.

The ERG focuses its critique from here onwards on the ERIVANCE and STEVIE studies as the ERG considers them to be the most relevant in addressing the final scope issued by NICE[1].

4.2.1 Trial conduct

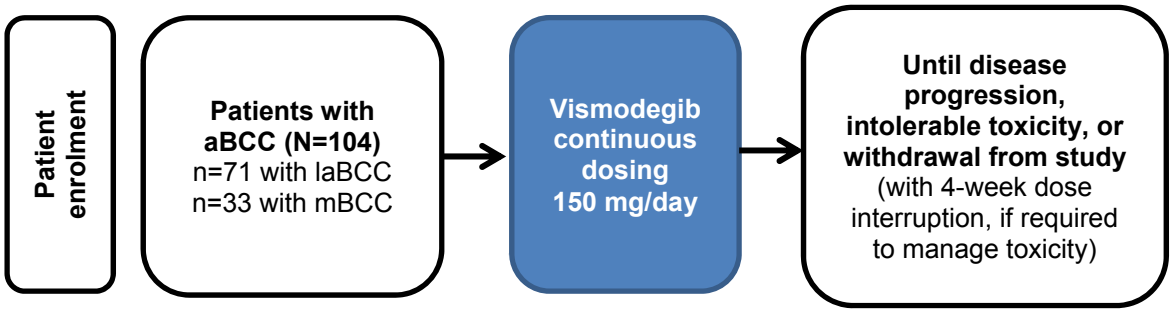
4.2.1.1 ERIVANCE

ERIVANCE (NCT00833417) was a multicentre international, open-label, single-arm, two-cohort clinical study comprising of patients with laBCC and mBCC. ERIVANCE was the key study used to gain conditional EU marketing authorisation for vismodegib. There were 104 patients (33 patients with mBCC and 71 patients with laBCC) enrolled in ERIVANCE across 31 study sites in the USA, England, France, Germany, Belgium, and Australia.[80] Vismodegib was given orally at the EU licensed dose of 150 mg/day in ERIVANCE until disease progression or study withdrawal for any reason including intolerable toxicity. The median duration of exposure to vismodegib in ERIVANCE was 13.3 months (range: 0.7 to 39.1) for patients with mBCC and 12.7 months (range: 1.1 to 47.1) for the laBCC group of patients. Vismodegib dose modifications were not allowed in ERIVANCE although treatment could be interrupted for up to four weeks for investigation of tolerability issues or if a patient was temporarily unable to swallow capsules, and for up to eight weeks for a planned surgical procedure. Concomitant therapy with other anti-tumour therapies was prohibited during the study although other therapies were unrestricted. The company reported that 95.2% of patients used at least one concomitant medication while on study, which was most commonly an analgesic. The most frequently reported concomitant medications included paracetamol (29.8%, 31 patients), multivitamins (20.2%, 21 patients), aspirin and ibuprofen (each with 19.2%, 20 patients).

Patients were followed up until disease progression, death, or withdrawal of consent. Tumour assessment was carried out every 8 weeks, and at the end of the study. The primary analysis in

ERIVANCE was at 9 months after the last patients were enrolled in the study (data cut-off: 26th November 2010)[68] with additional analyses 12 and 30 months later (data cut-offs 28th November 2011 and 30th May 2013, respectively).[57, 81] Figure 2 provides an overview of the study design of ERIVANCE.

Figure 2. Summary of ERIVANCE study design[68] (reproduced from CS, page 74, Figure 6)



The company reported that there was no control group in ERIVANCE because there was, "no accepted standard of care and no data suggesting spontaneous responses in advanced BCC". The ERG agree that there is likely to be variation in best supportive care (BSC) across the different sites of the trial and spontaneous resolution is not typical in BCC. However, the ERG considers an RCT design to be the preferred study design to enable a direct comparison between vismodegib and BSC. The ERG considers that a control group of physician's choice could potentially be used in an RCT to represent BSC as there is no universal standard definition of BSC in aBCC.

The inclusion and exclusion criteria for enrolment in ERIVANCE are summarised in Table 7. The ERG's clinical expert experts generally agree that these criteria appear reasonable and applicable to the patients likely to be selected for vismodegib treatment in the UK.

Table 7. Summary of inclusion and exclusion for the ERIVANCE study (Adapted from CS pages 75-76, Table 14)

Inclusion criteria	Exclusion criteria
• Men and women aged ≥ 18 years • Eastern Cooperative Oncology Group performance status of 0, 1, or 2 • mBCC patients: o Histologic confirmation of distant BCC metastasis (e.g., lung, liver, lymph nodes, bone), with metastatic disease that was RECIST measurable using CT or MRI. Patients with metastatic disease confined to bone were not considered eligible because of the lack of RECIST measurability • laBCC patients: o At least one histologically confirmed lesion ≥ 10 mm in the longest diameter that was considered to be inoperable or who had a medical contraindication to surgery, in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon. Acceptable medical contraindications to surgery included: • BCC that recurred in the same location after two or more surgical procedures, and curative resection was deemed unlikely	• Inability or unwillingness to swallow capsules • Prior treatment with vismodegib or other antagonists of the Hh pathway • Pregnancy or lactation • Life expectancy of < 12 weeks • Patients with superficial multifocal BCC considered unresectable because of breadth of involvement • Concurrent non-protocol-specified anti-tumour therapy

• Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, or eye; or requirement for limb amputation) • Other conditions considered to be medically contraindicated were discussed with the Medical Monitor before the patient was enrolled o Radiotherapy was previously administered for their locally advanced BCC, unless radiotherapy was contraindicated or inappropriate (e.g., hypersensitivity to radiation because of a genetic syndrome such as Gorlin syndrome, limitations because of location of tumour, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC was irradiated, disease had progressed after radiation o If a patient with locally advanced BCC also had a tumour that was not contiguous with cutaneous BCC, e.g., regional lymph nodes (if confirmed on biopsy as BCC and RECIST measurable), the patient was considered as having metastatic BCC and was enrolled in the metastatic cohort • Patients with Gorlin syndrome could have been enrolled in this study, but had to have met the criteria for locally advanced or metastatic disease listed above • Adequate haematopoietic capacity, defined by the following: o Haemoglobin >8.5 g/dL and not transfusion dependent; o Granulocyte count ≥1000/μL; and o Platelet count ≥75,000/μL • Adequate hepatic function, defined by the following: o Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3 × the upper limit of normal (ULN); and o Total bilirubin ≤1.5 × the ULN or within 3 × the ULN for patients with Gilbert disease • Women of childbearing potential, agreement to use two acceptable methods of contraception, including one barrier method, during the study and for 7 months after discontinuation of vismodegib • Men with female partners of childbearing potential, agreement to use a latex condom and to advise their female partner to use an additional method of contraception during the study and for 7 months after discontinuation of vismodegib • Agreement not to donate blood or blood products during the study and for at least 7 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 2 months after discontinuation of vismodegib	• Recent (within 4 weeks of Day 1), current, or planned participation in an experimental drug study • History of other malignancies within 3 years of Day 1, except for tumours with a negligible risk for metastasis or death • Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gave reasonable suspicion of a disease or condition that contraindicated use of an investigational drug
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BCC, basal cell carcinoma; CS, company submission; Hh, hedgehog; laBCC, locally advanced BCC; mBCC, metastatic BCC; RECIST, Response Evaluation Criteria In Solid Tumors; ULN, upper limit of normal.	

The primary efficacy endpoint in ERIVANCE was objective response rate (ORR) as determined by the independent review facility (IRF) for the primary analysis and 12-month analysis with the 30-month efficacy results based on investigator only assessment. Objective response was defined as a complete response (CR) or partial response (PR) on two consecutive assessments at least 4 weeks apart with patients with no baseline or post-baseline tumour assessment deemed to be non-responders in the analysis. Assessment of response in patients with mBCC was by the IRF according to RECIST[82] v1.0 criteria. A novel composite endpoint was created for assessment of response in patients with laBCC as the company reported there was, "no clinical or regulatory precedent for objective measurement of efficacy in patients with laBCC". The company also reported that the composite endpoint was created in consultation with the US FDA and informed by the Phase I study (SHH3925g) of vismodegib. It comprised of a photographic IRF (visual assessment of external tumour and ulceration), radiographic IRF (tumour imaging, if appropriate), and pathology IRF (tumour biopsy). The patients with either

mBCC or laBCC who did not meet criteria for response (CR or PR) or progressive disease (PD) were considered to have stable disease (SD). The ERG's clinical experts agree that the definitions of response used for laBCC and mBCC appear to be reasonable and the different definitions are required based on the differences in the clinical manifestation of the two diseases.

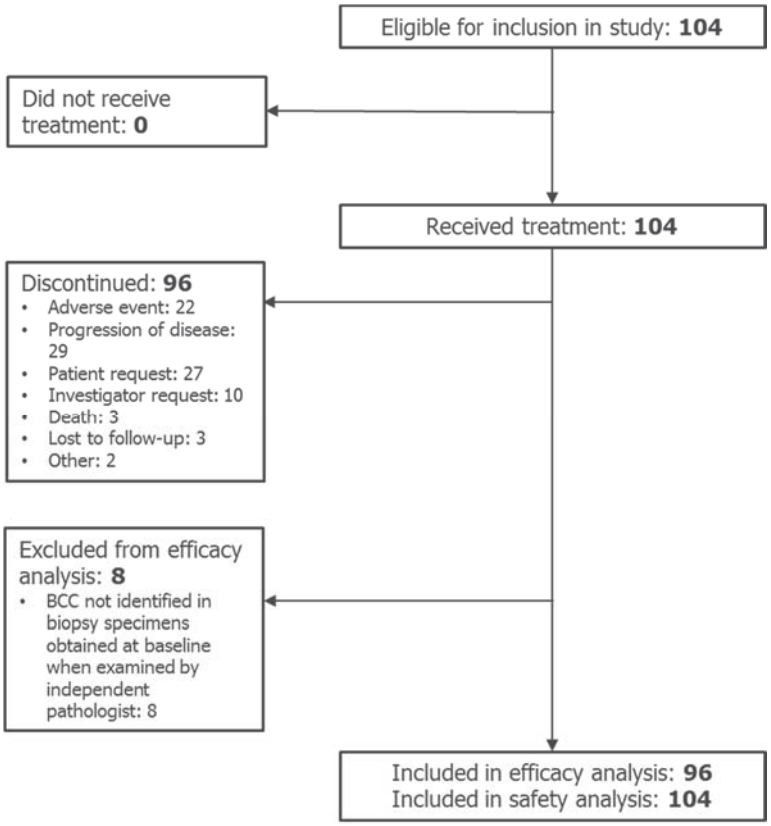
The secondary efficacy endpoints in ERIVANCE included:

- duration of objective response (defined as the time from the initial CR or PR to the earliest documented disease progression or death within 30 days of last exposure to study treatment);
- PFS (with duration of PFS defined as the time from first dose of vismodegib to the earliest documented disease progression or death within 30 days of last exposure to vismodegib);
- OS (with duration of OS defined as the time from first dose of vismodegib until death from any cause);
- change from Day 1 in patient-reported symptoms based on the SF-36 Health Survey (Version 2);
- histopathological response in terms of the absence of residual BCC in patients with locally advanced BCC (defined as post-baseline tissue samples that were found to be absent of residual BCC assessed by the independent pathologist).

The only pre-specified subgroup analyses in ERIVANCE were analyses for patients with laBCC and mBCC.

The patient flow in ERIVANCE were provided for the primary analysis and the 30-month follow-up (final) analysis in the CS with the only differences in the number of patients who had discontinued and so only the PRISMA diagram for the 30-month analysis is presented in this report (Figure 3). At the primary analysis 53 patients had discontinued, whereas at the 30-month follow-up all 96 patients suitable for the efficacy analysis had discontinued treatment. Also of note, three patients had died and three patients were lost to follow-up by the time of the primary analysis. The most common reason for discontinuation at the time of the primary analysis was patient request (38%). The most common reasons for discontinuation at the time of the 30-month analysis were disease progression (30%), patient request (28%) and adverse events (23%). In total, of the 104 patients enrolled in ERIVANCE, eight were excluded from the efficacy analyses due to concerns that BCC was not present in the baseline biopsy specimens following independent review. All enrolled patients were included in the safety analyses.

Figure 3. PRISMA diagram for ERIVANCE: 30-month analysis[81] (reproduced from CS, page 107, Figure 11)



The ERG requested clarification from the company on the details of the subsequent treatments (if any) used by patients discontinuing vismodegib as these are potential confounders when considering the results for overall survival. However, the company replied that no information on subsequent treatments were captured in ERIVANCE.

4.2.1.2 STEVIE

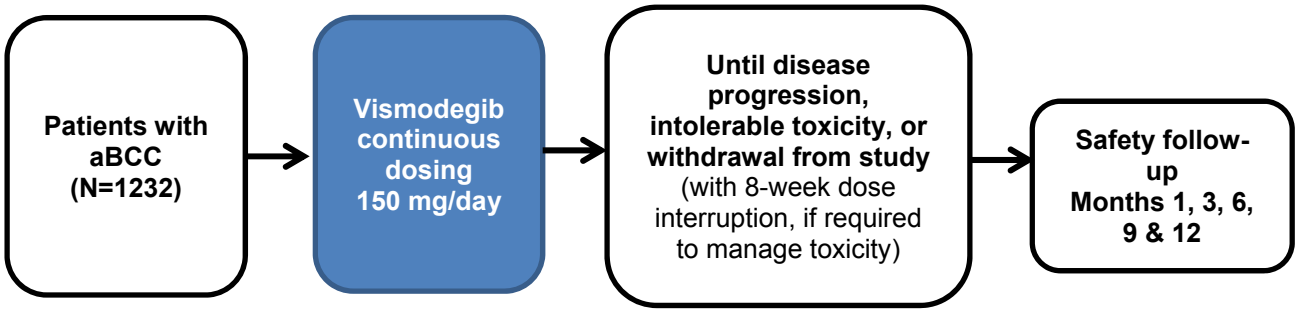
STEVIE was a multicentre international, open-label, single-arm, phase II clinical study comprising of patients with laBCC and mBCC. STEVIE was a post-approval safety study designed to fulfil one of the specific obligations required by the initial conditional marketing authorisation for vismodegib in the EU by providing further data on safety and data on efficacy in patients with symptomatic mBCC. STEVIE also included laBCC patients and thus also provided further evidence of vismodegib safety and efficacy in laBCC patients.

There were 1,232 patients enrolled in STEVIE across 152 sites in 36 countries that included Australia, Austria, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Finland, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Poland, Romania, Russian Federation, Serbia, Spain, Sweden, Turkey, and the UK. Treatment in STEVIE comprised of the EU licensed dose of oral vismodegib, 150mg daily, and was continued until disease progression,

intolerable toxicity, or withdrawal from the study for any reason. There were no dose alterations allowed although vismodegib treatment could be temporarily stopped for up to eight weeks for intolerable toxicity or if a patient became temporarily unable to swallow the capsules. The median duration of vismodegib treatment in STEVIE was 263 days (256 days for laBCC and 319 days for mBCC). Concomitant treatment with oral contraceptives, hormone-replacement therapy, or other maintenance therapy was allowed although use of St John's wort (Hypericum perforatum) and other anti-tumour therapies was prohibited. At least one concomitant medication was used while on study in STEVIE by 92.3% of patients with the most common classes of concomitant medications being vitamins and minerals (33.2%), analgesics (27.8%), proton-pump inhibitors (25.7%), and beta-adrenoceptor blocking agents (23.2%). The ERG's clinical experts report that these are to be expected in the age population being treated with vismodegib both in STEVIE and in clinical practice.

On discontinuation of treatment patients received a follow-up visit which was followed by a further five safety follow-up visits. Figure 4 provides more detail on the study design and patient journey in STEVIE.

Figure 4. Summary of STEVIE study design (CS, page 79, Figure 7)



Enrolment for STEVIE commenced on 30th June 2011 with the final patient enrolled on 2nd September 2014. There were six interim analyses planned in STEVIE and a final analysis. The final analysis was planned to be when whichever occurred first out of the following: the last patient in the study developed progressive disease (as determined by the investigator), unacceptable toxicity, withdrew consent, died or was deemed no longer to be benefiting from treatment according to the treating physician, or the study was terminated by the sponsor; or 12 months after the last dose of vismodegib in the last enrolled patient still on study. The six interim analyses were planned according to the number of patients enrolled in the study and required patients to have received at least three months treatment with the final interim analysis when 1,200 patients had been enrolled. This final interim analysis also comprised of an analysis of 500 enrolled patients who had been followed for at least 12 months. The data presented in the CS appear to correspond to the final interim analysis as it is reported in the CS that, "As of 6 November 2013, 499 patients had received study drug and had the potential to be followed up for 12 months or longer. 99 (20%) patients were receiving ongoing treatment with vismodegib" and, "As of 16 March

2015, 517/1215 patients (42.6%) had completed the study, and 375/1215 patients (30.9%) were still on study (147 [12.1%] on treatment and 228 [18.8%] in follow-up)".

The inclusion and exclusion criteria for enrolment in STEVIE are summarised in Table 8. The ERG's clinical experts agree that these criteria appear reasonable and applicable to the patients likely to be selected for vismodegib treatment in the UK (although they differ slightly from the inclusion criteria for ERIVANCE). The inclusion criteria in STEVIE were broader than that of ERIVANCE as STEVIE didn't restrict entry based on co-morbidities, other cancers and superficial multifocal BCC considered unresectable because of breadth of involvement.

Table 8. Summary of inclusion and exclusion for the STEVIE study (Adapted from CS page 81-82, Table 15)

Inclusion criteria	Exclusion criteria
• Men and women aged ≥18 years • Eastern Cooperative Oncology Group performance status of 0, 1, or 2 • mBCC patients: o Histologic confirmation of distant BCC • laBCC patients: o At least one histologically confirmed lesion ≥10 mm in the longest diameter that was considered to be inoperable or who had a contraindication to surgery, Acceptable medical contraindications to surgery included: o BCC that recurred in the same location after two or more surgical procedures, and curative resection was deemed unlikely o Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, or eye; or requirement for limb amputation) o Radiotherapy was previously administered for their locally advanced BCC, unless radiotherapy was contraindicated or inappropriate (e.g., hypersensitivity to radiation because of a genetic syndrome such as Gorlin syndrome, limitations because of location of tumour, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC was irradiated, disease had progressed after radiation • Patients with Gorlin syndrome could have been enrolled in this study, but had to have met the criteria for locally advanced or metastatic disease listed above • Adequate haematopoietic capacity, defined by the following: o Haemoglobin >8.5 g/dL and not transfusion dependent; o Granulocyte count ≥1000/μL; and o Platelet count ≥75,000/μL	• Inability or unwillingness to swallow capsules • Pregnancy or lactation • Concurrent non–protocol-specified anti-tumour therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy, including participation in an experimental drug study; note that treatment breaks up to 8 weeks for radiation therapy were allowed • Recent (within 21 days of Day 1) completion of anti-tumour therapy • Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics • History of other malignancies within 3 years of Day 1, except for tumours with a negligible risk for metastasis or death • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gave reasonable suspicion of a disease or condition that contraindicated use of an investigational drug • Patients with one of the following rare hereditary conditions: galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption

• Adequate hepatic function, defined by the following: o Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3 × the upper limit of normal (ULN); and o Total bilirubin ≤1.5 × the ULN or within 3 × the ULN for patients with Gilbert disease • Women of childbearing potential, agreement to use two acceptable methods of contraception, including one highly effective method and one barrier method, during the study and for at least 24 months after discontinuation of vismodegib • Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential could be included if they were either surgically sterile or had been postmenopausal for ≥1 year • Men with female partners of childbearing potential, agreement to use a condom with spermicide, even after vasectomy, during the study and for 2 months after discontinuation of vismodegib • Agreement not to donate blood or blood products during the study and for at least 7 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 2 months after discontinuation of vismodegib • Life expectancy ≥12 weeks	
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; ULN, upper limit of normal.	

The primary outcome in STEVIE was safety, defined as the incidence of adverse events until disease progression or unacceptable toxic effects as assessed by the investigator on day 1 of each 28-day treatment cycle. In addition, safety was assessed by number of patients experiencing any adverse effects (AEs), percentage of participants who experienced an AE (according to the NCI CTCAE, v4.03), Grade 3 or 4 AEs leading to drug interruptions or discontinuations,[83] and any serious AEs.[83]

The secondary endpoints in STEVIE included:

- Objective response rate defined according to RECIST v1.1 and investigator assessed. Best overall response rate (BORR) was defined as the number of patients whose best response was complete response (CR) or partial response (PR) divided by the total number treated. CR was defined as the disappearance of all target lesions and any pathological lymph nodes were required to have a reduction in short axis to less than 10 mm.[84] PR was defined as a 30% or greater reduction in the sum of the diameters of target lesions compared to baseline.[84]
- Time to response defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occurred first) and assessed by the investigator.

- Duration of response for patients whose confirmed best response was CR or PR defined as the time interval between the date of the earliest qualifying response and the date of PD or death from any cause as assessed by the investigator.
- Progression-free survival was assessed by the investigator and defined as the time interval between the date of the first dose and date of progression or death from any cause, whichever occurred first.
- Overall survival was defined as the time from the date of first treatment to the date of death from any cause.
- Patient quality of life assessed using:
    - the Skindex-16 questionnaire to assess the effects of skin disease on patients' HRQoL in both the laBCC and mBCC patients; and
    - the M.D. Anderson Symptom Inventory (MDASI) instrument to assess the impact of treatment on symptoms in patients with mBCC who were enrolled after a study protocol amendment.

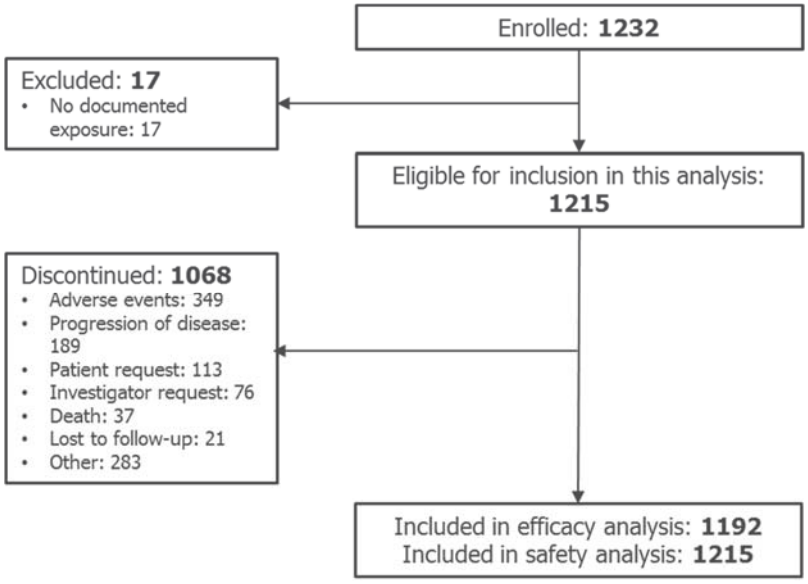
There was no central or independent review in STEVIE. Tumours were assessed every 4 to 8 weeks with CT and MRI scans done every 8 to 16 weeks as deemed necessary by the investigator.

The only pre-specified subgroup analyses in STEVIE were analyses for patients with laBCC and mBCC.

In summary, the outcomes in STEVIE were similar to those in ERIVANCE although the primary endpoint was safety in STEVIE and efficacy in ERIVANCE. Also, an IRF was used for the majority of the outcome assessments in ERIVANCE whereas STEVIE comprised only of investigator assessments and thus the results of STEVIE may be subject to assessor bias although the potential of impact of this is unknown.

The patient flow in the analysis of STEVIE presented in the CS is summarised in Figure 5. In summary, 1,215 of the 1,232 patients enrolled in STEVIE were included in the safety analysis and 23 of these were excluded from the efficacy analysis as they didn't have histologically confirmed disease and available measurable disease status at baseline. Of the patients eligible for inclusion in the analyses, 87.9% had discontinued treatment by the time of the analysis. The most common reason for discontinuation in STEVIE was due to AEs (28.7%). A higher proportion of patients discontinued due to AEs in STEVIE compared to in ERIVANCE (29% versus [vs] 23%, respectively) and a smaller proportion discontinued in STEVIE due to disease progression compared to in ERIVANCE (16% vs 30%, respectively).

Figure 5. PRISMA diagram for STEVIE[59] (reproduced from CS, page 108, Figure 12)



As for ERIVANCE, the ERG requested clarification from the company on the details of the subsequent treatments (if any) used by patients discontinuing vismodegib in STEVIE as they are potential confounders when considering the results for overall survival. However, the company replied that no information on subsequent treatments were captured in STEVIE or ERIVANCE and so the ERG is unsure whether any patients went on to receive subsequent treatments following vismodegib discontinuation. The ERG is thus unable to comment on what impact, if any, subsequent treatments may have had on the results of STEVIE and ERIVANCE.

4.2.2 Baseline characteristics

4.2.2.1 ERIVANCE

The baseline characteristics of patients enrolled in ERIVANCE are presented in Table 9 separately for the patients with laBCC and mBCC. There were minimal baseline characteristics presented in the CS and so the ERG requested further details at the clarification stage and has included the company's responses in Table 9. There were substantially more patients with laBCC than mBCC enrolled (n = 63 and n = 33, respectively) and more males than females with mBCC enrolled (73% and 27%, respectively). The ERG's clinical experts report that these differences are likely to be a natural reflection of clinical practice where you expect to see very few cases of mBCC compared to laBCC, and that patients with mBCC maybe more likely to be male. The clinical experts also reported that the population in ERIVANCE is, however, substantially younger than that expected in clinical practice as the median age in ERIVANCE was 62 years and in clinical practice patients are likely to be in their 70s. The ERG also considers it important to highlight that 21% of patients in ERIVANCE had Gorlin syndrome, which experts report is quite high compared to the prevalence in UK clinical practice. In addition, all the patients in ERIVANCE were of a white ethnic background and only 2% were enrolled from UK sites.

The ERG's clinical experts report that the UK population with BCC are typically but not exclusively white but the small number of UK patients in the study make it hard to draw any firm conclusions on the safety and efficacy of vismodegib in the UK population.

The ERG notes from the interim CSR for ERIVANCE (which was provided in response to a clarification question) that 49% of patients had more than one target lesion. The most common sites of laBCC target lesions were the scalp (28.6%), forehead (23.8%), and 'other' not further defined locations (30.2%). The lungs (66.7%), and lymph nodes (21.2%) were the most common sites for mBCC target lesions.

Table 9. Baseline characteristics of patients enrolled in ERIVANCE (Adapted from CS page 109, Table 22)

Baseline characteristic	**laBCC n=63**	**mBCC n=33**	**Total N=96**
Age, mean (SD); median (range)	61.4 (16.9); 62.0 (21 to 101)	61.6 (11.4); 62.0 (38 to 92)	NR
Gender, n (%) Male Female	 35 (56) 28 (44)	 24 (73) 9 (27)	 59 (61) 37 (39)
Race or ethnic background, White, n (%)	63 (100)	33 (100)	96 (100)
Enrolled at a UK site, n (%)	2 (6)	0	2 (2)
Gorlin syndrome, n (%)	20 (32)	0	20 (21)
Contraindications to surgery, n (%) Inoperable tumour Surgery inappropriate	 24 (38) 39 (62)	NA	NA
Prior radiotherapy, n (%) Yes Inappropriate or contraindicated	 13 (21) 50 (79)	NA	NA
Abbreviations: BCC, basal cell carcinoma; CS, company submission; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; SD, standard deviation.			

4.2.2.2 STEVIE

The baseline characteristics of patients enrolled in STEVIE are summarised in Table 10. Similar to ERIVANCE, minimal baseline characteristics were presented in the CS but the CSR was provided for STEVIE which enabled the ERG to review further baseline characteristics of potential importance. The median age in STEVIE was 72 years which clinical experts report is closer to what would be expected in UK clinical practice than the median age in ERIVANCE (62 years). In addition, there were substantially fewer patients with mBCC compared to with laBCC (96 and 1,119, respectively) as would be expected in clinical practice based on the incidence rates of laBCC and mBCC. In total only 3.1% of patients in STEVIE came from UK sites and 18.1% of patients in the whole study population had Gorlin syndrome. The number from UK sites is thus very low and, as it was an international study, it is difficult for the ERG to comment on the potential impact of this on the generalisability of the whole

trial results to the UK population. In addition, as for ERIVANCE, the ERG's clinical experts suggest that an incidence of 18.1% for Gorlin syndrome patients eligible for vismodegib in STEVIE is higher than expected in the UK. In the patients with laBCC, it was reported that 38.7% had baseline disease status that was considered inoperable, and surgery was medically contraindicated in 61.3% of patients.

The most frequent sites of disease were the head (74.9%) and trunk (21.9%) in patients with laBCC. In patients with mBCC, the most frequent sites of metastases were the lungs (65.6%), bone (32.3%) and lymph nodes (31.3%). The ERG's clinical experts report that these are in keeping with what would be expected in clinical practice although the number of patients with truncal laBCC is possibly higher than expected. The clinical experts reported that truncal BCC would usually be suitable for surgery or radiotherapy whereas lesions on the face are less likely to be suitable for these treatments. However, they also reported that the laBCC that were extensive multifocal superficial BCC, such as those that would be seen on the trunk of Gorlin patients are also more likely to be unsuitable for radiotherapy or surgery.

Table 10. Baseline characteristics of patients enrolled in STEVIE (Adapted from CS page 110, Table 23)

Baseline characteristic	laBCC (n=1,119)	mBCC (n=96)	Total (N=1,215)
Age, median (range)	72.0 (18 to 101)	67.0 (34 to 95)	72.0 (18 to 101)
Gender, n (%) Male	 634 (56.7)	 60 (62.5)	 694 (57.1)
Enrolled at a UK site, n (%)	NR	NR	38 (3.1)
ECOG score, n (%) 0 1 2	 662 (59.2) 316 (28.3) 138 (12.3)	 39 (40.6) 42 (43.8) 15 (15.6)	 701 (57.7) 358 (29.5) 153 (12.6)
Gorlin syndrome, n (%) Yes No	 214 (19.2) 899 (80.8)[a]	 5 (5.2) 91 (94.8)	 219 (18.1) 990 (81.9)[a]
Contraindications to surgery, n (%) Inoperable Surgery contraindicated	 433 (38.7) 686 (61.3)	 NA	 433 (35.6) 686 (56.5)
Prior radiotherapy, n (%) Yes No	 312 (27.9) 806 (72.0)	 59 (61.5) 37 (38.5)	 371 (30.5) 843 (69.4)

[a] Gorlin status not recorded for 6 patients
Abbreviations: BCC, basal cell carcinoma; CS, company submission; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; NR, not reported.

4.2.3 Description and critique of statistical approach used

4.2.3.1 ERIVANCE

The company reported that the null hypotheses for the primary analysis of ORR was that the ORR was 10% or less for mBCC with vismodegib and 20% or less for laBCC with vismodegib treatment.

Response rates of greater than 10% for mBCC and greater than 20% for laBCC were thus deemed to represent clinically meaningful benefits for patients. The company reported that these numbers were chosen based on there being no other therapeutic options for these patients and that aBCC is not known to spontaneously resolve. The ERGs clinical experts agree with the company that BCC is unlikely to resolve spontaneously and that patients eligible for vismodegib would be receiving palliative therapy as there are no other active therapies available at present. The magnitude of ORR was formally tested using one-sided exact binomial tests and 95% Blyth–Still–Casella exact confidence intervals calculated separately for laBCC and mBCC.

The sample size of 100 patients in ERIVANCE was chosen on the basis that it would enable the "adequate" detection of AEs and efficacy endpoints for vismodegib in aBCC. ERIVANCE was powered to have approximately 80% probability of rejecting the null hypothesis given a true ORR of 37% in the mBCC cohort (with 20 treated patients) and 34% in the laBCC cohort (with 80 treated patients). There were no planned interim analyses or stopping rules in ERIVANCE.

Duration of objective response was analysed only for responders in each cohort using the Kaplan–Meier method to estimate the median duration of objective response, and 95% confidence intervals calculated using the Brookmeyer and Crowley method. The responders without disease progression who had not died within 30 days of last exposure to vismodegib were censored at the time of the last tumour assessment.

The incidence of AEs was summarised by system organ class and preferred term with the maximum severity experienced by each patient used in the summary.

The HRQoL data captured through the SF-36 Health Survey (Version 2) and its associated subscales use at Day 1, Week 12, Week 24, and end of study or at the point of discontinuation were used to calculate the mean change from Day 1.

The efficacy analyses in ERIVANCE were performed using the efficacy-evaluable population which comprised of all treated patients who had a confirmed diagnosis of BCC from archival tissue or baseline biopsy as deemed by an independent pathologist. The safety analyses in ERIVANCE were performed using the all-treated patient population which comprised of all patients who received at least one dose of vismodegib.

Efficacy analyses were conducted separately for data from IRF assessment and that from investigator assessments although the 30-month follow-up analyses were based only on investigator assessments. The ERG also notes that the 12 and 30 month analyses were not pre-specified in the original protocol for ERIVANCE. The company provided a summary of the number of patients remaining on study at

the different analysis time-points but the ERG are unclear exactly how the 12 and 30-month follow-up analyses were selected and if it is related to the number of patients remaining in the study.

Table 11. Summary of analyses and data cut-offs for ERIVANCE (Adapted from CS page 115, Table 27)

Data cut-off date	26 November 2010[68]	28 November 2011[57]	30 May 2013[81]
Analysis time point	Primary analysis; 9 months after last patient enrolled	12-month follow-up	30-month follow up
% patients remaining on study	52.5%	27.9%	8.7%
Abbreviation: CS, company submission.			

4.2.3.2 STEVIE

The primary objective of STEVIE was to assess the safety of vismodegib in patients with laBCC or mBCC and there were no formal statistical hypothesis tests defined *a priori*. The original sample size was intended to be 150 patients but this was increased to around 1,200 to enable the AE incidence rate to be estimated to within 1.6 to 1.8% of the true adverse event rate, assuming an observed incidence of 10% (i.e. within a 95% Clopper–Pearson CI of 8.4 to 11.8) and a precision to estimate an AE occurring at a frequency of 1% to within 0.5 to 1% of the true adverse event rate.

The final analysis for safety and efficacy in STEVIE was planned to be performed when the later of the following occurred: the last patient on treatment developed progressive disease (as determined by the investigator) or unacceptable toxicity, withdrew consent, or died or the treating physician deemed the patient no longer benefited from treatment; or the study was terminated by the sponsor; or 12 months after the last dose of vismodegib in the last enrolled patient still on study. The six planned interim analyses for both safety and efficacy were planned to be when:

- first 75 patients enrolled have been treated for at least 3 months;
- first 150 patients enrolled have been treated for at least 3 months;
- first 300 patients enrolled have been treated for at least 3 months;
- first 550 patients enrolled have been treated for at least 3 months;
- first 800 patients enrolled have been treated for at least 3 months; and
- 1,200 patients enrolled have been treated for at least 3 months,
    - This last interim analysis was also planned to include the analysis of 500 enrolled patients who had been followed for at least 1 year.

The primary analysis for STEVIE as stated in Hansson *et al.* 2016 appears to correspond with the 6th interim analysis and is the analysis presented within the CS.

The primary outcome was the analysis of treatment-emergent AEs (TEAEs) and these were defined as AEs occurring between the first administration of study vismodegib and 30 days after the last dose.

TEAEs were also summarised for all patients and by disease cohort (laBCC and mBCC). Serious TEAEs and TEAEs were also captured and summarised.

For the efficacy outcomes of response and PFS patients were censored on the date of their last evaluable tumour assessment or last follow-up for progression of disease. A patient who died without a reported progression was considered as a PFS event on the date of death. For OS, patients were censored at the last date they were known to be alive or the time of first treatment with vismodegib if there was no post-baseline information.

Kaplan–Meier (KM) curves were used to generate survivor estimates for time-to-event endpoints, including PFS, OS, time to response, and DOR and estimates for the median time to event and the corresponding two-sided 95% confidence interval were calculated using the estimates for the other quartiles.

The Skindex-16 questionnaire for HRQoL was completed by patients with laBCC and patients with mBCC at selected sites at baseline, after Cycle 1, after Cycle 6, and at the end-of-treatment visit. A clinically meaningful improvement in HRQoL was defined as a decrease of ≥10 points from baseline.[85] Results from the Skindex-16 were tabulated and summarised through calculations of mean and median scores.

The MDSAI HRQoL data were collected at baseline and all subsequent visits including safety follow-up visits for up to 1 year in those patients with mBCC who enrolled following the implementation of protocol version 4. Results were summarised and tabulated with two separate analyses conducted according to the baseline score. A clinically meaningful change in MDASI score was estimated to be a 30% reduction in symptom severity and the company reported that this was based on evidence suggesting that a 3-point change on an 11-point numerical rating scale is meaningful.[86]

The analyses for AEs in STEVIE were done using the safety-evaluable population which was defined as all patients with documented exposure to vismodegib as determined by the return of the drug dispensed. The efficacy analyses in STEVIE were conducted for the efficacy-evaluable population which included all patients with documented exposure to vismodegib and as for the safety-evaluable population this was determined based on the return of drug dispensed. The safety and efficacy evaluable populations were thus comprised of the same patients. The ERG notes that the company's efficacy-analysis population in STEVIE was defined differently compared with in ERIVANCE and considers the definition in ERIVANCE to be more in line with an intention-to-treat analysis whereas the definition in STEVIE is closer to a per protocol analysis. The ERG thus considers it important to highlight that care should be taken when comparing the efficacy results from STEVIE and ERIVANCE.

4.2.4 Summary statement

In summary, the ERG considers that the company's systematic review of the literature followed recommended methodological practices. However, in the final scope issued by NICE, the comparator of interest was identified as best supportive care (BSC). The ERG notes that no trial level data were presented in the CS for BSC and that the company's search strategy would not have identified studies of BSC without vismodegib. This is a potential flaw in the company's systematic review.

Twelve studies identified in the systematic review met the company's inclusion criteria, although only five were presented in detail in the CS. The ERG considers the two studies that were used to gain the EU marketing authorisation for vismodegib, and that have been used to inform the economic model for this STA, to be the most relevant for the review of clinical effectiveness and so the focus of the ERG critique is on these two studies: ERIVANCE and STEVIE. ERIVANCE and STEVIE are both international multicentre, single arm studies of vismodegib in mixed populations of laBCC and mBCC adult patients with analyses presented separately for each population. The final scope issued by NICE specified the population of interest to be patients with symptomatic mBCC; or laBCC inappropriate for surgery or radiotherapy. The ERG considers the population in ERIVANCE and STEVIE to be relevant to the decision problem. The ERG also consider it important to highlight that STEVIE was designed primarily as a safety study although it also reported efficacy outcomes and it is still ongoing. The outcomes assessed in both ERIVANCE and STEVIE and presented in the CS are clinically relevant and address the decision problem as outlined in the final scope issued by NICE[1], with the exception of OS data for laBCC. The ERG considers that the company's discussion of the quality and validity of these trials in the CS was generally appropriate. The ERG considers both studies to be at a high risk of bias due to their observational nature and single-arm design. In addition, the ERG notes that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.

The ERG considers the baseline characteristics of STEVIE to be a closer match to that of UK patients likely to be treated with vismodegib, as the median age in ERIVANCE was much younger. The ERG also considers the number of patients with Gorlin syndrome in ERIVANCE and STEVIE to be higher than expected and that it is important to consider them as a separate subgroup, although only *post hoc* subgroup data from STEVIE are reported in the CS.

4.3 Clinical effectiveness results

4.3.1 ERIVANCE

The company presented efficacy results from the primary analysis, 12-month update and 30-month update in the CS (CS pages 118-119, Table 28). The ERG consider the 30-month data to be the most relevant to the decision problem and thus discusses only these data unless otherwise specified.

Table 12. Summary of clinical effectiveness data from ERIVANCE (Adapted from CS pages 118-119, Table 28)

Study arm	Primary outcomes (IRF-assessed) (data cut-off 26 November 2010)[68]			Outcomes from 12-month update (IRF-assessed) (data cut-off 28 November 2011)[57]			Further outcomes from 30-month update (investigator-assessed) (data cut-off 30th May 2013)[79, 81]		
	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	Patients with laBCC n=63	Patients with mBCC n=33	Total N=96	laBCC n=63	mBCC n=33	Total N=96
Response rate									
Objective response rate, n (%) [95% CI]	27 (43) [30 to 56]	10 (30) [16 to 48]	NR	30 (48) [36 to 61]	11(33) [19 to 52]	NR	38 (60.3) [47.2 to 71.7]	16 (48.5) [30.8 to 66.2]	54 (56.3) [45.7 to 66.4)]
Complete response, n (%)	13 (21)	0	NR	14 (22)	0	NR	20 (NR)	0 (0)	20 (NR)
Partial response, n (%)	14	10 (30)	NR	16 (25)	11 (33)	NR	18 (NR)	16 (NR)	34 (NR)
Stable disease, n (%)	24 (38)	21 (64)	NR	22 (35)	20 (60)	NR	15 (NR)	14 (NR)	29 (NR)
Progressive disease, n (%)	8 (13)	1 (3)	NR	8 (13)	1 (3)	NR	6 (NR)	2 (NR)	8 (NR)
Missing or NE, n (%)	4 (6)	1 (3)	NR	3 (5)	1 (3)	NR	4	1	5
Duration of response									
Median, months (range)	7.6 (1.0 to 12.9)	7.6 (2.1 to 11.1)	NR	9.5 (7.4 to 21.4)	7.6 (5.5 to 9.4)	NR	26.2 (9.0 to 37.6)	14.8 (5.6 to 17.0)	16.1 (9.5 to 26.2)
Tumour shrinkage									
n (%)	57 (NR)	24 (73)	NR			NR			
Progression-free survival									
Median, months (95% CI)	9.5 (7.4 to 11.9)	9.5 (7.4 to NE)	NR	9.5 (7.4 to 14.8)	9.5 (7.4 to 11.1)	NR	12.9 (10.2 to 28.0)	9.3 (7.4 to 16.6)	12.8 (9.5 to 26.2)
Overall survival									
Median OS, months (95% CI)	Data not mature	Data not mature	Data not mature	NE	24.1 (14 .3 to NE)	NR	NE (NE to NE)	33.4 (18.1 to NE)	NE (41.2 to NE)
1-year survival rate, % (95% CI)	91.6 (83.5-99.7)	75.5 (57.3-93.60	Not available	93.1 (86.6 to 99.6)	78.7 (64.7 to 92.7)	NR	93.2 (86.8 to 99.6)	78.7 (64.7 to 92.7)	NA

2-year survival rate, % (95% CI)	NA	NA	NA	85.4 (76.0 to 94.8)	60.3 (43.4 to 79.1)	NR	85.5 (76.1-94.8)	62.3 (45.4-79.3)	NA
Time to treatment discontinuation (reported as 'duration of treatment')									
Median, months (range)	9.7 (1.1 to 18.7)	10.0 (0.7 to 16.4)	NR	12.7 (1.1 to 30.6)	13.3 (0.7 to 24.8)	NR			NR
Duration of follow up									
Median, months (range) [95% CI]				21.7	22.4		39.1 (2.4 to 49.2) [37.8 to 40.3]	39.1 (6.7 to 43.4) [31.4 to 40.2]	39.1 (2.4 to 49.2) [37.8 to 39.6]
SF-36									
Mental component score, mean (95% CI) change from baseline at end of study, n=20	NR	NR	–3.80 (–10.55 to 2.96)	NR	NR	NR	NR	NR	NR
Physical component score, mean (95% CI) change from baseline at end of study, n=20	NR	NR	- 2.86 (–7.39 to 1.66)	NR	NR	NR	NR	NR	NR

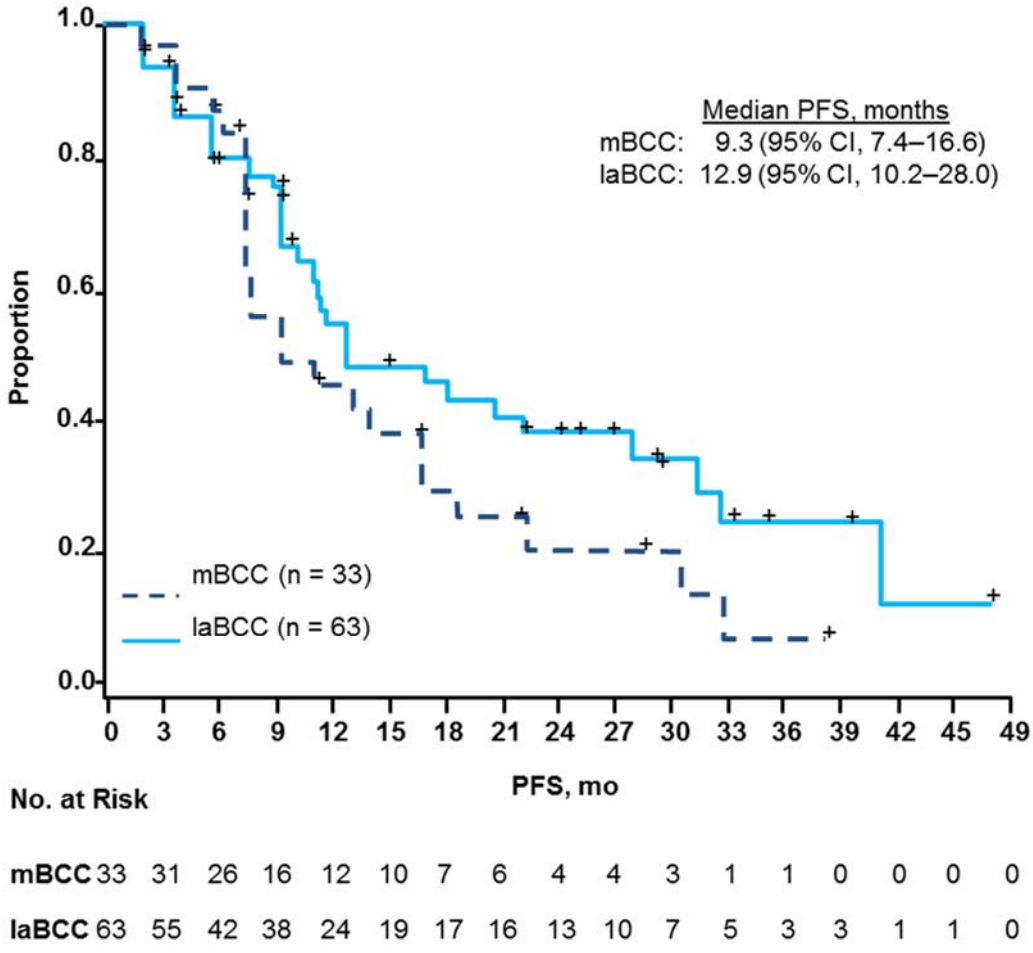
[a] Primary outcomes in ERIVANCE were from independent review; results from site investigators are also reported

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; CS, company submission; IRF, independent review committee; laBCC, locally advanced BCC; mBCC, metastatic BCC; NA, not applicable; NE, not evaluable; NR, not reported; OS, overall survival.

4.3.1.1 Progression-free survival

The ERG considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and so the data presented here should be interpreted with caution. Investigator assessed median PFS with vismodegib in the laBCC population was 12.9 months (95% confidence interval [95% CI]: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months, Figure 6). The ERG considers it important to note that the 95% CI for both the laBCC and mBCC populations are wide and so the point estimates are subject to a large amount of uncertainty. In addition, as the 95% CI of laBCC and mBCC are overlapping it is difficult to draw conclusions on the relative efficacy of vismodegib in the two populations. However, the median PFS is slightly longer in laBCC compared to in mBCC (12.9 months, and 9.3 months, respectively).

Figure 6. Kaplan-Meier plot for the 30-month investigator assessed PFS in ERIVANCE (reproduced from CS page 120, Figure 17)

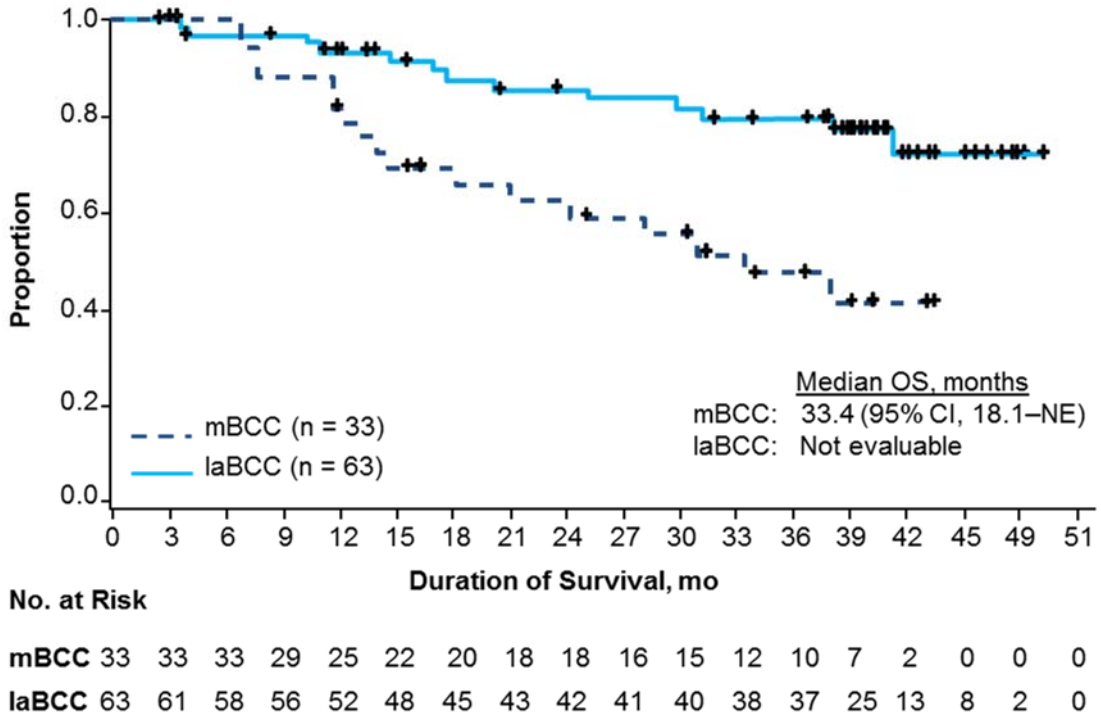


Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; PFS, progression free survival.

4.3.1.2 Overall survival

The ERG considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as OS and so the data presented here should be interpreted with caution. Investigator assessed median OS was not estimable for the laBCC population in ERIVANCE and so the only results available are for the mBCC population (Figure 7). The median OS for the mBCC patients in ERIVANCE was 33.4 months (95% CI: 18.1 months to not estimable [NE]). One-year and two-year survival rates were also reported for both the laBCC and mBCC populations; although the ERG notes that the one-year survival rates in the CS for the 30-month follow-up were transposed for laBCC and mBCC, and so the ERG has used the corrected values as confirmed by the CSR. The one-year survival for laBCC was 93.2% and the two-year survival rate had dropped slightly to 85.5%. In comparison the survival rates were lower for mBCC compared with laBCC with a greater drop between the first and second year (one-year survival 78.7%, and two-year survival 62.3% with mBCC).

Figure 7. Kaplan-Meier plot for the 30-month investigator assessed OS in ERIVANCE (reproduced from CS page 120, Figure 18)



Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; PFS, progression free survival.

4.3.1.3 Response rate

The investigator assessed ORR in ERIVANCE was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. The median duration of response

was 26.2 months for patients with laBCC and 14.8 months for patients with mBCC indicating that response is sustained for longer in patients with laBCC compared to those with mBCC.

4.3.1.4 Health-related quality of life

A summary of the SF-36 HRQoL data collected in ERIVANCE was provided in the CS with further details provided during clarification. The summary data provided in the CS were collected at the primary analysis and comprise of combined data from the laBCC and mBCC populations. The mean change from baseline in the mental component of the SF-36 was -3.80 (95% CI: -10.55 to 2.96), and -2.86 (95% CI: -7.39 to 1.66) for the physical component of the SF-36 (Table 13). It should be noted that each component is scaled from 0 to 100, with higher scores relating to higher or better HRQoL.

Table 13: Mental and physical component summary scores from SF-36 data collected in ERIVANCE (Adapted from CS page 211, Table 72)

Visit	N	Baseline	Value at visit	Change from baseline
Mental component				
Day 1	93	49.57 (11.57)	N/A	N/A
Week 12	82	49.24 (11.79)	51.44 (12.4)	2.20 (-0.22,4.62)
Week 24	75	49.38 (11.47)	51.67 (11.62)	2.29 (0.05,4.53)
End of study	20	49.90 (12.773)	46.11 (16.44)	-3.80 (-10.55,2.96)
Physical component				
Day 1	93	47.81 (9.907)	N/A	N/A
Week 12	82	49.14 (8.85)	47.89 (9.69)	-1.25 (-2.86,0.36)
Week 24	75	49.42 (8.70)	47.52 (9.87)	-1.90 (-3.75,-0.05)
End of study	20	45.72 (11.67)	42.85 (11.14)	-2.86 (-7.39,1.66)
Abbreviations: N/A, Not applicable; SD, Standard deviation.				

4.3.2 STEVIE

The company provide a summary of the efficacy data from the primary analysis of STEVIE using a data cut-off of 16th March 2015 in the CS (Table 14). All data reported in this report from STEVIE are based on this 16th March 2015 cut-off unless otherwise specified.

Table 14. Summary of clinical effectiveness data from STEVIE (Adapted from CS page 121, Table 29)

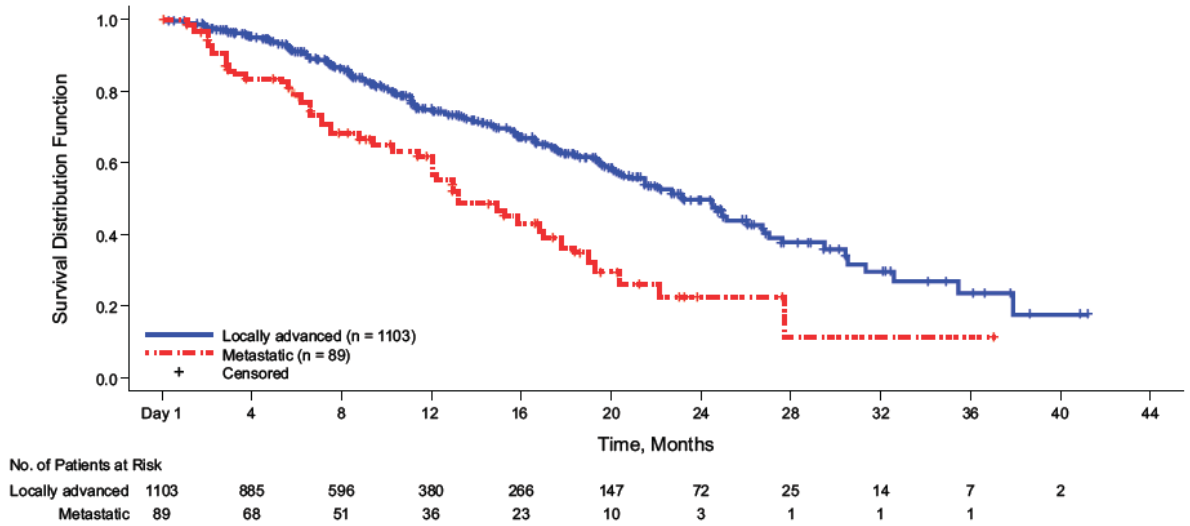
Study arm	Patients with laBCC n=1103	Patients with mBCC n=89	Total N=1192
Progression-free survival			
Median, months (95% CI)	23.2 [21.4 to 26.0]	13.1 [12.0 to 17.7]	22.1 [20.3 to 24.7]
	Outcomes among patients with measurable disease at baseline		
	n=1077	n=84	N=1161

Response rate			
Objective response rate, n (%) [95% CI]	738 (68.5) [65.66 to 71.29]	31 (36.9) [26.63 to 71.29]	769 (66.2) [63.43 to 68.96]
Complete response, n (%)	360 (33.4)	4 (4.8)	364 (31.4)
Partial response, n (%)	378 (35.1)	27 (32.1)	405 (34.9)
Stable disease, n (%)	270 (25.1)	39 (46.4)	309 (26.6)
Progressive disease, n (%)	21 (1.9)	9 (10.7)	30 (2.6)
Missing or NE, n (%)	48 (4.5)	5 (6.0)	53 (4.6)
Duration of response			
Median, months (95% CI)	23.0 (20.4 to 26.7)	13.9 (9.2 to NE)	22.7 (20.3 to 24.8)
Time to response			
Median, months [95% CI]	3.7 (2.9 to 3.7)	NE (5.5 to NE)	3.7 (3.5 to 3.7)
Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not evaluable.			

4.3.2.1 Progression-free survival

The ERG considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and so the data presented here should be interpreted with caution. The median PFS for patients with laBCC in STEVIE was 23.2 months (95% CI: 21.4 to 26.0) and 13.1 months (95% CI: 12.0 to 17.7) for patients with mBCC (Figure 8). The ERG notes that the PFS in STEVIE is substantially longer for laBCC patients compared to that seen in ERIVANCE (23.2 months vs 12.9 months, respectively). However, this is unlikely to be considered a statistically significant difference as the 95% CI for PFS in ERIVANCE includes the median PFS for STEVIE (ERIVANCE PFS 95% CI: 10.2 to 28.0 months).

Figure 8. PFS for patients with histologically confirmed disease in STEVIE (Reproduced from CS page 122, Figure 19)



4.3.2.2 Overall survival

Median OS was not estimable for either the laBCC or mBCC populations in STEVIE and the data are immature as only 9.0% of patients had died by the data cut-off date of 16th March 2015.

4.3.2.3 Response rate

The ORR in STEVIE was 68.5% (95% CI: 65.7% to 71.3%) in the laBCC population and 36.9% (95% CI: 26.6% to 71.2%) in the mBCC population. The ORR in STEVIE compared to in ERIVANCE was slightly higher for laBCC patients (68.5% and 60.3%, respectively) and slightly lower for mBCC patients (36.9% and 48.5%, respectively). Similar to for PFS, it is likely that the difference in ORR between ERIVANCE and STEVIE is unlikely to be considered statistically significant.

4.3.2.4 Health-related quality of life

Skindex-16

The Skindex-16 is a 16-item patient-completed questionnaire designed to measure QoL in patients suffering from skin disease and comprises of three domains: symptoms, emotions, and function. The 16 items are rated on a seven-point scale from zero (never bothered) to six (always bothered) and relate to the previous week. The Skindex-16 HRQoL data were reported in the CS as showing no clinically meaningful improvement defined as a decrease of ≥10 points from baseline) at any time point across all domains in patients with mBCC and the company reported that this was probably a result of the small sample size.

The Skindex-16 data for the laBCC population suggested clinically meaningful improvements in emotion scores with vismodegib (Figure 9). The differences were irrespective of gender, Gorlin status and lesion location. There were no clinically meaningful changes seen for functional scores (Figure 10) and there were no consistent changes seen for symptom scores (Figure 11) in the laBCC population. The company report that this could be a result of Skindex-16 being a dermatology focused instrument and thus does not detect other potentially important aspects of HRQoL that may be affected by vismodegib.

Figure 9. Change in emotional domain of Skindex-16 by subgroup in STEVIE (Reproduced from CS page 123, Figure 20)

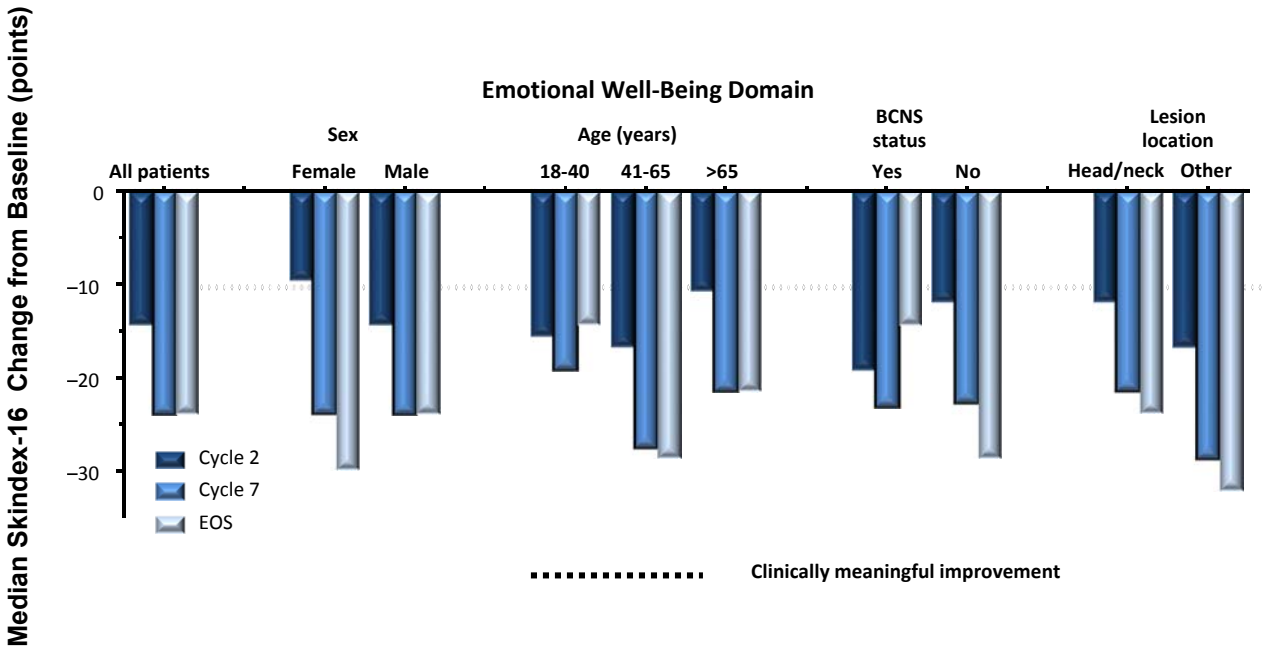


Figure 10. Change in function domain of Skindex-16 by subgroup in STEVIE (Reproduced from CS page 123, Figure 21)

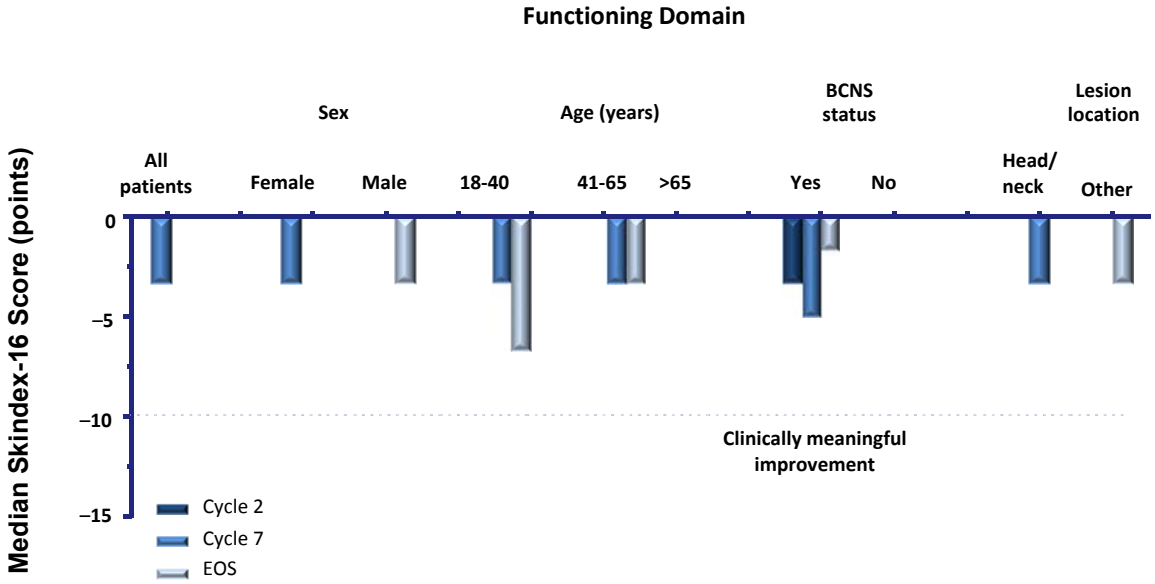
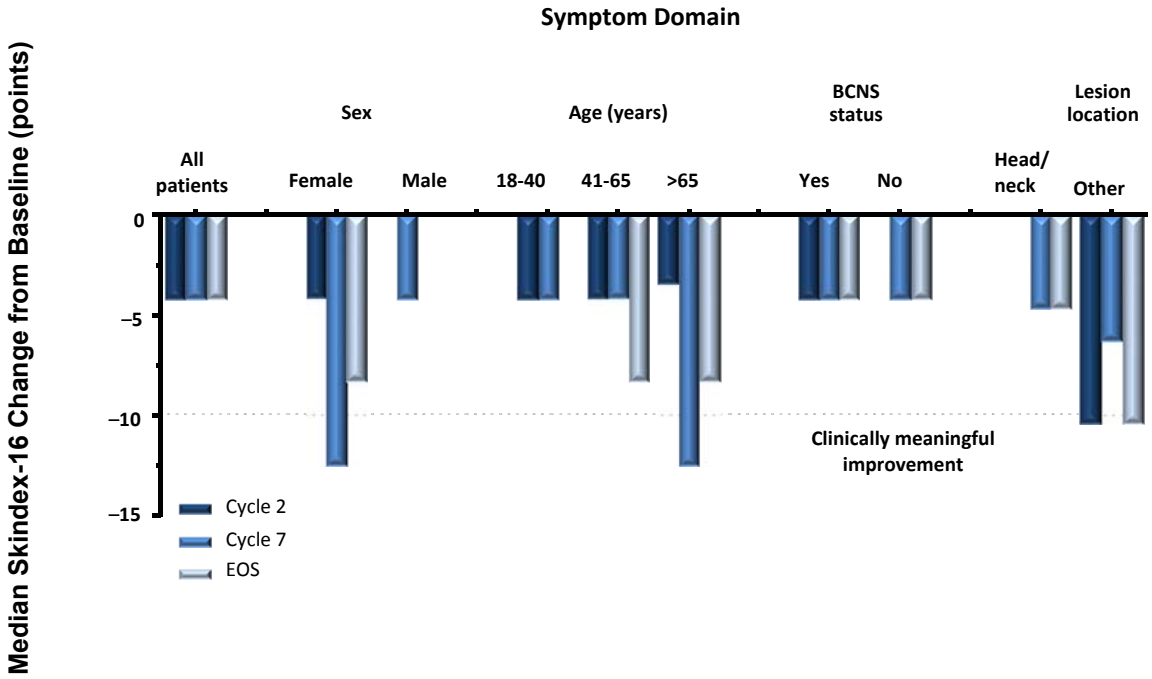


Figure 11. Change in symptom domain of Skindex-16 by subgroup in STEVIE (Reproduced from CS page 124, Figure 22)



MD Anderson Symptom Inventory (MDASI)

Patients with mBCC who were enrolled after the approval of Study Protocol Version 4.0 were asked to complete the MD Anderson Symptom Inventory (MDASI) in addition to the Skindex-16. The MDASI core instrument is a 19-item self-report questionnaire comprising of two scales, symptom severity and symptom interference. The baseline results of the MDASI revealed pain and fatigue were the worst symptoms experienced by mBCC patients (Table 15).

Table 15. Baseline MDASI scores for individual symptoms in mBCC (Adapted from CS page 209, Table 70)

MDASI symptom	**Baseline severity score (0 = Not Present; 10 = As Bad as You Can Imagine) Median (Range) (n = 15[a])**
Pain	3.0 (0-10)
Fatigue	4.0 (0-9)
Shortness of breath	2.0 (0-6)
Loss of appetite	0.0 (0-7)
Dry mouth	1.0 (0-9)
Coughing	0.0 (0-6)

a Baseline MDASI data were available for 15 of 17 eligible patients.
Abbreviations: MDASI, M.D. Anderson System Inventory.

There were 10 mBCC patients who had a baseline MDASI score of ≥ 4 at baseline and 6 (60%) of these achieved a greater than or equal to 30% reduction in disease-related symptoms according to the MDASI scale (Table 16).

Table 16. Patients with a baseline MDASI score ≥ 4 who achieved a ≥ 30% reduction in disease-related symptom (Adapted from CS page 209, Table 71)

	mBCC	Total
N	10	10
Yes	6 (60%)	6 (60%)
No	4 (40%)	4 (40%)
Notes: Baseline MDASI is defined as the last score prior to dosing within a given question. 30% reduction is at any on-treatment, post-baseline visit. A patient is considered to have had a 30% reduction if they had 4 points or more in a given question at baseline, and a 30% reduction in that question post baseline. Abbreviations: mBCC, metastatic basal cell carcinoma		

4.3.3 Subgroup analyses

The company reported that a subgroup analysis of patients with and without Gorlin syndrome in the STEVIE study had been presented at the ESMO 2016 congress.[87] There were 214 patients in the laBCC population and five in the mBCC population who met the eligibility criteria and had Gorlin syndrome. The results presented at ESMO were for the laBCC population, mBCC population, and whole trial population. The results discussed below and presented in the CS are for the whole trial population but the ERG notes that the results for the Gorlin subgroups in the laBCC and mBCC populations both show similar trends compared with the without Gorlin syndrome (non-Gorlin) subgroup. The baseline characteristics of the Gorlin syndrome subgroup compared with the non-Gorlin subgroup differed substantially with the Gorlin subgroup having:

- a lower median age (Gorlin syndrome: median 52.0 years [range 18 to 88]; non-Gorlin syndrome median 72.0 years [range 20 to 101]);
- a greater proportion of patients with an ECOG score of 0 (i.e. better performance status than non-Gorlin patients; ECOG Grade 0: 79.5% versus 53.0%, respectively); and
- a higher median number of target lesions (Gorlin syndrome median 3 [range 1 to 12], non-Gorlin median 1 [range 1-10]).

The investigator assessed ORR in the Gorlin syndrome subgroup was 81.7% which was higher than the 63% ORR in the non-Gorlin subgroup. The median duration of treatment was longer in the Gorlin syndrome subgroup compared to in the patients without Gorlin syndrome (12.3 months vs 8.1 months, respectively) and the median duration of response was also longer in the Gorlin subgroup (28.8 months, range 24.8 to NE, vs 18.5 months, range 16.4 to 20.8, respectively).

These results suggest that the Gorlin syndrome subgroup have a higher response rate and longer duration of response compared to non-Gorlin patients although the results are not statistically significant. These better responses could however be linked to the lower age and better baseline performance score of the Gorlin subgroup.

4.3.4 Adverse effects

4.3.4.1 ERIVANCE

The adverse events (AEs) reported in the CS from ERIVANCE were treatment-related adverse events (TRAEs) with aggregate data presented for the whole study population, not broken down for the laBCC and mBCC populations (Table 17). The ERGs clinical experts reported that this aggregate data for AEs was reasonable as there is no clinical expectation that the AEs would be different in people with laBCC compared to those with mBCC. The company did, however, provide data for serious adverse events (SAEs) and mortality for the separate laBCC and mBCC populations alongside the aggregate data.

The most frequently occurring AEs with vismodegib were muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%), and weight loss (51.9%). The highest Grade AE experienced by the majority of patients were either Grade 2 or 3 (71.2%) with 7.7% of the AEs resulting in death (8 patients). A Grade 3 or higher AE was experienced by over half of the study population (55.8%).

Table 17. Treatment-emergent AEs occurring in ≥10% of all treated patients in ERIVANCE (Adapted from CS page 131, Table 33)

AE, n (%)	**NCI CTCAE Grade (N = 104)**					
	Total	**1**	**2**	**3**	**4**	**5**
Any AE	104 (100.0)	-	-	-	-	-
Worst Grade AE experienced	-	8 (7.7)	37 (35.6)	37 (35.6)	13 (12.5)	8 (7.7)
Muscle spasms	74 (71.2)	45 (43.3)	23 (22.1)	6 (5.8)	0	0
Alopecia	69 (66.3)	49 (47.1)	20 (19.2)	NA	NA	NA
Dysgeusia	58 (55.8)	32 (30.8)	26 (25.0)	NA	NA	NA
Weight decreased	54 (51.9)	29 (27.9)	16 (15.4)	9 (8.7)	NA	NA
Fatigue	45 (43.3)	33 (31.7)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	29 (27.9)	19 (18.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	NA	NA
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	(3.8) 1	4 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	NA	NA

Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	NA	NA	NA
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	NA	NA	NA
Pruritus	11 (10.6)	8 (7.7)	2 (1.9)	1 (1.0)	NA	NA
Dyspepsia	11 (10.6)	8 (7.7)	3 (2.9)	0	NA	NA
Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.						

Serious adverse effects (SAEs) were experienced by 34.6% of patients in ERIVANCE with a higher proportion occurring in the laBCC population compared to in the mBCC population (39.4% versus 24.2%, respectively [Table 18]). The most frequently occurring SAEs were pneumonia and syncope (each in 4 patients [3.8%]); death and hip fracture (each in 3 patients [2.9%]); and cardiac failure, cellulitis, gastrointestinal haemorrhage, squamous cell carcinoma, pulmonary embolism, and deep vein thrombosis (each in 2 patients [1.9%]). The company reported that, "Medical review did not identify any pattern of association between SAE occurrence and duration of vismodegib treatment". The company also reported that it was possible that there were factors confounding the association between the AEs and vismodegib treatment although there were no further details on what they were in the CS.

Table 18. Serious adverse events by system organ class in ERIVANCE (Adapted from CS page 132, Table 34)

MedDRA System Organ Class	**laBCC (n=71)**	**mBCC (n=33)**	**All patients (N=104)**
All SAEs	28 (39.4)	8 (24.2)	36 (34.6)
Blood and lymphatic system disorders	1 (1.4)	0	1 (1.0)
Cardiac disorders	5 (7.0)	0	5 (4.8)
Eye disorders	1 (1.4)	1 (3.0)	2 (1.9)
Gastrointestinal disorders	4 (5.6)	0	4 (3.8)
General disorders and administration site conditions	5 (7.0)	2 (6.1)	7 (6.7)
Hepatobiliary disorders	1 (1.4)	0	1 (1.0)
Infections and infestations	8 (11.3)	1 (3.0)	9 (8.7)
Injury, poisoning and procedural complications	4 (5.6)	2 (6.1)	6 (5.8)
Metabolism and nutrition disorders	1 (1.4)	1 (3.0)	2 (1.9)
Musculoskeletal and connective tissue disorders	1 (1.4)	0	1 (1.0)
Neoplasms	6 (8.5)	1 (3.0)	7 (6.7)
Nervous system disorders	6 (8.5)	3 (9.1)	9 (8.7)
Psychiatric disorders	2 (2.8)	0	2 (1.9)
Renal and urinary disorders	1 (1.4)	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	3 (4.2)	1 (3.0)	4 (3.8)
Vascular disorders	4 (5.6)	1 (3.0)	5 (4.8)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

The company reported that there were 33 deaths in ERIVANCE (31.7%, [Table 19]) with more deaths in the mBCC population compared to the laBCC population (51.5% versus 22.5%). In addition, it was reported in the CS that none of the deaths in ERIVANCE were assessed by the investigator as related to vismodegib treatment and all patients who died during the study had significant pre-existing risk factors or co-morbidities at baseline.

Table 19. Summary of the deaths for all treated patients in ERIVANCE (Adapted from CS page 133, Table 35)

	laBCC (n=71)	mBCC (n=33)	All patients (N=104)
All deaths, n (%)	16 (22.5)	17 (51.5)	33 (31.7)
Time of death, n (%)			
Death on study drug	6 (8.5)	1 (3.0)	7 (6.7)
Death during survival follow up	10 (14.1)	16 (48.5)	26 (25.0)
Cause of death, n (%)			
Progressive disease	4 (5.6)	13 (39.4)	17 (16.3)
Adverse event	7 (9.9)	1 (3.0)	8 (7.7)
Other	5	3	8

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.

4.3.4.2 STEVIE

Treatment-emergent adverse events (TRAEs)

A total of 98% of patients in STEVIE experience a TEAE (defined as an AE occurring up until 30 days after the last administration of vismodegib) with 3.8% of the TEAEs resulting in death (Table 20). Similar to ERIVANCE, the TEAE data for STEVIE are presented for the whole trial population and for STEVIE they are only provided separately by Grade for Grade 3 and above AEs. The data for the laBCC and mBCC populations in STEVIE are limited to TEAEs leading to discontinuation, Grade 3 and above AEs, SAEs and deaths.

The most common TEAEs experienced in the whole trial (safety) population of STEVIE were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight loss (40.6%), and decreased appetite (24.9%). These AEs were similar to those seen in ERIVANCE. The ERG notes that Grade ≥ 3 TEAEs were reported in 43.7% of all patients in STEVIE which is lower than the proportion of people with Grade ≥ 3 TEAEs reported in ERIVANCE (55.8%).

Table 20. Summary of adverse events reported in >10% of patients in STEVIE (Adapted from CS page 136, Table 38)

Study arm	TEAEs, all patients N=1215	TEAEs leading to discontinuation		
		laBCC	mBCC	Total

		n=1119	n=96	N=1215
Any TEAE, n (%) All Grade 5 (fatal)	 1192 (98) 46 (3.8)	-	-	 380 (31) -
Ageusia, n (%) All Grade 3 Grade 4	 213 (17.5) 15 (1.2) 1 (<0.1)	 23 (2.1) - -	 0 - -	 23 (1.9) - -
Alopecia, n (%) All Grade 3 Grade 4	 747 (61.5) 15 (1.2) 1 (<0.1)	 39 (3.5) - -	 0 - -	 39 (3.2) - -
Arthralgia, n (%) All Grade 3 Grade 4	 124 (10.2) 4 (0.3) 0	 NR - -	 NR - -	 NR - -
Asthenia, n (%) All Grade 3 Grade 4	 291 (24.0) 22 (1.8) 1 (<0.1)	 35 (3.1) - -	 0 - -	 35 (2.9) - -
Decreased appetite, n (%) All Grade 3 Grade 4	 303 (24.9) 20 (1.6) 0	 37 (3.3) - -	 0 - -	 37 (3.0) - -
Diarrhoea, n (%) All Grade 3 Grade 4	 197 (16.2) 8 (0.7) 0	 NR - -	 NR - -	 NR - -
Dysgeusia, n (%) All Grade 3 Grade 4	 663 (54.6) 25 (2.1) 1 (<0.1)	 55 (4.9) - -	 0 - -	 55 (4.5) - -
Fatigue, n (%) All Grade 3 Grade 4	 201 (16.5) 19 (1.6) 1 (<0.1)	 25 (2.2) - -	 2 (2.1) - -	 27 (2.2) - -
Muscle spasm, n (%) All Grade 3 Grade 4	 807 (66.4) 94 (7.7) 1 (<0.1)	 84 (7.5) - -	 1 (1.0) - -	 85 (7.0) - -
Nausea, n (%) All Grade 3 Grade 4	 218 (17.9) 4 (0.3) 0	 12 (1.1) - -	 1 (1.0) - -	 13 (1.1) - -
Weight decreased, n (%) All Grade 3 Grade 4	 493 (40.6) 47 (3.9) 1 (<0.1)	 46 (4.1) - -	 1 (1.0) - -	 47 (3.9) - -
Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reported; TEAE, treatment-emergent adverse event.				

The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly higher proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively).

Table 21. Grade ≥ 3 Adverse events occurring in >2% patients in STEVIE (Adapted from CS page137, Table 39)

Adverse event	laBCC (n=1,119)	mBCC (n=96)	Total (N=1,215)
Total number of patients with ≥1 AE, n (%) Overall total number of events, n	484 (43.3) 949	47 (49.0) 85	531 (43.7) 1034
Muscle spasms	90 (8.0)	5 (5.2)	95 (7.8)
Weight decreased	44 (3.9)	4 (4.2)	48 (4.0)
Gamma-glutamyltransferase increased	28 (2.5)	2 (2.1)	30 (2.5)
Hypertension	23 (2.1)	4 (4.2)	27 (2.2)
Dysgeusia	25 (2.2)	1 (1.0)	26 (2.1)
Asthenia	23 (2.1)	1 (1.0)	24 (2.0)
Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.			

Hypertension was reported in the CS to be the only Grade ≥ 3 TEAEs occurring in >2% of patients that wasn't previously known to be associated with vismodegib treatment. The company reported that 70% of the patients had hypertension at baseline and only 22% of the Grade ≥3 hypertension TEAEs were deemed by the investigator to be related to vismodegib. The company also reported that the 6 patients with investigator assessed treatment related hypertension of Grade ≥ 3 all had confounding factors based on medical review including age, hypocholesterolaemia, and/or obesity.

Serious adverse events (SAEs)

SAEs were reported in 23.2% of patients with laBCC and 30.2% of patients with mBCC. The most frequently reported SAEs in patients with laBCC were pneumonia (1.5%), squamous cell carcinoma of the skin (SCC, 1.0%) and general physical health deterioration (1.0%). No SAE occurred in more than one patient in the mBCC population. The company reported that 6.8% of all patients experienced a SAE that was deemed by the investigator to be related to vismodegib.

Table 22. SAEs occurring in ≥0.5% patients in STEVIE (safety population) (Adapted from CS page 138, Table 40)

MedDRA Preferred Term	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Total number of patients with ≥1 AE, n (%) Overall total number of events	260 (23.2) 401	29 (30.2) 40	289 (23.8) 441
Pneumonia	17 (1.5)	1 (1.0)	18 (1.5)
Squamous cell carcinoma of skin	11 (1.0)	1 (1.0)	12 (1.0)
General physical health deterioration	11 (1.0)	1 (1.0)	12 (1.0)
Fall	9 (0.8)	0	9 (0.7)

Myocardial infarction	8 (0.7)	1 (1.0)	9 (0.7)
Gastroenteritis	5 (0.4)	1 (1.0)	6 (0.5)
Hip fracture	6 (0.5)	0	6 (0.5)
Syncope	6 (0.5)	0	6 (0.5)

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

Deaths

There were 110 deaths (9.1%) reported for patients on study or in follow-up in STEVIE by the 16th March 2015 data cut-off, and 8.2% of these were in laBCC patients and 18.8% in mBCC patients (Table 23). The ERG notes from Table 23 that there were four times as many deaths due to AEs compared to the number of deaths from disease progression. AEs were recorded as the primary cause of death in 71 patients although only 46 patients (3.8%) experienced a Grade 5 (fatal) TEAE (53 events). There were 25 deaths due to non-TEAEs (i.e. did not occur between first dose of vismodegib and 30-days following treatment discontinuation). Vismodegib was considered by the investigator to be related to the deaths of 7 patients (myocardial infarction [n = 2]; pancreatitis [n = 1], pulmonary embolism [n = 1], ischemic stroke [n = 1], cardiorespiratory arrest [n = 1], and renal failure [n = 1]). A total of 83.0% (44 of the 53) of the Grade 5 TEAEs were considered by the investigator to be unrelated to vismodegib.

Table 23. Summary of deaths in STEVIE (safety population) (Adapted from CS page138, Table 41)

Status	laBCC (n=1,119)	mBCC (n=96)	Total (N=1,215)
Number of patients who died, n (%)	92 (8.2)	18 (18.8)	110 (9.1)
Primary reason for death, n (%)			
Adverse event	65 (5.8)	6 (6.3)	71 (5.8)
Disease progression	15 (1.3)	12 (12.5)	27 (2.2)
Other[a]	12 (1.1)	0	12 (1.0)

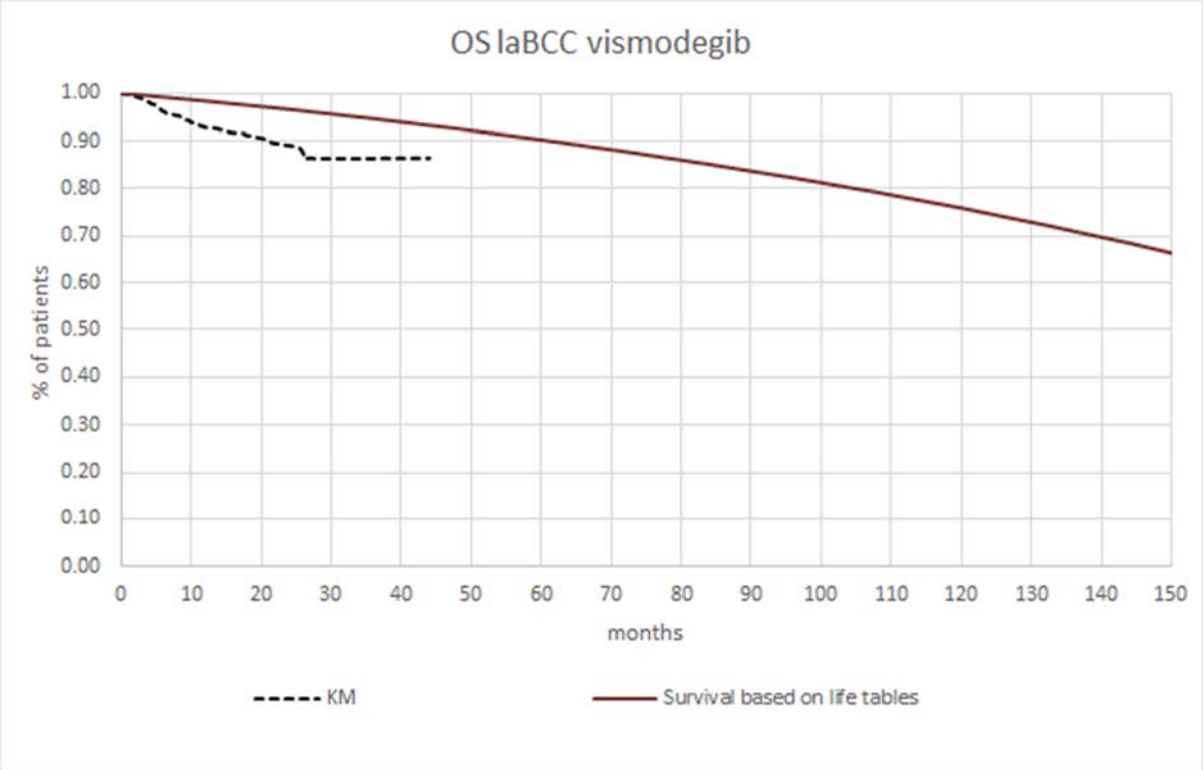
[a] Reasons for "other" included "unknown," "natural causes," "cardiac decompensation," "general state alteration," "deterioration of general state," "clinical deterioration taking into consideration patient's age," "old age," and "disease progression of mediastinal SCC

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; SCC, squamous cell carcinoma.

The ERG's clinical experts reported that patients with laBCC are unlikely to die as a result of laBCC. However, the ERG notes that the mortality rate of laBCC patients in STEVIE was higher than that seen in life tables for the UK general population (Figure 12). The ERG also notes that patients with BCC are likely to be at increased risk of death from other medical conditions including others which are related to sun-exposure such as melanoma and SCC. In addition, the ERG notes that only 3% of the population of STEVIE were from the UK and it is not clear where the remaining 97% of patients were recruited from. These factors may explain the observed increase in mortality in laBCC patients compared to the mortality rates seen in the UK general population. However, as all patients in the STEVIE study

received vismodegib, the ERG cannot rule out the possibility that vismodegib may increase mortality in laBCC patients. The ERG considers it important to note that 5.8% of vismodegib treated patients in STEVIE died due to an AE, albeit not necessarily considered by the investigator to be related to vismodegib treatment.

Figure 12. Kaplan Meier plot of deaths due to any cause during STEVIE compared to the background mortality rate for the overall population in the UK



Muscle spasm

Muscle spasm was the most commonly occurring AE in both STEVIE and ERIVANCE, affecting 66.4% and 71.2% of patients, respectively. Muscle spasm led to treatment discontinuation in 7% of patients in STEVIE. An exploratory analysis was conducted to identify baseline characteristics that could be related to the development of muscle spasm and the effects of vismodegib treatment interruption on muscle spasm using data from STEVIE. Sixteen baseline prognostic factors were chosen (Table 24) and assessed using logistic regression univariate and multivariate analyses.

Table 24. Prognostic factors for muscle spasm in STEVIE (Adapted from CS page 140, Table 44)

Type of prognostic factor	Prognostic factor
Demographic factors	Age Sex
Physical findings at baseline	BMI: grouped according to WHO guidelines

	ECOG PS
Tumour-related factors	Type of BCC (laBCC, mBCC) Gorlin syndrome
Biochemical and metabolic factors at baseline	Hyponatraemia Hypokalaemia Hypercreatinaemia Hyperbilirubinaemia Anaemia
Medical history at baseline	Diabetes Hypothyroidism
Concomitant medications at baseline	Statins Fibrates Diuretics
Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; CS, company submission; ECOG PS, Eastern Cooperative Oncology Group performance status; laBCC, locally advanced BCC; mBCC, metastatic BCC; WHO, World Health Organization.	

The results of the exploratory univariate and multivariate analyses suggested that the largest decrease in odds of muscle spasm while receiving vismodegib treatment occurred in older patients (≥70 years) and those with an ECOG PS ≥2. The largest increase in odds occurred in patients with increased BMI (obesity). In addition, Gorlin syndrome was associated with increased odds of muscle spasm in the univariate analysis.

Adverse events of special interest

There were seven AEs that were identified as potential risks associated with vismodegib treatment, and so they were analysed as part of the additional pharmacovigilance requirements specified in the Risk Management Plan for STEVIE. The seven AEs were:

- irregular menses/amenorrhoea;
- second primary malignancies (SPMs);
- skin squamous cell carcinoma (SCC);
- sudden death;
- keratitis;
- fractures; and
- venous thromboembolic events (VTEs).

The results of the analyses for these AEs are discussed briefly here.

There were 64 female patients at baseline who had menses in STEVIE and 28% of these experienced irregular menses or amenorrhea recorded as a TEAE. The company reported that there was, however, insufficient medical detail to enable the causality of the irregular menses/amenorrhea in these patients to be determined.

SPMs (excluding SCC) occurred in 2.6% of patients with only two of the 37 events investigator assessed as related to vismodegib. SCC occurred in 4.2% of patients with 60 events reported in 51 patients. The company reported that the majority of patients with SCC had risk factors and there was also a history of SCC in 35% of the patients who went on to develop SCC. The SCC completely resolved with no additional sequelae in 68.6% of patients by the data cut-off for this analysis although three patients (5.9%) had died as a result of SCC. The three SCC deaths were all deemed to be unrelated to vismodegib by the investigator as the patients had concurrent medical histories or other confounding factors.

Sudden death occurred in 2 patients (0.2%) with neither case considered by the investigator to be related to vismodegib.

Keratitis/ulcerative keratitis was reported in 10 patients (0.8%) and 80% of these were Grade 1 or 2 with the remaining 20% Grade 3. The keratitis resolved without sequelae in 70% of cases and 30% were investigator-assessed as related to vismodegib.

A fracture TRAE occurred in 36 patients (3.0%) with 39 fractures reported. The majority of the patients with a fracture TRAE were female (63.9%) and over 50 years old (72.2%), which are known risk factors for fracture development. The company reported that medical histories of 80.6% of the fracture patients confounded the assessment and attribution of the fracture TEAEs to vismodegib.

There were 12 TEAEs of VTE in 10 patients (0.8%) and these included deep vein thrombosis (n = 4) and pulmonary embolism (n = 3). Seven of the 12 events were assessed as serious and one patient had a Grade 5 (fatal) pulmonary embolism (PE). Two of the 12 events were considered by the investigator to be related to vismodegib treatment (a Grade 4 PE and the Grade 5 [fatal] PE). The company also reported that 90% of the patients who had a TEAE of VTE had risk factors confounding the assessment of causality.

The ERG considers the results of the analyses for these seven AEs of special interest to be inconclusive as patients generally had risk factors for the AE of interest. Further data on the safety of vismodegib is required to enable a more conclusive assessment of potential relationships between vismodegib treatment and any individual AE.

4.4 Landmark analysis

STEVIE and ERIVANCE were both single arm studies, and because no studies with a suitable comparator arm were identified in the systematic literature review there was no direct evidence available for the comparison of vismodegib with BSC. As a result, a landmark analysis was chosen by the company to enable the comparison of vismodegib with BSC in the CS. In the landmark method used

by the company, a Cox regression model with covariate adjustment for age and ECOG status at baseline was used to estimate the relative effect of non-responders versus responders for PFS and OS. The ERG also notes that the company preferred the use of a common treatment effect for laBCC and mBCC in its primary analysis (i.e. aBCC). The survival curves for the whole vismodegib population from STEVIE were used to estimate survival curves for BSC in the economic model using the hazard ratios estimated in the landmark approach. The landmark approach does not replace the randomisation in an RCT; it is used to generate estimates to inform comparative efficacy in the absence RCT data. The landmark analysis presented by the company to inform the comparison of vismodegib and BSC is based entirely on the use of a single arm interventional study and so constitutes observational data. The results of any analyses using the landmark approach should be considered low quality evidence. In addition, the landmark analysis estimates should be considered to have high uncertainty when extrapolating their results to inform the vismodegib versus BSC comparison in the economic model (Section 5). The ERG also considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS, and so the data presented from the landmark analysis should thus be interpreted with caution.

Prior to settling on a landmark analysis, the company considered using a matched adjusted indirect comparison (MAIC). This approach requires data on patients in the same population of interest who have received BSC as opposed to vismodegib therapy. The company deemed this approach to be unfeasible, "because of data limitations". The company discusses the unsuitability of using the eight patients that received BSC as their first treatment after laBCC diagnosis from RONNIE[53], a multi-centre retrospective chart review (Box 10), for an MAIC. However, no systematic literature review was conducted to identify any other potential studies suitable to use in an MAIC. The company reported that the definition of time to progression and death was different in RONNIE compared to in STEVIE. In RONNIE it was assessed from first diagnosis of laBCC rather than date of first treatment. In addition, in RONNIE progression was based on investigator assessment and defined as, "any increase in the sum of the sizes (longest diameters) or number of existing target lesions; recurrence of the primary lesion; and/or increase in the extent of the disease as noted by a physician in the medical record", whereas RECIST v1.1 criteria were used in STEVIE. The company reported that there were also differences in the follow-up amongst the patients in RONNIE which would make it difficult to analyse time-to-event data. The ERG considers that using the eight patients from RONNIE[53] would be associated with high uncertainty due to the small starting sample size. In addition, there are differences between RONNIE and STEVIE that would potentially confound the results of any analysis. The ERGs clinical experts were unable to cite any BSC studies in aBCC that would be suitable for use in an MAIC with

vismodegib. However, in the absence of a systematic literature review to identify BSC studies in aBCC, the ERG are unable to provide further critique on the suitability or unsuitability of an MAIC approach.

The company also considered analysing the relative efficacy in the Tang *et al.*[88] RCT of vismodegib versus placebo in 42 Gorlin syndrome patients with surgically eligible BCC, and applying it to the clinical data collected in the STEVIE study. However, the company reported they were unable to gain access to the complete Tang *et al.* dataset. The ERG notes that response rate, PFS and OS were not outcomes of interest specified in the protocol for the Tang *et al.* study[89], although disease progression and deaths were recorded as part of the study assessments and reasons for discontinuation. Deaths were also captured as part of the adverse events in the study. However, there was no PFS or OS data reported in the available publications of the Tang *et al.* study, and so the ERG agrees with the company that access to additional unpublished data would have been required. In addition, the ERG considers the Tang *et al.* study to be in a different population to STEVIE. This is because the patients in Tang *et al.* were required to have had at least 10 surgically eligible BCC in the two years prior to study entry whereas for entry in to STEVIE the patient was required to be unsuitable for surgery. There was also no minimum number of BCC required for entry into STEVIE. The ERG considers it to be unclear from the Tang *et al.* publication whether any patients had aBCC, so potentially they were also a less severe population than STEVIE. The ERG notes that the use of the Tang *et al.* study efficacy would have required the assumption that the relative efficacy of vismodegib and BSC is irrespective of Gorlin status if it was applied to the whole STEVIE population, which comprised of 82% non-Gorlin syndrome patients. In summary, the ERG agrees that the company would have been unable to perform an MAIC using the Tang *et al.*[88] study given the limited data available to them.

4.4.1 Landmark method

STEVIE was selected over ERIVANCE to provide the clinical data used to generate the responder versus non-responders HRs, partly due to it having a much larger patient population compared to ERIVANCE, and because it was considered more reflective of UK clinical practice. The company decided not to pool the data from STEVIE and ERIVANCE because of the differences in patient characteristics between the two studies. The ERG agrees with the company's decision to use only data from STEVIE for generating the estimates of OS and PFS for responders versus non-responders in their landmark analysis.

Non-responders

The classification of patients as a responder or non-responder was affected by the time point chosen as the landmark, with the landmark being the time onwards from which response was assessed with all

events prior to the landmark censored. The company reported that to minimise the bias introduced in the analysis, all patients who experienced the event of interest before the landmark were excluded from the analysis. However, this resulted in a different definition of responders and non-responders for the analysis of PFS compared to for the analysis of OS (Table 25). For PFS, non-responders included patients who had not progressed or died and who had stable disease as their best response until the landmark. Non-responders for OS included patients who had not died and who had either stable disease or progressive disease as their best response until the landmark. The company's rationale for this approach is provided in Box 14 but relates only to mBCC, and so the ERG considers it does not provide justification for using the same approach for the laBCC population. In addition, the ERG considers it important to highlight that it results in different responder and non-responder populations for the resulting OS and PFS HRs thus limiting the comparability and extrapolation of the results within the aBCC populations of interest.

Table 25. Definition of non-responders for the estimation of hazard ratios (Adapted from CS page 199, Table 66)

	Overall survival	Progression-free survival
Locally advanced	SD, PD (death until landmark excluded)	SD (PD & death until landmark excluded)
Metastatic	SD, PD (death until landmark excluded)	SD (PD & death until landmark excluded)

Abbreviations: CS, company submission; PD, progressed disease; SD, stable disease.

Box 14. Company's rationale for the use of different definiitons of non-responders for OS and PFS (CS page 198, Section 5.3.5)

> The exclusion of patients who progressed or died for both outcomes was deemed inappropriate because it would have left only patients with stable disease in the group of non-responders for both outcomes, and stable disease can be considered a sign of response in metastatic patients. The inclusion of metastatic patients who actually show signs of response would lead to an underestimation of the effect of response, and consequentially of the relative effects of vismodegib versus BSC. This underestimation is particularly pronounced in the estimation of OS hazard rates, which are much higher in metastatic patients.

Abbreviations: BSC, best supportive care; CS, company submission; OS, overall survival; PFS, progression-free survival.

Landmark

The choice of landmark should be done prospectively and based on a clinically meaningful time point to prevent the results from the landmark being used to inform the landmark chosen. However, the landmark in the CS was chosen retrospectively. The company's rationale for their choice of a 6-month landmark for their primary analysis was that it, "allowed for at least two assessments of all patients regardless of treatment duration". This is because in STEVIE study visits were planned to occur every 28 days (± 5 days) with safety follow-up visits at 1 month, 3 months, 6 months, 9 months, and 12 months

after the last dose of vismodegib. At the 6-month landmark all patients should have received the 1 and 3-month safety follow-up, even if they have discontinued study drug prior to the first 28-day follow-up. In their response to the clarification questions, the company reported that the median time to first confirmed response (investigator assessed complete or partial response) was 2.78 months (95% CI: not reported) for the 746 responders (efficacy evaluable patients with measurable disease status at baseline and histologically confirmed disease) in the laBCC population and 2.73 months (95% CIs not reported) for the 33 responders in the mBCC population. The mean time to first confirmed response for the same groups of patients were 3.40 months for laBCC and 3.44 months for mBCC (95% CIs not reported). The mean and median results suggest that a 6-month rather than a 3-month landmark is suitable for both the laBCC population and the mBCC population. In this specific example, the landmark needs to be late enough that most patients will have responded, but not so late that most patients in the non-responder group have already had the event of interest (i.e. progressed or died). Similarly, the landmark should be early enough so that most patients have not had the event of interest, but not so early that a high proportion of late responders are misclassified (and so analysed) as non-responders after the landmark. The choice of a 3-month landmark is thus likely to be too early as it is close to the median time to first response of 2.76 months and is less than the mean of 3.40 months for the combined aBCC population. As such a 3-month landmark is likely to misclassify a large proportion of subsequent responders as non-responders and thus overestimate the efficacy for non-responders. A 6-month landmark would thus appear to be more appropriate as it exceeds the mean and median time to first confirmed response.

Table 26 summarises the number of responders after the landmark in the non-responders group for the 3-month landmark and 6-month landmark using the company's preferred definition of non-responders. The proportion of responders after the landmark is lower at the 6-month landmark compared with the 3-month landmark, which adds further support to the selection of the 6-month landmark. The ERG's clinical experts reported that they would expect to see a treatment response with vismodegib for both laBCC and mBCC patients, on average, by 3-months. The ERG thus considers the data and clinical expert opinion supports the company's choice of a 6-month landmark for their primary analysis. The ERG notes that the company also conducted a scenario analysis using a 3-month landmark with results presented in the CS for both the 3 and 6-month landmarks.

Table 26. Number of responders/non-responders at landmark, who respond thereafter (Adapted from CS page 203, Table 68)

	3-month landmark		6-month landmark	
	Non-responders	**Response after landmark**	**Non-responders**	**Response after landmark**
Progression-free survival				

Locally advanced	493	294	213	102
Metastatic	50	14	31	6
Overall survival				
Locally advanced	545	295	274	102
Metastatic	61	14	39	6
Abbreviation: CS, company submission.				

Cox proportional hazard regression model

A semi-parametric Cox proportional hazard (PH) model was used to estimate the HRs for responders versus non-responders, however, it is important to note that it assumes proportional hazards hold between responders and non-responders (Section 5). The ERG notes that the HRs produced by the landmark approach are different at 6-months compared to 3-months and so do not provide evidence in support of proportional hazards. This potentially limits the applicability of the 6-month landmark analysis results in the economic model to only those patients defined at the 6-month landmark. The company reported that the validity of the assumption of PH could be, "assessed using a plot of the log cumulative hazard over log time for different values of independent variables, in this case an indicator of non-response". The results of the company's assessment of PH for the analyses of OS and PFS are presented in Box 15.

Box 15. Company's assessment of proportional hazards for the analysis of OS and PFS (CS page's 200-201, Section 5.3.5)

The proportionality assumption is deemed to hold if the log cumulative hazard curves for two values of an explanatory variable x are parallel. For PFS, the curves for responders and non-responders are generally parallel or overlap regardless of the landmark. For OS, the log cumulative hazard curves exhibit deviations from a parallel trend. The OS estimates are more uncertain than the PFS estimates because few events were observed. In addition, the diagnostic plots underline the low number of events observed in the group of metastatic patients. This low number of events leads to considerable uncertainty in the hazard ratio derivation and questions the use of an interaction term for the estimation of heterogeneous effects of response in laBCC and mBCC patients.
Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; OS, overall survival; PFS, progression-free survival.

The company reported that to account for the uncertainty in the HR for OS they used a common effect for both laBCC and mBCC patients with covariate adjustment for ECOG status and age in their primary analysis. The company also reported in the CS that an interaction term was used to estimate the HRs separately for laBCC and mBCC patients. However, no further details on the methodology for the use of the interaction term were provided in the CS, and so the ERG is unable to critique its suitability. The Cox PH model assumes that differences between individuals are the result of a proportional shift in the hazard function. The non-randomised method in which patients were selected as responders or non-

responders was likely to result in imbalances in prognostic factors between the two groups, and so the company included covariates in the model to adjust for imbalances in ECOG status and age. The company reported in the CS that, "ECOG status and age were selected because they are known predictors of progression-free and overall survival in skin cancer.[90, 91]" The ERG requested clarification from the company on their approach to the selection of these covariates and the company's response was that it was not a systematic approach (Box 16).

Box 16. Company's methodology for the selection of covariates (Company response to CQ's page 25, B10c)

No systematic approach was taken in the selection of the covariates. We included two clinically relevant prognostic factors (age and ECOG).[90, 91] No exclusion of covariates based on significance was performed in order to have a single consistent model across the different analysis (two endpoints, PFS and OS; two landmarks, 3 and 6 months and two cohorts, laBCC and mBCC).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; OS, overall survival; PFS, progression-free survival.

The ERG is concerned that other important potential covariates may have been omitted from the model and is unsure of the likely impact of these potential omissions on the overall results. The ERG's clinical experts reported that the presence of Gorlin syndrome, nerve infiltration, and the site of the target lesion are a few potential prognostic indicators in BCC that should have been considered as covariates in the model. In response to the ERG's clarification request the company provided an analysis including a covariate adjustment for Gorlin syndrome; the results of this analysis will be discussed in Section 4.4.2. The company also presented an unadjusted analysis in the CS where no covariates were applied.

4.4.2 Landmark analysis results

The company provided baseline characteristics for the responder and non-responder populations in response to a clarification question and the ones which relate to the 6-month landmark analyses where only patients with survival or PFS of at least 6 months were included, are presented in Table 27. These baseline characteristics are only applicable for the 6-month landmark PFS results presented in Table 28, and the results presented in Table 29, and Table 30.

The baseline characteristics of the responder and non-responders at the 6-month landmark presented in Table 27 suggest there is a higher proportion of patients with more than one lesion, and with Gorlin syndrome in the responder group compared to the non-responder group. The ERG considers this to highlight the importance of including Gorlin syndrome as a covariate in the analysis, and that number of target lesions at baseline should also ideally have been included as a covariate. In addition, the

responders group had a slightly higher median age at baseline, and a higher proportion of people with ECOG status ≥ 1 compared to the non-responders (Table 27). This highlights the importance of including the covariate adjustment for age and ECOG status in the landmark analyses.

Table 27. Baseline characteristics for responders and non-responders at 6-month landmark for patients with OS and PFS of 6-months (Company clarification response Question A2)

		Responders			**Non-responders**		
		mBCC (N = 32)	**laBCC (N = 523)**	**All Patients (N = 555)**	**mBCC (N = 31)**	**laBCC (N = 213)**	**All Patients (N = 244)**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Sex	Male	18 (56.3%)	293 (56.0%)	311 (56.0%)	20 (64.5%)	121 (56.8%)	141 (57.8%)
Number of target lesions	1	11 (34.4%)	234 (44.7%)	245 (44.1%)	6 (19.4%)	118 (55.4%)	124 (50.8%)
	2	7 (21.9%)	150 (28.7%)	157 (28.3%)	11 (35.5%)	52 (24.4%)	63 (25.8%)
	3	7 (21.9%)	36 (6.9%)	43 (7.7%)	7 (22.6%)	11 (5.2%)	18 (7.4%)
	3+	6 (18.8%)	99 (18.9%)	105 (18.9%)	4 (12.9%)	17 (8.0%)	21 (8.6%)
Race	White	32 (100%)	358 (68.5%)	390 (70.3%)	28 (90.3%)	151 (70.9%)	179 (73.4%)
	Non-white	0	165 (31.5%)	165 (29.7%)	3 (9.7%)	61 (28.6%)	64 (26.2%)
ECOG performance status	Grade 0	16 (50.0%)	332 (63.5%)	348 (62.7%)	14 (45.2%)	131 (61.5%)	145 (59.4%)
	Grade 1	14 (43.8%)	131 (25.0%)	145 (26.1%)	11 (35.5%)	62 (29.1%)	73 (29.9%)
	Grade 2	2 (6.3%)	59 (11.3%)	61 (11.0%)	6 (19.4%)	20 (9.4%)	26 (10.7%)
Gorlin syndrome	YES	4 (12.5%)	130 (24.9%)	134 (24.1%)	1 (3.2%)	34 (16.0%)	35 (14.3%)
	NO	28 (87.5%)	392 (75.0%)	420 (75.7%)	30 (96.8%)	177 (83.1%)	207 (84.8%)
Time from diagnosis to dose (years)	N	32	520	552	31	211	242
	Mean	13.35	12.93	12.96	11.25	12.12	12.01
	SD	11.98	12.49	12.45	7.64	10.83	10.47
	Median	10.34	8.83	8.93	10.42	9.59	9.9
	Min	0.04	0.01	0.01	0.19	0.01	0.01
	Max	46.22	61.8	61.8	30.87	55.98	55.98
Age at baseline (years)	N	32	523	555	31	213	244
	Mean	64.16	68.11	67.88	65.55	66.49	66.37
	SD	12.31	16.25	16.07	12.7	15.31	14.98
	Median	63	70	70	66	67	67
	Min	42	18	18	42	25	25
	Max	88	100	100	90	95	95

Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC; SD, standard deviation.

The results of the company's analysis of responders versus non-responders, using the landmark approach are presented in Table 28, for the 3-month and 6-month landmarks, with and without the covariate adjustments for age and ECOG status. However, the ERG considers it important to highlight that these results use different definitions of responders and non-responders for PFS and OS, and so the resulting hypothetical responder and non-responder populations are different depending on outcome assessed. Also of note, the covariate adjustment generally increased the HRs. This is because the non-responders group had more favourable baseline age and ECOG scores (younger age and lower ECOG score), and so the effect of "no response" was underestimated in the unadjusted analyses.

The HRs reported by the company when laBCC and mBCC were analysed as one population (aBCC) generally suggested that responders had more favourable PFS and OS HRs than non-responders, which would imply vismodegib was better than BSC. When analysed as separate populations, the HRs for the laBCC population were higher than for the combined aBCC population, whereas they were lower for the mBCC population. The HRs were <1 for mBCC patients suggesting that the non-responders with mBCC have a more favourable PFS and OS compared to mBCC responders. The company reported that this result is implausible and emphasised the considerable uncertainty in the analysis due to the small number of mBCC patients. The company highlighted that clinical opinion suggests the treatment effect with vismodegib should be similar between laBCC and mBCC patients. The ERG considers it difficult to draw conclusions based on the landmark analysis approach use; prefers the inclusion of additional covariates and the use of a coherent definition for non-responders for the primary analysis of PFS and OS.

Table 28. Conditional hazard ratios of non-responders versus responders estimated using the landmark approach (Adapted from CS page 202, Table 67)

	Progression-free survival		Overall survival	
	No covariates	**Covariates***	**No covariates**	**Covariates***
3-month landmark				
Common effect laBCC & mBCC (95% CI)	1.29 (1.018 to 1.636)	1.26 (0.977 to 1.626)	1.647 (1.061 to 2.556)	1.73 (1.091 to 2.744)
Separate effect laBCC (95% CI)	1.313 (1.02 to 1.691)	1.336 (1.02 to 1.75)	1.776 (1.108 to 2.844)	1.889 (1.15 to 3.103)
Separate effect mBCC (95% CI)	0.893 (0.446 to 1.788)	0.953 (0.404 to 2.247)	0.603 (0.176 to 2.062)	0.634 (0.173 to 2.321)
6-month landmark				
Common effect laBCC & mBCC (95% CI)	1.238 (0.952 to 1.61)	1.311 (0.985 to 1.746)	1.919 (1.159 to 3.177)	2.161 (1.27 to 3.676)
Separate effect laBCC (95% CI)	1.208 (0.908 to 1.608)	1.305 (0.959 to 1.776)	1.913 (1.106 to 3.309)	2.192 (1.225 to 3.922)
Separate effect mBCC (95% CI)	1.052 (0.523 to 2.113)	0.995 (0.411 to 2.408)	1.201 (0.322 to 4.478)	1.151 (0.296 to 4.473)

* Covariates included ECOG status and age at landmark
Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.

The ERG considers a coherent definition of non-responder for the landmark analyses a more appropriate approach (i.e. irrespective of outcome assessed), which is patients with stable disease where those who have progressed or died prior to the landmark were excluded from the analysis. This results in the same patients being assessed in the same groups for both outcomes (PFS and OS). In addition, the ERG considers it important to include a covariate adjustment for Gorlin syndrome as well as the ones applied by the company for age and ECOG status, as there were substantially more Gorlin patients in the responder group compared to the non-responder group at the 6-month landmark. The company provided the results of analyses meeting these criteria in their clarification responses, for OS (Table 29) and PFS (Table 30), along with results broken down for various combinations of applying/not applying the covariates of age, ECOG score and Gorlin status. It is important to note that the company have assumed a common effect for laBCC and mBCC in the analyses in Table 29 and Table 30.

The results of the analysis for OS with covariate adjustment for age, ECOG and Gorlin syndrome applied show a statistically significant increase in mortality for non-responders compared with responders for the laBCC population (HR 2.04, 95% CI: 1.09 to 3.82). The OS in the mBCC population also suggested a trend in favour of the responders (HR 1.04; 95% CI: 0.24 to 4.49). However, there was no statistically significant difference between non-responders compared with responders in the mBCC population, and the HR was associated with more uncertainty than the laBCC HR, as demonstrated by the wider 95% CIs.

Table 29. Results of covariate adjustment on OS at 6-month landmark excluding people who have progressed or died before the landmark (Company clarification response Question B10 d and e)

	laBCC			**mBCC**			**Combined**		
	HR	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**
Non-responders vs responders	1.826	1.019	3.275	1.105	0.276	4.422	1.793	1.048	3.068
Non-responders vs responders (adjusted for age and ECOG)	2.096	1.124	3.908	1.146	0.265	4.956	1.992	1.129	3.515
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**2.035**	**1.085**	**3.817**	**1.035**	**0.238**	**4.491**	1.937	1.091	3.438
Non-responders vs responders (adjusted for age)	2.176	1.176	4.027	0.959	0.237	3.878	2.091	1.193	3.666

Non-responders vs responders (adjusted for ECOG)	1.870	1.037	3.373	1.299	0.307	5.503	1.779	1.035	3.059
Non-responders vs responders (adjusted for Gorlin syndrome)	1.642	0.913	2.951	1.195	0.285	5.008	1.619	0.944	2.779
Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; laBCC, locally advanced BCC; LCL, lower confidence limit; mBCC, metastatic BCC; OS, overall survival; UCL, upper confidence limit.									

The results of the analysis of PFS at the 6-month landmark with the covariate adjustments for age, ECOG and Gorlin syndrome show no statistically significant difference between the non-responder and responder groups although the HR of 1.19 suggests a trend in PFS in favour of the responder group for the laBCC population (95% CI: 0.87 to 1.63). The HR for the mBCC population was 0.95 (95% CI: 0.39 to 2.33), implying the non-responders have a longer PFS than the responders (i.e. BSC better) although it is not statistically significant and may suggest there is no difference in PFS between responders and non-responders. However, the analysis is based on a very small number of patients with a wide 95% CI.

Table 30. Results of covariate adjustment on PFS at 6-month landmark excluding people who have progressed or died before the landmark (Company clarification response Question B10 d and e)

	Locally Advanced			**Metastatic**			**Combined**		
	HR	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**
Non-responders vs responders	1.208	0.908	1.608	1.052	0.523	2.113	1.238	0.952	1.61
Non-responders vs responders (adjusted for age and ECOG)	1.305	0.959	1.776	0.995	0.411	2.408	1.311	0.985	1.746
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**1.19**	**0.869**	**1.629**	**0.951**	**0.388**	**2.331**	1.204	0.9	1.611
Non-responders vs responders (adjusted for age)	1.314	0.966	1.787	0.91	0.40	2.069	1.329	0.999	1.768
Non-responders vs responders (adjusted for ECOG)	1.237	0.928	1.647	1.048	0.494	2.223	1.249	0.96	1.625
Non-responders vs responders (adjusted for Gorlin syndrome)	1.041	0.778	1.393	1.072	0.523	2.196	1.081	0.828	1.41
Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; laBCC, locally advanced BCC; LCL, lower confidence limit; mBCC, metastatic BCC; PFS, progression-free survival; UCL, upper confidence limit.									

The company also provided an exploratory analysis for OS and PFS for the Gorlin syndrome subgroup in their response to clarification questions (Table 31). The analysis assumed a common treatment effect for laBCC and mBCC as the company reported that stratifying would have resulted in extremely small sample sizes and greater uncertainty in the results. In addition, the company did not apply covariate adjustments for age and ECOG status in these analyses. The ERG agrees that an analysis of responder versus non-responder for the mBCC population at the 6-month landmark with the Gorlin subgroup would not have been feasible as there would only have been four responders and one non-responder in the analysis according to the baseline characteristics in Table 27. However, the ERG considers it would have been feasible to conduct a Gorlin subgroup analysis for laBCC patients using the 6-month landmark as there were 130 responders and 34 non-responders (Table 27). It is noteworthy that there would have been more patients in this analysis than in the mBCC analyses for the whole mBCC population (32 responders and 31 non-responders). In addition, the ERG would have preferred the results of the Gorlin subgroup analysis to have had appropriate covariates applied to adjust for baseline differences such as age and ECOG status.

The results for the Gorlin syndrome subgroup at the 6-month landmark suggest they may have improved OS compared to the non-Gorlin subgroup (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively). However, both Gorlin and non-Gorlin responders showed a statistically significant reduction in mortality compared to non-responders (Table 31). The results for PFS were not statistically significant for either the Gorlin or non-Gorlin subgroup analyses of responders versus non-responders, but the mean HR for the non-responders versus responders in the Gorlin syndrome subgroup was higher than for the non-Gorlin subgroup. These results suggest that the Gorlin syndrome subgroup may have a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

Table 31. Results of the landmark analysis for PFS and OS according to Gorlin syndrome status (Company clarification response Question A6)

	Progression-free survival, progression or death before landmark excluded	**Overall survival, death before landmark excluded**	**Overall survival, progression or death before landmark excluded**
	No covariates	**No covariates**	**No covariates**
3-month landmark			
With Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.221	4.212	4.16
	(0.746 to 1.998)	(0.894 to 19.842)	(0.883 to 19.599)
Without Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.219	1.45	1.394
	(1.018 to 1.46)	(1.054 to 1.997)	(0.998 to 1.946)

6-month landmark			
With Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.527	4.101	4.251
	(0.852 to 2.737)	(1.023 to 16.442)	(1.062 to 17.016)
Without Gorlin syndrome, common effect laBCC & mBCC (95% CI)	1.079	1.656	1.506
	(0.885 to 1.315)	(1.144 to 2.397)	(1.014 to 2.237)
Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; LCL, lower confidence limit; mBCC, metastatic BCC; OS, overall survival; PFS, progression free survival; UCL, upper confidence limit.			

4.5 Summary of clinical effectiveness

The results of ERIVANCE and STEVIE suggest that vismodegib is associated with favourable efficacy outcomes in terms of response rate although it is impossible to tell how it compares to BSC due to the efficacy data being only from single-arm studies. In addition, it should be remembered that vismodegib was associated with a high level of adverse events.

Investigator assessed ORR in ERIVANCE was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. Median investigator assessed progression-free survival (PFS) with vismodegib in the laBCC population was 12.9 months (95% CI: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months). Median OS for laBCC was not estimable (NE) but for the mBCC patients it was 33.4 months (95% CI: 18.1 months to NE). The mean change from baseline in the mental component and physical components of the health-related quality of life (HRQoL) SF-36 showed no statistically significant differences at the end of the study for the ERIVANCE combined (laBCC and mBCC) aBCC population ($p < 0.05$).

The ORR in STEVIE was 68.5% (95% CI: 65.7% to 71.3%) in the laBCC population and 36.9% (95% CI: 26.6% to 71.2%) in the mBCC population, and the median PFS for laBCC patients was 23.2 months (95% CI: 21.4 to 26.0) and 13.1 months (95% CI: 12.0 to 17.7) for mBCC patients. Median OS wasn't reached for either laBCC or mBCC patients. The only Skindex-16 HRQoL score for either mBCC or laBCC that showed a clinically meaningful change from baseline was the emotion score, which suggested an improvement with vismodegib. Efficacy results of STEVIE were thus in keeping with those of ERIVANCE, although PFS was longer for laBCC patients and shorter for mBCC patients.

The rate of AEs in both STEVIE and ERIVANCE was high, with 100% of patients in ERIVANCE and 98% in STEVIE experiencing an AE. Moreover, 55.8% of patients in ERIVANCE and 43.7% in STEVIE experienced a Grade 3 or higher treatment-emergent AE (TEAE). A total of 7.7% of the AEs in ERIVANCE and 3.8% in STEVIE resulted in death. The most frequently occurring AEs with vismodegib in both studies were muscle spasms (71.2% and 66.4%, ERIVANCE and STEVIE, respectively), alopecia (66.3% and 61.5%, respectively), dysgeusia (55.8% and 54.6%, respectively), and weight loss (51.9% and 40.6%, respectively).

The baseline characteristics of the Gorlin syndrome subgroup in STEVIE compared with the non-Gorlin subgroup differed substantially, with the Gorlin subgroup having:

- a lower median age (Gorlin syndrome: median 52.0 years [range 18 to 88]; non-Gorlin syndrome median 72.0 years [range 20 to 101]);
- a greater proportion of patients with an ECOG score of 0 (i.e. better performance status than non-Gorlin patients; ECOG Grade 0: 79.5% versus 53.0%, respectively); and
- a higher median number of target lesions (Gorlin syndrome median 3 [range 1 to 12], non-Gorlin median 1 [range 1-10]).

The *post hoc* Gorlin syndrome subgroup results from STEVIE also suggested that the Gorlin syndrome subgroup have a higher response rate (81.7% versus 63%) and longer duration of response (12.3 months versus 8.1 months) than non-Gorlin syndrome patients, although the results are not statistically significant ($p < 0.05$).

A landmark analysis was conducted by the company to inform the comparison of vismodegib with BSC, which the ERG considers to be of limited value in the evaluation of comparative clinical effectiveness as the analysis is based on the use of responder and non-responder data from vismodegib patients in STEVIE at a fixed point in time. Non-responders have received vismodegib and thus are not reflective of BSC patients. However, the absence of any comparative data on vismodegib makes meta-analysis unfeasible and thus alternative approaches, such as a landmark analysis or matched-adjusted indirect comparison (MAIC), are likely to be the only options to enable any comparison of vismodegib with BSC. The ERG notes that the company used a different definition to define responders in their analysis of PFS compared with the definition used for the analysis of OS. In this specific example, the landmark needs to be late enough that most patients will have responded, but not so late that most patients in the non-responder group have already had the event of interest (i.e. progressed or died). Similarly, the landmark should be early enough so that most patients have not had the event of interest, but not so early that a high proportion of late responders are misclassified (and so analysed) as non-responders after the landmark. The ERG agrees with the company's choice of a 6-month landmark for their primary analysis as it exceeds the mean and median time to first confirmed response in STEVIE. The company conducted sensitivity analyses using a 3-month landmark. However, the choice of a 3-month landmark is likely to be too early as it is close to the median time to first response of 2.76 months and is less than the mean of 3.40 months for the combined aBCC population (laBCC and mBCC). The company also included covariate adjustment for age and ECOG status at baseline. However, the ERG considers the company not to have fully explored other important covariates such as Gorlin syndrome status that may have impacted the results.

The landmark analysis results from the company's primary analysis at the 6-month landmark for PFS showed no statistically significant difference between non-responders and responders with laBCC (HR 1.31; 95% CI: 0.96 to 1.78) or with mBCC (HR 0.99; 95% CI: 0.41 to 2.41). There was a significantly higher risk of death in the non-responders compared with the responders who had laBCC (HR 2.19; 95% CI: 1.23 to 3.92), but no significant difference for those with mBCC (HR 1.15; 95% CI: 0.30 to 4.47).

Landmark analysis results using the ERG preferred coherent definition of non-response, covariate adjustment for baseline age, ECOG score and Gorlin status using the 6-month landmark were consistent with the company's primary analysis findings (PFS: HR 1.19, 95% CI: 0.87 to 1.63 for laBCC and HR 0.95, 95% CI: 0.39 to 2.33 for mBCC; OS: HR 2.04, 95% CI: 1.09 to 3.82 for laBCC and HR 1.04; 95% CI: 0.24 to 4.49 for mBCC).

The results provided by the company following a clarification question on the Gorlin syndrome subgroup at the 6-month landmark suggest people with Gorlin syndrome may have improved OS (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively) and a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

The ERG considers it important to highlight that the results of ERIVANCE, STEVIE and the landmark analysis all comprise evidence on vismodegib from single arm studies that is at high risk of bias and thus should be interpreted with caution. In addition, the results for the mBCC subgroup are based on small subgroups and so are subject to large amounts of uncertainty.

4.6 Conclusions of the clinical effectiveness section

- Vismodegib (Erivedge®) is approved in the EU for use in the treatment of adult patients with symptomatic metastatic basal cell carcinoma (mBCC); or locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy.

- The key studies providing the evidence of the clinical effectiveness of vismodegib are ERIVANCE and STEVIE, two single-arm studies of vismodegib in adults.

- Based on differences in baseline characteristics between ERIVANCE and STEVIE, the ERG considers STEVIE to be the most appropriate for the purposes of estimating clinical effectiveness of vismodegib.

- A landmark analysis was conducted by the company to inform the comparison of vismodegib with BSC although it is based on the use of responder and non-responder data from vismodegib patients in STEVIE at a fixed point in time.

- Efficacy results of ERIVANCE: Investigator assessed median PFS with vismodegib in the laBCC population was 12.9 months (95% CI: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months). Median OS for laBCC was not estimable (NE) but for the mBCC patients it was 33.4 months (95% CI: 18.1 months to NE). Investigator assessed ORR was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p < 0.05$).

- Efficacy results of STEVIE: The median PFS for laBCC patients was 23.2 months (95% CI: 21.4 to 26.0) and 13.1 months (95% CI: 12.0 to 17.7) for mBCC patients. Median OS wasn't reached for either laBCC or mBCC patients. ORR was 68.5% (95% CI: 65.7% to 71.3%) in the laBCC population and 36.9% (95% CI: 26.6% to 71.2%) in the mBCC population. The only Skindex-16 HRQoL score for either mBCC or laBCC that showed a clinically meaningful change from baseline was the emotion score which suggested an improvement with vismodegib.

- Results from STEVIE suggested that the Gorlin syndrome subgroup have a higher response rate (81.7% versus 63%) and longer duration of response (12.3 months versus 8.1 months) compared to non-Gorlin patients although the results are not statistically significant.

- AEs from STEVIE and ERIVANCE: 100% of patients in ERIVANCE and 98% in STEVIE experienced an AE with 55.8% of patients in ERIVANCE and 43.7% in STEVIE experiencing a Grade 3 or higher TEAE. 7.7% of the AEs in ERIVANCE and 3.8% in STEVIE resulted in death. The most frequently occurring AEs with vismodegib were muscle spasms (71.2% and 66.4%, ERIVANCE and STEVIE, respectively), alopecia (66.3% and 61.5%, respectively), dysgeusia (55.8% and 54.6%, respectively), and weight loss (51.9% and 40.6%, respectively).

- Landmark analysis results from company's primary analysis at the 6-month landmark for PFS showed no statistically significant difference between non-responders and responders for laBCC (HR 1.31; 95% CI: 0.96 to 1.78) or mBCC (HR 0.99; 95% CI: 0.41 to 2.41). There was a significantly higher risk of death in the non-responders compared to the responders for laBCC

(HR 2.19; 95% CI: 1.23 to 3.92), but no significant difference for mBCC (HR 1.15; 95% CI: 0.30 to 4.47).

- Landmark analysis results using the ERG preferred coherent definition of non-response, covariate adjustment for age, ECOG score and Gorlin status at the 6-month landmark were consistent with the company's primary analysis findings (OS: HR 2.04, 95% CI: 1.09 to 3.82 for laBCC and HR 1.04; 95% CI: 0.24 to 4.49 for mBCC; PFS: HR 1.19, 95% CI: 0.87 to 1.63 for laBCC and HR 0.95, 95% CI: 0.39 to 2.33 for mBCC).

- The results for the Gorlin syndrome subgroup at the 6-month landmark suggest they may have improved OS (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively) and a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

4.6.1 Clinical issues

- Evidence on clinical effectiveness of vismodegib is derived from two single-arm studies, and thus is based on observational data and is at a high risk of bias.

- Single-arm studies are not considered appropriate design to capture time to event outcomes such as PFS and OS.

- There were no estimates of the clinical effectiveness of vismodegib from head-to-head studies.

- The company's search strategy was not comprehensive enough to identify studies of BSC, the comparator of interest.

- The ERG has concerns around the generalisability of ERIVANCE and STEVIE to UK clinical practice as limited information was provided on the location of the patients enrolled. In addition, it is considered that a high proportion of patients in both studies had Gorlin syndrome.

- Gorlin syndrome patients in STEVIE were different to the non-Gorlin syndrome patients as they had a lower median age, a more favourable ECOG performance status and higher median number of target lesions.

- OS data are likely confounded by the use of subsequent treatment although no data on subsequent treatments were recorded as part of either ERIVANCE or STEVIE.

- There were high levels of AEs in ERIVANCE and STEVIE (100% and 98% of patients, respectively) and 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 addition, 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 based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies and the results for mBCC are based on small patient numbers (<100 patients) thus the evidence base is extremely limited for drawing any conclusions relating to vismodegib in mBCC.

- The Gorlin subgroup was not addressed adequately in the CS and the Gorlin subgroup results from the landmark analysis do not have any covariate adjustments for differences in baseline characteristics. In addition, they are not presented separately for the laBCC and mBCC populations.

- There is no data on the long-term safety and efficacy of vismodegib and data on OS in laBCC are immature.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© Excel based economic model.

5.2 Summary of the company's key results

Upon the clarification request from the ERG, the company corrected the mistake found in the model relating with using the cost of a dermatologist visit instead of a GP visit. The company's corrected deterministic base case results for vismodegib compared to BSC using the PAS price are reported in Table 32. The combined ICER weights the laBCC and the mBCC final ICERs by the proportion of patients in each group in STEVIE. The company's base case ICERs for laBCC and mBCC are reported in Table 33 and Table 34, respectively. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. Results are presented in Table 35.

Table 32. Base case results using list price

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 33. Base case results using list price for laBCC pateints

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£97,519	9.95	7.69	£27,345	1.16	0.90	£30,493
Vismodegib	£124,865	11.11	8.58				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 34. Base case results using list price for mBCC patients

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£40,813	4.28	2.95	£80,651	1.20	0.80	£100,615
Vismodegib	£121,465	5.48	3.75				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 35. Results of probabilistic sensitivity analysis using the corrected model

Treatment arm	Costs		QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA

	(deterministic)		(deterministic)		(deterministic)	
BSC	£93,352	£93,061	7.31	7.23	£35,251	£35,798
Vismodegib	£124,699	£124,553	8.20	8.11		

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a single search to identify economic evaluations; resource use and cost studies; and health state utility values (HSUVs) for patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). An overview of the search and details of the search terms, together with results are presented in Section 5.1 and Appendix 10 of the CS, respectively.

The company searched MEDLINE and MEDLINE In-process, Embase and the Cochrane Library (NHS Economic Evaluation Database, EconLit and the Health Technology Assessment database). The search was carried out on 25th November 2016 and no date restrictions were implemented. The search terms combined disease terms (basal cell carcinoma) with study outcome terms (cost-effectiveness, costs and quality of life).

The inclusion and exclusion criteria applied in the review are summarised in Table 58 of the CS. A total of 10 publications were reviewed for inclusion, resulting in two papers being included. The first is an abstract of an economic evaluation assessing the cost-effectiveness of sonodegib compared to vismodegib[92], and the second is a study reporting HSUVs in patients with advanced BCC.[93]

The ERG considers the search terms used by the company appropriate and sufficient to capture published studies of relevance in all the databases. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

The CS mentions economic evaluations assessing the cost-effectiveness of vismodegib submitted to the Canadian and Irish health technology assessment (HTA) bodies. However, these were not included in the cost-effectiveness evidence review, therefore the ERG requested the company to provide more detail on these at clarification stage. The ERG reviewed the HTA reports provided by the company and summarises the relevant aspects of these in Table 36.

Table 36. Summary of the Canadian and Irish HTAs for vismodegib

Author, Year	Intervention and comparator	Source for clinical effectiveness data for vismodegib	Method used for analysis of treatment effectiveness	Base case ICER	HTA review body ICER	Main issues raised in the HTA reports	Recommendation
Roche (Canada), 2013[94]	Vismodegib (150mg) and BSC	ERIVANCE	NR	laBCC: between $263,141 and $443,613 mBCC: between $162,646 and $172,464	laBCC: between $161,370 and $497,864 mBCC: between $147,860 and $656,314	• Based on input from the CGP, the EGP considered that the cost of wound management for PD was an overestimate of the wound care cost and conducted a reanalysis using an estimate that is 50% the value used by the submitter; • The EGP included wound management costs in the PFS health states of the model according to clinical expert opinion; • The EGP changed the time horizon of the analysis from 40 to 10 years. The 10-year time horizon was considered appropriate for the mBCC population as the expected survival of these patients is <10 years. For the laBCC patients, although their expected survival may be longer, the time horizon was also limited since based on extrapolation from the clinical trial data, at 10 years, almost all patients have progressed (only 0.2% progression-free), therefore, no additional benefit is expected from vismodegib after this point; • The uncertainty related to the quality of life data. The EGP was not able to reanalyse the model with quality of life data that were collected alongside the clinical trial, due to limitations of the quality of life instrument used – SF-36 (lack of sensitivity for this indication, ceiling effect for relatively healthy individuals at baseline) and the small size of the sample.	*"Recommended…conditional on the cost-effectiveness being approved to an acceptable level. Funding should be for patients with ECOG performance status ≤2 who have measurable mBCC or laBCC, which is considered inoperable or inappropriate for surgery and… radiotherapy."*
Roche (Ireland),	Vismodegib (150mg) and	ERIVANCE	NR	laBCC = € 556,657 mBCC = € 240,902	NR	• All patients receiving vismodegib were assumed to start in the PFS health state	Not recommended.

Author, Year	Intervention and comparator	Source for clinical effectiveness data for vismodegib	Method used for analysis of treatment effectiveness	Base case ICER	HTA review body ICER	Main issues raised in the HTA reports	Recommendation
2014[95]	BSC					whereas all patients in the BSC arm were assumed to start in the PD health state; • SF-36 quality of life data was collected during the pivotal phase II study but not used in the model. Instead, QALYs were valued using utilities measured in a time trade-off (TTO) study conducted by the company; • There were significant limitations associated with the submission, the most critical being the lack of evidence for additional benefits of vismodegib in prolonging PFS and OS compared with supportive care.	
Abbreviations used in the table: BSC: best supportive care; EGP: economic guidance panel; CGP: Clinical Guidance Panel							

Worthy of note is the fact that the ERIVANCE trial data was used to undertake the clinical and cost-effectiveness analyses in both CSs. Both the Canadian and the Irish HTA submission dates (2013 and 2014, respectively) were prior to the cut-off point for analysis in STEVIE (patient enrolment began on the 30th June 2011 and the clinical data cut-off was on the 16th March 2015), which might explain why ERIVANCE data were used instead of STEVIE data.

In the Canadian and Irish submissions, the analyses and the ICERs were reported separately for laBCC and mBCC, which contrasts with the CS to NICE, where a final common ICER is presented for both populations (although laBCC and mBCC patients are modelled separately albeit with a common treatment effect).

Finally, it should be highlighted that the CS to the Irish HTA body did not use the SF-36 data collected in ERIVANCE in its economic analysis, but instead a TTO analysis conducted by the company in the UK. It is unclear from the Canadian HTA document which data source was used to model quality of life in the cost-effectiveness model, however it seems to have been the Shingler *et al*. study, which the company includes as a scenario analysis in their CS to NICE.[93] The HTA report by the Economic Guidance Panel (EGP) states the following: "*Utility estimates that are more representative of the study populations would have been preferable. The quality of life data collected alongside the clinical trial could have provided such an estimate but a number of limitations related to the small sample of the study and the lack of sensitivity of the instrument used (SF-36) for this indication did not allow the EGP to use these data in the economic analysis. On the basis of this limited information, the overall quality of life observed in the ERIVANCE trial for both laBCC and mBCC populations was inconclusive."*

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 37 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.[1, 96]

Table 37. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes, however the ERG does not agree with the company's justification for not undertaking the subgroup analysis for Gorlin syndrome as stated in the NICE final scope. Nonetheless this analysis was undertaken upon a clarification request from the ERG.
Comparator(s)	Alternative therapies routinely used in the NHS	Unclear. The scarcity of literature on BSC for aBCC means that there is not a clear definition of BSC.
Perspective costs	NHS and Personal Social Services	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, however by the end of the 30-year time horizon (when modelled patients would be 100 years old), there are still 3% of patients alive in the vismodegib and BSC arms of the model for laBCC patients and 1% of patients alive in the vismodegib and BSC arms for mBCC patients. This seems unrealistic from a clinical point of view, especially for patients with metastatic disease. The mortality rate at this point in the model is defined by the background mortality rate taken from the UK life tables matched for age and gender in the overall population.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The model used EQ-5D values mapped from SF-36 data collected in the ERIVANCE trial using a published algorithm. Even though the mapping method employed by the company is robust, the underlying SF-36 data appears to carry a lot of uncertainty. The company used SF-36 values that mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values that suggest a decrease in patients' quality of life upon progression.
Benefit valuation	Time-trade off or standard gamble	EQ-5D UK TTO tariff (after mapping of SF-36 to EQ-5D).
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.4.2 Population

The population considered by the company for this STA comprises people with symptomatic laBCC or mBCC for whom surgery or radiotherapy is not appropriate. The company modelled the two populations separately, using laBCC and mBCC data, respectively, from the STEVIE trial. Nonetheless

the company used a common treatment effect measure for vismodegib (i.e. a common effect HR for laBCC and mBCC patients was assumed for vismodegib compared to BSC) and presented the economic results for the combined aBCC population.

The ERG considers that these two populations should be analysed separately from a clinical point of view, as well as from an economic perspective. The cost-effectiveness results should be considered in separation for each type of aBCC. Clinical expert opinion provided to the ERG explained that locally advanced and metastatic patients do not have similar prognosis, or disease pathways therefore the expected outcomes would differ in these populations. One of the key differences between these populations is the fact that mBCC patients will eventually die due to disease progression while laBCC patients are extremely unlikely to die of laBCC. It follows that while vismodegib might potentially have an impact on mBCC patients' mortality, it is less likely that the drug impacts mortality in laBCC patients.

Furthermore, while the overall incidence of the aBCC is low, this is particularly notable for mBCC patients, where the estimated incidence of disease is around 0.55% (please see Section 2.1 for more details). Out of the three clinical experts consulted by the ERG (two dermatologists and one oncologist) only one had knowledge of an mBCC patient in their practice. This reinforces the paramount level of uncertainty in the clinical and cost-effectiveness analysis of vismodegib in the mBCC population, discussed in the next sections of the report.

Adding to the low incidence of the disease is the fact that out of the 1,215 patients in STEVIE, only 38 (3%) were from the UK. This fact adds to the difficulty in evaluating the extent to which the company's analysis is generalizable to aBCC patients in the UK. For example, the fact that laBCC patients have a higher mortality rate than the average age and gender-matched population in the UK, when clinical expert opinion and the CS repeatedly state that laBCC is very unlikely to lead to an increase in mortality, might be related to the fact that only 3% of patients in the STEVIE trial came from the UK. 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 patients were enrolled from, the ERG cannot rule out the possibility that vismodegib may increase mortality in laBCC patients

Finally, the company decided to not run the subgroup analysis specified in the NICE final scope for Gorlin syndrome patients. The company reports that the number of Gorlin syndrome patients in STEVIE were too low and therefore insufficient to undertake a robust subgroup analysis. The ERG disagrees with the company assessment and finds it highly contradictory, considering that the number of patients with Gorlin syndrome in STEVIE [214 patients (19%) in the laBCC population and 5 patients

(5%) in the mBCC group] is more than double than the total number of patients in the mBCC group (96 patients). The ERG requested this subgroup analysis from the company at the clarification stage, and presents the results in Section 4 of the ERG report.

5.4.3 Interventions and comparators

The intervention and comparator considered in the economic model reflect those set out in the NICE final scope. The intervention under consideration is vismodegib, administrated orally in 150mg capsules. The recommended and modelled dose is one 150mg capsule daily. The clinical impact of receiving subsequent BSC after vismodegib is unknown as data on subsequent treatments were not collected in STEVIE or ERIVANCE. Considering that 31% of patients in STEVIE discontinued treatment due to adverse events (AEs), and assuming these patients would receive BSC after discontinuing treatment, data collection on subsequent BSC treatment could have served two important purposes: it would have helped to build the scarce evidence base on the definition and effectiveness of BSC in aBCC patients; and it would have helped clarify if the effectiveness of vismodegib in STEVIE was in any way confounded by BSC.

The comparator considered in the analysis is BSC. The definition of BSC is not explicitly reported as the evidence base around BSC in aBCC is rather weak. The company defined BSC as a non-active and non-curative treatment; as an option to manage patients' symptoms. Best supportive care mainly consists of wound management in the economic analysis.

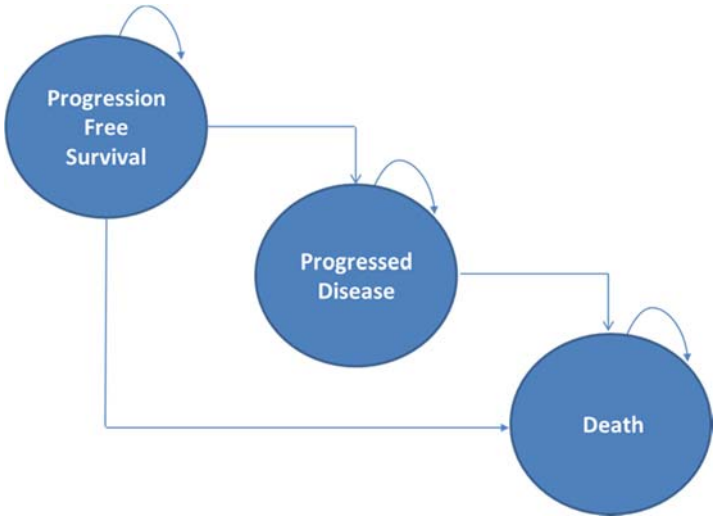
The clinical experts advising the ERG confirmed that literature around the definition of BSC for aBCC patients is scarce, and that it does not consist on a curative option. Nonetheless the clinical experts had issues related to the company's assumptions regarding resource use for BSC patients, especially with the company's assumption that a proportion of vismodegib patients will only need a lighter BSC regimen for the rest of their lifetime, after they discontinue vismodegib. The clinical experts disagreed with this assumption and explained that eventually all patients move on to receive a "standard" BSC regimen. This is discussed in detail in Section 5.4.9.

5.4.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of vismodegib in comparison with BSC in patients with symptomatic mBCC or laBCC who cannot have curative surgery or radiotherapy. The model is a cohort-based partitioned survival model (presented in Figure 13) which includes three health states: progression-free survival (PFS), progressed disease (PD), and death. The company reports that aBCC patients receive treatment with vismodegib until disease progression or unacceptable toxicity.

The cohort is allocated to the PFS state at the beginning of the economic analysis and is assumed to initiate treatment with vismodegib or with BSC. Patients occupying the PFS state are at risk of disease progression or death. Patients in the PD state are also at risk of death and cannot enter remission in the model. Progressed vismodegib patients are assumed to receive BSC as a subsequent treatment in the economic analysis. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

Figure 13. Model structure



A life time horizon of 30 years is adopted in the model and time is discretised into weekly cycles. A half-cycle correction was applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[96]

The company used the same model structure and modelling approach to estimate the cost-effectiveness of vismodegib for laBCC and mBCC (albeit two different models, with different data inputs). The output of the economic model is an overall ICER combining laBCC and mBCC patients. In order to estimate a single final ICER the company weighted the individual ICERs resulting from the laBCC and mBCC models by the proportion of laBCC and mBCC patients in the STEVIE trial.

ERG critique

The ERG is generally satisfied with the model structure and the patients' flow through the model. Patients discontinuing treatment due to treatment toxicity was captured through time to treatment discontinuation (TTD) data but not explicitly through the health states included in the economic model.

Vismodegib patients who have progressed are assumed to receive subsequent BSC, which is in line with clinical expert opinion provided to the ERG. Patients who progress are assumed to start subsequent treatment as soon as they enter the progression state.

The partitioned survival approach employed by the company is appropriate. A life time horizon of 30 years is adopted in the model, which seems reasonable considering the mean age of patients at baseline of 70 years. Nonetheless, by the end of the 30-year time horizon (when these patients would be 100 years old), there are still 3% of patients alive in the vismodegib and BSC arms of the model for laBCC patients and 1% of patients alive in the vismodegib and BSC arms for mBCC patients. This seems unrealistic from a clinical point of view, especially for patients with metastatic disease. This could suggest an overestimation of survival tails in the long-term of the economic analysis, however the mortality rate at this point in the model is defined by the background mortality rate taken from the UK life tables matched for age and gender in the overall population.[97] This issue is further discussed in Section 5.4.7 of the ERG report.

Considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. The ERG removed the half-cycle correction from the model as an exploratory analysis and presents the results of the analysis in Section 6.

The ERG agrees with the company's decision to build two separate models, one for laBCC and the other for mBCC. However, the ERG disagrees with the decision of using a common treatment effect for vismodegib and reporting an aggregated ICER for laBCC and mBCC. As discussed in Section 5.4.2, and according to clinical expert opinion provided to the ERG, these are two different populations in terms of disease prognosis and clinical outcomes, and should therefore be considered separately. To also note is the fact the CS to the Canadian and Irish HTA bodies reported two individual ICERs for laBCC and mBCC, respectively.

5.4.5 Treatment effectiveness

The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or chemotherapy and so are left with no other treatments options at this point in the clinical pathway. The company adds that vismodegib offers clinical benefit in terms of delay of disease progression and survival, with a manageable safety profile.

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS, PFS and TTD data from STEVIE to determine mortality, disease progression and time on treatment for each cycle of the economic model, respectively. The company

built two separate models, one for laBCC and the other for mBCC. STEVIE data were therefore used according to the type of aBCC, in each model, separately.

In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to STEVIE Kaplan-Meier (KM) data. The company reports fitting clinical data with exponential, Weibull, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Technical Support Document (TSD) 14. [98]The company also explored the option of including KM curves with a parametric tail used for extrapolation in their sensitive analyses. The fit of each parametric model was compared with the observed KM data and statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Once the best-fitting model was selected, survival curves for vismodegib were derived through the use of survival functions and were then used to estimate the proportion of patients in each health state for every cycle of the vismodegib laBCC and mBCC models. The company did not report how the estimated survival curves for vismodegib were used to derive the proportion of patients in each health state of the model, therefore the ERG investigated the economic model and reports the formulae used by the company below. The company's model used the following equations:

- PFS = P(PFS);
- PD = P(OS)-P(PFS);
- Death = 1-P(OS).

Where P(PFS) is the proportion of progression-free patients taken from the PFS curve and P(OS) is proportion of patients alive taken from the OS curve.

To obtain OS and PFS curves for BSC, the HRs derived from the landmark approach (Section 4) were applied to the estimated vismodegib PFS and OS survival curves. Even though the company built two separate models, using separate data for laBCC and mBCC, the common effect (laBCC and mBCC) HR derived through the landmark approach was applied to the laBCC and the mBCC curves. Patients on BSC were assumed to be on a specific BSC treatment regimen until progression, and on a different BSC regimen after disease progression (Section 5.4.9).

The company's base case model assumes that the proportional hazards (PH) assumption holds for the responders compared to non-responders in STEVIE. The company provided that log-cumulative hazard plots for OS and PFS data for responders and non-responders in the STEVIE study. The company did

not undertake an assessment of the proportional odds (PO) or accelerated failure time (AFT) assumptions.

ERG critique

The ERG has several concerns with the estimation of relative treatment effectiveness in the model. These issues are similar across OS and PFS outcomes and apply to both laBCC and mBCC patients, even though the concerns for mBCC patients are reinforced by an extremely small number of patients included in the analysis. The issues are enumerated here and discussed in turn below:

1. The adjustment of the landmark HRs undertaken by the company, to try and reflect the relative treatment effectiveness of vismodegib compared with BSC patients (and not the relative treatment effectiveness of responders vs non-responders in STEVIE);

2. The assessment of PH;

3. The selection of HRs to be used in the economic model:

    a. The use of a common treatment effect HR;

    b. The process for selecting prognostic factors as covariates;

4. The plateau observed in the KM curves.

5.4.5.1 Company's adjustment of HRs

In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to STEVIE KM data. Although it is not clear from the CS, at the clarification stage the company explained that the baseline curves fitted for vismodegib in the economic model are based on the ITT population data, instead of the responders in STEVIE. Given that the ITT population includes vismodegib responders and non-responders, similar to what would be observed in clinical practice, the ERG agrees with the inclusion of the ITT population data in the vismodegib models.

Nonetheless, the use of the ITT data to model the vismodegib arms of the economic model raises an important issue. The landmark approach taken by the company derived a HR for responders vs non-responders in the STEVIE study. Therefore, the estimated HR reflects the relationship between vismodegib responders and non-responders, and not between vismodegib and BSC patients, which is the population included in the economic model. The company tried to address this issue by adjusting the HR obtained in the landmark approach to reflect the HR of non-responders vs ITT patients, as

reported in the company's clarification document. The ERG reproduces the company's explanation for the adjustment made to the landmark HR below.

"Let h_{itt} be the hazard rate in the ITT population, h_r the hazard rate in the responder group, h_{nr} the hazard rate in the non-responder group, and p_r the proportion of responders in the ITT population.

1) $\log(h_{itt}) = p_r \times \log(h_r) + (1 - p_r) \times \log(h_{nr})$

To obtain the HR of non-responders versus ITT patients as a function of the HR of non-responders versus responders we first subtract the log hazard rate in the non-responder group from both sides of the above equation and multiply the entire equation by minus 1.

2) $\log(h_{nr}) - \log(h_{itt}) = p_r \times [\log(h_{nr}) - \log(h_r)]$

The differences in the log hazard rates can then be re-written as log HRs.

3) $\log\left(\frac{h_{nr}}{h_{itt}}\right) = p_r \times \log\left(\frac{h_{nr}}{h_r}\right)$

This relationship indicates that the log HR of non-responders versus ITT patients is the log hazard ratio of non-responders versus responders multiplied by the proportion of responders in the ITT population, or equivalently, that the HR of non-responders versus ITT patients equals the HR of non-responders versus responders in the power of the proportion of responders in the ITT population.

4) $\frac{h_{nr}}{h_{itt}} = \left(\frac{h_{nr}}{h_r}\right)^{p_r}$

Because non-responders die at higher rates than responders the proportion of responders in the ITT population increases over time. The HR between non-responders and ITT patients $HR_{nr-itt}(t)$ is thus modelled to vary over time dependent on the time-invariant average HR of responders versus non-responders HR_{nr-r} and the time-varying proportion of responders in the ITT population, $p_r(t)$."

5) $HR_{nr-itt}(t) = HR_{nr-r}^{p_r(t)}$

While the calculations undertaken by the company are sound, the ERG disagrees with the theoretical and methodological implications of the adjustment process. The final HR used by the company in the model is a time-varying HR (as can be seen by the time element in Equation 5), as it depends on the change in the proportion of responders in the ITT population over time. The manipulation of the relationship between the hazard in the responders and non-responders undertaken by the company is not evidence or methodologically-based, as the company is imposing a time-varying component in a

HR that was derived as a time-invariant HR with a Cox proportional hazards model (described in Section 4).

If the company had reasons to believe that there is evidence of a time-varying treatment effect, then a different modelling approach could have been explored. The company could have explored fitting the responders and non-responders data from STEVIE independently or fitted the dataset with a time-varying model. If on the contrary, the evidence does not substantiate the existence of a time-varying HR, then this time dependency should not be forced into the HR, which is what the company's approach implies.

Worth noting is the fact that fitting responders and non-responders data independently would have raised a different issue. Using these populations as proxies for a vismodegib and a BSC arm, respectively, would have introduced bias in the analysis and overestimated the effectiveness of vismodegib and the effectiveness of BSC. This is because using the responders in STEVIE as a proxy for vismodegib patients will artificially create a "perfect response" vismodegib group, as everyone included will respond to the drug. Similarly, using the non-responders in STEVIE as a proxy for BSC patients will artificially create a group with a better prognosis than BSC patients, as these patients still received vismodegib in practice. Also depending on the definition of the landmark, non-responders might eventually respond to vismodegib after the chosen landmark, and these events will be counted under the effectiveness of BSC.

Applying the "unadjusted" HR resulting from the landmark approach to the ITT population in STEVIE also partially carries the same flaw. The HR reflects the relationship between a "perfect response" vismodegib group and a BSC group with potentially better outcomes than a real BSc group. However, if one hypothesises that the upwards bias introduced in this analysis cancels out (meaning that the overestimation of vismodegib effectiveness cancels out the overestimation of BSC effectiveness), then applying this HR to the ITT population, could approximate the analysis to what would be observed in a typical two-arm trial, comparing vismodegib with BSC.

Even though the ERG does not agree with the company's adjustment made to the HRs derived with the landmark approach, it notes that adjusting the HRs is in detriment of the company's analysis as this decreases the HRs used in the model, therefore increasing the final ICER. The results of removing the adjustment to the landmark HR are reported in Section 6.

5.4.5.2 Proportional hazards

Related to the issue discussed in the previous section is the assessment of PH in the clinical events observed in the responders and non-responders groups in STEVIE. To obtain survival curves for BSC,

the HRs derived from the landmark approach (Section 4) 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 to non-responders in STEVIE. Assessment of the log-cumulative hazard plots for OS and PFS data for responders and non-responders in the STEVIE study, provided to the ERG after the clarification stage, suggest that the assessment of PHs might change depending on the landmark used, and on the clinical outcome considered.

Analysis of the log-cumulative hazard plots for PFS outcomes in laBCC and mBCC patients, when a 3-month and a 6-month landmark approach are used, suggests that:

1) For laBCC it is not unreasonable to assume PH, regardless of the landmark used;

2) For mBCC, PH does not seem to hold for a 3-month landmark, which becomes even more apparent at the 6-month landmark. Thus the assumption of PH for PFS in mBCC patients at a 6-month landmark is unlikely to hold.

Analysis of the plots also suggests that the existence of constant hazards is not unreasonable, and that a Weibull curve might be appropriate to model PFS for laBCC. Analysis of the log-cumulative hazard plots for OS outcomes in laBCC and mBCC patients, when a 3-month and a 6-month landmark approach are used, suggests that:

1) For the 3-month landmark, it is not unreasonable to assume PH, regardless of the type of BCC (i.e. laBCC and mBCC);

2) For the 6-month landmark, PH does not seem to hold for laBCC or for mBCC.

The analysis of the plots was based on the responders and non-responders groups defined as per the ERG's request at clarification. This means that OS events were analysed using the same definition of non-responders as for PFS (please see Section 4 of the report for more details). However, this also means that the analysis was based on smaller numbers of patients, especially for mBCC patients (Table 38).

Table 38. Number of patients in the analysis of PFS and OS data at a 6-month landmark

PFS/OS populations	laBCC	mBCC
Responders (n)	523	32
Non-responders (n)	213	31

Considering the methodological approach undertaken (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 is meaningful in this case. Although the initial tests (visual inspection of log-cumulative hazard plots) seem to indicate that PH does not hold for OS or for PFS (for mBCC at 6 months), this could be a product of the combination of the landmark method of analysis and the extremely small numbers observed for mBCC patients. 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 much larger sample size, nonetheless the assessment suffers from the same underlying issue in study design.

5.4.5.3 Hazard ratios used in the analysis

The ERG disagrees with the company's approach of using a common effect (laBCC and mBCC) HR (PFS HR of 1.311, 95% CI: 0.985 to 1.746 and OS HR of 2.161, 95% CI: 1.270 to 3.676). The company built two separate models, using separate data for laBCC and mBCC but decided to use a common treatment effect HR in both models. Due to the differences in the populations (discussed in Section 5.4.2) the ERG considers that the two patient groups should be analysed separately, as should be the effectiveness of vismodegib. For example, while it is plausible to assume that vismodegib has a survival benefit for mBCC patients (who eventually die from their disease), it is less likely that vismodegib has a survival benefit on laBCC patients (who are unlikely to die from their disease).

Furthermore, the company decided to include age and ECOG as covariates in the estimation of the HRs. The ERG asked the company to demonstrate that a systematic approach had been taken to select the prognostic factors included in the analysis. The ERG also requested the results of the stepwise selection process for covariates for the separate mBCC and laBCC models. The company replied that no systematic approach had been taken to select covariates 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 should have been taken to ensure that no selection bias was introduced in the analysis and that all clinically relevant and statically significant prognostic factors were captured. Clinical experts advising the ERG noted that other baseline

characteristic are likely to be relevant prognostic factors, such as Gorlin syndrome, nerve infiltration and BCC location (e.g. head, neck, etc.).

Table 39 and Table 40 report the unadjusted HRs, together with the adjusted HRs for age, ECOG and Gorlin (together and separately but not the full step-wise approach), for OS and PFS, respectively. The results reported for OS are based on patients who survived and are progression-free at the 6 months landmark. The company included Gorlin syndrome as a covariate as per the ERG request during the clarification stage. As explained in Section 4, the ERG's preferred HR adjusts at least for Gorlin syndrome, age and ECOG. However, it should be emphasised that these HRs might still not include all the relevant prognostic factors and therefore may be biased.

To note is that none of the mBCC HRs are statistically significant. This is not surprising considering the very limited number of patients observed in the group. The PFS HR for mBCC adjusted for age, ECOG and Gorlin syndrome is below one, indicating that vismodegib is worse than BSC at delaying progression. The ERG's clinical experts do not consider this a clinically plausible scenario therefore a HR of 1 was used instead of the 0.95 reported below. Interestingly the PFS HR for laBCC is also not statistically significant, despite the relatively large sample size in this population (736 patients overall).

Table 39. Hazard ratios for OS for responders compared to non-responders when adjusting fro different prognostic factors

	Locally Advanced			**Metastatic**			**Combined**		
	HR	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**
Non-responders vs responders	1.826	1.019	3.275	1.105	0.276	4.422	1.793	1.048	3.068
Non-responders vs responders (adjusted for age and ECOG)	2.096	1.124	3.908	1.146	0.265	4.956	1.992	1.129	3.515
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**2.035**	**1.085**	**3.817**	**1.035**	**0.238**	**4.491**	1.937	1.091	3.438
Non-responders vs responders (adjusted for age)	2.176	1.176	4.027	0.959	0.237	3.878	2.091	1.193	3.666
Non-responders vs responders (adjusted for ECOG)	1.870	1.037	3.373	1.299	0.307	5.503	1.779	1.035	3.059
Non-responders vs responders (adjusted for Gorlin syndrome)	1.642	0.913	2.951	1.195	0.285	5.008	1.619	0.944	2.779
Abbreviations used in the table: HR: hazard ratio; LCL; lower confidence limit; UCL; upper confidence limit.									

Table 40. Hazard ratios for PFS for responders compared to non-responders when adjusting fro different prognostic factors

	Locally Advanced			Metastatic			Combined		
	HR	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**	**HR**	**95% LCL**	**95% UCL**
Non-responders vs responders	1.208	0.908	1.608	1.052	0.523	2.113	1.238	0.952	1.61
Non-responders vs. responders (adjusted for age and ECOG)	1.305	0.959	1.776	0.995	0.411	2.408	1.311	0.985	1.746
Non-responders vs responders (adjusted for age, ECOG and Gorlin syndrome)	**1.190**	**0.869**	**1.629**	**0.951**	**0.388**	**2.331**	1.204	0.9	1.611
Non-responders vs responders (adjusted for age)	1.314	0.966	1.787	0.91	0.40	2.069	1.329	0.999	1.768
Non-responders vs responders (adjusted for ECOG)	1.237	0.928	1.647	1.048	0.494	2.223	1.249	0.96	1.625
Non-responders vs responders (adjusted for Gorlin syndrome)	1.041	0.778	1.393	1.072	0.523	2.196	1.081	0.828	1.41
Abbreviations used in the table: HR: hazard ratio; LCL; lower confidence limit; UCL; upper confidence limit.									

In conclusion, there is a very high degree of uncertainty in the measure of relative treatment effectiveness of vismodegib compared with BSC. The method used to derive the HRs for OS and PFS introduces uncertainty in the analysis which is only reinforced by the small number of patients in the mBCC group. To these issues, adds the non-systematic selection process of prognostic factors in the HR estimations, which potentially introduced further uncertainty and bias in the analysis. Assuming PH holds in the analysis is also likely to introduce further uncertainty in the results, particularly of OS data.

It is the ERG view that for mBCC patients, the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib in terms of OS and PFS outcomes. With regards to laBCC patients, the only statistically significant HR resulting from the landmark analysis is for OS outcomes.

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

5.4.5.4 Kaplan-Meier curves

Figure 14 and Figure 15 reproduce the KM curves for OS, PFS and TTD for laBCC and mBCC patients. There is an unusual plateau at the end of the OS and TTD KM curves for laBCC and mBCC patients. The ERG investigated the KM data provided by the company in the economic model and reports the

KM data reported by the company in Table 41 and Table 42 for laBCC and mBCC, respectively. The KM curves and the data suggest that for laBCC patients, there were no death or discontinuation events for approximately 1.5 years before the end of the follow-up period. The same is true for mBCC patients where for approximately 16 months before the end of the follow-up period there were no deaths or discontinuation events. The ERG asked the company to confirm if this had been the case or if the follow-up period had been shorter than the last data entry in the KM data (44 months for laBCC and 38 months for mBCC). The company confirmed that the 44 months for laBCC and 38 months for mBCC data points correspond to the entire follow-up period in STEVIE and that no events were observed from the previous date point in the KM curves till the end of the follow-up (Table 41 and Table 42).

By 26 months patients in STEVIE would be, on average, 74 years. The KM tails imply that no patient with mBCC would die for 18 months, which the ERG finds this unlikely from a clinical point of view. The long tails of the TTD curves suggest that patients continued treatment after progression in the mBCC population. At 22 months, when there were still around 30% on treatment (8 patients at risk), about 23% of patients were free from progression (6 patients at risk). Although the numbers at risk are small, the curves cross much earlier, 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.

With regards to laBCC patients, while it appears implausible that patients would not discontinue treatment for 1.5 years, the fact that the TTD and the PFS curves cross at around month 38 could be an artefact of the small number of patients in the PFS curve at this point in time (three patients). To also note is that the definition of treatment discontinuation in STEVIE was based on discontinuing vismodegib for longer than eight weeks. Any treatment breaks shorter than eight weeks would not be considered as discontinuation for the purpose of estimating TTD. This is likely to be different to what would be seen in clinical practice, where patients are expected to be kept on a three months on and three months off treatment regimen, according to clinical expert opinion provided to the ERG.

Figure 14. KM curves for laBCC patients

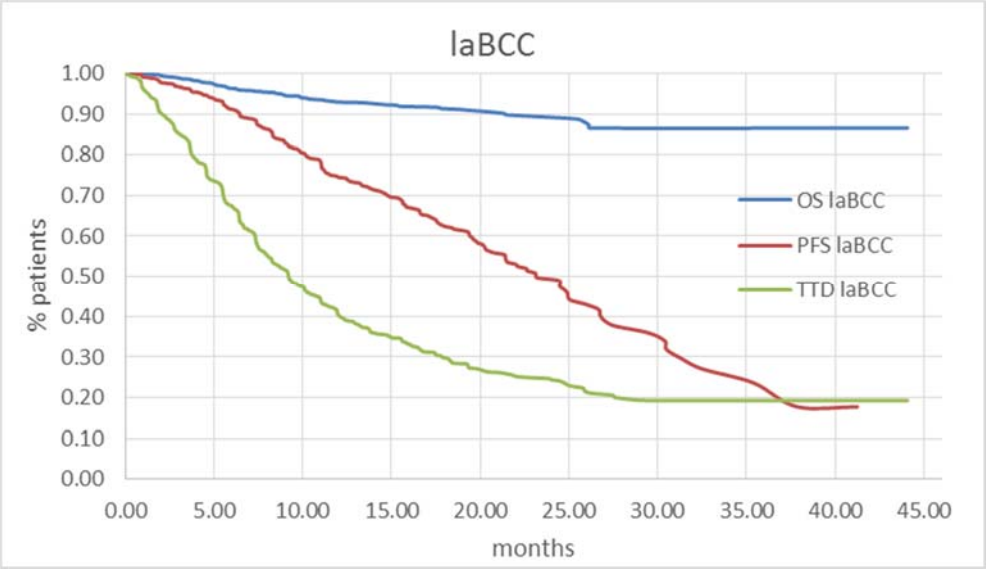


Table 41. KM data for OS, PFS and TTD for laBCC

Outcome/months	Percentage of patients	Number of patients at risk	Number of patients failed
OS			
26.12 months	87%	115	89
26.15 months	86%	114	90
44.06 months	86%	0	90
TTD			
27.60 months	20%	37	769
29.40 months	19%	26	770
44.06 months	19%	0	770
PFS			
35.38 months	24%	7	287
37.85 months	18%	3	288
41.23 months	18%	0	288

Figure 15. KM curves for mBCC patients

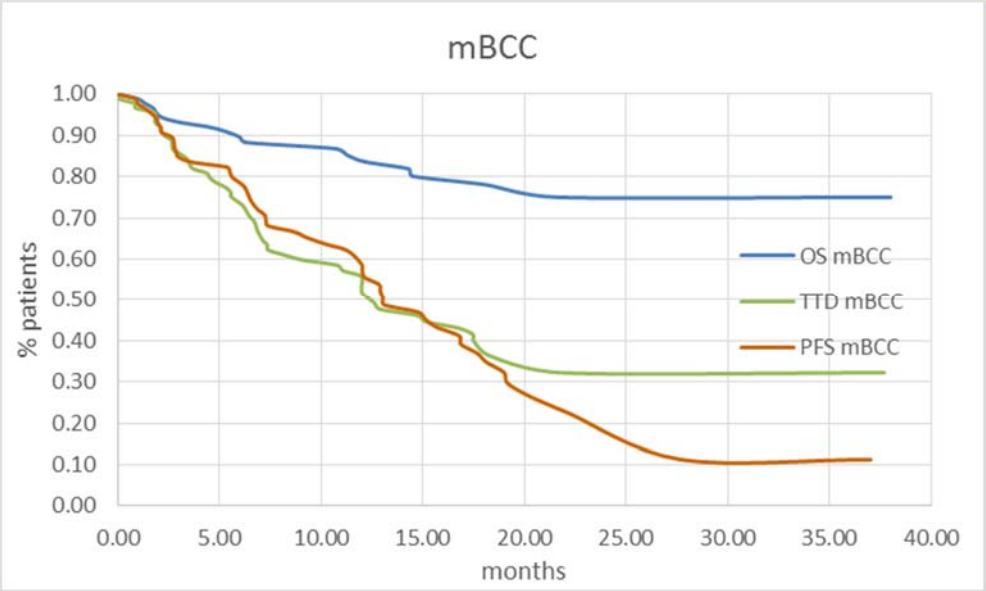


Table 42. KM data for OS, PFS and TTD for mBCC

Outcome/months	Percentage of patients	Number of patients at risk	Number of patients failed
OS			
18.14 months	78%	37	16
21.65 months	75%	25	17
38.01 months	75%	0	17
TTD			
18.33 months	36%	20	51
21.82 months	32%	8	52
37.68 months	32%	0	52
PFS			
35.38 months	23%	6	49
37.85 months	11%	1	50
41.23 months	11%	0	50

5.4.6 Progression-free survival

The company used KM data from STEVIE to model PFS for vismodegib in the base case economic model. Based on the AIC and BIC criteria reported in Table 43 and on clinical plausibility of the curves, the company concluded that the best fitting model is the Weibull, both for the laBCC and mBCC clinical data.

Table 43. Goodness of fit statistics for PFS data

	AIC		BIC	
	Locally advanced	**Metastatic**	**Locally advanced**	**Metastatic**
Exponential	1'503.05 (5)	203.97 (6)	1'508.06 (6)	206.45 (1)
Weibull	**1'444.66 (1)**	**201.94 (1)**	**1'454.67 (1)**	**206.91 (2)**
Log-logistic	1'448.69 (4)	203.22 (3)	1'458.71 (2)	208.20 (4)
Log-normal	1'475.24 (3)	203.07 (2)	1'485.25 (5)	208.05 (3)
Gamma	1'446.63 (2)	203.67 (5)	1'461.65 (3)	211.14 (6)
Gompertz	1`459.73 (6)	203.53 (4)	1'469.74 (4)	208.50 (5)

ERG critique

The PFS HR obtained by the company for laBCC patients is not statistically significant (1.305, 95% CI: 0.959 to 1.776), which is also the case for the PFS HR adjusted for Gorlin syndrome, together with ECOG and age (HR 1.190, 95% CI: 0.869 to 1.629).

This analysis needs to be caveated by the uncertainty in the HR introduced by the landmark approach method and the non-systematic selection process of prognostic factors in the HR estimation, which potentially introduced further uncertainty and bias in the analysis. It is difficult to anticipate the direction and the extent of the methodological uncertainty associated with the estimation of the PFS and OS HRs.

Despite the lack of statistical significance in the PFS HRs and the lack of robustness in the methods used to analyse the relative effectiveness of vismodegib, the ERG ran a scenario analysis using the HRs adjusted for ECOG, age and Gorlin syndrome for the laBCC population, considering its larger sample size.

It is the ERG view that for mBCC patients, the evidence base is not robust enough to draw conclusions on the effectiveness of vismodegib in terms of OS and PFS outcomes. Furthermore, the mean PFS HR for mBCC is below one, indicating that vismodegib is worse than BSC at delaying progression. The ERG's clinical experts do not consider this a clinically plausible scenario therefore a HR of 1 was used instead of the 0.95 HR. Results of the ERG's scenario analysis are reported in Section 6.

5.4.7 Time to treatment discontinuation

Patients in STEVIE received treatment until progression or unacceptable toxicity. Treatment duration with vismodegib in the model was defined through the use of TTD data from STEVIE. Based on the AIC and BIC criteria reported in Table 44, the log-logistic model is the best statistical fit for the laBCC and mBCC data. Nonetheless the company decided to fit a Weibull model to the vismodegib arms of the model. The CS justifies this decision with the fact that using a log-logistic curve causes the estimated TTD and the PFS curves to cross for laBCC patients (Figure 16) and similarly the log-logistic fitted TTD curves for laBCC and mBCC cross for vismodegib patients (Figure 17). The company deemed the scenario in Figure 16 clinically implausible and the scenario portrayed in Figure 17 a poor representation of the KM curves (which do not cross). As such, the company decided to fit a Weibull model to TTD data for laBCC and mBCC patients.

Table 44. Goodness of fit statistics for TTD data

	laBCC	mBCC	Locally advanced	Metastatic
Exponential	3'112.46 (5)	239.94 (2)	3'117.46 (4)	242.43 (1)
Weibull	**3'112.02 (4)**	**241.92 (3)**	**3'122.03 (5)**	**246.90 (3)**
Log-logistic	3'043.02 (1)	239.66 (1)	3'053.03 (1)	244.64 (2)
Log-normal	3'061.75 (3)	242.74 (5)	3'071.76 (2)	247.71 (5)
Gamma	3'058.96 (2)	N/A	3'073.98 (3)	250.10 (6)
Gompertz	3'114.46 (6)	241.94 (4)	3'124.47 (6)	246.92 (4)

Figure 16. Vismodegib TTD and PFS curves for laBCC and mBCC patients (CS, Figure 33)

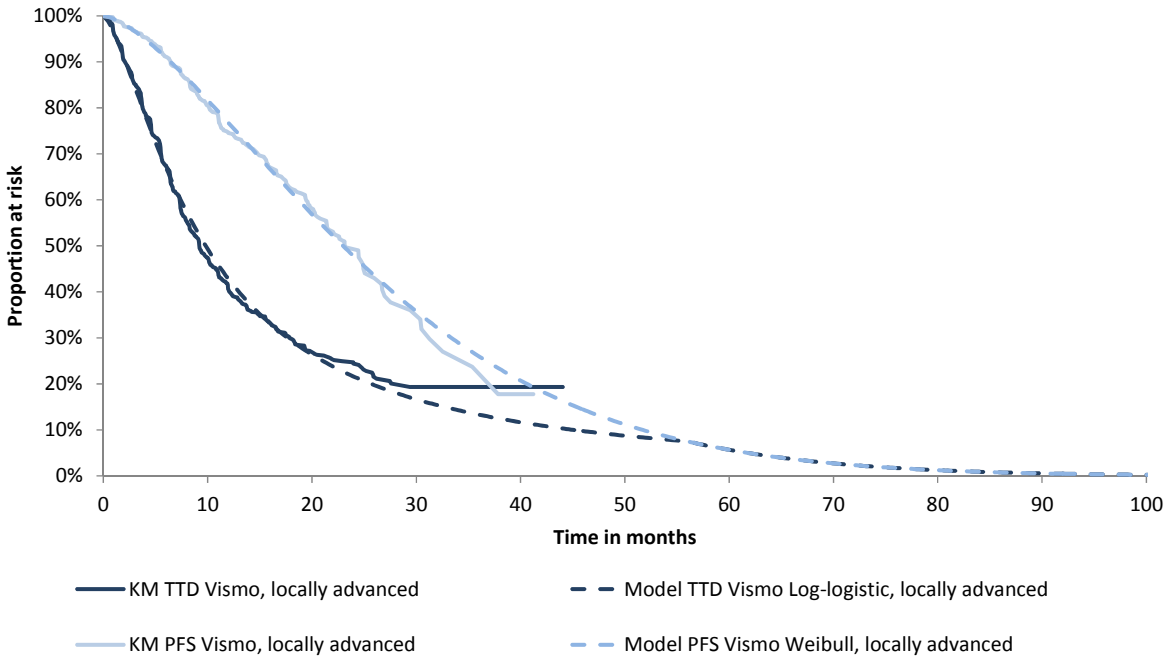
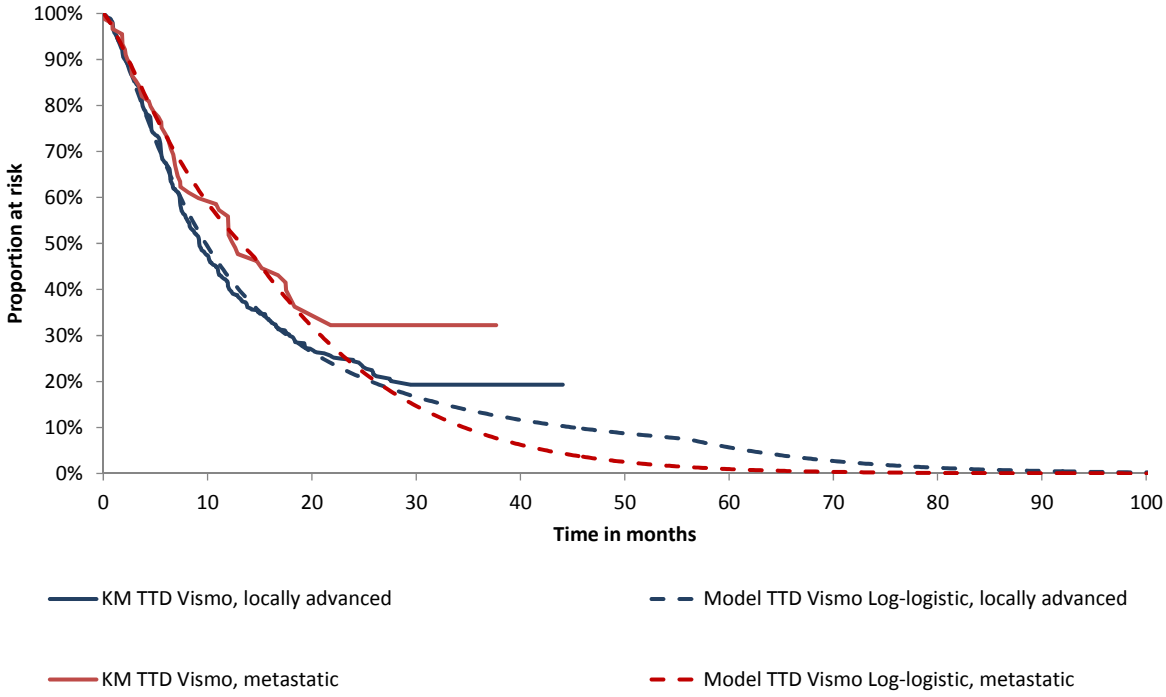


Figure 17. Vimsodegib TTD curves for laBCC and mBCC patients (CS, Figure 32)



ERG critique

As acknowledged by the company, vismodegib patients discontinue treatment for reasons other than disease progression or death. Treatment discontinuation in STEVIE was defined as dose interruptions longer than eight weeks, which means that patients stopping treatment for up to eight weeks were not considered to discontinue treatment. Clinical expert opinion provided to the ERG advised that patients are unlikely to tolerate vismodegib for long periods of time, requiring treatment breaks and eventually discontinuing treatment. Clinical experts added that in UK clinical practice, vismodegib patients are usually kept on a treatment regimen of three months on active treatment followed by three months off treatment, on a continuous basis, before disease progression or unacceptable toxicity. It was also reported that patients are unlikely to tolerate vismodegib for longer than 6 months without treatment breaks.

Considering the frequent treatment breaks required by vismodegib patients, the ERG agrees with the company's approach of using TTD data to capture treatment costs in the model. However, the definition of treatment discontinuation in STEVIE might not be an accurate representation of treatment discontinuation in clinical practice. While STEVIE patients were considered to discontinue treatment after two months off treatment, in clinical practice patients seem to have three month breaks in their treatment regimens before continuing treatment. Considering the expected vismodegib treatment

regimen in the UK, both STEVIE and the economic model are unlikely to reflect clinical practice in terms of treatment costs and benefits.

The ERG has some concerns regarding the estimation of TTD curves in the laBCC and mBCC vismodegib models. These are summarised and discussed in turn below:

1. The company's decision to use a Weibull instead of a log-logistic model to estimate TTD in the laBCC and mBCC models;

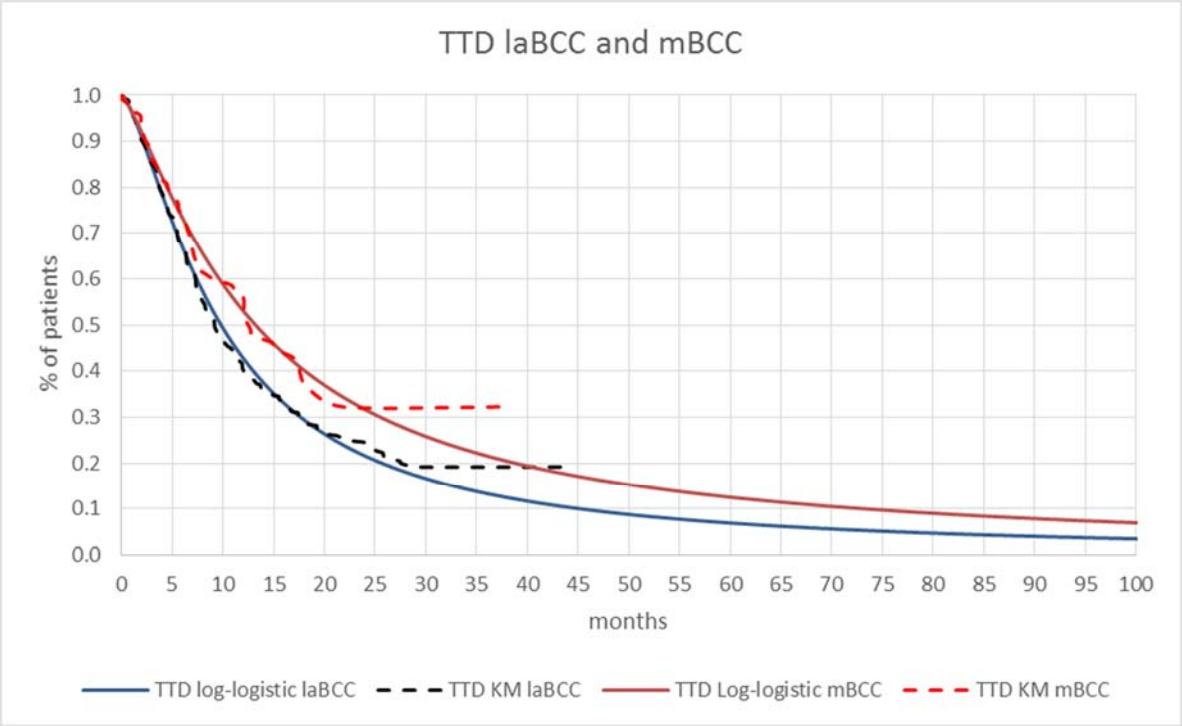
2. The KM TTD laBCC and mBCC curves crossing;

3. The KM TTD curve crossing the KM PFS curve for mBCC patients.

The company reports AIC and BIC statistics, together with a log survival odds over log time plot to justify that the log-logistic model is the best fit for both laBCC and mBCC. However, because the company's claim that the fitted log-logistic curves for laBCC and mBCC cross, while the KM curves for the corresponding data don't (Figure 17 above), together with the fact that the log-logistic TTD and the PFS curves cross for laBCC patients (Figure 16 above), the company decided to use a Weibull model instead.

The fact that the laBCC and mBCC TTD log-logistic curves cross in the model is caused by the company's approach to modelling the TTD curves, and has nothing to do with the fit of the log-logistic curves. The reason why the TTD log-logistic curves cross for laBCC and mBCC, when the corresponding KM curves do not, is due to the company's decision to cap the TTD curves to the PFS curves for laBCC and mBCC, and does not indicate a bad fit of the log-logistic curves. When the ERG plotted the uncapped log-logistic curves against the KM curves for TTD data for laBCC and mBCC patients, it obtained the curves shown on Figure 18. The ERG's plotted log-logistic curves do not cross each other, which differs from the crossing log-logistic curves reported by the company.

Figure 18. TTD curves for laBCC and mBCC



Furthermore, looking at Table 44 above, 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 earlier in Section 5.4.5.4, 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 at the tail (Figure 19). Figure 19 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 use of the Weibull curve brings no benefits to the modelling exercise.

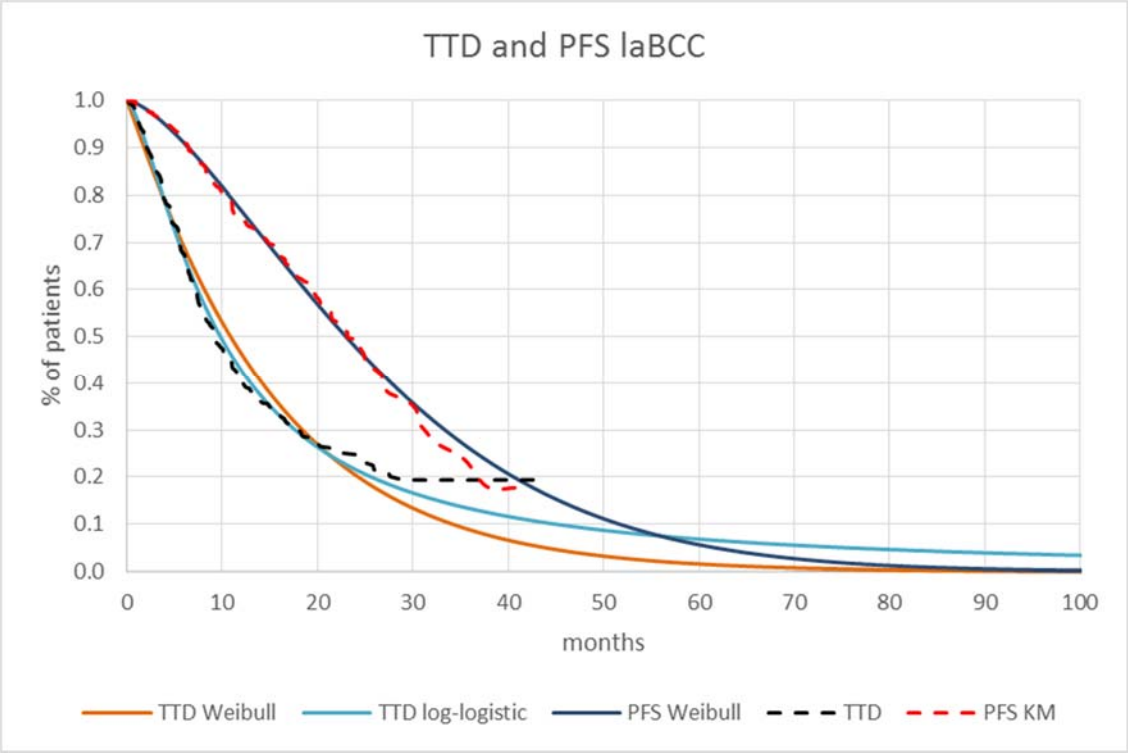
The ERG agrees with the company that the TTD curve for vismodegib should not cross the PFS curve as treatment beyond progression was not allowed for patients in STEVIE. However, the non-crossing of the curves should be reflected in the KM curves, and should only be a curve fitting problem in the case where KM curves do not cross, themselves. The company has dealt with the issue of TTD and PFS crossing curves by capping the TTD curves (even when fitted with a Weibull curve) 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.

With regards to laBCC patients, the reason why the KM TTD and the PFS curves cross at around month 38 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 on the model time horizon, the proportion of patients left in the log-logistic TTD curve (and the PFS curve) at 5 years is 7%. Considering the small percentage of patients, the ERG's preferred approach would still be to use a better fitting curve 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 (for 3 years) the 7% of patients left in the TTD curve only discontinue treatment due to death or progression.

The formulae used in the estimation of time on treatment in the company's model already accommodates for capping the TTD curve by the PFS curve therefore the ERG's preferred approach only required changing the Weibull to a log-logistic TTD curve in the model. Results are presented in Section 6.

Figure 19. TTD and PFS curves for laBCC



With regards to mBCC patients, and as explained in Section 5.4.5.4, the long tails of the KM TTD curves suggest that metastatic patients continued treatment after progression in STEVIE. The TTD and the 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.

The CS does not to report the issue of TTD and PFS curves crossing for mBCC patients (it only reports this as an issue for laBCC patients). The ERG investigated the KM and fitted curves in the model and reports these in Figure 20. As mentioned previously, in the mBCC population, the KM curves for TTD and PFS cross at around month 15 and separate until around month 38. 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, it 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 therefore no clinical rationale was provided. 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.

Regardless of the cause leading to KM curves crossing, the company's approach to solving this problem for the estimated curves was to cap the estimated TTD curve by the PFS curve (the Weibull curve also presented the same crossing problem, as can be observed in Figure 20). This means that from month 12 and for the remaining of the economic analysis (for about 4 years, given that there are no patients left in the TTD curve at year 5), PFS and TTD curves overlap. This implies that the 54% of patients in the TTD curve at year 1 only discontinue due to death or progression in the next 4 years. This is the same scenario that the company deemed implausible when making modelling decisions for the laBCC model. Page 188 of the CS states that, *If TTD was to be equal to the PFS, it would imply that patients discontinue treatment because of progression or death only. However, from what we have observed in the previous 30 months of follow-up, where the PFS KM is a lot higher than the TTD KM, it does not seem plausible that the TTD would reach PFS"*. Therefore, there is a high degree of inconsistency and a lack of clarity in the company's modelling approach for laBCC and mBCC models.

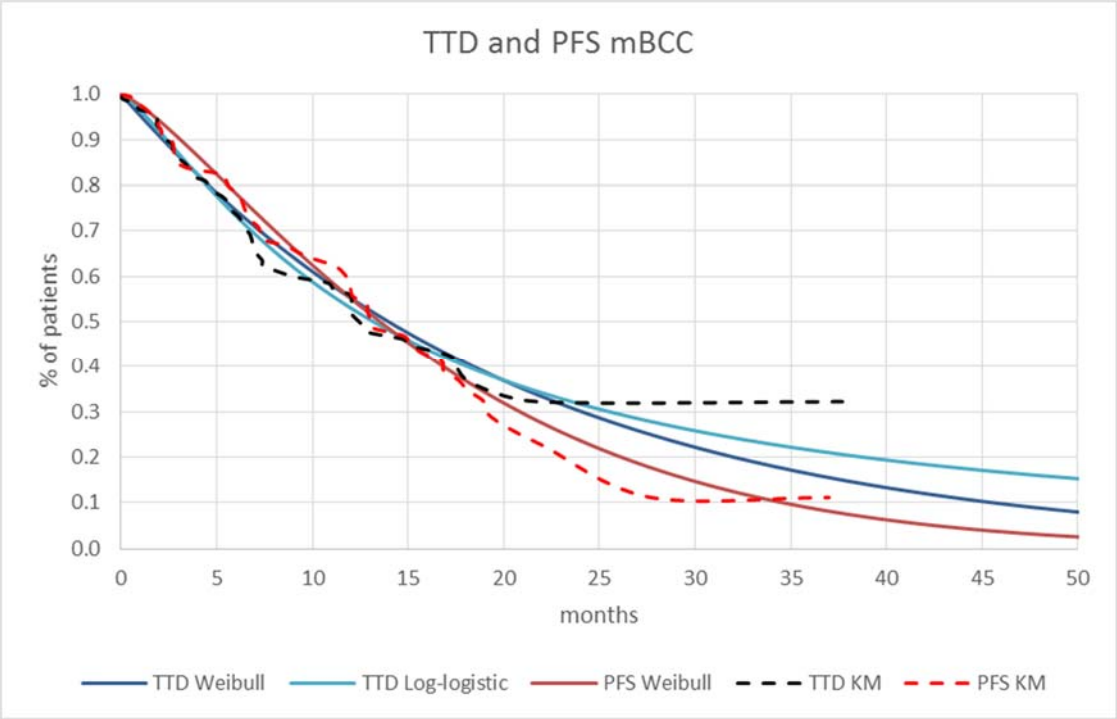
It remains unclear to the ERG if capping the TTD curves (regardless of the distribution used to model these) to the PFS curves for laBCC and mBCC patients translates into a clinically plausible scenario or not. It could be hypothesised that metastatic patients die and progress quicker, therefore their time to experience AEs and discontinue treatment is shorter, compared with locally advanced patients. The data reported in the STEVIE CSR indicates that only 5% of mBCC patients discontinued treatment due to death (compared with 3% in laBCC patients) and that disease progression led to 39% of metastatic patients discontinuing treatment (compared with 14% of laBCC patients). The STEVIE CSR also reports that 16% of mBCC patients discontinued treatment due to AEs, while 33% of laBCC patients discontinued for the same reason.

Similar to the laBCC model, the ERG does not consider that the company has presented a valid argument for changing the log-logistic distribution to a Weibull one to model TTD curves in the mBCC model, considering that the log-logistic curve is the best fitting to the TTD KM data. 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 impact on the final ICER from using a log-logistic model is reported in Section 6 of the report.

The mean treatment duration estimated in the model is 15 months for laBCC (17 with a log-logistic model) patients and 16 months for mBCC patients (16 with a log-logistic model). These estimates compare with 11 months for laBCC and 12 months for mBCC patients in the STEVIE study. This suggests that time on treatment is slightly overestimated in the economic model. The fact that on average, metastatic patients seem to stay on treatment for longer than locally advanced patients seems

counterintuitive from a clinical point of view, considering the higher mortality expected in mBCC patients.

Figure 20. TTD and PFS curves for mBCC



5.4.8 Adverse events

To model vismodegib-related AEs in the model, the company included Grade 3 or higher treatment-emergent adverse events (TEAEs) observed in ≥ 2% of patients in STEVIE. The TEAEs included in the model are dysgeusia, increased gamma-glutamyltransferase (GGT), muscle spasms, and decreased weight. The company reports that although 2.2% of patients in STEVIE experienced Grade ≥3 hypertension, these events were considered to be unrelated with treatment with vismodegib and so were not included in the model. The TEAEs included in the economic analysis are summarised in Table 45. The costs of adverse events included in the model are discussed in Section 5.4.11. The impact of AEs in patients' quality of life is discussed in Section 5.4.10.

Table 45. Adverse event rates used in the model (Adapted from CS, Table 39, pg 137)

Adverse event	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Muscle spasms	90 (8.0%)	5 (5.2%)	95 (7.8%)
Weight decreased	44 (3.9%)	4 (4.2%)	48 (4.0%)
Gamma-glutamyltransferase increased	28 (2.5%)	2 (2.1%)	30 (2.5%)
Dysgeusia	25 (2.2%)	1 (1.0%)	26 (2.1%)
Abbreviations in table: laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; n,N=number.			

ERG critique

The ERG considers the company's approach to be generally reasonable. Clinical expert opinion provided to the ERG confirmed that hypertension is unlikely to be caused by vismodegib. Clinical experts added that most patients will discontinue vismodegib at some point as its adverse events (although not easily quantifiable in terms of impact on costs to the NHS and impact on patients' quality of life) have a considerable impact on patients' wellbeing. For example, 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.

5.4.9 Mortality

The company used KM data from STEVIE to model OS in the vismodegib arms of the economic model. Based on the AIC and BIC criteria reported in Table 46, the company concluded that the Gamma distribution was the best fitting model for the laBCC population and that the lognormal was best fitting one for the mBCC data. The CS notes the lack of maturity in OS data, with only 9% of patients having died in STEVIE at the data cut-off point. Therefore, the CS notes that the extrapolated tails of the OS curves carry a high level of uncertainty in the economic analysis, regardless of the distribution used.

Table 46. Goodness of fit statistics for OS data

	AIC		BIC	
	Locally advanced	**Metastatic**	**Locally advanced**	**Metastatic**
Exponential	783.93 (3)	128.77 (3)	788.93 (2)	131.25 (1)
Weibull	785.92 (5)	129.93 (5)	795.93 (5)	134.91 (4)
Log-logistic	784.87 (4)	129.49 (4)	794.88 (4)	134.46 (3)
Lognormal	778.48 (2)	**128.19 (1)**	788.49 (1)	**133.17 (2)**
Gamma	**775.49 (1)**	128.52 (2)	**790.51 (3)**	135.98 (6)
Gompertz	785.93 (6)	130.77 (6)	795.94 (6)	135.74 (5)

The company plotted the best-fitting curves (Gamma for laBCC patients and lognormal for mBCC patients) against the respective OS KM curves and the mortality in the UK general population (Office of National Statistics, 2013–2015), matched for gender and age. The ERG shows these curves, together with all the other models considered for fitting OS in Figure 21 and Figure 22 for laBCC and mBCC, respectively.

The CS reports that the mortality rates observed in the STEVIE trial do not reflect the increase in mortality rates at older ages and, therefore, the OS fitted curves are likely to overestimate long-term survival in the laBCC and the mBCC populations (Figure 21 and Figure 22), when compared with the survival of the general population. The company reinforces the view that mortality directly attributed to laBCC is incredibly rare and that laBCC patients are usually elderly and are often suffering from other co-morbidities. Nonetheless, the company adds that patients diagnosed with non-melanoma skin cancer (including BCC and SCC) have a 10-year lower life expectancy than the general population. With regards to mBCC patients, the CS states that these patients' prognosis is poor, with mortality being higher than that for the general population.

The company sought clinical expert opinion and was informed that patients with mBCC have excess disease mortality and should not reach background mortality at any point in the extrapolation. Therefore, the company considered parametric models with a "lighter" tail, such as the Weibull, exponential, or Gompertz models. Given that the exponential distribution incorporates a hazard function that is constant over time and that the Gompertz model converged almost to an exponential model (theta parameter = 0.00000001), the company chose a Weibull model in the base case analysis of OS for the mBCC group.

For the laBCC group, clinical opinion provided to the company suggested that patients at lower ages are more likely to have a slight excess mortality directly attributable to laBCC. However, as patients get older, it is more likely that they die from other comorbidities and not from laBCC. Therefore, the company used the Gamma function adjusted for background mortality in the base case analysis. Two methods were evaluated in order to prevent OS extrapolations exceeding background mortality rates in the model. These methods have implications on the evaluation of the relative treatment effectiveness of vismodegib compared to BSC. These are discussed below.

Figure 21. Survival curves and KM curve for OS laBCC

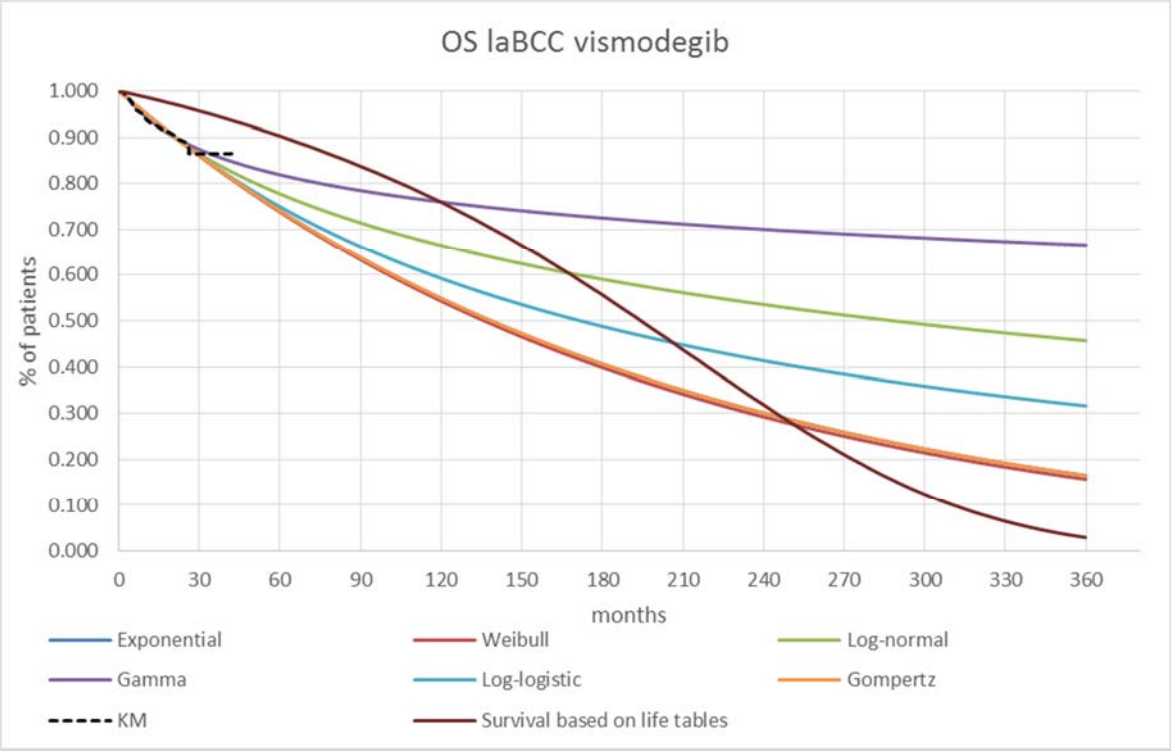
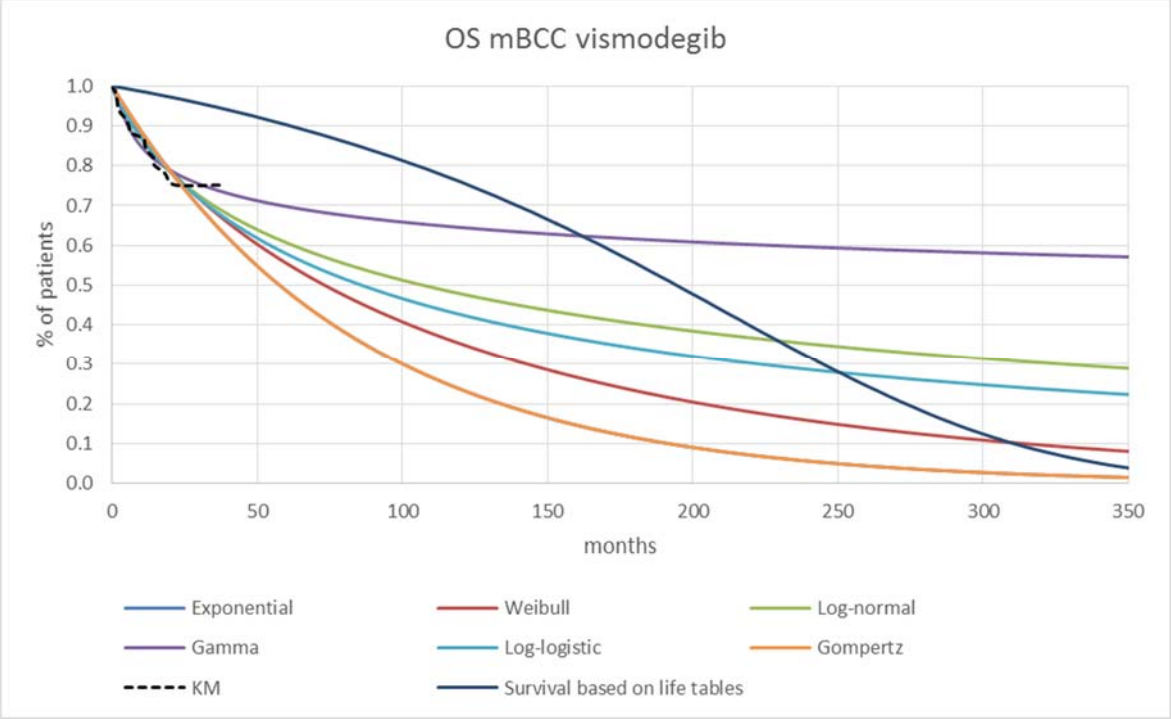


Figure 22. Survival curves and KM curve for OS mBCC

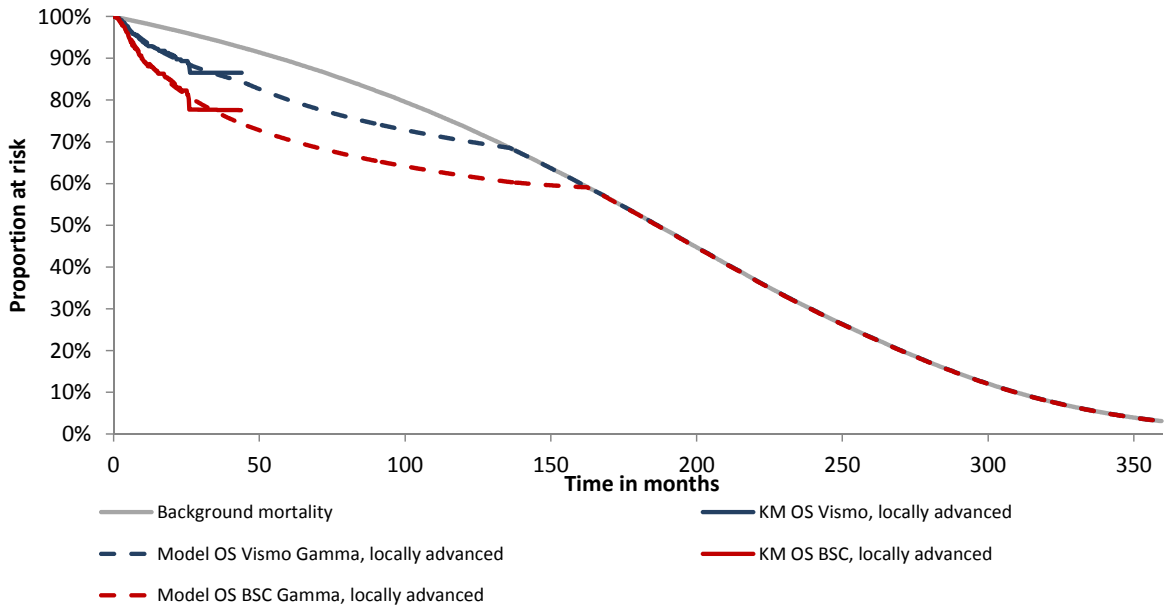


To estimate OS in the BSC arms of the model, the company applied the HRs derived from the landmark approach to the Gamma vismodegib OS curve for laBCC patients and to the Weibull vismodegib OS

curve for mBCC patients. The company considered that it would be unrealistic to assume a life-long treatment effect with vismodegib and so applied the relevant HRs for 44 months in the laBCC model and until month 38 in the mBCC population. These time points correspond to the maximum follow-up times in STEVIE. After these time points, the company used the hazard rate from the BSC arm to model OS for vismodegib patients.

In order to adjust the laBCC OS curve to background mortality, the company took two alternative approaches. The first option consists on capping the OS vismodegib curve with the background mortality curve. This option implies that the OS rates in patients with laBCC are calculated as the minimum between the OS fitted curve and the background mortality survival rates. When this option is used the difference in survival probabilities between vismodegib and BSC diminishes once the vismodegib curve crosses the background mortality curve and disappears entirely when the BSC survival curve crosses the background mortality survival curve (because the background mortality survival curve effectively becomes the same OS curve for vismodegib and BSC patients, Figure 23). According to clinical opinion provided to the company this translates into an unrealistic scenario. Therefore, the company did not use this approach in their base case analysis, but included it as scenario analysis.

Figure 23. Modelling of overall survival curves as the minimum of parametric extrapolations and background mortality survival (Figure 38, CS page 205).

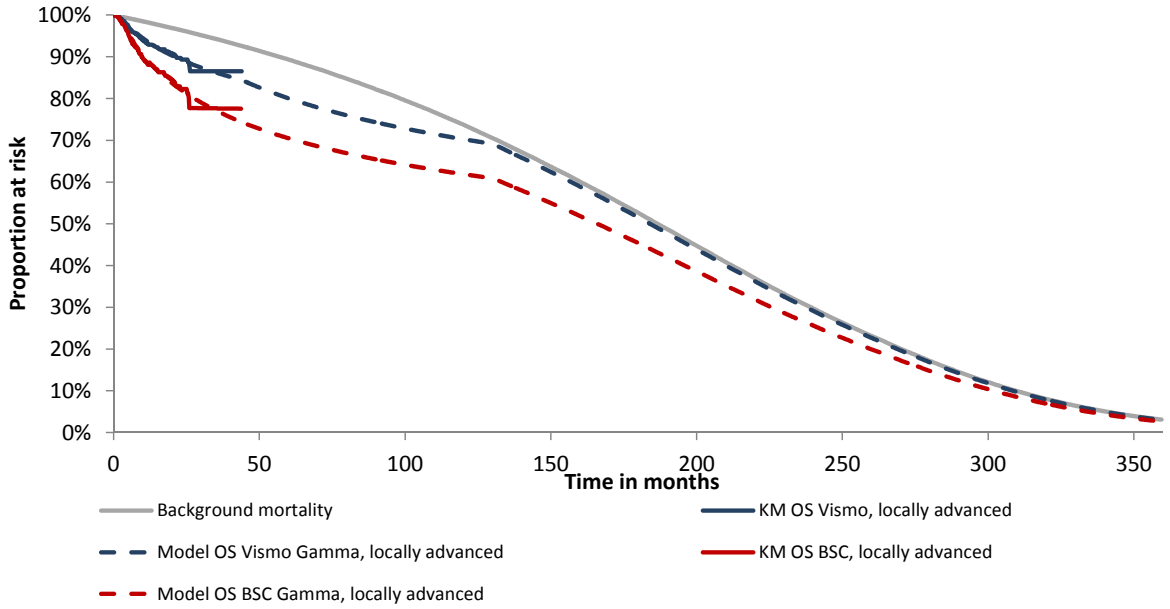


The second option, and the one used by the company in their base case analysis, consists of applying uniform background mortality rates to the OS curves in the vismodegib and BSC model arms after a user-defined point in time. The company states that this option still assumes that the treatment effect

will cease at the end of the STEVIE follow up period. The cut-off point, at which background mortality applies, was selected at the point where the extrapolated vismodegib curve crosses the background mortality curve, which is approximately 147 months (12.25 years).

This approach assumes that after a certain point, patients in the BSC arm would have the same risk of dying as the general UK population (Figure 24). However, in contrast to the previous approach, the BSC curve lies below the general UK population, as shown Figure 39, i.e. patients who would get BSC have a reduced life expectancy compared to general UK population over the entire time horizon.

Figure 24. Modelling of overall survival curves using uniform background mortality rates after a user-defined timepoint (Figure 39, CS page 206).



ERG critique

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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these data will carry a high degree of uncertainty. Therefore, the ERG considers that even though the traditional steps in validating curve fit and extrapolations should be undertaken, clinical expert opinion might be of more value in this instance given the lack of robust OS data. This is only caveated by the fact that out of the three clinical experts contacted by the ERG (two dermatologists and one oncologist), only one had had contact with an mBCC patient. As mentioned in

Section 4, the incidence of mBCC is extremely low, and therefore clinical expert opinion given for mBCC also carries considerable uncertainty.

The ERG splits its review of the company's approach to modelling OS data by laBCC and mBCC, due to the difference in these populations but also the difference in opinions provided by the clinical experts advising the ERG.

5.4.9.1 Mortality in laBCC patients

When shown Figure 21, the clinical experts advising the ERG reached a similar conclusion. The three experts reported that they would expect the OS curve for vismodegib to be closer (if not the same) to the background survival curve seen for the average UK population. Clinical experts stated that patients are highly unlikely to die from laBCC, as acknowledged by the company in several instances in the CS. One clinical expert added that the advantage of vismodegib in laBCC patients is in preventing progression, but that once that point is reached then the journey of the patient is the same, irrespective of treatment. However, as raised by the ERG in Section 5.4.5.3, the PFS HR for laBCC is not statistically significant in the landmark approach.

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 landmark approach method and the non-systematic selection process of prognostic factors in the HR estimation, which potentially introduced further uncertainty and bias in the analysis. It is difficult to anticipate the direction and the extent of the methodological uncertainty associated with the estimation of the PFS and OS HRs.

The CS does 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 also interesting to note that for the first five cycles in the economic model, the company used the background survival curve to model OS for vismodegib (instead of the Gamma model), as the survival predicted by the Gamma model was higher than the background survival for the matched UK population.

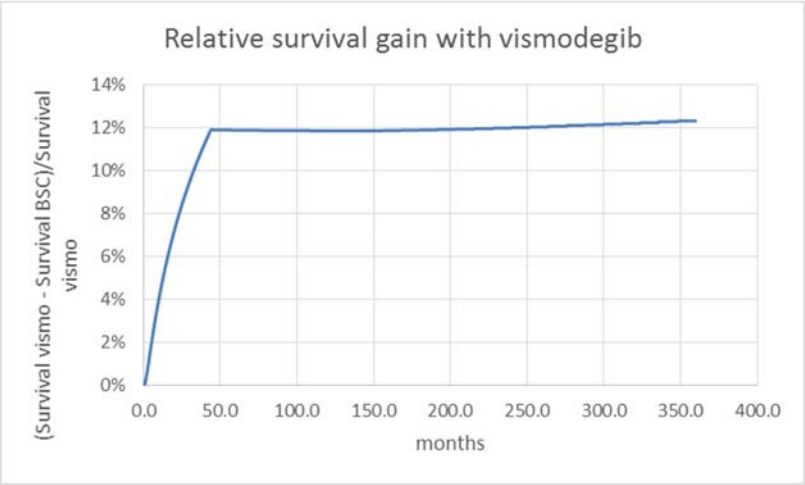
The ERG ran a scenario analysis using the OS HRs adjusted for ECOG, age and Gorlin syndrome for the laBCC population, despite the clinical inconsistency in the statistical significance found for the OS and PFS HRs. Considering the consistent feedback from clinical experts and the statements included in the CS, the ERG also ran a conservative scenario analysis where the mortality for laBCC patients with vismodegib was assumed to be the same as the background mortality for the UK population. This implies that the there is no mortality gain with vismodegib compared with BSC, as there is no mortality loss associated with laBCC. This is an important analysis as it reflects a scenario where laBCC is not

associated with reduction in patients' survival. Results of this scenario analysis are reported in Section 6 of the ERG report.

The company made two different adjustments to the vismodegib OS survival curve. Firstly, the company assumed that the treatment duration with vismodegib ends at 44 months and so adjusted the OS curve after this point. The probability of a patient being alive in the vismodegib OS curve at cycle 44+1 in the model was calculated as the probability of the patient being alive at cycle 44 times the probability of a BSC patients remaining alive from cycle 44 to cycle 44+1. The same calculations were applied to all following cycles.

This approach requires the use of the OS BSC arm, which in the model is derived through taking the OS vismodegib arm to the power of the estimated OS HR. Therefore, while the transition probability applied in the OS vismodegib curve after month 44 might come from the transition probability of survival in the BSC curve, the BSC curve is still derived from a HR which assumes that there is a relative treatment gain resulting from using vismodegib, compared with BSC. Furthermore, the adjustment carried means that from month 44 onwards the relative treatment effectiveness with vismodegib is approximately maintained, but does not diminish (Figure 25).

Figure 25. Relative survivall gain with vismodegib over time



Secondly, the company adjusted the laBCC survival curve to reflect the background mortality in the UK population, given that survival with the extrapolated vismodegib curves in the long term is higher than the background survival for the average UK population (regardless of the distribution used to model survival). The company chose the second adjustment approach over the first one (reported in the previous section). However, the ERG prefers the first approach which consists of capping the OS vismodegib curve with the background mortality curve. When this option is used the difference in survival probabilities between vismodegib and BSC diminishes once the vismodegib curve crosses the

background mortality curve and disappears entirely when the BSC survival curve crosses the background mortality survival curve (as the background mortality survival curve effectively becomes the OS curve for vismodegib and BSC patients, Figure 26). According to clinical expert opinion provided to the ERG, this translates a realistic scenario as patients are expected to become resistant to vismodegib over time, and the duration of the treatment effect is not a life-long one.

Nonetheless, the ERG also acknowledges the theoretical consequence pointed by the company resulting from using this approach. When this option is used the difference in survival probabilities between vismodegib and BSC diminishes once the vismodegib curve crosses the background mortality curve and disappears entirely when the BSC survival curve crosses the background mortality survival curve. This implies either an improvement in BSC patients' health or a more accentuated decrease in vismodegib's patients' health status, when compared with BSC patients. While the former is unlikely, the latter could be hypothesized maybe the case where vismodegib acts as a delaying factor in patients' progression but once patients progress there is a "rebound effect", where the effect of vismodegib is no longer observed and so patients become equivalent to BSC patients, in terms of survival. This is the equivalent to saying that once patients progress on vismodegib, their survival effectively becomes that of BSC patients at the beginning of the OS curve, where a steeper drop in survival is observed (Figure 24). This would then compare to the survival of BSC patients later in the OS curve, where a smoother curve is observed.

Clinical expert opinion provided to the ERG disagreed with the company's method for adjusting the OS vismodegib curve to the background mortality as it implies that patients who received vismodegib will carry a survival gain throughout their lifetime, compared with BSC (Figure 24 and Figure 25). The company applied uniform background mortality rates to the OS curves in the vismodegib and BSC model arms after 147 months (12.25 years) in the model. The company also explains that this approach assumes that after a certain point patients on the BSC arm would have the same risk of dying as the general UK population (Figure 24) but that patients who get BSC have a reduced life expectancy compared to general UK population over the entire time horizon. Even if this is a plausible assumption, using this adjustment method leads to the estimation of a constant benefit with vismodegib from month 44 onwards, which is not clinically plausible.

In summary, the ERG acknowledges the flaws in both approaches, but considers that given the uncertainty around the shape of the "real" OS curve for vismodegib and the duration of treatment benefit in clinical practice, the preferred approach would be to assume that when the OS curves for vismodegib and BSC cross the background survival curve, the survival for vismodegib and BSC patients becomes the same as for the background population (orange and red curves in Figure 27). This approach reflects

a scenario where the mortality for vismodegib and BSC patients eventually becomes the same, which is plausible from a clinical point of view.

It is difficult to evaluate the extent to which the company's analysis is generalizable to laBCC patients in the UK. For example, the fact that laBCC patients have a higher mortality rate than the average age and gender-matched population in the UK, when clinical expert opinion and the CS repeatedly state that laBCC is very unlikely to lead to an increase in mortality, might be related to the fact that only 3% of patients in the STEVIE trial came from the UK. Given these patients age, and the possibility that patients' co-morbidities is the main cause of death, it could be hypothesised that the other 97% of the STEVIE population had higher mortality rates due to different co-morbidities from the ones observed in the UK for the gender and age matched average population, or due to different management/treatment options for these conditions in other health care systems.

Figure 26. Relative survival gainwith vismodegib over time when OS curves are capped by background mortality rates

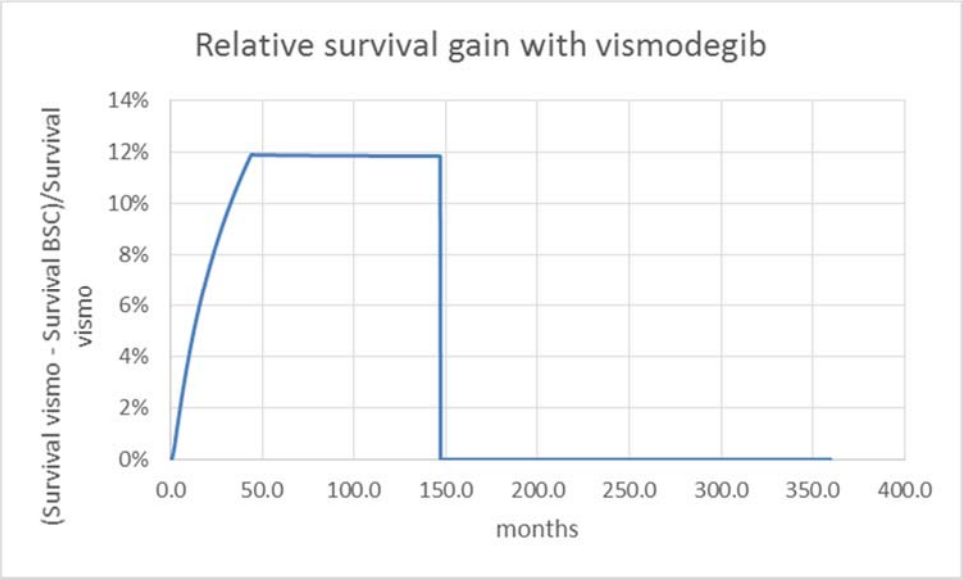
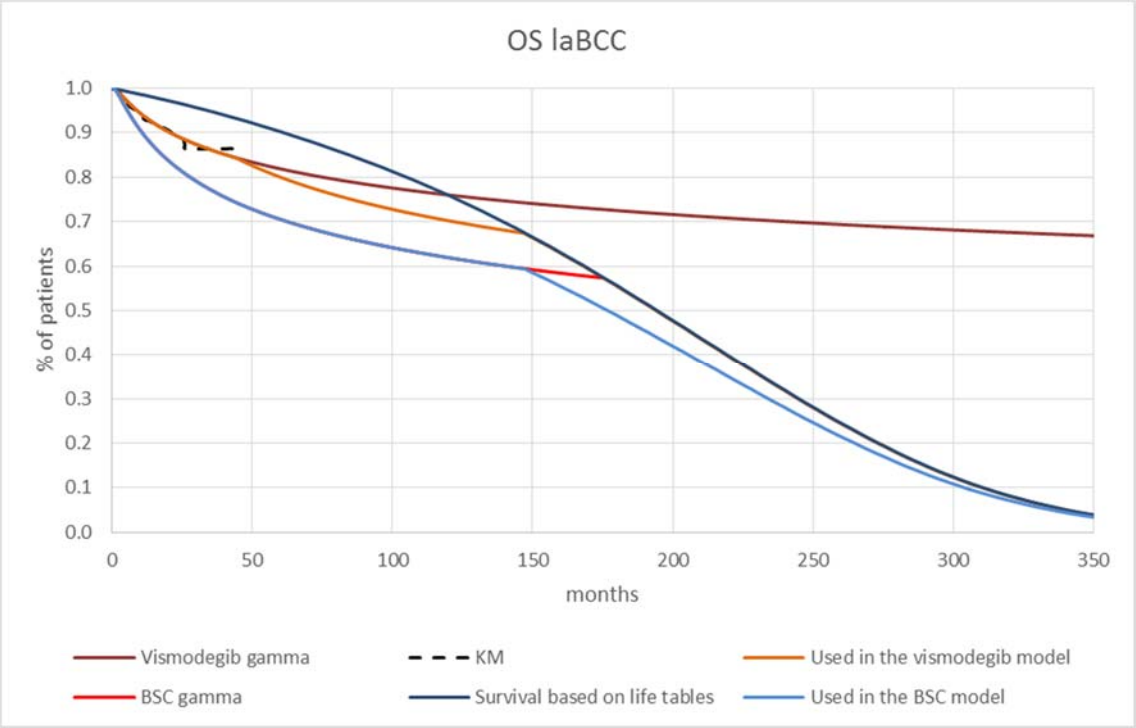


Figure 27. Alternative approaches for modelling mortality in laBCC patients



5.4.9.2 Mortality in mBCC patients

When shown Figure 22, the clinical experts advising the ERG had different reactions. Even though the three experts agreed that (unlike for laBCC), patients will die from mBCC, there was not a consistent view on which curve was a better representation of the vismodegib OS curve for mBCC. Nonetheless, all the clinical experts expected mortality to be much higher than that reflected with the Gamma distribution.

As mentioned previously, the ERG agrees with the company's assessment regarding the lack of mature OS data. For mBCC patients, this problem is exacerbated by the small sample size observed in STEVIE. Therefore, the ERG considers that even though the traditional validation methods for curve fit and extrapolation are important, clinical expert opinion might be of more value in this instance given the lack of robust OS data. This is only caveated by the fact that out of the three clinical experts contacted by the ERG (two dermatologists and one oncologist), only one had had contact with an mBCC patient.

The company chose the Weibull distribution to model OS for the mBCC population. Two of the clinical experts advising the ERG considered the lognormal to be a better reflection of what OS with vismodegib for mBCC would look like. One clinical expert added that the Weibull curve would be a better representation for the BSC OS curve. The third clinical expert's opinion was that none of the curves were accurate representations of mortality for mBCC patients as it was expected that most mBCC

patients die between 12 to 24 months and it was unrealistic to assume that patients would survive for more than 10 years. This is consistent with the view of the EGP in Canadian HTA body, who considered that mBCC patients were expected to survive for less than 10 years.

Determining a clinically realistic survival curve for mBCC patients is extremely difficult, as is determining the relative treatment effect of vismodegib compared with BSC for these patients. The ERG asked the company to use the McCusker *et al.* paper to conduct a validation exercise on the modelled BSC arm for mBCC as this study appears to be the only available evidence for BSC-related mortality in aBCC patients. [26]

The company aggregated the distant and regional metastatic KM OS curves from McCusker *et al.* as requested by the ERG and used it to fit BSC OS curves in the economic model for mBCC patients.[26] The company then applied the inverse HR obtained through the landmark approach to derive an mBCC vismodegib curve. Figure 28 shows that the modelled survival curves from STEVIE (i.e. ITT population curve for vismodegib patients and BSC curve estimated by applying the landmark HR to the ITT vismodegib curve) and the McCusker *et al.* curves (i.e. the observed BSC curve for mBCC patients and the vismodegib curve estimated by applying the landmark HR to the McCusker *et al.* curve) are similar (red and blue curves compared with yellow and pink curves). [26]This is not unexpected, considering that the same HR was used to derive the comparator curve in each case (i.e. the BSC curve in STEVIE data and the vismodegib curve in the McCusker *et al.* data).[26] As the observed curves (i.e. ITT curve in STEVIE and BSC curve in McCusker *et al.*) are not comparable, the difference in these curves cannot be validated by any other data source.[26] However, Figure 28 also shows the difference between the non-responders in STEVIE and the BSC patients in the McCusker *et al.* paper (dark green and pink curves).[26] This shows that the non-responders group in STEVIE and the BSC patients in McCusker *et al.* have very different survival prognosis.[26] This analysis is caveated by the fact that the number of patients in the non-responders group in STEVIE is incredibly small (31 patients) and that only four patients died. It should also be noted that patients in McCusker *et al.* are younger than in STEVIE, which would suggest that patients would have a better survival prognosis instead of worse outcomes.[26]

Figure 28. Survival in mBCC patients

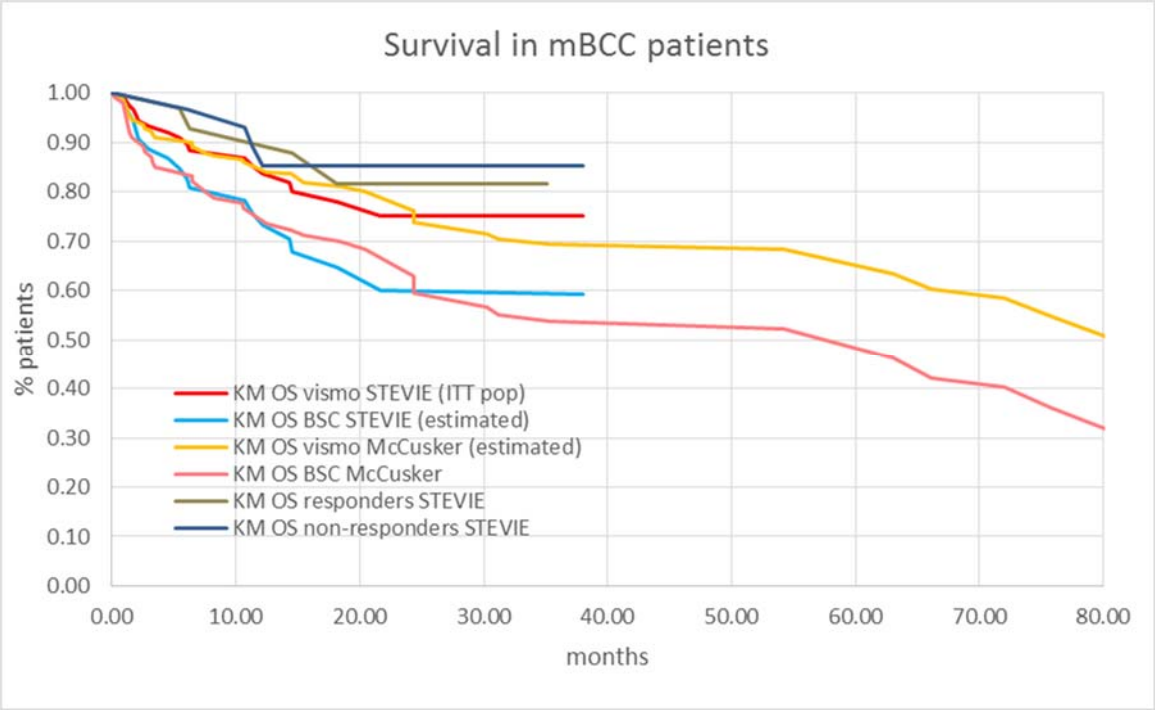
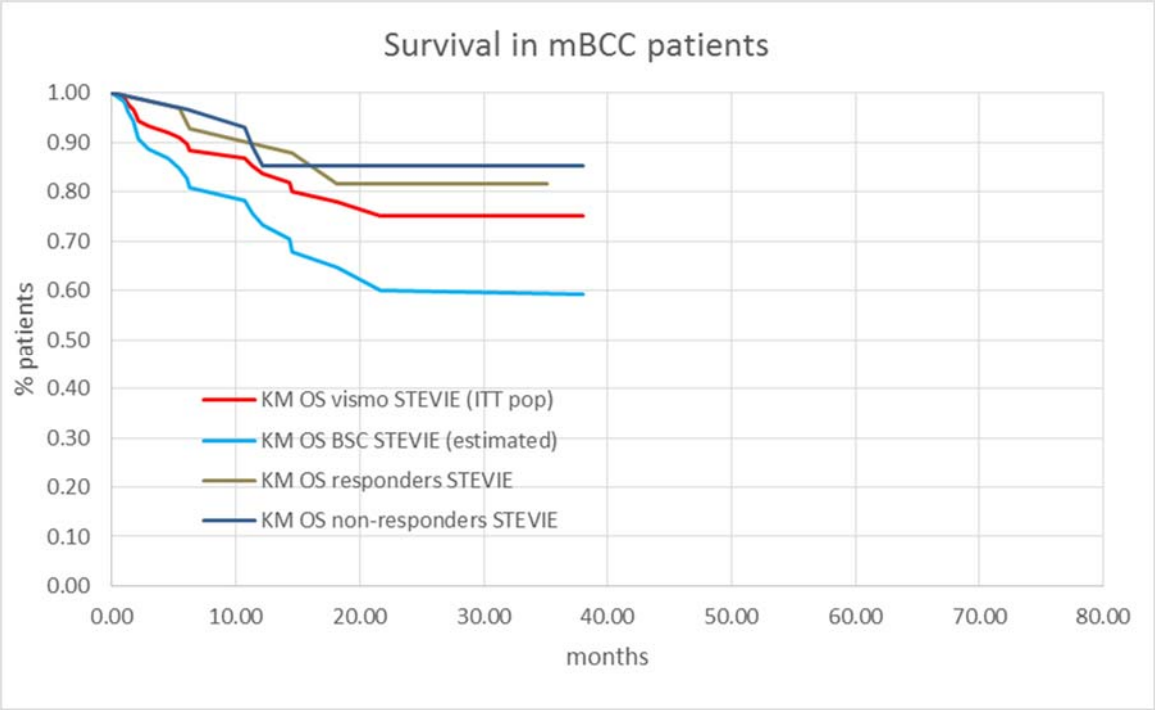


Figure 29 shows how the responders and non-responders groups from STEVIE compare with the modelled vismodegib and BSC curves for mBCC. The difference is these curves is overwhelming and it goes beyond the fact that the baseline curve (i.e. the vismodegib curve) changes its position from the ITT to the responders analysis. While the responders and non-responders KM curves clearly reflect the lack of statistical significance encountered in the landmark HR for OS in mBCC patients (as they cross and overlap a few times), the ITT and estimated BSC curves do not, and show a clear separation of the curves throughout the entire time horizon of the model. This is worrying as it reveals the lack of robust evidence substantiating the vismodegib and BSC estimated curves and the contradiction between observed and estimated outcomes.

Figure 29. Survival in STEVIE for mBCC patients



In summary, the ERG does not consider that the evidence provided by STEVIE or clinical experts (due to the very low incidence of mBCC cases) is robust enough to draw conclusions on the effectiveness of vismodegib in the mBCC population. For inclusiveness, the ERG ran a scenario analysis where the OS HR for mBCC patients was assumed 1 to reflect the lack of statistical significance, and evidence, on the relative effectiveness of vismodegib. Given that a similar analysis was ran for PFS outcomes, this reduces the economic analysis in the mBCC population to cost-minimisation. To model OS, the ERG used the Weibull model selected by the company and presents the results of the analysis in Section 6.

5.4.10 Health-related quality of life

5.4.10.1 Systematic literature review for HRQoL studies

The systematic review carried out by the company to identify studies reporting health-state utility values (HSUVs) for patients with aBCC is described and critiqued in Section 5.3.

The systematic literature review identified one study,[93] which is a vignette time trade-off (TTO) study in patients with aBCC, carried out in the UK. Health state vignettes were developed based on a systematic literature review and clinicians' feedback. The HSUVs were elicited for nine aBCC health states by carrying out a valuation exercise using the EQ-5D questionnaire on a sample of 100 members of the UK general population. The HRQoL results from the study were reported to be slightly better

compared to those seen in the UK general population, which are reported in Kind *et al.* [93, 99]. The HSUVs are reported in Table 47.

Table 47. HSUVs reported in Shingler *et al.*(CS, pg 219, Table 78)

Health state	Utility value (SD)[93]
Complete response	0.94 (0.08)
Post-surgical state	0.72 (0.24)
Partial response with small growth (2 cm)	0.88 (0.12)
Partial response with large growth (6 cm)	0.82 (0.16)
Stable disease with small growth (2 cm)	0.82 (0.16)
Stable disease with multiple growths (2 cm)	0.80 (0.20)
Stable disease with large growth (6 cm)	0.76 (0.20)
Progressed disease with small growth (2 cm)	0.74 (0.21)
Progressed disease with large growth (6 cm)	0.67 (0.25)
Abbreviations in table: cm, centimetre.	

Although this is not explicitly stated in the CS, nor in the Canadian and Irish HTA submissions, the ERG has reasons to believe that the Shingler *et al.* study[93] is the same TTO vignette study reported in the Canadian and Irish HTAs, which is used to model cost-effectiveness in the base case analysis. The company used the utility values reported in the study Shingler *et al.* study identified in the systematic literature review in a scenario analysis.[93]

5.4.10.2 Health state utility values used in the model

Utility data in STEVIE were captured with the Skindex-16 instrument. Given the lack of a published algorithm to map Skindex-16 into EQ-5D data, the company could not use the utility data captured in STEVIE. The HSUVs used in the model are based on SF-36 data collected in the ERIVANCE trial. The SF-36 data were mapped to EQ-5D tariff scores, using a mapping algorithm published by Rowen *et al.*[100] In ERIVANCE, SF-36 data were collected on Day 1, at Week 12, Week 24, and at the end of study or early termination visit. The company reports that only patients who completed the SF-36 on Day 1 were included in the final QoL analysis, in accordance with the predefined missing data rules. During the clarification stage, the company provided the ERG with descriptive statistics for all eight dimensions of the SF-36 data collected in the ERIVANCE study by study visit.

The Rowen *et al.* study reports five models to map SF-36 to EQ-5D data. These consist of three random effects generalized least squares (GLS) models, a tobit and a censored least absolute deviation (CLAD) model. According to the paper, the GLS model which included all dimensions of the SF-36 scale, squared and interaction terms, provided the most accurate prediction of EQ-5D data, based on mean absolute error and mean squared error.[100] The company selected this model to map the SF-36 data from

the ERIVANCE trial into EQ-5D tariff scores. A description of how the SF-36 data were used and mapped to EQ-5D values is presented in Box 17.

Box 17. Mapping of SF-36 data from the ERIVANCE trial to estimate HSUVs in the model (CS, pg 211- 212)

The general model reported in the paper is given below in Equation 6 Equation 6 $\gamma_i = \alpha + \beta x_{ij} + \theta r_{ij} + \delta z_{ij} + \varepsilon_{ij}$; where i = 1,2,..., n represents individual respondents and j = 1,2,..., m represents the eight different dimensions. The dependent variable, γ, represents the EQ-5D utility score, x represents the vector of SF-36 dimensions, r represents the vector of squared terms, z represents the vector of interaction terms and ε_{ij} represents the error term. Mapping was carried out on data collected in ERIVANCE up until the 28th November 2011. To be included in this analysis, patients must have completed the SF-36 at least twice - at baseline and one other follow-up assessment. Patients must also have complied with the missing data rules of the SF-36, as defined in the SF-36, Version 2, scoring manual. Instances where these two criteria were not fulfilled were classified as "missing data". No missing data was imputed in this analysis. The average EQ-5D utilities in the progression-free and post progression states were calculated as the raw means of the data collected from patients in these health states. The analysis was conducted separately for locally advanced and metastatic patients.
Abbreviations:

The resultant HSUVs used in the model are summarised in Table 48. Different utility values are applied in the model based on progression status and type of aBCC.

Table 48. Health state utility values used in the model (CS, pg 212, Table 73)

Health state	laBCC (95% confidence intervals)	mBCC (95% confidence intervals)
Progression-free survival	0.839 (0.81-0.87)	0.819 (0.79-0.85)
Progressive disease	0.757 (0.68-0.83)	0.639 (0.42-0.85)
Abbreviations in table: laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; SE, standard error.		

Utility decrements due to AEs were also considered in the model. The company used values reported in a study assessing the impact of treatment for advanced melanoma on quality of life for Australian and UK patients.[101] The company considered this paper to be the best available evidence given the paucity of data and the fact that melanoma is a similar disease area to BCC. Utility decrements in the study were not estimated for specific AEs, but instead a mean decrement was estimated for Grade 3 and Grade 4 events overall. All the Grade 3 events related with melanoma treatment in the study required 1 day of inpatient or outpatient stay while the Grade 4 events reported required a 2-5 day hospitalisation. A utility decrement of 0.13 (SE 0.01) is applied in the model for Grade 3 events, and a decrement of

0.17 (SE 0.01) for Grade 4 events.[101] Grade 3 adverse events are assumed to have a duration of 7 days in the model, while Grade 4 events are assumed to last for 14 days.

5.4.10.3 ERG critique

The quality of life data incorporated in the model are from the ERIVANCE trial, while the clinical effectiveness data used in the model are based on the STEVIE trial. The ERG acknowledges that there are no published algorithms for mapping quality of life data captured through the Skindex instrument into EQ-5D values, therefore using data from the STEVIE trial was not an option. Nonetheless, using ERIVANCE quality of life data raises several issues:

- The population in the ERIVANCE trial is generally younger than the STEVIE population therefore, and according to the ERG's clinical experts, this patient group is fitter and likely to experience better quality of life compared with STEVIE patients. This is potentially overestimating the quality of life of patients in the analysis, when compared to the source of the clinical effectiveness data used in the analysis;

- 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 on average 70 years old, which compares to a baseline median age of 62 years in ERIVANCE (72 years in STEVIE). This leads to a potential overestimation of utility values in the economic analysis, when compared to what is expected to be observed in clinical practice;

- Progression was assessed in different ways in the two trials. In STEVIE, progression was assessed using the RECIST v1.1 criteria, while in ERIVANCE a novel composite method was used to determine progression in the laBCC population. It is difficult to anticipate the impact that the difference in progression criteria could have on the cost-effectiveness results. However, it can be hypothesised that if the criteria applied in ERIVANCE lead to patients being classified as progressed at a later point in their disease than patients in the STEVIE trial, this could potentially lead to an underestimation of the utility associated with the PFS state in STEVIE patients, and therefore in the model. It is also not unreasonable to assume that the average utility associated with the PD state could be underestimated when using the ERIVANCE utility data in STEVIE, as patients would reach the PD state later in ERIVANCE than in STEVIE (therefore with a poorer prognosis).

- The Canadian HTA body also raised some valid points on the uncertainty of the SF-36 data from ERIVANCE. They point to the lack of sensitivity of the SF-36 instrument for this indication, the ceiling effect for relatively healthy individuals at baseline and the small sample size in ERIVANCE.

The descriptive statistics provided by the company at clarification stage are reported in Table 49. According to the values reported, the mean change from baseline in SF-36 values for all the dimensions does not seem to be 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) for the physical functioning and vitality components seems to be statistically significant. All of the other dimensions do not seem to show statically significant reductions at the end of the study.

The lack of statistical significance in the results might be related with the points raised by the Canadian HTA body, which noted 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.

Table 49. Descriptive statistics for SF-36 data collected in ERIVANCE (Company's clarification responses) – laBCC and mBCC patients combined

SF-36 dimension	Visit	n	Mean	Lower limit (95% CI)	Upper limit (95% CI)	Mean change	Lower limit (95% CI)	Upper limit (95% CI)
Bodily pain	Day 1	95	74.15	68.93	79.37	-	-	-
General health	Day 1	94	67.60	63.37	71.82	-	-	-
Mental health	Day 1	94	75.50	71.57	79.42	-	-	-
Physical functioning	Day 1	95	75.20	69.72	80.68	-	-	-
Role physical	Day 1	95	71.25	64.98	77.52	-	-	-
Role-emotional	Day 1	95	80.53	74.99	86.06	-	-	-
Social functioning	Day 1	95	77.37	71.96	82.78	-	-	-
Vitality	Day 1	95	62.11	57.78	66.43	-	-	-
Bodily pain	Week 12	84	71.06	65.28	76.84	-3.48	**-9.51**	**2.55**
General health	Week 12	83	70.64	66.11	75.16	2.48	**-1.02**	**5.98**
Mental health	Week 12	82	78.26	73.72	82.81	2.90	**-0.87**	**6.66**
Physical functioning	Week 12	84	78.33	73.22	83.45	-1.47	**-4.86**	**1.91**
Role physical	Week 12	84	74.11	67.70	80.51	-1.64	**-7.70**	**4.43**
Role-emotional	Week 12	84	83.53	77.37	89.69	2.88	**-3.66**	**9.41**
Social functioning	Week 12	84	83.78	78.93	88.63	5.36	0.53	10.18
Vitality	Week 12	83	63.40	58.44	68.37	-0.23	**-4.59**	**4.14**
Bodily pain	Week 24	76	72.92	67.61	78.24	-1.42	**-6.96**	**4.11**
General health	Week 24	76	69.25	64.28	74.22	0.68	**-3.29**	**4.66**

Mental health	Week 24	75	78.33	73.92	82.75	2.93	**-0.24**	**6.11**
Physical functioning	Week 24	76	77.69	72.10	83.28	-3.29	**-7.78**	**1.21**
Role physical	Week 24	76	72.29	65.88	78.69	-3.95	**-10.19**	**2.29**
Role-emotional	Week 24	76	84.21	78.47	89.95	3.07	**-2.57**	**8.71**
Social functioning	Week 24	76	81.74	76.10	87.39	1.97	**-3.14**	**7.08**
Vitality	Week 24	76	64.72	59.79	69.65	0.16	**-4.73**	**5.06**
Bodily pain	EOT	35	56.89	47.29	66.48	-14.89	**-26.72**	**-3.05**
General health	EOT	34	62.82	55.52	70.12	-9.00	**-16.29**	**-1.71**
Mental health	EOT	35	70.43	63.08	77.78	-6.33	**-12.69**	**0.03**
Physical functioning	EOT	34	64.56	53.47	75.65	-12.76	-21.74	-3.77
Role physical	EOT	35	64.23	53.47	74.98	-8.63	**-18.15**	**0.89**
Role-emotional	EOT	35	70.48	59.23	81.72	-10.71	**-22.36**	**0.94**
Social functioning	EOT	35	68.57	56.91	80.23	-6.79	**-17.77**	**4.20**
Vitality	EOT	35	53.21	44.67	61.76	-8.39	-15.63	-1.16
Abbreviations in table: EOT, end of treatment; n, number. Values in bold show confidence intervals containing 0.								

Regarding the approach taken by company in mapping the SF-36 data from the ERIVANCE trial, the ERG considers that the method used (reported in the Rowen *et al.* paper) is reasonably robust.[100] One of the reported disadvantages of all the models explored in the paper is the potential for over predicting utility values for more severe conditions, where patients have an EQ-5D utility value of less than 0.5. Although there is no EQ-5D data available for aBCC, the SF-36 values reported at baseline in the ERIVANCE trial are generally in line with the UK population norms for the age-matched population, which seems to indicate that aBCC would not fall under the umbrella of severe conditions.[102]

Even though the mapping method employed is robust, the underlying SF-36 data seems to carry a lot of uncertainty. The company used SF-36 values that mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values that suggest a decrease in patients' quality of life upon progression.

The company carried out a scenario analysis based on the study by Shingler *et al.*[93] However, this is of limited value as the estimates elicited in the study are based on responses from members of the general population and not on responses obtained directly from patients and, therefore, not in line with the NICE reference case.[96] Furthermore, the values in the paper are reported to be higher than the age matched UK general population values.

The utility decrements applied in the model for AEs are based on a study in patients with melanoma. Despite the company's consideration that melanoma and aBCC are similar diseases, the AEs listed in Beusterian *et al*. study do not match the AEs of interest reported in either STEVIE or ERIVANCE. Also

Grade 4 events in the Beusterian *et al*. required hospitalisation, while the Grade 3 events were assumed to require an inpatient/outpatient stay.[101] The ERG's clinical experts explained that AEs experienced with vismodegib are generally managed by discontinuing treatment and would not require hospitalisation. This renders the Grade 3 and Grade 4 events reported in Beusterian *et al*. not representative of the Grade 3 and 4 events in STEVIE. Furthermore, it is likely that the SF-36 data collected in the ERIVANCE trial somewhat captures the impact of AEs on patients' QoL. Therefore, applying AE-related utility decrements potentially double counts the impact of these in the economic analysis. Nonetheless, removing AEs-related utility decrements in the model has a negligible impact on the final cost-effectiveness results.

5.4.11 Resources and costs

The costs included in the economic analysis fall within three cost categories: pharmacological, disease management, and adverse event costs. The estimates used are based on the 2015/2016 price year, with unit costs obtained from published sources such as the NHS national schedule of reference costs[103], the Personal Social Services Research Unit (PSSRU)[104] and the British National Formulary (BNF)[105], which is in line with the NICE reference case.[96]

5.4.11.1 Pharmacological costs

The pharmacological costs considered in the model consist of the cost of vismodegib. Vismodegib is administered orally and so is not assumed to incur an administration cost. In order to estimate the cost of treatment with vismodegib for each cycle in the economic model, the proportion of patients receiving treatment each cycle (based on TTD curves for laBCC and mBCC from the STEVIE trial) is multiplied by £1,571, the estimated weekly cost of vismodegib.

The daily dose of vismodegib considered in the model is 150mg, which is in line with the recommended dosage of vismodegib in the summary of product characteristics (SmPC).[106] The estimation of the weekly cost of vismodegib in the economic analysis is summarised in Table 50.

Table 50. Vismodegib acquisition costs (Adapted from CS, Table 82, pg 223)

Drug	Formulation	Cost per pack[105]	Caps per pack	Cost per mg	Cost per weekly cycle
Vismodegib	150mg	£6,285.00	28	£1.50	£1,571.25
Abbreviations in table: caps, capsules; mg, milligrams.					

5.4.11.2 Disease management costs

Vismodegib arm

Patients in the vismodegib arm of the model are assumed to have oncologist visits and blood tests every 4 weeks prior to progressing. Once patients progress, they are allocated to one of the two management pathways considered by the company, with 67% of patients being monitored by oncologists and GPs and 33% of patients proceeding to receive BSC after vismodegib. Best supportive care for progressed vismodegib patients consists of oncology and GP visits, combined with wound management and palliative radiotherapy. All patients switching to BSC after vismodegib are assumed to receive wound management, while only 50% are assumed to receive palliative radiotherapy.

Wound management cost includes the cost of a tissue viability nurse (TVN) delivering the wound management service and the actual would management (bandages, dressings, etc.). Palliative radiotherapy is not curative and is intended as an option for disease management. Based on clinical expert opinion, the company assumes that 20% of patients receive complex palliative radiotherapy, and that 30% get basic palliative radiotherapy. The cost of radiotherapy is applied as a one-off cost in the model as patients are assumed to receive the regimen once in their lifetime. Resource use and unit costs for disease management in vismodegib patients is reported in Table 51 and Table 52 below.

Best supportive care arm

Patients in the BSC arm of the model are assumed to have dermatologist and GP visits prior to and after progression. Best supportive care patients have a more intensive regimen of wound management while palliative radiotherapy is assumed to be received by 50% of patients, similar to vismodegib patients. Resource use and unit costs for disease management in BSC patients are reported in Table 51 and Table 52 below.

Table 51. Costs of radiotherapy applied in the model (CS, Table 85, pg 228)

Item	% of patients in BSC arm	Description	Unit cost	Reference[103]	Regimen	One-off model cost
Palliative RT	30%	A fraction of treatment on a MV machine	£107.00	NHS reference schedule - SC22Z	20 Gray in 5 fractions	£160.50
Complex palliative RT	20%	A fraction of complex treatment on a MV machine	£153.00	NHS reference schedule-SC23Z	20 Gray in 5 fractions	£153.00
Abbreviations in table: BSC, best supportive care; MV, megavoltage; NHS, National Health Service; RT, radiotherapy.						

Table 52. Resource use assumed in the model for disease management (Adapted from CS Table 86, pg 230)

Model arm	Health state	Item	Unit cost	Reference	Schedule	Frequency per cycle	Cycle cost
Vismodegib	Progression-free survival	Blood test	£1.18	NHS Reference	Every 4 weeks	0.25	£0.30

				schedule-DAPS04			
		Oncologist visit	£163.00	NHS Ref. schedule - WF01A-370	Every 4 weeks	0.25	£40.75
		Total per model cycle	**£41.05**				
	Progressed disease (Monitoring only – 67% of vismodegib patients)	Oncologist visit	£163.00	NHS Ref. schedule - WF01A-370	Every 12 weeks	0.083	£13.58
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks	0.250	£9*
		Total per model cycle	**£15.13***				
	Progressed disease (Switch to BSC – 33% of vismodegib patients)	Oncologist visit	£163.00	NHS Ref. schedule - WF01A-370	Every 12 weeks	0.083	£13.58
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks	0.250	£9.00*
		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Once per week	1	£50.65
		Wound management	£10.00	Clinical expert opinion	Once per week	1	£10.00
		Total per model cycle	**£27.47***				
BSC	Progression-free survival	Dermatologist visit	£99.00	NHS Ref. schedule - WF01A-330	Every 12 weeks	0.083	£8.25
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks	0.250	£9.00*
		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Twice per week	2	£101.30
		Wound management	£10.00	Clinical expert opinion	Twice per week	2	£20.00
		Total per model cycle	**£138.55***				
	Progressed disease	Dermatologist visit	£99.00	NHS Ref. schedule WF01A-330	Every 12 weeks	0.083	£8.25
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks	0.250	£9*

		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Three times per week	3	£151.95
		Wound management	£10.00	Clinical expert opinion	Three times per week	3	£30.00
		Total per model cycle	**£199.20***				
Abbreviations in table: GP, General Practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TVN, tissue viability nurse. * These are based on ERG corrections. The original values reported in Table 86 of the CS where based on including the cost of a dermatologist visit, incorrectly used instead of a GP visit cost							

5.4.11.3 Adverse event costs

The costs of adverse events applied in the economic model are summarised in Table 53. No costs are attributed to the treatment of dysgeusia and increased GTT.

Table 53. Adverse event costs (CS, Table 87, pg 231)

Adverse reactions	Treatment	Unit cost	Treatment regimen	Weekly cost
Dysgeusia	No treatment available	N/A	N/A	£0.00
GGT increased	No treatment available	N/A	N/A	£0.00
Muscle spasms	Quinine sulphate	£2.17[105]	200mg, once daily	£0.54
Weight decreased	Dietician (Band 3)	£30.00[104]	Monthly visit	£7.50
Abbreviations in table: GGT, gamma-glutamyltransferase; mg, milligram; N/A, not applicable.				

ERG critique

Resource use estimates applied in the model are based on feedback from the company's clinical experts as there are no known sources for resource use in the study population. The ERG validated the unit costs used in the model across the various published sources and also verified that discounting was applied correctly in the model. The ERG's clinical experts confirmed that the assumptions made in the model surrounding pharmacological costs are reasonable. However, there are some concerns surrounding the company's assumptions for estimating disease management costs. More specifically these are related with:

- The company's assumption that 67% of patients who progress after receiving vismodegib are on a monitoring regimen for the remainder of their lifetime and never receive BSC. The ERG's clinical experts explained that even if these patients need a less intensive regimen for managing disease progression after vismodegib, they will eventually go on to receive BSC as their disease progresses. Clinical experts' input indicates that the duration of the watchful waiting period is highly volatile and depends on the location 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, progressed patients will eventually move to BSC;

- The company's assumption on the frequency of wound management and TVN visits. There was no consensus amongst the clinical experts advising the ERG with regards to the frequency of wound management in the PD and in the PFS states for BSC patients. While one clinical expert agreed with three visits for the PD state and two visits for the PFS state, the other two clinical experts suggested that a less intense regimen would be more plausible (two visits for the PD state and one visit for the PFS state);

- The company's assumption that the post-progression BSC regimen for vismodegib patients differs from the post-progression BSC regimen for BSC patients. Clinical expert opinion provided to the ERG was consensual that once vismodegib patients progress and require BSC, the treatment schedule for these patients is the same as the one required by patients on the BSC treatment arm who have progressed.

In order to reflect clinical expert opinion provided to the ERG and exploring the impact of changing the company's assumptions surrounding resource use for disease management, the ERG has carried out scenario analyses reflecting the aforementioned changes. This entailed assuming that:

- Vismodegib patients who have progressed stay on the monitoring regimen for three months after progression, but then move to BSC;

- Vismodegib patients who have progressed stay on the monitoring regimen for six months after progression, but then move to BSC;

- Vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed;

- Decreasing the frequency of wound management in the PD and the PFS health states.

The ERG's clinical experts also reported that a small proportion of patients receive salvage surgery as part of managing their disease, which has not been considered by the company in the model. The magnitude of the impact of excluding this cost from the analysis on the overall results is unclear. The resource use assumed by the ERG in its scenario analysis is summarised in Table 54 , and the results of the scenario analysis are reported in Section 6.

Table 54. Alternative resource use estimated by the ERG

Model arm	Health state	Item	Unit cost	Reference	Schedule	Alternative value	Frequency per cycle	Cycle cost
Vismodegib	Progression-free survival	Blood test	£1.18	NHS Reference	Every 4 weeks	n/a	0.25	£0.30

				schedule-DAPS04				
		Oncologist visit	£163.00	NHS Ref. schedule - WF01A-370	Every 4 weeks	n/a	0.25	£40.75
		Total per model cycle	**£41.05**					
	Progressed disease (Monitoring only – 67% of vismodegib patients)	Oncologist visit	£163.00	NHS Ref. schedule - WF01A-370	Every 12 weeks		0.083	£13.58
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks		0.250	£9.00*
		Total per model cycle	**£15.13**					
	Progressed disease (Switch to BSC – 33% of vismodegib patients)	Dermatologist visit	£99.00	NHS Ref. schedule - WF01A-330	Every 12 weeks		0.083	£8.25
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks		0.250	£9.00
		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Three times per week		3	£30.00
		Wound management	£10.00	Clinical expert opinion	Three times per week		3	£151.95
		Total per model cycle		**£199.20**				
BSC	Progression-free survival	Dermatologist visit	£99.00	NHS Ref. schedule - WF01A-330	Every 12 weeks		0.083	£8.25
		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks		0.250	£9.00
		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Twice per week		2	£101.30
		Wound management	£10.00	Clinical expert opinion	Twice per week		2	£20.00
		Total per model cycle		**£138.55**				
	Progressed disease	Dermatologist visit	£99.00	NHS Ref. schedule WF01A-330	Every 12 weeks		0.083	£8.25

		GP visit	£36.00	PSSRU 2016 - page 145	Every 4 weeks		0.250	£9.00
		Tissue viability nurse visit	£50.65	NHS Ref. schedule - N25AF	Three times per week		3	£30.00
		Wound management	£10.00	Clinical expert opinion	Three times per week		3	£151.95
		Total per model cycle		**£199.20**				
	Abbreviations in table: GP, General Practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TVN, tissue viability nurse.							

With respect to the estimation of AE costs, and as mentioned in Section 5.4.8, even though vismodegib is expected to have a considerable impact on patients' QoL, this is not easily quantifiable. The same applies for the estimation of the impact of vismodegib AEs on costs. The majority of the AEs related to vismodegib do not have any treatment available, and will most likely be managed by stopping the treatment. Furthermore, according to the ERG's clinical experts patients with weight loss are not usually referred to a dietician. The cost of excluding this from the model is negligible.

The ERG discovered a minor error in the estimation of costs of GP visits in the model, where the unit cost of a dermatologist visit (£99) was applied instead of a GP visit (£36). The company corrected this during the clarification stage.

5.5 Results included in company's submission

5.5.1 Base case results

Upon the clarification request from the ERG, the company corrected the mistake found in the model relating with using the cost of a dermatologist visit instead of a GP visit. The company's corrected deterministic base case results for vismodegib compared to BSC using the PAS price are reported in Table 55. The combined ICER weights the laBCC and the mBCC final ICERs by the proportion of patients in each group in STEVIE. According to the company's analysis, vismodegib is expected to extend patients' lives by around 14 months compared to BSC with a gain of 0.89 QALYs. The incremental cost-effectiveness ratio for vismodegib compared with BSC is of £35,251 per QALY gained. The company's base case ICERs for laBCC and mBCC are reported in Table 56 and Table 57, respectively.

Table 55. Base case results using list price

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251

Vismodegib	£124,699	10.66	8.20				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 56. Base case results using list price for laBCC pateints

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£97,519	9.95	7.69	£27,345	1.16	0.90	£30,493
Vismodegib	£124,865	11.11	8.58				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 57. Base case results using list price for mBCC patients

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£40,813	4.28	2.95	£80,651	1.20	0.80	£100,615
Vismodegib	£121,465	5.48	3.75				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

The breakdown of QALYs accumulated in the model according to health state is presented in Table 58. Most of the incremental QALY gain for vismodegib against BSC stems from the PD health state, for both laBCC and mBCC patients. This is related with the mortality benefit seen in the company's model, as patients in the vismodegib arm live longer than in the BSC arm, therefore accruing more QALYs while in the PD state.

Table 58. QALY breakdown according to health state (CS, pg 240, Table 90)

Health state	QALYs BSC	QALYs vismodegib	Increment	QALYs BSC	QALYs vismodegib	Increment
	laBCC patients			mBCC patients		
PFS	1.57	1.79	0.22	0.95	1.11	0.16
PD	6.12	6.79	0.67	1.99	2.63	0.64
AEs	0.00	0.00	0.00	0.00	0.00	0.00
Total	7.69	8.59	0.90	3.75	3.75	0.80
Abbreviations in table: AEs, adverse events; BSC, best supportive care; PD, progressed disease; PFS, progression-free survival.						

5.5.2 Sensitivity analysis

5.5.2.1 Scenario analysis

The company carried out a range of scenario analyses exploring the impact of changing assumptions surrounding the following parameters:

- Time horizon;
- Clinical inputs;
    - Parametric distributions for: TTD, PFS, and OS

- Landmark
- HR estimation procedure
- Covariate adjustment
- Duration of treatment effect cut-off point
- Starting point to apply background mortality

- Health state utilities;

- Costs and resource use.

Nonetheless, the company did not provide the results for the scenario analyses after correcting their base case model, as a result of the clarification stage. The base case ICER in the original model was £34,407 (compared with £35,798 in the corrected model) per QALY gained. The ERG presents the results of the scenario analysis carried out in the company's original model and presents the results in Table 59 and Table 60. Even though the final results are not for the corrected model, these show the impact of changing the parameters listed above on the company's results.

Table 59. Results of scenario analyses for costs and utilities using vismodegib list price (CS, pg 246, Table 98)

Parameter	Value	Vismodegib vs BSC			
		Life years	QALYS	Costs	ICER
Wound care cost per visit	£0.00	1.16	0.89	£43,048	£48,409
	£20.00	1.16	0.89	£18,146	£20,406
	£40.00	1.16	0.89	-£6,756	Dominant
	£60.00	1.16	0.89	-£31,657	Dominant
TVN frequency in PD for vismodegib arm	1	1.16	0.89	£30,597	£34,407
	3	1.16	0.89	£48,539	£54,583
TVN frequency in PFS for BSC arm	1	1.16	0.89	£36,329	£40,853
	3	1.16	0.89	£24,865	£27,962
	5	1.16	0.89	£13,402	£15,071
TVN frequency in PD for BSC arm	1	1.16	0.89	£79,279	£89,151
	3	1.16	0.89	£30,597	£34,407
	5	1.16	0.89	-£18,084	Dominant
Utilities	Shingler	1.16	0.86	£30,597	£35,445
	ERIVANCE	1.16	0.89	£30,597	£34,407
TTD distribution laBCC	Exponential	1.16	0.89	£32,429	£36,468
	Weibull	1.16	0.89	£30,597	£34,407
	Log-normal	1.16	0.89	£43,270	£48,661
	Gamma	1.16	0.89	£40,279	£45,296
	Log-logistic	1.16	0.89	£40,384	£45,415
	Gompertz	1.16	0.89	£32,429	£36,468

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; laBCC, locally advanced basal cell carcinoma; PD, progressed disease; PFS, progression-free survival; QALY, quality adjusted life years; TTD, time to treatment discontinuation; TVN, tissue viability nurse.

Table 60. Results of scenario analyses for efficacy using vismodegib list price (CS, pg 247, Table 99)

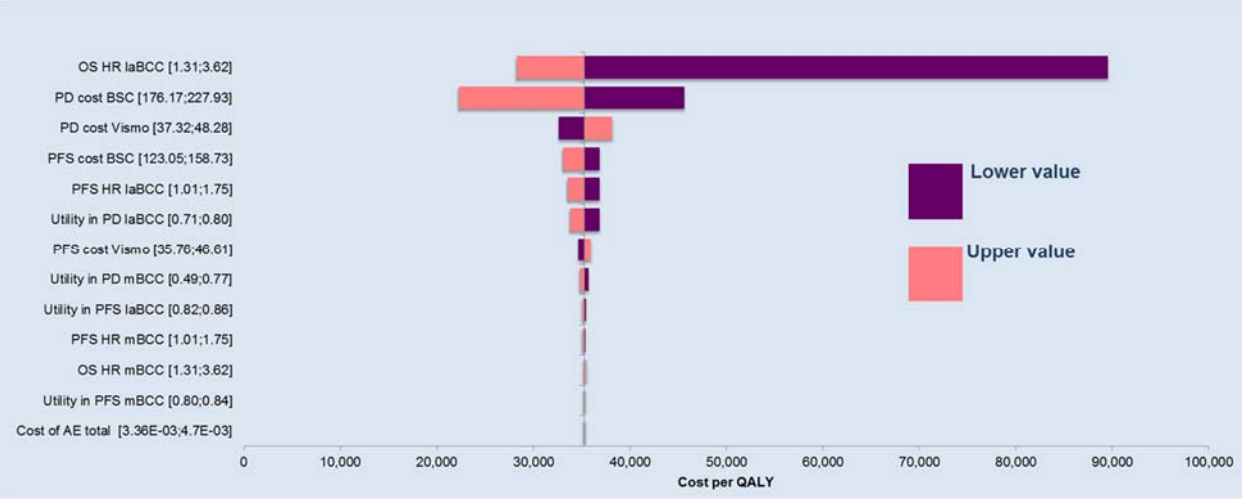
Parameter	Value	Vismodegib vs. BSC			
		Life Years	QALYS	Costs	ICER
PFS distribution laBCC	Exponential	1.16	0.91	£31,813	£34,971
	Weibull	1.16	0.89	£30,597	£34,407
	Lognormal	1.16	0.92	£32,061	£34,727
	Gamma	1.16	0.89	£30,619	£34,410
	Log-logistic	1.16	0.91	£31,358	£34,280
	Gompertz	1.16	0.88	£28,592	£32,361
OS distribution laBCC	Exponential	1.02	0.78	£51,188	£65,367
	Weibull	1.02	0.78	£51,668	£66,221
	Lognormal	1.14	0.88	£40,804	£46,481
	Gamma	1.16	0.89	£30,597	£34,407
	Log-logistic	1.09	0.83	£47,585	£56,996
	Gompertz	1.02	0.78	£51,188	£65,367
OS treatment effect cut-off laBCC	20	0.74	0.57	£29,025	£50,771
	40	1.11	0.85	£30,393	£35,841
	60	1.26	0.97	£30,973	£32,052
	80	1.33	1.02	£31,242	£30,584
	100	1.37	1.05	£31,371	£29,929
OS background mortality cut-off laBCC	0	0.11	0.09	£13,270	£145,472
	75	1.11	0.85	£33,533	£39,315
	150	1.13	0.87	£30,270	£34,866
	225	0.89	0.68	£27,538	£40,273
	300	0.89	0.68	£27,538	£40,273
	375	0.89	0.68	£27,534	£40,281

Abbreviations in table BSC, best supportive care; ICER, incremental cost-effectiveness ratio; laBCC, locally advanced basal cell carcinoma; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life years.

5.5.2.2 One-way sensitivity analysis

The results of the company's one-way sensitivity analysis (OWSA) on the corrected model are presented in Figure 30. According to the analysis the main drivers of the model are the hazard ratio for OS for patients with laBCC, and the cost for progressed disease for patients in the BSC arm of the model. Using the upper and lower limits of the OS hazard ratios for laBCC patients causes the ICER to range from £28,318 to £88,336 per QALY gained.

Figure 30. One-way sensitivity sensitivity analysis – corrected model



5.5.2.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results across 1,000 iterations are presented in Table 61 for the corrected model. The PSA results produced a mean ICER of £35,798 per QALY gained for vismodegib compared to BSC. The scatterplots, and cost-effectiveness acceptability curves when the list price for vismodegib is used are presented in Figure 30 and Figure 31, respectively. The probability of vismodegib at list price being cost-effective at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY is around 10%, and 30% respectively.

Table 61. Results of probabilistic sensitivity analysis using the corrected model

Treatment arm	Costs		QALYs		ICERs	
	Base case (deterministic)	PSA	Base case (deterministic)	PSA	Base case (deterministic)	PSA
BSC	£93,352	£93,061	7.31	7.23	£35,251	£35,798
Vismodegib	£124,699	£124,553	8.20	8.11		

Figure 31. Distribution of cost-effectiveness simulation on the cost-effectiveness plane for vismodegib vs BSC using corrected model

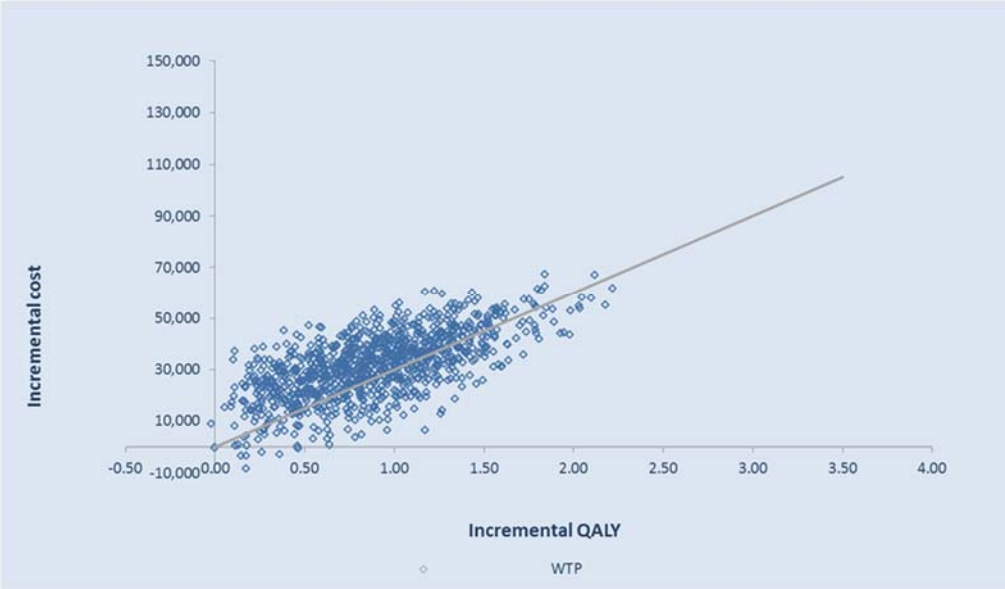
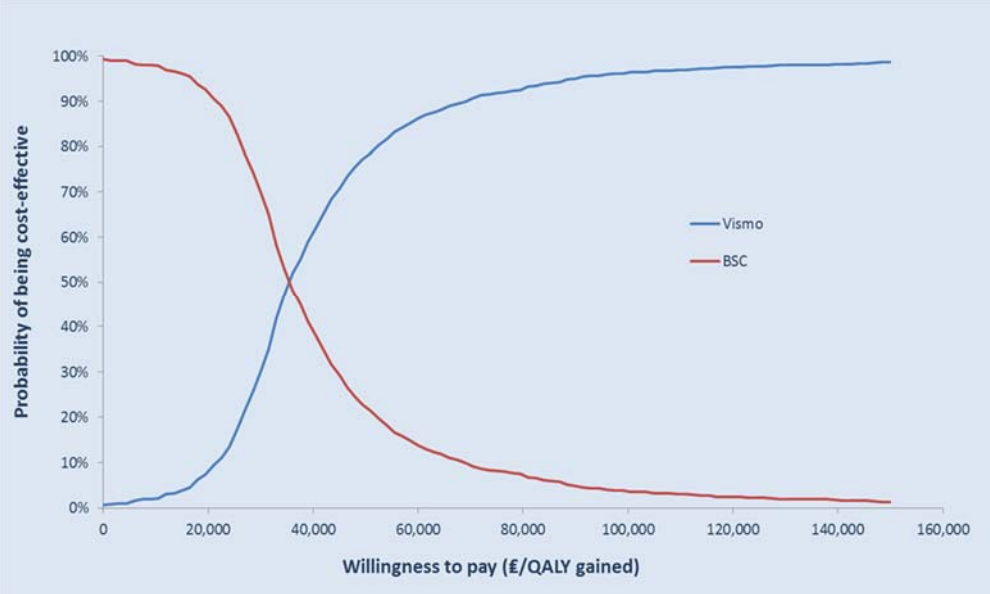


Figure 32. Cost-effectiveness acceptability curves using corrected model



5.5.3 Model validation

The company reports undertaking an external advisory board meeting where four practising clinicians and three external health economists were present. It is stated that range of topics were discussed at this meeting, with the purpose of validating the assumptions made by the company. Some of these included the utilities used in the model, the choice of comparator, the observed excess disease mortality for

laBCC and the decision to not model Gorlin syndrome patients as a subgroup. Details on the discussions undertaken at the meeting can be found in the CS, from page 249 to page 254.

Furthermore, the CS reports that an internal quality control and validation of the model was conducted by an external consultancy. Validation processes included cell by cell validation (including formula checking), cell references and all aspects of model functionality. A number of 'pressure tests' were conducted, often using extreme values.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. Some of the exploratory analyses (such as the ones relating to using the PFS and OS HRs) are still based on some flawed assumptions or methods (for example assuming PH), however provide a step in the right direction compared with the company's base case approach.

The ERG notes that all exploratory analyses conducted for mBCC patients are an academic exercise to explore the possible direction of the change in the final ICER and the overall impact of changes when considered together. Nonetheless, the ERG stresses its opinion that for mBCC patients, the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib compared to BSC.

Results of the exploratory analyses are reported in Table 62 for laBCC patients while Table 63 presents the results for mBCC patients. The company's corrected base case ICER is also presented separately for the two populations, as these estimates were calculated separately in the company's economic model. The analyses undertaken by the ERG consist on the following:

1. Considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. Therefore, the ERG removed the half-cycle correction from the model;

2. The ERG removed the company's adjustment made to the HRs derived with the landmark approach, to reflect a HR of non-responders vs ITT patients, instead of a non-responders vs responders HR;

3. Despite the lack of statistical significance in the PFS HRs and the lack of robustness in the methods used to analyse the relative effectiveness of vismodegib, the ERG ran a scenario analysis using the PFS HR adjusted for ECOG, age and Gorlin syndrome for the laBCC population, considering its larger sample size;

4. The ERG ran a scenario analysis using a PFS HR of 1 for mBCC patients to reflect the uncertainty in the mBCC analysis and to account for the fact that the mean PFS HR for mBCC in the company's analysis is below one, indicating that vismodegib is worse than BSC at delaying progression, which is deemed clinically implausible in light of the PFS results for laBCC;

5. The ERG ran a scenario analysis using the OS HRs adjusted for ECOG, age and Gorlin syndrome for the laBCC and the mBCC populations;

6. Considering the consistent feedback from clinical experts and the statements included in the CS, the ERG also ran a conservative scenario analysis where the mortality for laBCC patients with vismodegib was assumed to be the same as the background mortality for the UK population. This implies that the there is no mortality gain with vismodegib compared with BSC, as there is no mortality loss associated with laBCC or BSC;

7. For inclusiveness, the ERG ran a scenario analysis where the OS HR for mBCC patients was assumed 1 to reflect the lack of statistical significance, and evidence, on the relative effectiveness of vismodegib;

8. Capping the OS vismodegib curve by the background mortality curve (this is an issue mainly for laBCC OS curves). This replaces the company's approach of applying uniform background mortality rates to the OS curves in the vismodegib and BSC model arms after a user-defined point in time;

9. The ERG changed the Weibull to a log-logistic TTD curve in the laBCC and mBCC models;

10. The ERG removed the AEs-related utility decrements in the model;

11. In order to reflect clinical expert opinion provided to the ERG and exploring the impact of changing the company's assumptions surrounding resource use for disease management, the ERG has carried out scenario analyses reflecting the following changes:

    a) Vismodegib patients who have progressed stay on the monitoring regimen for three months after progression, but then move to BSC;

    b) Vismodegib patients who have progressed stay on the monitoring regimen for six months after progression, but then move to BSC;

    c) Vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed;

    d) Decreasing the frequency of wound management in the PD and the PFS health states for BSC patients.

12. Furthermore, according to the ERG's clinical experts' patients with weight loss are not usually referred to a dietician. The ERG excluded this cost from the economic model.

The ERG's exploratory analysis shows that both the laBCC and mBCC results are most sensitive to the assumptions made around disease-related mortality and vismodegib's survival benefit, as well as the assumptions surrounding the costs of BSC.

When the ERG assumed that there is no mortality associated with laBCC, therefore assuming that there is no survival benefit with vismodegib compared with BSC, the ICER for laBCC patients increased from £30,493 to £435,402 per QALY gained. The assumptions made around the BSC regimen patients receive after vismodegib is also a key driver of the economic model. When the BSC regimen for vismodegib progressed patients was assumed to be the same as the one received for BSC progressed patients (as supported by the clinical experts advising the ERG) the ICER increased from £30,493 to £50,474 per QALY gained. Similarly, when all progressed vismodegib patients were assumed to eventually move to a BSC regimen (after three or six months) the final ICERs increased to £46,523 and £46,100 per QALY gained, respectively.

For mBCC patients, when the ERG replaced the company's HR adjusted for ECOG and age by the company's HR adjusted for ECOG, age and Gorlin syndrome, the ICER increased from £100,615 to £791,095 per QALY gained. Similar to what is observed in the laBCC population, the assumptions made around BSC costs for vismodegib progressed patients are key drivers of the economic analysis.

Removing the AE-related disutilities and the cost of a dietician from the model had a negligible impact on the model results for both laBCC and mBCC patients.

Table 62. Results of the ERG's scenario analysis for laBCC patients

Analysis from list	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's corrected base case for laBCC patients**			
	Total costs (£)	£124,865	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER		**£30,493**	
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£126,135	£97,558	£28,577
	QALYs	8.59	7.69	0.90
	ICER		**£31,880**	
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			

Analysis from list	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	Total costs (£)	£124,214	£89,170	£35,045
	QALYs	8.36	7.05	1.31
	ICER		**£26,820**	
3	**Replacing the company's PFS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 1.311) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 1.19)**			
	Total costs (£)	£124,865	£97,214	£27,651
	QALYs	8.58	7.69	0.89
	ICER		**£31,107**	
5	**Replacing the company's OS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 2.035)**			
	Total costs (£)	£124,929	£99,278	£25,651
	QALYs	8.60	7.81	0.79
	ICER		**£32,442**	
6	**Assuming that mortality for laBCC patients with vismodegib and BSC is to be the same as the background mortality for the UK population (i.e. no survival gain with vismodegib)**			
	Total costs (£)	£126,490	£117,138	£9,352
	QALYs	9.14	9.11	0.02
	ICER		**£435,402**	
8	**Using alternative approach to model mortality**			
	Total costs (£)	£124,869	£100,607	£24,262
	QALYs	8.58	7.91	0.67
	ICER		**£36,028**	
9	**Changing the Weibull to a log-logistic model to estimate the TTD curve**			
	Total costs (£)	£135,491	£97,519	£37,972
	QALYs	8.58	7.69	0.90
	ICER		**£42,344**	
10	**Removing the AE-related disutilities from the model**			
	Total costs (£)	£124,865	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER		**£30,482**	
11 a)	**Assuming that vismodegib patients move to BSC three months after progression**			
	Total costs (£)	£139,240	£97,519	£41,721
	QALYs	8.58	7.69	0.90
	ICER		**£46,523**	
11 b)	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£138,861	£97,519	£41,341
	QALYs	8.58	7.69	0.90
	ICER		**£46,100**	
11 c)	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			

Analysis from list	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	Total costs (£)	£142,784	£97,519	£45,264
	QALYs	8.58	7.69	0.90
	ICER		**£50,474**	
11 d)	**Decreasing the frequency of wound management in the PD and the PFS health states for BSC patients**			
	Total costs (£)	£124,865	£66,029	£58,836
	QALYs	8.58	7.69	0.90
	ICER		**£65,607**	
12	**Removing the cost from a consult with a dietician from the model**			
	Total costs (£)	£124,864	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER		**£30,492**	
Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.				

Table 63. Results of the ERG's scenario analysis for mBCC patients

Analysis from list	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's corrected base case for mBCC patients**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER		**£100,615**	
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£122,243	£40,870	£81,373
	QALYs	3.75	2.95	0.80
	ICER		**£101,550**	
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs. non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£120,524	£33,729	£86,794
	QALYs	3.48	2.49	0.99
	ICER		**£87,939**	
4	**Using a PFS HR of 1 in the mBCC model**			
	Total costs (£)	£121,465	£40,187	£81,278
	QALYs	3.75	2.98	0.77
	ICER		**£106,092**	
5	**Replacing the company's OS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for mBCC patients (HR of 1.035)**			
	Total costs (£)	£125,063	£69,528	£55,535
	QALYs	4.78	4.71	0.07
	ICER		**£791,095**	

Analysis from list	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
7	**Using a OS HR of 1 in the mBCC model**			
	Total costs (£)	£125,212	£70,805	£54,407
	QALYs	4.82	4.79	0.03
	ICER		**£1,580,078**	
8	**Using alternative approach to model mortality**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER		**£100,615**	
9	**Changing the Weibull to a log-logistic model to estimate the TTD curve**			
	Total costs (£)	£120,573	£40,813	£79,760
	QALYs	3.75	2.95	0.80
	ICER		**£99,502**	
10	**Removing the AE-related disutilities from the model**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER	**£100,586**		
11 a)	**Assuming that vismodegib patients move to BSC three months after progression**			
	Total costs (£)	£126,639	£40,813	£85,825
	QALYs	3.75	2.95	0.80
	ICER		**£107,070**	
11 b)	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£126,325	£40,813	£85,512
	QALYs	3.75	2.95	0.80
	ICER		**£106,679**	
11 c)	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			
	Total costs (£)	£129,687	£40,813	£88,874
	QALYs	3.75	2.95	0.80
	ICER		**£110,873**	
11 d)	**Decreasing the frequency of wound management in the PD and the PFS health states**			
	Total costs (£)	£121,465	£27,267	£94,197
	QALYs	3.75	2.95	0.80
	ICER		**£117,514**	
12	**Removing the cost for a consult with a dietician from the model**			
	Total costs (£)	£121,464	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER		**£100,615**	

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

6.2 ERG exploratory ICER

In this section the ERG reports two ICERs reflecting two different scenarios for laBCC patients. One scenario assumes there is no mortality loss associated with laBCC (conservative scenario) while the other reports an ICER assuming a survival benefit with vismodegib, portraying a less conservative scenario.

For mBCC patients, the ERG ran a cost minimisation analysis, to reflect the fact that the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib compared to BSC in terms of OS and PFS outcomes, and the fact that all HRs derived for mBCC are not statistically significant.

The ERG caveats the analysis presented with the very high degree of uncertainty embedded in the company's landmark method used to derive the HRs for OS and PFS, which is only exacerbated by the small number of patients in the mBCC group. To these issues, adds the non-systematic selection process of prognostic factors in the HR estimations, which potentially introduced further uncertainty and bias in the analysis. Assuming PH holds in the analysis is also likely to introduce further uncertainty in the results, particularly for OS data. The common assumptions made for both the laBCC and mBCC models are:

1. Considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. Therefore, the ERG removed the half-cycle correction from the model;

2. The ERG removed the company's adjustment made to the HRs derived with the landmark approach, to reflect a HR of non-responders vs ITT patients, instead of a non-responders vs responders HR;

3. The ERG changed the Weibull to a log-logistic TTD curve in the laBCC and mBCC models;

4. Capping the OS vismodegib curve by the background mortality curve (this is an issue mainly for laBCC OS curves). This replaces the company's approach of applying uniform background mortality rates to the OS curves in the vismodegib and BSC model arms after a user-defined point in time;

5. In order to reflect clinical expert opinion provided to the ERG the following changes were made in the model:

e) Vismodegib patients who have progressed stay on the monitoring regimen for six months after progression, but then move to BSC;

a) Vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed.

The specific assumptions made for laBCC patients are the following:

6. Despite the lack of statistical significance in the PFS HRs and the lack of robustness in the methods used to analyse the relative effectiveness of vismodegib, the ERG used the PFS HR adjusted for ECOG, age and Gorlin syndrome for the laBCC population;

7. Considering the consistent feedback from clinical experts and the statements included in the CS, the ERG assumed that mortality for laBCC patients with vismodegib is the same as the background mortality for the UK population. This implies that the there is no mortality gain with vismodegib compared with BSC, as there is no mortality loss associated with laBCC;

8. As an alternative to the analysis described in the previous bullet point, the ERG used the OS HRs adjusted for ECOG, age and Gorlin syndrome for the laBCC population, to reflect a gain in survival with vismodegib for this population.

The specific assumptions made for mBCC patients are:

6. Using a PFS HR of 1 for mBCC patients to reflect the uncertainty in the mBCC analysis and to account for the fact that the mean PFS HR for mBCC in the company's analysis is below one, indicating that vismodegib is worse than BSC at delaying progression, which is deemed clinically implausible;

7. Assuming that the OS HR for mBCC patients is 1 to reflect the lack of statistical significance and evidence, on the relative effectiveness of vismodegib. Given that a similar analysis was ran for PFS outcomes, this reduces the economic analysis in the mBCC population to cost-minimisation.

The results for the laBCC population are reported in Table 64. When the ERG assumes there is no mortality associated with laBCC, therefore assuming to survival gain with vismodegib, the final ICER for vismodegib compared with BSC is £5,203,675. The ICER for vismodegib compared with BSC when assuming the existence of laBCC-related mortality and a gain in survival with vismodegib compared with BSC is £106,569.

Table 64. ERG base case ICER for laBCC patients

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's base case for laBCC patients**			
	Total costs (£)	£124,865	£97,519	£27,345
	QALYs	8.58	7.69	0.90
	ICER			**£30,493**
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£126,135	£97,558	£28,577
	QALYs	8.59	7.69	0.90
	ICER (compared with base case)			£31,880
	ICER with all changes incorporated			**£31,880**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£124,214	£89,170	£35,045
	QALYs	8.36	7.05	1.31
	ICER (compared with base case)			£26,820
	ICER with all changes incorporated			**£27,772**
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£135,491	£97,519	£37,972
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£42,344
	ICER with all changes incorporated			**£35,888**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£124,869	£100,607	£24,262
	QALYs	8.58	7.91	0.67
	ICER (compared with base case)			£36,028
	ICER with all changes incorporated			**£39,597**
5a	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£138,861	£97,519	£41,341
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£46,100
	ICER with all changes incorporated			**£52,356**
5b	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			
	Total costs (£)	£142,784	£97,519	£45,264
	QALYs	8.58	7.69	0.90
	ICER (compared with base case)			£50,474
	ICER with all changes incorporated			**£95,164**

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
6	**Replacing the company's PFS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 1.311) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 1.19)**			
	Total costs (£)	£124,865	£97,214	£27,651
	QALYs	8.58	7.69	0.89
	ICER (compared with base case)			£31,107
	ICER with all changes incorporated			**£96,352**
7	**Assuming that mortality for laBCC patients with vismodegib and BSC is to be the same as the background mortality for the UK population (i.e. no survival gain with vismodegib)**			
	Total costs (£)	£126,490	£117,138	£9,352
	QALYs	9.14	9.11	0.02
	ICER (compared with base case)			£435,402
	ICER with all changes incorporated			**£5,203,675**
8	**Replacing the company's OS HR (responders vs non-responders) from the landmark approach adjusting for age, ECOG (HR of 2.161) with the company's HR adjusting for age, ECOG and Gorlin syndrome for laBCC patients (HR of 2.035)**			
	Total costs (£)	£124,929	£99,278	£25,651
	QALYs	8.60	7.81	0.79
	ICER (compared with base case)			£32,442
	ICER with all changes incorporated			**£106,569**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

As previously explained, due to the level of uncertainty and the lack of robust mBCC data, the ERG conducted a cost minimisation analysis for this population. The results are shown in in Table 65. When the ERG assumed a PFS and OS HR of 1, the final ICER for vismodegib vs BSC became dominated, with a zero QALY gain and an additional cost of £89,323 (total costs for vismodegib £159,547 and £70,224 for BSC).

Table 65. ERG base case ICER for mBCC patients

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's base case for mBCC patients**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER			£100,615
1	**Removing the half-cycle correction from the model**			
	Total costs (£)	£122,243	£40,870	£81,373

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£101,550
	ICER with all changes incorporated			**£101,550**
2	**Removing the PFS and OS HRs adjustment made by the company (ITT population vs non-responders) and using the company's HR (responders vs non-responders) from the landmark approach controlling for age and ECOG status**			
	Total costs (£)	£120,524	£33,729	£86,794
	QALYs	3.48	2.49	0.99
	ICER (compared with base case)			£87,939
	ICER with all changes incorporated			**£88,698**
3	**Changing the Weibull to a log-logistic curve to model TTD**			
	Total costs (£)	£120,573	£40,813	£79,760
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£99,502
	ICER with all changes incorporated			**£87,795**
4	**Using alternative approach to model mortality**			
	Total costs (£)	£121,465	£40,813	£80,651
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£100,615
	ICER with all changes incorporated			**£87,795**
5a	**Assuming that vismodegib patients move to BSC six months after progression**			
	Total costs (£)	£126,325	£40,813	£85,512
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£106,679
	ICER with all changes incorporated			**£92,161**
5b	**Assuming that vismodegib patients moving to BSC receive the same treatment regimen as BSC patients who have progressed**			
	Total costs (£)	£129,687	£40,813	£88,874
	QALYs	3.75	2.95	0.80
	ICER (compared with base case)			£110,873
	ICER with all changes incorporated			**£109,503**
6	**Using a PFS HR of 1 in the mBCC model**			
	Total costs (£)	£121,465	£40,187	£81,278
	QALYs	3.75	2.98	0.77
	ICER (compared with base case)			£106,092
	ICER with all changes incorporated			**£115,545**
7	**Using a OS HR of 1 in the mBCC model**			
	Total costs (£)	£125,212	£70,805	£54,407

	Results per patient	Vismodegib (1)	Best supportive care (2)	Incremental value (1-2)
	QALYs	4.82	4.79	0.03
	ICER (compared with base case)			£1,580,078
	ICER with all changes incorporated			**Vismodegib dominated**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

7 END OF LIFE

The company reported in the CS that the only one of the three End-of-Life criteria met by vismodegib is that, "the treatment is licensed or otherwise indicated, for small patient populations" (Table 66). The ERG agrees with the company's assessment and thus does not consider vismodegib to meet all of the criteria specified by NICE for a treatment to be considered as an end-of-life treatment.

Table 66: Company's assessment of vismodegib for end-of-life (Adapted from: CS page 167, Table 56)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	No
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No – clinical study data included in this submission relate to single-arm, non-randomised, non-comparator studies. There are no studies assessing vismodegib vs current NHS treatment (best supportive care)
The treatment is licensed or otherwise indicated for small patient populations	Yes – advanced BCC is very rare with fewer than 500 patients estimated to have received treatment in England since launch in August 2013
Abbreviations: BCC, basal cell carcinoma.	

8 OVERALL CONCLUSIONS

Clinical

The CS contained a systematic review that addressed the population and intervention specified in the decision problem outlined in the final scope issued by NICE. The company's search strategies were well designed for identifying studies of vismodegib but the ERG is concerned that the company's search strategy omitted search terms for BSC, the key comparator of interest in the final scope issued by NICE. This is a concern because one of the main limitations of the submission is the lack of direct randomised evidence comparing vismodegib versus BSC, and a further limitation is that the key data for vismodegib were from single-arm studies. The ERG is not qualified to comment on the feasibility of an RCT of vismodegib in the population of interest in this decision problem although the ERG does consider a comparative study design to be preferable. The ERG considers a potential comparator of physician's choice could have been used in an RCT to represent BSC. In addition, the ERG considers the company's rationale that it would be difficult to recruit sufficient patients due to the limited aBCC population to be unjustified given the size of the STEVIE study.

The ERG considers that the available evidence on the clinical efficacy of vismodegib for the treatment of symptomatic mBCC and laBCC inappropriate for surgery or radiotherapy is of limited quality due to the single-arm non-randomised study design of ERIVANCE and STEVIE. However, the ERG also acknowledges that ERIVANCE and STEVIE at this time, represent the best available evidence on the clinical effectiveness of vismodegib. In addition, the ERG considers it important to highlight that there are no data on the long-term safety and efficacy of vismodegib and the data on OS in laBCC are immature. The ERG has further concerns about the data on vismodegib in mBCC patients, as they are based on small patient numbers (96 patients in STEVIE and 33 patients in ERIVANCE), and so any estimates of efficacy are associated with large amounts of uncertainty.

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 and less than 5% of patients in either study were recruited from the UK. In addition, the ERG's clinical experts considered that a high proportion of patients in both studies had Gorlin syndrome and the ERIVANCE study had a lower median age than expected in UK patients. The ERG thus considers that STEVIE is more representative of the UK population likely to be eligible for vismodegib, based on it having a higher median age at baseline. The ERG also noted that there was no information on subsequent treatments received following study drug discontinuation in either ERIVANCE or STEVIE although it is likely that patients went on to receive BSC. The impact of these

potential subsequent treatments is thus unknown, although it is likely they would only affect estimates of OS and AEs. As a result, the ERG considers that OS data in the landmark analysis are likely to be confounded by the use of subsequent treatments. The ERG also notes that there is guidance from the FDA suggesting that single-arm studies shouldn't be used for capturing time-to-event data such as OS and PFS and so the ERG considers the data presented in the CS for OS and PFS for vismodegib from ERIVANCE, STEVIE and the landmark analysis should be interpreted with caution.

The ERG considers it important to highlight that there were high levels of AEs in ERIVANCE and STEVIE (100% and 98% of patients, respectively). In addition, compared to comparable 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 patients were enrolled from, the ERG cannot rule out the possibility that vismodegib may increase mortality in laBCC patients.

The ERG has further 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 the results of the landmark analysis should be interpreted with caution because they are based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions should not be made from the results of single-arm studies. The results for mBCC from the landmark analysis are based on small patient numbers (<100 patients) and thus as already discussed, the evidence base is extremely limited for drawing any conclusions relating to vismodegib in mBCC.

Finally, the ERG does not consider the Gorlin syndrome subgroup to have been addressed adequately in the company submission (CS) although the Gorlin syndrome subgroup in STEVIE was larger than the subgroup of mBCC patients in ERIVANCE. The ERG notes that Gorlin syndrome patients in STEVIE were different to the non-Gorlin syndrome patients as they had a lower median age, a more favourable ECOG performance status and higher median number of target lesions. The ERG therefore considers them to be an important subgroup and notes that the Gorlin subgroup results from the landmark analysis are not adjusted for differences in baseline characteristics which limits their usefulness. In addition, the Gorlin syndrome subgroup results are not presented separately for the laBCC and mBCC populations.

Economic

The ERG is concerned with the extremely high degree of uncertainty embedded in the analysis of relative treatment effectiveness of vismodegib compared with BSC. The landmark method used to derive the HRs for OS and PFS introduces uncertainty in the analysis, which is only exacerbated by the small number of patients in the mBCC group. To these issues, are added the non-systematic selection process of prognostic factors in the HR estimations, which potentially introduced further uncertainty and bias in the analysis. Assuming PH holds in the analysis is also likely to introduce further uncertainty in the results, particularly for OS data.

It is the ERG view that, in particular for mBCC patients, the evidence base is not robust enough to draw conclusions on the relative effectiveness of vismodegib compared to BSC in terms of OS and PFS outcomes. With regards to 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 PFS and OS HRs.

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

Below the ERG discusses the particularities of the STA and its issues in more detail:

- The landmark approach undertaken by the company produced a HR for responders vs non-responders in the STEVIE study. Therefore, the company adjusted the HR obtained in the landmark approach to reflect the HR of non-responders vs ITT patients, as a proxy of the measure of relative effectiveness for vismodegib compared with BSC. The ERG disagrees with the theoretical and methodological implications of the adjustment made by the company. The final HR used in the model is a time-varying HR, which resulted from the company imposing a time-varying component in the landmark HR that was derived as a time-invariant HR, with a Cox proportional hazards model. If the company had reasons to believe that there is evidence of a time-varying treatment effect, then a different modelling approach should have been explored. The company could have explored fitting the responders and non-responders data from STEVIE independently or fitted the dataset with a time-varying model. If on the contrary,

the evidence does not substantiate the existence of a time-varying HR, then this time dependency should not be forced into the HR, which is what the company's approach implies. Even though the ERG does not agree with the company's adjustment made to the HRs, it notes that adjusting the HRs is in detriment of the company's analysis as this decreases the HRs used in the model, therefore increasing the final ICER. Worth noting is also the fact that fitting responders and non-responders data independently would have raised a different issue. Using these populations as proxies for a vismodegib arm and a BSC arm, respectively, would have introduced bias in the analysis and overestimated the effectiveness of vismodegib and the effectiveness of BSC.

Applying the "unadjusted" HR resulting from the landmark approach to the ITT population in STEVIE is also partially flawed. The HR reflects the relationship between a "perfect response" vismodegib group and a BSC group with potentially better outcomes than a real BSC group. However, if one hypothesises that the upwards bias introduced in this analysis cancels out (meaning that the overestimation of vismodegib effectiveness cancels out the overestimation of BSC effectiveness), then applying this HR to the ITT population, could approximate the analysis to what would be observed in a comparative trial, evaluating vismodegib vs BSC. This was the approach followed by the ERG in its exploratory analysis.

- Related to this issue is the assessment of PH in the clinical events observed in the responders and non-responders groups of STEVIE. 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 to 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. Although the initial tests (visual inspection of log-cumulative hazard plots) seem to indicate that PH does not hold for OS or for PFS for mBCC patients, this could be a product of the combination of the method of analysis and the extremely small numbers of mBCC patients. 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. The HRs and the methods used to model treatment with vismodegib and BSC in the cost-effectiveness analysis (dependant fit and

assumption of PH) carry a high degree of uncertainty. This, in turn, adds substantial uncertainty in the final ICERs.

- The ERG disagrees with the company's approach of using a common treatment effect (laBCC and mBCC) HR in the model. The company built two separate models, using separate data for laBCC and mBCC patients but decided to use a common treatment effect HR in both models. Due to the clinical and prognostic differences in the populations (discussed in Section 5.4.2), the ERG considers that the two patient groups should be analysed separately, as should the effectiveness of vismodegib in these populations. For example, while it is plausible to assume that vismodegib has a mortality benefit for mBCC patients (who eventually die from their disease), it is less likely that vismodegib has a mortality benefit on laBCC (who are unlikely to die from their disease).

- The company decided to include age and ECOG as covariates in the estimation of the landmark HRs. The ERG asked the company to confirm that a systematic approach had been taken to select the prognostic factors included in the analysis. The company replied that no systematic approach had been taken to select covariates 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 characteristic are likely to be relevant prognostic factors, such as Gorlin syndrome, nerve infiltration and BCC location (i.e. head, neck, etc.).

- The mBCC HRs are not statistically significant for OS or PFS outcomes. This is not surprising considering the very limited number of patients observed in the group. Interestingly the PFS HR for laBCC is also not statistically significant, despite the considerably larger sample size in this population (736 patients overall). The only HR that is statistically significant in the company's analysis is the OS HR for laBCC patients.

- There is an unusual plateau at the end of the OS and TTD KM curves for laBCC and mBCC patients. The KM curves and the data suggest that for laBCC patients, there were no death or discontinuation events for approximately 1.5 years before the end of the follow-up period. The same is true for mBCC patients where for approximately 16 months before the end of the follow-up period there were no deaths or discontinuation events. The ERG asked the company

to confirm if this had been the case in STEVIE and the company confirmed that the 44 months for laBCC and 38 months for mBCC data points correspond to the entire follow-up period in STEVIE and added that no events were observed from the previous date point in the KM curves till the end of the follow-up. By 26 months patients in STEVIE would be, on average, 74 years. The OS KM tails imply that no patient with mBCC would die for 18 months, which the ERG finds implausible from a clinical point of view. The long tails of the TTD curves suggest that patients continued treatment after progression in the mBCC population. This is difficult to explain as STEVIE patients could not continue treatment after progression.

- The ERG has some concerns regarding the estimation of TTD curves in the laBCC and mBCC vismodegib models:

    - The company's decision to use a Weibull instead of a log-logistic model to estimate TTD: the ERG considers that there is no robust evidence to suggest using a Weibull over a log-logistic distribution to estimate TTD in the economic analysis 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;

    - The KM TTD laBCC and mBCC curves crossing: the fact that the laBCC and mBCC TTD log-logistic curves cross in the model is entirely based on the company's approach to modelling the TTD curves, and has nothing to do with the fit of the log-logistic curves. The reason why the TTD log-logistic curves cross for laBCC and mBCC, when the corresponding KM curves do not, is due to the company's decision to cap the TTD curves to the PFS curves for laBCC and mBCC, and does not indicate a bad fit of the log-logistic curves. The ERG's plotted log-logistic curves do not cross each other, thus differing from the crossing log-logistic curves reported by the company. Therefore, the ERG disagrees with the company's use of this argument to justify the selection of a Weibull instead of a log-logistic model.

    - The KM TTD curve crossing the KM PFS curve for mBCC patients: 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. The company has dealt with the issue of TTD and PFS crossing curves by capping the 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.

With regards to laBCC patients, the fact that the KM TTD and the PFS curves cross at around month 38 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 7%. Considering the small percentage of patients, the ERG's preferred approach would still be to use a better fitting curve 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, and as explained in Section 5.4.5.4, the long tails of the KM TTD curves suggest that metastatic patients continued treatment after progression in STEVIE. 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. 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 it 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 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.

- 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. Due to this, clinical expert opinion might be of more value than the traditional curve fitting validation exercises. This is only caveated by the fact that out of the three clinical experts contacted by the ERG (two dermatologists and one oncologist), only one had had contact with an mBCC patient. As mentioned in Section 4, the incidence of mBCC is extremely low, and therefore clinical expert opinion given for mBCC data also carries considerable 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. One clinical expert added that the advantage of vismodegib in laBCC patients is in preventing progression, but that once that point is reached, then the journey of the patient is the same irrespective of treatment.

The CS does 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 also interesting to note that for the first five cycles in the economic model, the company used the background survival curve to model OS for vismodegib (instead of the Gamma model), as the survival predicted by the Gamma model was higher than the background survival for the matched UK population. It is therefore difficult to understand the extent to which the company's analysis is generalizable to laBCC patients in the UK. For example, the fact that laBCC patients have a higher mortality rate than the average age and gender-matched population in the UK might be related to the fact that only 3% of patients in the STEVIE trial came from the UK. 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 patients were enrolled from, the ERG cannot rule out the possibility that vismodegib may increase mortality in laBCC patients

With regards to mBCC-related mortality, the clinical experts advising the ERG presented different views. Even though the three experts agreed that (unlike for laBCC), patients will die from mBCC, there was not a consistent view on which curve was a better representation of the vismodegib OS curve for mBCC. One clinical expert's opinion was that none of the curves were accurate representations of mortality for mBCC patients as it was expected that most

mBCC patients die between 12 to 24 months and so it was unrealistic to assume that patients would survive for more than 10 years. This is consistent with the view of the Economic Guidance Panel for the Canadian HTA body, which considered that mBCC patients would be expected to survive for less than 10 years.

The ERG asked the company to use the McCusker *et al.* paper to conduct a validation exercise on the modelled BSC arm for mBCC as this study appears to be the only available evidence for BSC-related mortality in aBCC patients.[26] The company aggregated the distant and regional metastatic KM OS curves from McCusker *et al.* as requested by the ERG and used it to fit BSC OS curves in the economic model for mBCC patients.[26] The company then applied the inverse HR obtained through the landmark approach to derive an mBCC vismodegib curve. The modelled survival curves from STEVIE (i.e. ITT population curve for vismodegib patients and BSC curve estimated by applying the landmark HR to the ITT vismodegib curve) and the McCusker *et al.* curves (i.e. the observed BSC curve for mBCC patients and the vismodegib curve estimated by applying the landmark HR to the McCusker *et al.* curve) are similar, which is not unexpected, considering that the same HR was used to derive the comparator curve in each case (i.e. the BSC curve in STEVIE data and the vismodegib curve in the McCusker *et al.* data).[26] As the observed curves (i.e. ITT curve in STEVIE and BSC curve in McCusker *et al.*) are not comparable, the difference in these curves cannot be validated by any other data source. Figure A also shows the difference between the non-responders in STEVIE and the BSC patients in the McCusker *et al.* source (dark green and pink curves).[26] This shows that the non-responders group in STEVIE and the BSC patients in McCusker *et al.* have very different survival prognosis.[26] This analysis is caveated by the fact that the number of patients in the non-responders group in STEVIE is incredibly small (31 patients) and that only four patients died. It should also be noted that patients in McCusker *et al.* are younger than in STEVIE, which suggests patients would have a better survival prognosis instead of worse survival outcomes, when compared with STEVIE.[26]

Figure A. Survival in mBCC patients

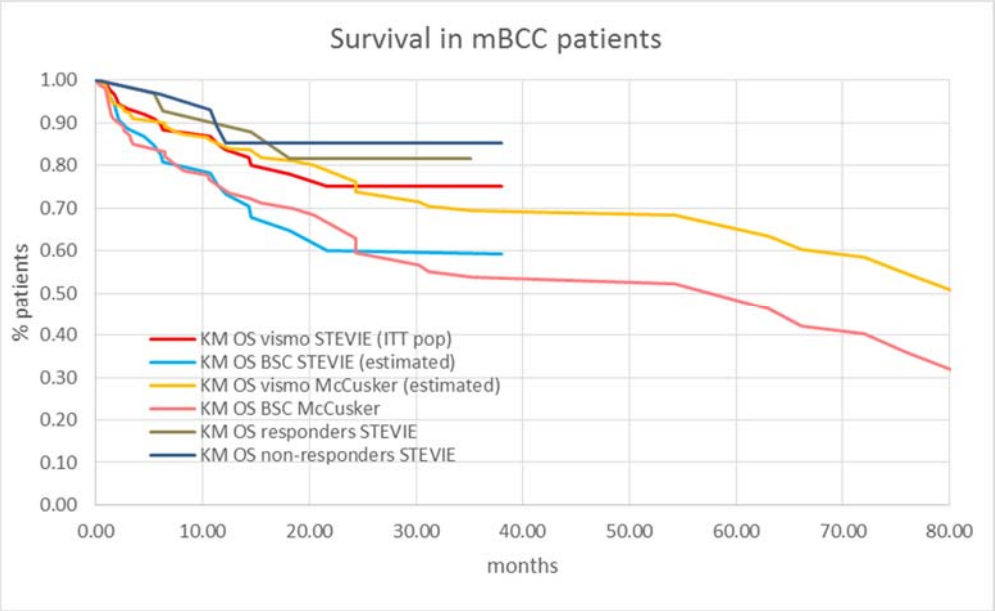
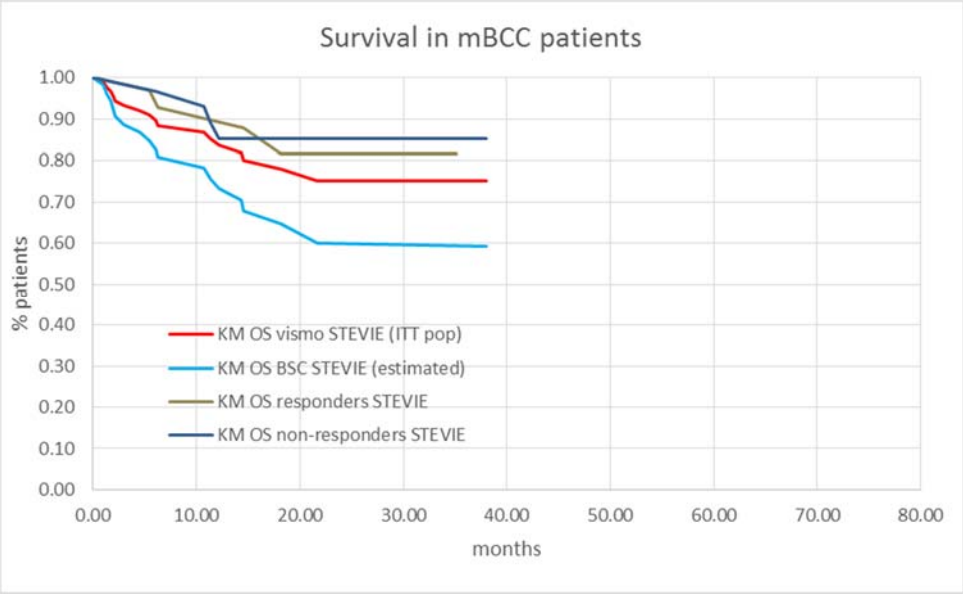


Figure B shows how the responders and non-responders groups from STEVIE compare with the modelled vismodegib and BSC curves for mBCC. The difference is these curves is overwhelming. While the responders and non-responders KM curves clearly reflect the lack of statistical significance encountered in the landmark HR for OS in mBCC patients (as they cross and overlap a few times), the ITT and estimated BSC curves do not, and show a clear separation of the curves throughout the entire time horizon of the model. This is worrying as it reveals the lack of robust evidence substantiating the vismodegib and BSC estimated curves and the contradiction between observed and estimated outcomes. The ERG does not consider that the evidence provided by STEVIE or clinical experts (due to the very low incidence of mBCC cases) is robust enough to make conclusions on the effectiveness of vismodegib in the mBCC population.

Figure B. Survival in STEVIE for mBCC patients



- The quality of life data incorporated in the model are from the ERIVANCE trial, while the clinical effectiveness data used in the model are based on the STEVIE trial. The ERG acknowledges that there are no published algorithms for mapping quality of life data captured through the Skindex-16 instrument into EQ-5D values, therefore using data from the STEVIE trial was not an option. Nonetheless using ERIVANCE quality of life data raises several issues:

  - 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 on average 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 to the observed clinical practice, but also when compared with the STEVIE population, who was on average 10 years older than the population in ERIVANCE;

  - Progression was assessed in different ways in the two trials. In STEVIE, progression was assessed using the RECIST v1.1 criteria, while in ERIVANCE a novel composite method was used to determine progression in the laBCC population. It is difficult to anticipate the impact that the difference in progression criteria could have on the cost-effectiveness results;

- The Canadian HTA body also raised some valid points on the uncertainty of the SF-36 data from ERIVANCE. They point to the lack of sensitivity of the SF-36 instrument for this indication, the ceiling effect for relatively healthy individuals at baseline and the small sample size in ERIVANCE.

According to the descriptive statistics provided by the company at clarification stage, the mean change from baseline in SF-36 values for all the dimensions does not seem to be 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) for the physical functioning and vitality components seems to be statistically significant. All the other dimensions do not seem to show statically significant reductions at the end of the study. The lack of statistical significance in the results might be related with the points raised by the Canadian HTA body, which noted 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 is robust, the underlying SF-36 data seems to carry a lot of uncertainty. The company used SF-36 values who mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values who suggest a decrease in patients' quality of life upon progression.

- The utility decrements applied in the model for AEs are based on a study in patients with melanoma. Despite the company's consideration that melanoma and aBCC are similar diseases, the AEs listed in Beusterian *et al*. study do not match the AEs of interest reported in either STEVIE or ERIVANCE. Also Grade 4 events in the Beusterian *et al*. required hospitalisation, while the Grade 3 events were assumed to require an inpatient/outpatient stay.[101] The ERG's clinical experts explained that AEs experienced with vismodegib are generally managed by discontinuing treatment and would not require hospitalisation. This renders the Grade 3 and Grade 4 events reported in Beusterian *et al*. not representative of the Grade 3 and 4 events in vismodegib. Nonetheless, removing AEs-related utility decrements in the model has a negligible impact on the final cost-effectiveness results.

- Resource use estimates applied in the model are based on feedback from the company's clinical experts as there are no known sources for resource use in the study population. The ERG's clinical experts confirmed that the assumptions made in the model surrounding pharmacological costs are reasonable. However, there are some concerns surrounding the company's assumptions for estimating disease management costs. More specifically these are related with:

- The company's assumption that 67% of patients who progress after receiving vismodegib are on a monitoring regimen for the remainder of their lifetime and never receive BSC. The ERG's clinical experts explained that even if these patients require a less intensive regimen for managing disease progression after vismodegib, they will eventually go on to receive BSC as their disease progresses. Clinical experts' input indicates that the duration of the watchful waiting period is highly volatile and depends on the location 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, progressed patients will eventually move to BSC;

- The company's assumption on the frequency of wound management and TVN visits. There was no consensus amongst the clinical experts advising the ERG with regards to the frequency of wound management in the PD and in the PFS states for BSC patients. While one clinical expert agreed with three visits for the PD state and two visits for the PFS state, the other two clinical experts suggested that a less intense regimen would be more plausible (two visits for the PD state and one visit for the PFS state);

- The company's assumption that the post-progression BSC regimen for vismodegib patients differs from the post-progression BSC regimen for BSC patients. Clinical expert opinion provided to the ERG was consensual that once vismodegib patients progress and require BSC, the treatment schedule for these patients is the same as the one required by patients on the BSC treatment arm who have progressed.

The ERG's exploratory analysis has shown that both the laBCC and mBCC results are most sensitive to the assumptions made around disease-related mortality and vismodegib's survival benefit, as well as the assumptions surrounding the costs of BSC. Removing the AE-related disutilities and the cost of a dietician from the model had a negligible impact on the model results for both laBCC and mBCC patients.

When the ERG assumed that there is no mortality associated with laBCC, therefore assuming to survival gain with vismodegib, the final ICER for vismodegib compared with BSC is £5,203,675. The ICER for vismodegib compared with BSC when assuming the existence of laBCC-related mortality and a gain in survival with vismodegib compared with BSC is £106,569.

As previously explained, due to the level of uncertainty and the lack of robust mBCC data, the ERG conducted a cost minimisation analysis for this population. When the ERG assumed a PFS and OS HR

of 1, the final ICER for vismodegib vs. BSC became dominated, with a zero QALY gain and an additional cost of £89,323 (total costs for vismodegib £159,547 and £70,224 for BSC).

8.1 Implications for research

The ERG notes that there are several ongoing clinical studies of vismodegib including:

- STEVIE which is ongoing to further evaluate safety and efficacy of vismodegib in aBCC; and
- RegiSONIC which is an ongoing observational study of treatment patterns, effectiveness, and safety outcomes in aBCC and basal cell naevus syndrome (BCNS) patients.

The ERG considers there is a need for further research to:

- confirm the relative effectiveness of vismodegib compared with BSC, in particular, from a randomised controlled trial;
- confirm the efficacy and safety of vismodegib in the population of England and Wales;
- confirm the efficacy and safety of vismodegib in people with mBCC as well as the subgroups of people with laBCC and Gorlin syndrome, and mBCC and Gorlin syndrome;

provide long-term efficacy and safety data on vismodegib, in particular, to confirm its impact on OS.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

ID 1043 - Vismodegib in advanced basal cell carcinoma (aBCC)

You are asked to check the ERG report from BMJ-TAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 9th June, 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Section 1 - Summary

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
1	Page 17, Section 1.2, 6th paragraph Page 134, Section 5.4.5, 1st paragraph "The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or chemotherapy and so are left with no other treatments options at this point in the clinical pathway." The company submission, and vismodegib license, actually states that vismodegib is to be used when surgery and radiotherapy have been deemed inappropriate, not chemotherapy.	"The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or radiotherapy and so are left with no other treatments options at this point in the clinical pathway."	Incorrect statement	The ERG agrees with the company and has made the proposed amendments.
2	Page 18, Section 1.3, 6th paragraph "The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the lognormal was best fitting model for the OS mBCC data." Incorrect statement, The Weibull distribution was used to model OS in the mBCC population, not the lognormal.	"The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the Weibull distribution was the best fitting model for the OS mBCC data."	Incorrect statement	The ERG agrees with the company and has made the proposed amendments.
3	Page 21, Section 1.4.2, 1st paragraph Page 65, Section 3.3, 1st paragraph "In addition, the ERG considers the company's rationale that it would be difficult to recruit sufficient patients due to the limited aBCC population to be unjustified given the size of the STEVIE study." It should be noted that this was not the only factor involved in the decision to conduct a randomised clinical trial. The	Phrasing taken from ERIVANCE protocol: This study is designed to demonstrate the efficacy and assess the safety of GDC-0449 given as a single agent in patients with locally advanced or mBCC. These populations were chosen for study based on unmet	Misleading statement	Not a factual error

	phase I study reported a response rate of around 80%. It was therefore viewed as unethical to conduct a randomised, placebo controlled trial. In addition, the following was taken from the ERIVANCE CSR: "The population of patients with metastatic or locally advanced BCC was chosen on the basis of the scientific rationale (i.e., presence of Hh pathway activation in the majority of BCCs), evidence of drug activity in these populations in the Phase I study (SHH3925g), and the lack of other therapeutic alternatives for these patients. A control group was not used, given that there is no accepted standard of care and no data suggesting spontaneous responses in advanced BCC."	medical need and evidence of efficacy observed in the Phase I study. A control group was not used, as there is no accepted standard of care and no data suggesting spontaneous responses in advanced BCC.		
4	Page 21, Section 1.4.2, 4th paragraph "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 company believes this to be an unfair statement. The language used implies a lack of cooperation by the company. During the clarification question stage of this appraisal, the company provided the numbers of patients registered at each UK centre in both the ERIVANCE and STEVIE clinical trials.	Suggest removal of statement	Incorrect statement	Not a factual error
5	Page 21, Section 1.4.2, 5th paragraph "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." A single-arm study with a response rate endpoint was deemed by investigators and experts in the field, as well as	Removal of statement	Misleading statement	Not a factual error

	the US FDA, to be the most appropriate and feasible design in this rare aBCC population with unmet medical need.			
6	Page 21, Section 1.4.2, 6th paragraph "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." Whilst this statement is true, in the original submission the company failed to include salient details associated with deaths due to vismodegib in STEVIE. The following excerpt is taken from Page 71 of the STEVIE CSR: "The age range of patients with Grade 5 TEAEs of general physical health deterioration was 84 to 88 years, and all patients had significant comorbidities at baseline, which confounds the assessment of relationship to vismodegib.".	Suggest incorporation of phrase taken from the STEVIE CSR.	Misleading statement	Not a factual error. The additional information provided by the company does not suggest any difference between the STEVIE population and the population that the background mortality rate data is taken from as patients in this age range would generally be expected to have comorbidities.
7	Page 22, Section 1.4.2, 3rd paragraph "The Gorlin subgroup results from the landmark analysis are not adjusted for differences in baseline characteristics. In addition, they are not presented separately for the laBCC and mBCC populations." A subgroup analysis of Gorlin versus non-Gorlin patients within laBCC and mBCC patients would have lessened the mBCC sample size even further. Given that the ERG already highlighted the small sample size for mBCC	Add context surrounding the appropriateness of including separate laBCC and mBCC results for Gorlin vs. non-Gorlin patients	Further clarification	Not a factual error
8	Page 23, Section 1.4.2, 1st bullet point "The ERG disagrees with the theoretical and methodological implications of the adjustment made by the company. The final HR used in the model is a time-varying	Review further clarification provided by the company.	ERG has misunderstood an aspect of the methodology	Not a factual error.

	HR, which resulted from the company imposing a time-varying component in the landmark HR that was derived as a time-invariant HR, with a Cox PH model. If the company had reasons to believe that there is evidence of a time-varying treatment effect, then a different modelling approach should have been explored. The company could have explored fitting the responders and non-responders data from STEVIE independently or fitted the dataset with a time-varying model. If, on the contrary, the evidence does not substantiate the existence of a time-varying HR, then this time dependency should not be forced into the HR, which is what the company's approach implies." The hazard ratio of non-responders versus the entire intent-to-treat population was obtained through an adjustment of the hazard ratio of non-responders versus responders by the proportion of non-responders in the intent-to-treat population. The reason for the change of the hazard ratio of non-responders versus intent-to-treat patients over time was the fact that the proportion of non-responders changes in the intent-to-treat population. This modelling step was not motivated by a hypothesis that the hazard ratio of non-responders versus responders changed over time. The company believes that an adjustment of the compositional changes in the vismodegib arm in the model is unrelated to the estimation procedure of the hazard ratio of non-responders versus responders and would be necessary even when time varying hazard ratios of non-responders versus responders were estimated. Because the hazard ratio of non-responders versus the intent-to-treat population could not be estimated directly the true effect of compositional changes in the intent-to-treat population could not be assessed empirically.			
9	Page 27, Section 1.4.2, 2nd paragraph	Remove statement	Misleading statement	Not a factual error.

	"One clinical expert added that the advantage of vismodegib in laBCC patients is in preventing progression, but that once that point is reached, then the journey of the patient is the same irrespective of treatment." Company disagrees with this statement, as do all clinical experts consulted during the development of the CS. Vismodegib has been shown to heal wounds and shrink tumours. A patient who has progressed would not have the same outlook regardless of whether they received vismodegib or not.			
10	Page 28, Section 1.4.2, 1st paragraph "The expert indicated that most mBCC patients would be expected to die between 12 and 24 months" Misleading statement. Is this statement referring to those with no active treatment? This has been disproved by STEVIE	"The expert indicated that most mBCC patients would be expected to die between 12 and 24 months if not active intervention was received" – or remove statement	Misleading/inaccurate statement	Not a factual error.
11	Page 29, Section 1.4.2, 1st paragraph "It should also be noted that patients in McCusker et al. are younger than in STEVIE, which suggests patients would have a better survival prognosis instead of worse survival outcomes, when compared with STEVIE." This can also be interpreted that advances in therapy including vismodegib to which our non-responders were exposed. Thus, the McCusker exercise actually shows that our BSC arm is rather conservative.	Include additional interpretation provided by the company	Misleading statement	Not a factual error.
12	Page 32, Section 1.4.2, 2nd paragraph Page 130, Section 5.4.1, "Health states for QALYs" Page 174, Section 5.4.10, 2nd paragraph	Remove statement	Incorrect/misleading statement	Not a factual error.

	“The company used SF-36 values who mainly do not show a statistically significant change in quality of life over time and derived EQ-5D values who suggest a decrease in patients’ quality of life upon progression.” Misleading statement. The ERG questions the fact that no statistically significant differences in SF-36 results still somehow translated into meaningful differences in pre and post progression HSUVs. The company considers this comparison unjust. SF-36 is measured across visits (baseline vs end of treatment) whereas for utilities are measured across health states (progression free vs progression). The two sets of values are not comparable.			

Issue 2 Section 2 - Background

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
1	Page 40, Section 2, 1st paragraph "The ERG considers it important to highlight that while NMSC includes BCC, it also comprises of squamous cell carcinoma (SCC), which is known to be faster growing than BCC.29 The prognosis and economic impact for BCC are thus unclear and the information presented in Box 7 should be interpreted with caution."	"The ERG considers it important to highlight that while NMSC includes BCC, it also comprises of squamous cell carcinoma (SCC), which is known to be faster growing than BCC. It is recognised that the company have included a statement acknowledging that SCC is more agressive than BCC. The prognosis and economic impact for BCC are thus unclear and the information presented in Box 7 should be interpreted with caution"	Roche believe that the statement "NMSC incorporates both BCC and the typically more aggressive SCC." in box 7 covers the issue highlighted by the ERG and would like to ensure that the reviewers were not of the opinion that Roche aimed to mislead the panel.	Not a factual error
2	Page 46, Section 2.2, 3rd paragraph “The ERG’s clinical experts agree with the company’s proposed resource use for vismodegib although they consider that follow-up may actually be two weekly for the first six weeks of treatment with a blood test for liver function at two weeks. Clinical experts reported that routinely patients would then be seen monthly while on the drug, with monthly blood tests (full blood count, urea and electrolytes, and liver function tests).” Given that this area is not officially addressed in the Summary of Product Characteristics document for	Add acknowledgement that follow-up routines are at the discretion of the treating physician and can vary case by case.	Further clarity	Not a factual error

	vismodegib, the company understands follow-up routine to be at the discretion of the physician.			
3	Page 48, Section 2.2, 1st paragraph “The company’s estimate is thus that 426 patients would be eligible for vismodegib in 2018. However, the ERG notes that the company also report that vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013 and up until the end of August 2016 only 352 requests had been made for CDF funding for vismodegib. The company is thus suggesting that more patients would receive vismodegib in a one-year period compared to in a 3-year period while it has been available via the CDF. The ERG and its clinical experts are unclear why more patients would be expected to be treated with vismodegib if it were approved by NICE as the indication would remain the same.” From this statement, it appears that the ERG has misunderstood the values reported in Table 2 of their report. The company believes that a total of 426 patients will have either mBCC or laBCC inappropriate for surgery or radiotherapy in 2018. This figure is the total number of patients in England and Wales that are within the licensed indication and are therefore eligible for vismodegib therapy. It is unreasonable to assume that 100% of the eligible patients would receive vismodegib, therefore we have weighted the population using a market uptake percentage of 35%, which was calculated based on extrapolation of the CDF data. Please refer to Section 6 of the CS for a more in-depth explanation of the methodology.	Remove this statement	Incorrect statement	The ERG agrees with the company. The text has been amended to reflect the market uptake percentage and incorrect text deleted, “The company’s estimate is thus that 426 patients would be eligible for vismodegib in 2018. However, the ERG notes that the company also report that vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013 and up until the end of August 2016 only 352 requests had been made for CDF funding for vismodegib. The company reported that the market uptake percentage is expected to be only 35% based on extrapolation of the CDF data.”

Issue 3 Section 3 - Critique of Company's Decision Problem

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
1	Page 54, Section 3.2, 1st paragraph “The All Wales Medicines Strategy Group (AWMSG) are due to re-appraise vismodegib on 26th April 2017 as Roche were unable to provide a complete submission in time for the previously scheduled appraisal in August 2016.” This statement is not reflective of the entire situation. On the 15th July, 2016, Roche were informed that the Welsh government had instructed AWMSG to conduct a technology appraisal of vismodegib. AWMSG expected evidence of both clinical and cost-effectiveness to be submitted to them by August 5th, 2016. Roche felt that 3 weeks was both an unreasonable and impossible amount of time in which to develop a *de novo* cost-effectiveness model, and therefore only provided AWMSG with clinical evidence. The formal meeting to discuss this appraisal took place on 26th April, 2017. There was no re-appraisal; this was all part of a single appraisal in which Roche were unable to offer any cost-effectiveness evidence due to severely contracted timelines.	Use information in “Description of problem” field to give a clearer timeline of events.	Further clarity	The ERG acknowledges that the text is incorrect and has amended the sentence to, “The All Wales Medicines Strategy Group (AWMSG) were due to appraise vismodegib on 26th April 2017 although the ERG notes that Roche were unable to provide a complete submission by the AWMSG deadline of 5th August 2016.”
2	Page 55, Section 3.3, 1st paragraph "The ERG considers a potential comparator of physician’s choice could have been used in an RCT to represent BSC" As stated earlier in section 3.3, "no standard treatment options were identified for either laBCC or mBCC patients based on a literature review of the previous 30 years" - hence inclusion of a control arm in which clinicians were able to select their own BSC (not including surgery or	Removal of statement	Unfeasible suggestion	Not a factual error

	radiotherapy) would have impacted on the validity of the trial.			

Issue 4 Section 4 - Clinical effectiveness

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
1	Page 58, Section 4.1.1, 3rd paragraph "The ERG notes that no search terms were used to identify the comparator treatment outlined in the decision problem, best supportive care (BSC). The ERG considers the company's search strategy to be appropriate for identifying studies of vismodegib but does not consider it suitable for identifying studies for the comparator, BSC. The ERG finds it particularly unusual that the company didn't search for studies of BSC given that their key studies for vismodegib were single arm studies and so they knew that data for BSC would be required to enable a comparison to address the decision problem in the final scope issued by NICE" The company believes this to be an unfair statement, as it has already been established in section 3.3, "no standard treatment options were identified for either laBCC or mBCC patients based on a literature review of the previous 30 years" Further, the statement on page 58 is at odds with statement page 59 "The ERG agrees that the lack of search terms for comparators in the search strategy is appropriate given that the comparator of interest in the final scope issued by NICE is BSC, which can consist of a multitude of different treatments "	Remove statement	Incorrect statement	Not a factual error. However, the ERG has added the following sentence to page 60, "However, to enable studies of BSC to have been identified, the ERG considers that the search should not have been limited to studies of vismodegib".
2	Page 58, Section 4.1.1, 4th paragraph "The ERG might agree with the conferences identified by the company if they were justified as the most relevant conferences to include. However, the company provided no	Remove statement	Incorrect statement	Not a factual error

	rationale as to how these particular conferences were identified and chosen over others. " The company believe this to be self-explanatory - the most relevant conferences were chosen. No clarification question was asked of the company.			
3	Page 59, 1st paragraph beneath bullets "The company outline that despite identifying conferences that were relevant and should be searched, not all titles were included in the manual search process. The company justify the exclusion of these conferences due to the proceedings not being freely available. The conferences not searched include the following: European Academy of Dermatology and Venereology; British Oculoplastic Surgery Society; Winter Clinical Dermatology Conference; Fall Clinical Dermatology Conference; World Cutaneous Malignancies Conference. The ERG notes that identifying these conferences as relevant for the disease area and then subsequently not searching them for relevant evidence is a limitation to the company's search. The ERG is unable to comment on the likely impact this selective searching has on the results of the literature review." As indicated in the original submission, the proceedings of some conferences were not freely available, and thus it was not possible to search these for relevant evidence. The EADV abstract books for 2015 & 2016 are not published in the JEADV. The searchable abstracts (not abstract books) are available to EADV members only via exclusive access on EADV.org with login details: full access is limited to members Fall and Winter Clinical Dermatology Conferences: abstract books could not be located online	Amend statement to make more reflective of limitations of searches	Misleading statement	Not a factual error

	British Oculoplastic Surgery Society: member access only, for abstracts (not abstract book) World Cutaneous Malignancies Congress: 'highlights' available online, but no full abstract book			
4	Page 59, 3rd paragraph "The ERG considers the methods used to search for relevant conference proceedings to lack transparency by the company and the selective searching procedures of these conferences to be problematic." As above, the company believes they have been as transparent as possible in explaining the limitations of searching for some conference proceedings	Remove statement	Unfair statement	Not a factual error
5	Page 61, Section 4.1.3, 1st paragraph "Therefore the ERG considers the eligibility criteria outlined by the company to be appropriate for identifying relevant evidence aligned with the NICE final scope for vismodegib but not for identifying studies of BSC." The company believes this is unfair, as the ERG have already acknowledged on page 59 the difficulty in identifying a comparator, as there is no one BSC.	Remove last part of statement relating to BSC	Unfair statement	Not a factual error
6	Page 61, Section 4.1.3, 2nd paragraph "The company provide no details of how these records were identified. A total of 49 records which reported results from 12 unique studies were included in the review. The ERG notes that the company report a disparity in the number of included studies from their database searches in the CS: in Section 4.1.4 of the CS the company suggest a total of 33 records were identified however these numbers do not	Add further information for clarification	Further clarification	Not a factual error

	correlate with those presented in the company's PRISMA diagram, shown in Figure 1 of the ERG report." Whilst it was not possible to search an abstract book for some of the conferences identified, the company were aware of abstracts that they had submitted to these conferences. Therefore, these were available to the company for consideration in the submission. - Durrani (BOPSS 2015): abstract book not available online, but Roche had submitted this abstract and thus had available - Basset-Seguiin (EADV 2016): abstract book not available online, but Roche had submitted this abstract and thus had available - Tang (WCDC 2015; 2 abstracts): abstract book not available online, but Roche had submitted these abstract and thus had available - Tang (WCDC 2016): abstract book not available online, but Roche had submitted this abstract and thus had available - Hansson (EADV 2015: abstract book not available online, but Roche had submitted this abstract and thus had available - Dummer (EADV 2015): abstract book not available online, but Roche had submitted this abstract and thus had available - Sekulic (ASCO 2014): this abstract fell outside the limits of the congress search (2015-2017) thus was not picked up in the SLR. However, as the results were deemed relevant (first presentation of the 30-month results for ERIVANCE), this was added - Chang (Oncotarget 2016): company recognises that this should have been listed in the SLR instead of as provided by Roche - Lacoutre (EADO 2015): company recognises that this			

	should have been listed in the SLR instead of as provided by Roche			
7	Page 62, Section 4.1.3, 3rd paragraph: "However, the ERG notes there is a lack of clarity with regards to the number of records retrieved from the search and screening process with inconsistent reporting between the text and the PRISMA diagram presented in the CS." If explanatory statement above is accepted by the ERG, this statement should be removed.	Possible removal of statement	Incorrect given previously proposed amendments	Not a factual error
8	Page 64, Section 4.1.4, 3rd paragraph: "The ERG considers the inclusion of approximately 20% of patients with Gorlin syndrome in both the ERIVANCE and STEVIE study's to be an over-representation of Gorlin patients compared to UK clinical practice" Roche agree that the incidence of Gorlin syndrome versus the general population is over-represented in the studies included in the review (Gorlin incidence has been reported as 1 in 30 827 in England; Evans DG, Howard E, Giblin C et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010; 152: 327–332.) However there are clinics specialising in the treatment of patients with Gorlin syndrome and due to the pathophysiology of BCC development this cohort of patients is particularly relevant to receive vismodegib treatment.	"The ERG considers the inclusion of approximately 20% of patients with Gorlin syndrome in both the ERIVANCE and STEVIE study's to be an over-representation of Gorlin patients compared to UK clinical practice. However there are clinics specialising in the treatment of patients with Gorlin syndrome and due to the pathophysiology of BCC development this cohort of patients is particularly relevant to receive vismodegib treatment."	Misleading statement	Not a factual error
9	Page 79, Section 4.2.1.2, 3rd paragraph "..., an IRF was used for the majority of the outcome assessments in ERIVANCE whereas STEVIE comprised	Add information provided by company in in "Description of problem" field of this comment	Misleading statement as not all information has been reported	Not a factual error

	only of investigator assessments and thus the results of STEVIE may be subject to assessor bias although the potential of impact of this is unknown." Further clarification - clinical experts consulted by Roche suggested that investigator assessment of skin cancers, where a clinical examination was made holistically (including the texture/feel of surrounding tissue and scar tissue) was potentially more accurate/realistic than an independent review of images of BCCs.			
10	Page 102, Section 4.3.4, 1st paragraph “The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly higher proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively).” Incorrect statement. 43.3% < 49.0%	“The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly lower proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively).”	Incorrect statement	The ERG acknowledges that the sentence should read, “. . . slightly lower proportion of these events in laBCC”. The sentence has been corrected accordingly.
11	Page 104, Section 4.3.4, 1st paragraph “In addition, the ERG notes that only 3% of the population of STEVIE were from the UK and it is not clear where the remaining 97% of patients were recruited from.” The CS provides a list of countries with more than one centre on page 78. In addition, all patients along with their Centre number are listed from page 1,235 to page 1,316 of the STEVIE CSR. Through cross referencing this listing with a list of the Centre locations and numbers (begins on page 9,360 of CSR) it can be deduced how many patients were enrolled in each country.	Remove statement	Incorrect statement	Not a factual error

12	Page 121, Section 4.6, 5th bullet point "Efficacy results of ERIVANCE: Investigator assessed median PFS with vismodegib in the laBCC population was 12.9 months (95% CI: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months). Median OS for laBCC was not estimable (NE) but for the mBCC patients it was 33.4 months (95% CI: 18.1 months to NE). Investigator assessed ORR was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p < 0.05$)." Typographical error. Sentence should read "The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p > 0.05$)" – if the ERG are trying to say there was no significant difference.	"The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p > 0.05$)"	Typographical error	The ERG acknowledges that the sentence should read ($p > 0.05$). The sentence has been corrected accordingly.

Issue 5 Section 5 - Cost-effectiveness

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
1	Page 125, Section 5.2, 1st paragraph. "The company's corrected deterministic base case results for vismodegib compared to BSC using the PAS price are reported in Table 32" This statement is incorrect. The results reported in Table 32 of the ERG report are based on the list price of vismodegib, not the PAS price.	""The company's corrected deterministic base case results for vismodegib compared to BSC using the vismodegib list price are reported in Table 32. Please refer to the PAS appendix of this report for economic results generated using the confidential PAS price"	Statement is incorrect.	The ERG agrees with the company. The sentence, "The company's corrected deterministic base case results for vismodegib compared to BSC using the vismodegib list price are reported in Table 32." has been added.
2	Page 129, Section 5.3, 3rd paragraph "The HTA report by the Economic Guidance Panel (EGP) states the following: "Utility estimates that are more representative of the study populations would have been preferable. The quality of life data collected alongside the clinical trial could have provided such an estimate but a number of limitations related to the small sample of the study and the lack of sensitivity of the instrument used (SF-36) for this indication did not allow the EGP to use these data in the economic analysis. On the basis of this limited information, the overall quality of life observed in the ERIVANCE trial for both laBCC and mBCC populations was inconclusive."" The company appreciates that this is a quote taken from another source and perhaps not the views of the ERG, however there is an issue surrounding the "lack of sensitivity" comment in relation to the SF-36. As far as we are aware, there has been no published evidence conclusively documenting the lack of sensitivity of	Either provide a credible reference for this statement, or remove the quote from the report.	Statement is conjecture and could be misleading to readers.	Not a factual error.

	the SF-36 questionnaire in advanced basal cell carcinoma (aBCC).			
3	Page 129, Section 5.4.1, Table 37 Page 131, Section 5.4.2, 5th paragraph "Yes, however the ERG does not agree with the company's justification for not undertaking the subgroup analysis for Gorlin syndrome as stated in the NICE final scope." According to the Final Scope for this appraisal, the Gorlin syndrome subgroup was only to be considered "If the evidence allows". The phrasing of the ERG's statement in the table implies that this subgroup was definitely to be included in the analysis and therefore that the company has ignored the Final Scope of the appraisal.	"Yes, however the ERG does not agree with the company's justification for not undertaking the subgroup analysis for Gorlin syndrome"	Misleading statement	Not a factual error.
4	Page 143, Section 5.4.5.4, 2nd paragraph "The KM tails imply that no patient with mBCC would die for 18 months, which the ERG finds this unlikely from a clinical point of view." This is not what is implied. 25 mBCC patients were at risk (not lost to either death or follow-up) at 21.6 months and all of them were lost to follow-up at 38 months. We have partial information about those patients: they were known to be alive up to the point we last contacted them but we do not know what happened to them afterwards (see KM below)	Remove statement	Incorrect statement	The ERG acknowledges that the sentence should read 16 months instead of 18 months (as there were no death events from around month 22 to month 38). The sentence has been corrected accordingly.
5	Page 155, Section 5.4.8, 2nd paragraph "For example, 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."	"For example, vismodegib can occasionally cause hair and appetite loss, which has a considerable impact on patients' quality of life, despite not being costly or captured through the QALY analysis."	Misleading statement	Not a factual error.

	It is true that vismodegib therapy may cause hair or appetite loss. However, the occurrences of such events are rare. In STEVIE, of the 1,215 patients treated with vismodegib only 1 (0.08%) appetite disorder and 17 instances of hair loss were reported (1.48%). The language used in the ERG report implies that appetite and hair loss are almost inevitable when being treated with vismodegib, when in actual fact this is far from true.			
6	Page 161, Section 5.4.9, 3rd paragraph "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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these data will carry a high degree of uncertainty." The figures quoted in this section of text are incorrect. According to the STEVIE CSR (page 70): - laBCC 92 patients out of 1119 died (8.2%) - mBCC 18 patients out of 96 died (18.8%) In the KM curves only Efficacy-Evaluable Patients with Measurable Disease Status at Baseline and Histologically Confirmed Disease were included: - laBCC 90 patients out of 1103 died (8.2%) - mBCC 17 patients out of 89 died (19.1%)	"The OS KM curve for laBCC patients shows that 8.2% of patients had died at the end of the 44-month follow-up period, while 18.8% of mBCC patients had died at the end of the 38-month follow-up period in STEVIE."	Incorrect statement	The ERG acknowledges an error in the sentence as this should read, "The OS KM curve for laBCC patients shows that **14%** 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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these data will carry a high degree of uncertainty." However, the ERG disagrees with the

				company's proposed amendment as for the purpose of this analysis the relevant percentage of deaths is the one shown in the KM curves, used to extrapolate survival curves.
7	Page 171, Section 5.4.10.3, 2nd bullet point "Clinical experts reported that aBCC patients are on average 70 years old," The company finds it highly implausible that clinical experts are able to accurately report the mean age of a patient group of approximately 900 patients, across three countries based solely on their own clinical experience. Whilst a reasonably accurate estimate may be possible, the language used here implies it as fact. It is unacceptable to argue that there is an overestimation of utility values in the economic analysis compared to clinical practice based on a guess derived from what is assumed to be a relatively limited sample size.	Statement should either be removed or a credible, confirmatory reference should be added.	Possibly incorrect statement	Not a factual error.
8	Page 172, Section 5.4.10.3, 4th bullet point "The Canadian HTA body also raised some valid points on the uncertainty of the SF-36 data from ERIVANCE. They point to the lack of sensitivity of the SF-36 instrument for this indication" This issue has been addressed in a previous comment within this response. No published evidence is available regarding the lack of sensitivity of the SF-36 questionnaire in aBCC	Either remove this statement or find a valid reference.	Incorrect statement	Not a factual error.

9	Page 181, Section 5.5.1, Table 58 caption “QALY breakdown according to health state (CS, page 240, Table 90)” Inaccurate caption. The values reported in Table 58 of the ERG report are adapted from Table 94 on page 240 of the CS, not Table 90.	“QALY breakdown according to health state (CS, page 240, Table 94)”	Incorrect caption	The ERG has made the amendments requested by the company.

Issue 6 Section 6 - Additional work undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment
No issues	N/A	N/A

Issue 7 Section 7 - End of life

Description of problem	Description of proposed amendment	Justification for amendment
No issues	N/A	N/A

Issue 8 Section 8 - Overall conclusions

Description of problem	Description of proposed amendment	Justification for amendment
No issues in addition to those addressed in previous sections	N/A	N/A

Vismodegib for treating basal cell carcinoma
ERRATUM

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

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
17, 132	The sentence "The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or chemotherapy and so are left with no other treatments options at this point in the clinical pathway." was replaced with "The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or radiotherapy and so are left with no other treatments options at this point in the clinical pathway."
18	The sentence "The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the lognormal was best fitting model for the OS mBCC data." has been amended to "The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the Weibull was best fitting model for the OS mBCC data."
47	The text has been amended to reflect the market uptake percentage and incorrect text deleted. The text has been amended to, "The company's estimate is thus that 426 patients would be eligible for vismodegib in 2018. However, the ERG notes that the company also report that vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013 and up until the end of August 2016 only 352 requests had been made for CDF funding for vismodegib. The company reported that the market uptake percentage is expected to be only 35% based on extrapolation of the CDF data."
52	The sentence, "The All Wales Medicines Strategy Group (AWMSG) are due to re-appraise vismodegib on 26th April 2017 as Roche were unable to provide a complete submission in time for the previously scheduled appraisal in August 2016." has been replaced with "The All Wales Medicines Strategy Group (AWMSG) were due to appraise vismodegib on 26th April 2017 although the ERG notes that Roche were unable to provide a complete submission by the AWMSG deadline of 5th August 2016."
60	The sentence, "However, to enable studies of BSC to have been identified, the ERG considers that the search should not have been limited to studies of vismodegib." has been added.
101	The sentence, "The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly higher proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively)." has been amended to "The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly lower proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively)."
120	The sentence, "The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p < 0.05$)." has been amended to "The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p > 0.05$)."
123	The sentence "The company's corrected deterministic base case results for vismodegib compared to BSC using the PAS price are reported in Table 32" has been amended to "The company's corrected deterministic base case results for vismodegib compared to BSC using the list price are reported in Table 32".
141	The sentence "The KM tails imply that no patient with mBCC would die for 18 months, which the ERG finds this unlikely from a clinical point of view." has been amended to "The KM tails imply that no patient with mBCC would die for 16 months, which the ERG finds this unlikely from a clinical point of view."
158	The sentence "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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these

	data will carry a high degree of uncertainty." has been replaced with "The OS KM curve for laBCC patients shows that 14% 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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these data will carry a high degree of uncertainty."
179	Table 58 has been labelled as "QALY breakdown according to health state (CS, page 240, Table 94)".

is likely to be too early as it is close to the median time to first response of 2.76 months and is less than the mean of 3.40 months for the combined aBCC population (laBCC and mBCC). The company also included covariate adjustment for age and ECOG status at baseline. However, the ERG considers the company not to have fully explored other important covariates such as Gorlin syndrome status that may have impacted the results.

The landmark analysis results from the company's primary analysis at the 6-month landmark for PFS showed no statistically significant difference between non-responders and responders with laBCC (HR 1.31; 95% CI: 0.96 to 1.78) or with mBCC (HR 0.99; 95% CI: 0.41 to 2.41). There was a significantly higher risk of death in the non-responders compared with the responders who had laBCC (HR 2.19; 95% CI: 1.23 to 3.92), but no significant difference for those with mBCC (HR 1.15; 95% CI: 0.30 to 4.47).

Landmark analysis results using the ERG preferred coherent definition of non-response, covariate adjustment for baseline age, ECOG score and Gorlin status using the 6-month landmark were consistent with the company's primary analysis findings (PFS: HR 1.19, 95% CI: 0.87 to 1.63 for laBCC and HR 0.95, 95% CI: 0.39 to 2.33 for mBCC; OS: HR 2.04, 95% CI: 1.09 to 3.82 for laBCC and HR 1.04; 95% CI: 0.24 to 4.49 for mBCC).

The results provided by the company following a clarification question on the Gorlin syndrome subgroup at the 6-month landmark suggest people with Gorlin syndrome may have improved OS (HR 4.25 vs HR 1.51, for Gorlin vs non-Gorlin, respectively) and a greater PFS benefit with vismodegib compared with the non-Gorlin subgroup (HR 1.53 vs HR 1.08, Gorlin vs non-Gorlin, respectively).

The ERG considers it important to highlight that the results of ERIVANCE, STEVIE and the landmark analysis all comprise evidence on vismodegib from single arm studies that is at high risk of bias and thus should be interpreted with caution. In addition, the results for the mBCC subgroup are based on small subgroups and so are subject to large amounts of uncertainty.

The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or radiotherapy and so are left with no other treatments options at this point in the clinical pathway. The company adds that vismodegib offers clinical benefit in terms of delay of disease progression and survival, with a manageable safety profile.

1.3 Summary of cost effectiveness evidence submitted by the company

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS, PFS and time-to-treatment discontinuation (TTD) data from STEVIE to determine mortality, disease progression and time on treatment for each cycle of the economic model,

respectively. The company built two separate models, one each for laBCC and mBCC. Data from STEVIE were therefore used according to the type of aBCC, in each model, separately.

In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to STEVIE Kaplan-Meier (KM) data. The company also explored the option of including KM curves with a parametric tail used for extrapolation in their sensitivity analyses. Once the best-fitting model was selected, survival curves for vismodegib were derived through the use of survival functions, and were then used to estimate the proportion of patients in each health state for every cycle of the vismodegib laBCC and mBCC models.

To obtain OS and PFS curves for BSC, the HRs derived from the landmark approach were applied to the estimated vismodegib PFS and OS survival curves. Even though the company built two separate models, using separate data for laBCC and mBCC, the common effect (laBCC and mBCC) HR derived through the landmark approach was applied to the laBCC and the mBCC curves. Patients on BSC were assumed to be on a specific BSC treatment regimen until progression, and on a different BSC regimen after disease progression.

The company's base case model assumes that the proportional hazards (PH) assumption holds for the responders compared with non-responders in STEVIE. The company provided log-cumulative hazard plots for OS and PFS data for responders and non-responders in the STEVIE study. The company did not undertake an assessment of the proportional odds (PO) or accelerated failure time (AFT) assumptions.

Patients in STEVIE received treatment until progression or unacceptable toxicity. Treatment duration with vismodegib in the model was defined through the use of TTD data from STEVIE. The company decided to model TTD curves with a Weibull model. The company also used a Weibull model to estimate PFS for laBCC and mBCC patients.

The company concluded that the Gamma distribution was the best fitting model for OS in the laBCC population and that the Weibull was best fitting model for the OS mBCC data. The CS notes the lack of maturity in OS data, and the fact that the extrapolated tails of the OS curves carry a high level of uncertainty in the economic analysis, regardless of the distribution used.

The CS reports that the mortality rates observed in the STEVIE trial do not reflect the increase in mortality rates at older ages and, therefore, the OS fitted curves are likely to overestimate long-term survival in the laBCC and the mBCC populations, when compared with the survival of the general population. The company reinforces the view that mortality directly attributed to laBCC is incredibly rare and that laBCC patients are usually elderly and are often suffering from other co-morbidities. Nonetheless, the company adds that patients diagnosed with non-melanoma skin cancer (including BCC

- The population of England and Wales was obtained from ONS, 2014-based National Population Projections (published 29-Oct-2015);
- Trends in incidence of skin basal cell carcinoma obtained from a UK primary care database study[41] and extrapolated using linear regression;
- Incidence and prevalence of BCC and laBCC was obtained from a retrospective cohort study of a large commercially insured population in the United States[12].

Applying the proportions obtained in the retrospective US insurance claims publication enabled the estimation of the numbers of laBCC and mBCC in England and Wales.

Abbreviations: BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC; ONS, Office of National Statistics.

The company's resulting estimate for the number of patients potentially eligible for vismodegib in England and Wales is presented in Table 2 and assumes everyone with mBCC and those with laBCC inappropriate for curative surgery or radiotherapy would be eligible for vismodegib. The company's estimate is thus that 426 patients would be eligible for vismodegib in 2018. However, the ERG notes that the company also report that vismodegib has been available on the Cancer Drugs Fund in England since the UK launch of vismodegib in August 2013 and up until the end of August 2016 only 352 requests had been made for CDF funding for vismodegib. The company reported that the market uptake percentage is expected to be only 35% based on extrapolation of the CDF data.

Table 2. Company's estimate of the number of patients with laBCC and mBCC in England and Wales (Adapted from CS, page 52, Table 10)

	2014	2015	2016	2017	2018	2019	2020	2021
Female laBCC	441	456	471	486	502	517	532	548
Male laBCC	442	456	471	485	499	513	527	542
Female mBCC	4	4	4	4	4	4	4	4
Male mBCC	19	20	20	21	22	22	23	23
laBCC incidence	883	912	942	971	1,000	1,030	1,060	1,090
laBCC inappropriate for surgery or radiotherapy (assumption: 40% of laBCC are inappropriate)	353	365	377	388	400	412	424	436
mBCC incidence	23	23	24	25	26	26	27	28

Abbreviations BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.

The ERG agrees with the company's findings of no data on the current incidence of laBCC or mBCC in England and Wales and agrees with the approach taken by the company to source suitable data from other countries. The ERG notes that both the incidence of laBCC and mBCC have been based on US incidence data and the ERG are unsure of exactly how much these would differ to those in England and Wales. The ERG's clinical experts report that the incidence of BCC may be higher in the US than in

- a safety update comprising of the pooled safety population using the final data from ERIVANCE and an interim analysis of STEVIE of 500 patients with a potential one year follow up; and

- data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of STEVIE.

The Committee for Medicinal Products for Human Use (CHMP) issued a positive recommendation on 15th September 2016 following the review of the additional data and vismodegib was granted full approval by the EMA on 14th November 2016. Vismodegib is approved in the EU for use in the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma (mBCC); or

- locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy.

The recommended dose in the summary of product characteristics (SPC) is one 150 mg capsule once daily. Vismodegib treatment should only be prescribed by or under the supervision of a specialist physician experienced in the management of aBCC. There are no specific monitoring requirements for vismodegib other than regular pregnancy testing for women of childbearing potential and routine monitoring for adverse events. Vismodegib is contraindicated to people who demonstrate hypersensitivity to it or to any of its excipients. In addition, vismodegib is contraindicated in women who are pregnant or breast-feeding, women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme, and patients receiving co-administration of St John's wort (Hypericum perforatum). The Pregnancy Prevention Programme was implemented as part of a requirement of the vismodegib marketing authorisation due to the teratogenicity of vismodegib. It requires women of childbearing potential to undergo monthly medically-supervised pregnancy tests within a maximum of seven days of prescription of vismodegib with prescriptions of vismodegib limited to 28 days' supply in these patients.

Vismodegib has been available via the Cancer Drugs Fund (CDF) in England since August 2013. The company reported in the CS that since the UK launch, up until the end of August 2016 there had been 352 requests for funding of vismodegib via the National Cancer Drugs Fund.[65]

The company reports in the CS that vismodegib has marketing authorisation in approximately 40 countries outside the EU and the United States (US), and that authorisation in the US was granted on 30th January 2012. The All Wales Medicines Strategy Group (AWMSG) were due to appraise vismodegib on 26th April 2017 although the ERG notes that Roche were unable to provide a complete submission by the AWMSG deadline of 5th August 2016.

specified. The outcomes of interest are relevant to those listed in the NICE final scope[1]. The study design was not limited to RCT studies which the ERG considers to be appropriate due to the limited available evidence in this disease area, with the available evidence known to consist mostly of single arm studies. There was no language restriction applied which ensured no relevant evidence was excluded. Therefore the ERG considers the eligibility criteria outlined by the company to be appropriate for identifying relevant evidence aligned with the NICE final scope for vismodegib1 but not for identifying studies of BSC. However, to enable studies of BSC to have been identified, the ERG considers that the search should not have been limited to studies of vismodegib.

4.1.3 Critique of screening process

The company outlines the methods implemented to screen the studies retrieved by the systematic search of the literature and the methods are in line with those recommended by the Centre for Reviews and Dissemination.[67] The record screening at title and abstract stage as well as full text were carried out by two independent reviewers. Any disputes relating to eligibility of records were resolved between the reviewers or under the consultation of a third reviewer. Data extraction was carried out by one reviewer and reviewed by a second reviewer for accuracy.

The database search in November 2016 retrieved 230 unique study records, 46 of which were selected for full text review and 30 were deemed as relevant. Conference searches and reference list searches resulted in identification of 57 records of which 9 were included as relevant. An additional 10 unpublished records were supplied by the company for inclusion. The company provide no details of how these records were identified. A total of 49 records which reported results from 12 unique studies were included in the review. The ERG notes that the company report a disparity in the number of included studies from their database searches in the CS: in Section 4.1.4 of the CS the company suggest a total of 33 records were identified however these numbers do not correlate with those presented in the company's PRISMA diagram, shown in Figure 1 of the ERG report.

The company report the study methods and results of five unique studies investigating vismodegib (NCT00607724 [Phase 1 SHH3935g],[39] NCT01367665 [STEVIE],[59] NCT00833417 [ERIVANCE],[68] NCT01160250 [EAS],[69] NCT01604252 [RegiSONIC][70]). Therefore, seven studies identified in the search were not included as supporting evidence in the CS by the company. The details of these seven studies are outlined in the CS, Appendix 8. The company's reasoning for not including six of the studies in the review was due to small sample sizes. The sample size of these six studies[71,72,73,74,75,76] was between 7 and 24 patients. The ERG notes that the company does not provide an *a priori* sample size requirement as an inclusion/exclusion criterion for the review. The remaining study, Alkeraye 2015[77], was not included due to a lack of relevant outcome measures other than the incidence of a specific adverse events, alopecia. The ERG considers this to be a relevant reason for exclusion, however based

The company provide a summary of the Grade ≥ 3 TEAEs reported in STEVIE which showed there was a slightly lower proportion of these events in laBCC patients compared to in mBCC patients (43.3% and 49.0%, respectively).

Table 21. Grade ≥ 3 Adverse events occurring in >2% patients in STEVIE (Adapted from CS page137, Table 39)

Adverse event	laBCC (n=1,119)	mBCC (n=96)	Total (N=1,215)
Total number of patients with ≥1 AE, n (%) Overall total number of events, n	484 (43.3) 949	47 (49.0) 85	531 (43.7) 1034
Muscle spasms	90 (8.0)	5 (5.2)	95 (7.8)
Weight decreased	44 (3.9)	4 (4.2)	48 (4.0)
Gamma-glutamyltransferase increased	28 (2.5)	2 (2.1)	30 (2.5)
Hypertension	23 (2.1)	4 (4.2)	27 (2.2)
Dysgeusia	25 (2.2)	1 (1.0)	26 (2.1)
Asthenia	23 (2.1)	1 (1.0)	24 (2.0)
Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CS, company submission; laBCC, locally advanced BCC; mBCC, metastatic BCC.			

Hypertension was reported in the CS to be the only Grade ≥ 3 TEAEs occurring in >2% of patients that wasn't previously known to be associated with vismodegib treatment. The company reported that 70% of the patients had hypertension at baseline and only 22% of the Grade ≥3 hypertension TEAEs were deemed by the investigator to be related to vismodegib. The company also reported that the 6 patients with investigator assessed treatment related hypertension of Grade ≥ 3 all had confounding factors based on medical review including age, hypocholesterolaemia, and/or obesity.

Serious adverse events (SAEs)

SAEs were reported in 23.2% of patients with laBCC and 30.2% of patients with mBCC. The most frequently reported SAEs in patients with laBCC were pneumonia (1.5%), squamous cell carcinoma of the skin (SCC, 1.0%) and general physical health deterioration (1.0%). No SAE occurred in more than one patient in the mBCC population. The company reported that 6.8% of all patients experienced a SAE that was deemed by the investigator to be related to vismodegib.

Table 22. SAEs occurring in ≥0.5% patients in STEVIE (safety population) (Adapted from CS page 138, Table 40)

MedDRA Preferred Term	laBCC (n=1119)	mBCC (n=96)	Total (N=1215)
Total number of patients with ≥1 AE, n (%) Overall total number of events	260 (23.2) 401	29 (30.2) 40	289 (23.8) 441
Pneumonia	17 (1.5)	1 (1.0)	18 (1.5)
Squamous cell carcinoma of skin	11 (1.0)	1 (1.0)	12 (1.0)
General physical health deterioration	11 (1.0)	1 (1.0)	12 (1.0)
Fall	9 (0.8)	0	9 (0.7)

- A landmark analysis was conducted by the company to inform the comparison of vismodegib with BSC although it is based on the use of responder and non-responder data from vismodegib patients in STEVIE at a fixed point in time.

- Efficacy results of ERIVANCE: Investigator assessed median PFS with vismodegib in the laBCC population was 12.9 months (95% CI: 10.2 to 28.0 months) and in the mBCC population it was 9.3 months (95% CI: 7.4 to 16.6 months). Median OS for laBCC was not estimable (NE) but for the mBCC patients it was 33.4 months (95% CI: 18.1 months to NE). Investigator assessed ORR was 60.3% (95% CI: 47.2% to 71.7%) in patients with laBCC, and 48.5% (95% CI: 30.8% to 66.2%) in patients with mBCC. The HRQoL SF-36 mean change from baseline in the mental component and physical components showed no statistically significant differences at the end of the study for the ERIVANCE combined aBCC population ($p > 0.05$).

- Efficacy results of STEVIE: The median PFS for laBCC patients was 23.2 months (95% CI: 21.4 to 26.0) and 13.1 months (95% CI: 12.0 to 17.7) for mBCC patients. Median OS wasn't reached for either laBCC or mBCC patients. ORR was 68.5% (95% CI: 65.7% to 71.3%) in the laBCC population and 36.9% (95% CI: 26.6% to 71.2%) in the mBCC population. The only Skindex-16 HRQoL score for either mBCC or laBCC that showed a clinically meaningful change from baseline was the emotion score which suggested an improvement with vismodegib.

- Results from STEVIE suggested that the Gorlin syndrome subgroup have a higher response rate (81.7% versus 63%) and longer duration of response (12.3 months versus 8.1 months) compared to non-Gorlin patients although the results are not statistically significant.

- AEs from STEVIE and ERIVANCE: 100% of patients in ERIVANCE and 98% in STEVIE experienced an AE with 55.8% of patients in ERIVANCE and 43.7% in STEVIE experiencing a Grade 3 or higher TEAE. 7.7% of the AEs in ERIVANCE and 3.8% in STEVIE resulted in death. The most frequently occurring AEs with vismodegib were muscle spasms (71.2% and 66.4%, ERIVANCE and STEVIE, respectively), alopecia (66.3% and 61.5%, respectively), dysgeusia (55.8% and 54.6%, respectively), and weight loss (51.9% and 40.6%, respectively).

- Landmark analysis results from company's primary analysis at the 6-month landmark for PFS showed no statistically significant difference between non-responders and responders for laBCC (HR 1.31; 95% CI: 0.96 to 1.78) or mBCC (HR 0.99; 95% CI: 0.41 to 2.41). There was a significantly higher risk of death in the non-responders compared to the responders for laBCC

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© Excel based economic model.

5.2 Summary of the company's key results

Upon the clarification request from the ERG, the company corrected the mistake found in the model relating with using the cost of a dermatologist visit instead of a GP visit. The company's corrected deterministic base case results for vismodegib compared to BSC using the list price are reported in Table 32. The combined ICER weights the laBCC and the mBCC final ICERs by the proportion of patients in each group in STEVIE. The company's base case ICERs for laBCC and mBCC are reported in Table 33 and Table 34, respectively. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. Results are presented in Table 35.

Table 32. Base case results using list price

Therapy	Total costs	Total Lys	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£93,352	9.50	7.31	£31,347	1.16	0.89	£35,251
Vismodegib	£124,699	10.66	8.20				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 33. Base case results using list price for laBCC pateints

Therapy	Total costs	Total Lys	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£97,519	9.95	7.69	£27,345	1.16	0.90	£30,493
Vismodegib	£124,865	11.11	8.58				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 34. Base case results using list price for mBCC patients

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£40,813	4.28	2.95	£80,651	1.20	0.80	£100,615
Vismodegib	£121,465	5.48	3.75				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 35. Results of probabilistic sensitivity analysis using the corrected model

Treatment arm	Costs		QALYs		ICERs	
	Base case (deterministic)	PSA	Base case (deterministic)	PSA	Base case (deterministic)	PSA

Vismodegib patients who have progressed are assumed to receive subsequent BSC, which is in line with clinical expert opinion provided to the ERG. Patients who progress are assumed to start subsequent treatment as soon as they enter the progression state.

The partitioned survival approach employed by the company is appropriate. A life time horizon of 30 years is adopted in the model, which seems reasonable considering the mean age of patients at baseline of 70 years. Nonetheless, by the end of the 30-year time horizon (when these patients would be 100 years old), there are still 3% of patients alive in the vismodegib and BSC arms of the model for laBCC patients and 1% of patients alive in the vismodegib and BSC arms for mBCC patients. This seems unrealistic from a clinical point of view, especially for patients with metastatic disease. This could suggest an overestimation of survival tails in the long-term of the economic analysis, however the mortality rate at this point in the model is defined by the background mortality rate taken from the UK life tables matched for age and gender in the overall population.[97] This issue is further discussed in Section 5.4.7 of the ERG report.

Considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. The ERG removed the half-cycle correction from the model as an exploratory analysis and presents the results of the analysis in Section 6.

The ERG agrees with the company's decision to build two separate models, one for laBCC and the other for mBCC. However, the ERG disagrees with the decision of using a common treatment effect for vismodegib and reporting an aggregated ICER for laBCC and mBCC. As discussed in Section 5.4.2, and according to clinical expert opinion provided to the ERG, these are two different populations in terms of disease prognosis and clinical outcomes, and should therefore be considered separately. To also note is the fact the CS to the Canadian and Irish HTA bodies reported two individual ICERs for laBCC and mBCC, respectively.

Treatment effectiveness

The CS reports that vismodegib offers a treatment option for patients with laBCC or mBCC who are unsuitable for surgery and/or radiotherapy and so are left with no other treatments options at this point in the clinical pathway. The company adds that vismodegib offers clinical benefit in terms of delay of disease progression and survival, with a manageable safety profile.

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS, PFS and TTD data from STEVIE to determine mortality, disease progression and time on treatment for each cycle of the economic model, respectively. The company

KM data reported by the company in Table 41 and Table 42 for laBCC and mBCC, respectively. The KM curves and the data suggest that for laBCC patients, there were no death or discontinuation events for approximately 1.5 years before the end of the follow-up period. The same is true for mBCC patients where for approximately 16 months before the end of the follow-up period there were no deaths or discontinuation events. The ERG asked the company to confirm if this had been the case or if the follow-up period had been shorter than the last data entry in the KM data (44 months for laBCC and 38 months for mBCC). The company confirmed that the 44 months for laBCC and 38 months for mBCC data points correspond to the entire follow-up period in STEVIE and that no events were observed from the previous date point in the KM curves till the end of the follow-up (Table 41 and Table 42).

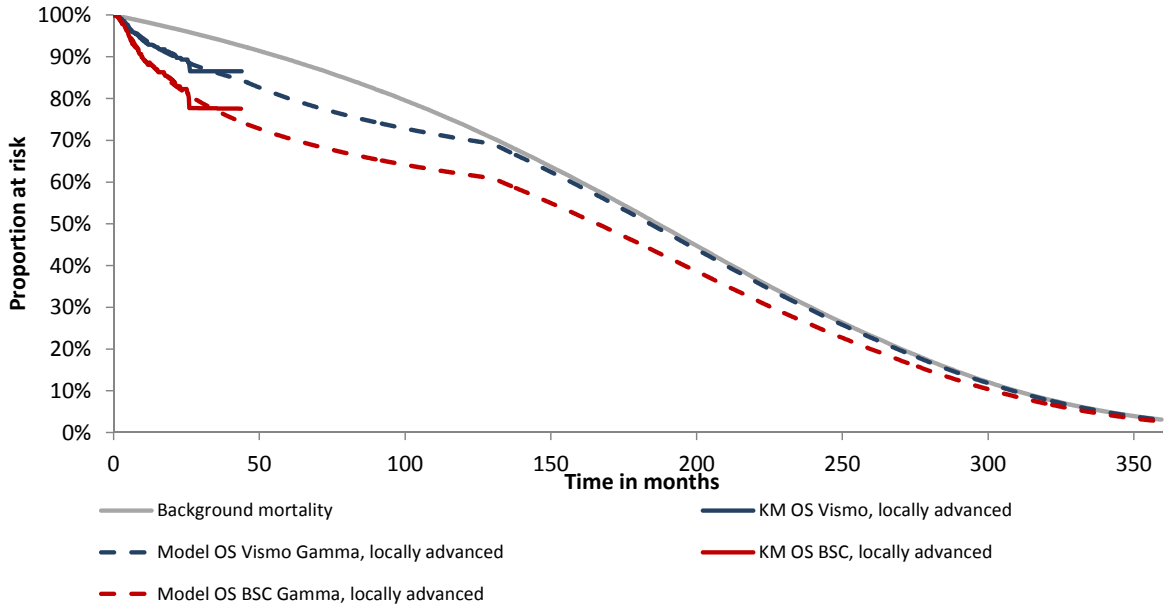
By 26 months patients in STEVIE would be, on average, 74 years. The KM tails imply that no patient with mBCC would die for 16 months, which the ERG finds this unlikely from a clinical point of view. The long tails of the TTD curves suggest that patients continued treatment after progression in the mBCC population. At 22 months, when there were still around 30% on treatment (8 patients at risk), about 23% of patients were free from progression (6 patients at risk). Although the numbers at risk are small, the curves cross much earlier, 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.

With regards to laBCC patients, while it appears implausible that patients would not discontinue treatment for 1.5 years, the fact that the TTD and the PFS curves cross at around month 38 could be an artefact of the small number of patients in the PFS curve at this point in time (three patients). To also note is that the definition of treatment discontinuation in STEVIE was based on discontinuing vismodegib for longer than eight weeks. Any treatment breaks shorter than eight weeks would not be considered as discontinuation for the purpose of estimating TTD. This is likely to be different to what would be seen in clinical practice, where patients are expected to be kept on a three months on and three months off treatment regimen, according to clinical expert opinion provided to the ERG.

will cease at the end of the STEVIE follow up period. The cut-off point, at which background mortality applies, was selected at the point where the extrapolated vismodegib curve crosses the background mortality curve, which is approximately 147 months (12.25 years).

This approach assumes that after a certain point, patients in the BSC arm would have the same risk of dying as the general UK population (Figure 24). However, in contrast to the previous approach, the BSC curve lies below the general UK population, as shown Figure 39, i.e. patients who would get BSC have a reduced life expectancy compared to general UK population over the entire time horizon.

Figure 24. Modelling of overall survival curves using uniform background mortality rates after a user-defined timepoint (Figure 39, CS page 206).



ERG critique

The ERG agrees with the company's assessment regarding the lack of mature OS data. The OS KM curve for laBCC patients shows that 14% 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. The ERG is unclear why the company reports that only 9% of patients died in STEVIE at the data cut-off points, however, it agrees that survival data from STEVIE in not mature and any curve fitting and extrapolation exercise using these data will carry a high degree of uncertainty. Therefore, the ERG considers that even though the traditional steps in validating curve fit and extrapolations should be undertaken, clinical expert opinion might be of more value in this instance given the lack of robust OS data. This is only caveated by the fact that out of the three clinical experts contacted by the ERG (two dermatologists and one oncologist), only one had had contact with an mBCC patient. As mentioned in

Vismodegib	£124,699	10.66	8.20				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 56. Base case results using list price for laBCC pateints

Therapy	Total costs	Total Lys	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£97,519	9.95	7.69	£27,345	1.16	0.90	£30,493
Vismodegib	£124,865	11.11	8.58				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 57. Base case results using list price for mBCC patients

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£40,813	4.28	2.95	£80,651	1.20	0.80	£100,615
Vismodegib	£121,465	5.48	3.75				
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

The breakdown of QALYs accumulated in the model according to health state is presented in Table 58. Most of the incremental QALY gain for vismodegib against BSC stems from the PD health state, for both laBCC and mBCC patients. This is related with the mortality benefit seen in the company's model, as patients in the vismodegib arm live longer than in the BSC arm, therefore accruing more QALYs while in the PD state.

Table 58. QALY breakdown according to health state (CS, pg 240, Table 94)

Health state	QALYs BSC	QALYs vismodegib	Increment	QALYs BSC	QALYs vismodegib	Increment
	laBCC patients			mBCC patients		
PFS	1.57	1.79	0.22	0.95	1.11	0.16
PD	6.12	6.79	0.67	1.99	2.63	0.64
AEs	0.00	0.00	0.00	0.00	0.00	0.00
Total	7.69	8.59	0.90	3.75	3.75	0.80
Abbreviations in table: AEs, adverse events; BSC, best supportive care; PD, progressed disease; PFS, progression-free survival.						

5.5.2 Sensitivity analysis

1.4.1.1 Scenario analysis

The company carried out a range of scenario analyses exploring the impact of changing assumptions surrounding the following parameters:

- Time horizon;
- Clinical inputs;
    - Parametric distributions for: TTD, PFS, and OS