Projector and public slides

Lead team presentation Vismodegib for treating basal cell carcinoma – STA

1st Appraisal Committee meeting, 28 June 2017

Background and Clinical Effectiveness

Committee D

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ERG: BMJ

NICE technical team: Aimely Lee, Raisa Sidhu

Company: Roche

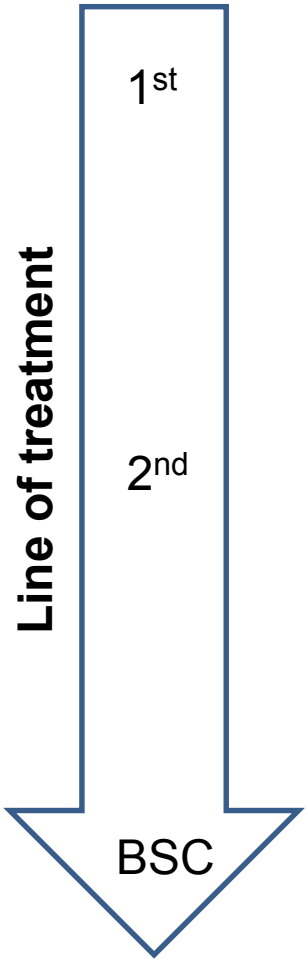
Basal Cell Carcinoma
Disease background

- BCC is a non-melanoma skin cancer (NMSC) that develops in the deep basal cell layer of the epidermis around a hair follicle.
- Most common form of NMSC (75% NMSC is BCC)
- Early treatment is generally curative, however if untreated, it can become advanced (aBCC), either locally advanced (laBCC) or metastatic (mBCC), potentially causing extensive tissue destruction and disfigurement
- Approx. 53,000 new cases of BCC occur every year in the UK with around 10% becoming aBCC
- Of the BCC cases, up to 1% are laBCC and up to 0.55% are mBCC
- BCC is more common in:
  - People with Gorlin syndrome
  - Males
  - People with fair skin, blond or red hair, blue, green or grey eyes, increasing age, or family history

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) Confidential patient access scheme available; results presented in part 2
CDF	Available on the CDF – 352 requests until Aug 2016

Treatment pathway – Basal cell carcinoma



Surgical techniques

Non-surgical techniques
(e.g. radiotherapy, topical and photodynamic therapies)

Best supportive care* (BSC)

BSC includes monitoring by dermatologists several times a year, palliative radiotherapy when required, or referral for consideration for major surgery to resect locally advanced disease

Vismodegib?

Clinician perspective
(BASCSN and RCP)

- Patients are often elderly and frail with number of comorbidities, on medications, making surgery and radiotherapy challenging.
- There is no established systemic management for people with laBCC or mBCC
- Vismodegib:
  - Provides a palliative treatment option for patients who cannot have surgery or radiotherapy.
  - Oral tablet taken once a day only.
  - Expected duration of response range from 12 to 18 months.
  - Prescribed in secondary or tertiary care with specialists and nursing input.
  - Generally well tolerated but has the potential to cause significant side effects with toxicity prompting interruption or treatment discontinuation in some patients.

- *No submissions from patient organisations*

Decision problem
Deviations from final scope

	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	
Intervention	Vismodegib	
Comp.	Best supportive care (BSC)	No relevant RCTs were identified in the company's systematic literature review. A landmark approach was therefore used to derive a proxy for BSC (using non-responders in STEVIE)
Outcomes	• PFS and OS • response rates • adverse effects of treatment • health-related quality of life	As per scope, except OS data not mature 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

Clinical evidence - ERIVANCE (basis for conditional MA Aug 2013)

Study type	• Phase II (n=104), international, multicentre (UK 6%), non-randomised, open-label, single-arm, two-cohort study	
Population	• Adults: enrolled median age (range): 62 years (laBCC: 21-101; mBCC: 38-92) • ECOG PS≤ 2 • mBCC: n=33 • laBCC: n=63 inappropriate for surgery or radiotherapy (previously administered unless inappropriate) • laBCC with Gorlin syndrome: n= 20 *(32%)*	***ERG highlighted:*** *Only 6% of patients came from UK sites.* *Younger age and higher prevalence of gorlin syndrome than in UK practice*
Intervention	Oral vismodegib 150 mg/day until disease progression, intolerable toxicity, or withdrawal (with up to 4-weeks dose interruption if required to manage toxicity or up to 8 weeks for a planned surgical procedure)	
Primary endpoint	Objective response rate (complete or partial responses)	
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	

Clinical evidence - STEVIE (led to full MA Sept 2016)

Study type	• Phase II post-approval safety study (n=1232) • International, multi-centre (UK 3%), open-label, non-comparative study	
Population	• Adults: enrolled median age (range): 72 years (laBCC: 18-101; mBCC: 34-95) • ECOG PS≤ 2 • mBCC: n=96 • laBCC: n=1,119 inappropriate for surgery or radiotherapy (previously administered unless inappropriate) • 38.7% baseline disease status considered inoperable, and surgery medically contraindicated in 61.3% • laBCC with Gorlin syndrome: n= 214 *(19.2%)* • mBCC with Gorlin syndrome: n= 5 (5.2%)	***ERG highlighted:*** *Only 3% of patients from UK sites. Median age close to expectation in UK clinical practice but higher prevalence of gorlin syndrome*
Intervention	Oral vismodegib 150 mg/day until disease progression, intolerable toxicity, or withdrawal from study (with up to 8-weeks dose interruption if required to manage toxicity)	
Primary endpoint	• Incidence of treatment-emergent AEs (TEAEs)	
Time points	6 interim and 1 final analysis; safety follow-up: months 1, 3, 6, 9 & 12	

ERIVANCE and STEVIE
Summary results

- Overall survival data not mature and not evaluated for laBCC
  - For mBCC, ERIVANCE OS data at 30 months presented: median OS 33.4 months

	ERIVANCE (30 month data)		STEVIE	
	laBCC	mBCC	laBCC	mBCC
PFS (median, months; 95% CI)	12.9 (10.2 - 28.0)	9.3 (7.4 - 16.6)	23.2 (21.4 to 26.0)	13.1 (12.0 to 17.7)
ORR (n(%); 95% CI	38 (60.3) (47.2 - 71.7)	16 (48.5) (30.8 - 66.2)	738 (68.5) (65.66 to 71.29)	31 (36.9) (26.63 to 71.29)

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. Definition of non-responder varied depending on outcome assessed:
  - **Overall survival:** people who had not died and who had either stable disease of 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 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

Vismodegib vs. BSC
'Landmark' approach – ERG concerns

- Definitions of responders and non-responders **-** not reflective of all patients on vismodegib and BSC (treatment-naïve) population, respectively
- Appropriateness of the chosen 6-month landmark **–** chosen prospectively and other possible landmarks (apart from 3-month) not explored; agree 3 month not appropriate
- Use of a common treatment effect (aBCC) HR – laBCC and mBCC are both clinically and prognostically different
- The non-systematic selection process and limited number of covariates included **–>** important covariates may have been omitted (e.g. Gorlin syndrome)

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)
No. 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)

ERG: Gorlin syndrome and target lesions at baseline should also have been included as covariates

Conditional HR of non-responders vs. responders estimated at 6-month landmark

	Progression-free survival		Overall survival	
	No covariates	**Covariates***	**No covariates**	**Covariates***
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.

ERG's key concerns:

- Use of different definitions of responders and non-responders for PFS and OS
- HRs not adjusted for Gorlin syndrome
- Lack of mature OS data - Only 9% of people had died in STEVIE at the data cut-off point
- Very small number of people with mBCC (n=96)
- HRs were <1 for people with mBCC -> non-responders performed better - plausible?

ERG exploration PFS and OS at 6-month landmark

Preferred definition of non-response, covariate adjustment including Gorlin syndrome*

	laBCC	mBCC	Combined
	HR (95% CI)	HR (95% CI)	HR (95% CI)
OS			
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)
PFS			
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)

*people with stable disease where those who have progressed or died prior to the landmark were excluded; Red denotes statistically significant differences between non-responders and responders (>1 favours responders)

Landmark analysis for PFS and OS according to Gorlin syndrome status at 6-month landmark (post-hoc)

	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
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)

ERG highlighted the following:

- A lower median age in people with Gorlin syndrome: 52 years [range 18-88] vs. 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): 79% vs 53%
- A higher median number of target lesions in people with Gorlin syndrome: 3 [range 1-12] vs 1 [1-10]
- HRs are not adjusted for differences in the above baseline characteristics
- Results for people with laBCC and mBCC are not presented separately

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)

ERG notes:

- High levels of AEs in both studies
- Vismodegib considered by the investigator to be related to 7/71 deaths in STEVIE and none in ERIVANCE

Key clinical issues

- 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?
- Is there an increased mortality risk in people with aBCC, and is vismodegib associated with a survival benefit?

Lead team presentation Vismodegib for treating basal cell carcinoma - STA

1st Appraisal Committee meeting

28 June 2017

Cost-effectiveness

Committee D

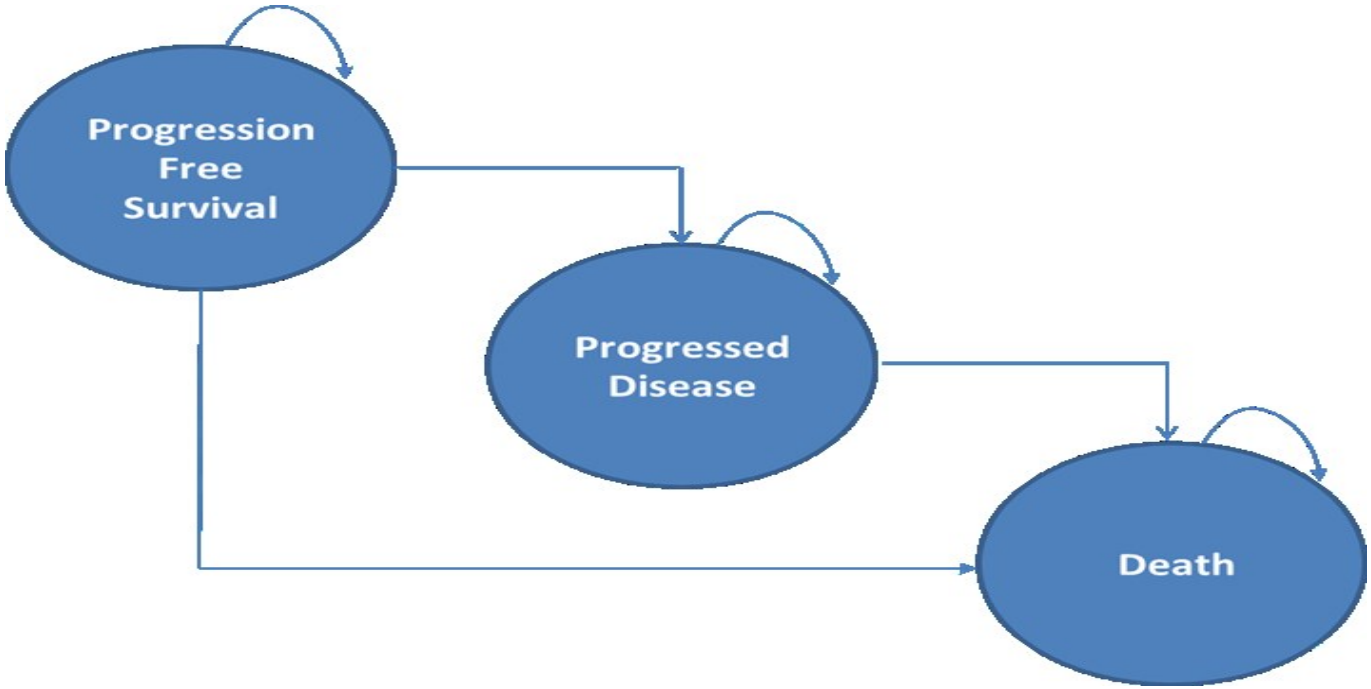
Lead team: Matt Bradley, Peter Hall and Rebecca Harmston

ERG: BMJ

NICE technical team: Aimely Lee, Raisa Sidhu

Company: Roche

Company model: 3-state partitioned survival model



- 30 year time-horizon
- Weekly cycle (with half cycle correction)
- Utilities and costs discounted at 3.5%
- NHS and personal and social services (PSS) perspective

Modelling clinical outcomes and extrapolation

Company approach

- The conditional HRs obtained from the landmark analysis were adjusted with a time-varying component to reflect the HRs of non-responders vs. ITT population
- It is assumed that there is a time-varying treatment effect between responders and non-responders in the ITT population over time

ERG comments

- Limitations of the landmark approach (see clinical slides) carry through to the model and results resulting in substantial uncertainty in the final ICERs
- The adjustment of HRs is not evidence or methodologically-based but note adjustment is conservative as it reduces HRs

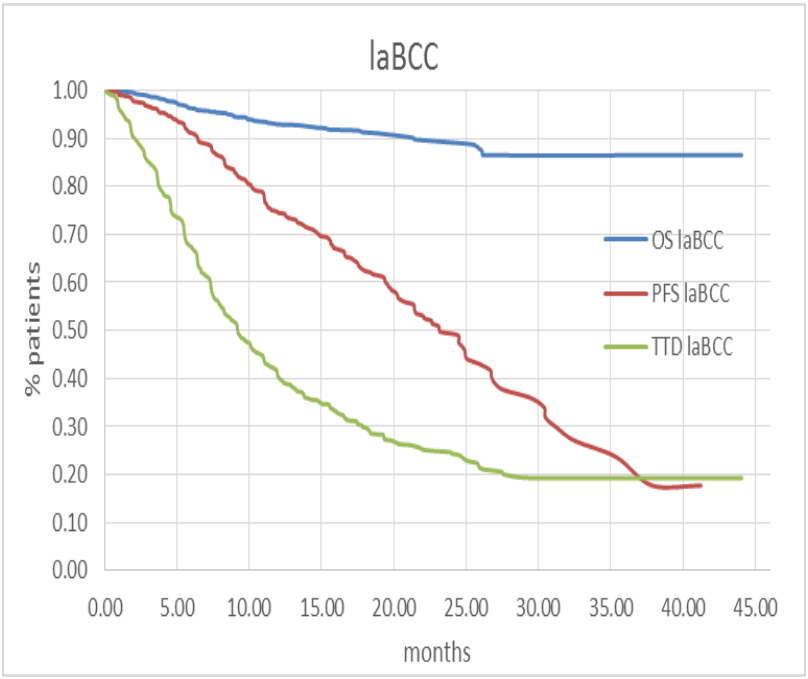
Company approach

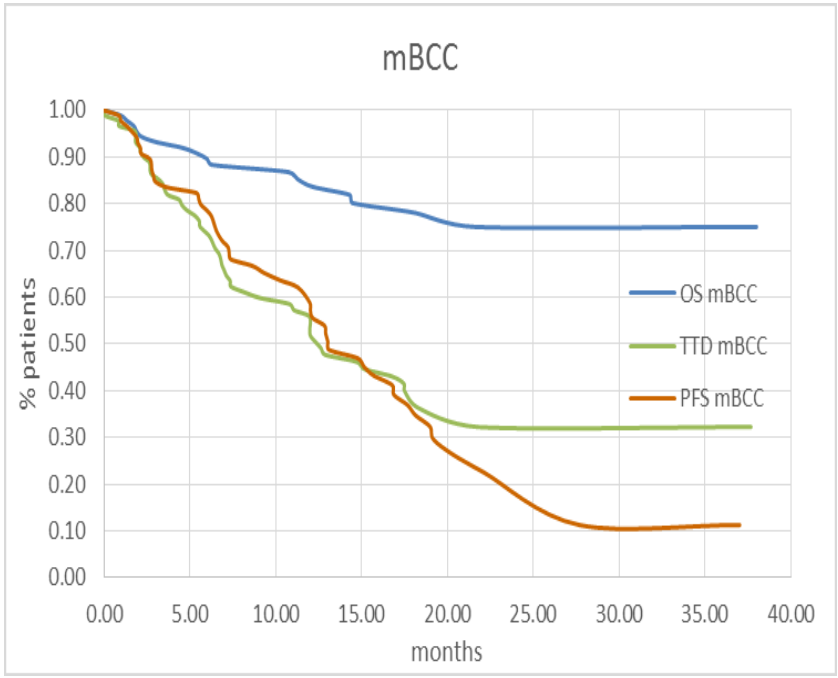
- Generally selected the best-fitting model, comparing with observed KM data and using AIC and BIC
- For TTD, log-logistic best fit but Weibull used because fitted log-logistic curves for laBCC and mBCC cross, while the KM curves for the corresponding data do not, and the fitted TTD and the PFS curves cross for laBCC patients

ERG comments

- Log-logistic best fit to KM data for TTD and not the reason for curves crossing

KM curves

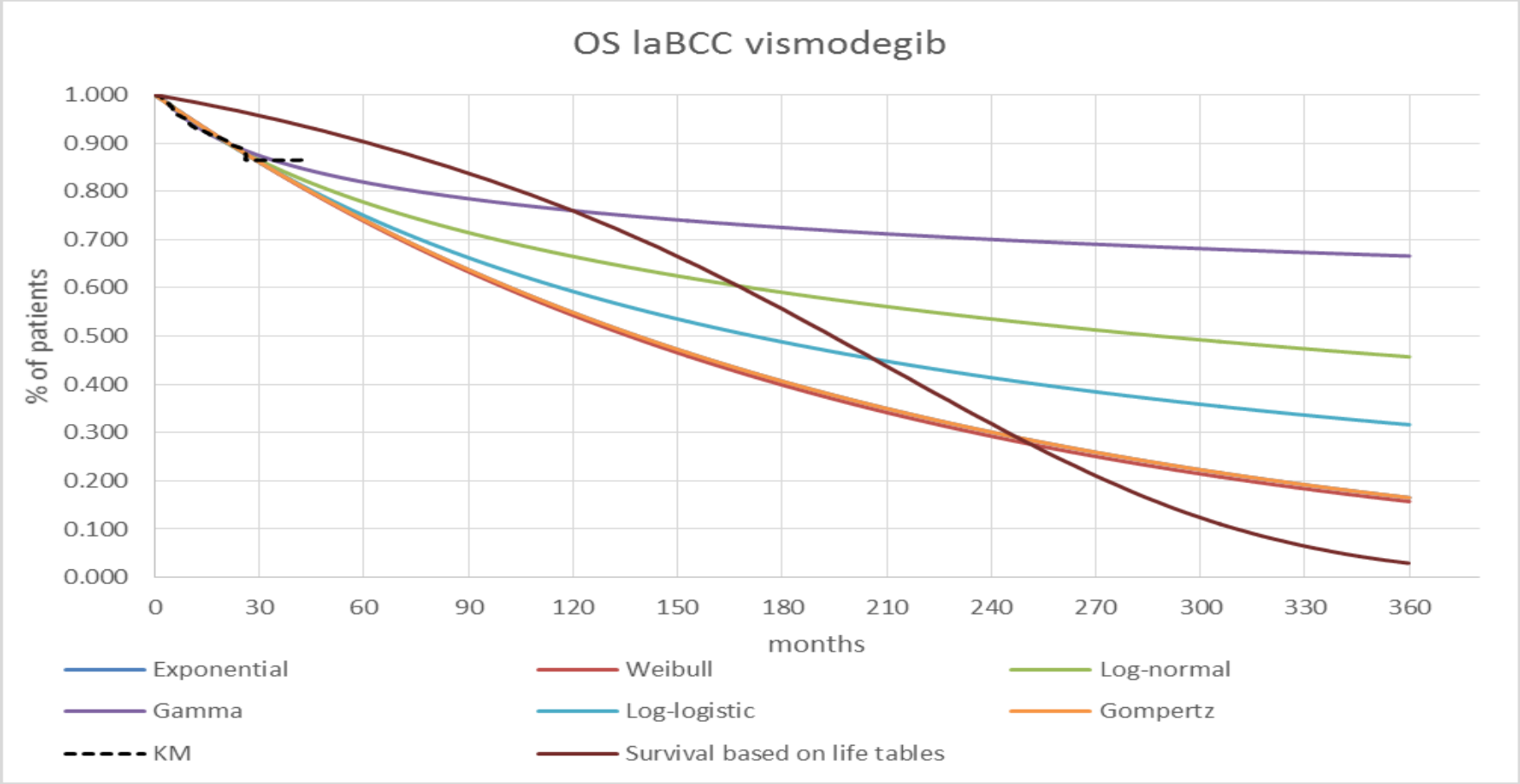




ERG comments

- OS KM tails imply that no patients with laBCC or mBCC would die or discontinue treatment for 18 or 16 months, respectively, before end of follow-up (44 months laBCC, 38 months mBCC).
  - plausible considering by 26 months people in STEVIE would be on average 74 years? Plausible that no mBCC patients would die for 18 months?
- KM TTD curve crossing the KM PFS curve suggests that people continued treatment after progression (not allowed in STEVIE). No explanation has been provided for this.
- Very small number of people with mBCC (n=96)

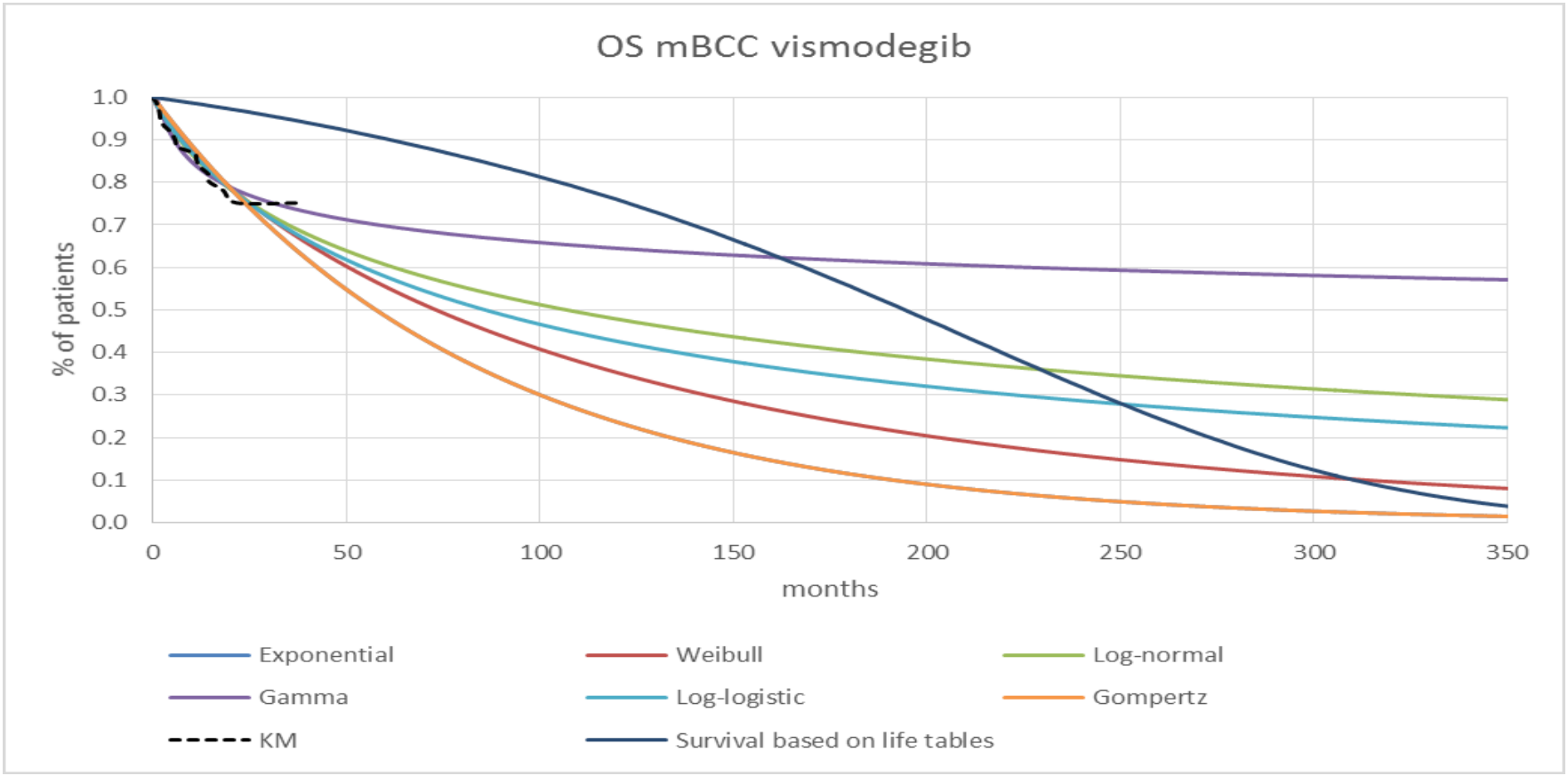
OS curves for people with laBCC vs. background mortality rate for the overall UK population



ERG comments

- The OS curves suggest that there is an increased mortality risk in people with laBCC vs. the average UK population (age and gender-matched) – plausible?

OS curves for people with mBCC vs. background mortality rate for the overall UK population



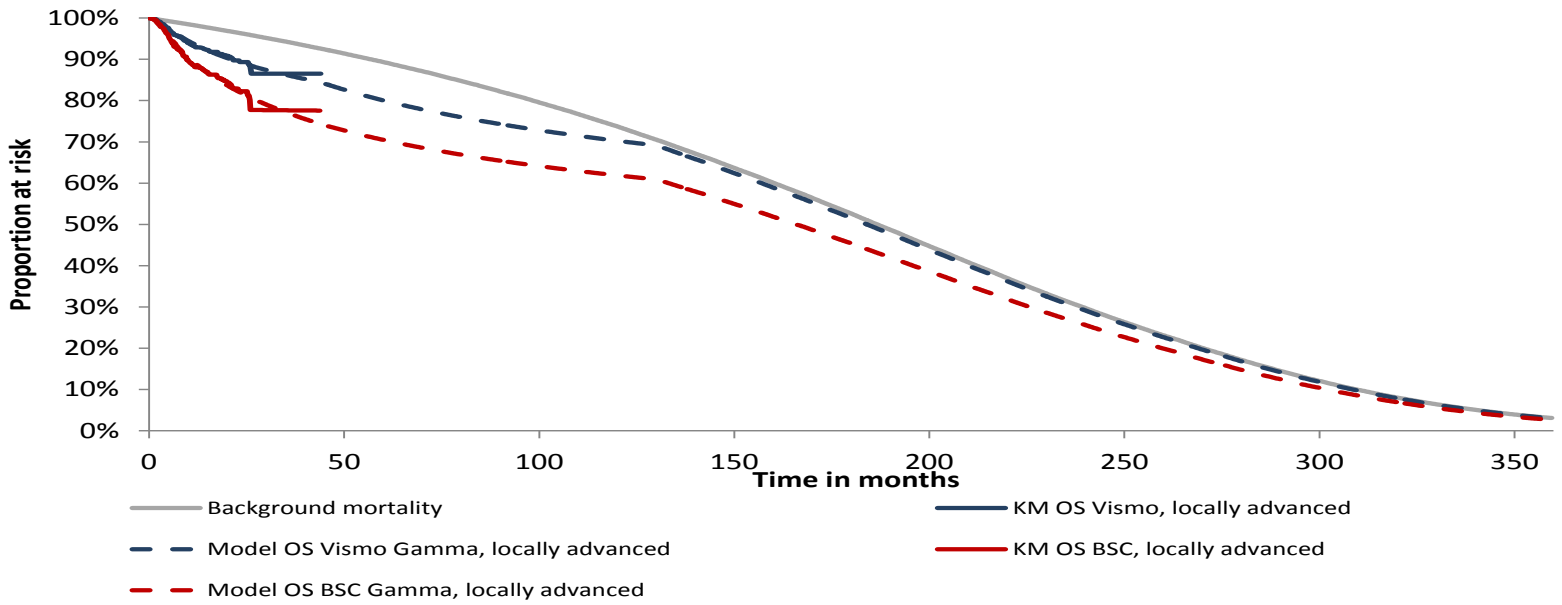
ERG comments

- None of the curves appear to accurately reflect mortality for people with mBCC. It is underestimated by the assumption that they would survive for >10 years in the model (estimated survival: 1-2 years post diagnosis)

Modelling of OS curves

Company approach

Uniform background mortality rates were applied to the OS curves after the extrapolated vismodegib curve crossed the background mortality curve – approx. 147 months (12.25 years)



ERG comments

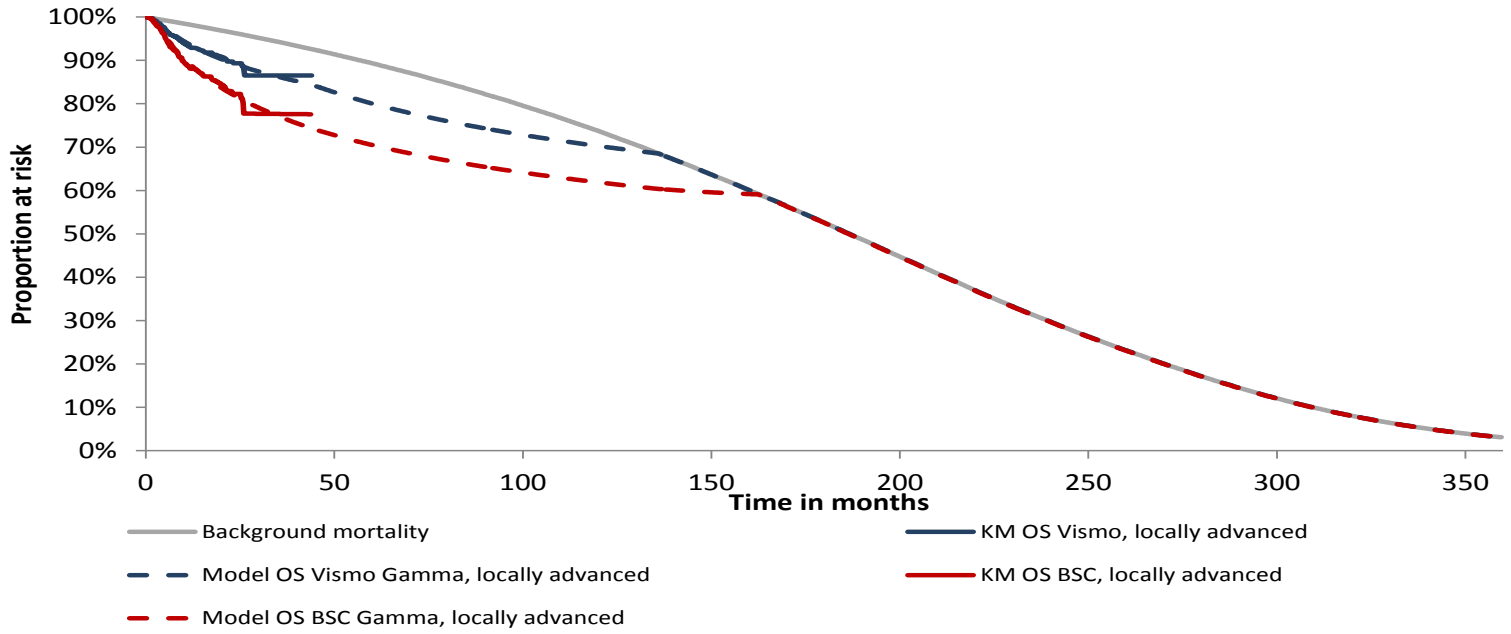
- The BSC curve lies below the UK population -> implies that people who would get BSC have a reduced life expectancy compared to the UK population over the entire time horizon

Modelling of OS curve – alternative approach

Preferred option by ERG

ERG comments

- Capping the OS vismodegib curve with the background mortality curve to imply that the OS rates in patients with laBCC are calculated as the minimum between the OS fitted curve and the background mortality curves:
  - 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 curve



Utility estimates

Company approach

- SF-36 data from ERIVANCE trial mapped to EQ-5D
- Different utility values were applied in the model consistently over time based on progression status and type of aBCC

ERG comments

- The population baseline age in ERIVANCE (median:62 yrs) is not reflective of patients in STEVIE (~72 yrs) or UK clinical practice (~70 yrs)
- The assessment of response/progression differ between ERIVANCE and STEVIE (novel composite method vs. RECIST V1.1 criteria)
- The underlying SF-36 data seems to carry a lot of uncertainty:
  - Mainly insignificant changes in QoL observed in ERIVANCE over time – potentially due to small sample size or lack of sensitivity of the SF-36 for aBCC?
  - Despite mainly insignificant changes observed in ERIVANCE, the derived EQ-5D values still suggest a decrease in patients QoL upon progression

Costs and resource use assumptions (base case): **Vismodegib arm**

Health state	Item	Unit cost	Schedule	Cycle cost
PFS	Technology	£6,285.00	150 mg daily	£1,571.25
	Oncologist visit	£163.00	Every 4 wks*	£40.75
	Total per model cycle: £1,612.00			
PD (Monitoring only, 67%)	Oncologist visit	£163.00	Every 12 wks*	£13.58
	GP visit	£36.00	Every 4 wks	£24.75
	Total per model cycle: £25.68¥			
PD (Switch to BSC, 33%)	Oncologist visit	£163.00	Every 12 wks*	£13.58
	GP visit	£36.00	Every 4 wks	£24.75
	TVN visit	£50.65	Once per wk*	£50.65
	Wound mgmt.	£10.00	Once per wk*	£10.00
	Total per model cycle: £32.66¥			

***** **=** Assumption

¥ = Base case patient weightings have been applied. i.e. it has been assumed that 33% of patients switch to BSC, 67% monitoring only.

Costs and resource use assumptions (base case): **BSC arm**

Health state	Item	Unit cost	Schedule	Cycle cost
PFS	Dermatologist visit	£99.00	Every 12 wks*	£8.25
	GP visit	£36.00	Every 4 wks	£24.75
	TVN visit	£50.65	Twice per wk*	£101.30
	Wound mgmt.	£10.00	Twice per wk*	£20.00
	Total per model cycle: £154.30			
PD	Dermatologist visit	£99.00	Every 12 wks*	£8.25
	GP visit	£36.00	Every 4 wks	£24.75
	TVN visit	£50.65	Three times per wk*	£151.95
	Wound mgmt.	£10.00	Three times per wk*	£30.00
	Total per model cycle: £214.95			
*** =** Assumption				

Costs and assumptions related to palliative radiotherapy: **One-off model cost**

- It is assumed that approximately 50% of patients on BSC would in their lifetime undergo one course of palliative radiotherapy

Item	% of patients in BSC arm	Description	Unit cost	Regimen	One-off model cost
Palliative RT	30%	A fraction of treatment on a MV machine	£107.00	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	20 Gray in 5 fractions	£153.00 * 5 = £765 £765 * 0.2 = £153.00

ERG comments on costs and resource use

ERG comments

- Assuming 67% of people who progress after vismodegib never receive BSC unrealistic
  - **ERG's clinical experts:** after the monitoring regimen begins, people will eventually go on to receive BSC
- Frequency of wound management and TVN visits uncertain
  - **ERG's clinical experts:** uncertain; no consensus was reached amongst the ERG's clinical experts
- Assuming post-progression BSC regimen for people receiving vismodegib differs from the post-progression BSC regimen for people receiving BSC inaccurate
  - **ERG's clinical experts:** post-progression BSC schedule for the two groups are the same

Company base case model results (list price)

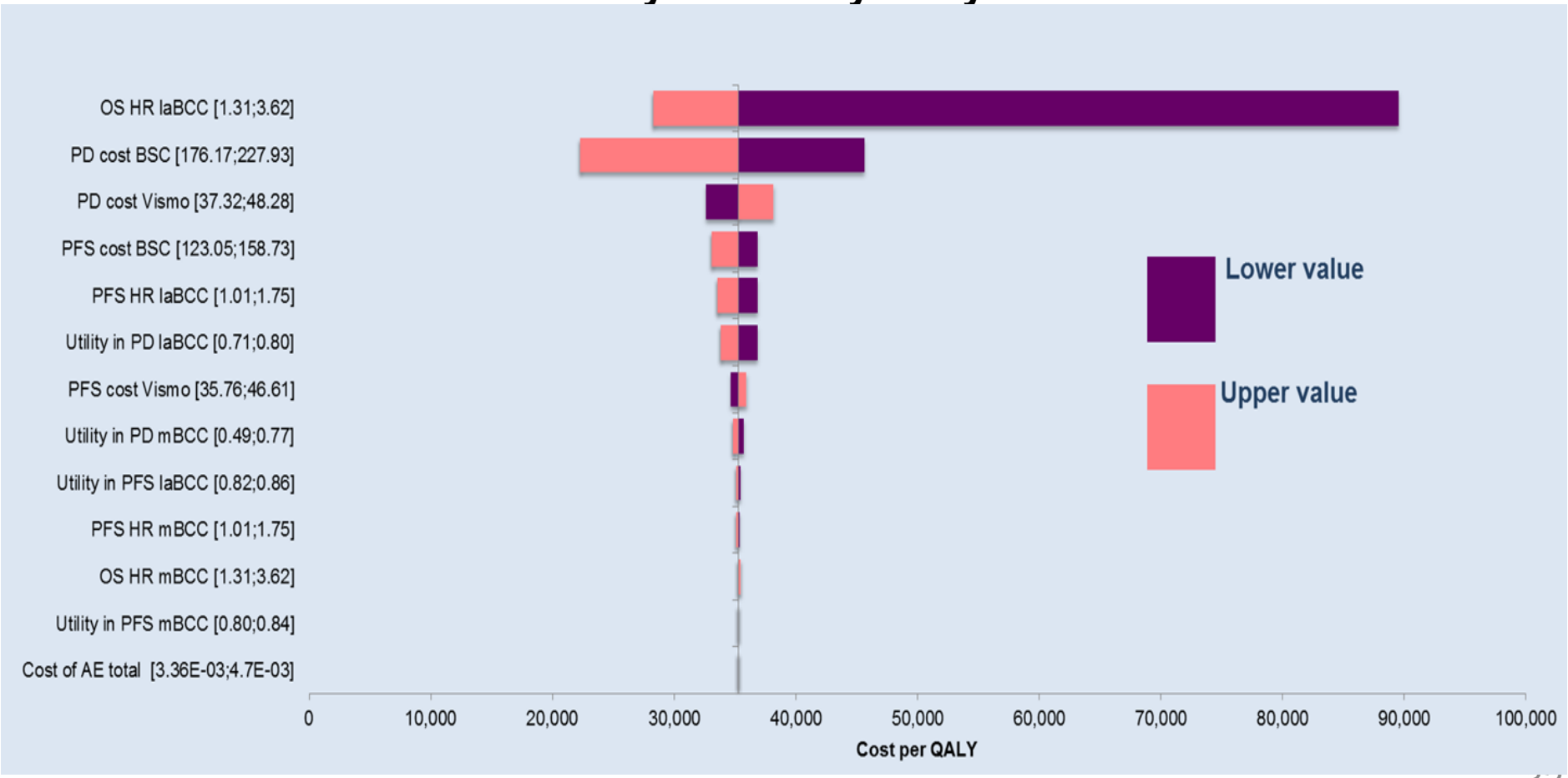
Results were calculated separately for laBCC and mBCC, then weighted by the percentage of laBCC (92.1%) and mBCC (7.9%) patients in STEVIE to represent the aBCC population

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

Confidential PAS based results presented in part 2

Deterministic sensitivity analyses showed that survival with laBCC is main driver of company model (vismodegib list price)

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



ERG preferred results

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

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

ERG changes to the base case	ICER vs base case	ICER*
Company's base case for laBCC	**£30,493**	
1. Half-cycle correction removed	£31,880	£31,880
2. PFS and OS HRs adjustment removed & used the unadjusted HRs	£26,820	£27,772
3. Changed the Weibull to a log-logistic curve to model TTD	£42,344	£35,888
4. Capped the OS vismodegib curve by the background mortality curve	£36,028	£39,597
5. Assumed that people on vismodegib move to BSC six months after progression	£46,100	£52,356
6. Assumed that people on vismodegib moving to BSC received the same treatment regimen as people on BSC who have progressed	£50,474	£95,164
** ICER with all changes incorporated*		

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

ERG changes to the base case	ICER vs base case	ICER*
Company's base case for laBCC	**£30,493**	
7. Replaced the company's PFS HR 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)	£31,107	£96,352
8a. Assumed no survival gain with vismodegib vs. BSC (i.e. same as background mortality for the UK population)	£435,402	**£5,203,675**
8b. Assumed there is a survival benefit with vismodegib, incorporated using HR adjusted for age, ECOG and Gorlin syndrome	£32,442	**£106,569**
** ICER with all changes incorporated*		

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

ERG changes to the base case	ICER vs base case	ICER*
Company's base case for laBCC	**£100,615**	
1. Half-cycle correction removed	£101,550	£101,550
2. PFS and OS HRs adjustment removed & used the unadjusted HRs	£87,939	£88,698
3. Changed the Weibull to a log-logistic curve to model TTD	£99,502	£87,795
4. Capped the OS vismodegib curve by the background mortality curve	£100,615	£87,795
5. Assumed that people on vismodegib moved to BSC six months after progression	£106,679	£92,161
** ICER with all changes incorporated*		

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

ERG changes to the base case	ICER vs base case	ICER*
Company's base case for laBCC	**£100,615**	
6. Assumed that people on vismodegib moving to BSC received the same treatment regimen as people on BSC who have progressed	£110,873	£109,503
7. Using a PFS HR of 1 in the mBCC model	£106,092	£115,545
8. Using a OS HR of 1 in the mBCC model	£1,580,078	**Vismodegib Dominated**
** ICER with all changes incorporated*		

- Cost minimisation:
  - when ERG assumed a PFS and OS HR of 1, the final ICER for vismodegib vs BSC became dominated, with a **0 QALY gain and an additional cost of £89,323**
  - Total costs for vismodegib was £159,547 and £70,224 for BSC

Key cost-effectiveness issues

- Landmark approach
  - 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?
- Is the log-logistic curve more appropriate for extrapolating TTD?
- Are the assumptions plausible?
  - 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
- What is the committee's view on the mapped EQ-5D data?
- Does the committee agree with the ERG's explorations? If so, which of the 2 final ICERs does the committee consider to be most plausible?