Projector and public slides

Chair's presentation Vismodegib for treating basal cell carcinoma

2nd Appraisal Committee meeting, 30 August 2017

Committee D

Lead team: Matt Bradley, Peter Hall and Rebecca Harmston

ERG: BMJ

NICE technical team: Aimely Lee, Raisa Sidhu

Company: Roche

Key issues for discussion

- Should a Weibull or Log-logistic distribution be used to model TTD in the economic model?
- When are patients who have progressed on vismodegib likely to move on to receive the same BSC regimen as patients who have progressed and never received vismodegib?
  - 6 months or 6 years?
- Are quality of life benefits likely to be underestimated?
- Is there a survival benefit with vismodegib?
- Does the committee maintain that the results of the landmark analysis are not sufficiently robust for decision-making?

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

ACD: preliminary recommendation

Vismodegib is not recommended within its marketing authorisation for treating symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma that is inappropriate for surgery or radiotherapy, in adults.

ACD committee conclusions (1)

Clinical need	Valuable to have alternative treatment options that improve quality of life
Comparator	Best supportive care
Trial data	STEVIE study most representative of UK clinical practice and appropriate for decision making

Effectiveness of vismodegib	**Uncertain:**
	• Single-arm study, high risk of bias
	• OS data immature
	• Concerns with the landmark approach:
	  • use of non-responder data as proxy for BSC
	  • choice of landmark (6-month),
	  • limited number of covariates included

Subgroup analysis	Population with Gorlin syndrome was too small for separate consideration

ACD committee conclusions (2)

Utilities	• Uncertainty with applying ERIVANCE-derived utilities to STEVIE study population as the population baseline age in ERIVANCE is not reflective of patients in STEVIE or UK clinical practice and the assessment of response/progression in each trial is also different • Concerns with the lack of sensitivity of the SF-36 for aBCC
Model: **Clinical inputs**	**Uncertain:** • limitations of landmark approach carried through to model
Model: **BSC assumptions**	• Accepted ERG scenario that people on vismodegib move to BSC 6 months after progression • Agreed that people on vismodegib moving to BSC receive the same treatment regimen as people on BSC who have progressed

ACD committee conclusions (3)

Model: Cost-effectiveness (CE)	• Considered combined results (laBCC and mBCC) from the model so as not to disadvantage the very small number of patients with mBCC
	• Agreed that most plausible ICER would be between 2 different scenarios:
	  • No survival gain with vismodegib
	  • Survival gain with vismodegib incorporated using HR adjusted for age, ECOG and Gorlin syndrome

Results	• Plausible ICERs for aBCC compared with BSC (list price):
	  • £106,810/QALY gained when a survival benefit was assumed
	  • £5,658,289/QALY gained when no survival benefit was assumed

ACD consultation responses

- **Consultee comments from:**
  - Roche (including additional evidence)

- **Clinical expert comments from:**
  - National Cancer Research Institute – Advanced Care Planning – Royal College of Physicians (NCRI-ACP-RCP)

- **Web comments from:**
  - 1 NHS professional
    - Consultant clinical oncologist
  - 1 patient

Company consultation comments

Selection of Landmark point (6-month)

- **ACD:**
  - Further exploration around the landmark would have increased its confidence in the analysis

- **Roche:**
  - Further exploration around the landmark is not plausible:
    - Time points between 3- and 6-months do not align with STEVIE's assessment schedule
    - Beyond the 6-month landmark, majority of non-responders would have progressed or died **->** final analysis would have been based on a small number of patients **->** ↑ uncertainty

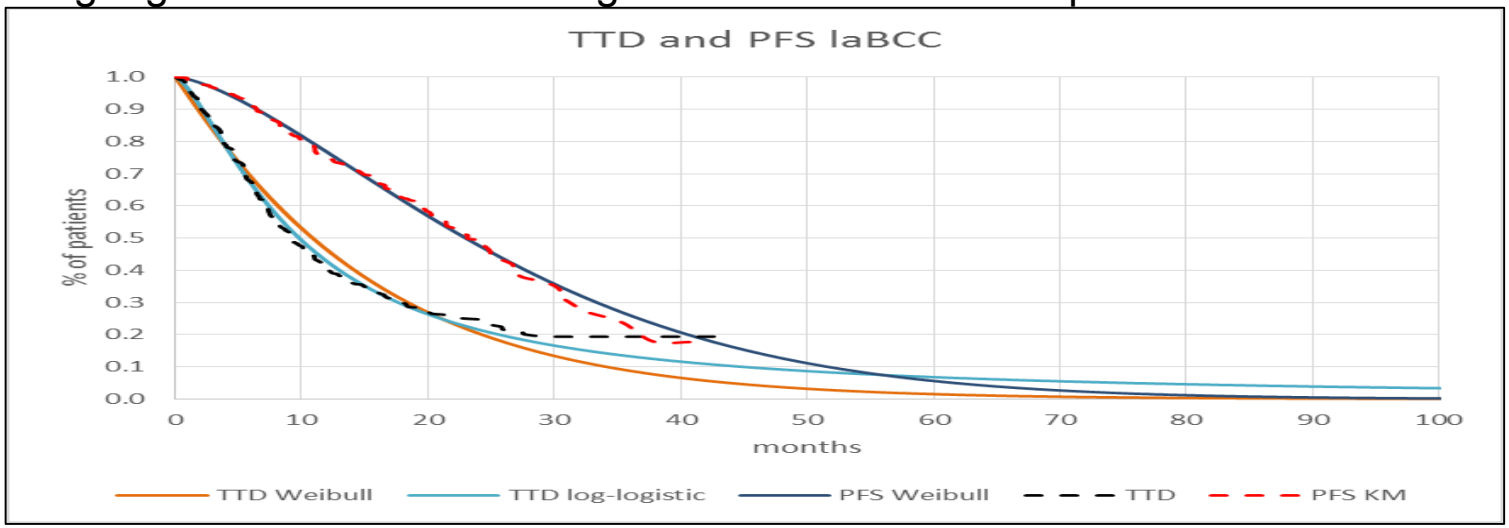
Extrapolation of time to treatment discontinuation (TTD)

- **ACD:**
  - Committee preferred log-logistic function to company's choice of Weibull for extrapolating TTD, which is a worse fit to KM data based on AIC values
  - ERG explained log-logistic function is not the reason for TTD and PFS curves crossing, it is dependent on the modelling approach

- **Roche:**
  - Disagrees with this TTD extrapolation choice:
    - AIC values do not address the appropriateness of the overall extrapolation beyond the observed KM data (~13% of the model time horizon) -> closeness of fit (log-logistic) is over-interpreted
    - The difference in fit between Weibull and log-logistic throughout the observed time period is small: <5% difference for 40 months
    - To prevent TTD and PFS curves from crossing, the log-logistic curve must be capped from year 5 to 8 **->** patients left on treatment (7%) can only discontinue due to progression or death **–>** Clinically implausible. No capping required with Weibull.

ERG critique: extrapolation of TTD

- Based on AIC and BIC, log-logistic best fit for laBCC and mBCC data (Weibull is one of the worst fitting curves for laBCC data); curves crossing issue does not favour either curve
- For laBCC: although capping TTD by PFS curve is required with a log-logistic model, it is still preferred over Weibull considering the small % patients left from year 5 and the uncertainty in the long-term predictions of the economic analysis
- For mBCC: curves cross using Weibull (and log-logistic) but the company has not provided an explanation for using Weibull over alternative better fitting models (log-logistic)
- Visual inspection (laBCC):
  - Tails of the KM curves – a smoother drop with log-logistic curves vs. Weibull curves (sharper drop) -> replicating the plateau from month 30 for patients with laBCC
  - Log-logistic is a better fit throughout the observed data period in the KM curve for



Intensity of post-progression BSC regimen in economic analysis

- **ACD:**
  - Accepted ERG scenario assuming that patients (67%) on vismodegib who have progressed stay on the monitoring regimen for 6 months after progression and then move to BSC, and this regimen will be the same irrespective of prior vismodegib treatment
- **Roche:**
  - Disagree, assuming a 6-month delay is highly conservative
  - Clinical expert opinion that patients who receive vismodegib can expect a delay up to 10 years before receiving the same BSC treatment as a patient who is not treated, although this is highly variable
- **ERG:**
  - Agree that delay periods are highly variable and depend on location and type of BCC and other factors
  - But company's assumption of 6-10 year estimate implausible, particularly for patients with mBCC with an average life expectancy of 10 years

    → ERG's preferred assumption of 6 months remain

Clinical expert and web comments

Clinical need	• Patients value alternative treatment options • Many patients are elderly • Patients face living with 'living with a disfiguring, painful, weeping, smelly tumour' or alternatively life changing and mutilating surgery, for example removal of a nose, eye or ear. The surgery is very expensive and can involve protracted hospital stays.
Survival benefit	• OS benefit difficult to demonstrate as mBCC is extremely rare and death from laBCC or it's complications are relatively rare
Use of vismodegib	• Frequently used for short periods (e.g. 6 months) and can be used again when cancer recurs -> better palliation for patients in terms of side-effects and more cost-effective • Remissions can be long lasting • Useful in patients with advanced Gorlin syndrome who may otherwise have 30+ procedures/year

Revised company base case vs. ERG's alternative base case (list price)

The assumptions that differ in the company's revised base case compared to the ERG's are:

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

Company's revised base case (when a survival benefit is assumed (aBCC))

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

ERG's preferred base case (when a survival benefit is assumed (aBCC))

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

ERG's preferred base case (when no survival benefit is assumed (aBCC))

Incr. costs	Incr. QALYs	ICER
£93,727	0.02	**£5,658,289**

Scenario analysis: BSC delay post-progression
(ICERs including an assumption of survival benefit - list price)

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

ERG''s assumption

Company's assumption

Scenario analysis: Utilities in the economic model (list price)

- The company states that its original model is likely to have underestimated HrQoL benefit with vismodegib because of:
  - lack of sensitivity of the SF-36 for aBCC
  - the model applied health-state utilities across treatment arms
    - Patients on vismodegib in the PFS or PD state are likely to have smaller tumours than PFS or PD patients receiving BSC -> better QoL
- **Updated scenario analysis:**
  - differential health-state utilities are applied across treatment arms **->** this highlights the sensitivity of the model to this difference in HrQoL
    - utilities applied in the BSC arm were derived by multiplying the SF-36 utilities by a user-modifiable factor

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

ERG critique: utilities in the economic model (scenario analysis)

- Agree that using the same values for vismodegib and BSC may underestimate patients' QoL on vismodegib in the PFS state
- Disagree that this benefit with vismodegib would last forever
  - patients who progress on vismodegib will eventually progress to a state that is equivalent to patients who progressed on BSC

  -> *Overestimation of the impact of treatment-specific HSUVs on the final ICERs*
- Vismodegib-related AEs (e.g. hair loss, appetite loss) are not captured in the analysis (not easily quantifiable) → negative impact of vismodegib-related AEs on QoL is underestimated
- Agree that the company's exploratory analysis should only be taken as an academic exercise due to it not being evidence-based

Overall survival

- Overall survival (OS) data immature
- Mortality directly attributed to laBCC is rare but compared with background mortality in general population, there appears to be an ↑ mortality risk in people with laBCC, which has not been explained - could be because only 3% of the STEVIE population were from UK?
- Mortality directly attributable to mBCC is plausible but the OS analysis is based on a very small sample size (n=96)

ERG's preferred adjusted HRs at 6-month landmark

Plausible?

	laBCC	mBCC	Combined
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
OS at 6-month landmark			
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 at 6-month landmark			
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)
Red denotes statistically significant differences between non-responders and responders (>1 favours responders)			

Key issues for discussion

- Should a Weibull or Log-logistic distribution be used to model TTD in the economic model?
- When are patients who have progressed on vismodegib likely to move on to receive the same BSC regimen as patients who have progressed and never received vismodegib?
  - 6 months or 6 years?
- Are quality of life benefits likely to be underestimated?
- Is there a survival benefit with vismodegib?
- Does the committee maintain that the results of the landmark analysis are not sufficiently robust for decision-making?