Slides for public

Sorafenib for treating advanced hepatocellular carcinoma

Cancer Drug Fund Reconsideration of TA189

3rd CDF committee meeting: 1 February 2017, Manchester

Evidence Review Group: NICE Decision Support Unit (DSU), University of Sheffield Iñigo Bermejo and Sabine Grimm

Chair: Amanda Adler

Lead Team (NICE TA189, Committee C): Matt Stevenson, Philip Rutledge

NICE Technical Team: Martyn Burke, Frances Sutcliffe

Company: Bayer

History of Appraisal

2009/4	1st appraisal committee meeting
	Appraisal Consultation Document (ACD) – not recommended
2009/6	2nd appraisal committee meeting
2009/8	3rd appraisal committee meeting
	2nd ACD – not recommended
2009/10	4th appraisal committee meeting
	Final appraisal determination issued: not recommended
2010/2	Appeal: 4 points. All dismissed
2010/5	Final guidance reissued: not recommended
2016/7	1st CDF reconsideration meeting - New price and new data to validate time beyond trial
	ACD: not recommended
2016/11	2nd CDF reconsideration meeting
	2nd ACD: recommended in the CDF
2017/2	3rd meeting: New price, new data on treatment duration

Preview - Issues for discussion

- What is the appropriate function with which to extrapolate treatment costs with sorafenib?
- Is matched GIDEON satisfactory to validate SHARP
  - with respect to cost of treatment?
- How does the CDF data from the King audit of UK sorafenib use inform the committee's decision?
- Is it reasonable to make a decision on an ICER based on a midpoint between a lognormal and Weibull for overall survival extrapolation?
- Would this treatment have been considered innovative?

Sorafenib and decision problem TA189

Sorafenib	
Marketing authorisation	'for the treatment of hepatocellular carcinoma' (and renal cell and thyroid carcinoma)
Mechanism	'Multikinase' inhibitor
Administration	Oral – twice daily
Indications	Renal cell carcinoma, differentiated thyroid carcinoma

Decision problem	
Population	Patients with advanced stage hepatocellular carcinoma who have failed or are unsuitable for surgical or loco-regional therapies
Intervention	Sorafenib
Comparators	Best supportive care

Evidence Randomised Controlled Trial 'SHARP'

Population

- 602 patients
- Not previously treated
- Life expectancy ≥ 12 weeks
- ECOG 0 to 2
- Child-Pugh function **grade A**

Intervention + comparison

Sorafenib 400 mg

Placebo

Outcome

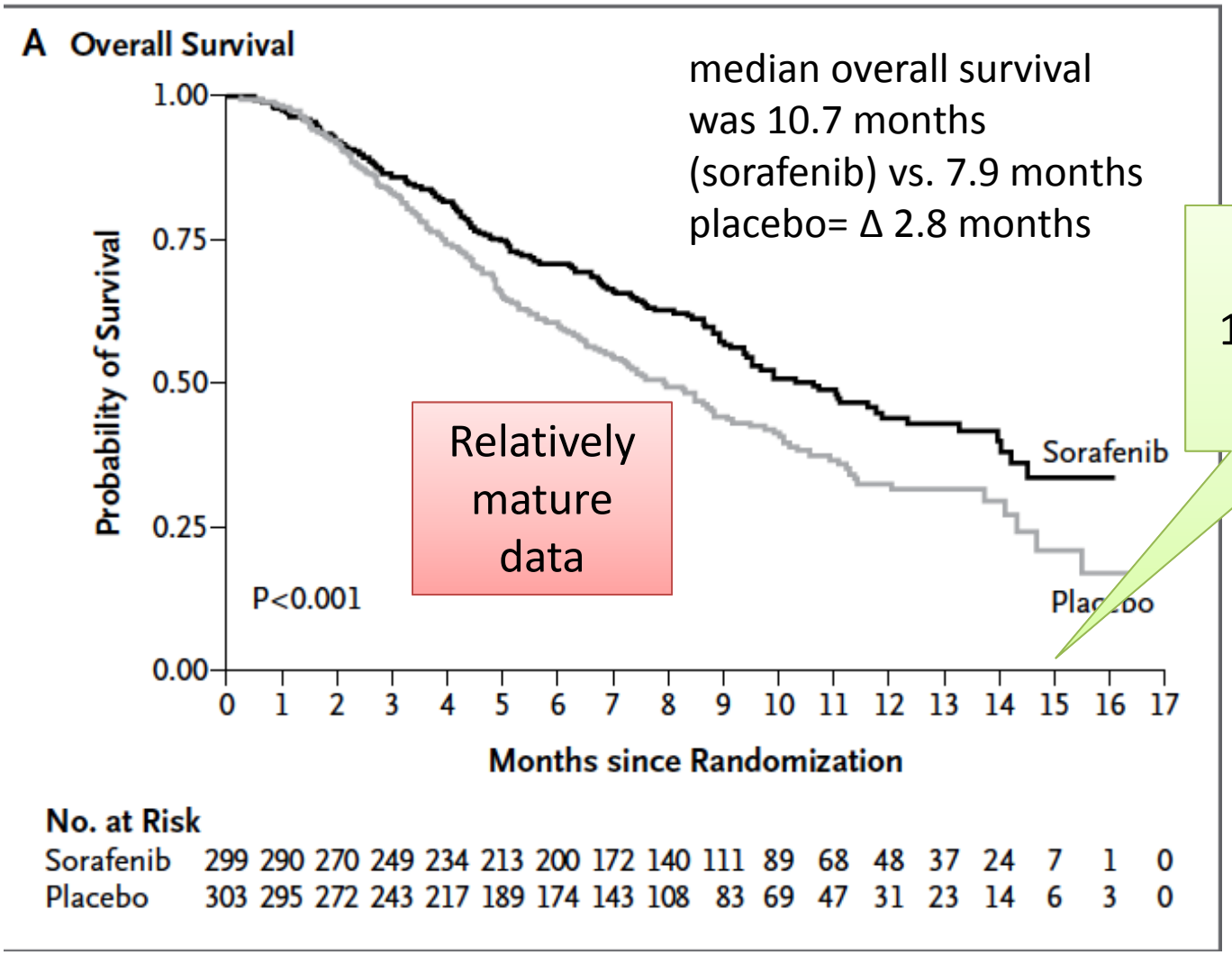
Two 1° endpoints:

1. overall survival
2. time to symptomatic progression

- Treat to radiographic progression (7.7% continued beyond)
- Trial stopped early
- Utility: FACT-hep mapped to EQ-5D

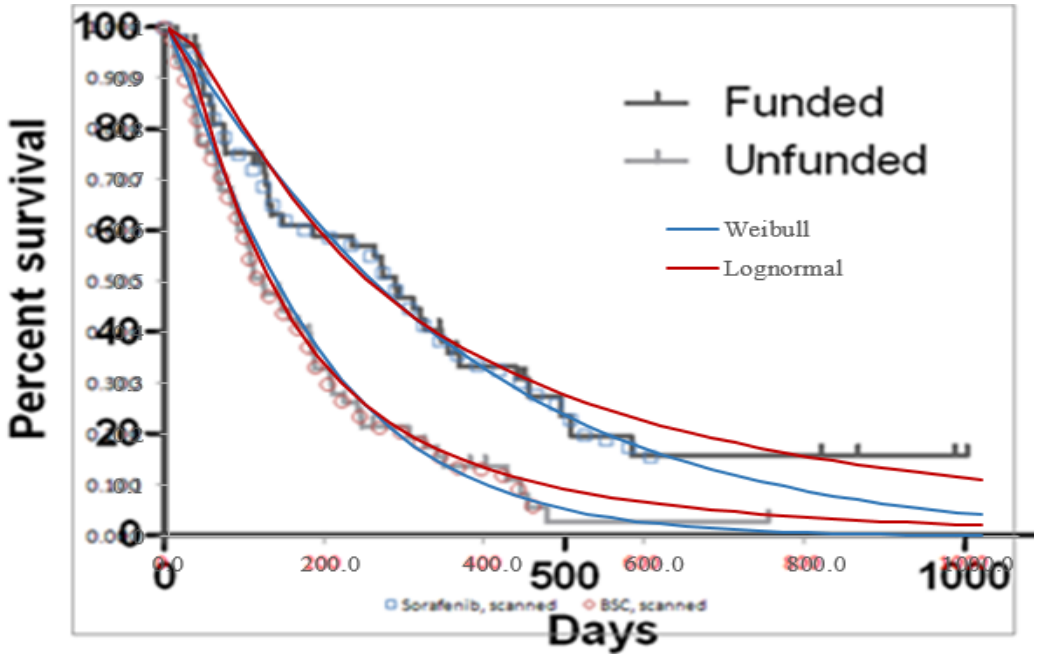
- *Eastern Cooperative Oncology Group performance status (0: fully active to 5: dead)*
- *Child-Pugh based on serum bilirubin, serum albumin, prothrombin time, ascites, enchephalopathy; 96% of SHARP Child-Pugh function grade A. FACT-hep Functional assessment of cancer therapy - hepatobiliary*

Results overall survival
N Engl J Med 2008;359:378-90.



To validate survival beyond SHARP uncontrolled retrospective UK observational study Palmer *et al.* 2013

- Comparing 'funded' (n=57) vs. 'unfunded' (n=76)
- Numbers at risk, statistical methods not presented
- Plateau at tail = high uncertainty
- Weibull likely to be well within confidence intervals
- Confounding



Source: Figure 1, page 16 of ERG report

To validate survival beyond end of SHARP company provided GIDEON an uncontrolled safety study

"3213 patients, 50% died, 50% censored in median [AIC] days"

Overall Survival

Unresectable HCC, candidates for systemic therapy, life expectancy of > 8 weeks

Source: Figure 3 of company's submission

Committee considerations by meeting

	Original TA189	CDF reconsideration		
Meeting:	FAD	1st	2nd	New today
Clinical effectiveness	Child–Pugh grade A liver function (95% SHARP) + good performance			–
	TTP differs if determined centrally or locally			–
Extrapolation	OS and TTP extrapolation 'key drivers'			–
Time to progression (TTP)	Log-normal			–
OS	**Log-normal** fits SHARP observed data better than **Weibull**, but not necessarily thereafter. Consider **BOTH**	GIDEON data does not match SHARP population – different risk of death?	GIDEON matched to age, Child-Pugh, ECOG sex. 3:1 – Statistically, log normal fits data best. Visually log normal **over-estimates** and Weibull **underestimates** OS; Committee: **closer to lognormal than Weibull**	–

	TA189	CDF reconsideration		
	FAD	1st	2nd	New today
Palmer et al	Not available	Likely confounded		_
Costs – treatment beyond progression	1st meeting: treat beyond progression (per SHARP) 2nd meeting: no	Beyond progression		_
Treatment duration with sorafenib	Based on proxy of time to progression	Based on patient-level SHARP data rather than proxy of time to progression Company chooses LOG NORMAL (statistical fit) DSU: Weibull and Gompertz distributions were most plausible (visually, external data) Committee LOG NORMAL better (on BIC) than Weibull Committee heard from clinician about 10% still on treatment at 3 years; chose LOGNORMAL		Data from matched GIDEON

	TA189	CDF reconsideration		
	FAD	1st	2nd	New today
Resource use	Original estimate	Should pool original and CDF estimates because based on few clinicians	Company said no because 'clinical practice has changed'	Company has pooled data
Sorafenib wastage	No	Committee concluded account for drug wastage	Committee concluded company's new evidence from 2 NHS Trusts OK	–
End of life	Yes. Median survival gain >2.8 months Mean from company's model 6.1 months			–
Price sorafenib	Complex PAS	CMU Price 1	CMU Price 2	CMU Price 3 (27 01 17)
Decision	Not cost effective	Not cost effective	Not cost effective – CDF funding	Company declines CDF

SHARP data on time to treatment discontinuation for treatment duration: Company's 'fully parametric' approach – 2nd ACM

Kaplan-Meier curve incomplete so company extrapolated using 5 parametric models – company preferred log normal on statistical fit						
Months	KM	Expo-nential	Weibull	Log logistic	Gom-pertz	Log-normal
Median	[AIC]	[AIC]	[AIC]	[AIC]	[AIC]	[AIC]
Mean	[AIC]	[AIC]	[AIC]	[AIC]	[AIC]	[AIC]

ERG: 1. AIC BIC differences in Weibull, Gompertz + log normal small 2. Weibull and Gompertz more plausible for extrapolation than log normal based upon visual inspection and external data

SHARP vs GIDEON
Overall survival Kaplan–Meier graph
Matched (3:1) GIDEON dataset to SHARP patients – 2nd ACM

Source: Figure 3 of company's response to the ACD

Choice of survival extrapolation: GIDEON – 2nd ACM

Source: page 9, figure 1, ERG critique of company response to ACD

Company's ICERS revised price – 2nd ACM

Scenario	Details	Cost/QALY
Company base case	• Treatment costs from investigator-determined time to progression (TTP) • Log normal for extrapolating overall survival • Updated resource use data only • No wastage	£35,695
Appraisal committee's preferred assumptions for treatment costs	• Treatment duration based on SHARP time to treatment discontinuation with company's choice of 'hybrid' extrapolation • Independent assessment of progression • Pooled resource use • No wastage	£47,852
Scenario for treatment costs; including wasting	• Duration of treatment based on SHARP data (fully parametric curve, log normal) • Independent assessment of progression • Pooled resource use • 7 days wastage	£49,060
Company's base case plus Weibull for overall survival	• Treatment costs based on investigator-determined time to progression (TTP) • Weibull for extrapolating overall survival • Updated resource use data only • No wastage	£52,056

ERG's exploratory base case analysis: Based on the "ACD preferred assumptions" – 2nd ACM

Base case assumptions:

- Extrapolating overall survival on log normal distribution
- Time to progression based on independent reviewer assessment
- Treatment duration extrapolation based on patient level data for treatment duration from SHARP
  - fully parametric curve = log normal
- Resource use: pooled estimates from the original appraisal and the new submission
- Up to 7 days of wastage

ERG's exploratory analyses – 2nd ACM

	Scenario (source: pages 17–18, table 2 of the ERG's critique of the company's response to the ACD)	ICER (£/QALY)
	ERG's base case (log normal, 7 days wastage)*	£49,299
	ERG's base case* (probabilistic)	£49,239
1	Extrapolation of overall survival: Weibull	£87,091
2	Extrapolation of treatment duration: Weibull	£41,935
3	Combining 1 and 2: Weibull overall survival and duration of treatment	£72,596
4	Wastage: half a pack (14 days)	£50,884

* Equivalent to the "ACD preferred assumptions" in the company's response to the ACD, but with an adverse costing error fixed.

Abbreviations: ACD = appraisal consultation document; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year.

CDF reconsideration meeting: Committee's key conclusions ACD2 (1)

Validation of the overall survival extrapolation	• 3 data sets (SHARP, GIDEON, and Palmer et al.) for informing the choice of survival distribution did not conclusively favour one single distribution • The log normal function used to extrapolate survival beyond SHARP fitted GIDEON better than the Weibull function, but that the Weibull function was still plausible
Treatment duration	• **Preferred using effectiveness and cost estimates from the same source** • Estimates of mean and median treatment duration reported in clinical practice were inconclusive • Company's fully parametric method using the log normal distribution reflected the most robust estimate of treatment duration (SHARP data)

CDF reconsideration meeting: Committee's key conclusions ACD2 (2)

Resource use	• Resource use data not robust and further data would increase certainty in the ICER • Pooled estimates preferred
Treatment wastage	• Appropriate to account for 7 days of drug wastage
Most plausible ICER	• Preferred ICER range between £49,500 to £87,000 • Most plausible ICER likely to be lower than the mid-point of the its preferred ICER range (that is, lower than approximately £68,250 per QALY gained), but would be higher than ICERs previously accepted for technologies that had met the end-of-life criteria
Cancer Drugs Fund	• Considerable uncertainty about the relationship between length of treatment and its effectiveness • Company's resource use estimates had considerable impact on the ICER and this had potential for further data collection in CDF

Summary of preferred extrapolations

	Company	Committee
Treatment duration	Weibull	Lognormal
Overall survival	Lognormal	Between lognormal and Weibull - closer to lognormal

ACD2 recommendation

Sorafenib is recommended for use within the Cancer Drugs Fund as an option for treating advanced hepatocellular carcinoma in adults only if:

- surgical or locoregional therapies have failed or are not suitable **and**
- the company submits a proposal for sorafenib to be included in the Cancer Drugs Fund

Consultation comments after 2nd CDF reconsideration

ACD2 consultation responses

- Consultees:
  1. British Liver Trust
  2. Royal College of Physicians
  3. NHS England (Professor Peter Clark)
  4. Bayer (sorafenib)
     - New PAS
     - New data on treatment duration from GIDEON
- Web comments
  - None

Comments British Liver Trust

- Want patients to have access to sorafenib
- Sorafenib is the only treatment available
- Highlight the “immense benefits of not only prolonging life but also the improved symptom control and quality of life that can be achieved”
- Sorafenib is available to patients in Scotland and Wales - unfair not to give equal access to patients in England

Comments Royal College of Physicians RCP (1)

- Without sorafenib, England risks becoming an international outlier and an inappropriate place to conduct clinical research in hepatocellular carcinoma
- GIDEON was a global study and do not believe there were any UK centres, therefore, the King et al. UK audit data may be relevant (next slide)
- Broadly consistent findings across the studies:
  - poorer outcomes for Child-Pugh B
  - daily dose
  - duration of treatment

Comments RCP (2)
UK Sorafenib Audit (King et al 2016)
similar to CDF data

- n=448 from 15 hospitals
- Retrospective analysis of patients in Cancer Drugs Fund and local databases
- Median age 68 years (range 17–89), 75% performance status ≤1, **77% were Child-Pugh A and 16.1% were Child-Pugh B**
  - N.B. does not match SHARP
- Median time on treatment 3.6 months (lower than SHARP)
- Mean daily dose of 590 mg (lower than SHARP)
- Median overall survival 8.5 months, Child-Pugh A compared with Child-Pugh B (9.5 compared with 4.6 months)
- For Child-Pugh A patients with good performance status, survival outcomes were similar to those reported in global RCTs
- “Patients with Child-Pugh B or poor performance status seem to derive limited benefit from sorafenib and may be better managed with best supportive care”

Comments NHS England

- Child Pugh A is the appropriate populations for this recommendation – SHARP was meant only to enroll Child Pugh A
- Summary of product characteristics acknowledges limited data for Child Pugh B
- Child Pugh B perform less well than A
- Separating sources of data ‘increases uncertainty’
- Oncologists have ‘learned to use sorafenib better’ than when SHARP occurred (2008) and clinical practice
  - starting dosage in the UK is likely to be lower – 38% in UK CDF audit had lowering starting dosages than SHARP
  - Now more likely to have dose reductions

Comments summary company – by topic

Topic	Company response
Areas of uncertainty	1. duration of treatment 2. overall survival 3. resource use
Cancer Drug Fund	Chooses not to participate GIDEON provide better data than the CDF could generate
Price of sorafenib	New price – bigger discount 'Lowest price in Europe' Sorafenib patent expires in 5 years
Overall costs of treatment – treatment duration	New data from matched GIDEON

Comments Company Duration of treatment

- Some patients in SHARP did not stop treatment but all patients in GIDEON did
- GIDEON larger than SHARP
- Unrestricted mean duration of treatment in the matched GIDEON population is lower than the Appraisal Committee's preferred extrapolation the log-normal

Source: Table 1, page 4 of company's response to ACD2	GIDEON n=895		SHARP n=299
	Mean (95 CI%)	Median (IQR)	Mean
Duration of treatment (months)	[AIC]	[AIC]	Weibull: [AIC] **Lognormal:** [AIC]
Mean daily dose intensity (mg)	[AIC]	[AIC]	[AIC]

Abbreviations: CI, confidence intervals; IQR, interquartile range; mg, milligram. Values rounded.

Kaplan-Meier analysis for treatment discontinuation GIDEON matched to SHARP

⊙ What distribution is this consistent with?

Comments company duration treatment (2)

- People lived longer in matched GIDEON (median [AIC] days) than in SHARP (median 324 days).
  - But shorter treatment and lower doses [AIC] in GIDEON vs [AIC] in SHARP) did not shorten lives
    - N.b. committee chose not to separate source of effectiveness and costs
  - Therefore, combining data from SHARP and GIDEON is ‘conservative’ (see slide 37)

Comments Company duration treatment (3)

Supportive evidence

- Over [AIC] patients had access to sorafenib via CDF – therefore, unlike for new treatments, there is published evidence on duration of treatment derived from use in NHS

Table: Empirical estimates of treatment duration in UK clinical practice

Publication	Sample size (n=)	Duration of treatment (months)	
		Median	Mean
J King et al (2013)	379	3.2	NR
GIDEON (total population)	3,202	3.5	5.5
GIDEON (matched population)	895	[AIC]	[AIC]
J King et al (2016)	484	3.6	NR
Ziogas et al (2017)	Age≤ 75: 151 Age>75: 31	Age ≤75: 3.0 Age >75: 5.1	NR

Numbers rounded. NR, not reported. Source: table 4, page 9 of company's response to ACD2

Comments company duration treatment (4)

- "The use of the statistical fit criteria published by Kass et al (1995), used by the Committee to determine the selection of the log-normal extrapolation of treatment duration is not appropriate."
- Statistical fit should not be used in isolation to decide on model fit
  - Committee selected log-normal based heavily on statistical fit
  - Weibull and Gompertz both appear to fit latter part of KM curve better than log normal upon visual inspection
  - n.b. ACD2 4.26:
    - log normal distribution was the best statistical fit of the 5 distributions explored
    - heard from the clinical expert that based on UK audit data 10% of patients survived for 3 years, which supported the log normal
- NICE technical support document 14 provides no guidance on inferring differences in AIC/BIC statistics to inform model selection
- If Kass applies to choice of model for treatment duration, Committee should also use it for choice of model for overall survival

Comments company overall survival

- "Unfortunately" SHARP did not follow-up overall survival past 19 months
- If committee were to apply criteria in Kass (1995) to extrapolation of overall survival to matched GIDEON population, this indicates that Weibull does not fit the data – a difference twice that seen for extrapolation of treatment duration ([AIC])

Table 1	Kass et al. (1995) criteria
ΔBIC	Evidence against higher BIC
0 to 2	Not worth more than a mention
2 to 6	Positive
6 to 10	Strong
>10	Very Strong

Table 2	Differences in BIC across datasets (rounded)
Source	ΔBIC: Lognormal & Weibull
Matched GIDEON	[AIC]
SHARP (modelling)	[AIC]
Palmer 2013	Not reported

- 3 data sets the company had presented for informing the choice of survival distribution did not conclusively favour 1 single distribution

Comments company resource use

- Company did not identify any new evidence that offers comparative data
- Company accepts the committee's preferred assumption to pool original and updated resource use data

Keeping sources together

SHARP data

- PFS
- Treatment duration
- Overall survival

Extrapolate PFS, TD, OS from SHARP

- Assess each for best parametric curve:
  - Statistical fit to SHARP
  - Visual fit to ‘over-lain’ matched GIDEON data (rather than fitted to GIDEON per se)

Choose best parametric curve for each

- Calculate ICERs

Comments: Company new ICER estimates

- Include following appraisal committee preferred assumptions:
  - Independent assessment of progression
  - Wastage (up to 7 days)
  - Pooled resource use estimates

Effectiveness data from SHARP Source: Table 8, page 14 of company's response to ACD2		**Duration of treatment**			
		Matched GIDEON mean ([AIC]months)		Weibull SHARP mean ([AIC]months)	
		[AIC]	[AIC]	[AIC]	[AIC]
Overall survival	Log-normal	£32,819	£36,050	£37,202	£41,073
	Weibull	£54,929	£61,290	NR	NR
	Midpoint	**£43,874**	**£48,670**	£50,380	£56,125

Abbreviations: NR, not reported. Note (mean daily dose): a = Matched GIDEON; b = SHARP.

ERG comments

- Choose curves based on statistical fit to real data and visual inspection of extrapolated portion
- Use treatment effectiveness and cost data from the same source
  - committee already concluded to:
    - Extrapolate overall survival curve from SHARP
    - Extrapolate data from SHARP to estimate duration and total cost of treatment
  - Using costs from GIDEON and effectiveness from SHARP is ‘potentially misleading’

Treatment duration versus overall survival of sorafenib studies referred to by the company

Source: Figure 1, ERG critique of company's response to ACD2

ERG's exploratory analyses new CMU price

- Includes following appraisal committee preferred assumptions:
  - Independent assessment of progression
  - Wastage (up to 7 days)
  - Pooled resource use estimates

Source: Table 2, page 10 of ERG critique of company's response to ACD2

Overall survival	DoT		Total QALYs	Inc. QALYs	Total costs	Inc. costs	ICER
Lognormal	Log normal	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
Weibull		BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
Lognormal	Weibull	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
Weibull		BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]

Abbreviations: DoT: Duration of treatment, BSC: best supportive care; Inc, incremental.

ERG's exploratory analyses new CMU price: Midpoint and weighted averaged results for sorafenib vs BSC with different parametric curves for overall survival

- Includes following appraisal committee preferred assumptions:
  - Independent assessment of progression
  - Wastage (up to 7 days)
  - Pooled resource use estimates

Source: Table 3, page 10 of ERG critique of company's response to ACD2

Overall survival	DoT		Total QALYs	Inc. QALYs	Total costs	Inc. costs	ICER
50% lognormal 50% Weibull	Log normal	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
	Weibull	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
75% lognormal 25% Weibull	Log normal	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]
	Weibull	BSC	[AIC]		[AIC]		
		Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	[AIC]

Abbreviations: DoT: Duration of treatment, BSC: best supportive care; Inc, incremental.

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- Is matched GIDEON satisfactory to validate SHARP
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- How does the CDF data from the King audit of UK sorafenib use inform the committee's decision?
- Is it reasonable make a decision on an ICER based on a midpoint between a lognormal and Weibull for overall survival extrapolation?
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