NICE National Institute for Health and Care Excellence

CDF Rapid Reconsideration

Sorafenib for advanced hepatocellular carcinoma (Cancer Drugs Fund reconsideration of TA189)

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Sorafenib for advanced hepatocellular carcinoma (Cancer Drugs Fund reconsideration of TA189)

Contents:

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

Slides for public

Cancer Drug Fund Reconsideration of TA189 sorafenib for treating advanced hepatocellular carcinoma

CDF Committee Meeting: 26 July 2016, Manchester

Single Technology Appraisal

Evidence Review Group: NICE Decision Support Unit (DSU), University of Sheffield

Chair: Amanda Adler

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

NICE Technical Team: Martyn Burke, Fay McCracken, Frances Sutcliffe

Company: Bayer

General issues for discussion

- Have all the committee's preferred assumptions been sufficiently addressed?
- What is the most plausible ICER?
- Should sorafenib be:
  - recommended for routine commissioning in the NHS?
  - not recommended for routine commissioning in the NHS?
  - recommended for use in the Cancer Drug Fund (CDF)?

TA189 sorafenib history

- 1st appraisal committee meeting: 8 April 2009
- Appraisal consultation document 1 issued: Not recommended
- 2nd appraisal committee meeting: 11 June 2009
- 3rd appraisal committee meeting: 12 August 2009
- Appraisal consultation document 2 issued: Not recommended
- 4th appraisal committee meeting: 14 October 2009
- Final appraisal determination issued: Not recommended
- Appeal hearing: 26 February 2010: Dismissed
- Final guidance published: 26 May 2010: **Not recommended**

Question today: Does the new Commercial Medicines Unit price and new data to validate time beyond trial allow the committee to recommend sorafenib for routine commissioning in the NHS?

TA189: Appeal

Grounds	Decision
Committee failed to explain why it changed its conclusions with respect to the modelling, in the absence of new data to support doing so and by not stating the degree to which they considered evidence received during the appraisal regarding appropriate survival extrapolation methods	Rejected
Committee devoted insufficient time to considering the responses to consultation at the meeting prior to publication of the FAD	Rejected
Committee failed to place adequate weight on innovation	Rejected
Committee failed to consider the cost effectiveness of sorafenib similarly to previous compounds when applying end of life criteria	Rejected

Sorafenib & decision problem in TA189

Sorafenib	
Marketing authorisation	‘for the treatment of hepatocellular carcinoma’ (and renal cell and thyroid carcinoma)
Mechanism	‘Multikinase’ inhibitor
Administration	Oral

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

No changes to the scope of the appraisal are considered for CDF reconsideration

Comparators and evidence in TA189: 1st line treatment

Advanced hepatocellular carcinoma not previously treated

Doxorubicin occasionally used

Local resection, radiofrequency ablation, chemoembolisation

Best supportive care

Sorafenib

Committee concluded outside decision problem

Committee accepted as comparator

Evidence Randomised Controlled Trial

Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP)

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

Sorafenib 400 mg

Placebo

1° endpoint: Combined overall survival and time to symptomatic progression

Treat until radiographic progression RECIST; however, in SHARP 7.7% of patients continued beyond progression

Trial stopped early
Published in 2008
Functional assessment of cancer therapy - hepatobiliary [FACT-hep] mapped to EQ-5D

Child-Pugh based on serum bilirubin, serum albumin, prothrombin time, ascites, enchephalopathy; 7

Committee conclusions TA189 final guidance

Population	Child–Pugh grade A liver function (95% SHARP) + good performance
Clinical effectiveness	SHARP stopped early; potentially underestimates survival benefit
	Radiological disease progression differed by who assessed it;11.7 weeks longer when assessed independently, 5.1 weeks by investigator for sorafenib compared with placebo
Cost effectiveness	Company chose log-normal to extrapolate overall survival and progression free survival; key drivers of cost effectiveness
	Log-normal provided slightly better fit to observed data than Weibull, it could not be accepted as the definitive function to extrapolate beyond the data, therefore both distributions should be considered
	1st model included treating beyond progression (per SHARP); later model with PAS did not include costs beyond progression
	In SHARP a cycle lasted 31.5 days, but in model lasted 30.4 days
	Complex patient access scheme introduced
ICER	Lower range of ICER was £52,600 per QALY gained; key drivers OS, PFS, utility
End of life	Yes. Increased median survival >2.8 months, and the company's model predicted a mean gain in overall survival of 6.1 months

CDF reconsideration: Company rationale for investigator review

- Time on treatment and not time to progression affects cost effectiveness.
- In the SHARP study it was the investigator who made treatment decisions based on patient scans and their own assessment of whether the cancer had progressed or not. The outcomes observed in the SHARP study are a direct result of the actual treatment received as determined by the investigator, and not a longer duration of treatment as 'predicted' by independent review.
- The decision to continue/discontinue treatment was not based on independent assessment of patient scans. The independent assessment was conducted in order to centralise and standardise patient scans for the purposes of regulatory approval. Whilst independent assessment is appropriate for regulatory approval it is not appropriate for the assessment of cost-effectiveness for the following reasons:
  - Using the independent assessment of PFS results in an estimation of treatment duration that exceeds the actual duration of treatment as observed in the trial.
  - The outcomes in the SHARP trial reflect the treatment received. The outcomes do not reflect those of a predicted longer duration of treatment i.e. treatment continuing until progression as determined by the independent review.
  - In real-life clinical practice assessment of progression and the suitability for treatment is determined by the clinician (synonymous with the investigator). Scans are not sent for centralised review. The investigator assessment of PFS is therefore aligned with what will happen in clinical practice

- Despite some limitations, patient numbers from the CDF (which might help establish the duration of treatment) suggest any increase from the actual treatment length as measured in the SHARP study would not be valid.

- There are two additional real world evidence studies involving sorafenib - time on treatment from these is:
  - In the Palmer study (reported in our submission) the average length of treatment on sorafenib was 5.1 months.
  - Gideon, (also reported in our submission) identified the median treatment duration as 3.5 months.

- These data would suggest that any increase in the treatment duration based on the independent time to progression would not reflect clinical practice.

n.b. for committee information – please refer to the table document

CDF reconsideration: Overview of company's submission

TA189 conclusions	Company
Child–Pugh grade A liver function is population	New populations not limited to grade A
SHARP stopped early	No new updated analyses
Radiological disease progression differed by who assessed it	All results investigator-assessed
Extrapolation key driver of cost effectiveness; curves other than log-normal fit extrapolated portion better; consider Weibull and log-logistic	New observational data to validate company's choice curves for overall survival
Treating beyond progression	Now included
Cycle length	Amended

⊙ Which is more appropriate for committee to address 'investigator' or 'independent' review?

What is new?

Patient access scheme replaced by Commercial Medicines Unit price

UK real-life clinical data; reference = Palmer et al 2013

GIDEON observational study; reference = 'data on file'

Characteristics of patients
GIDEON, Palmer *et al.* (2013) and SHARP

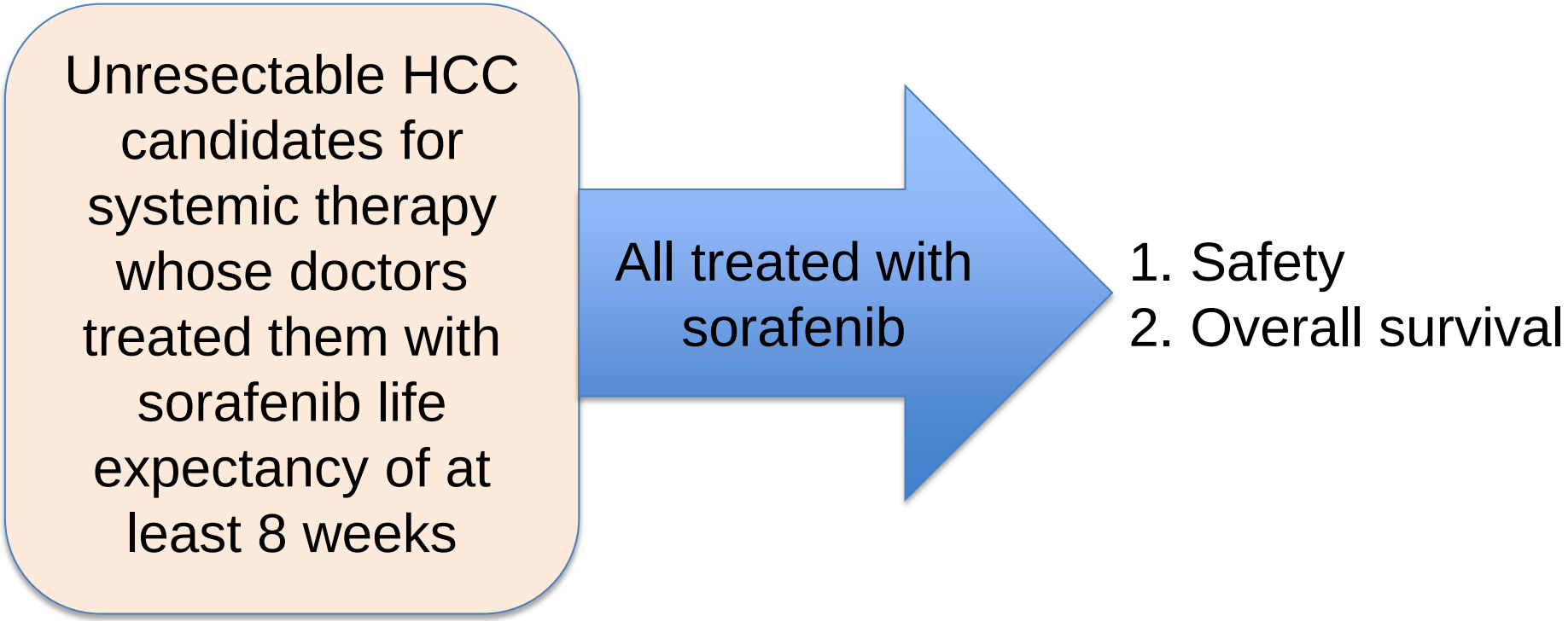
	SHARP N=602	GIDEON N=3213	PALMER N=133
Mean age (years)	65.6	61.9	62 (*n.b.* median)
Male	87%	82.2%	81.2%
Child-Pugh status A	96.5%	61.5%	82%
ECOG 0	54%	42.6%	19%
ECOG 1	38%	39.7%	49%
BCLC B (intermediate)	17.4%	19.8%	NR
BCLC C (advanced)	82.4%	52.0%	NR
BCLC D (end stage)	0.2%	NR	NR

⊙ Are patients in GIDEON in line with population in decision problem? Are SHARP and GIDEON populations similar? Are differences likely to modify effect? Did the company consider matching?

Abbreviations: BCLC, Barcelona Clinic Liver Cancer ; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NR, not reported.*Source (s): NICE technology appraisal guidance 189, Bayer original submission, SHARP publication (NEJM), tables 15 and 19 company's CDF submission*

Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON)

Observational uncontrolled study n=3,202



GIDEON maturity of data

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

	Median
SHARP Weibull	[AIC]
SHARP Lognormal	[AIC]
GIDEON	[AIC]

*Kaplan Meier OS data ITT analysis visual inspection (approximate survivors)

	80%
SHARP Weibull	[AIC]
SHARP Lognormal	[AIC]
GIDEON	[AIC]

Source: Figure 3 of company's submission

Numbers at risk not provided

- Why is median visualised if half of patients have died? Does this data validate the company's use of the lognormal function?

ERG's critique: GIDEON

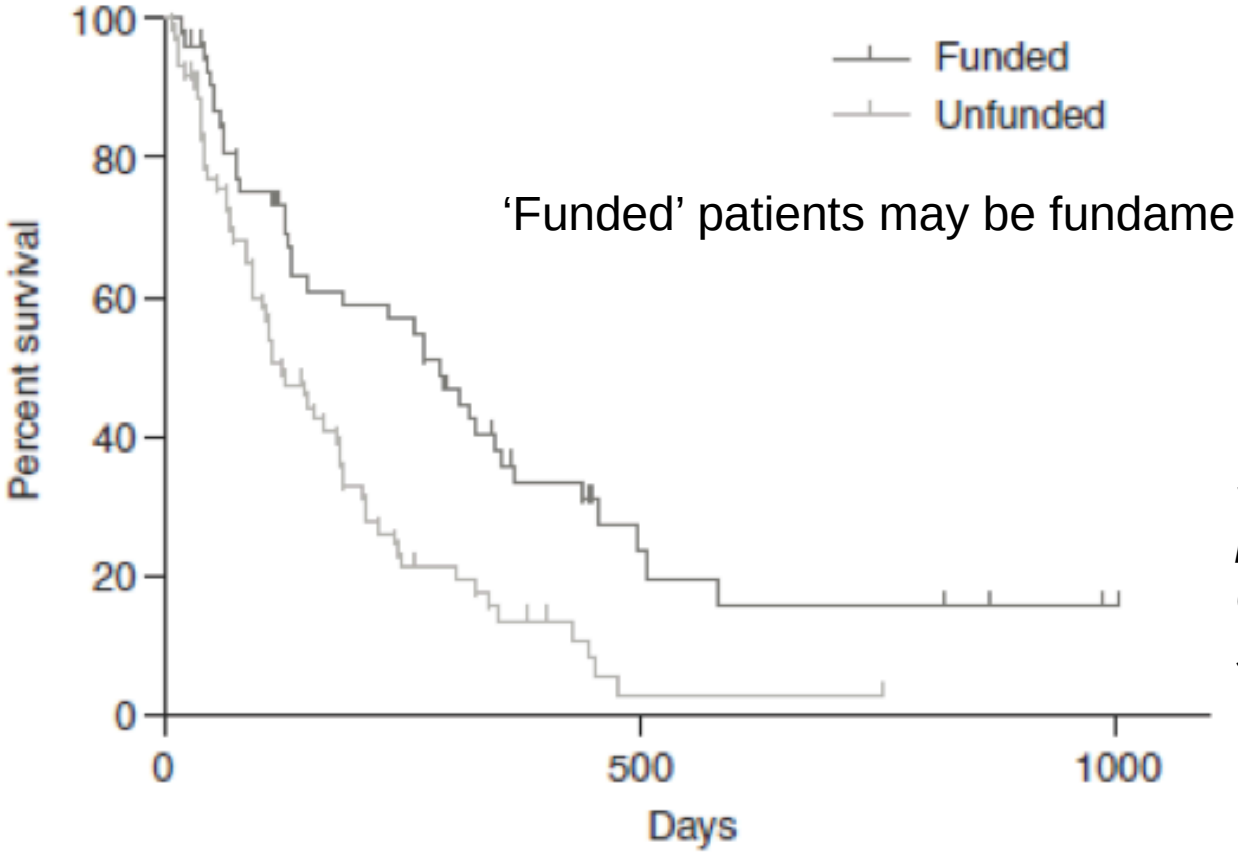
- Company excluded single-arm studies like GIDEON from its own literature review
- Lognormal (yellow) fits better than the Weibull (green) to GIDEON (red), but
- Important differences between GIDEON and SHARP in study design and population

Source: Figure 7, page 39 of ERG report

⊙ Numbers at risk? Which curve provides the better fit? Is GIDEON an appropriate choice for validation? Why or why not?

Palmer et al. (2013)

Retrospective unpublished UK observational study comparing ‘funded’ (n=57) vs. ‘unfunded’ (n=76)



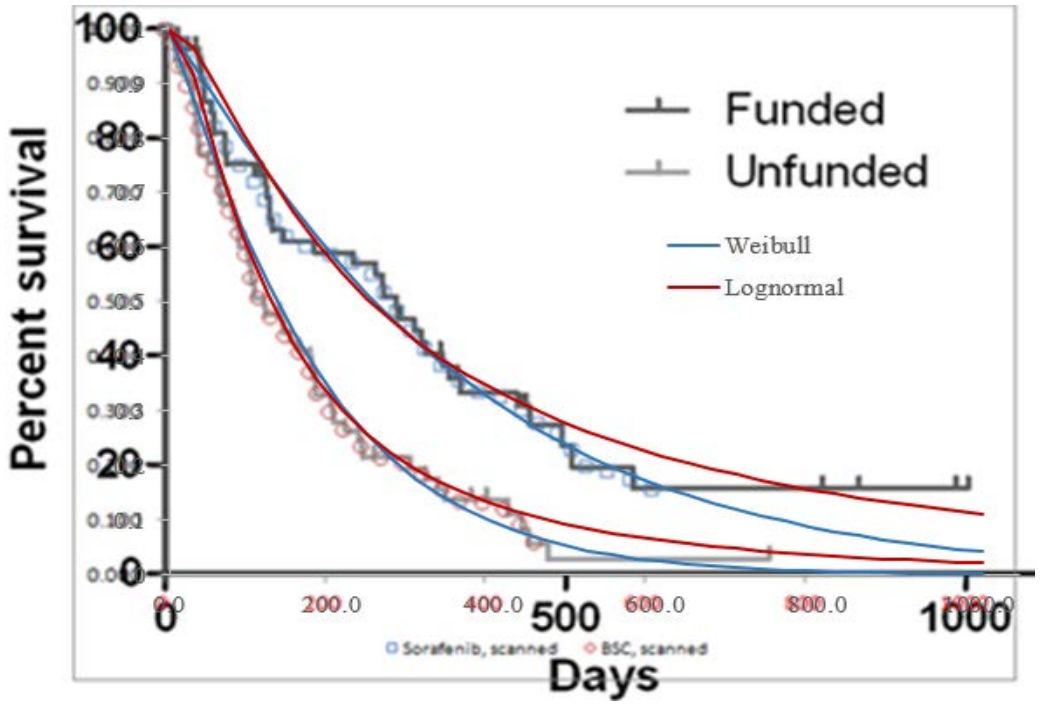
‘Funded’ patients may be fundamentally healthier?

Source: Figure 4, page 51 of company CDF submission

- Numbers at risk not presented
- Statistical methods not presented

ERG's critique: Palmer *et al.* 2013

- High risk of bias (not suitable for decision-making)
- Small number of patients (n=57 on sorafenib)
- On visual inspection, the Weibull fits the events better
- Plateau at the tail is an approximation with high uncertainty and Weibull likely to be well within the confidence intervals



⊙ Numbers at risk? Which curve provides the better fit? Is Palmer an appropriate choice for validation? Why or why not?

Source: Figure 1, page 16 of ERG report

Company's revised base case with Commercial Medicines Unit contract price

- CMU price: national available price negotiated through 4 regions in the NHS
- Base case cost effectiveness results based on SHARP trial

	Sorafenib	BSC	Incremental
Total costs (£)	[CIC]	[AIC]	[CIC]
Life years gained	[AIC]	[AIC]	[AIC]
QALYs	[AIC]	[AIC]	[AIC]
ICER (£/QALY)			£43,808

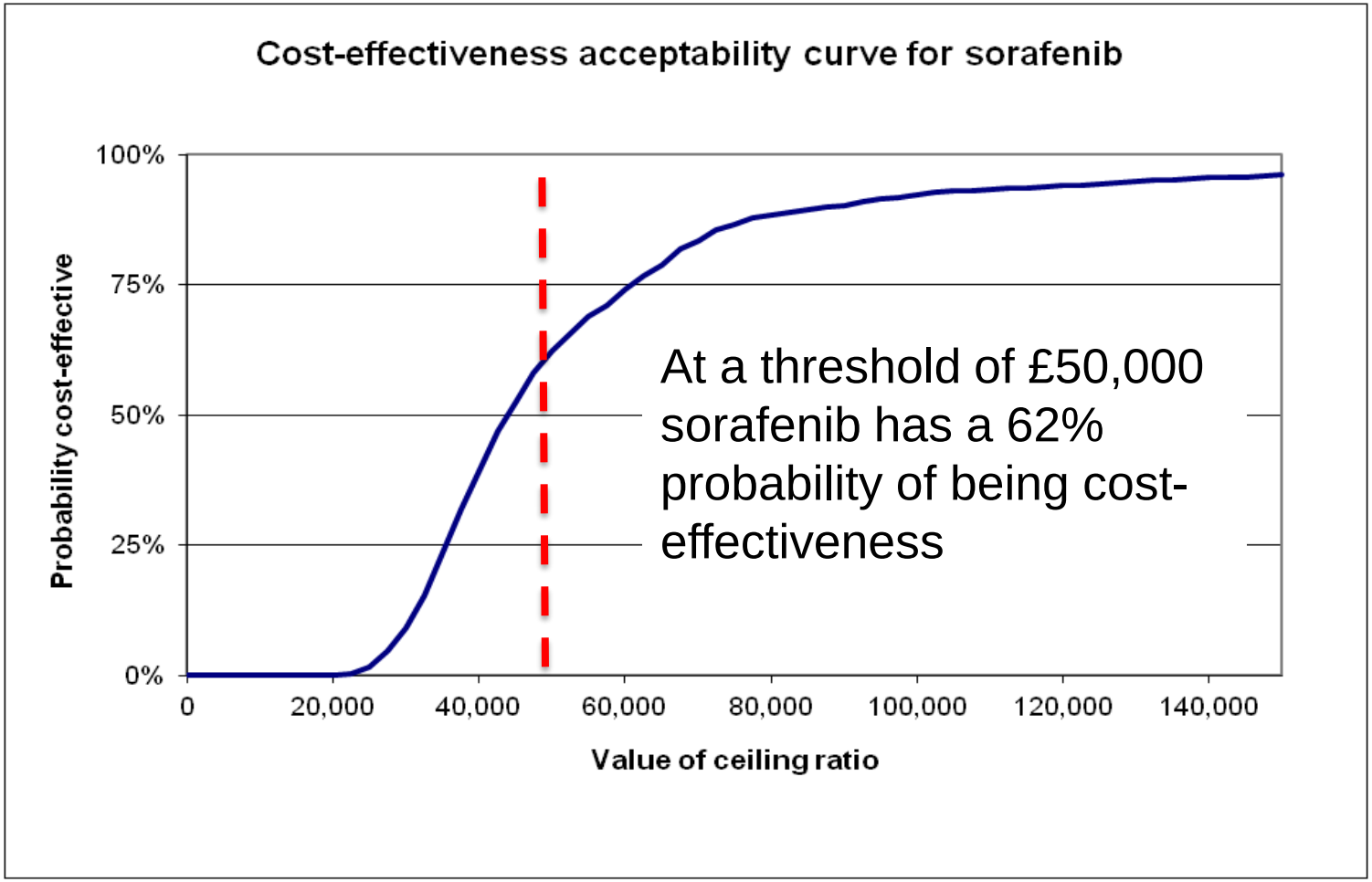
Abbreviations: BSC, best supportive care; CMU, commercial medicines unit; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

Source: Table 6, page 23 of the company submission.

Company's one-way sensitivity analysis with CMU price (base case £43,808)

Variable (table 7, company's submission)	Low value 95%	High value 95%	Low	High
			ICER (£/QALY)	
Overall survival sorafenib lognormal mean	[AIC]	[AIC]	[AIC]	[AIC]
Overall survival Sorafenib lognormal standard deviation	[AIC]	[AIC]	[AIC]	[AIC]
Overall survival BSC lognormal mean	[AIC]	[AIC]	[AIC]	[AIC]
Overall survival BSC lognormal sigma	[AIC]	[AIC]	[AIC]	[AIC]
Utility during first-line treatment with sorafenib before progression	[AIC]	[AIC]	[AIC]	[AIC]
Utility during BSC before progression	[AIC]	[AIC]	[AIC]	[AIC]
Time-to-progression sorafenib mean	[AIC]	[AIC]	[AIC]	[AIC]
Utility during best supportive care	[AIC]	[AIC]	[AIC]	[AIC]
Cost of routine follow-up for patients on active treatment after progression	[AIC]	[AIC]	[AIC]	[AIC]
Time-to-progression sorafenib sigma	[AIC]	[AIC]	[AIC]	[AIC]

Company's probabilistic sensitivity analysis with CMU contract price



Probabilistic base case

ICER = £43,408

Source: Table 10 and Figure 1, pages 28–29 of the company's submission

Company's "additional supporting analyses" with CMU contract price, 2014-15 costs and updated resource use

- Supporting analysis 1:
  - SHARP trial (original submission), committee's preferred TA189 treatment cost assumptions
  - ICER = £39,162 per QALY gained
  - See Appendix 6 of company's submission
- Supporting analysis 2:
  - Real world study (Palmer et al. 2013)
  - Committee's preferred TA189 treatment cost assumptions
  - ICER = £20,556 per QALY gained
  - See Appendices 3 and 5 of company's submission

ERG's exploratory analyses

- New evidence submitted by the company (Palmer, GIDEON) could be used only in a supportive manner and not in the model
- Log-normal might fit better in some cases but Weibull still retains plausibility and should be considered
- ERG's preferred assumptions (SHARP trial data):
  - Updated costs: costs relevant to time decision is made
  - Pooled resource use: likely to be more robust than new (opinion of 3 physicians) and original estimates (4 physicians)
  - Independent assessment of time to progression: less prone to bias, and published
- Scenario analyses using SHARP trial data:
  - Pooled old and new resource use estimates
  - Weibull distribution for overall survival
  - Independent assessment of time to progression

⊙ Is it appropriate to pool estimates? Weibull or log-normal? Investigator or independent assessment?

ERG's exploratory analyses

Source: table 16, page 46 of the ERG report		QALYs		Costs(£)		ICER (£/QALY)
		Total	Inc.	Total	Inc.	
Company's base case (investigator assessment + updated costs + resource use)	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£39,162
Weibull	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£58,287
Independent assessment	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£45,468
Using pooled resource use estimates						
Lognormal	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£45,372
Weibull	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£66,873
ERG's preferred assumptions (independent assessment + pooled resource use estimates)						
Lognormal	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£51,208
Weibull	BSC	[AIC]		[AIC]		
	Sorafenib	[AIC]	[AIC]	[CIC]	[CIC]	£71,276

Issues for discussion

Generalisability

- Extrapolation was a key driver of cost effectiveness - the company has tried to validate modelling choices –
  - do the 2 new studies reflect the population in SHARP?

Extrapolation

- Which extrapolation best fits the data?
  - log-normal to extrapolate overall survival and progression free survival as per company?
  - Weibull to extrapolate overall survival and progression free survival as per ERG?
- What uncertainties or omissions remain?
  - investigator or independent assessment?

General issues for discussion

- Have all the committee's preferred assumptions been sufficiently addressed?
- What are the most plausible ICER plausible?
- Should sorafenib be:
  - recommended for routine commissioning in the NHS?
  - not recommended for routine commissioning in the NHS?
  - recommended for use in the Cancer Drug Fund (CDF)?
- Is there a case to be made for inclusion in the CDF?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Submission for the re-consideration of sorafenib (TA189) for the treatment of advanced hepatocellular carcinoma under the proposed CDF criteria

26 February 2016

Contents

Abbreviations

AC	Appraisal Committee
AE	Adverse Event
AIC	Akaike Information Criteria
BCLC	Barcelona Clinic Liver Cancer (classification system)
BIC	Bayesian Information Criterion
BSC	Best supportive care
CDF	Cancer Drugs Fund
CR	Complete response
CMU	Commercial Medicines Unit
FACT-Hep	Functional Assessment of Cancer Therapy - Hepatobiliary (questionnaire)
FHSI-8	Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index Questionnaire
GIDEON	A Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
KM	Kaplan Meier
LYs	Life-years
LYG	Life-years gained
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RWE	Real-world-evidence
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TTP	Time to progression
UK	United Kingdom

Executive summary

Sorafenib (Nexavar®) was assessed by NICE for use in hepatocellular carcinoma (HCC) in 2009 using evidence from the SHARP study (1). The 'most plausible' ICER for sorafenib was above the £50K/QALY threshold at the list price (£64,800/QALY) and original PAS price (£52,600/QALY).

This submission presents the cost-effectiveness of sorafenib using a new CMU contract price (representing a [redacted] discount to the list price) and uses the Appraisal Committee's preferred assumptions to provide an updated 'most plausible' ICER. The updated cost per QALY is £43,808 which represents a 16.7% improvement compared to 2009.

During the 2009 appraisal the extrapolation curve was highlighted as an area of uncertainty. The lognormal curve was accepted by the Appraisal Committee and was used in the base case, however, it was commented that the Weibull curve might also provide an acceptable fit to the data. The evidence base has grown since 2009 and two pieces of real-life data are presented in this re-submission

1) UK real-life clinical data (Palmer et al 2013)

2) The GIDEON observational study (data on file)

Both data sources show that a small proportion of patients survive for an extended period of time, indicating that the Weibull curve does not fit with the survival observed in clinical practice and that the lognormal curve is indeed a better fit. This new survival data provides confidence in the base case results originally presented.

The UK real-life data published by Palmer (2013) also provides the best indication of the effectiveness of sorafenib as it would be used in the NHS. A cost-effectiveness analysis using the efficacy data from this study, the Appraisal Committees preferred assumptions and updated resource use data and costs, provides an ICER of £20,556. The improved ICER compared to the SHARP study is due to the better overall survival results observed in clinical practice.

Treatment with sorafenib is recognised as the standard of care for patients with advanced HCC (2-4) and is still the only treatment for this population that has proven

a survival benefit in a clinical trial. Other than best-supportive care there are no options other than sorafenib for this patient group.

Using the new CMU contract price the most plausible ICER is £43,808 which supports it as a cost-effective use of NHS resources. Clinical experience gained over the last 6-7 years supports the significant benefit sorafenib provides for this patient group.

1 Introduction

1. All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2. In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3. The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4. The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5. A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6. Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7. The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8. Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9. The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

Brand name	Nexavar®
UK approved name	Sorafenib
Therapeutic class	Multikinase inhibitor

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

A Commercial Medicines Unit (CMU) Framework Agreement was developed in order to replace a previous complex patient access scheme (PAS), submitted to support the original submission in 2009 for sorafenib in patients with advanced HCC who are not suitable for treatment with surgical or loco-regional therapies. Details of the framework agreement can be found in Appendix 8.

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

The current list price for a 112-tab pack of 200mg of sorafenib (28-day supply) is £2980.47. A nationally available discount to the list price is available through a CMU Framework Agreement. Sorafenib is currently available via this contract at a price of [redacted] excluding VAT. Full details of the CMU Framework Agreement can be found in Appendix 8.

Upon a positive recommendation there will be a further reduction via the CMU Framework Agreement, resulting in a contract price of [redacted] excluding VAT.

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

The CMU Framework Agreement applies to the whole licensed population.

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Not applicable.

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The CMU Framework Agreement applies to the whole licensed population.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

The CMU Framework Agreement is not restricted to a sub-population.

3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

The CMU contract price is a discounted purchase price and does not require rebates

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional collection of information will be required.

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

Not applicable as the CMU contract price represents a discount to the list price

3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

The CMU contract price will be in place from the date of guidance publication, until NICE next reviews the guidance for sorafenib and a final decision has been published on the NICE website. Please note, the review date specified in the technology appraisal guidance indicates the date that the guidance is eligible for review.

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues are foreseeable under the CMU Framework Agreement.

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration

forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Before being told the discount price trusts will be required to sign a simple confidentiality agreement in line with the CMU Framework Agreement process.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

Not applicable.

4 Cost effectiveness

Introduction

To allow consideration of both the base case of the original 2009 economic model (stipulated by the guidance), and new evidence that became available subsequent to the 2009 original submission, this document presents two sets of analyses:

1. New Commercial Medicines Unit (CMU) contract price in the original model with the Appraisal Committee preferred assumptions

In line with the methodological requirements for this appraisal, the base case of this analysis (presented in this chapter) is based on the economic model submitted for the original appraisal in 2009, with the exception of the following changes only:

- implementation of a new CMU contract price (detailed in Section 3.3)
- implementation of the Appraisal Committee's preferred assumptions for the 2009 original submission, presented in Table 1.

Results from these analyses are presented in Section 4.6- 4.9

2. Additional supporting analysis

To allow further exploration of uncertainty (whilst adhering to the Appraisal Committee's preferred assumptions), an adaptation of the original model has been provided, which provides cost-effectiveness evidence based on the model described above, with the following additional changes:

- Updated with 2015 resource utilisation evidence and 2014-2015 unit costs (2016 treatment costs) (see Appendix 4 for methodology)
- Updated to allow consideration of an independent RWE comparative study, Palmer (2013), conducted in UK clinical practice (Appendix 3), which was identified as part of the clinical systematic review (SR) update (findings of the SR are reported in Appendix 7)

Results from these analyses are presented in Appendix 5 (Palmer 2013) and Appendix 6 (SHARP)

Two economic models have therefore been submitted to inform this appraisal:

- Nexavar_HCC_2009_base_case_ACIC.xls corresponds with the base case analysis; i.e. the original model submitted in 2009.
- Nexavar_HCC_2016_scenario_ACIC.xls corresponds with the updated model; i.e. updated resource use and costs

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

4.1.1 Changes in line with Appraisal Committee's preferred assumptions

The changes made to the 2009 economic model carried out in line with the Appraisal Committee's preferred assumptions are presented in Table 1.

Table 1: Changes to clinical and cost assumptions of 2009 sorafenib model in line with Appraisal Committee's comments

Original sorafenib model, 2009	Appraisal Committee's preferred assumption	Changes made to sorafenib model
Sorafenib treatment costs were not accounted for post-progression	*"The Committee considered that the cost of post-progression sorafenib treatment was removed from the model but that the benefits were not adjusted. It agreed that, because in clinical practice the benefit from post-progression treatment is likely to be small, retaining the benefits in the model would have a minimal effect on the ICER."*	Post-progression costs have been incorporated into the original 2009 model. • The costs for 7.7% of patients who continued sorafenib treatment post-progression in the SHARP (1) trial have been incorporated • Changes have been implemented in cell AV247 of the 'Model' tab.
Treatments costs were calculated for 30 day periods rather than the actual cycle length (30.44 days)	*"The Appraisal Committee agreed that treatment costs should be based on the actual length of the model cycle."*	Treatment costs calculated based on the actual model cycle length (30.44 days) have been incorporated into the original 2009 model • Changes have been implemented in cell R24 of the 'Default_cost' tab.

In addition to the changes outlined in Table 1, one further change included the incorporation of an updated CMU contract price, which is described in Section 3.3. Details of the cost of sorafenib (per cycle) with the previous complex PAS (as offered in the original submission) and new CMU contract price are presented in Table 2.

Table 2: Comparison of sorafenib treatment cost with old PAS (2009 submission) and new CMU contract price (2016 submission) with cycle length changed in line with AC preferred assumptions

Submission	Cost (£) per cycle with commercial agreement
2009	[redacted]
2016	[redacted]β

Based on a cycle of 30.4 days, and a mean dose of sorafenib of 710.5mg per day per patient per day (observed during the SHARP study(1)); ¶ PAS: Patient access scheme; β: Commerical Medicines Unit contract price

4.1.2 Other areas of uncertainty highlighted by Appraisal Committee in 2009 submission

For other assumptions where the Committee has highlighted uncertainty, but where no preferred assumption was stated, no changes to the model have been made, however, further information has been provided to support the manufacturer's original assumptions (Table 3, Appendix 1 (data from the original submission), Appendix 2 (details of the GIDEON (5) study) and Appendix 3 (details of Palmer 2013 (6)).

Table 3: Responses to other preferred assumptions of Appraisal Committee

<table>
<tr><th>Assumptions, manufacturer's 2009 economic model</th><th>Appraisal Committee's Comments</th><th>Method to address uncertainty for 2016 submission</th></tr>
<tr><td>Extrapolation of OS /TTP: The lognormal distribution was used to extrapolate survival data and TTP for base case results</td><td>"The Committee concluded that, although the lognormal curve provided a slightly better fit to the observed data, it could not be accepted as the definitive function to extrapolate beyond the data.
The Weibull distribution, which also provided an acceptable fit, should also be considered in any consideration of uncertainty."</td><td>Changes to model: none

Justification for lognormal distribution: New evidence
Since the original submission in 2009, RWE, relevant to UK clinical practice (identified systematically and previously unpublished) has been included that supports the use of the lognormal curve.

• GIDEON (5): Survival data from the GIDEON study (a large long-term prospective observational study of over 3000 patients treated with sorafenib) was used to compare the extrapolated curves employed within the model as a validation exercise to identify the most appropriate distribution.

• The GIDEON data show that the Weibull distribution curve consistently underestimates the actual survival observed in the study. Full details of the GIDEON study and analyses conducted are presented in Appendix 2.

Comparison of SHARP (1) vs. GIDEON: Overall survival
<table>
<tr><th rowspan="2">Parametric distributions</th><th>SHARP RCT 50% survival</th><th>SHARP RCT 30% survival</th><th>SHARP RCT 20% survival</th><th>GIDEON study 50% survival *</th><th>GIDEON study 30% survival *</th><th>GIDEON study 20% survival *</th></tr>
<tr><th>Days+</th><th>Days+</th><th>Days+</th><th>Days</th><th>Days</th><th>Days</th></tr>
<tr><td>Weibull</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td></tr>
<tr><td>Lognormal</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="7">*Kaplan Meier OS data ITT analysis visual inspection (approximate survivors)</td></tr>
</table>
• Palmer 2013 (6): Palmer (2013), is an independent retrospective study of patients treated with sorafenib in the two largest specialist hepatobiliary oncology units in the UK. Follow up in this study was longer than in the SHARP study and also suggests that use of the Weibull curve to extrapolate survival from the SHARP trial is overly pessimistic. Details of the Palmer 2013 study and the methodology behind these analyses are presented in Appendix 3, with a scenario analysis considering cost-effectiveness utilising the Palmer 2013 efficacy data presented in Appendix 5.</td></tr>
<tr><td>TTP assessment: The base case was based on investigator assessment</td><td>"The Appraisal Committee noted that the ICER presented in the manufacturer's base case was dependent on investigator assessment</td><td>Changes to model: none
As per the original submission the investigator assessment adopted is supported by the following:
• The investigator assessment was based on a higher number of progression events (independent assessment n=107 investigator assessment n= 181).</td></tr>
</table>

Assumptions, manufacturer's 2009 economic model	Appraisal Committee's Comments	Method to address uncertainty for 2016 submission
	(rather than independent assessment, which was the primary analysis in the SHARP study)"	• The independent assessment was stopped at the first interim analysis as specified in the study protocol.

AIC: Akaike's Information Criteria; BIC: Bayesian Information Criterion; ICER: Incremental cost-effectiveness ratio OS: overall survival; RWE: Real-world evidence; TTP: Time-to-progression; UK: United Kingdom

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

Not applicable.

4.3 Please provide a summary of the clinical [and cost] effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

A summary of clinical and cost-effectiveness parameters are detailed in Table 4.

Table 4: Summary of clinical and cost-effectiveness parameters used in the 2009 model (with incorporation of Appraisal Committee's assumptions)

Clinical evidence	As detailed in the 2009 submission (no changes).
Costs/Resource use	As detailed in original 2009 submission. One change only with regard to comment from Appraisal Committee (Post-progression costs have been incorporated into the 2016 model, Table 1).
Health-Related Quality of Life	As detailed in 2009 submission (no changes).

4.4 Please list any implementation and operation of the patient access scheme/ costs associated with the commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'

There are no additional costs associated with the implementation or operation of the CMU Framework Agreement.

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No additional treatment-related costs are incurred by implementing the CMU Framework Agreement.

Summary cost effectiveness results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

Cost-effectiveness results from the base case (2009 model incorporating the Appraisal Committee's preferred assumptions) using the price in the published 2009 appraisal, and new CMU contract price, are presented in Table 5 and Table 6, respectively. Sorafenib resulted in higher life-years (LYs) and quality-adjusted life-years (QALYs) gained compared with best supportive care (BSC), but had higher overall costs, which resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY using the old PAS price, and an ICER of £43,808 per QALY with the new CMU contract price.

Table 5: Base-case cost-effectiveness results using the old PAS as in the published technology appraisal (2009 model AC preferred assumptions)

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	[redacted]

BSC: best supportive care; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6: New base-case cost-effectiveness results using the new CMU contact price (2009 model AC preferred assumptions)

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	£43,808

BSC: best supportive care; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.7 Please present in separate tables the incremental results as follows.

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance.

Only one relevant comparator has been identified relevant to the decision problem, for incremental results please refer to Table 5 and Table 6.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

One-way sensitivity analysis (OWSA)

A range of one-way sensitivity analyses (OWSA) were undertaken to determine if the base case results (2009 model incorporating Appraisal Committee's preferred assumptions) with the new CMU contract price were sensitive to variations in parameter values independently. As per the original submission, upper and lower bounds for parameters varied within the one-way sensitivity analysis were determined using the 95% confidence intervals for the efficacy parameters, standard deviations for the utilities, and ±30% for disutility estimates and costs. Parameters found to be most sensitive to variation and the resultant effects on the ICER are listed in Table 7.

Table 7: One-way sensitivity analysis (new CMU contract price)

Variable	Low value	High value	Low variation	High variation
			ICER (£/QALY)	ICER (£/QALY)
Overall survival Sorafenib mu	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival Sorafenib sigma	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival BSC mu	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival BSC sigma	[redacted]	[redacted]	[redacted]	[redacted]
Utility during first-line treatment with sorafenib before progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC before progression	[redacted]	[redacted]	[redacted]	[redacted]
TTP Sorafenib mu	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients on active treatment after progression	[redacted]	[redacted]	[redacted]	[redacted]
TTP Sorafenib sigma	[redacted]	[redacted]	[redacted]	[redacted]

The model results were most sensitive to variation in the parameters used within the survival analyses, utility values, and cost of patient follow up. Other parameter variations had smaller impact on the ICER.

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

4.9.1 PSA methodology

The variables included in the probabilistic sensitivity analysis (PSA) are presented in Table 8. Individual parameters were sampled including costs, utilities and adverse events. When no measure of variability was available a standard deviation of +/-30% of the mean was assumed. The extrapolated data for TTP and OS were also sampled using the covariance matrix for each distribution type for TTP and OS in each arm (Table 9).

Table 8: Parameters varied in PSA

Parameter	Mean	SD	Distribution	Alpha	Beta	Source
Utilities						
Utility of sorafenib (first line)	0.6885	0.1183	Beta	9.86	4.46	Bayer data on file 2007 (7)
Utility of sorafenib (after progression)	0.7111	0.1262	Beta	8.46	3.44	Bayer data on file 2007 (7)
Utility of BSC (before progression)	0.6885	0.1183	Beta	9.86	4.46	Bayer data on file 2007 (7)
Utility of BSC (after first line)	0.7111	0.1262	Beta	8.46	3.44	Bayer data on file 2007 (7)
Disutility due to AEs (sorafenib)	-0.0087	-0.00261	Beta	11.22	-1300.47	Calculation (mean), assumption (SD)

Parameter	Mean	SD	Distribution	Alpha	Beta	Source
Disutility due to AEs (BSC)	-0.0087	-0.00261	Beta	11.22	-1300.47	Calculation (assumption), assumption (SD)
Costs						
Active Tx (routine)						
Hospitalisation	£65	£19.43	Gamma	11.11	5.83	£ per cycle/per month (aggregate sum of all resource costs)
Medical staff visits	£230	£69.10	Gamma	11.11	20.73	
Lab tests	£124	£37.24	Gamma	11.11	11.17	
Radiological tests	£61	£18.22	Gamma	11.11	5.47	
Active Tx (after progression)						
Hospitalisation	£266	£79.87	Gamma	11.11	23.96	£ per cycle/per month (aggregate sum of all resource costs)
Medical staff visits	£480	£143.88	Gamma	11.11	43.16	
Lab tests	£30	£9.11	Gamma	11.11	2.73	
Radiological tests	£78	£23.44	Gamma	11.11	7.03	
At progression - one off cost						
Hospitalisation	£0	£0.00	n/a	n/a	n/a	n/a
Medical staff visits	£0	£0.00	n/a	n/a	n/a	
Lab tests	£104	£31.34	Gamma	11.11	9.40	£ per cycle/per month (aggregate sum of all resource costs)
Radiological tests	£134	£40.09	Gamma	11.11	12.03	
BSC – first line						

Parameter	Mean	SD	Distribution	Alpha	Beta	Source
Hospitalisation	£151	£45.36	Gamma	11.11	13.61	£ per cycle/per month (aggregate sum of all resource costs)
Medical staff visits	£225	£67.61	Gamma	11.11	20.28	
Lab tests	£124	£37.24	Gamma	11.11	11.17	
Radiological tests	£61	£18.22	Gamma	11.11	5.47	
BSC – (prior to disease progression)						
Hospitalisation	£386	£115.77	Gamma	11.11	34.73	£ per cycle/per month (aggregate sum of all resource costs)
Medical staff visits	£364	£109.34	Gamma	11.11	32.80	
Lab tests	£30	£9.11	Gamma	11.11	2.73	
Radiological tests	£78	£23.44	Gamma	11.11	7.03	
Probability of adverse events						
Sorafenib	0.069	0.005	Beta	160	2174.67	per cycle
BSC	0.056	0.005	Beta	118	1972.23	
Adverse event costs						
Sorafenib	£131.58	£39.47	Gamma	11.11	11.84	£ per cycle/per month (weighted average cost per treatment arm from SHARP trial (1))
BSC	£216.96	£65.09	Gamma	11.11	19.53	
Death	£0.00	£0.00	n/a	n/a	n/a	N/A

AEs: adverse events; BSC: best supportive care; SD: standard deviation.

Table 9: Variance covariance matrices used to sample lognormal regression (TTP and OS)

	Sorafenib		BSC	
TTP	***const***	***ln sigma***	***const***	***ln sigma***
const	0.004267		0.002534	
ln sigma	0.000836	0.002994	0.000283	0.002373
OS	***const***	***ln sigma***	***const***	***ln sigma***
const	0.00701893		0.00449	
ln sigma	0.00241541	0.0041413	0.001211	0.003221

OS: overall survival; TTP: time to progression

4.9.2 PSA results

Using the new CMU contract price, probabilistic outputs are aligned with deterministic, resulting in an ICER of £43,408. Probabilistic sensitivity analysis results are presented in Table 10.

Results of the PSA are illustrated on the cost-effectiveness plane (Figure 1), and the cost-effectiveness acceptability curve (Figure 2).

At a willingness-to-pay threshold of £50,000 sorafenib is 62.2% likely to be cost-effective with the new CMU contract price.

Table 10: Probabilistic sensitivity analysis results (new CMU contract price)

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	£43,408

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Figure 1: Cost effectiveness scatter plane (new CMU contract price) - £50,000/QALY threshold

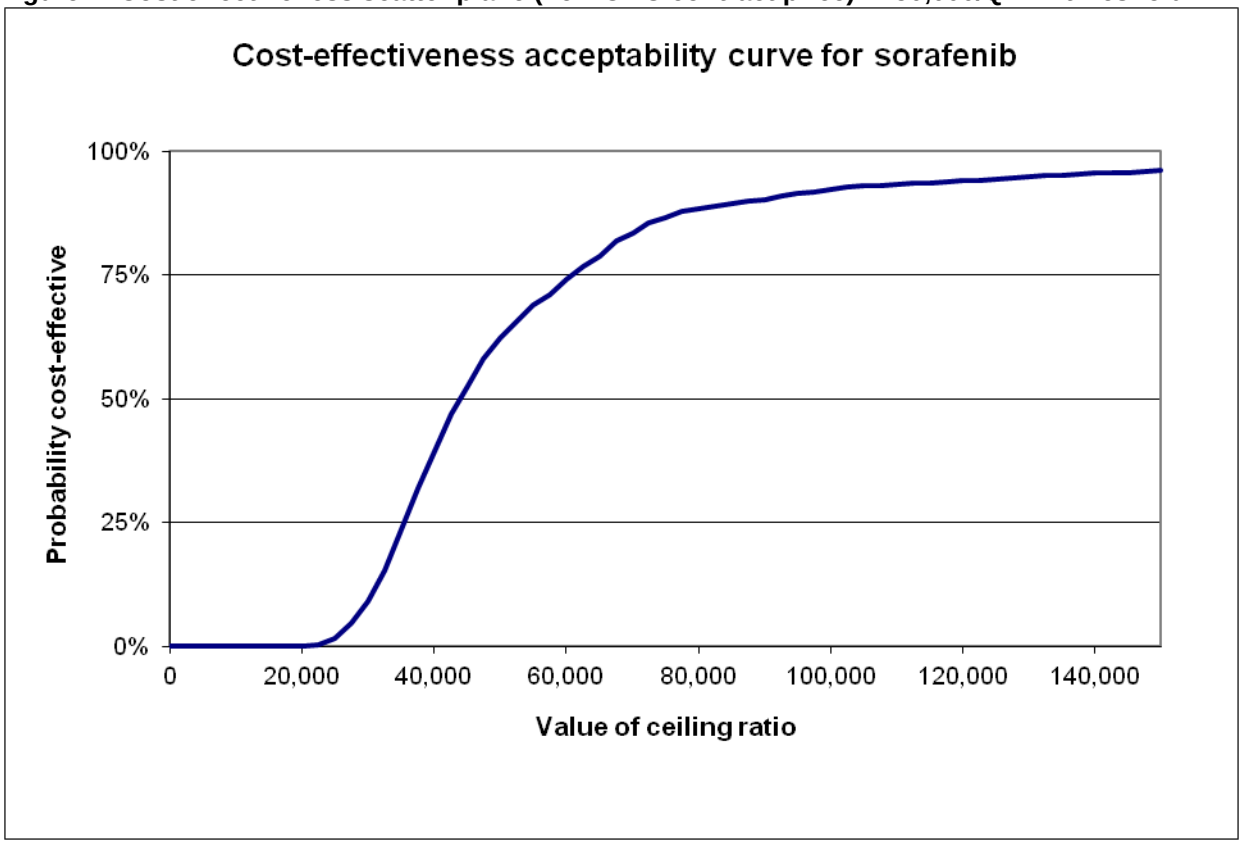
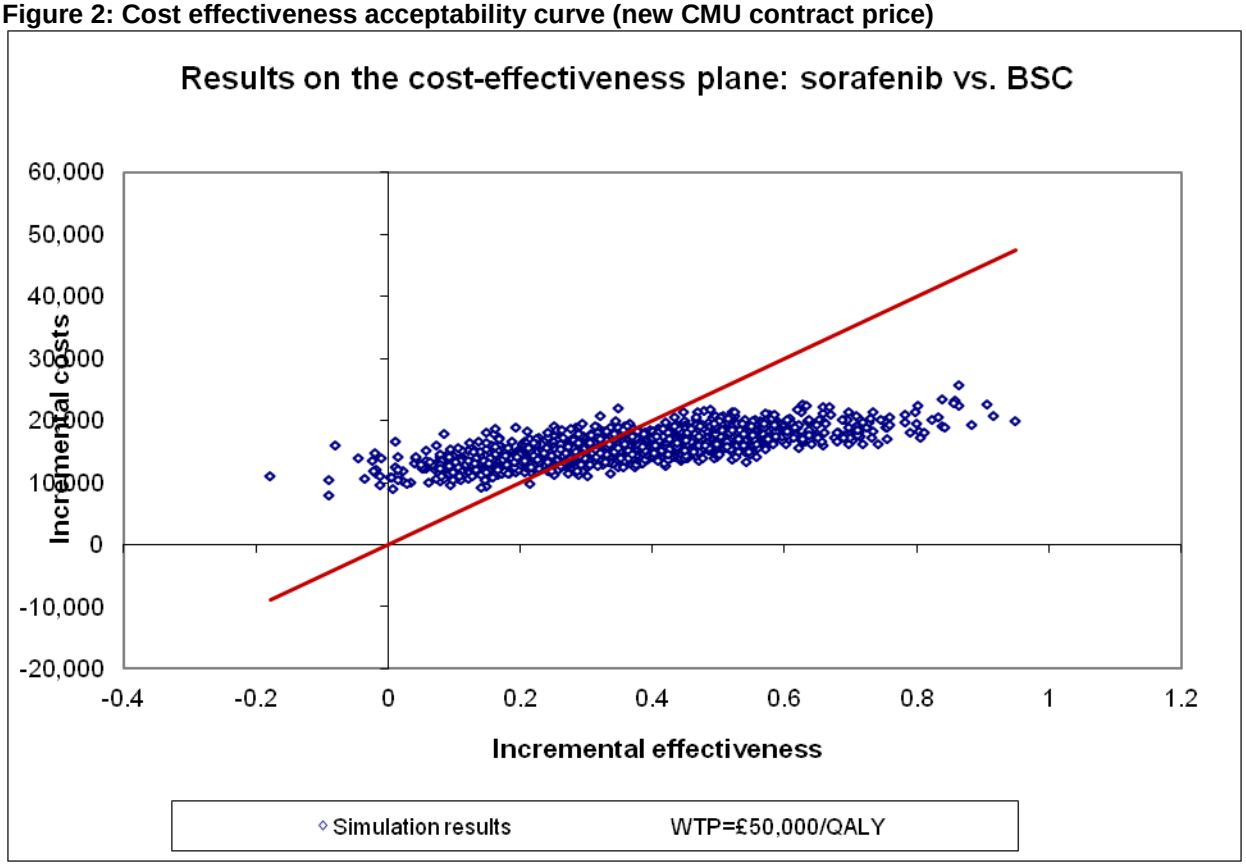


Figure 2: Cost effectiveness acceptability curve (new CMU contract price)



4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not currently available.

5.3 Details of outcome-based schemes

5.4 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.5 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.6 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.
- Not applicable

5.7 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.8 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.9 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.9.1 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)

- the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
- the anticipated results based on the expected new evidence and the proposed higher price.2

Not applicable.

5.9.2 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted. List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

Appendix 1: Data from the original submission to support the selection of distribution curves for OS

Data from the orignal submisison in support of the lognormal are summarised below and further supporting evidence from the GIDEON (5) and Palmer 2013 (6) studies are presented in Appendix 2 and Appendix 3 respectively.

SHARP study, validation of lognormal curve

AIC and BIC

The Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC) results for overall survival (OS) for lognormal and Weibull are presented in Table 11. As indicated by the lower AIC and BIC values, the lognormal provided the closest fit.

Table 11: AIC and BIC results from the extrapolation of the OS SHARP (1) trial data for sorafenib versus best-supportive care

	Sorafenib		Best supportive care	
	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike's Information Criteria; BIC: Bayesian Information Criterion.

Model validation - Overall Survival

Data points from the fitted model and observed outcomes from the SHARP (1) OS Kaplan-Meier were compared as a validation exercise. Approximately half ([redacted] for sorafenib, [redacted] for BSC) of the patients died by [redacted] and [redacted] months ([redacted] and [redacted] days) in the sorafenib and best supportive care (BSC) arm of the model respectively, which compares well to the median survival of [redacted] and [redacted] days for sorafenib and BSC respectively in the clinical trial (Table 12).

Table 12: Median Overall survival

	OS (SHARP trial) (days)	OS from model (days)
Sorafenib	[redacted]	[redacted]
BSC	[redacted]	[redacted]

BSC: best supportive care; OS: overall survival

The lognormal curve was found to be superior to the Weibull curve in the objective statistical goodness-of-fit tests conducted, resulting in both lower AIC and BIC values. A further validation of the fitted lognormal curve against OS outcomes observed in the SHARP trial confirms lognormal as the most appropriate fit.

Appendix 2: GIDEON: A Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (5)

1.1 Overview

Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) (5), was an international prospective, open-label, multi-centre, non-interventional study conducted in over 3,000 outpatients globally with unresectable hepatocellular carcinoma (HCC).

Participants were candidates for systemic therapy in whom a decision to treat with sorafenib had been made. Patients were followed from the start of therapy with sorafenib to withdrawal of consent, death, or end of study.

Long-term survival data addresses uncertainties highlighted by the Appraisal Committee regarding the extrapolation of overall survival (OS) from the SHARP trial (1). Currently the findings presented are unpublished and available as a clinical study report only.

A validation exercise conducted confirms the alignment between projected survival using the lognormal distribution and that observed within the GIDEON study. Extrapolations presented using both the lognormal and Weibull curves provides further evidence of the appropriateness of using the lognormal to extrapolate OS data for this population.

These findings strengthen the robustness of the extrapolations from SHARP generated using the lognormal distribution, with analyses showing a minority of patients surviving for substantially longer than the median, and provide further evidence of the appropriateness of extrapolation using the lognormal as opposed to the Weibull.

Section 1.2-1.7 provides a summary of the study, with Section 1.8 presenting the economic analysis.

1.2 Summary methodology for non-randomised/ controlled studies

The primary objective of the study was to evaluate the safety of sorafenib in patients with unresectable HCC who were candidates for systemic therapy under real-life practice conditions.

The secondary objectives included evaluating long-term efficacy including overall survival (OS), progression free survival (PFS) and time to progression (TTP). Table 13 provides a summary of the methodology employed.

Table 13: Summary of methodology for GIDEON

Methodology	GIDEON (5)
Location	International: 376 sites in 39 countries. Countries with highest contribution: United States (17.6%), (15.9%), South Korea (15.1%) and China (10.3%).
Trial design	Multicentre prospective, open-label, non-interventional study.
Eligibility criteria for participants	Outpatients with histologically/cytologically documented or radiographically diagnosed unresectable HCC who were candidates for systemic therapy and for whom a decision to treat with sorafenib had been made.
Settings and locations where data were collected	Conducted in 39 countries and 376 study sites.
Trial drugs Intervention (s) (n=[x] and comparators (n=[x]	Sorafenib: n= 3202, non-comparative study.
Permitted and disallowed concomitant medication	Permitted concomitant medication: Not reported Concomitant medication at baseline was reported for 80.1%, with the most common medications at ATC level 1 addressing alimentary tract and metabolism (54.3%), followed by cardiovascular system (51.9%), anti-infectives for systemic use (26.4%), and blood and blood forming organs (23.4%) Concomitant systemic anti-cancer therapy after initiation of study drug was reported by 5.7% of patients. Concomitant non-systemic treatments (post treatment initiation until end of treatment) were reported for 497 patients (15.5%).
Primary outcomes (including scoring methods and timings of assessments)	Safety: Follow-up visits could be scheduled every eight weeks or at intervals the prescribing physician usually used.
Secondary outcomes (including scoring methods and timings of assessments)	Overall survival, progression-free survival (PFS), time to progression (TTP)

1.3 Inclusion/ Exclusion criteria

At the commencement of study all patients had to meet the inclusion and exclusion criteria are presented below in Table 14.

Table 14: Inclusion/Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Outpatients with histologically/cytologically documented or radiographically diagnosed unresectable HCC who were candidates for systemic therapy and for whom a decision to treat with sorafenib had been made. Radiographic diagnosis needed typical findings of HCC by radiographic method i.e. on multidimensional dynamic computerized tomography (CT), CT hepatic arteriography (CTHA)/CT arterial portography (CTAP) or Magnetic Resonance Imaging (MRI). *2.* Patients had to have signed an informed consent form. 3. Patients had to have a life expectancy of at least 8 weeks. 4. The patient's physician had to be willing to complete and submit CRFs. 5. The physician had to be willing to submit to a site audit with verification of source documents and validation of data reported.	Exclusion criteria had to follow the approved local product information

1.4 Statistical Analysis

All variables were analysed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum were calculated for metric data. Frequency tables were generated for categorical data.

Dropouts, defined as subjects who withdrew from study before reaching the predefined criteria for end of follow-up in the observational period (i.e. adverse event (AE), withdrawal of consent or patient is lost to follow-up), were not replaced for the safety or efficacy evaluations. All safety analyses were based on the safety population which was composed of all patients who received at

least one dose of sorafenib and underwent at least one assessment for follow-up after initiating study medication.

Efficacy analyses were based on the intent-to-treat population, which comprised all patients who received at least one dose of sorafenib (with the exception that, as noted in the statistical analysis plan, missing data were not estimated or carried forward in any statistical analysis).

Sample size determination was based on the primary objective. The plan to enrol and collect data from 3,000 patients with unresectable HCC treated with sorafenib globally was to allow for sufficient evaluation of safety monitoring of all treated patients as well as different subsets of patients enrolled.

Based on other previously conducted large, global, multi-centre sorafenib studies for HCC, specific AEs that were identified as being of interest for further safety monitoring in the GIDEON study had observed overall incidence rates of approximately 1-2%. With this number of patients, it is possible to observe at least 25 patients with a particular AE if the true incidence rate for the AE is 1% (1:100) with approximately 84% probability.

1.5 Patient characteristics

The vast majority of patients (82.2%) in this study were male. Almost half of the patients included in this study (47.1%) were Asian and 40.0% were White. Patients had a mean age of 61.9 ± 12.1 years with a mean body mass index (BMI) of 25.0 ± 4.62 kg/m^2. A large portion of patients had Eastern Cooperative Oncology Group (ECOG) scores of 0 (42.6%) or 1 (39.7%).

At start of therapy the most frequently reported Barcelona-Clinic Liver Cancer (BCLC) stage was C (52.0%), followed by B (19.8%). In 44.3% of patients HCC was confined to liver, in 39.7% extrahepatic spread and in 22.2% of patients vascular invasion was reported. Tumour status at start of therapy was progressive disease in 67.2% of patients, followed by stable disease in 26.5% of patients. The median duration of stable disease at start of therapy was 2.0 months.

At start of therapy, most frequently Child-Pugh status A (1968 patients, 61.5%) and Child-Pugh status B (666 patients, 20.8%) were documented. A total of 74 patients (2.3%) had Child-Pugh status C. The mean Model for End-stage Liver Disease (MELD) score was 9.862 ± 3.791 and the MELD-Na score was 5.043 ± 7.928. The most common MELD and MELD-Na category in patients for which data were available was <10 (MELD: 46.8%; MELD-Na: 52.5%), followed by 10 to < 20 (MELD: 24.3%; MELD-Na: 11.7%).

With regard to the etiology of the underlying disease, most frequently the underlying disease originated from hepatitis B infection (36.5%), followed by hepatitis C infection (32.9%) and alcohol use (26.0%). A summary of patient baseline characteristics is listed in Table 15.

Table 15: Patient baseline characteristics

GIDEON Baseline characteristic	Sorafenib treatment group
Age	61.9 ± 12.1 years
Gender	82.2% male
BMI	25.0 ± 4.62 kg/m²
Ethnicity	Asian (47.1%) White (40.0%)
ECOG score	0 (42.6%), 1 (39.7%)
BCLC stage	C (52.0%), B (19.8%)
CLIP score	Not evaluable (26.6%), followed by 1 (21.7%) and 2 (19.4%)

1.6 Quality assessment of GIDEON

GIDEON provides an opportunity to evaluate and understand global treatment patterns in clinical practice for the treatment of unresectable HCC in a large population.

Whilst the study is not intended to inform estimations of comparative efficacy versus best supportive care (BSC), the large sample and long-term follow-up provide valuable information on long-term outcomes for patients treated with sorafenib which could not be captured in the relevant randomised controlled trials (RCTs).

The international nature of the study means there is scope for heterogeneity versus the relevant RCTs, however when considering the robust sample size and nature of the analyses presented, the study offers a valuable validation of methodology employed for the original submission.

1.7 Results

1.2.1 Primary outcome: Safety

Though this study included patients who could be excluded from clinical trials according to protocols, the overall safety profile of sorafenib observed in this study (conducted in the real life practice, including broader populations than those enrolled in clinical trials) is consistent with the known profile. The treatment-emergent adverse event (TEAE) incidences reported in this study were not remarkably higher than the incidences in other sorafenib studies as well. TEAEs were reported for [redacted] of patients and drug-related TEAEs were reported in [redacted] of patients. The most frequent TEAEs and drug-related TEAEs were diarrhoea [redacted], hand-foot skin reaction [redacted] and fatigue [redacted]. This TEAE profile is in line with the results of the clinical program.

Treatment-emergent serious adverse events (TESAE) were documented in [redacted] of patients. The most frequently experienced were liver dysfunction [redacted] followed by encephalopathy [redacted].

Various TEAEs leading to discontinuation were reported for a total of [redacted] of patients.

Grade 3 AEs were observed in [redacted] patients [redacted] including [redacted] patients [redacted] with drug-related Grade 3 AEs. Grade 4 AEs were observed in [redacted] patients [redacted]. Drug related grade 4 TEAEs were generally low ([redacted] patients ; [redacted]) consistent with previous studies with sorafenib, though this study included poorer and more advanced conditioned patients treated in real practice (including Child-Pugh B patients) who are generally excluded from clinical trials in HCC patients. Unexpected adverse events or substantially higher risk exposure were also not observed.

1.2.2 Overall survival

A summary of efficacy outcomes are presented in Table 16.

The median TTP and OS were [redacted] days and [redacted] days respectively (comparable to the median OS of 10.7 months reported in SHARP (1)). A Kaplan-Meier curve of overall survival is displayed in Figure 3 demonstrating a long survival 'tail' with a percentage of patients surviving for considerably longer than the average, an analysis of this is provided in the following economic analysis (Appendix 2, Section 1.8).

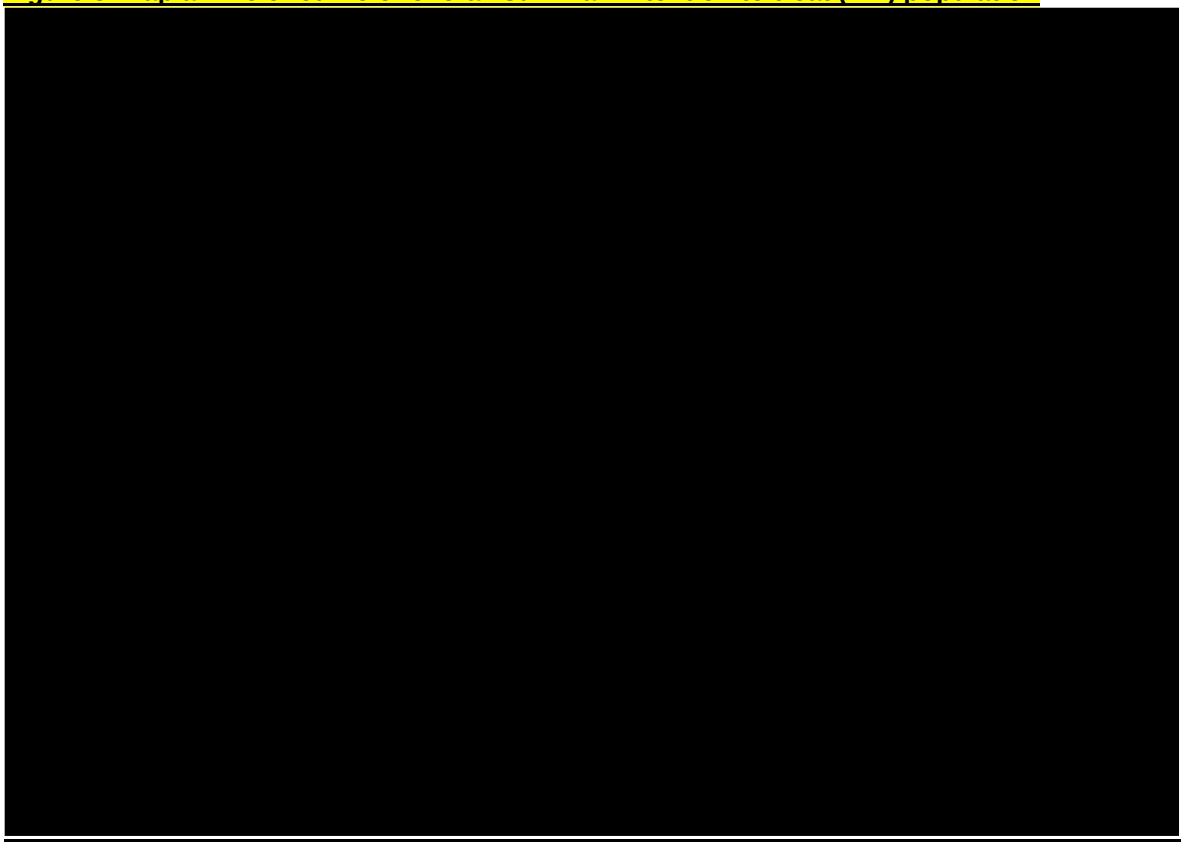
In the absence of long term data this provides a robust estimate and potentially validation of the modelling approach utilised for clinical outcomes that fall outside of the trial period.

Table 16: Summary of outcome variables: Overall survival, progression-free survival and time to progression- ITT

Time to events	N	Number failed	Number censored	Median (days)	95% CI Median (days)
Overall survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Progression free survival determined as disease progression or death (if death occurred before progressive disease), where progression is radiological or clinical progression, whichever is earlier. For time to progression only radiological progression was determined as disease progression.

Figure 3: Kaplan-Meier curve of overall survival- Intention to treat (ITT) population



1.8 Economic evidence

1.8.1 Extrapolation of overall survival

Survival data from the GIDEON study was used to compare the extrapolated curves employed within the model as a validation exercise to assess the suitability of the parametric extrapolations conducted. As per NICE TSD 14 (8) recommendations, a visual inspection using the GIDEON OS Kaplan-Meier graph was carried out to compare the OS modelled for each distribution included in the updated model versus OS observed in the GIDEON study.

As can be seen in Table 17, at median survival (50%) both the lognormal and Weibull distributions are similarly aligned when considered against the observational data. However, at 30% survival, the lognormal distribution provides a much closer alignment to OS as reported from GIDEON. As the survival drops further (20% survival) the relative difference between the observational data and the Weibull curve increases substantially relative to the lognormal curve, which at this point offers a much closer fit.

Though no formal statistical comparison could be conducted and there is heterogeneity between the trial populations from the SHARP (1) and the GIDEON studies, the alignment between projected survival using the lognormal distribution and that observed within the GIDEON trial strengthens the robustness of the results generated using the lognormal distribution.

Table 17: GIDEON study 50%, 30% and 20% survival versus lognormal and Weibull estimated using parametric models with the OS SHARP (1) trial data.

Parametric distributions	SHARP RCT 50% survival	SHARP RCT 30% survival	SHARP RCT 20% survival	GIDEON study 50% survival *	GIDEON study 30% survival *	GIDEON study 20% survival *
	Days+	Days+	Days+	Days		
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]			

*Kaplan Meier OS data ITT analysis visual inspection (approximate survivors)

Appendix 3: Palmer et al. (2013) (6)

Palmer et al (6) is a comparative, independent, real-world UK study that compares OS in patients approved for funding of sorafenib versus those in which funding was declined, and was identified as a relevant study in a systematic literature review conducted (in February 2016) to establish the current clinical evidence base for this submission (Appendix 7).

In this appendix, Sections 1.1-1.6 provide full details of the study and methodology employed, whilst Section 1.7 considers the application of economic evidence and its role in addressing uncertainties previous highlighted by the Appraisal Committee.

Cost-effectiveness results using adjusted extrapolations in place of the SHARP (1) data resulted in £20,556 per QALY for the new CMU contract price, providing further evidence of cost-effectiveness in a UK clinical setting. These are presented in Appendix 5.

1.1 Clinical evidence

Study methodology for non-randomised / non-controlled study is listed in Table 18.

Table 18: Summary of methodology for Palmer (2013) study

Methodology	Palmer 2013 (6)
Location	United Kingdom (UK).
Trial design	Multicentre retrospective study.
Eligibility criteria for participants	Advanced HCC, not suitable for loco-regional therapies, compensated chronic liver disease, performance status 0-2.
Settings and locations where the data were collected	The two largest specialist hepatobiliary oncology units in UK (Kings College Hospital, London, and Queen Elizabeth Hospital, Birmingham).
Trial drugs Intervention (s) (n=[x] and comparators (n=[x]	Sorafenib (patients receiving funding): n=57 (43%). Best supportive care (patients who were declined funding): n=76 (57%).
Permitted and disallowed concomitant medication	Not reported.
Primary outcomes (including scoring methods and timings of assessments)	Overall survival from date of application (of funding for sorafenib therapy).
Secondary / tertiary outcomes (including scoring methods and timings of assessments)	Overall survival in those receiving at least one dose of sorafenib.
Pre-planned subgroups	Not reported.

1.2 Statistical analysis

The primary population for efficacy analysis was the intent-to-treat (ITT) population, those receiving funding (n=57) and those not receiving funding (n=76).

Statistical methodology was not reported in the study publication. The groups were well balanced in terms of baseline characteristics. In order to check for confounding factors, or biases, the authors performed sensitivity analyses with regard to metastatic disease and fibrolamellar variant.

1.3 Patient characteristics

Key demographic and prognostic factors are summarised in Table 19. In general, these were balanced between the two groups and between the two centres, and statistical comparison of each variable revealed no significant differences. Notably, the cohort had a number of adverse prognostic features: patients were predominantly performance status (PS) 1–2; the majority had multifocal disease with the largest lesion being >5 cm; and macroscopic vascular invasion, metastases, and AFP >1000 ng ml^{-1} were each present in approximately one-third of cases. The median time from application to funding decision was 17 days (range 3–260 days).

Table 19: Patient demographic and prognostic factors

	All patients	**Sorafenib funded**	**Best supportive care (i.e. Sorafenib not funded)**
Number of patients	133	57	76
Kings	71	30	41
Birmingham	62	27	35
Male: Female	108 : 25	52 : 5	56 : 20
Median age (range)	62 (16 – 86)	61 (16 – 82)	62 (17 – 86)
PS 0 : 1 : 2 (%)	19 : 49 : 32	20 : 48 : 32	18 : 48 : 34
Child-Pugh A	82%	84%	80%
AFP ≥1000	31%	30%	31%
Multifocal	70%	65%	75%
Largest lesion >5cm	68%	78%	60%
Macroscopic vascular invasion	34%	41%	29%
Extrahepatic metastases	39%	30%	46%

1.4 Quality assessment

The study is a ‘real world’ observational study comparing the overall survival in patients given sorafenib with patients unable to obtain funding for sorafenib who received only best supportive care (BSC).

All patients enrolled in the study came from the UK and, thus, the methodology and results are directly applicable to clinical practice in the UK and the decision problem within this submission. Patients were treated at the two largest specialist hepatobiliary oncology units in UK, where expertise and familiarity with the disease and its treatment options can be expected to be similar and high.

Patients were not randomised to treatment, however, at the outset; neither patient nor clinician would have any knowledge of the treatment they were to receive, as the funding decision was not within their remit. All funding applications were carried out in the same manner. The criteria for application were uniform across both centres and comprised clinical information to indicate that, in the treating clinician’s opinion, sorafenib was the most appropriate therapy – that is, it had a good PS (WHO PS 0–2); well-compensated background chronic liver disease; not a suitable candidate for loco-regional therapies (surgery, transplantation, local ablation, and TACE). On this basis, decisions on whether to fund were not apparently based on clinical variables.

Both patient and investigator would have known what treatment was being given, so there was no blinding of treatment allocation.

The primary population for efficacy analysis was the intent-to-treat (ITT) population, those receiving funding (n=57) and those not receiving funding (n=76).

Baseline demographic and prognostic factors were balanced between the two groups and between the two centres.

The quality of the study was assessed using the Downs and Black checklist (9), a validated checklist for assessing the risk of bias for observational

studies and non-randomised studies (see Appendix 3.1 for checklist questions). The studies were evaluated for: quality of reporting (10 items); external validity (3 items); bias (7 items); and confounding (6 items) using the sub scales of Downs and Black scoring system. The quality index score on the 27-item Downs and Black checklist was 12 out of a possible 30 points (Table 20).

Table 20: Summary of Downs and Blacks Checklist (9) score for Palmer 2013 study

	Reporting										Score
Study name	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Palmer 2013	1	1	1	1	2	1	1	0	0	0	8
	External Validity			**Internal validity - bias**							Score
Study name	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Palmer 2013	0	0	0	0	0	0	0	1	0	1	2
	Internal validity – confounding (selection bias)						**Power**				Score
Study name	**21**	**22**	**23**	**24**	**25**	**26**	**27**				
Palmer 2013	1	1	0	0	0	0	0				2
										Total score	**12**

1.5 Results

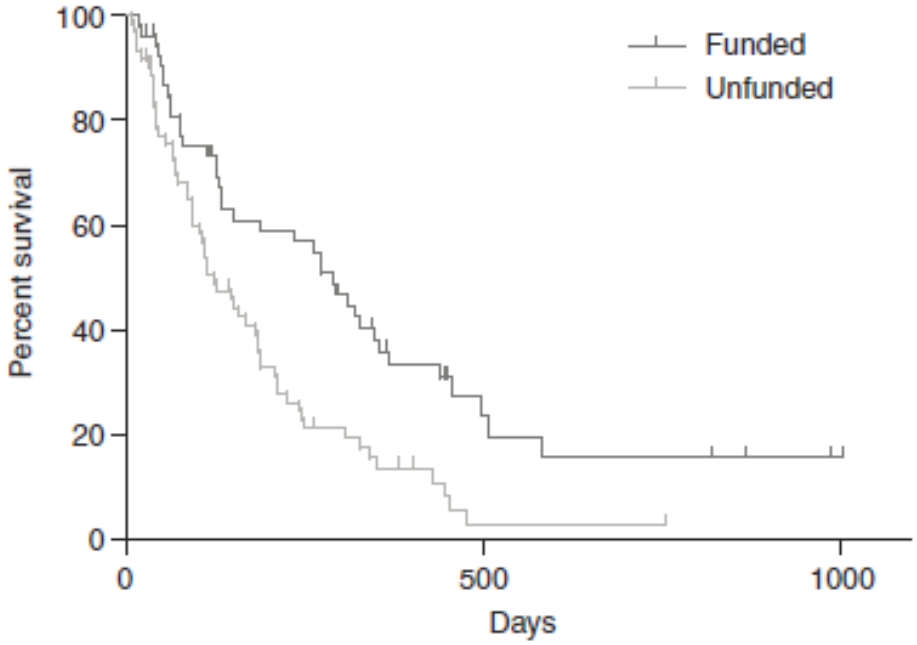
For the primary 'intention-to-treat' analysis, the median overall survival was 4.1 months when funding was declined, and 9.5 months when funding was approved (hazard ratio (HR) 0.48; 95% CI 0.3186–0.7267; P=0.0005; Figure 4).

In 14 of the 57 cases where funding was approved, in the time awaiting the funding body decision, the clinical condition deteriorated such that treatment could not be commenced.

The median survival for the 43 patients who received at least one dose of sorafenib was 10.7 months (HR 0.38; 95% CI 0.25–0.59; P<0.0001). In those receiving sorafenib, the median duration of treatment was 5.1 months. There was a higher proportion of patients with metastatic disease in the unfunded group, which conceivably could negatively influence the survival in this group. However, a sensitivity analysis excluding all patients with metastases did not significantly affect the data, again indicating that differences in survival are

likely due to treatment effects rather than due to imbalances in prognostic variables between the two groups (non-metastatic patients, median survival funded vs unfunded: 8.95 vs 3.7 months; HR 0.51, 95% CI 0.32–0.82; P=0.0061).

Figure 4: Survival proportions in patients for whom an application for sorafenib funding was made



1.6 Authors discussion and conclusion

This study suggests a similar benefit for patients in the UK versus those in trials from Europe and the Far East. Notably, these patients had a number of adverse prognostic features compared with those recruited to the phase III trials, including poorer PS and greater tumour burden. Despite this, the survival advantage for these patients compares favourably to the randomised trials. Of note, the hazard ratio (HR) reported here (0.48) is somewhat better than that reported in the SHARP trial (0.69). This may, in part, be due to the relatively worse outcome for untreated patients reflecting a number of adverse prognostic variables present in this study population, and additionally may reflect the experience of two high-volume liver units and the evolution of experience in managing toxicities and maintaining dose intensity for sorafenib treated patients since the original publication of the trial data. Although

treatment in this study was not randomly assigned, the funding applications were made using the same criteria for suitability for sorafenib, and the baseline demographics between the two groups were generally balanced, suggesting that the improved outcome was due to a treatment effect rather than due to confounding prognostic variables. The data reported here support the use of sorafenib for patients with advanced HCC as clinical and cost-effective interventions.

1.7 Economic evidence

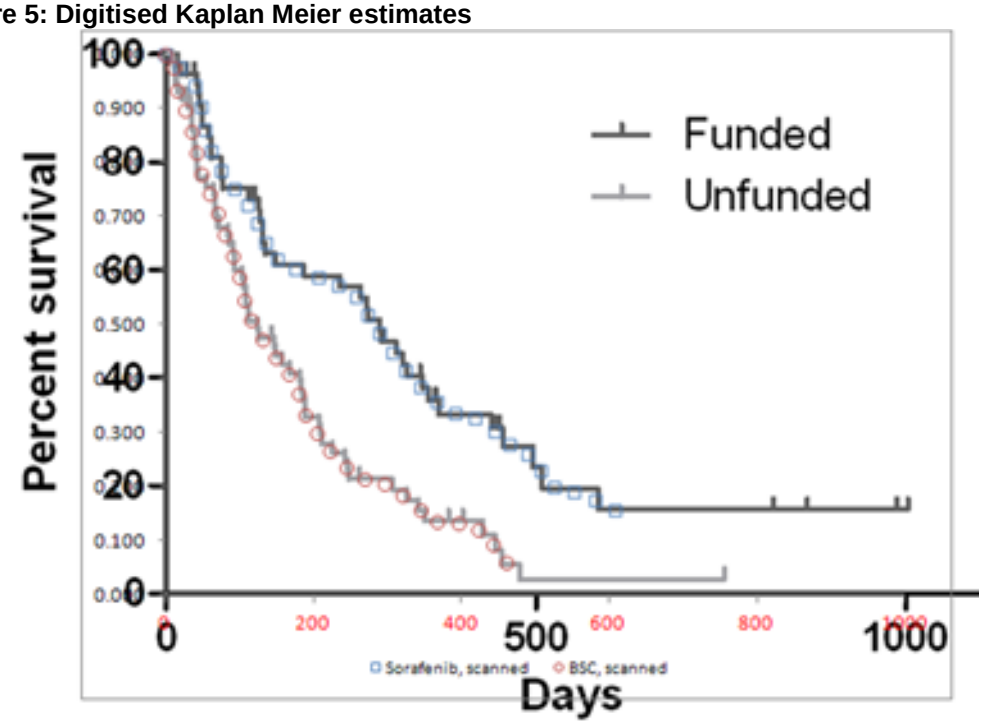
A scenario analysis was undertaken using results from the study to inform alternative parametric extrapolations and the impact of using these modified curves on model results. Kaplan-Meier (KM) estimates for survival were reported as presented in Figure 4.

Time to progression and the mean amount of sorafenib given to patients in the treatment arm were not reported; hence assumptions were required to incorporate this data, as described below.

Based on the overall survival Kaplan-Meier survival analysis and the hazard ratio (HR) of 0.48, it was possible to estimate the mean lifetime OS for the treatment group by estimating a suitable parametric survival model for the BSC group and applying the HR. In order to apply the HR, a parametric function had to be chosen that met the proportional hazards requirement.

The Kaplan-Meier graph reported was scanned, with the precision corresponding to the quality of presentation of the graph in the manuscript. The graph below shows the original KM estimates with the digitized values (shown as O and [illegible] superimposed (Figure 5).

Figure 5: Digitised Kaplan Meier estimates



Subsequently, a lognormal distribution was fitted to the Kaplan Meier estimates for the sorafenib and BSC arms. Figure 6 shows the Kaplan-Meier graph with superimposed lognormal distribution for the sorafenib and BSC arms. Visually, the curves fit the empirical estimates reasonably well with the lognormal distribution fitting closer at the end of the Kaplan-Meier plot, and less accurately at the beginning. Due to a decreasing hazard function with the lognormal distribution, the mean life expectancy estimated with the lognormal approach is longer. A comparison of the fitted model and Kaplan-Meier is presented in Table 21.

Figure 6: Fitting of the lognormal distribution to the sorafenib and BSC arms

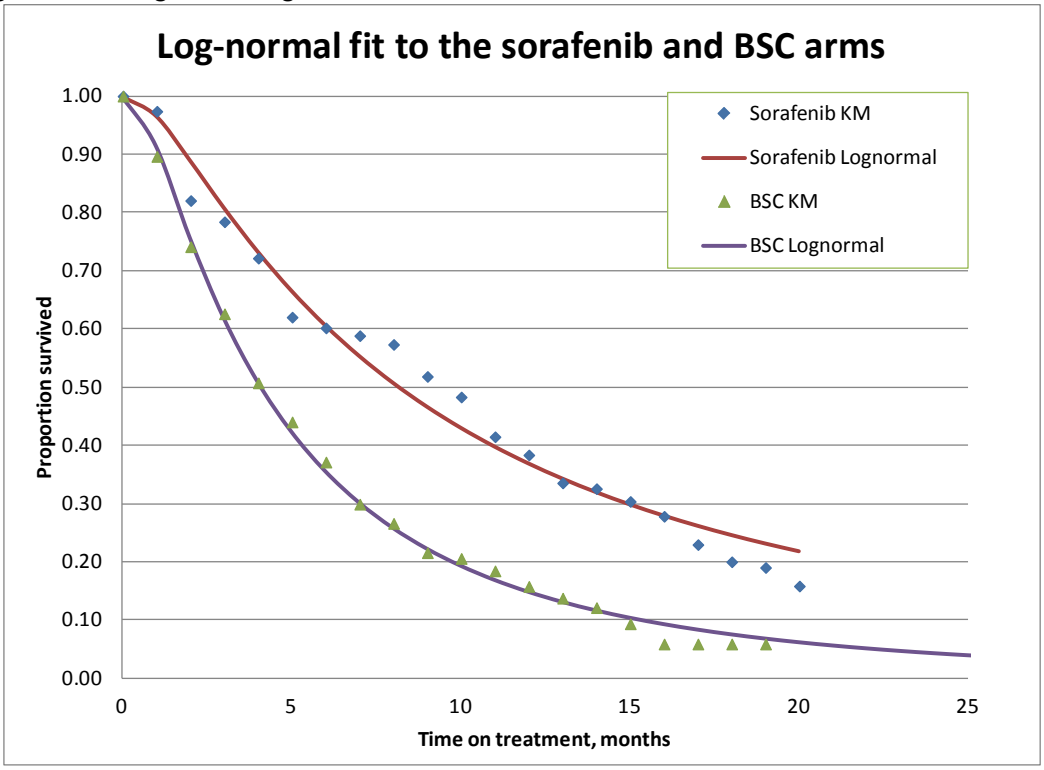


Table 21: Lognormal distribution

	Parametric	Kaplan-Meier
OS BSC, median	[redacted]	[redacted]
OS Sorafenib, median	[redacted]	[redacted]
OS difference median	[redacted]	[redacted]
OS BSC, mean at 14 years	[redacted]	N/A
OS Sorafenib, mean at 14 years	[redacted]	N/A
OS BSC, mean lifetime	[redacted]	N/A
OS Sorafenib, mean lifetime	[redacted]	N/A
OS difference, mean, at 14 year time horizon, years	[redacted]	N/A
OS difference, mean, months	[redacted]	N/A
OS difference (Lognormal, base case)	[redacted]	

Weibull, exponential and log-logistic distributions were also fitted to the Kaplan Meier estimates for the sorafenib and BSC arms. The charts below show the fitted curves for the Weibull, exponential and loglogistic distributions for the sorafenib and BSC arms (Figure 7 and Figure 8).

Figure 7: **Fitting of the Weibull, exponential and loglogistic distributions to the sorafenib arm**

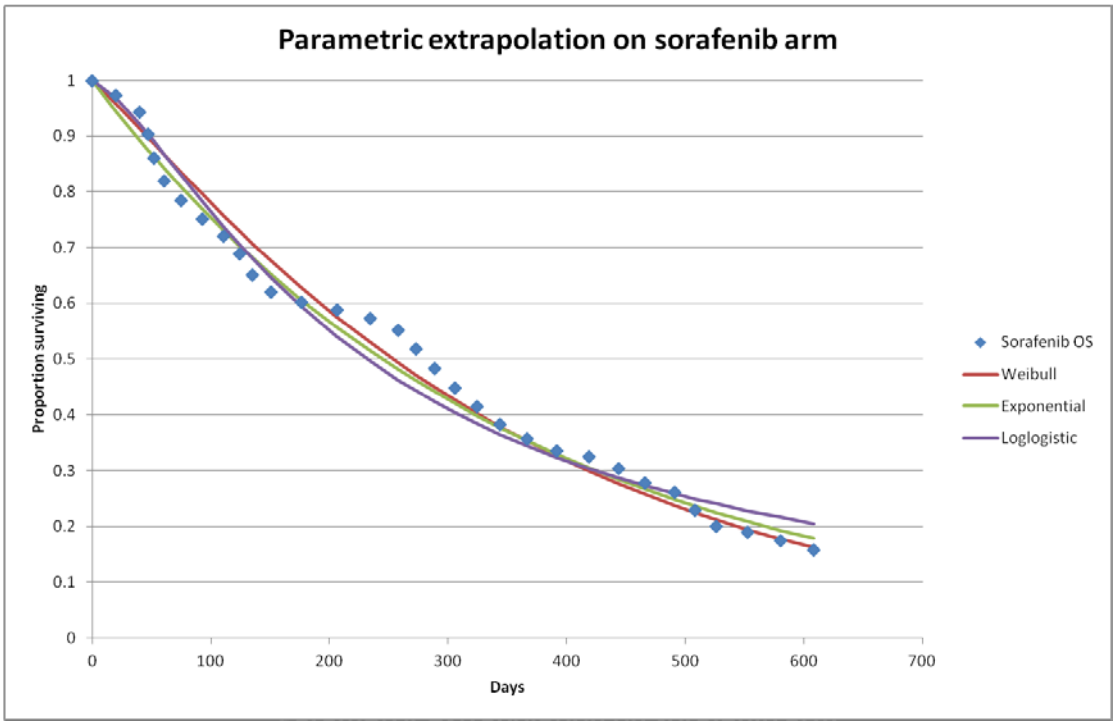
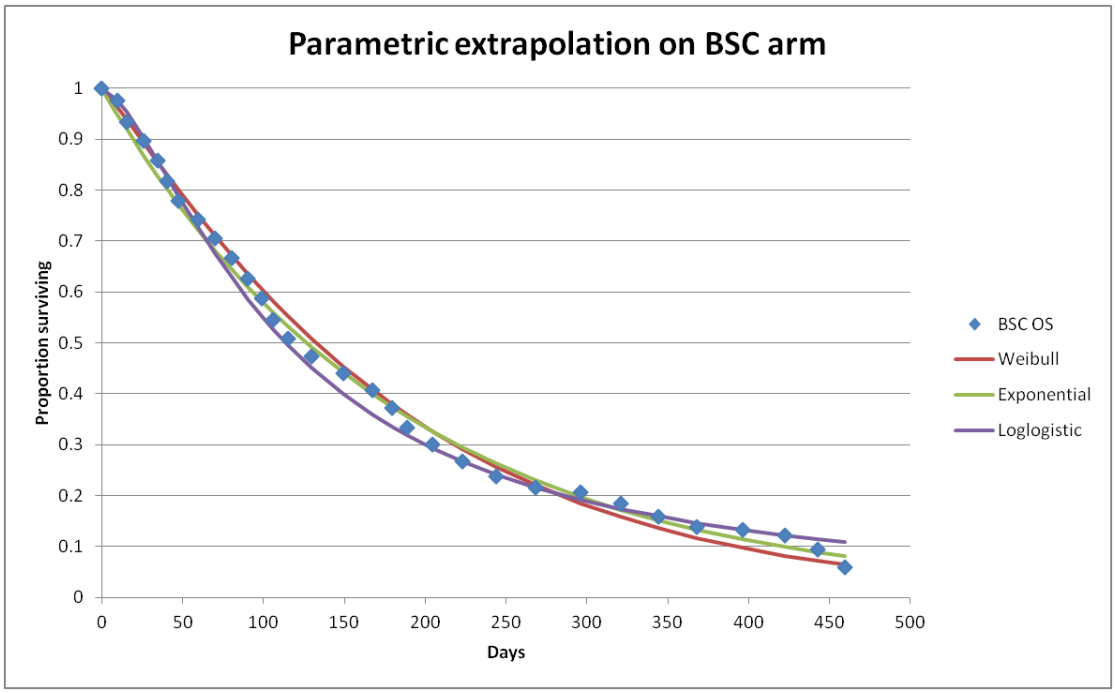


Figure 8: Fitting of the Weibull, exponential and loglogistic distributions to the BSC arm



Visually, all the curves fit the empirical estimates reasonably well; due to a decreasing hazard function with the lognormal distribution, the mean life time estimated with the lognormal approach is longer.

For the current curve fitting exercise, the lognormal and Weibull curves provide better visual fits at different time points when superimposed onto the KM curves, and because a similar proportion of patients survive with each fit until the end of the observed data period, an important element in choosing the most appropriate curve would be the long term disease prognosis.

As indicated by Figure 4, which provides longer term observed data for patients for whom an application for sorafenib funding was made, at around 600 days survival was observed to plateau in patients funded to use sorafenib, corresponding to approximately 18% survival. As evident from these curves it appears that a small proportion of HCC patients treated with sorafenib who survive beyond 600 days may be expected to maintain survival for extended periods (the last observation was made at 1000 days).

As the lognormal curve plateaus faster than the Weibull, this would appear to represent better clinical plausibility in relation to the observations from Figure 4 where no patients died after 600 days, compared with survival decreasing from 22% to 11% with the lognormal, and an even more rapid decline when using the Weibull.

Overall, in both the SHARP (1) and the Palmer study (which had a longer follow-up), the lognormal distribution is considered to be the better fit (using both visual inspection for this study and the AIC and BIC[1] criteria/visual inspection for SHARP). The consistent superior fit of the lognormal distribution could be considered verification that it represents the best form of parametric function to extrapolate the SHARP trial data past the trial observation window.

Further to the above, cost-effectiveness outputs were formally generated using the Palmer adjusted extrapolations in place of the SHARP data alone, resulting in ICERs of £20,556 per QALY for the new CMU contract price, as presented in Table 22. As can be noted, use of the Palmer adjusted data

[1] It was not possible to conduct AIC/BIC analysis on the digitalised OS Kaplan-Meier

resulted in lower ICERs than presented in the base case. Full results are available in Appendix 5.

Table 22: SA cost-effectiveness results using the RWE Palmer study and the CMU contract price for sorafenib

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	£20,556

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Appendix 3.1: Black and Downs checklist questions (9)

The Black and Downs checklist questions used to assess the quality of the study are presented in Table 23.

Table 23: Black and Downs checklist questions

Reporting: "Yes=1," "No=0"	
1	Is the hypothesis /aim /objective of the study clearly described?
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3	Are the characteristics of the patients / samples included in the study clearly described?
4	Are the interventions of interest clearly described?
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? "Yes=2," "Partially=1," "No=0"
6	Are the main findings of the study clearly described?
7	Does the study provide estimates of the random variability in the data for the main outcomes?
8	Have all important adverse events that may be a consequence of the intervention been reported?
9	Have the characteristics of patients lost to follow-up been described?
10	Have actual probability values been reported (e.g. 0.035 rather than <0.5) except where the probability value is less than 0.001?
External validity: "Yes=1," "No=0," "Unable to determine=0"	
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
Internal validity - bias: "Yes=1," "No=0," "Unable to determine=0"	
14	Was an attempt made to blind study subjects to the intervention they have received?
15	Was an attempt made to blind those measuring the main outcomes of the intervention?
16	If any of the results of the study were based on "data dredging" was this made clear?
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18	Were the statistical tests used to assess the main outcomes appropriate?
19	Was compliance with the intervention/s reliable?
20	Were the main outcome measures used accurate (valid and reliable)?
Internal validity - confounding (selection bias): "Yes=1," "No=0," "Unable to determine=0"	
21	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?
22	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?
23	Were study subjects randomized to intervention groups?
24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26	Were losses of patients to follow-up taken into account?
Power: "No=0", "Yes, one measure=1" "Yes, two or more measures=2"	
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%

Appendix 4: Updated costs and resource utilisation

2015 resource utilisation costs

Health state costs

Since the original submission and the subsequent launch of sorafenib, clinicians have had increased experience of using sorafenib in routine UK clinical practice. Revised estimates of resource utilisation were generated based on feedback from a panel of physicians (n=3), to generate up to date estimates of resource use in the model. These revised estimates can be located within the 'Default_cost' tab of the model.

A copy of the resource use survey is provided in Appendix 4.1 along with mean values, standard deviations and lower and upper estimates calculated on the basis of the clinician responses.

Adverse events

Grade 3/4 AE costs were also updated based on the resource use reported by the physicians and publicly available unit costs these are presented in Table 24.

Table 24: Adverse event costs

Adverse events	Total cost (£), 2016	Source
Rash/desquamation	67.65	Calculated based on resource use and cost for staff using 2015 resource use questionnaire and NHS reference unit costs 2014-2015 (10)
Hypertension	188.51	
Fatigue	57.15	
Weight loss	159.02	
Alopecia	17.69	
Diarrhoea	136.15	
Nausea/vomiting	78.20	

Adverse events	Total cost (£), 2016	Source
Hand-foot skin reaction	90.48	
Pain, abdomen	40.15	
Hemorrhage, any event	0.00	

Unit cost update

Unit costs were updated with the most recently available source. Drug costs were extracted from the British National Formulary (version 70, January 2016) (11), whereas all other unit costs were obtained from the following sources National Schedule of Reference Costs (2014-2015) (10) or Personal Social Services Research Unit (PSSRU) (2015) (12).

Unit costs associated with health state resource use are presented in Table 25. Costs of medications are presented Table 26 and Table 27 presents the aggregated cost per month (per cycle) for each treatment phase.

Table 25: Unit costs associated with health state resource use

Resource	Cost (£)	Unit	Source
Medical staff visits			
Oncologist	170.85	Per cycle	NHS National Schedule of Reference Costs 2014-15
Hepatologist	223.35	Per cycle	NHS National Schedule of Reference Costs 2014-15
Gastroenterologist	139.83	Per cycle	NHS National Schedule of Reference Costs 2014-15
Specialist nurse/Macmillan nurse	44.00	Per cycle	PSSRU 2015
Radiologist	137.00	Per cycle	PSSRU 2015
GP	40.00	Per cycle	PSSRU 2015

District nurse	44.00	Per cycle	PSSRU 2015
Palliative care team	144.79	Per cycle	NHS National Schedule of Reference Costs 2014-15
Specialist visit	167.96	Per cycle	NHS National Schedule of Reference Costs 2014-15
Dietician	34.00	Per cycle	PSSRU 2015
Oncologist	170.85	Per cycle	NHS National Schedule of Reference Costs 2014-15
Acute care			
ICU	938.75	Per cycle	NHS National Schedule of Reference Costs 2014-15
General ward	559.94	Per cycle	NHS National Schedule of Reference Costs 2014-15
A&E Admission	131.92	Per cycle	NHS National Schedule of Reference Costs 2014-15
Medical oncology	562.12	Per cycle	NHS National Schedule of Reference Costs 2014-15
Laboratory tests			
AFP Test	1.19	Per cycle	NHS National Schedule of Reference Costs 2014-15
Liver Function Test	1.19	Per cycle	NHS National Schedule of Reference Costs 2014-15
INR	1.19	Per cycle	NHS National Schedule of Reference Costs 2014-15
Complete blood count	3.01	Per cycle	NHS National Schedule of Reference Costs 2014-15
Complete metabolic panel/Biochemistry	16.66	Per cycle	NHS National Schedule of Reference Costs 2014-15

Microbiological examination	6.89	Per cycle	NHS National Schedule of Reference Costs 2014-15
IV rehydration	0.30	Per cycle	BNF January 2016 (accessed February 2016)
Urea and electrolytes (blood urea nitrogen)	1.19	Per cycle	NHS National Schedule of Reference Costs 2014-15
Urea and electrolytes (urine)	1.19	Per cycle	NHS National Schedule of Reference Costs 2014-15
Endoscopy	428.15	Per cycle	NHS National Schedule of Reference Costs 2014-15
Radiological tests			
CT scan: abdominal	101.2	Per cycle	NHS National Schedule of Reference Costs 2014
MRI: abdominal	157.4	Per cycle	NHS National Schedule of Reference Costs 2014
Ultrasound: abdominal	60.7	Per cycle	NHS National Schedule of Reference Costs 2014

Table 26: Cost of medications

Treatment	Cost per mg (£)	Pack price (£)	Pack size	Source
Loperamide (2mg)	0.0358	2.15	30	BNF January 2016 (accessed February 2016)
Metoclopramide (10mg)	0.0033	0.93	28	BNF January 2016 (accessed February 2016)
Domperidone (10mg)	0.0043	1.28	30	BNF January 2016 (accessed February 2016)
Morphine sulphate (10mg)	0.0087	5.20	60	BNF January 2016 (accessed February 2016)
Methylphenidate	0.0183	5.49	30	BNF January 2016 (accessed February 2016)
E45 cream*	5.62	1.00	500	BNF January 2016 (accessed February 2016)
Amlodipine	0.0065	0.91	28	BNF January 2016 (accessed February 2016)
Ensure	2.2600	2.26	1	BNF January 2016 (accessed February 2016)
Codeine phosphate	0.0017	1.40	28	BNF January 2016 (accessed February 2016)
Cyclizine hydrochloride	0.0021	10.65	100	BNF January 2016 (accessed February 2016)
Paracetamol	0.0001	0.94	32	BNF January 2016 (accessed February 2016)

Table 27: Health state costs included in the model

Resource	Cost (£)	SD
Active treatment – routine are		
Medical staff visits	87.62	26.29
Laboratory tests	288.24	86.47
Radiological tests	23.24	6.97
Hospitalisation	39.13	11.74
Active treatment – after progression		
Medical staff visits	64.40	19.32
Laboratory tests	194.68	58.40
Radiological tests	17.41	5.22
Hospitalisation	16.70	5.01
At progression – one-off cost		
Medical staff visits	0.00	0.00
Laboratory tests	0.00	0.00
Radiological tests	22.84	6.85
Hospitalisation	67.46	20.24
BSC – first line		
Medical staff visits	570.37	171.11
Laboratory tests	315.09	94.53
Radiological tests	18.81	5.64
Hospitalisation	16.70	5.01

BSC (palliative)		
Medical staff visits	570.37	171.11
Laboratory tests	289.86	86.96
Radiological tests	3.17	0.95
Hospitalisation	5.84	1.75

Appendix 4.1: Resource questionnaire

IMS works under the rules of the EphMRA International Code of Conduct.

We are currently undertaking an investigation into resource usage during the treatment of advanced hepatocellular carcinoma (HCC) patients that are either unsuitable for surgical or loco-regional treatments or their HCC has progressed after surgery or loco-regional therapies and would very much appreciate your co-operation. These patients are referred to as advanced HCC hereafter.

Our intention is not to sell you anything.

We will comply with all UK laws protecting your personal data and the British Healthcare Business Intelligence Association guidelines. Your responses will be used by us and the sponsoring pharmaceutical company for HTA submissions. Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.

Please be informed that we use your personal data limited to contact details and information about your specialisation in order to conduct market research. We will send you written information about this use.

You can withdraw from the market research at anytime, and you have the right to withhold information, i.e. not answer a question should you wish

All answers that you provide will be treated in the strictest confidence and your identity will not be revealed to any third parties. The results from your interview will be aggregated with those provided by other respondents.

You are about to enter a market research interview. We are now required to pass on to our client details of adverse events that are raised during the course of market research interviews. Should you raise an adverse event in a specific patient or group of patients, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be contacted to ask whether or not you are willing to waive the

confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you contribute during the course of the interview will continue to remain confidential. Are you happy to proceed with the interview on this basis?

Yes [ ] No [ ]

Objectives

To obtain data about the resource use associated with the treatment of patients with non-curative hepatocellular carcinoma (HCC) in the UK.

Background

This questionnaire relates to patients with advanced HCC that are either unsuitable for surgical or loco-regional treatments or their HCC has progressed after surgical or loco-regional therapies We would like you to have this patient group in mind throughout all the questions you see.

We are interested in the resources consumed during two phases of further treatment that a patient may receive. We have classified these as the “pre-progression” and “post-progression” phases of treatment. We are also interested in the resources consumed at the time of progression for those patients on sorafenib which is applied as a one-off cost.

In this questionnaire, we refer to the typical “pre-progression” patient as the patient who hasn’t had further progression from the state described above (patients with advanced HCC that are either unsuitable for surgical or loco-regional treatments or their HCC has progressed after loco-regional therapies.

We then refer to the typical “post-progression” patient who has experienced progression from this state.

Distinguishing between the “pre-progression” and “post-progression” phases of treatment for this patient group will allow us to discern to some extent how resource usage patterns may vary as a patient’s condition and cancer treatment changes.

Structure of the questionnaire

The questionnaire you are about to complete asks first about your specialism and experience. This is followed by a section in which we ask you to think about treatment regimens associated with care for “pre-progression” patients both on sorafenib and best supportive care (BSC) and address resource use associated with testing in this group.

The questionnaire continues with a similar section in which we ask you to consider your “post-progression” patients who have failed on, or discontinued, their “pre-progression” treatment to help us define what treatments and resource usage are given in this group for patients on sorafenib or BSC.

In turn the questionnaire includes a section around the cost at the time of progression for those patients on sorafenib which is considered to be a one off cost.

Finally we go on to ask you about how your patients are managed at the end of their lives. Here we ask you to think about the care given in the home and other settings associated with death.

We would like you to consider typical patient experiences and metrics and so throughout this survey please consider a representative patient within each category. You might like to think of this patient as the ‘average or typical’ patient.

Questionnaire

The following sections represent the body of the questionnaire.

Q1) How many advanced HCC patients have you personally and directly managed in the past 12 months?

Q2) In which country are you based?

Q3) What is your profession/specialism?

‘**Pre-progression’ patients**

This set of questions relates to a typical ‘pre-progression’ patients defined here as patients who haven’t had further progression from the state described previously.

Drug treatment

Q4) Thinking now about a typical ‘pre-progression’ advanced HCC patients. What proportion, if any, are receiving each of the following treatments directly related to their advanced HCC and what dosing regimens are associated with each of the following therapies? How frequently would your average or typical ‘pre-progression’ advanced HCC patient receiving treatment be seen on a scheduled out-patient basis per month?

Treatment	% of ‘pre-progression’ patients	Average therapy dose	Frequency	Treatment duration
Sorafenib				
Other (specify)				
No active treatment (Best supportive care -BSC)				

Medical Staff Visits

Q5) Furthermore, when thinking about a typical ‘pre-progression’ advanced hepatocellular carcinoma patients, on average how many and which type of physician, nurse and GP visits do they receive per month. If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3). Please keep in mind that this section is referring to any visits that would be planned (elective).

Physician visits	Average number of visits (per month) and specialty if required
Pre-progression patients treated with sorafenib	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	

GP visit	
Other physician visit (please specify)	
Pre-progression patients on BSC	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	

Acute Care

Q6a) Still thinking about a typical 'pre-progression' advanced HCC patients, what proportions of patients receiving treatment or taking no other active treatment (BSC) require each of the following resources as part of acute care?

Acute Care	Average proportions for 'pre-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)		
Proportion requiring A&E admissions (per month)		
Acute Care	Average proportions for 'pre-progression' patients	Length of Stay (days)
Proportion requiring general ward admittance (per month)		
Proportion requiring ICU admittance (per month)		

Acute Care	Average proportions for 'pre-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)		
Proportion requiring A&E admissions (per month)		
Acute Care	Average proportions for 'pre-progression' patients	Length of Stay (days)
Proportion requiring general ward admittance (per month)		
Proportion requiring ICU admittance (per month)		

Q6b) Once patients have been released from hospital is there normally a follow up visit from a physician? If so, what type of professional do they see and how many follow-up visits on average do they receive?

Laboratory and Radiological tests

Q7) Still thinking about a typical 'pre-progression' advanced HCC patient. What proportions of patients receiving treatment or taking no other active therapies (BSC) require each of the following resources? (Please include 0% for no proportion). What is the frequency of these patients receiving these laboratory and radiological tests?

Test	Average proportions for 'pre-progression'' patients	Frequency of testing for 'pre-progression'' patients (per month)
Laboratory tests		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Biochemistry		
Other (please specify)		
Radiological tests		
Abdominal CT		
Abdominal MRI		
Other (please specify)		

Test	Average proportions for 'pre-progression'' patients	Frequency of testing for 'pre-progression'' patients (per month)
Laboratory tests		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Biochemistry		
Other (please specify)		
Radiological tests		

Test	Average proportions for 'pre-progression'' patients	Frequency of testing for 'pre-progression'' patients (per month)
Abdominal CT		
Abdominal MRI		
Other (please specify)		

'Post-progression' patients

This set of questions relates to a typical 'post-progression' patient defined here as patients who have progressive disease and have left the 'pre-progression' stable disease state.

Drug treatment

Q8) Thinking now about a typical 'post-progression' advanced hepatocelluar carcinoma patient. What proportion, if any, are receiving each of the following treatments directly related to their advanced HCC and what dosing regimens are associated with each of the following therapies? How frequently would your average or typical 'post-progression' advanced HCC patient receiving treatment be seen on a scheduled out-patient basis per month?

Treatment	% of 'post-progression' patients	Average therapy dose	Frequency	Treatment duration
Sorafenib				
Other (specify)				
No active treatment (BSC)				

Medical Staff Visits

Q9) Furthermore, when thinking about a typical 'post-progression' advanced hepatocelluar carcinoma patients on active treatment or on BSC, on average how many and which type of physician, nurse and GP visits do they receive per month? If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3). Please keep in mind that this section is referring to any visits that would be planned (elective).

Physician visits	Average number of visits (per month) and specialty if required
Post-progression patients treated with sorafenib	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	
Post-progression patients on BSC	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	

Acute Care

Q10a) Still thinking about a typical 'post-progression' advanced HCC patients, what proportions of patients receiving treatment or taking no other active treatment require each of the following resources as part of acute care?

Acute Care	Average proportions for 'post-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)		
Proportion requiring A&E admissions (per month)		
Acute Care	Average proportions for 'post-progression' patients	Length of Stay (days)
Proportion requiring general ward admittance (per month)		
Proportion requiring ICU admittance (per month)		

Acute Care	Average proportions for 'post-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)		
Proportion requiring A&E admissions (per month)		
Acute Care	Average proportions for 'post-progression' patients	Length of Stay (days)
Proportion requiring general ward admittance (per month)		
Proportion requiring ICU admittance (per month)		

Q10b) Once patients have been released from hospital is there normally a follow up visit from a physician? If so, what type of professional do they see and how many follow-up visits on average do they receive?

Laboratory and Radiological tests

Q11) Still thinking about a typical 'post-progression' advanced HCC patients. What proportions of patients receiving treatment or taking no other active therapies require each of the following resources? (Please include 0% for no proportion). What is the frequency of these patients receiving these laboratory and radiological tests?

Test	Average proportions for 'post-progression'' patients	Frequency of testing for 'post-progression'' patients (per month)
Laboratory tests		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Biochemistry		
Other (please specify)		
Radiological tests		
Abdominal CT		
Abdominal MRI		
Other (please specify)		

Test	Average proportions for 'post-progression'' patients	Frequency of testing for 'post-progression'' patients (per month)
Laboratory tests		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Biochemistry		
Other (please specify)		
Radiological tests		
Abdominal CT		
Abdominal MRI		
Other (please specify)		

At time of progression – sorafenib patients

Laboratory and Radiological tests

Q12) At the time of progression a one-off cost is applied for patients treated with sorafenib. These costs refer to laboratory and radiological test that are undertaken at the time of progression. What proportions of patients receiving treatment require each of the following resources? (Please include 0% for no proportion). What is the frequency of these patients receiving these laboratory and radiological tests?

Test	Average proportions for 'pre-progression'' patients	Frequency of testing for 'pre-progression'' patients
Laboratory tests		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Biochemistry		
Other (please specify)		
Radiological tests		
Abdominal CT		
Abdominal MRI		
Other (please specify)		

Adverse Events

Resource use associated with adverse events due to HCC active treatment

Q13) Whilst on treatment patients may experience adverse events. We would like to find out about how certain adverse events associated with HCC therapies are treated, irrespective of their incidence. Please indicate how you would manage the following adverse events. What percentage of patients experiencing an adverse event would require hospitalisation, a GP visit, medication etc.

Adverse Events Associated With HCC Therapies	% of patients with AE hospitalised as an inpatient due to AE	Avg. length of hospital stay (days)	% of patients with AE treated as outpatients	Avg. No. of outpatient specialist visits per patient related to AE	Avg. No. of GP visits per patient related to AE	Tests/ Procedures (please list)	Medications/Treatment (include dose and duration of medications)
Fatigue							
Weight loss							
Diarrhoea							
Nausea/vomiting							
Abdominal pain							
Alopecia							
Rash							
Hand-foot skin reaction							
Hypertension							

Thank you for your time and valuable contribution.

Resource estimates used in the economic model

Resource use per cycle for sorafenib (first line treatment, no progression)

Resource item	Mean	SD
Physician visits (N)		
Oncologist	[redacted]	[redacted]
Gastroenterologist	[redacted]	[redacted]
Clinical Nurse Specialist	[redacted]	[redacted]
Hepatologist	[redacted]	[redacted]
Palliative Care Physician / Nurse	[redacted]	[redacted]
Macmillan Nurse	[redacted]	[redacted]
Radiologist	[redacted]	[redacted]
Laboratory tests (% of patients)		
AFP test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Liver function test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
INR		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Complete blood count		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Biochemistry		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Endoscopy		
Mean proportion of patients utilising	[redacted]	[redacted]

Resource item	Mean	SD
Mean number of tests per cycle	[redacted]	[redacted]
Radiological tests (% of patients)		
CT scan: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
MRI: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Hospitalisation		
Proportion of patients requiring hospitalisation	[redacted]	[redacted]
Number of hospitalisations	[redacted]	[redacted]
Oncology ward stay (days)	[redacted]	[redacted]
Proportion of A&E admissions	[redacted]	[redacted]
Follow-up visits		
Specialist follow-up per hospitalisation	[redacted]	[redacted]
GP follow-up per hospitalisation	[redacted]	[redacted]
Nurse follow-up per hospitalisation	[redacted]	[redacted]

Additional resource use per cycle for sorafenib at time of progression

Resource item	Mean	SD
Laboratory tests (% of patients)		
AFP test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Liver function test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
INR		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Complete blood count		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Biochemistry		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Radiological tests (% of patients)		
CT scan: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
MRI: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]

Resource use per cycle for best supportive care (first line treatment)

Resource item	Mean	SD
Physician visits (N)		
Oncologist	[redacted]	[redacted]
Gastroenterologist	[redacted]	[redacted]
Clinical Nurse Specialist	[redacted]	[redacted]
Hepatologist	[redacted]	[redacted]
Macmillan Nurse	[redacted]	[redacted]
Other (Palliative Care Team)	[redacted]	[redacted]
Laboratory tests (% of patients)		
AFP test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Liver function test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
INR		

Resource item	Mean	SD
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Complete blood count		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Biochemistry		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Endoscopy		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Radiological tests (% of patients)		
CT scan: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
MRI: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Hospitalisation		
Proportion of patients requiring hospitalisation	[redacted]	[redacted]
Number of hospitalisations	[redacted]	[redacted]
Oncology ward stay (days)	[redacted]	[redacted]
Proportion of A&E admissions	[redacted]	[redacted]
Follow-up visits		
Specialist follow-up per hospitalisation	[redacted]	[redacted]
GP follow-up per hospitalisation	[redacted]	[redacted]
Nurse follow-up per hospitalisation	[redacted]	[redacted]

Resource use per cycle for best supportive care (palliative)

Resource item	Mean	SD
Physician visits (N)		
Oncologist	[redacted]	[redacted]
Clinical Nurse Specialist	[redacted]	[redacted]
Hepatologist	[redacted]	[redacted]
Macmillan Nurse	[redacted]	[redacted]
Other (Palliative Care Team)	[redacted]	[redacted]
Laboratory tests (% of patients)		
AFP test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Liver function test		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
INR		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Complete blood count		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Biochemistry		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
Radiological tests (% of patients)		
CT scan: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]
Mean number of tests per cycle	[redacted]	[redacted]
MRI: abdominal		
Mean proportion of patients utilising	[redacted]	[redacted]

Resource item	Mean	SD
Mean number of tests per cycle	[redacted]	[redacted]
Hospitalisation		
Proportion of patients requiring hospitalisation	[redacted]	[redacted]
Number of hospitalisations	[redacted]	[redacted]
Oncology ward stay (days)	[redacted]	[redacted]
Proportion of A&E admissions	[redacted]	[redacted]
Follow-up visits		
Specialist follow-up per hospitalisation	[redacted]	[redacted]
GP follow-up per hospitalisation	[redacted]	[redacted]
Nurse follow-up per hospitalisation	[redacted]	[redacted]

Source: Physician survey of 3 medical oncologists

Appendix 5: Palmer (2013) (6) cost-effectiveness results and sensitivity analysis using updated costs and resource use

A systematic review (SR) was conducted in 2015 and updated in February 2016 to identify clinical evidence (randomised and non-randomised) for sorafenib in the treatment of advanced HCC (Appendix 7). One study, in addition to the pivotal SHARP trial (1) was identified (UK real world evidence: Palmer et al 2013 (6)) was considered relevant to the decision problem. An overview of Palmer (2013) is available in Appendix 3.

Along with updated resource utilisation and unit costs, (methods described in Appendix 4) the model employed for these analyses (whilst maintaining the Appraisal Committee's preferred assumptions) also has the functionality to incorporate results of an independent retrospective study performed in the two largest specialist hepatobiliary oncology units in the UK. The cost effectiveness results of a further scenario analysis based on the updated costs, resource use, and new CMU contract price, but based on the efficacy results from the observational Palmer 2013 study, as opposed to the SHARP RCT, are presented in Table 28. Based on this UK real-word study, updated resource use and costs, sorafenib results in an ICER of £20,556 using the new CMU contract price.

Table 28: SA cost-effectiveness results using the RWE Palmer study and the new CMU conract price for sorafenib

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	£20,556

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

One-way sensitivity analysis

A range of OWSA were undertaken to determine if the results were responsive to variations in parameter values independently. The parameters varied along with the values tested for each parameter are shown in Table 29 using new CMU contract price. The sensitivity analysis presented shows that results are robust to changes in the key parameters.

Table 29: One-way sensitivity analysis (new CMU contract price) conducted on scenario analysis using updated costs and resource use data

Variable	Low Value	High Value	Low variation	High variation
			ICER (£/QALY)	ICER (£/QALY)
Time to progression investigator - sorafenib mu	[redacted]	[redacted]	[redacted]	[redacted]
Time to progression investigator - sorafenib sigma	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients BSC before progression	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients undergoing active treatment after progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility during first-line treatment with sorafenib before progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC before progression	[redacted]	[redacted]	[redacted]	[redacted]
Cost of progression	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients BSC after progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility during first-line treatment with sorafenib after progression	[redacted]	[redacted]	[redacted]	[redacted]

Summary

Cost-effectiveness results presented utilising efficacy data from Palmer 2013 suggest that sorafenib is cost-effective treatment for patients with advanced HCC in UK clinical practice. Sensitivity analyses show that results are robust to changes in the key parameters.

Appendix 6: SHARP cost-effectiveness results and sensitivity analysis using updated costs and resource use

Cost-effectiveness results with application of updated costs, and resource utilisation are presented below. The model employed for these analyses applied the following additional changes, whilst maintaining the Appraisal Committee's preferred assumptions (Tables 1 and 3, Section 4.1):

- Updated 2009 model to 2014-2015 unit costs (2016 treatment costs)
- Updated 2009 model to 2015 resource utilisation evidence

A summary of the updated costs and resource utilisation applied as part of the scenario analysis, and the methods surrounding the identification and calculation of these is presented in Appendix 4.

Cost-effectiveness results incorporating the Appraisal Committee's preferred assumptions, and using the updated costs and resource use with the new CMU contract price are reported in Table 30. There were higher LYs and QALYs within the Sorafenib arm, but higher overall costs, generating an ICER of £39,162 per QALY when using the new PAS price.

Table 30: Base-case cost-effectiveness results using the new CMU contract price and 2016 costs and updated resource use

	Intervention	BSC
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	[redacted]	[redacted]
LYG difference	NA	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	NA	[redacted]
ICER (£)	NA	£39,162

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

One-way sensitivity analysis

A range of OWSA were undertaken to determine if the results were responsive to variations in parameter values independently. The parameters varied along with the values tested for each parameter are shown in Table 31 using new CMU contract price.

Table 31: One-way sensitivity analysis (new CMU contract price) conducted on scenario analysis using updated costs and resource use data

Variable	Low value	High value	Low variation	High variation
			ICER (£/QALY)	ICER (£/QALY)
Overall survival Sorafenib mu	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival Sorafenib sigma	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival BSC mu	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival BSC sigma	[redacted]	[redacted]	[redacted]	[redacted]
Utility during first-line treatment with sorafenib before progression	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients BSC before progression	[redacted]	[redacted]	[redacted]	[redacted]
TTP Sorafenib mu	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC before progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility during BSC	[redacted]	[redacted]	[redacted]	[redacted]
Cost of routine follow-up for patients BSC after progression	[redacted]	[redacted]	[redacted]	[redacted]

Summary

Updated resource use and unit costs factor in changes to clinical practice that have occurred since the original submission in 2009. Cost-effectiveness results presented add to the robustness of results (presented in the base case and from Palmer 2013 (Appendix 5)) under alternative assumptions.

Appendix 7: Clinical systematic literature review

This appendix contains details of a systematic literature review originally conducted in April 2015 and subsequently updated in February in 2016 to identify evidence regarding the clinical efficacy, safety and tolerability of sorafenib (monotherapy) in patients with advanced HCC who are unsuitable for surgical or loco-regional therapies.

1.1 Identification and selection of relevant studies

A broad search was conducted on 1 February 2016 to identify RCTs and real-world evidence comparing sorafenib (monotherapy) with any comparator in patients with advanced HCC who are unsuitable for surgical or loco-regional therapies.

Details of the search strategy are provided below, and the search strategy, including search terms employed, is presented in Appendix 7.1.

1.1.1 Data Sources

- Medline (from database inception to 1/2/16)
- Embase (from database inception to 1/2/16)
- Medline in process (from database inception to 1/2/16)
- Cochrane Central Register of Controlled Trials (CENTRAL - from database inception to 1/2/16)

In addition, four conferences were hand-searched (last three years) for relevant abstracts/posters, to include results of recent and updated trials:

- International Liver Cancer Association (ILCA) (Annual meeting – 2013, 2014, 2015)
- European Society for Medical Oncology Congress (ESMO Congress – 2013, 2014, 2015)
- American Society of Clinical Oncology (ASCO) (Annual meeting – 2013, 2014, 2015)
- American Society of Clinical Oncology (ASCO) (Gastrointestinal Cancer Symposium – 2014, 2015, 2016)

1.2 Study selection

Studies were considered relevant if they met the eligibility criteria presented in Table 32. Citation screening was conducted by two independent reviewers with differences reconciled by a third independent reviewer. Publications that appeared to be potentially relevant on the basis of abstract and title were ordered for a full review of the text and assessed for inclusion independently by two reviewers. A flow diagram of the numbers of records included and excluded at each stage is provided in Figure 9 of this appendix. A log of excluded publications following full paper review was kept along with a rationale for the exclusion and is presented in Appendix 7.1. Data extraction of the included studies was undertaken by one reviewer, quality assessed by an independent reviewer, and any differences were reconciled by the project lead.

RCTs were quality assessed using the NICE checklist, and observational studies using the Black and Downs checklist (9).

Table 32: Eligibility criteria

Clinical evidence	Inclusion	Exclusion
Patient population	Adult patients with advanced HCC (unresectable)	Response to prior sorafenib therapy: Patients should not have expeirenced progression on prior sorafenib treatment
Interventions	Sorafenib	-
Comparators	Placebo Best Supportive Care (BSC) Sorafenib in combination with another agent	-
Outcome measures	Efficacy outomes e.g. overall survival, Time to symptomatic progression, Time to progression, progression-free survival, response rate. Safety outcomes e.g. adverse events	-

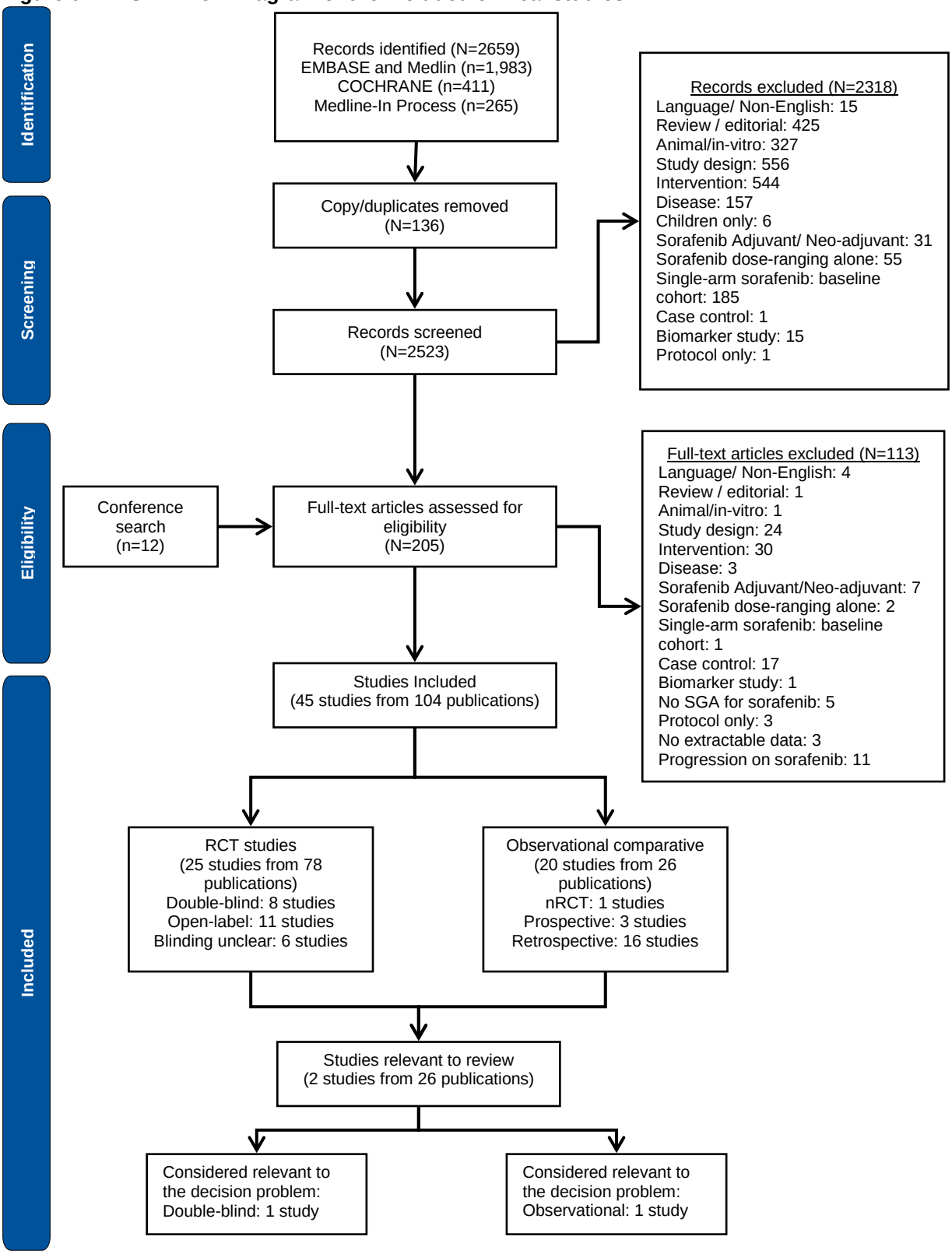
Clinical evidence	Inclusion	Exclusion
	Health-Related quality of life (HRQoL)	
Study design	Randomised controlled trial irrespective of blinding status Comparative observational studies (prospective or retrospective)	Dose ranging with no active comparator
Restrictions	Language: English	Non-English studies Protocol only (no extractable data)

1.3 Results

Across both the original and updated systematic literature review, the electronic databases yielded a total of 2659 articles. Following the removal of duplicates, 2523 abstracts were screened, of which 205 were considered potentially relevant on the basis of information reported in the abstract and title. Additionally, 12 conference abstracts meeting the inclusion criteria for this review were included after hand searching of four conference proceedings. In total 45 relevant studies from 104 publications were identified. Of these, 25 were RCTs (double-blind, n=8, blinding unclear, n=6, open-label, n= 11), and 20 were observational studies. A list of the publications excluded at full-text stage, along with the rationale for exclusion is provided in Appendix 7.1.

With reference to the decision problem (i.e. indication, intervention, comparator) 'the use of sorafenib, as a monotherapy, compared with best supportive care (BSC) in advanced HCC for patients unsuitable for surgical or loco-regional therapies' only 4 studies remained relevant: the 'SHARP study (1)', Palmer 2013 (6) , the 'Asian-Pacific study' (13) and Ji 2014 (14). Table 42 and Table 43 (Appendix 7.1) present the studies assessed against criteria used to refine to studies relevant to the decision problem.

Figure 9: PRISMA Flow Diagram of the included clinical studies



ASCO: American Society of Clinical Onclogy; ESMO: European Society for Medical Oncology; ILCA: International Liver Cancer Association; nRCT: non-Randomized Controlled Trial; RCT: Randomized Controlled Trial; SGA: Subgroup Analysis

Results from two of the four studies were subsequently considered not relevant to the decision problem as they focused on Chinese patients only, ('Asian-Pacific study', Ji 2014) resulting in only one RCT and one observational study being considered relevant to support this submission.

The remaining 21 RCTs did not include a BSC or placebo treatment arm, and were therefore considered irrelevant. A list of the 24 RCTs not considered relevant is presented in Appendix 7.1 (Table 42), along with the rationale for exclusion.

1.2 List of relevant randomised controlled trials

One study identified by the systematic review was considered relevant to this submission. SHARP (1) was a phase III multicentre, international, double-blind study that investigated the clinical benefits of sorafenib versus placebo in advanced HCC. The study was considered to be of moderate/low risk of bias. Details of the study are presented in Table 33 (and a full write-up can be found in the original submission)

Table 33: RCTs considered relevant to decision problem

Trial	Population	Intervention	Comparator	Primary study ref
SHARP Trial (1)	advanced HCC ineligible for surgery or loco-regional treatment, with no prior systemic treatment, ECOG performance status 0-2 and Child-Pugh status A.	Sorafenib N=299	Placebo N=303	Llovet 2008

BSC=Best supportive care; ECOG= Eastern Cooperative Oncology Group, HCC=hepatocellular cancer; NR=not reported;

1.3 Non-randomised and non-controlled evidence

1.3.1 Relevant non-randomised and non-controlled evidence

Although not considered as robust as double-blind RCTs, evidence of the efficacy of treatments in the clinical setting is becoming increasingly important. Of the 20 identified observational studies, only four included a BSC comparator, however only one of these was conducted in the UK and considered relevant to UK clinical practice. A list of observational studies identified by the systematic review but not considered relevant to inform this submission is presented in Appendix 7.1 along with a rationale for that decision.

Table 34 shows that the one study met all of these criteria (Palmer et al, 2013). A full clinical summary of Palmer 2013 can be found in Appendix 3 with results of a scenario analysis considering the cost-effectiveness using this data presented in Appendix 5.

Table 34: Observational studies found relevant to the decision problem

Trial	Population	Intervention	Comparator	Primary study ref.
Palmer 2013 (6)	Advanced HCC unsuitable for loco-regional therapy.	Received funding (sorafenib) N=57	Did not receive funding (BSC) N=76	Palmer (2013)

BSC=Best supportive care; HCC=hepatocellular cancer

Appendix 7.1: Search strategy for relevant studies

1.1 Original review conducted in April 2015

Table 35: Search strategy Embase® and MEDLINE® using Embase.com platform searched on 06 April 2015

No.	Search terms	Facet	Hits
#1	'liver cell carcinoma'/exp OR hcc:ab,ti	Disease	108,934
#2	hepatic:ab,ti OR hepatocellular:ab,ti OR liver:ab,ti		949,303
#3	cancer:ab,ti OR carcinoma:ab,ti		1,846,938
#4	#2 AND #3		156,003
#5	#1 OR #4		192,200
#6	advanced:ab,ti OR unresectable:ab,ti OR inoperable:ab,ti	Disease stage	400,542
#7	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	Study design (RCTs and observational study)	6,274,555
#8	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti		5,813,761
#9	#7 OR #8		9,284,814
#10	'sorafenib'/syn OR 'sorafenib'	Intervention	17,286
#11	#5 AND #6 AND #9 AND #10	Combination facet	2,104
#12	#11 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	Limits	27
#13	#11 AND ([conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)		473
#14	#12 OR #13		500
#15	**#11 NOT #14**	**Sorafenib trials**	**1,604**

Table 36: Search strategy Cochrane database searched on 06 April 2015

No.	Search terms	Facet	Hits
#1	Liver OR hepat* OR hepatocellular	Disease Facet	43,648
#2	Carcinoma OR cancer OR neoplas*		99,229
#3	#1 AND #2		8,403
#4	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees		1,153
#5	(primary near/4 (liver or hepati*) or (primary near/3 (cancer or carcinom* or neoplas*)		3,540
#6	HCC		1,091
#7	#3 OR #4 OR #5 OR #6		11,323
#8	("sorafenib" or sorafenib) or ("nexavar" or Nexavar) or ("bay 43 9006" or "bay 43- 9006" or "bay 439006" or "bay43 9006" or "bay43-9006" or "bay439006")	Intervention Facet	438
#9	#7 AND #8	Combination facet	179
#10	**#9 in Trials**	**Sorafenib trials**	**139**

Table 37: Search Strategy MEDLINE® In-process searched on 06 April 2015

No.	Search terms	Facet	Hits
#1	Liver OR hepat* OR hepatocellular	Disease Facet	1,101,793
#2	carcinoma OR cancer OR neoplas*		3,177,946
#3	#1 AND #2		250,385
#4	HCC OR "hepatocellular carcinoma" OR hepatoma		93,161
#5	#3 OR #4		2,58,614
#6	Sorafenib OR Nexavar OR "bay 43 9006" OR "bay43-9006" OR "bay 439006" OR "bay43 9006" OR "bay43-9006" OR "bay439006"	Intervention Facet	31,840
#7	#5 AND #6	Combination facet	2,120
#8	**#7 AND (inprocess[sb] OR pubstatusaheadofprint)**	**Sorafenib trials**	**264**

1.2 Updated searches conducted February 2016

Table 38: Search strategy Embase® and MEDLINE® using Embase.com platform searched on 01 February 2016

No.	Search terms	Facet	Hits
#1	'liver cell carcinoma'/exp OR hcc:ab,ti	Disease	118,425
#2	hepatic:ab,ti OR hepatocellular:ab,ti OR liver:ab,ti		1,001,587
#3	cancer:ab,ti OR carcinoma:ab,ti		1,988,978
#4	#2 AND #3		170,284
#5	#1 OR #4		208,583
#6	advanced:ab,ti OR unresectable:ab,ti OR inoperable:ab,ti	Disease stage	435,957
#7	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	Study design (RCTs and observational study)	6,669,470
#8	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti		6,194,229
#9	#7 OR #8		9,866,355
#10	'sorafenib'/syn OR 'sorafenib'	Intervention	19,289
#11	#5 AND #6 AND #9 AND #10	Combination facet	2,529
#12	#11 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	Limits	31
#13	#11 AND ([conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)		538
#14	#12 OR #13		569
#15	**#11 NOT #14**	**Sorafenib trials**	**1,960**
#16	**#15 AND [6-4-2015]/sd**		**379**

Table 39: Search strategy Cochrane database searched on 01 February 2016

No	Search terms	Facet	Hits
#1	Liver OR hepat* OR hepatocellular	Disease Facet	48,010
#2	Carcinoma OR cancer OR neoplas*		109,935
#3	#1 AND #2		9,638
#4	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees		1,282
#5	(primary near/4 (liver or hepati*) or (primary near/3 (cancer or carcinom* or neoplas*))		3,949
#6	HCC		1,282
#7	#3 OR #4 OR #5 OR #6		12,881
#8	("sorafenib" or sorafenib) or ("nexavar" or Nexavar) or ("bay 43 9006" or "bay 43- 9006" or "bay 439006" or "bay43 9006" or "bay43-9006" or "bay439006")	Intervention Facet	545
#9	#7 AND #8	Combination facet	232
#10	**#9 in Trials Publication Date from Apr 2015 to Feb 2016**	**Sorafenib trials**	**1**

Table 40: Search Strategy MEDLINE® In-process searched on 01 February 2016

No	Search terms	Facet	Hits
#1	Liver OR hepat* OR hepatocellular	Disease Facet	1,141,770
#2	carcinoma OR cancer OR neoplas*		3326489
#3	#1 AND #2		263149
#4	HCC OR "hepatocellular carcinoma" OR hepatoma		99170
#5	#3 OR #4		271672
#6	Sorafenib OR Nexavar OR "bay 43 9006" OR "bay43-9006" OR "bay 439006" OR "bay43 9006" OR "bay43-9006" OR "bay439006"	Intervention Facet	34804
#7	#5 AND #6	Combination facet	2,486
#8	**#7 AND (inprocess[sb] OR pubstatusaheadofprint)**	**Sorafenib trials**	**272**

1.3 Conference search

Table 41 lists the methodology used for searching conferences.

Table 41: Conference search strategy used to identify relevant studies

Conference name	Year	Search terms	Abstracts screened
International Liver Cancer Association	2013	All abtracts published in online abstract book were screened.	253
	2014		228
	2015		382
American Society of Clinical Oncology (ASCO) (Annual meeting)	2013	All abtracts available under sub heading “Hepatobiliary Cancer” from “Gastrointestinal (Noncolorectal) Cancer” heading were searched.	70
	2014		85
	2015		78
American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium	2014	All abtracts available under “Cancers of the Esophagus and Stomach” heading were searched.	208
	2015		278
	2016		184
European Society for Medical Oncology (ESMO) Congress	2013	All abtracts available under “Gastrointestinal Malignancies − Noncolorectal Cancer” heading were searched.	215
	2014		134
	2015		207

1.4 Excluded studies

Table 42: RCTs that met the inclusion criteria of the systematic review but were not considered relevant to support the submission

Trial	Population	Intervention	Comparator	Primary study ref.	Reason for exclusion
RCTs					
Asian-Pacific Trial (13)	advanced (unresectable or metastatic) hepatocellular carcinoma, who had not received previous systemic therapy	Sorafenib N=150	Placebo N=76	Cheng 2009	Met inclusion criteria but subsequently excluded as based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population.
Abou-Alfa (15)	advanced HCC, Eastern Cooperative Oncology Group performance status 0 to 2, Child-Pugh A status, and no prior systemic therapy	Sorafenib + doxorubicin N=47	Doxorubicin N=49	Abou-Alfa 2010	Not monotherapy; No BSC control arm
BRISK FL study (16)	advanced HCC with no prior systemic therapy	Sorafenib N=578	Brivanib N=577	Johnson 2013	No BSC control arm
Kudo (17)	unresectable HCC, Child-Pugh class A cirrhosis and ≥25% tumour necrosis/shrinkage 1-3 months after 1 or 2 TACE sessions	Sorafenib N=458	-	Kudo 2011	Adjunctive therapy to TACE; Wrong patient population; No BSC control arm
SEARCH Trial (18)	advanced HCC and underlying Child-Pugh class A cirrhosis, who were naive to systemic treatment	Sorafenib N=358	Sorafenib + erlotinib N=362	Zhu 2015	No BSC control arm
Torre (19)	NR	Sorafenib	Sorafenib + Propanolol +Etodolac	Torre 2015	Patient population not reported; No BSC control arm

Trial	Population	Intervention	Comparator	Primary study ref.	Reason for exclusion
RCTs open label					
Yen 2013 (20)	Sorafenib Nintedanib	Sorafenib N=32	Nintedanib N=63	Yen 2013	No BSC control arm
Thomas 2015 (21)	Sorafenib Bevacizumab + Erlotinib	Sorafenib N=43	Bevacizumab + Erlotinib N=47	Thomas 2015	No BSC control arm
Ji 2014 (14)	Sorafenib BSC	Sorafenib N=95	BSC N=94	Ji 2014	Met inclusion criteria but subsequently excluded as based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population.
Cainap 2015 (22)	Sorafenib Linifanib	Sorafenib N=521	Linifanib N=524	Cainap 2015	No BSC control arm
Cheng 2013 (23)	Sorafenib Sunitinib	Sorafenib N=544	Sunitinib N=530	Cheng 2013	No BSC control arm
Ettrich 2015 (24)	Sorafenib Sorafenib + Doxorubicin	Sorafenib N=15	Sorafenib + doxorubicin N=15	Ettrich 2015	No BSC control arm
Cheng 2015a (25)	Sorafenib Sorafenib + tigatuzumab dose 1 Sorafenib + tigatuzumab dose 2	Sorafenib N=55	Sorafenib + tigatuzumab dose 1, N= 53, dose 2, N=54	Cheng 2015a	No BSC control arm
Cheng 2015b (26)	Sorafenib Dovitnib	Sorafenib N=82	Dovitinib N=83	Cheng 2015b	No BSC control arm
Abdel-Rahman 2013 (27)	Sorafenib Capecitabine	Sorafenib N=82	Capecitabine N= 26	Abdel-Rahman 2013	No BSC control arm
Palmer 2015 (28)	Sorafenib Nintedanib	Sorafenib N=62	Nintedanib N=31	Palmer 2015	No BSC control arm
Lee 2014 (29)	Sorafenib	Sorafenib	AEG35156 + Sorafenib	Lee 2014	No BSC control arm

Trial	Population	Intervention	Comparator	Primary study ref.	Reason for exclusion
	AEG35156 + Sorafenib	N=17	N=31		
RCTs blinding unclear					
Koeberle 2014 (30)	Sorafenib Sorafenib + Everolimus	Sorafenib N=43	Sorafenib + Everolimus N=60	Koeberle 2014	No BSC control arm
Georgescu 2011a (31)	Sorafenib Sorafenib +Lovastatin	Sorafenib N=33	Sorafenib +Lovastatin = 39	Georgescu 2011a	No BSC control arm
Ciuleanu 2016 (32)	Sorafenib Sorafenib + Mapatumumab	Sorafenib N=51	Sorafenib + Mapatumumab N=51	Ciuleanu 2016	No BSC control arm
Assenat 2013 (33)	Sorafenib Sorafenib + Gemox	NR	NR	Assenat 2013b	No BSC control arm
Bhattacharyya 2014 (34)	Sorafenib Sorafinib + Propranolol + Etodolac	NR	NR	Bhattacharyya 2014	No BSC control arm
Li 2015 (35)	Sorafenib Sorafenib + tiopronin	Sorafenib N=42	Sorafenib + tiopronin N=40	Li 2015	No BSC control arm
Abou-Alfa 2016 (36)	Sorafenib Sorafenib + doxorubicin	Sorafenib N=173	Sorafenib + doxorubicin N=173	Abou-Alfa 2016	No BSC control arm

*Despite meeting the criteria of the decision problem Ji (2014) and the 'Asian-Pacific study' were subsequently considered not relevant due to considering a Chinese population only.

Table 43: Observational studies that met the inclusion criteria of the systematic review but were not considered relevant to support the submission

Study / Primary study reference	Objective	Population	Intervention / Comparator	Justification for inclusion
Cebollero 2012 (37)	Evaluate efficacy of sorafenib +/- bevacizumab in HCC	Not reported	Sorafenib +/- Bevacizumab	Excluded – Not UK based; no BSC control arm; unclear as to patient population
Chen 2015 (38)	Evaluate changes of DCE-MRI in patients with advanced HCC	Advanced HCC	Sorafenib + UFUR / Vandetnib / Best supportive care	Excluded – Not UK based; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy; no monotherapy arm
Doi 2014 (39)	Assess impact of interferon added to sorafenib treatment in advanced HCC	Advanced HCC failed ≥1 loco-regional therapies	Sorafenib / Sorafenib + interferon	Excluded – Not UK based; no BSC control arm;
Daniel (2015) (40)	Compare survival rates of liver transplantation patients receiving Sorafenib or BSC	Not reported	Sorafenib / Best supportive care	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Feng 2015 (41)	Evaluate the efficacy of sorafenib + cyproheptadine versus sorafenib alone in advanced HCC	Advanced HCC	Sorafenib / Sorafenib +cyproheptadine	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Haruna 2013 (42)	Evaluate the efficacy of sorafenib + vitamin K analogue in HCC	BCLC B	Sorafenib / Sorafenib + vitamin K analogue	Excluded – Not UK based; no BSC control arm; Intermediate HCC
Haruna 2015 (42)	To evaluate vitamin K dosing during sorafenib treatment for HCC	BCLC B/C	Sorafenib / Sorafenib + Vitamin k	Excluded – Not UK based; no BSC control arm;
Huang 2016 (43)	Evaluate outcomes of different modalities on long-term survival	Recurrence of HCC post liver transplantation	Sorafenib + sirolimus / Best supportive care	Excluded – Not UK based; no monotherapy arm, no BSC control arm; patients suitable for surgical / loco-regional therapy
Kim 2013 (44)	Evaluation of the outcomes and prognostic factors of systemic chemotherapy in patients with	Post liver transplantation HCC recurrence	Sorafenib	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for

Study / Primary study	Objective	Population	Intervention	Justification for inclusion
	post liver transplantation HCC recurrence		Cytotoxic chemotherapy	surgical / loco-regional therapy
Lee 2012 (45)	Compare sorafenib with conventional cytotoxic therapy in advanced HCC	Advanced HCC unsuitable for surgical or loco-regional therapies	Sorafenib Cytotoxic therapy	Excluded – Not UK based; no BSC control arm;
Lv 2014 (46)	Compare efficacy of sorafenib vs. S-1 + oxaliplatin in HCC	Advanced HCC	Sorafenib S1 + oxaliplatin	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Mehta 2013 (47)	Evaluate different therapeutic approaches in infiltrative HCC	Infiltrative HCC	Sorafenib Placebo	Excluded – not UK based; no BSC control arm; patients suitable for surgical / loco-regional therapy
Nakashita 2013 (48)	Evaluate sorafenib vs. sorafenib + vit K analogue in patients with unresectable HCC who have responded to TACE	Unresectable HCC	Sorafenib Sorafenib + vitamin K analogue	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Naganuma 2015 (49)	Evaluate the effect of an oral nutrition supplement on hand-foot syndrome in advanced HCC.	Advanced HCC	Sorafenib Sorafenib + nutritional supplement	Excluded– Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Parikh 2015 (50)	Examine outcomes of elderly patients with advanced HCC in the US	Advanced HCC	Sorafenib No treatment	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Salguero 2013 (51)	Evaluation of different therapies in HCC	HCC mixed population	Sorafenib Idarubicin TACE+doxorubicin	Excluded – Not UK based; no BSC control arm; unclear breakdown of patient population
Tao 2014 (52)	Compare the effects of no treatment with sorafenib or sorafenib combination treatment in advanced HCC	Advanced HCC	Sorafenib Control Sorafenib +interventional therapy	Excluded – Not UK based; no BSC control arm; Advanced HCC but unclear if unsuitable for surgical / loco-regional therapy
Yang 2011 (53)	compare the overall survival of patients who were first treated with TARE, sorafenib, or best supportive care	NR	Sorafenib BSC	Excluded – not UK based; Unclear if monotherapy and also if advanced HCC unsuitable for surgical or loco-regional therapy

Study / Primary study	Objective	Population	Intervention	Justification for inclusion
Yoon 2012 (54)	To compare the efficacy and safety of systemic cytotoxic chemotherapy with sorafenib	Advanced HCC	Sorafenib Cytotoxic therapy	Excluded – not reported to be UK based; Unclear if monotherapy and also if patients unsuitable for surgical or loco-regional therapy; no BSC control arm

1.5 List of excluded studies following full paper review

Table 44: Clinical search- Summary of excluded publications at full-text stage (also see Table 42 and Table 43)

Study name	Reference	Exclusion reason
Abou-Alfa 2014	Phase II study of first-line trebananib plus sorafenib in patients with advanced hepatocellular carcinoma (HCC). Abou-Alfa G.K., Blanc J.-F., Miles S., et. al. J Clin Oncol (2014); 32 (3)	Case control
Adhoute 2014	N.I.A.C.E score: A new tool to better distribute advanced hepatocellular carcinoma (BCLC C). Results from four French cohorts comprising 703 patients. Adhoute X., Penaranda G., Blanc J.-F., et al. Hepatology (2014); 60: 838A-839A	Intervention
Alkhatib 2015	Real Life Treatment of Hepatocellular Carcinoma: Impact of Deviation from Guidelines for Recommended Therapy.	Study design
Alsina 2013	Improved survival with sorafenib and multimodality therapy in recurrent hepatocellular carcinoma following liver transplantation: A preliminary report. Alsina A.E., Franco E.S., Makris A.M., et al. Am J Transplantation (2013); 13: 81	Case control
Avila 2015	Making Sorafenib Irresistible: In Vivo Screening for Mechanisms of Therapy Resistance in Hepatocellular Carcinoma Hits on Mapk14. Avila M and Berasain C. Hepatology (2015);	Animal/in-vitro
Balsom 2010	A single-institute experience with sorafenib in untreated and previously treated patients with advanced hepatocellular carcinoma. Balsom S.M., Li X., Trolli E., et al. Oncology (2010); 78 (42067): 210-212.	Study design
Berk 2013	Efficiency and side effects of sorafenib therapy for advanced hepatocellular carcinoma: a retrospective study by the anatolian society of medical oncology. Berk V., Kaplan M.A., Tonyali O., et al. APJCP (2013); 14 (12):7367-7369	Study design
Bettinger 2011	Prognostic factors in patients with hepatocellular carcinoma (HCC) and sorafenib treatment: Experience from a single center retrospective study. Bettinger D., Schultheiss M., Knuppel E., et al. Hepatology (2011); 54: 1406A.	Study design
Bitzer 2010	First clinical data of resminostat, a novel oral histone deacetylase (HDAC) inhibitor, in patients with hepatocellular carcinoma (HCC): The SHELTER study	Progression on sorafenib
Bitzer 2011	Clinical update on the SHELTER study: A phase I/II trial of the HDAC inhibitor resminostat in patients with sorafenib-resistant hepatocellular carcinoma (HCC)	Progression on sorafenib
Bitzer 2012	Efficacy, safety, tolerability, and PK of the HDAC inhibitor resminostat in sorafenib-refractory hepatocellular carcinoma (HCC): Phase II SHELTER study	Progression on sorafenib
Bitzer 2013	Subgroup analysis of prognostic factors for overall survival in the SHELTER trial evaluating resminostat in advanced hepatocellular carcinoma (HCC) - The SHELTER Study Group	Progression on sorafenib

Study name	Reference	Exclusion reason
Bitzer 2013	Resminostat in advanced hepatocellular carcinoma (HCC): Overall survival subgroup analysis of prognostic factors in the SHELTER trial	Progression on sorafenib
Brau 2010	Improved survival of hepatocellular carcinoma (HCC) in HIV-infected patients with undetectable HIV RNA. Brau N., Kikuchi L., Nunez M., et al. J Hepatol (2010); 52 : S219.	Intervention
Brunot 2013	Implementation of a nurse-driven educational program improves management of sorafenib`s toxicities in hepatocellular carcinoma. Brunot A., Le Roy F., Lesourd S., et al. Eur J Cancer (2013); 49: S629-S630.	Study design
Cabibbo 2014	Personalized therapy with sorafenib for hepatocellular carcinoma. Cabibbo G., Iavarone M., Maida M., et al. J Hepatol (2014): 60 (1): S397.	Case control
Chelis 2013	Circulating biomarkers of sorafenib efficacy in advanced HCC. Chelis L., Anagnostopoulos K., Trypsianis G., et al. J Clin Oncol (2013): 31 (4)	Case control
Chelis 2015	Serum mass spectrometry analysis in hepatocellular carcinoma (HCC) patients treated with sorafenib (S)	No Extractable data
Chen 2014	Efficacy of sorafenib in patients with pulmonary metastatic hepatocellular carcinoma after liver transplantation. Chen Y., Luo W., Ju W., He X., Zhu X. Liver Transplantation (2014); 20: S256.	Disease
Chen 2014	Efficacy of sorafenib in patients with pulmonary metastatic hepatocellular carcinoma after liver transplantation. Chen Y., Ju W., Zhu X., He X., Guo Z. Transplantation (2014); 98: 699.	Sorafenib Adjuvant/Neoadjuvant
Cheng 2015	Efficacy and safety of nintedanib versus sorafenib in caucasian and Asian patients with advanced hepatocellular carcinoma: Combined analysis of two randomised phase II trials	Study design
Cheng 2015	Retrospective pooled analysis of advanced HCC patients in sharp and AP randomized clinical trials	Study design
Cho 2010	Comparison of sorafenib and radiotherapy in unresectable hepatocellular carcinoma patients whom transcatheter arterial chemoembolization was ineffective or unsuitable. Cho S.B., Rew H.S., Seo T.J., et al. Hepatology International (2010); 4 (1):302.	Intervention
Colombo 2009	Sorafenib in Advanced Hepatocellular Carcinoma: A Further Step Toward Personalized Therapy of Liver Cancer. Colombo M. Gastroenterology (2009); 136 (5):1832-1835.	Review / editorial
Daniele 2012	A randomized phase III trial comparing sorafenib plus best supportive care (BSC) versus BSC alone in Child-Pugh B patients (pts) with advanced hepatocellular carcinoma (HCC): The BOOST study. Daniele B., Di Maio M., Gallo C., et al. J Clin Oncol (2012); 30 (15).	Protocol only

Study name	Reference	Exclusion reason
De 2011	Metronomic capecitabine as second-line treatment for patients with hepatocellular carcinoma with preserved liver function: A phase II study. De Rosa F., Agostini V., Di Girolamo S., et al. J Clin Oncol (2011); 29 (15).	Study design
De'Angelis 2014	Treatments of hepatocellular carcinoma recurrence after liver transplantation: A single center experience. De`Angelis N., Laurent A., Azoualy D. Liver Transplantation (2014); 20: S371.	Sorafenib Adjuvant/Neoadjuvant
Detry 2009	Palliative management of hepatocarcinoma with sorafenib (nexavar (registered trademark)). Results of the sharp study (sorafenib hepatocarcinoma assessment randomized protocol trial). Detry O., Delwaide J., De Roover A., et al. Revue Medicale de Liege (2009); 64 (3): 168-170.	Language/ Non-English
Dharancy 2009	Safety profile of sorafenib (SO) in patients with hepatocellular carcinoma (HCC): A prospective evaluation. Dharancy S., Cattan S., Romano O., et al. Hepatology (2009); 50:1099A.	Case control
Di 2015	Sorafenib off-target effects predict outcomes in patients treated for hepatocellular carcinoma. Di Costanzo GG, de Stefano G, Tortora R, et al. Future Oncol (2015); 11 (6): 943-951.	Study design
Dimitroulopoulos 2013	Demographic profile and outcome of 126 consecutive HCC cirrhotic patients treated with Nexavar. A 5 year Greek multicentrer study. Dimitroulopoulos D., Protopappas A., Karatapanis S., et al. Hepatology (2013); 7: S634.	Case control
Dimitroulopoulos 2013	A 5-year Greek Observational Multicentre Study of 126 consecutive HCC cirrhotic patients treated with Nexavar. Demographic profile, outcome and quality of life results. D. Dimitroulopoulos, A. Fotopoulou, A. Protopappas, et al. ILCA Annual Conference (2013).	Case control
Elmashad 2015	Predictive value of serum insulin-like growth factor-1 in hepatocellular carcinoma	Intervention
Finn 2011	Phase I study of everolimus in combination with sorafenib in patients with advanced hepatocellular carcinoma (HCC). Finn R.S., Poon R.T.P., Yau T., et al. J Clin Oncol (2011); 29 (15).	Sorafenib dose-ranging alone
Finn 2014	A multicenter, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib (E7080) versus sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma. Finn R.S., Cheng A.-L., Ikeda K., et al. J Clin Oncol (2014); 32 (15).	Protocol only
Fu 2014	Sorafenib continuation after first disease progression could reduce disease flares and provide survival benefits in patients with hepatocellular carcinoma: a pilot retrospective study. Fu S.-R., Zhang Y.-Q., Li Y., et al. APJCP (2014); 15 (7): 3151-3156.	Intervention

Study name	Reference	Exclusion reason
Fukubayashi 2015	Evaluation of sorafenib treatment and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma: a comparative study using the propensity score matching method.	Intervention
Furuse 2011	Controversies in the treatment indication of TACE and sorafenib for advanced HCC	Intervention
Garcovich 2011	Systemic endothelial dysfunction as a predictor of hypertension development in cirrhotic patients with hepatocellular carcinoma (HCC) undergoing therapy with sorafenib. Garcovich M., Zocco M.A., Lupascu A., et al. Hepatology (2011); 54 : 1394A.	Case control
Garcovich 2012	Systemic endothelial dysfunction as a predictor of hypertension development in cirrhotic patients with hepatocellular carcinoma (HCC) undergoing therapy with sorafenib. Garcovich M., Zocco M.A., Lupascu A., et al. Digestive and Liver Disease (2012); 44: S139.	Case control
Ghimire 2013	Survival trends among patients with advanced hepatocellular carcinoma in the United States. Ghimire K.B., Shah B.K., and Nepal B. J Clin Oncol (2013); 31 (4).	Intervention
Gholam 2011	Outcomes of planned multimodality therapy for unresectable, untransplantable hepatocellular carcinoma. Gholam P.M., Lie K., Azar N., et al. Hepatology (2011); 54: 1403A-1404A.	Intervention
Godin 2015	Biomarkers of apoptosis and necrosis in patients with hepatocellular carcinoma treated with sorafenib. Godin C, Louandre C, Bodeau S, et al. Anticancer Res (2015); 35 (3): 1803-1808.	Case control
Goldwasser 2011	Reversible decrease of portal venous flow in cirrhotic patients: a positive side effect of sorafenib. Goldwasser F. PloS one (2011); 6 (2): e16978.	Case control
Guarino 2015	Lack of evidence that adherence to standard of care therapy improves survival in subjects with hepatocellular carcinoma in clinical practice	Study design
Hiramine 2013	Efficacy and optimal treatment sequence of Sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. Hiramine Y., Tamai T., Imamura Y., et al. Acta Hepatologica Japonica (2013); 54 (4): 233-248.	Language/ Non-English
Iliescu 2014	The evolution and treatment of hepatocellular carcinoma. Iliescu L., Toma L., Orban C., and Tanase A. Hepatology International (2014); 8 (1): S285.	No SGA for sorafenib
Iliescu 2014	Management of hepatocellular carcinoma - Experience of a single center. Iliescu L., Mindrut E., Grasu M., et al. Chirurgia (Romania) (2014); 109 (2):204-207.	No SGA for sorafenib
Imanaka 2015	Impact of branched-chain amino acid supplementation on the survival in patients with advanced hepatocellular carcinoma treated with sorafenib; a multicenter retrospective cohort study.	Intervention

Study name	Reference	Exclusion reason
Jeong 2012	The efficacy of hepatic arterial infusion chemotherapy as an alternative treatment for sorafenib in advanced hepatocellular carcinoma. Jeong S.W., Jang J.Y., Bok G.H., et al. Hepatology International (2012); 6 (1): 203.	Intervention
Jeong 2012	The efficacy of hepatic arterial infusion chemotherapy as an alternative to sorafenib in advanced hepatocellular carcinoma. Jeong S.W., Jang J.Y., Lee J.E., et al. Asia-Pacific Journal of Clinical Oncology (2012); 8 (2): 164-171.	Intervention
Johnson 2015	Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach-The ALBI Grade. Johnson PJ, Berhane S, Kagebayashi C, et al. J Clin Oncol (2015); 33 (6): 550-558.	Single-arm sorafenib: baseline cohort
Kasai 2013	Combination therapy of intra-arterial 5-fluorouracil and systemic pegylated interferon alpha-2b for advanced hepatocellular carcinoma. Kasai K., Sawara K., Suzuki K. J Clin Oncol (2013); 31 (4).	Intervention
Kasai 2013	Combination therapy of intra-arterial 5-fluorouracil and systemic pegylated interferon (alpha)-2b for advanced hepatocellular carcinoma. Kasai K. Gastroenterology (2013); 144 (5): S1035 - S1036.	Intervention
Kikuchi 2015	Sorafenib therapy in HIV-infected patients with hepatocellular carcinoma (HCC)	Intervention
Kim 2011	Survival of patients with advanced hepatocellular carcinoma: Sorafenib versus other treatments. Kim H.Y., Park J.-W., Nam B.-H.,et al. Journal of Gastroenterology and Hepatology (Australia) (2011); 26 (11): 1612 - 1618.	Intervention
Kim 2013	Sorafenib versus cytotoxic chemotherapy for patients with recurrent hepatocellular carcinoma after liver transplantation. Kim B.H., Woo S.M., Kim S.H., et al. Hepatology (2013); 58 (4): 1239A.	Sorafenib Adjuvant/Neoadjuvant
Kim 2015	The role of 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) for accurate staging and optimal treatment planning in patients with hepatocellular carcinoma	Intervention
Kohli 2014	Sorafenib but not locoregional therapy improves survival in patients with hepatocellular carcinoma recurrence after orthotopic liver transplantation. Kohli R., Lopez R., Romero-Marrero C., et al. Gastroenterology (2014); 146 (5): S913 - S914.	Sorafenib Adjuvant/Neoadjuvant
Kondo 2013	Sorafenib for survival post-progression in advanced hepatocellular carcinoma unresponsive to hepatic arterial infusion chemotherapy. Kondo M., Morimoto M., Moriya S., et al. Journal of Gastroenterology and Hepatology Research (2013); 2 (4): 520 - 525.	Intervention
Kuzuya 2010	Efficacy of sorafenib, molecular targeting drug, for advanced hepatocellular carcinoma. Kuzuya T., Tsuchiya K., Izumi N. Gan to kagaku ryoho. Cancer & chemotherapy (2010); 37 (10): 1883 - 1886.	Language/ Non-English

Study name	Reference	Exclusion reason
Le 2015	Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial	Disease
Lencioni 2016	Sorafenib or Placebo plus TACE with Doxorubicin-Eluting Beads for Intermediate-Stage HCC: Phase II, Randomized, Double-Blind SPACE Trial.	Intervention
Lesmana 2012	Influence of the sorafenib patients assistance program on treatment compliance and overall survival of unresectable hepatocellular carcinoma patients. Lesmana L.A., Gani R.A., Hasan I., et al. Acta medica Indonesiana (2012); 44 (3): 228 - 232.	Case control
Li 2014	Combination of individualized local control and target-specific agent to improve unresectable liver cancer managements: a matched case-control study. Li J, Zhang F, Yang J, Zhang Y, Wang Y, et al. Target Oncol (2014);	Intervention
Liepa 2013	Characteristics and treatment patterns of patients potentially eligible for further therapy after discontinuation of first-line sorafenib for advanced hepatocellular carcinoma (HCC): An EU perspective. Liepa A.M., Mitra D., D`yachkova Y., et al. Eur J Cancer (2013); 49: S594.	No SGA for sorafenib
Lin 2014	High serum transforming growth factor (beta)1 levels associated with poor survivals in patients with advanced hepatocellular carcinoma. Lin T.-H., Shao Y.-Y., Chan S.-Y., et al. Cancer Research (2014); 74 (19).	Study design
Lin 2015	Computed tomography response criteria in patients with advanced hepatocellular carcinoma receiving anti-angiogenic therapy in clinical trials	No SGA for sorafenib
Lu 2010	A pilot study: Sorafenib in patients with post liver transplant recurrence of HCC. Lu M., Chen Y., Cai C.,et al. Liver Transplantation (2010); 16: S191.	Sorafenib Adjuvant/Neoadjuvant
Lu 2014	Clinical characteristics of advanced hepatocellular carcinoma patients with prolonged survival in the era of anti-angiogenic targeted-therapy. Lu L.-C., Shao Y.-Y., Chan S.-Y., et al. Anticancer Research (2014); 34 (2); 1047 - 1052.	Study design
Mahgoub 2014	Outcomes in veterans with hepatocellular carcinoma (HCC)-a single center experience over 10 years. Mahgoub A., Peeraphatdit T., Maust T.J., et al. Gastroenterology (2014); 146 (5): S994.	Intervention
Mehta 2011	Infiltrative hepatocellular carcinoma: Prognostic factors and positive impact of tumor directed therapy. Mehta N., Fidelman N., Yao F.Y. Hepatology (2011); 54:1368A.	Study design
Mohamed 2015	Microvessel Density Analysis in Patients with Viral Hepatitis-Related Hepatocellular Carcinoma. Mohamed A, Chenna A, Abdelfatah M, et al. J Gastrointest Cancer (2015).	Intervention
Nakazawa 2014	Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: Propensity score analysis. Nakazawa T., Hidaka H., Shibuya A., et al. BMC Gastroenterology (2014); 14 (1).	Intervention

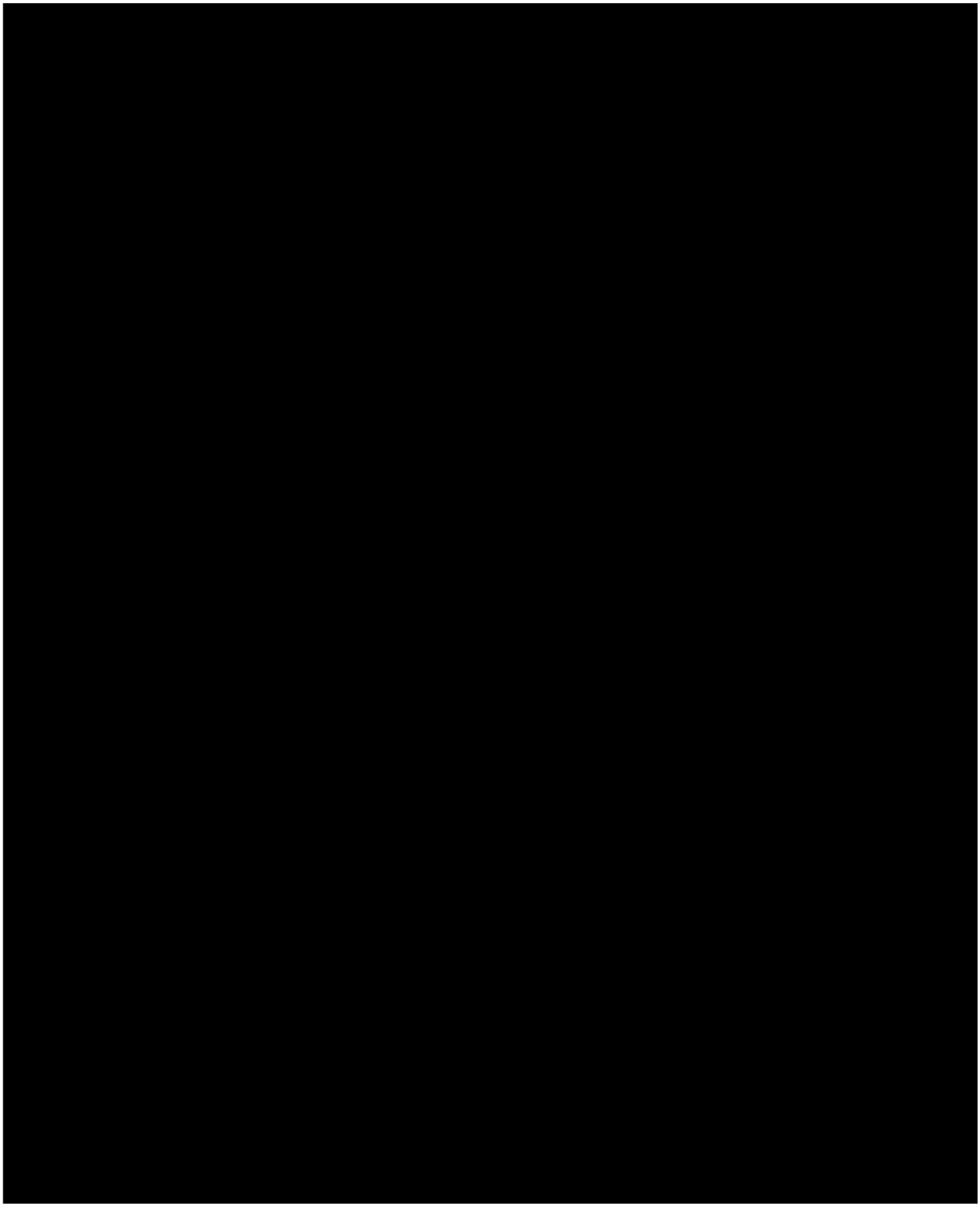
Study name	Reference	Exclusion reason
Negri 2015	Expression of pERK and VEGFR-2 in advanced hepatocellular carcinoma and resistance to sorafenib treatment. Negri FV, Dal Bello B, Porta C, et al. Liver Int (2015) Jan 5.	Biomarker study
Olowokure 2014	Sorafenib (S) in HCC: Is there a role for starting at a total daily dose of 400mg? Olowokure O.O., Singeltary B., Ghose A., et al. J Clin Oncol (2014); 32 (15).	Case control
Pfeiffenberger 2013	Sorafenib treatment is save and may affect survival of recurrent hepatocellular carcinoma after liver transplantation. Pfeiffenberger J., Koschny R., Hoffmann K., et al. Langenbeck`s Archives of Surgery (2013); 398 (8); 1123 - 1128.	Sorafenib Adjuvant/Neoadjuvant
Pinter 2011	Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. Pinter M., Sieghart W., Hucke F.,et al. Alimentary Pharmacology and Therapeutics (2011); 34 (8): 949 - 959.	Case control
Puzanov 2010	Safety and pharmacokinetics (PK) of AMG 479 in combination with erlotinib (E) or sorafenib (S) in patients (pts) with advanced solid tumors. Puzanov I., Sarantopoulos J., Gilbert J., et al. J Clin Oncol (2010); 28 (15).	Disease
Qin 2014	A multicenter, randomized, phase Ib/II trial of the oral c-Met inhibitor MSC2156119J as monotherapy versus sorafenib in Asian patients with MET-positive (MET+) advanced hepatocellular carcinoma (HCC) and Child-Pugh Class A liver function. Qin S., Cheng A.-L., Lim H.Y., et al. J Clin Oncol (2014); 32 (15).	Protocol only
Radu 2013	Treatment of hepatocellular carcinoma in a tertiary Romanian center. Deviations from BCLC recommendations and influence on survival rate. Radu P., Ioana G., Iancu C., et al. Journal of Gastrointestinal and Liver Diseases (2013); 22 (3): 291 - 297.	Study design
Romano 2009	Prospective evaluation of sorafenib (SO) in patients with hepatocellular carcinoma (HCC): Does child score B influence safety? Romano O., Cattan S., Dharancy S., et al. J Hepatology (2009); 50: S28.	Case control
Sangiovanni 2015	Natural history of portal vein thrombosis, evaluated by contrast enhanced ultrasonography (CEUS), in patients with hepatocellular carcinoma	No Extractable data
Santoro 2011	Phase II randomized trial on dose-escalated sorafenib (S) versus best supportive care (BSC) in patients with advanced hepatocellular carcinoma (HCC) with disease progression on prior S treatment.	Progression on sorafenib
Santoro 2013	A phase II randomized dose escalation trial of sorafenib in patients with advanced hepatocellular carcinoma.	Progression on sorafenib
Schmidt 2014	Addition of local hepatic therapy to sorafenib in patients with advanced hepatocellular carcinoma (stage BCLC C). Schmidt L, op den Winkel M, Fischer K, et al. Digestion (2014); 90 (4):219 - 228.	Intervention
Seong 2011	Early experience of combination treatment of sorafenib and radiotherapy in patients with advanced hepatocellular carcinoma (HCC). Seong J. J Clin Oncol (2011); 29 (4 suppl 1).	Sorafenib dose-ranging alone

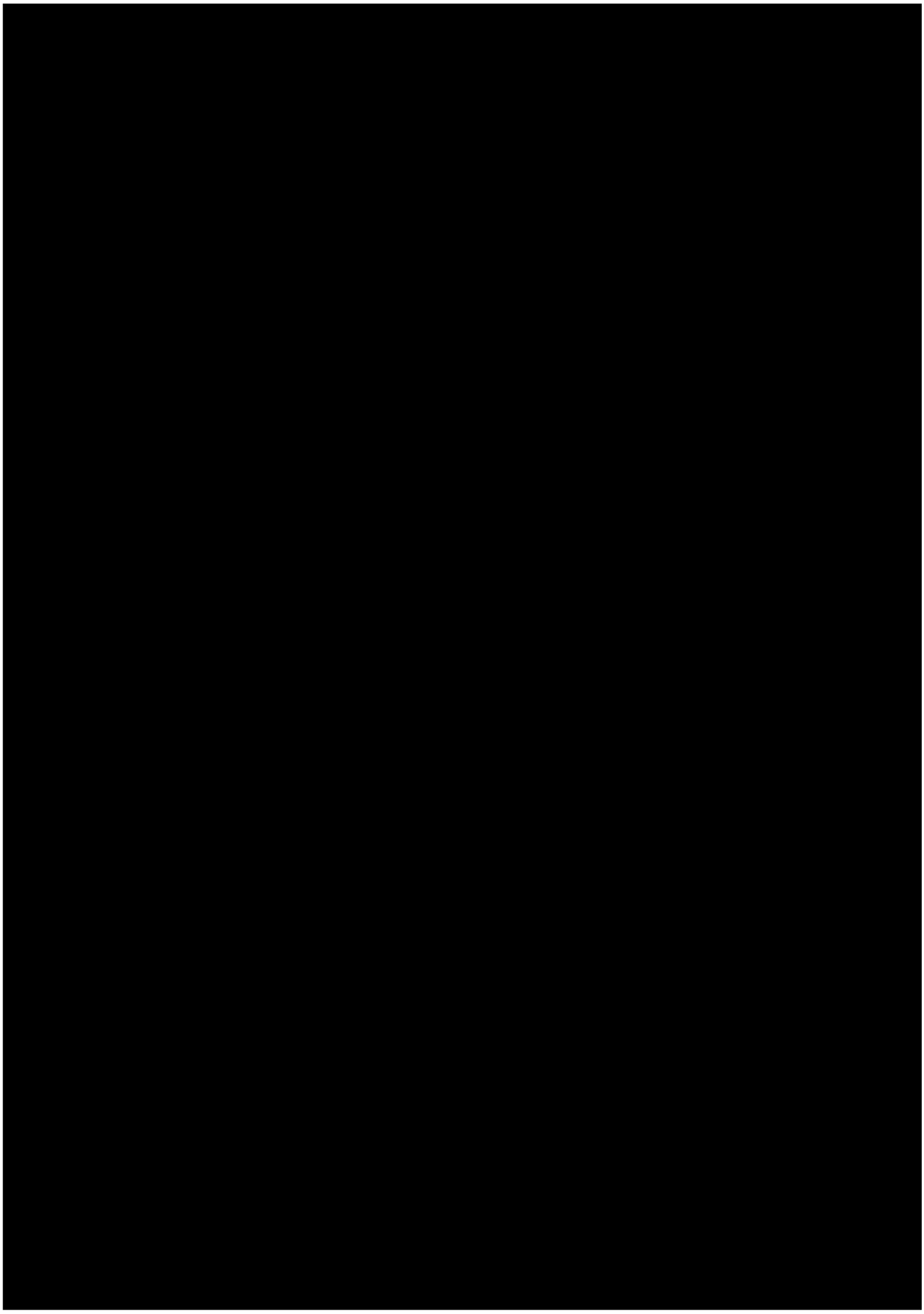
Study name	Reference	Exclusion reason
Shah 2012	Staging of advanced hepatocellular carcinoma patients in the targeted therapy era. Shah N.N., Hassan M., Xiao L., et al. J Clin Oncol (2012); 30 (4).	Study design
Shao 2010	Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. Shao Y.-Y., Lin Z.-Z., Hsu C., et al. Cancer (2010); 116 (19): 4590 - 4596.	Study design
Shao 2013	The BIM deletion polymorphism not associated with treatment efficacy of sorafenib for advanced hepatocellular carcinoma. Shao Y.-Y., Chang Y.-L., Huang C.-Y.,et al. Cancer Res (2013); 73 (8).	Study design
Shao 2014	Prognosis of patients with advanced hepatocellular carcinoma who failed first-line systemic therapy. Shao Y.-Y., Wu C.-H., Lu L.-C., et al. J Hepatol (2014); 60 (2):313 - 318.	Study design
SHELTER trial NCT00943449	Investigation of the HDAC inhibitor resminostat in patients with sorafenib-resistant hepatocellular carcinoma (HCC): Clinical data from the phase I/II SHELTER study	Progression on sorafenib
Staufer 2012	High toxicity of sorafenib for recurrent hepatocellular carcinoma after liver transplantation. Staufer K., Fischer L., Seegers B., et al. Transplant International (2012); 25 (11): 1158 - 1164.	Sorafenib Adjuvant/Neoadjuvant
Subbiah 2013	Characteristics and outcomes of patients with advanced hepatocellular carcinoma treated on phase I trials. Subbiah I.M., Janku F., Tsimberidou A.M., et al. J Clin Oncol (2013); 31 (4).	No SGA for sorafenib
Takashi 2015	Prospective cohort study for evaluating clinical effects and safety of intra-arterial infusion therapy of cisplatin suspension in lipiodol combined with 5-fluorouracil and sorafenib for advanced hepatocellular carcinoma with macroscopic vascular invasion	Intervention
Takeda 2015	Proposal of Japan Red Cross score for sorafenib therapy in hepatocellular carcinoma. Takeda H, Nishikawa H, Osaki Y, et al. Hepatol Res (2015) Jan 11.	Study design
Thiruvenkatachari 2011	Limitations of antineoplastic therapy for hepato cellular carcinoma in a low resource developing country like India. Thiruvenkatachari M. Hepatology International (2011); 5 (1): 458.	No Extractable data
Triolo 2013	Multimodality treatment of hepatocellular carcinoma in a single tertiary referral centre. Triolo M., Sangiovanni A., Manini M.A., et al. Hepatology (2013); 58 (4): 1262A.	Study design
Trojan 2015	Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: Analysis of the European multicentre trial SORAMIC. Trojan J. Liver International (2015); 35 (2): 620 - 626.	Intervention
Uchino 2012	Sorafenib for advanced hepatocellular carcinoma: Comparison with systemic combination therapy of intravenous continuous 5-fluorouracil and pegylated interferon as a historical control. Uchino K., Obi S., Asaoka Y., et al. Hepatology (2012); 56: 461A.	Case control
Ueshima 2011	Phase I/II study of sorafenib in combination with low-dose cisplatin and fluorouracil	Intervention

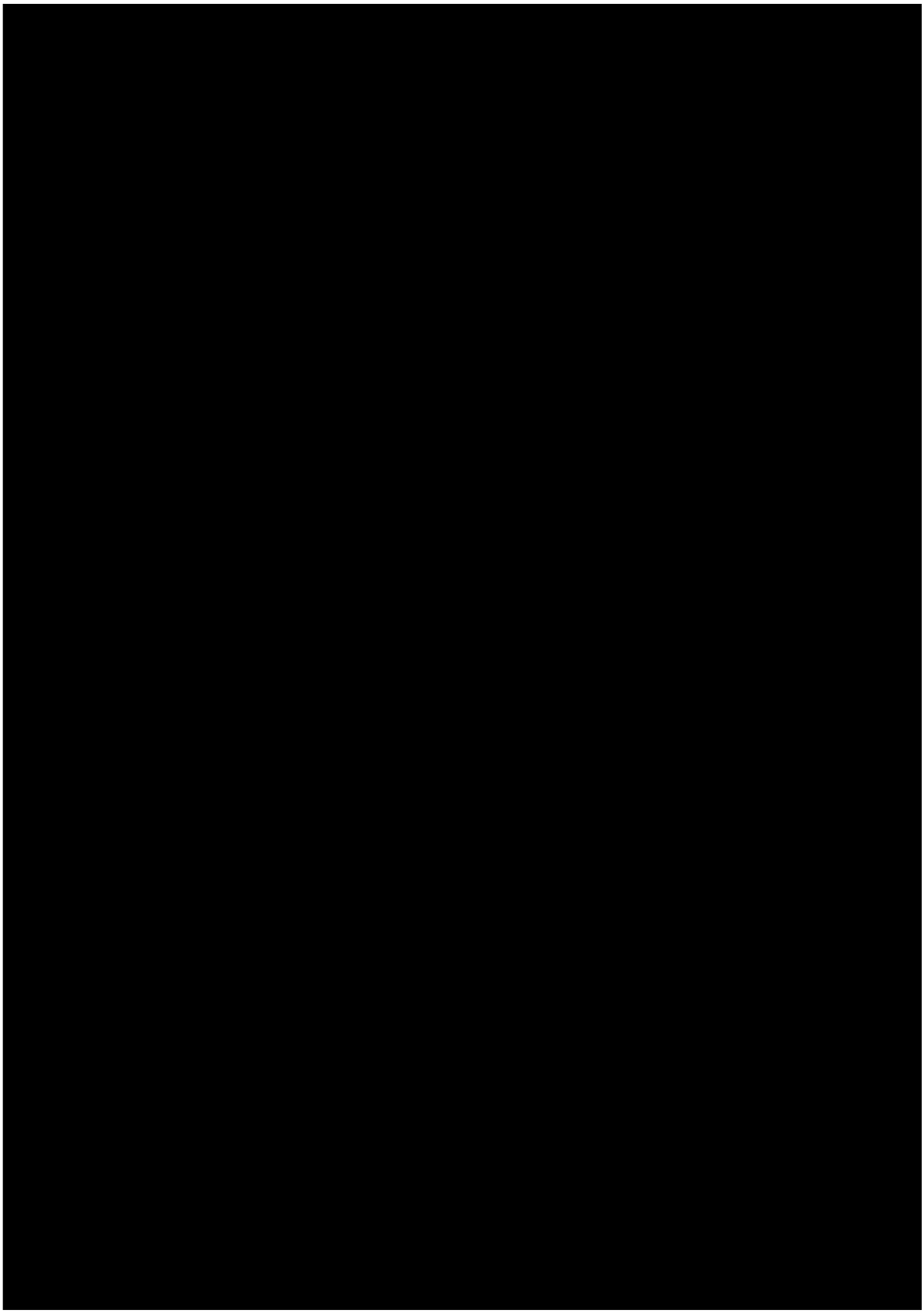
Study name	Reference	Exclusion reason
	intra-arterial infusion chemotherapy	
Vilgrain 2013	Advanced Hepatocellular Carcinoma: early evaluation of response to targeted therapy and prognostic value of Perfusion CT and Dynamic Contrast Enhanced-Ultrasound. Preliminary results. Vilgrain V. Eur J Radiol (2013); 82 (5):e205-211.	Study design
Wada 2016	The Efficacy of Continued Sorafenib Treatment after Radiologic Confirmation of Progressive Disease in Patients with Advanced Hepatocellular Carcinoma.	Progression on sorafenib
Waghray 2012	Safety and efficacy of sorafenib for the treatment of recurrent hepatocellular carcinoma after liver transplantation. Waghray A., Balci B., El-Gazzaz G., et al. Hepatology (2012); 56: 463A - 464A.	Sorafenib Adjuvant/Neoadjuvant
Wang 2014	The combination of HTATIP2 expression and microvessel density predicts converse survival of hepatocellular carcinoma with or without sorafenib. Wang W.-Q., Liu L., Xu H.-X., et al. Oncotarget (2014); 5 (11): 3895 - 3906.	Intervention
Wang 2014	The combination of HTATIP2 expression and microvessel density predicts converse survival of hepatocellular carcinoma with or without sorafenib. Wang WQ, Liu L, Xu HX, et al (2014 Jun 15); 5 (11): 3895 - 3906.	Study design
Woo 2011	Clinical course of sorafenib resistant hepatocellular carcinoma patients	Progression on sorafenib
Woo 2012	Clinical course of sorafenib treatment in patients with hepatocellular carcinoma	Progression on sorafenib
Wu 2015	The effects and adverse reaction of Sorafenib in treating middle and advanced hepatocellular carcinoma	Language/ Non-English
Xu 2015	Antiviral therapy improves survival of patients with hepatitis B virus-related hepatocellular carcinoma who treated with sorafenib. Xu L, Gao H, Huang J, et al. J Gastroenterol Hepatol (2015 Jan 30).	Intervention
Yoon 2013	The comparison of sorafenib and systemic cytotoxic chemotherapy in patients with advanced hepatocellular carcinoma: Results from the historical control group. Yoon E.L., Yeon J.E., Lee H.J., et al. Hepatology International (2013); 7: S591-S592.	Case control
Yoon 2014	Systemic cytotoxic chemotherapy of patients with advanced hepatocellular carcinoma in the era of sorafenib nonavailability. Yoon E.L., Yeon J.E., Lee H.J., et al. J Clin Gastroenterol (2014); 48 (3):e22 - e29.	Case control
Zee 2012	Multistage phase II design for mixed tumor response and time-to-event endpoints: An application for screening new drugs in hepatocellular carcinoma (HCC). Zee B.C.Y., Lai X., Lee A.S., et al. J Clin Oncol (2012); 30 (15).	Study design
Zimmermann 2009	Eligibility of patients with hepatocellular carcinoma for systemic treatment with sorafenib. Zimmermann L.C., Schuette K., Borschein J., et al. J Clin Oncol (2009); 27 (15): e15673.	Study design
Zolfino 2011	Sorafenib and locoregional treatment in patients with stage B and stage C HCC: Sardinian experience. Zolfino T., Piras M.R., Zaru S., et al. J Clin Oncol (2011); 29	Intervention

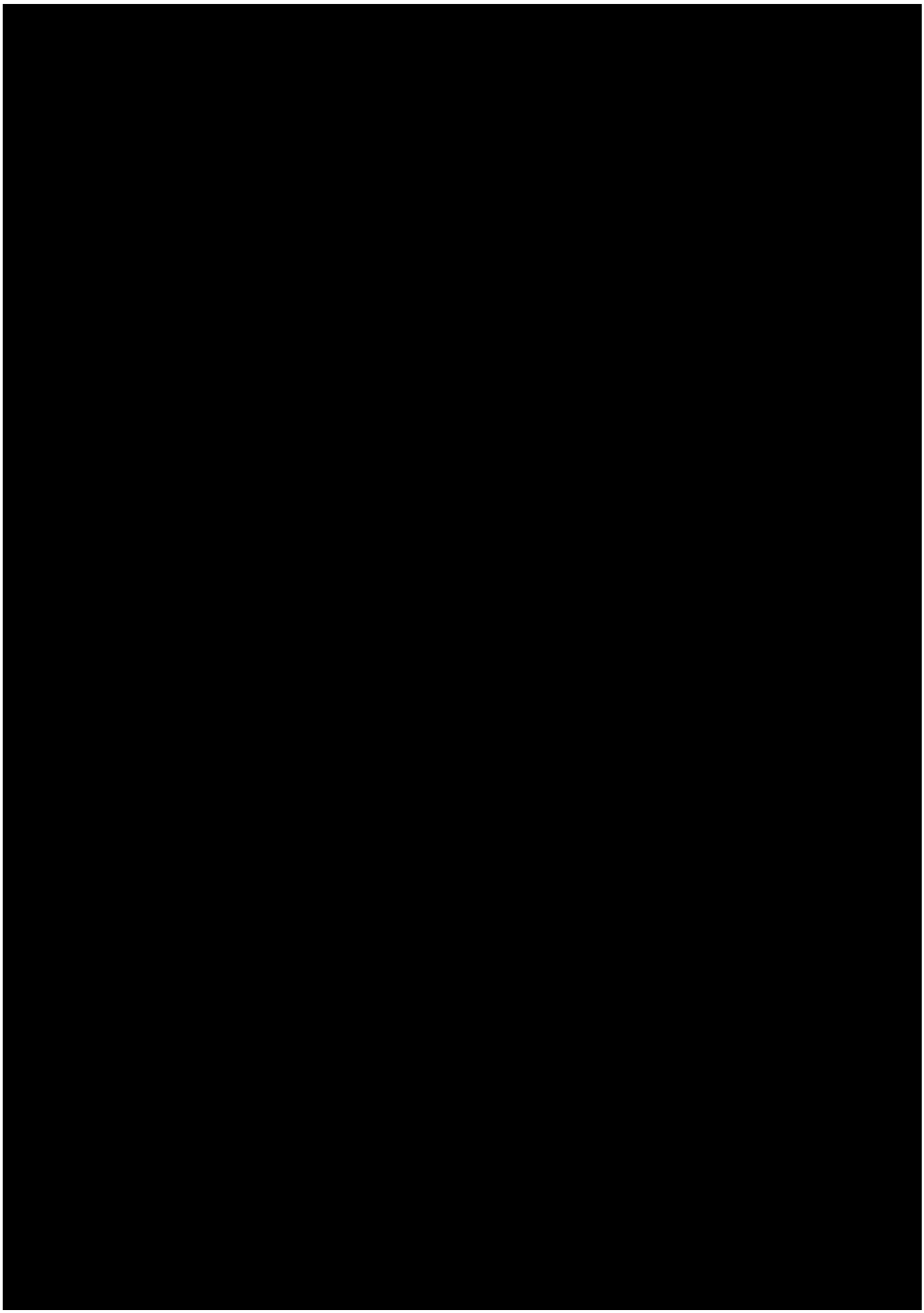
Appendix 8: Commerical Medicines Unit Agreement

8.1 Covering letter: NHS Framework Agreement









8.2 Nexavar® CMU Framework Agreement

Document No. 02

Framework Agreement

for framework agreements/unspecified quantities over a stated contract period where the awarding authority is The Secretary of State for Health acting through the Commercial Medicines Unit (part of the Department of Health) on behalf of the NHS [and other participating authorities]

Contract reference number: CM/PHR/13/5415

THIS FRAMEWORK AGREEMENT is made the 24th day of April 2014

BETWEEN:

(1) **The Secretary of State for Health acting through the Commercial Medicines Unit (part of the Department of Health)** whose principal office is at **Richmond House, 79 Whitehall, London SW1A 2NS (the Authority)**; and

(2) **Bayer Plc** whose registered office is at Bayer House, Strawberry Hill Newbury Berkshire RG14 1JA ('the Supplier').

Individually referred to as a "Party" and together referred to as "the Parties"

WHEREAS:

(A) An advertisement was placed by the Authority in the Official Journal of the European Union on 3 December 2013, reference **2013/S 236-409695** in respect of a framework agreement for the supply of **Proprietary Pharmaceuticals to all Regions (National)** to Participating Authorities (as defined below). Therein the Authority invited offers from economic operators to participate in a competitive tender.

(B) On the basis of its offer, the Authority has selected the Supplier (and may have appointed other suppliers) to provide the Goods/Services (as defined below) to Participating Authorities in the manner and on the terms described herein.

NOW IT IS HEREBY AGREED as follows:

1. **DEFINITIONS**

In this Agreement the following words and phrases shall have the following meanings:

"Agreement"	Means this framework agreement including the appendices hereto and any other documents incorporated by reference herein.
"Commercially Sensitive Information"	means the information (i) listed in the Commercially Sensitive Information Schedule; or (ii) notified to the Authority in writing (prior to the commencement of this Agreement) which has been clearly marked as Commercially Sensitive Information comprised of information: (a) which is provided by the Supplier to the Authority in confidence for the period set out in that Schedule or notification; and/or (b) that constitutes a trade secret.
"Confidential Information"	means any information, which has been designated as confidential by either Party in writing or that ought reasonably to be considered as confidential however it is conveyed, including information that relates to the business, affairs, developments, trade secrets, know-how, personnel and suppliers of the Supplier, including IPRs, together with all information derived from the above, and any other information clearly designated as being confidential (whether or not it is expressly marked as "confidential") or which ought reasonably to be considered to be confidential;
"Electronic Trading System(s)"	means such electronic data interchange system and/or world wide web application and/or other application with such message standards and protocols as the Authority may specify from time to time.
"Employment Legislation"	means the, Equality Act 2010, Part Time Workers (Prevention of Less Favourable Treatment) Regulations 2000, the Fixed Term Employees (Prevention of Less Favourable Treatment) Regulations 2002 or any equivalent legislation applicable in Scotland, Northern Ireland and/or Wales or any other relevant legislation relating to discrimination in the employment of employees, or any other relevant legislation in the United Kingdom relating to discrimination in the employment of

employees.

"Goods / Services"	means the goods and services more particularly described in the Specification.
"Insolvent"	means:

(a) if the Supplier is an individual, that individual or where the Supplier is a partnership, any partner(s) in that firm becomes bankrupt or shall have a receiving order, administration order or interim order made against him, or shall make any composition or scheme of arrangement with or for the benefit of his creditors, or shall make any conveyance or assignment for the benefit of his creditors, or shall purport to do so, or any application shall be made for sequestration of his estate, or a trust deed shall be granted by him for the benefit of his creditors;

(b) if the Supplier is a company, the passing by the Supplier of a resolution for its winding-up or the making by a court of competent jurisdiction of an order for the winding-up of the Supplier or the dissolution of the Supplier, or if an administrator is appointed, or documents are filed with the court for the appointment of an administrator or notice of intention to appoint an administrator is given by the Supplier or its directors or by a qualifying floating charge holder (as defined in paragraph 14 of Schedule B1 to the Insolvency Act 1986), or the appointment of a receiver over, or the taking possession or sale by an encumbrancer of any of the Supplier's assets, or if the Supplier makes an arrangement with its creditors generally or makes an application to a court of competent jurisdiction for protection from its creditors generally; and

(c) any event in any jurisdiction other than England and Wales which is analogous to any of (a) and (b) above.

"Invitation to Offer"	means the invitation to offer issued by the Authority as referred to in Recital (A) comprising the documents listed in the Authority's cover letter to the Supplier.
"Mini-Competition"	means the reopening of competition between the Suppliers appointed to this Framework Agreement in accordance with Article 32 of Directive 2004/18/EC (as implemented by Regulation 19 of the Public Contracts

	Regulations 2006).
"NHS Conditions of Contract"	means the NHS terms and conditions of contract for the purchase of goods (supplementary) February 2012. Included with the Invitation to offer and which will govern any Order raised by a Participating authority.
"the Offer"	means the offer submitted by the Supplier as referred to in Recital (B).
"Order"	means an order raised by a Participating Authority for the supply the Goods/Services pursuant to this Framework Agreement.
"Participating Authorities"	means all or any of the bodies listed in Appendix One and any successor to any such body together with all other bodies incumbent within the listed NHS Pharmacy Purchasing Group or any other bodies authorised by virtue of their inclusion in the relevant OJEU notice to participate in the Framework Agreement.
"Product Information"	means information concerning the Goods/Services supplied by the Supplier to the Authority in accordance with clause 10 for inclusion in the Commercial Medicines Unit's product catalogue from time to time.
"Specification"	Means the specification for the Goods/Services included in the Invitation to offer.
"Supplementary Conditions of Contract"	means the set of supplementary conditions of contract included with the Invitation to offer.
"Terms of Offer"	means the document entitled Terms of offer issued by the Authority as part of the Invitation to offer.

2. DURATION AND SCOPE

2.1 This Framework Agreement shall commence on the dates stated in the Award schedule – Appendix Two below, and shall continue in force until the date stated in the Award schedule, Appendix Two, unless the Authority no later than 3 months prior to the specified dates exercises by notice in writing to the Supplier its option to extend the Framework Agreement. Such extension shall apply to all of the Goods/Services or to such units or parts of the Goods/Services as the Authority may specify in the notice given under this Clause 2.1.

3. OBLIGATIONS OF THE SUPPLIER

3.1 In consideration of (a) the Authority agreeing to appoint the Supplier to this Framework Agreement and (b) the Authority agreeing to pay £5 (five pound) to the Supplier, receipt of which is hereby acknowledged by the Supplier, the Supplier

undertakes to supply Goods/Services of the exact quality, type and price specified in Appendix Two, in such quantities, to such extent and at such times and locations as may be ordered pursuant to this Framework Agreement, in accordance with the terms of the Offer and the NHS conditions of contract for the purchase of goods (supplementary). In the event of any inconsistency between the Terms of the offer and the terms of Appendix Two, the latter shall prevail.

3.2 The Supplier will accept orders pursuant to this Framework Agreement for the Goods/Services from any Participating Authority.

3.3 The Supplier agrees that the NHS conditions of contract for the purchase of goods (supplementary), and the NHS supplementary conditions of contract for the purchase of pharmaceuticals shall apply to all supplies of the Goods/Services made by the Supplier to Participating Authorities pursuant to this Framework Agreement. The Supplier agrees that it will not in its dealings with Participating Authorities seek to impose or rely on any other contractual terms which in any way vary or contradict the NHS conditions of contract for the purchase of goods (supplementary) or the NHS supplementary conditions of contract for the purchase of pharmaceuticals

3.4 The Supplier warrants that in submitting the Offer it has complied with the terms of the Invitation to offer (including in particular but not limited to the Terms of offer). The Supplier also agrees that it will continue to comply with the following provisions of the Terms of Offer throughout the duration of this Framework Agreement:

3.4.1 paragraph 4 (Freedom of Information Act 2000);

3.4.2 paragraph 11 (contract monitoring); and

and that breach of this clause 3 shall constitute a material breach which will entitle the Authority to terminate this Framework Agreement in accordance with clause 14.

4. **PRICE**

4.1 The Supplier acknowledges and agrees that the Authority has entered into this Framework Agreement on the basis of the pricing information supplied to and accepted by the Authority as specified in Appendix Two. The Supplier shall not offer Goods/Services the subject of this Framework Agreement to Participating Authorities at a lower price than has been accepted by the Authority as specified by the Supplier in Appendix Two unless in accordance with Appendix Three or by way of a Mini-Competition conducted in accordance with Regulation 19 of the Public Contracts Regulations 2006 and:

(a) such lower price is not derived via a Mini-Competition from terms which were capable of being fixed and determined at the time of, or before, the Framework Agreement was concluded; and

(b) the resulting price from a Mini-Competition supplements – as an increase or decrease – the price in the concluded Framework Agreement.

4.2 If the Supplier offers Goods/Services the subject of this Framework Agreement to a Participating Authority at a lower price than that specified in Appendix Two, in breach of Clause 4.1 above, this breach shall be deemed to be a material breach of this Framework Agreement, and shall entitle the Authority to terminate this Framework Agreement in accordance with clause 14.

4.3 The right to terminate this Framework Agreement given by Clause 4.2 above shall be without prejudice to any other right or remedy of the Authority in respect of the breach concerned or any other breach.

4.4 The Authority may, at its sole discretion, decide to accept the Supplier's breach of Clause 4.1 above and instead of terminating this Framework Agreement the Authority shall substitute the lower price offered by the Supplier in breach of Clause 4.1 above for the original price specified in Appendix Two.

4.5 Any waiver by the Authority of Clause 4.2 above, pursuant to Clause 4.4 above, shall not be considered as a waiver of any subsequent breach of the same or any other provision of this Framework Agreement.

5. THE POSITION OF PARTICIPATING AUTHORITIES

5.1 Other suppliers, in addition to the Supplier, may have been awarded the right to participate in a framework agreement as a result of the procurement process the subject of the Invitation to offer. Further suppliers may be appointed in the future to supply Goods/Services of the same type as those that are the subject of this Framework Agreement. Accordingly, the Supplier acknowledges that Participating Authorities are under no obligation to place any, or any particular level or volume of Orders with the Supplier under or pursuant to this Framework Agreement. The Supplier accepts that the Authority shall have no liability to it in respect of or arising out of the volume of Orders received by the Supplier during the continuance of this Framework Agreement.

6. THE POSITION OF THE AUTHORITY AND THE COMMERCIAL MEDICINES UNIT

6.1 The Secretary of State acting through the Commercial Medicines Unit, a part of the Department of Health, has established this Framework Agreement as a central purchasing body for and on behalf of such Participating Authorities as may from time to time be Participating Authorities. The supply contracts resulting from such Orders will be between the Supplier and the Participating Authorities concerned and the Authority shall not be a party thereto nor shall the Authority have any liability arising out of the acts or omissions of Participating Authorities in connection with such contracts.

7. ASSIGNMENT

7.1 This Framework Agreement is personal to the Supplier. The Supplier shall not assign, novate, sub-contract or otherwise dispose of this Framework Agreement or any part of it or the benefit or advantage of this Framework Agreement or any part of it without the previous written consent of the Authority.

8. PRE-CONTRACTUAL STATEMENTS

8.1 (Save in the case of fraud) no statements made by or on behalf of the Authority at any time before, during or after the competition leading to conclusion of this Framework Agreement shall add to or vary this Framework Agreement or be of any force or effect unless any such pre-contractual statements are expressly set out in this Framework Agreement. The Supplier waives any right it may have to make any claim whatsoever in connection with any non-fraudulent pre-contractual statements made by or on behalf of the Authority. This waiver shall be unconditional and irrevocable, but it is expressly agreed that it shall not exclude any liability of the Authority for pre-contractual statements made fraudulently.

8.2 Without prejudice to the generality of clause 8.1 the Supplier acknowledges that it has not been induced to enter into this Framework Agreement by any indication as to the volume or content of Orders which might be placed by Participating Authorities.

9. WARRANTY

The Supplier warrants to the Authority that it has all necessary corporate standing and authorisation to enter into and be bound by the terms of this Framework Agreement. At all times in connection with this Framework Agreement, the Supplier shall be an independent contractor and nothing in this Framework Agreement shall create a relationship of the Authority or partnership or a joint venture as between the Supplier and the Authority and accordingly the Supplier shall not be authorised to bind the Authority.

10. ELECTRONIC PRODUCT INFORMATION

10.1 The Supplier shall provide the Authority the Product Information in such manner and upon such media as agreed between the Supplier and the Authority from time to time, for the sole use by the Authority.

10.2 The Supplier warrants that the Product Information is and will be complete and accurate as at the date upon which it is delivered to the Authority and that the Product Information does not contain any data or statement which gives rise to any liability on the part of the Authority following publication of the same in accordance with this clause 10.

10.3 In the event the Product Information ceases to be complete and accurate, the Supplier shall promptly notify the Authority in writing of any modification or addition to or any inaccuracy or omission in the Product Information.

10.4 The Supplier grants the Authority a non-exclusive royalty free licence in perpetuity to use and exploit the Product Information and any intellectual property therein for the purpose of illustrating the range of goods and services (including, without limitation, the Goods/Services the subject of this Framework Agreement) available pursuant to the Authority's contracts from time to time. No right to illustrate or advertise the Product Information is granted to the Supplier by the Authority as a consequence of the licence conferred by this clause 10.4 or otherwise under the terms of this Framework Agreement.

10.5 The Authority may reproduce for its sole use the Product Information provided by the Supplier in the Commercial Medicines Unit's product catalogue from time to time which shall be made available on the National Health Service internal communications network in electronic format or made available on the Commercial Medicines Unit's external website or any other electronic media of the Commercial Medicines Unit from time to time.

10.6 Before any publication of the Product Information (electronic or otherwise) is made by the Authority, it will submit a copy of the relevant sections of its product catalogue to the Supplier for approval, such approval not to be unreasonably withheld or delayed. For the avoidance of doubt the Supplier shall have no right to compel the Authority to exhibit the Product Information in any product catalogue as a result of the approval given by it pursuant to this clause 10.6 or otherwise under the terms of this Framework Agreement.

10.7 If requested in writing by the Authority, the Supplier and the Authority shall forthwith negotiate in good faith an agreement to use the Electronic Trading System.

11. SALES INFORMATION

11.1 If requested by the Authority, the Supplier shall provide the Authority with statements giving accurate and complete details of the quantity and value of the Goods/Services supplied by the Supplier to Participating Authorities pursuant to this Framework Agreement. The frequency, format and level of detail to be included in such statements shall be as specified by the Authority in the Invitation to offer, or as otherwise agreed between the Authority and the Supplier.

11.2 The Supplier shall keep at its normal place of business detailed, accurate and up to date records of the quantity and value of the Goods/Services sold by it to any Participating Authority pursuant to this Framework Agreement, together with accurate details of the identity of the Participating Authority to which such Goods/Services were sold. Subject to any other auditing process being agreed between the Authority and the Supplier in writing, the Authority shall be entitled by prior appointment to enter the Supplier's normal place of business during normal office hours and to inspect such records in order to verify whether any statement supplied by the Supplier to the Authority pursuant to clause 11.1 is accurate and complete.

12. TRANSPARENCY

12.1 The Parties acknowledge that, except for any information which is exempt from disclosure in accordance with the provisions of the FOIA and or the Environmental Information Regulations, the content of this Framework Agreement is not Confidential Information. The Authority shall be responsible for determining in its absolute discretion whether any of the content of this Framework Agreement is exempt from disclosure in accordance with the provisions of the FOIA and or the Environmental Information Regulations. Notwithstanding any other term of the Framework Agreement, the Supplier hereby gives its consent for the Authority to publish the Framework Agreement in its entirety (but with any information which is exempt from disclosure in accordance with the provisions of the FOIA and or the Environmental Information Regulations redacted), including from time to time any agreed changes to the Framework Agreement, to the general public.

12.2 The Authority may, at its sole discretion, redact information from the Framework Agreement prior to publishing for one or more of the following reasons:

(a) national security;

(b) personal data;

(c) information protected by intellectual property law;

(d) confidentiality including third party confidential information;

(e) IT security;

(f) prevention of fraud; and/or

(g) commercial sensitivity.

12.3 The Authority may consult with the Supplier to inform its decision regarding any redactions but the Authority shall have the final decision in its absolute discretion.

13. EQUALITY AND NON-DISCRIMINATION

13.1 In fulfilling its obligations under this Framework Agreement the Supplier shall ensure that it complies with all current Employment Legislation and in particular, does not unlawfully discriminate in breach of any Employment Legislation.

13.2 The Supplier shall take all reasonable steps (at its own expense) to ensure that any employees employed to fulfil the Supplier's obligations under this Framework Agreement do not unlawfully discriminate in breach of any Employment Legislation.

13.3 In the management of its affairs and the development of its equality and diversity policies, the Supplier shall co-operate with the Authority in light of the Authority's obligations to comply with statutory equality duties. The Supplier shall take such steps as the Authority considers appropriate to promote equality and diversity, including race equality, equality of opportunity for disabled people, gender equality, and equality relating to religion and belief, sexual orientation and age in the fulfilment of its obligations under this Framework Agreement.

14. TERMINATION BY THE AUTHORITY

14.1 The Authority may terminate this Framework Agreement by serving written notice on the Supplier in any of the following circumstances:

14.1.1 a material failure by the Supplier to perform any obligation of the Supplier under this Framework Agreement provided that (if capable of remedy) such failure has not been remedied to the Authority's reasonable satisfaction within a period of 30 days following written notice demanding remedy of the failure in question being served by the Authority on the Supplier; or

14.1.2 the Supplier fails to perform any material obligation of the Supplier under this Framework Agreement on more than three occasions; or

14.1.3 the Supplier becomes Insolvent or otherwise ceases to be capable of supplying the Goods/Services the subject of this Framework Agreement; or

14.1.4 the Supplier is in default of any duty of care or any fiduciary or statutory duty owed to the Authority and/or any employee or agent of the Authority; or

14.1.5 there is a change of ownership or control of the Supplier which, in the reasonable opinion of the Authority will have a material impact on the supply of the Goods/Services the subject of this Framework Agreement or the image of the Authority; or

14.1.6 the Supplier purports to dispose of this Framework Agreement in breach of clause 7; or

14.1.7 the Supplier shall have offered or given or agreed to give to any person any gift or consideration of any kind as an inducement or reward for doing or forbearing to do, or for having done or forborne to do, any action in relation to the obtaining or execution of this Framework Agreement or any contract with a Participating Authority pursuant to this Framework Agreement, or for showing or forbearing to show favour or disfavour to any person in relation to this Framework Agreement or any contract with a Participating Authority

pursuant to this Framework Agreement; or similar acts have been done by any person employed by it or acting on its behalf (whether with or without the knowledge of the Supplier); or

14.1.8 if in relation to this Framework Agreement or any contract with a Participating Authority pursuant to this Framework Agreement, the Supplier or any person employed by it or acting on its behalf shall have committed any offence under the Prevention of Corruption Acts 1889 to 1916, or shall have given any fee or reward to any officer of the Authority which shall have been exacted or accepted by such officer under colour of his office or employment and is otherwise than such officer's proper remuneration.

14.2 The Supplier agrees and acknowledges that the Authority is entitled to recover any costs the Authority, and/or any Participating Authorities, may incur in consequence of the Authority terminating this Framework Agreement pursuant to this clause 14.

14.3 The Supplier agrees that upon termination for any reason or expiry of this Framework Agreement it shall not be entitled to make a claim against the Authority in relation to costs incurred by the Supplier in providing the Goods/Services or costs incurred in acquiring equipment and/or materials used in the provision of the Goods/Services or in engaging third parties in connection with the Goods/Services the subject of this Framework Agreement.

14.4 Where the Authority terminates this Framework Agreement under this clause 14 this shall not in any way affect the validity of any Order raised by a Participating Authority prior to the date of such termination.

15. **GENERAL**

15.1 The parties accept the exclusive jurisdiction of the English courts in respect of any disputes that may arise out of this Framework Agreement and agree that this Framework Agreement is to be governed and construed in accordance with English law.

15.2 Any notice to be given pursuant to this Framework Agreement shall be in writing and shall be deemed duly served four days after it has been sent by pre-paid registered post to the address of the other party set out above or to such other address as may be notified by the recipient to the sender for the purposes of this clause.

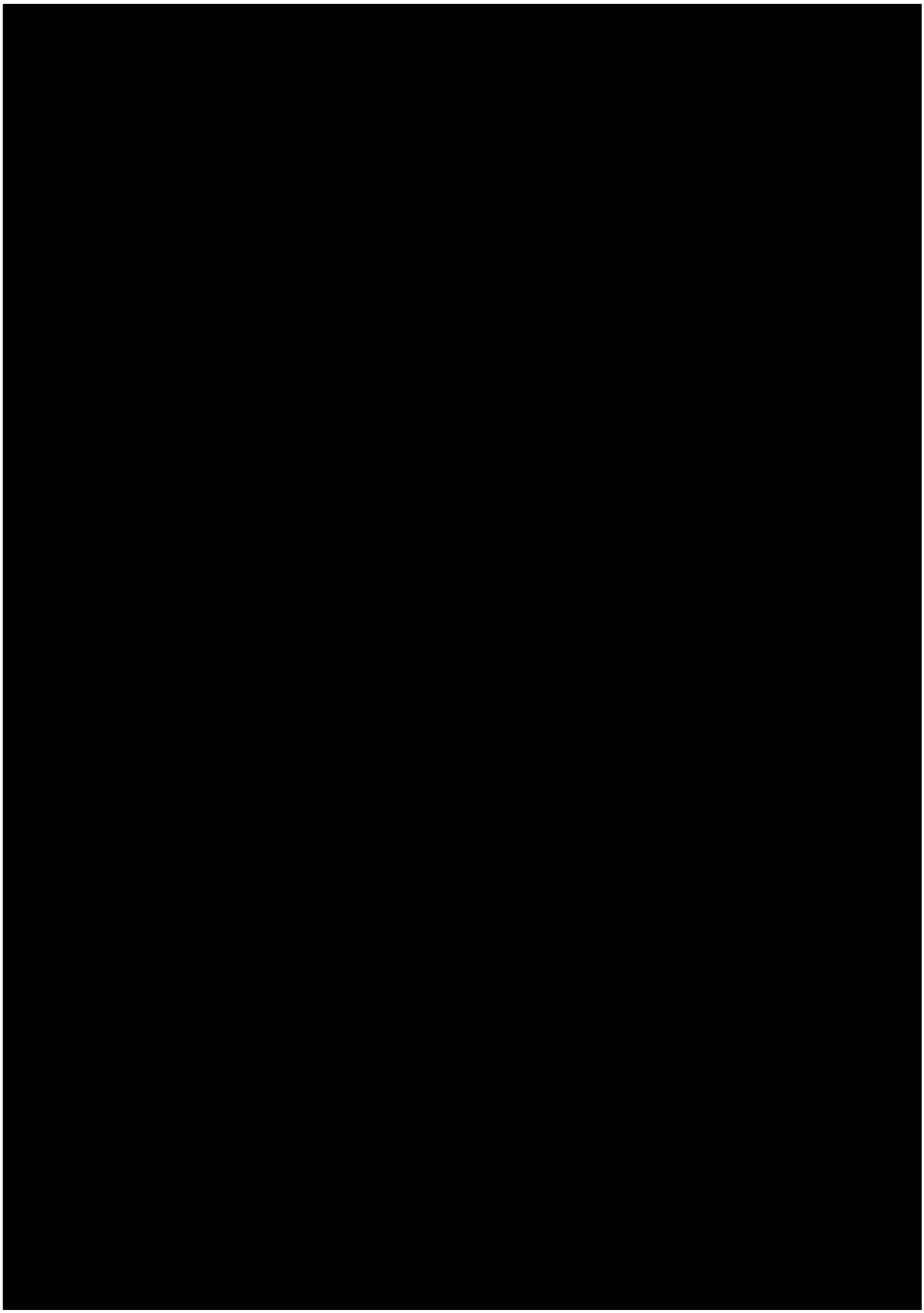
15.3 No amendment of this Agreement shall be valid unless agreed in writing by a duly authorised representative of each of the parties.

15.4 The failure by the Authority or the Supplier to insist upon the strict performance of any provision, term or condition of this Framework Agreement or to exercise any right or remedy consequent upon the breach thereof shall not constitute a waiver of any such breach or any subsequent breach of such provision, term or condition.

SIGNED by and on behalf of the Parties on the date which first appears in this Agreement.

APPENDIX ONE
Participating Authorities

APPENDIX TWO
Details of Goods/Services and Prices



APPENDIX THREE

Framework Agreement Price Variation and Additional Goods

1. Price Variations

1.1 At the end of every Pricing Period, the Authority may review the prices payable from time to time for the Goods ("the Review"). The Authority shall be entitled to increase or decrease the price of the Goods/Services in the event that such price does not in the reasonable opinion of the Authority reflect the market price. In assessing the market price under this paragraph 1.1, the Authority shall take into account the prices payable by other health authorities and NHS Trusts for goods which are reasonably equivalent to the Goods, but such market price shall be decided without reference to the prices then payable for the Goods under this Framework Agreement.

1.2 Within one month of the end of the relevant Pricing Period, the Authority may increase or decrease the price of the Goods by giving the Supplier not less than 1 month's written notice of such increase or decrease ("the Review Notice") and the Review Notice shall stipulate the new prices as varied pursuant to the Review ("the Revised Prices") and the reasons for this. The Supplier shall be entitled to supply the Goods at the revised prices as soon as it receives the Review Notice but otherwise the Revised Prices shall take effect automatically upon expiry of the Review Notice (unless the Supplier serves notice to terminate under paragraph 1.3 below in which case paragraph 1.4 below shall apply).

1.3 The Supplier may terminate this Framework Agreement by giving to the Authority not less than three months' notice in writing, such notice to be given within 14 days of its receipt of a Review Notice under paragraph 1.2 above.

1.4 For the avoidance of doubt, if the Supplier serves notice to terminate under paragraph 1.3 above until such notice expires, the prices shall remain fixed at the price payable immediately preceding the Review to which the Review Notice relates.

1.5 For the further avoidance of doubt, if the Supplier serves notice to terminate under paragraph 1.3 above the Supplier shall be obliged to supply the Goods in accordance with the terms of this Framework Agreement and any order that may be placed prior to the date of termination.

1.6 For the purpose of this paragraph 1, "Pricing Period" means:-

1.6.1 in the case of the first Review to be carried out by the Authority, the period ending at the end of the [fifth/eleventh] month after the date of this Framework Agreement; or

1.6.2 in the case of the second or any subsequent Review to be carried out by the Authority, a consecutive period of four calendar months after the first Review carried out pursuant to paragraph 1.6.1.

2. Additional Goods

2.1 Goods may be added to this Framework Agreement if they are within the same product range as any goods supplied from time to time under this Framework Agreement. The additional goods will be deemed to be within such product range if they are made with the same active ingredient(s) and the Supplier is the sole source of supply of such additional goods. Provided that each proposal for the supplier to provide additional goods shall be assessed by the Authority and this shall not place any obligation on the Authority to purchase such additional goods from the Supplier in breach of any law relating to public procurement. In all other cases where supply of additional goods is available from third parties, the Authority shall apply the statutory procedures to enable the Supplier and any third parties to participate in such exercise.

2.2 If the Supplier wishes to add additional goods to this Framework Agreement, it shall give the Authority one-month prior notice in writing of the identity and price of the additional goods.

2.3 The Authority reserves the right not to add the additional goods (being the subject matter of the notice given by the Supplier under paragraph 2.2 above) to this Framework Agreement. If the Authority wishes to exercise this right, it shall, within 14 days of the notice given by the Supplier under paragraph 2.2 above, give the Supplier notice in writing to that effect.

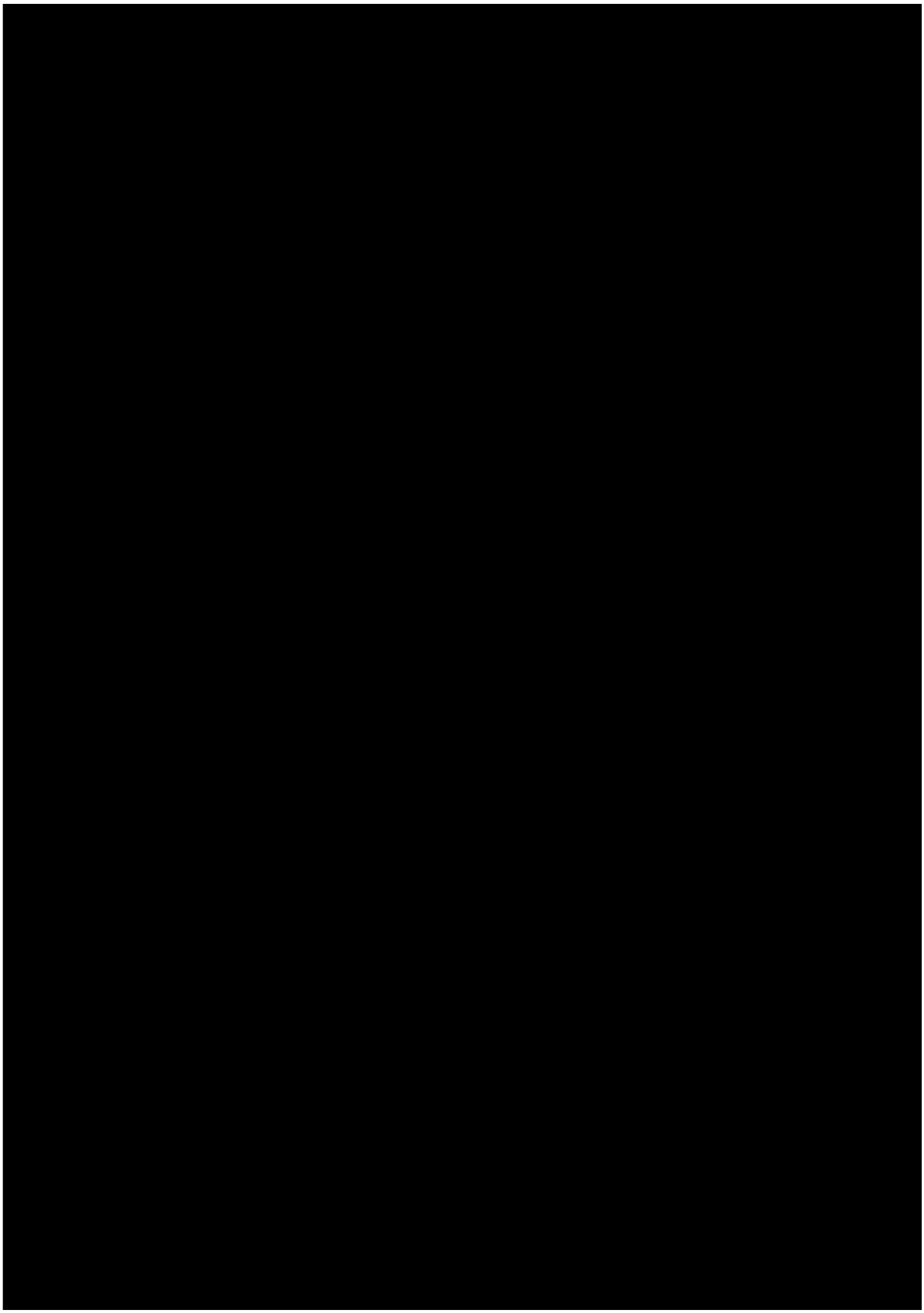
2.4 The price of the additional goods shall be the price offered by the Supplier under paragraph 2.2 above.

3. Termination by Supplier

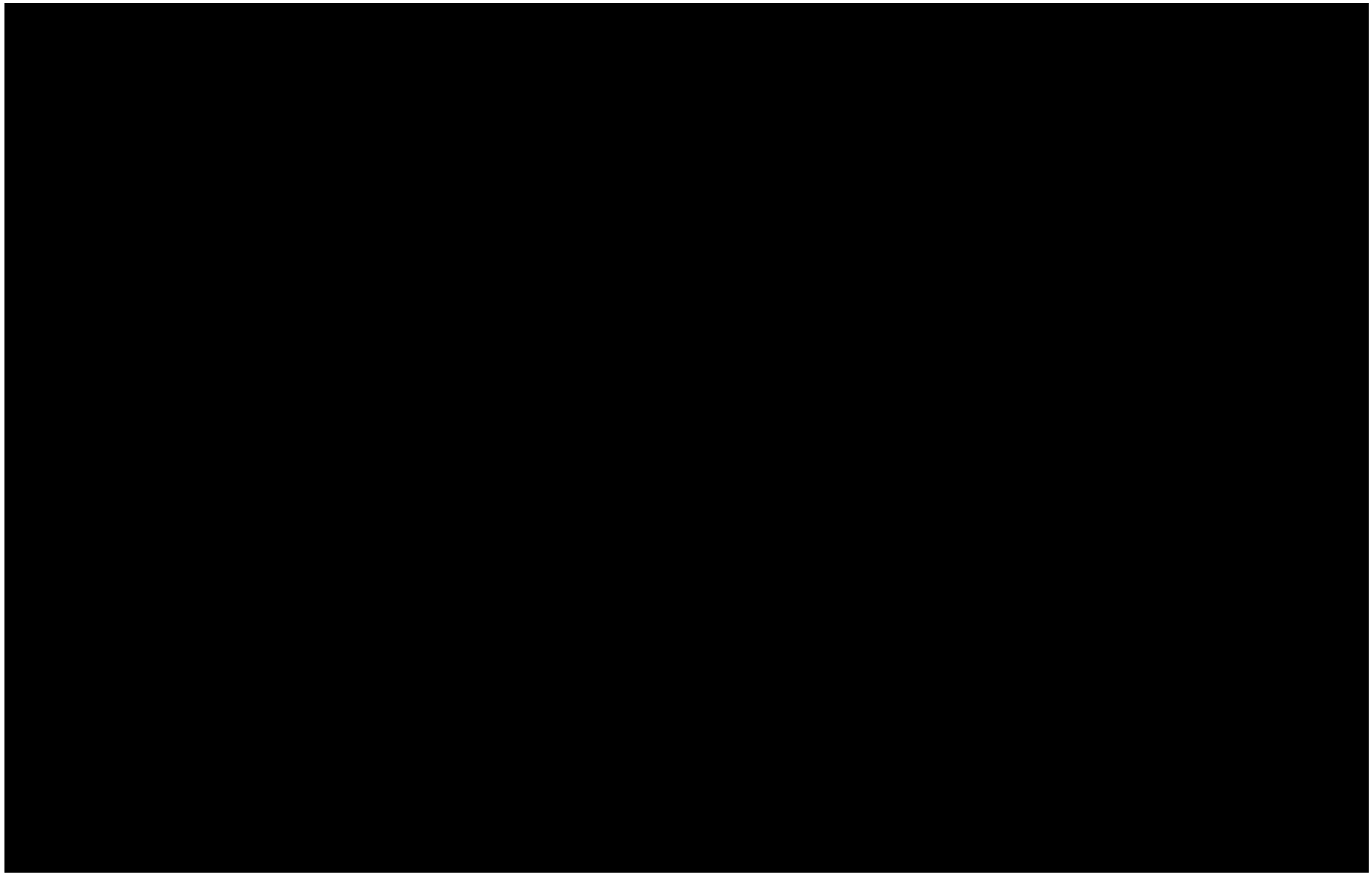
3.1 The Supplier may terminate this Framework Agreement by giving to the Authority not less than three months' notice in writing, such notice to be given within fourteen days of its receipt of either of the notices referred to in Clause 2.1 of this Framework Agreement.

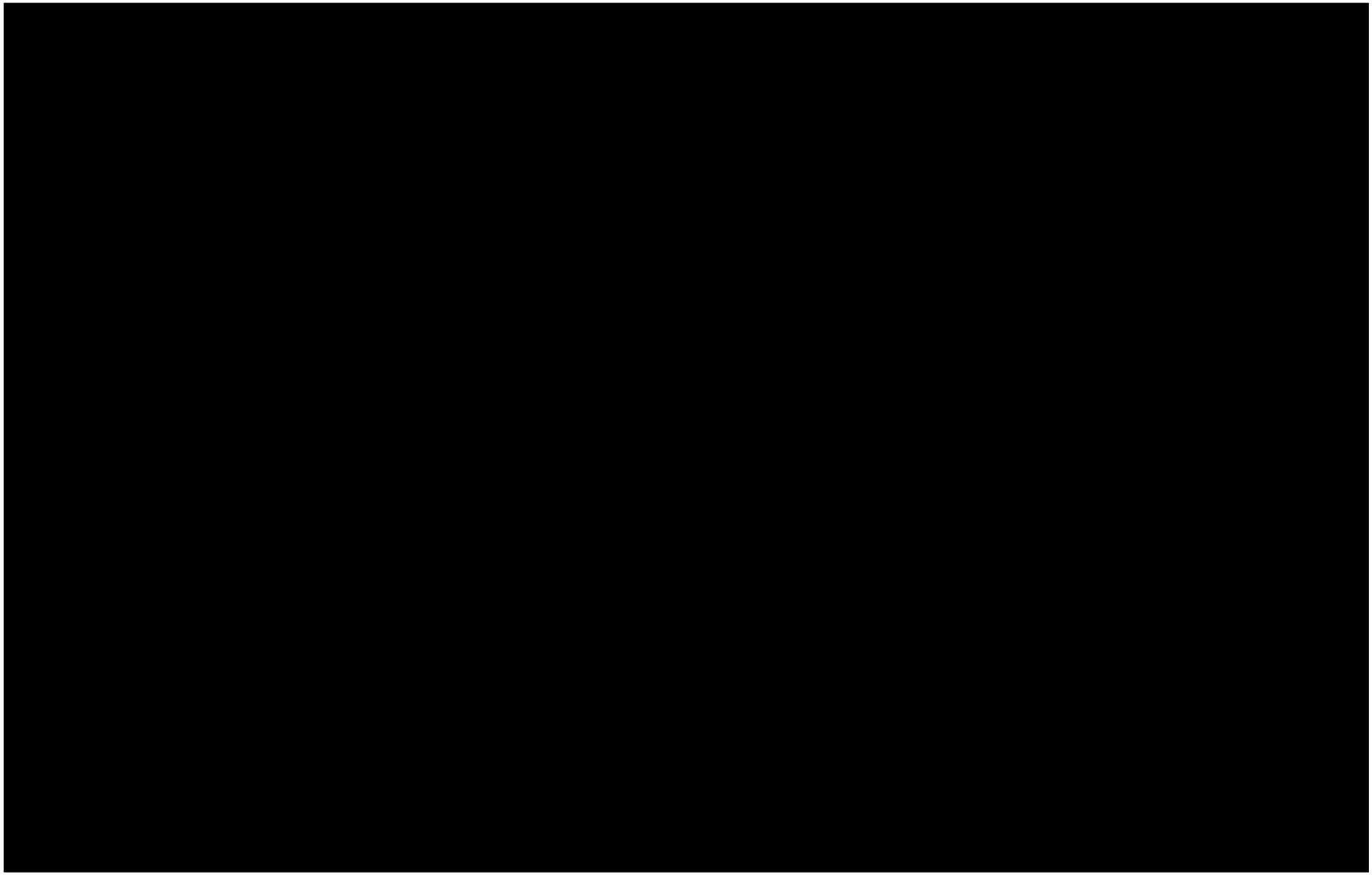
3.2 In the event that the Supplier (acting reasonably and in good faith) intends to cease to manufacture or to market any particular product line of the Goods in the United Kingdom the Supplier may terminate the supply under this Framework Agreement of such product line by giving three months' written notice to the Authority to such effect. The Supplier shall give reasonable details in its notice of the grounds for ceasing to manufacture or market the product line in the United Kingdom.

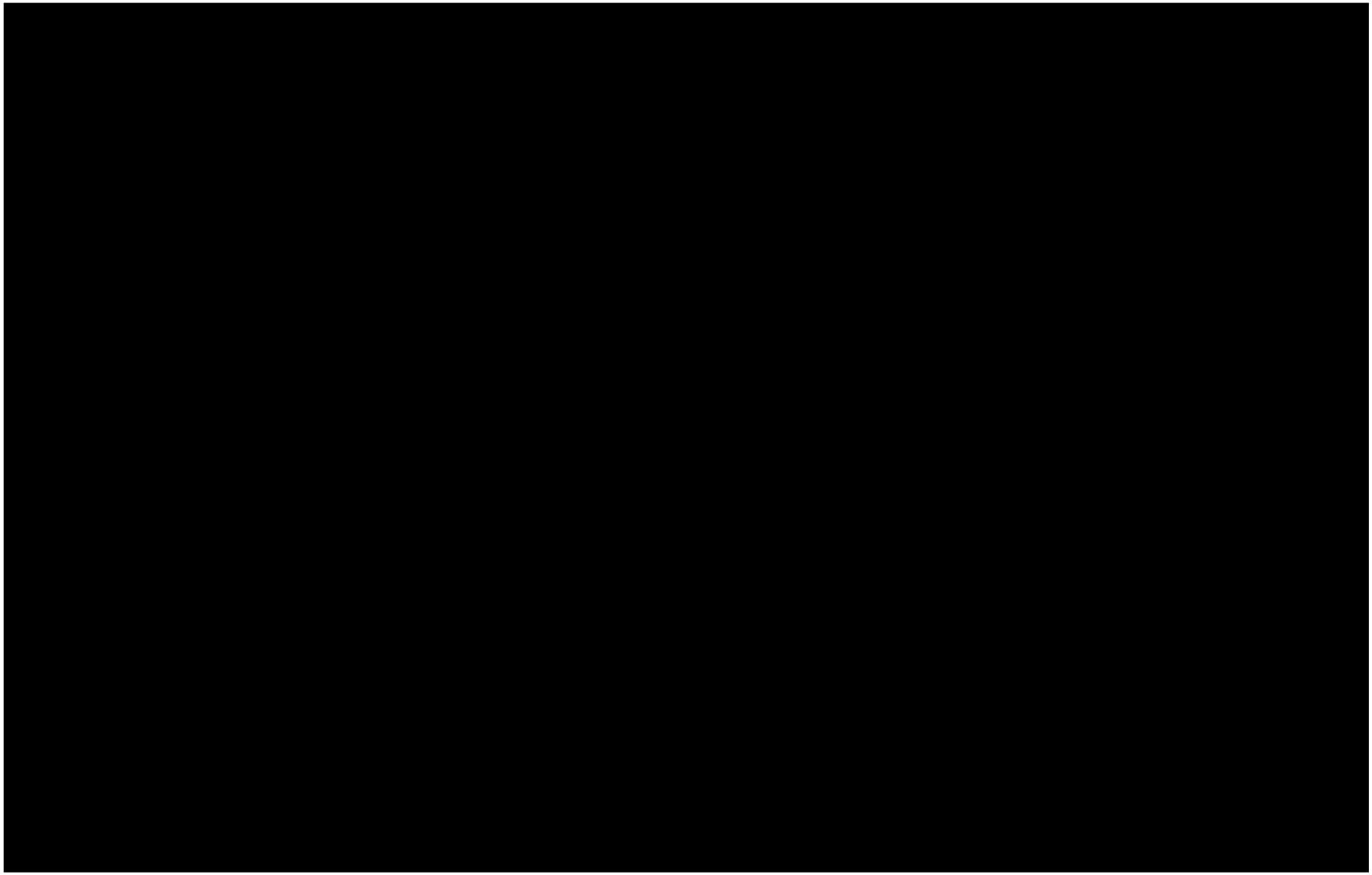
3.3 For the avoidance of doubt, in the event that the Supplier gives notice under paragraph 3.1 or paragraph 3.2 above, the Supplier shall be obliged to supply the Goods (in accordance with the terms of this Framework Agreement) pursuant to any Order that may be placed by, or on behalf of, customers prior to the expiry of the notice.

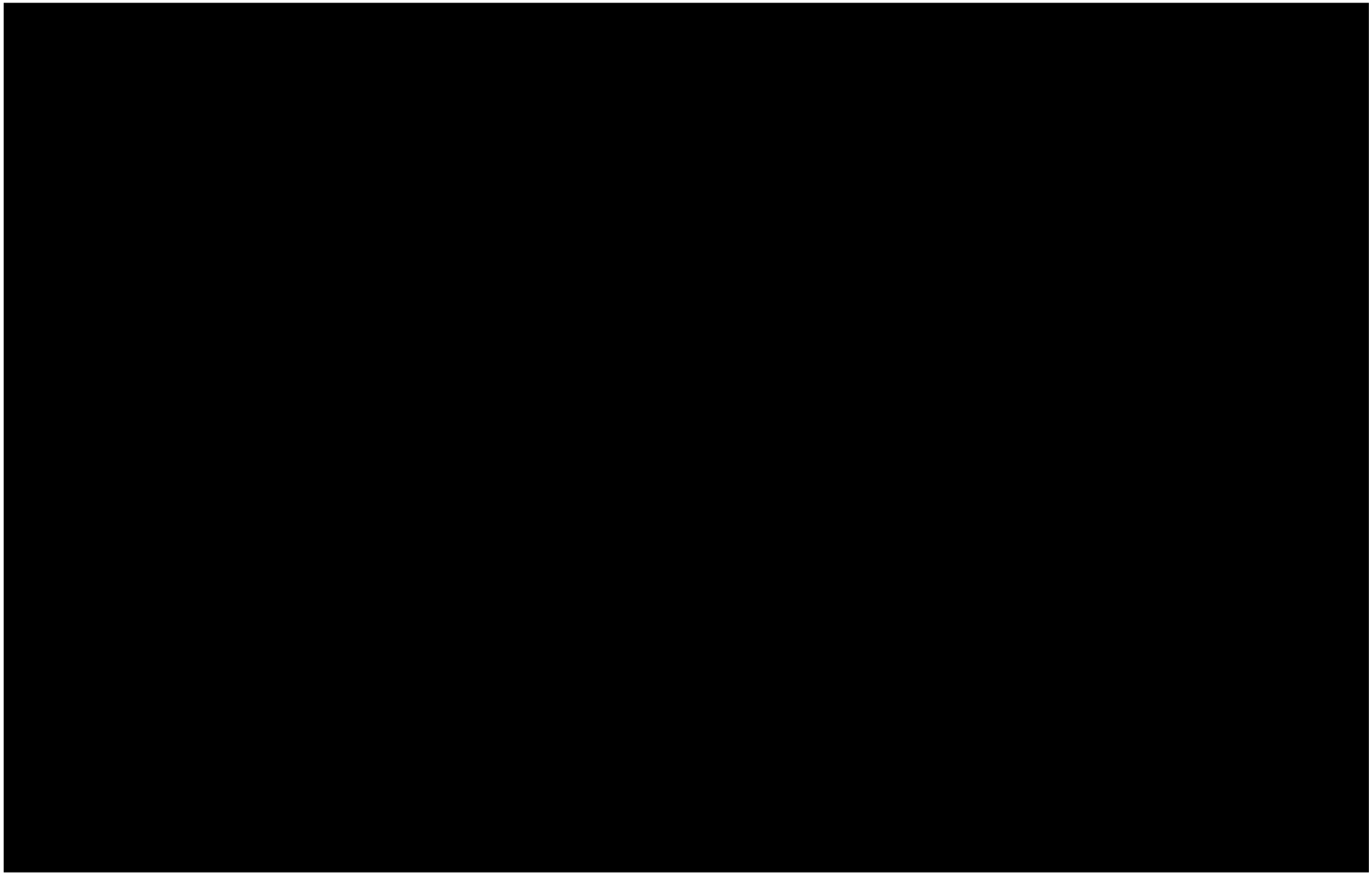


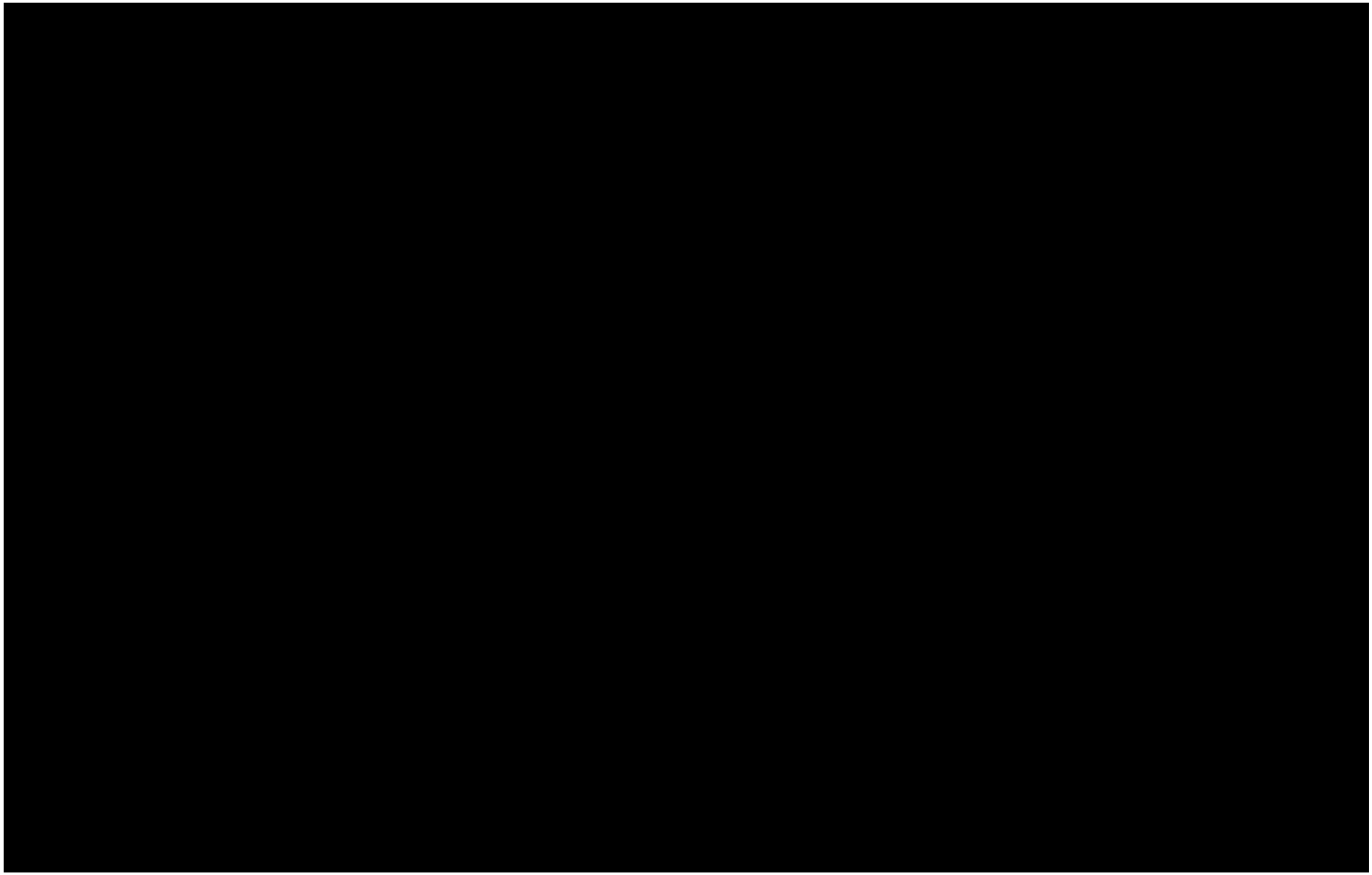
8.3 CMU Framework Participants

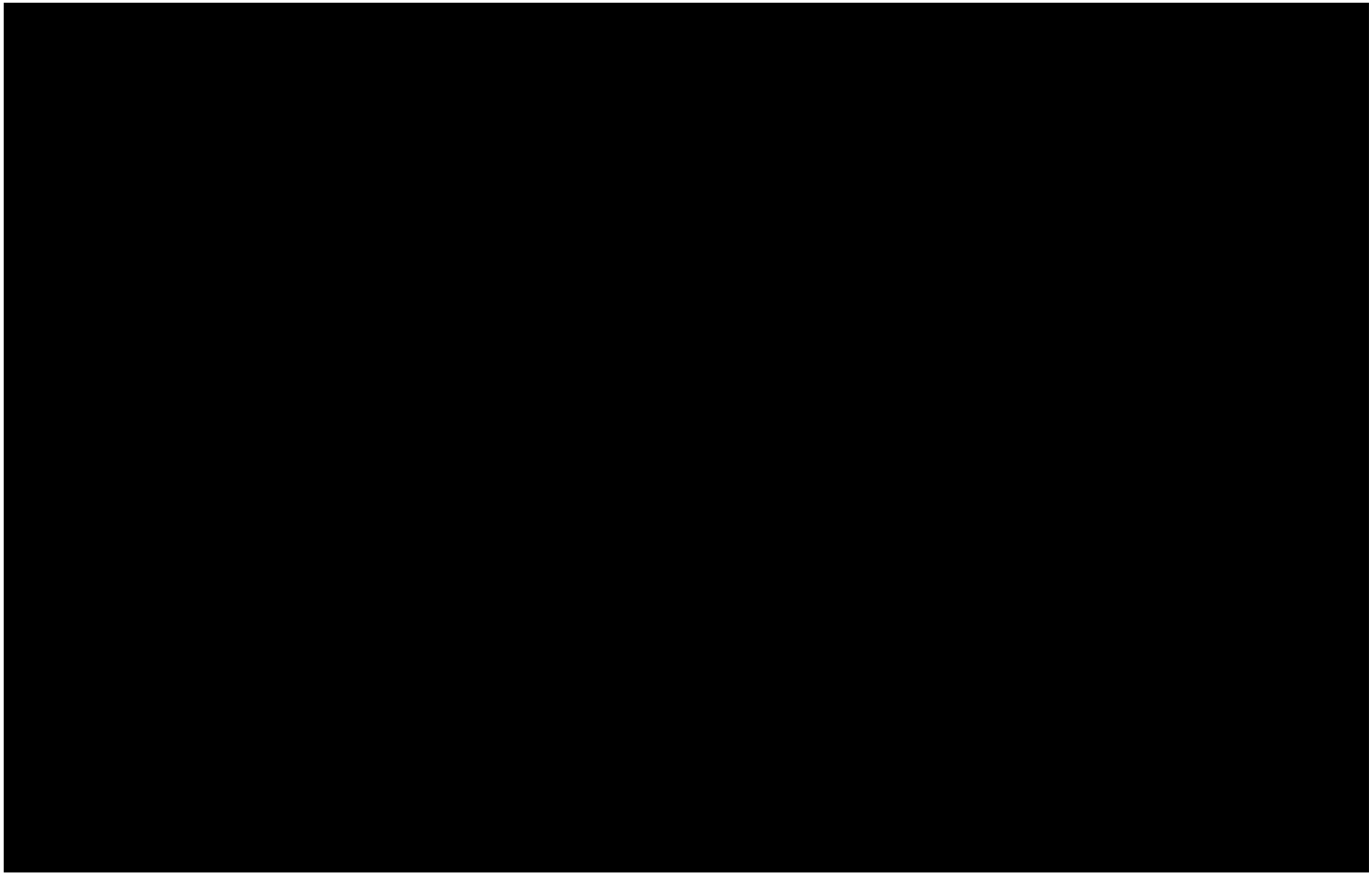


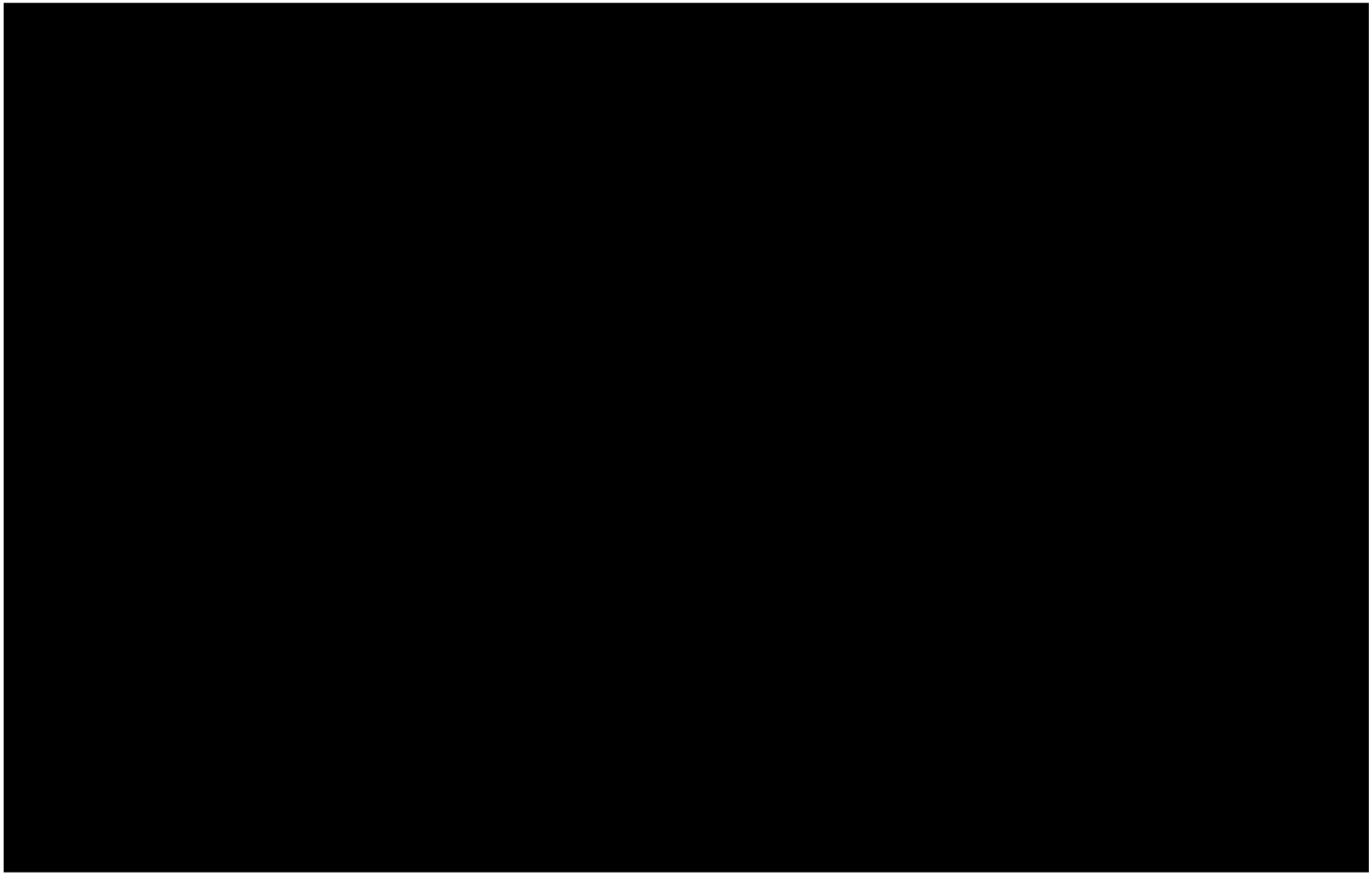


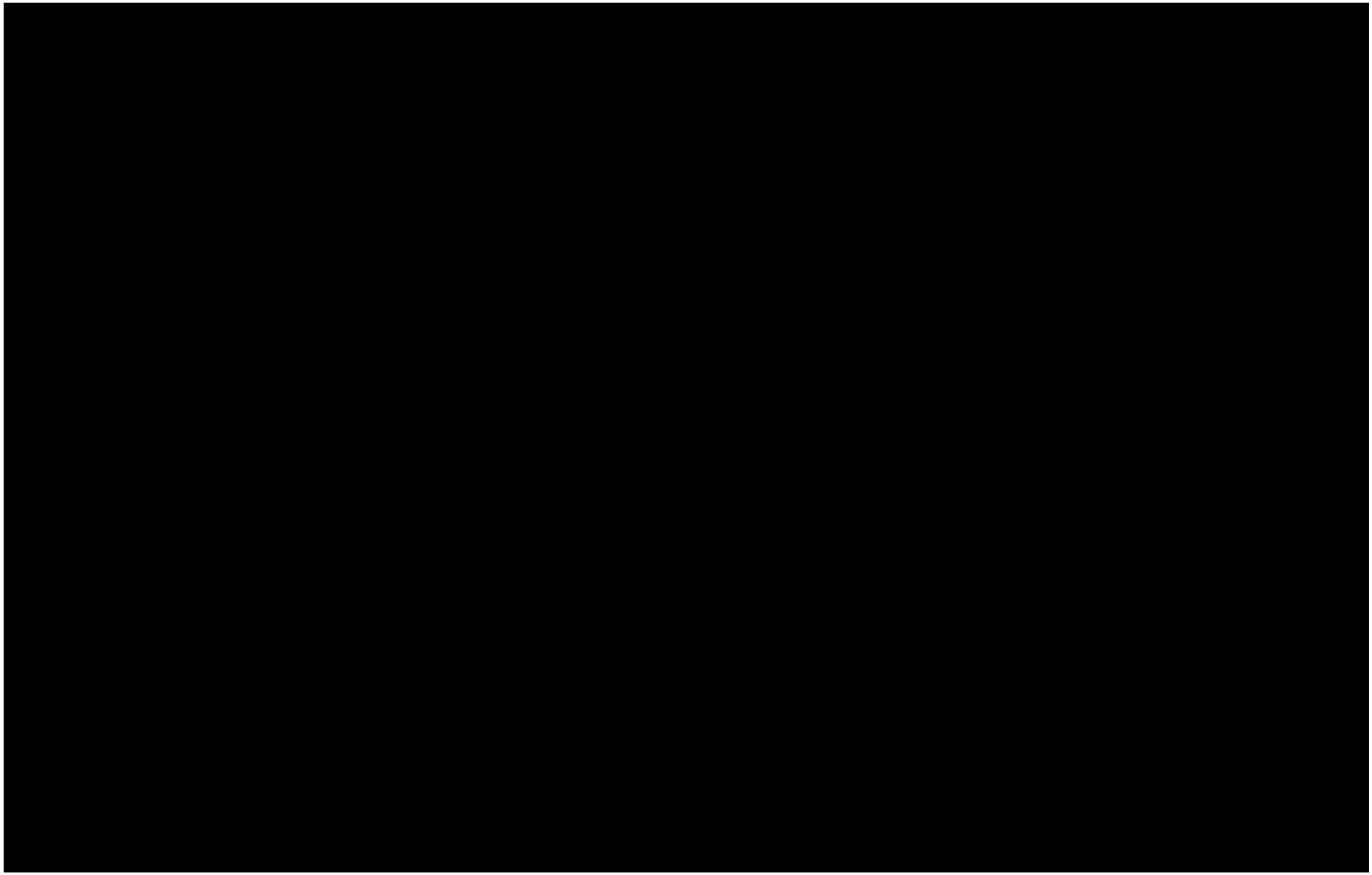


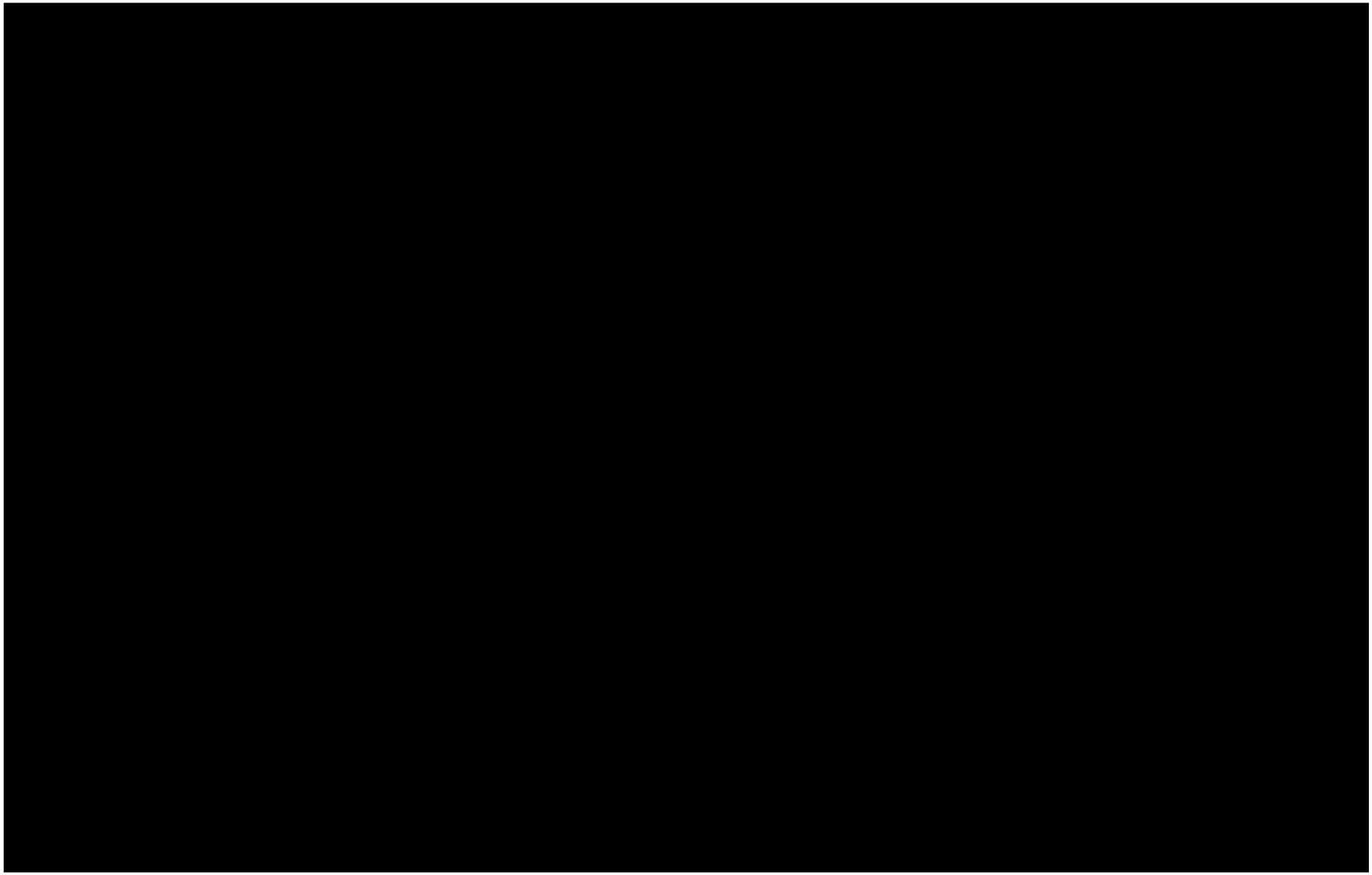


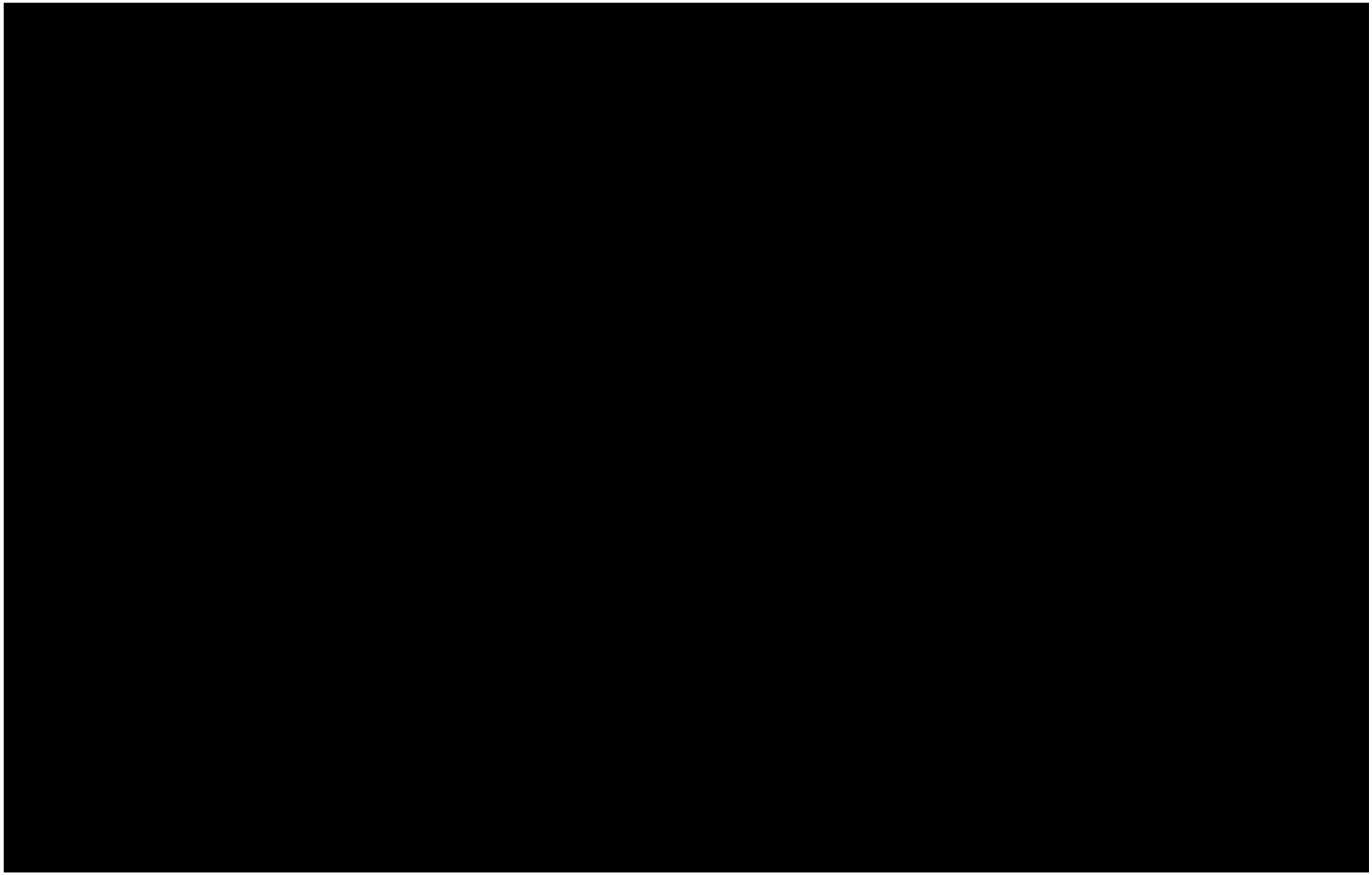


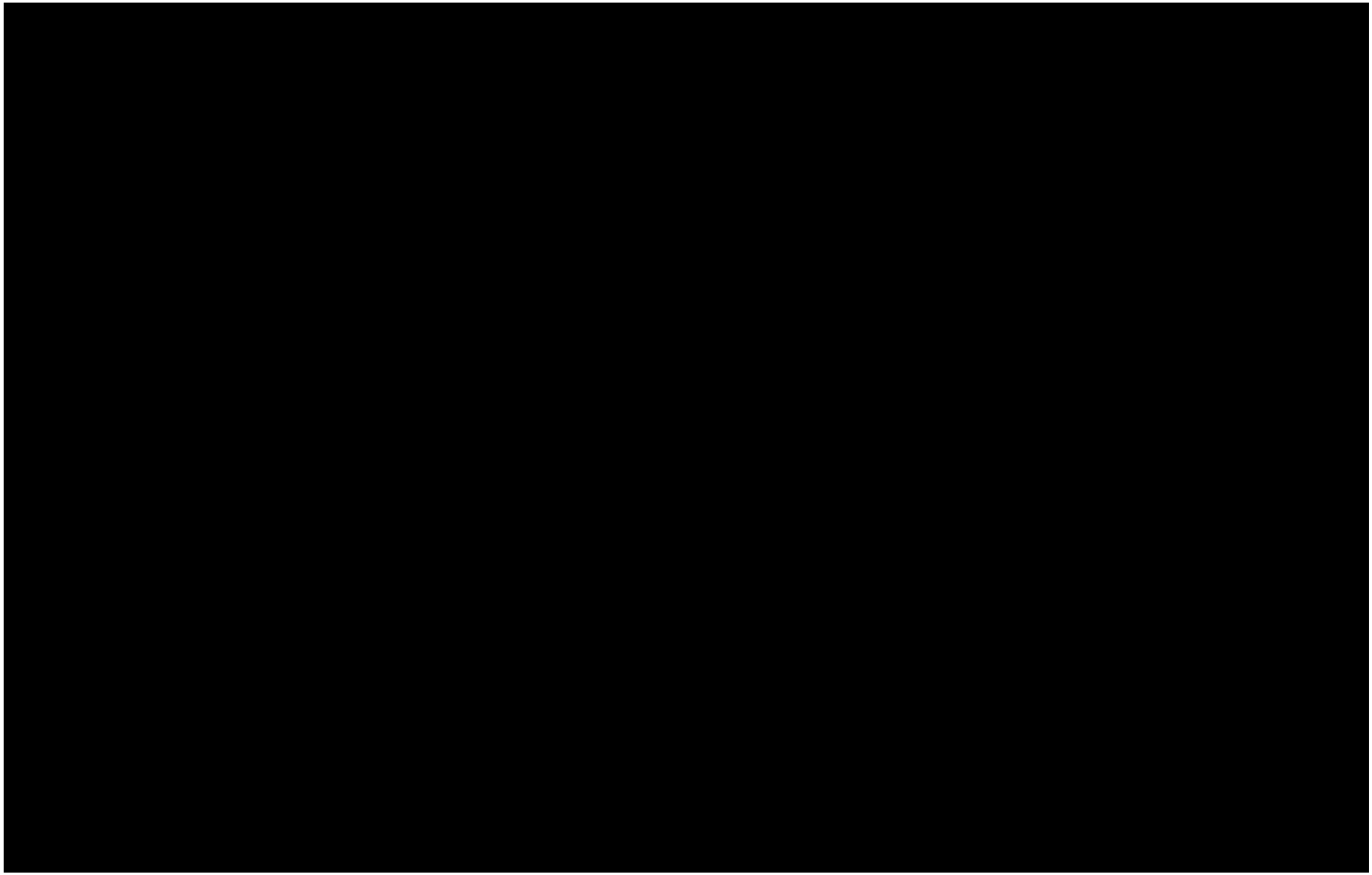


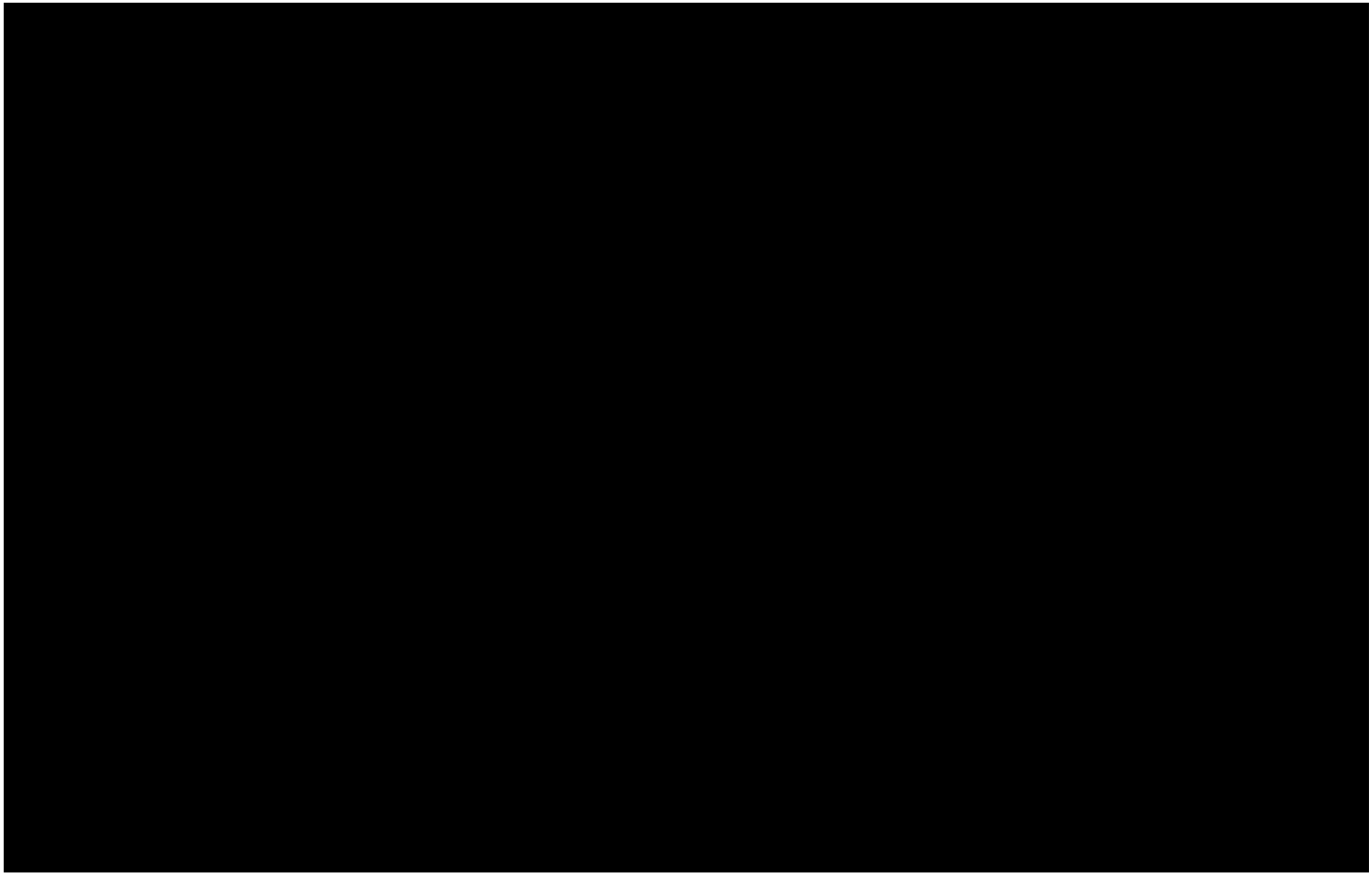


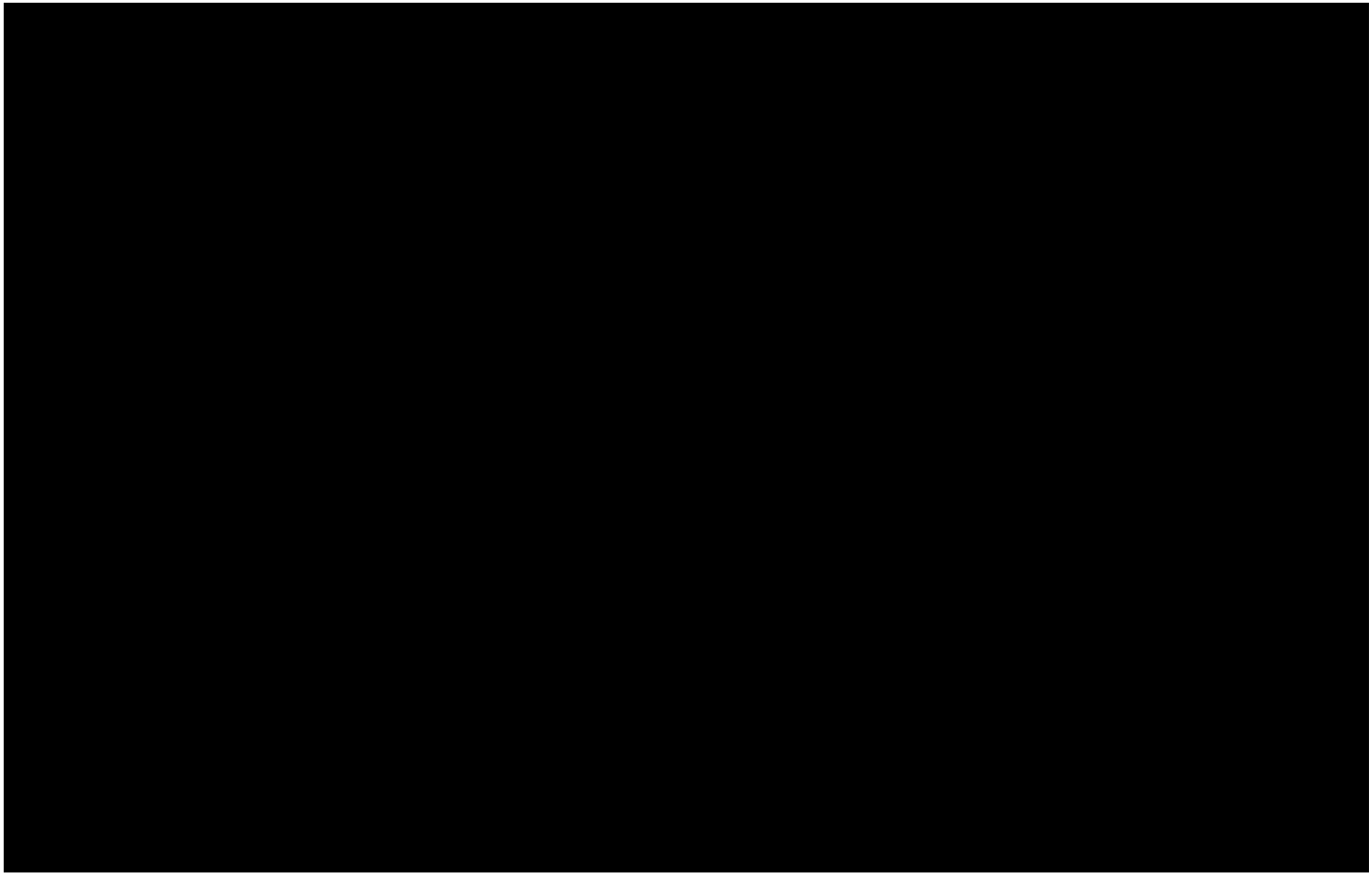


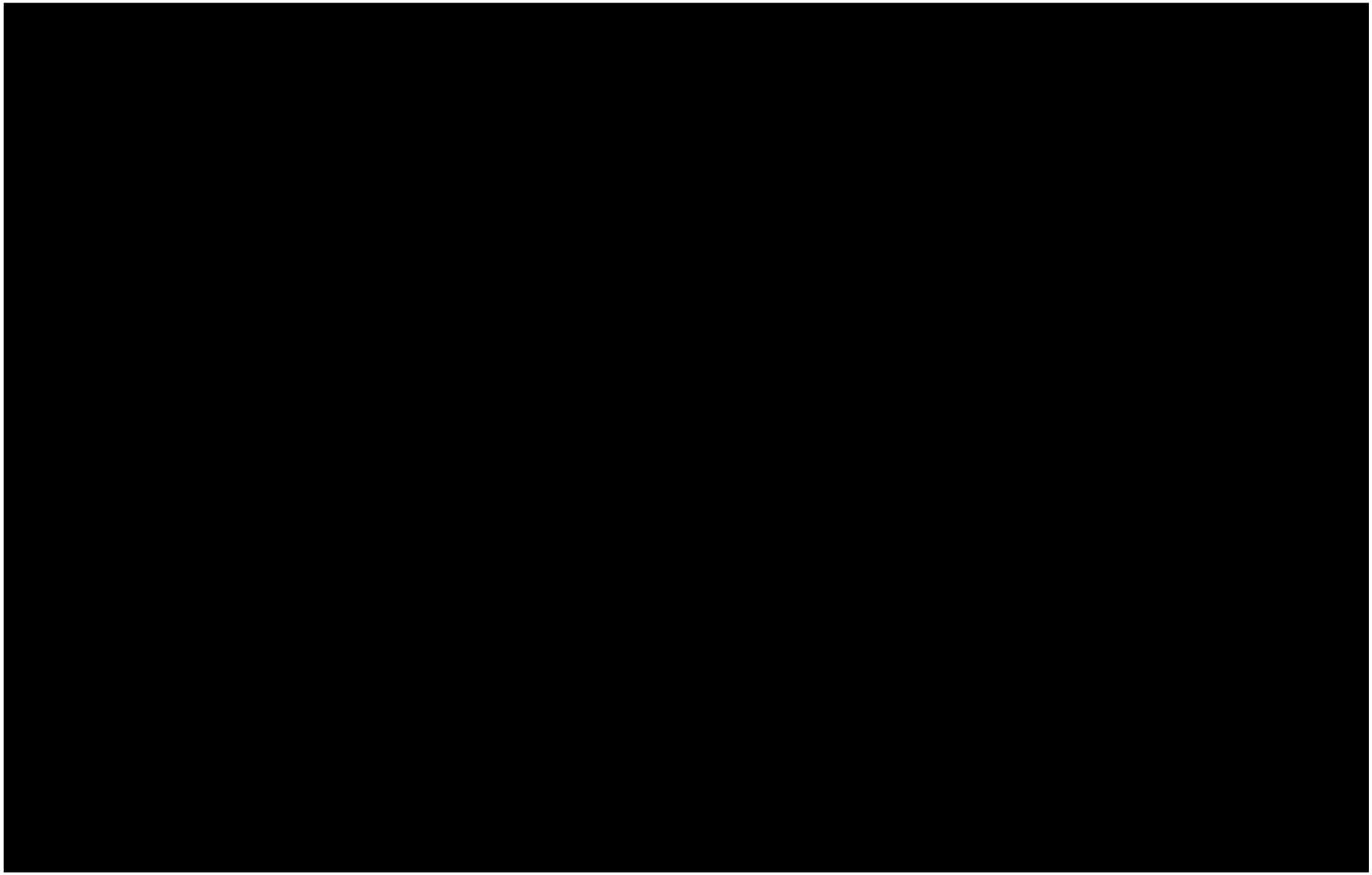


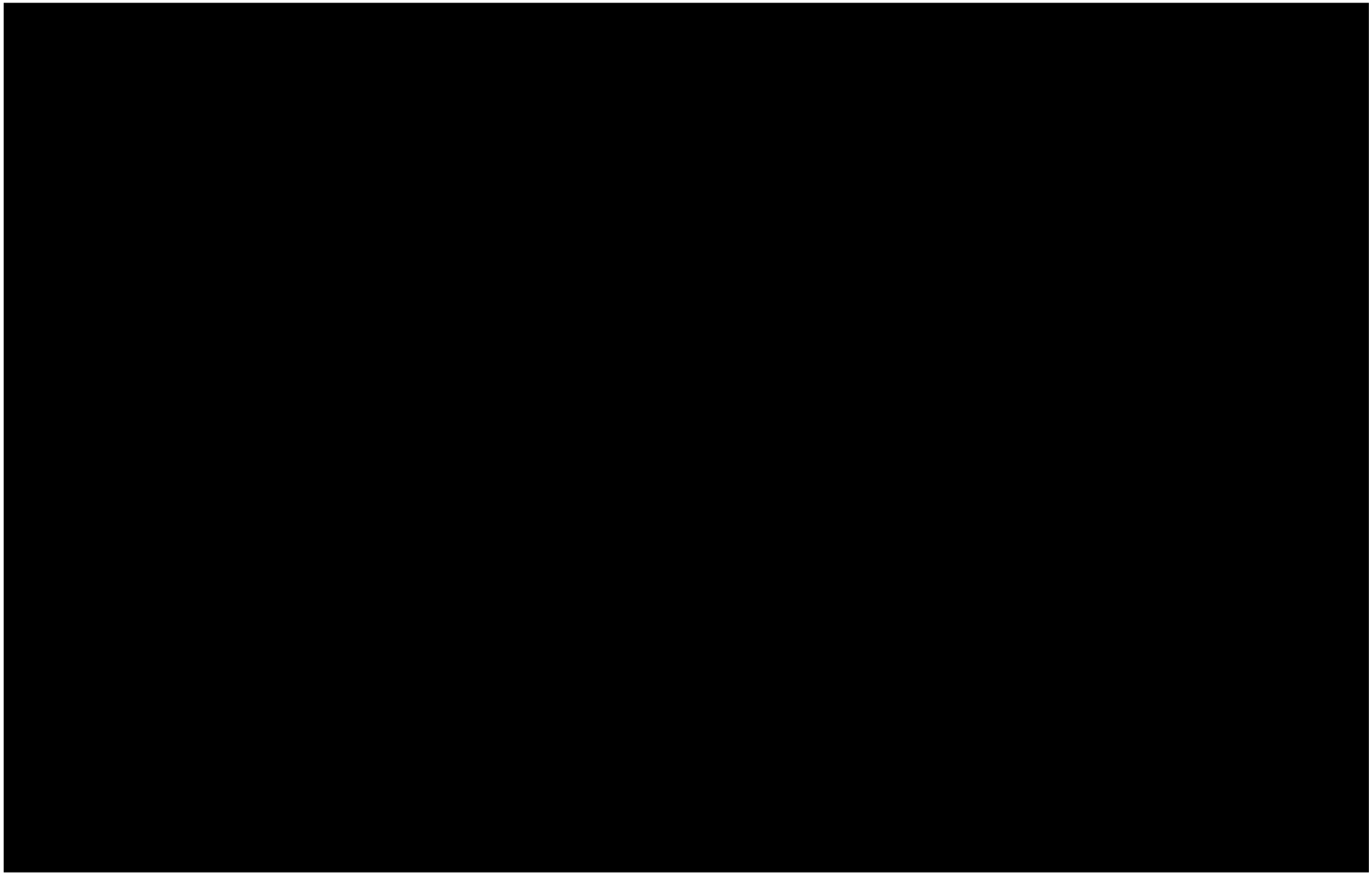


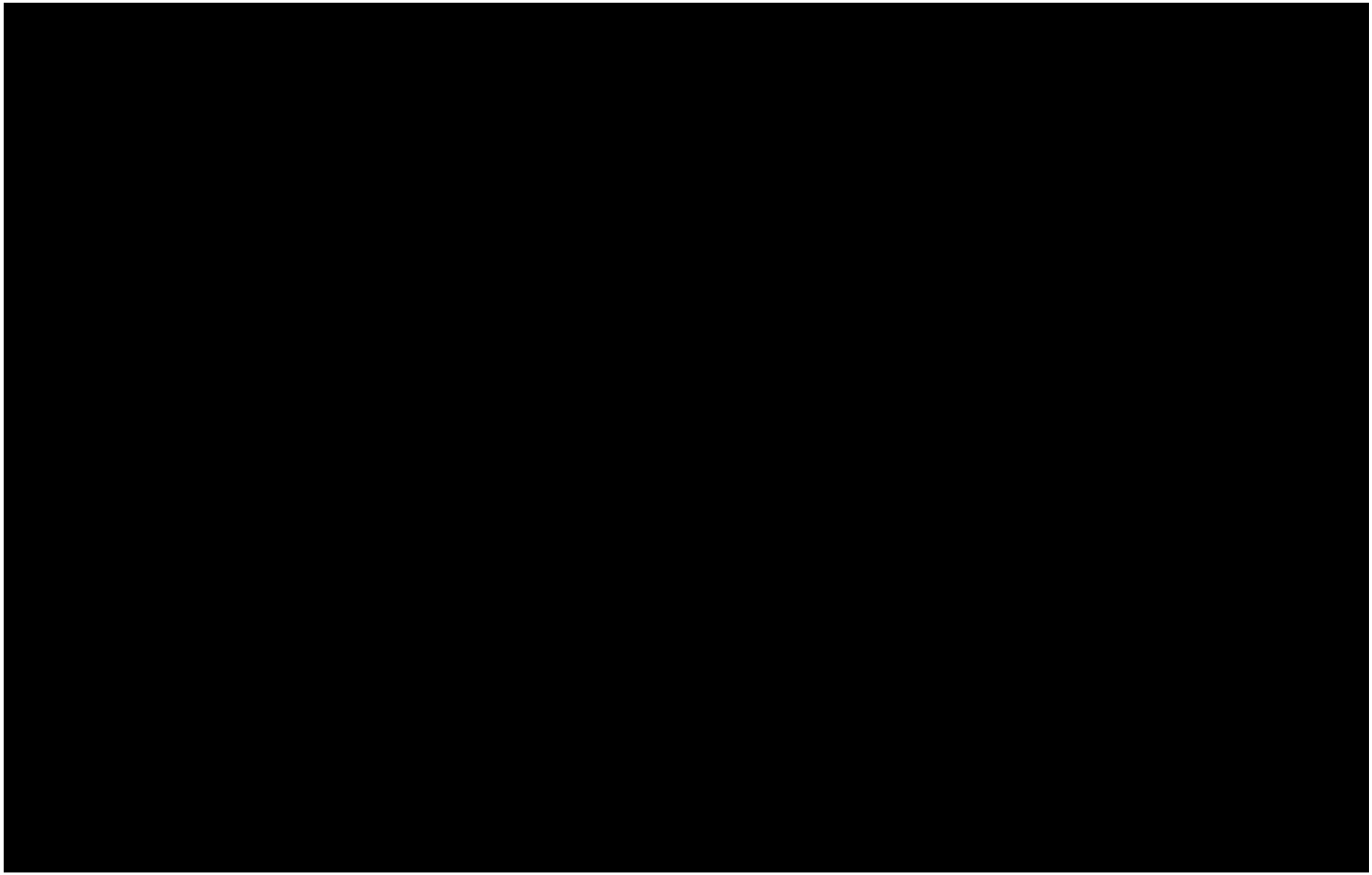


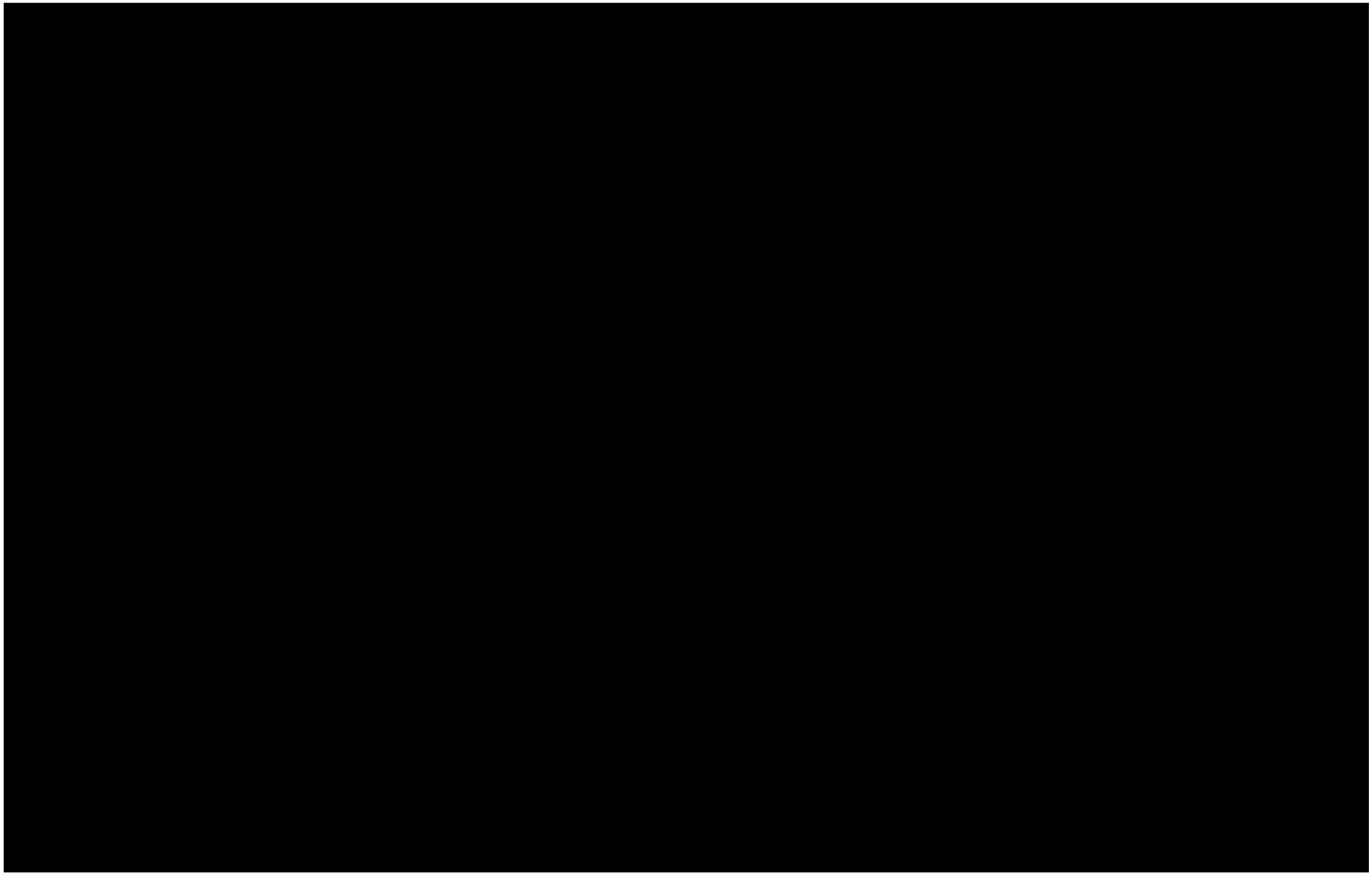


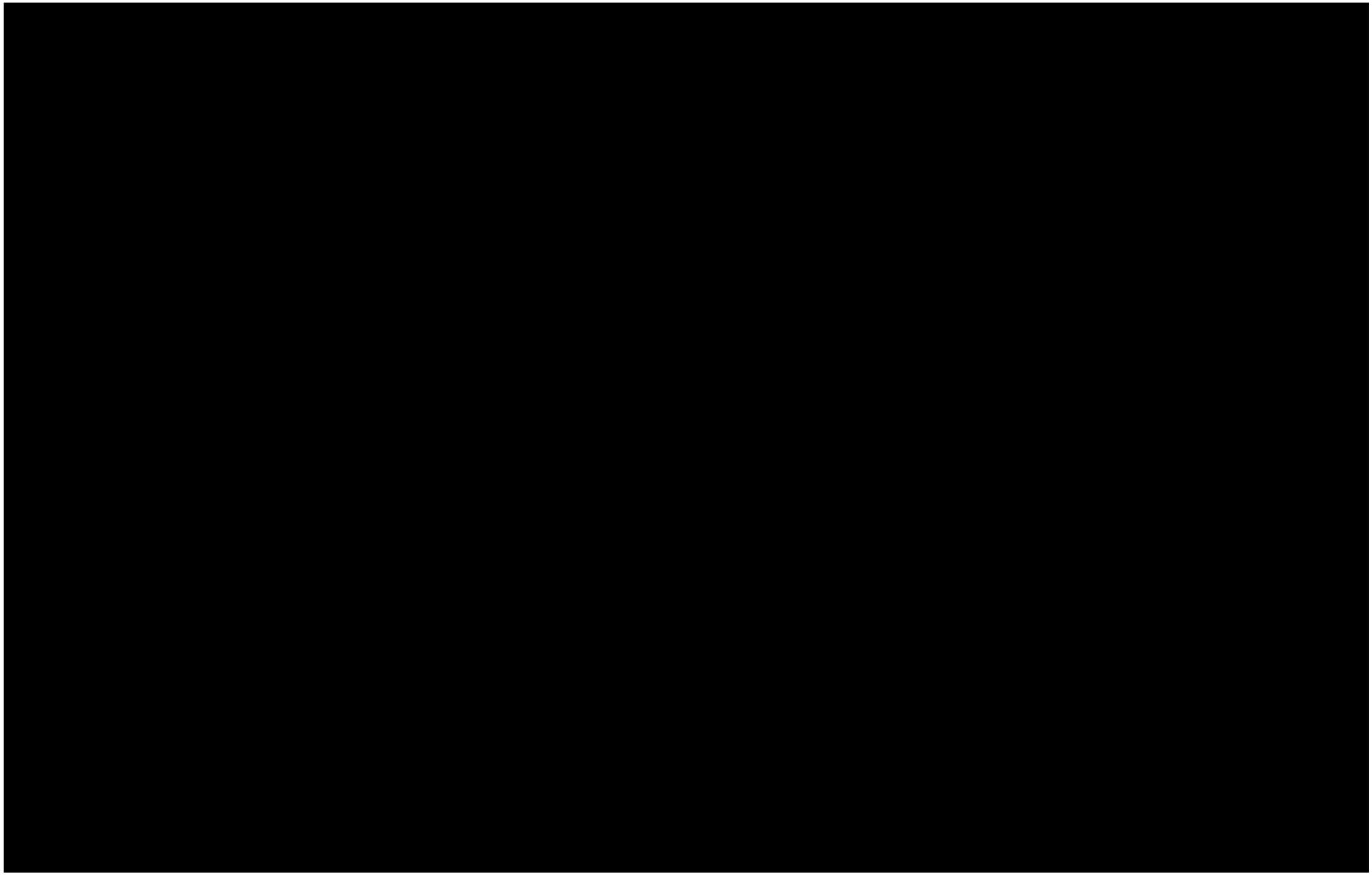


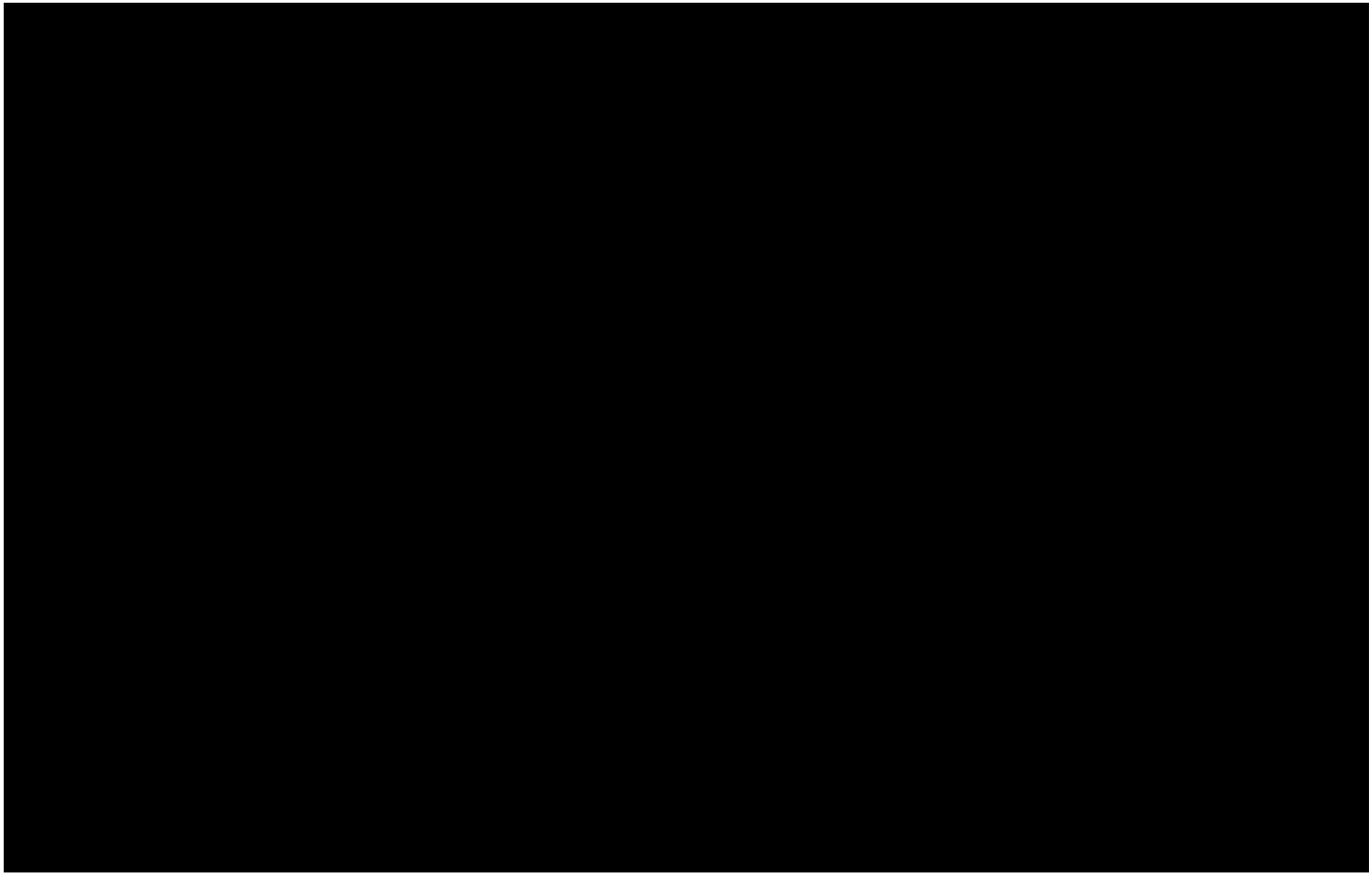


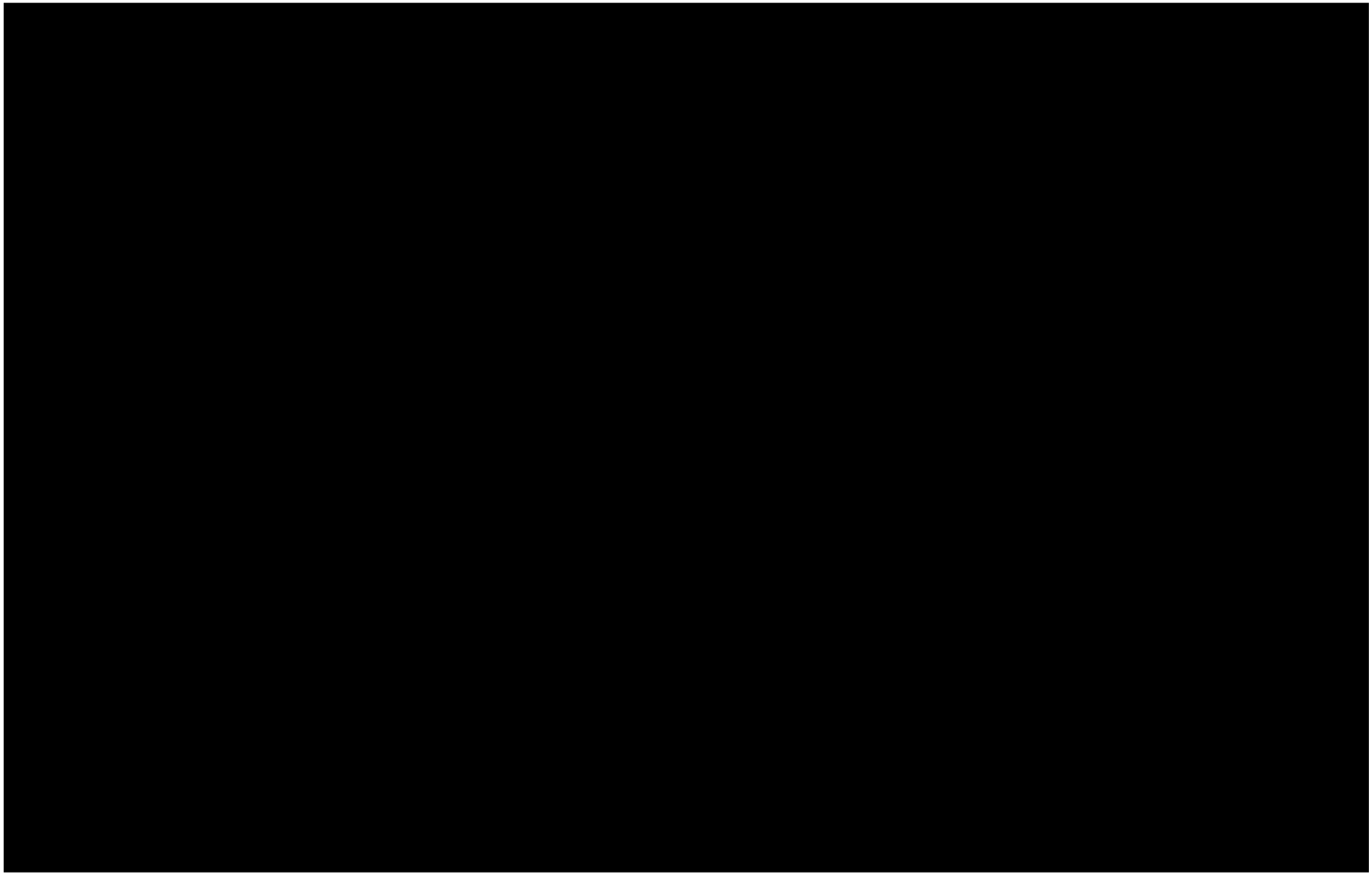


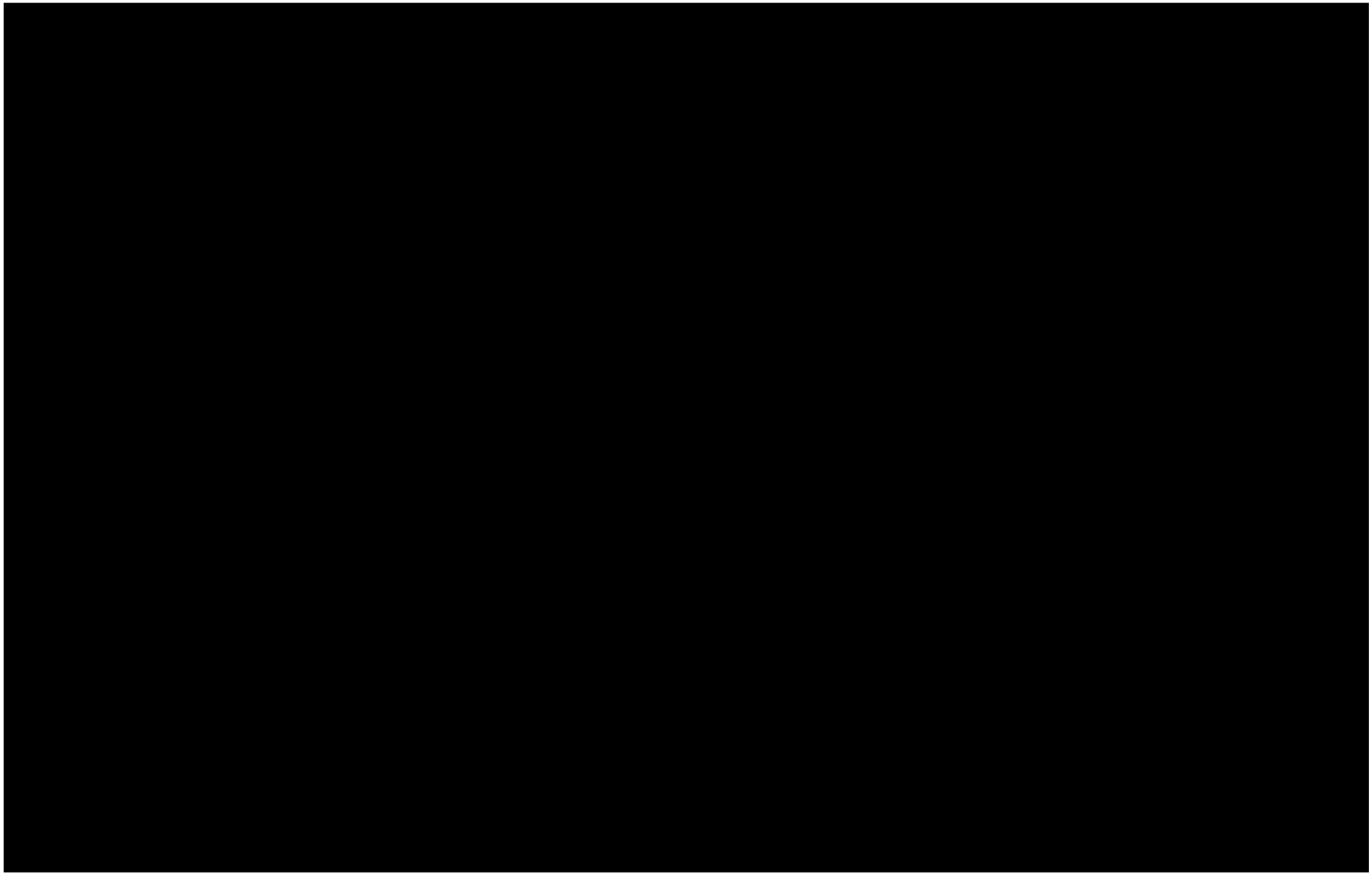












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Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA189 - Sorafenib for advanced hepatocellular carcinoma

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: BASL / HCC UK LTD
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)?
- 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

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA189 - Sorafenib for advanced hepatocellular carcinoma

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?

Sorafenib is the current standard of care for patients with advanced hepatocellular carcinoma not suitable for loco-regional therapies and with adequate liver function and performance status. The drug is currently available throughout NHS England via the Cancer Drug Fund. It is currently the only licenced systemic therapy for this indication such that there are currently no alternative therapies available.

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?

The survival benefit for sorafenib in advanced HCC has been demonstrated in two large, well-conducted placebo-controlled double blind randomised phase III clinical trials, one in predominantly European patients with background alcoholic liver disease, NASH and chronic hepatitis C virus infection, and the other in the Asia-Pacific region with predominantly chronic hepatitis B virus infection. Subgroup analyses suggested a similar magnitude of benefit across all subgroups. Subsequent reports have suggested there may be a greater benefit for patients with underlying hepatitis C virus infection. However, this has not been tested prospectively and the Asia-Pacific study reported an identical hazard ratio to the European study, indicating sorafenib to be similarly efficacious in a non-HCV population.
There are no data to suggest a greater risk for any subgroup.

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)?

HCC is complicated by underlying cirrhosis in the majority of cases such that it should be managed by multidisciplinary teams with the necessary expertise and experience including hepatologists and oncologists with an interest in HCC. The potentially chronic nature of sorafenib therapy with its associated side effects is such that specialist nursing input for dynamic management of toxicities is desirable.

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?

At present, sorafenib is available in NHS England via the CDF. This availability is more restrictive than the licenced indication but does reflect the evidence base for its potential benefit (advanced HCC not suitable for loco-regional or surgical therapies, good PS, good liver function).

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA189 - Sorafenib for advanced hepatocellular carcinoma

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.

Sorafenib for advanced HCC is recommended in both US (AASLD) and European Guidelines (EASL) based on the high quality randomised phase III trials described above.
UK HCC guidelines have not been updated since sorafenib data became available.

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?

As already discussed, sorafenib is currently available via the CDF and there are currently no proven alternative therapies for patients with advanced HCC.

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.

Sorafenib for HCC requires adequate liver function and performance status. Its use should be restricted to those with Child-Pugh A cirrhosis and PS 0-2. Duration of treatment in the phase III trials was not dictated by radiological evidence of disease progression. Thus, decision making for stopping therapy requires clinical judgement of the balance of risk and benefit.

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 clinical trials for sorafenib in HCC were well designed and conducted as already described. The primary endpoint was overall survival. Current UK use via the CDF is appropriately restricted to patients with good PS and good liver function, reflecting the eligibility criteria for these trials. Similar survival times to those reported in the clinical trials have been reported in UK audits of sorafenib use, indicating the applicability of these trial data to the UK population.

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 side effect profile of sorafenib is predictable and manageable in experienced hands and reflects that reported in the clinical trials. This does require oncologists and specialist nurses with appropriate experience and interest in HCC.

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.

UK audits of sorafenib for HCC have been conducted and published and should be readily accessible (e.g. Palmer DH et al Br J Cancer, 2013; King J et al ESMO meeting, 2014).

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)?

Since sorafenib is already available via CDF, no additional resource for its ongoing use within similar criteria should be required.

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.

None known

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

CDF rapid reconsideration of TA189 - Sorafenib for advanced hepatocellular carcinoma

Thank you for agreeing to give us your views on this LIVER CANER treatment that is being appraised by NICE. Patients, carers and patient organisations are asked for their unique perspective on HCC, being at risk of it and its treatment

- the experience of having the condition or caring for someone with the condition
- the experience of having specific treatments for the condition
- expectations about the risks and benefits of the treatment.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: HBV Trust
Your position in the organisation: [redacted]
Brief description of the organisation: We care via national helpline website and materials for 500,000 HBV patients and deal with the booming numbers being diagnosed and have much experience (10 years) of end stage with liver cancer. There is no public funding for our work since 2010 so patients and staff fund the organisation

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately.

- [redacted]

All can explain how HCC is vastly up to 200 times increased for their patient populations due to lack of care. Eg 800,000 undiagnosed heppers equals 40,000 getting HCC from alcohol and 40,000 getting it from binge medicating and 20,000 from overeating as we write. I can vouch for the fact that 21 units is odds on cirrhosis in 5 years for the undiagnosed.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No NB smoking does not cause liver cancer, the question should be about **paracetamol and the 20 genuses of liver cancer causing medications** commonly killing undiagnosed heppers! This is an important point substantial numbers are being given meds that speed them to cirrhosis and HCC in months not decades. Many hep patients have an ALTs reaction to painkillers that indicates a poisoning event 500 to 1500. One caller bled from orifices for 3 years on paracetamol. Leukaemia treatment is always an ambulance to an icu within hours. The under 16 cases of HBV HCC need auditing for meds especially. We need to monitor speed to cirrhosis and HCC again entirely.

Over 7 years, 10,000 calls from patients, the fibrosis, cirrhosis and HCC patient status clearly mirrors the prescription load rather more than the viral load. If there's one parked prescription 1 year plus we expect fibrosis 1, if say 5 a F3 to 4 decompensated cirrhosis score would be very common to normal. We have asked every patient to self study their ALTs re meds and to ask their liver monitoring team to keep an eye on their prescription load and ALTs also so they have more back up during adverse events. This community is often challenged also in care, the demented, Alzheimer's, sectioned. I remember an A n E call where the patient had a sock in his mouth as the prescriptions plus HIV and HCV where making him hallucinate and jump off buildings. He is still bullied by locums to take them.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

The key emotional experiences of our HBV HCC endemic migrants and exposed staff

1 STIGMA. Our manufactured "It's a gay junkie plague and its kisses kill!" by the politically correct Equality Mob causes even patients told they are dying of HCC, to dash around trying to have a family as they die. Patients loved all their lives have died isolated, the last hung himself with a note I'm innocent for the wife told he has rent boys maybe by the GP. This is especially hard for migrants with strong cultural trends to sobriety and fidelity. For staff there is a feeling if blood kills like coal dust and asbestos, if a nurse dies daily of HBV in the US, why does no one know?

2 CONFUSION. With Sorafenib or any do or die end stage treatment that involves multiple symptoms rapidly changing and 40 new health workers saying hello, utter patient bewilderment is common. These poor people are diagnosed dying or with serious and poor prognosis, of usually 4 things they have never heard of viral hepatitis, fibrosis, cirrhosis and HCC or the other kidney etc cancers. It's human nature we can endure hugely if we understand why, yet the bulk of callers are without any understanding of what helps and what harms them both with medical and lifestyle care. We find they need 1 to 2 hours of education for them to understand how to fight for their lives. [redacted] has lost a cousin and

a brother to HBV HCC and has it himself, yet so many migrant patients end up facebooking everyone they had sex with saying I'm dying of the HBV HCC sex disease and leaving a relative odds on for Hep HCC. I remember at BASL a doctor needing time as his 2 medical trainee roommates from 1989 had both just died of HBV HCC. So deep clear data on this is the best options for care and diet, an explanation of scans and tests, a chance to own our files and see improvements. Helps.

3 ANGER. the sheer numbers diagnosed end stage with a 1% survival cancer, the stupidity of it. 90% are not living with a condition, they are dying. It is always idiotic to die of a cancer that takes 50 years on average to occur when a one pound finger blot test is available now for 27 years and nearly all the dying are WHO indicated for testing for 27 years. We briefed 600 MP's in 2004 that Liver cancer and cirrhosis will boom 500% regardless of alcohol use from 1970 to date if we fail to test. The horror of being just plain left to die is so strong as they die, many desperately use the moments trying to warn their professions or communities and families. Border testing and child vaccinations, the care our 20 million migrants from endemic areas need, is only available AFTER infection and 40% of the time at Cirrhosis and HCC stages.

4. FEAR of the HCC is a condition. We have 200,000 being monitored for hep HCC...the scale of the boom to 1 million heppers out there now, at high 200 fold risk, there are 800,000 people with hepatitis b or c mainly long term undiagnosed with under the radar work, healthcare and childhood infections. They are dying of hep HCC yet the scale of the dying is completely hidden, both cirrhosis and cancer hep kills are loaded en masse into alcohol figures

5. DEPRESSION. Kidney, bile duct, blood cancers especially NHL, the hep carcinogens are good at these kills and all are booming , the 10% who survive and also the NHL, Kidney and Bile Duct cancer survivors all had a real positive attitude in common since we started measuring that KPI in helpline callers. Yet seeing 44% of survival chances deemed too expensive how can we create that? Both me the CEO and the MD here have had Hep cancers and flatlined during care and come back to fight for care and sorafenib with the CDF and [redacted]. They won't admit the infections prevalence, they won't vaccinate the 4 million children at risk they won't test for the 3% HBV positive at the borders and we are discussing removing 44% of current cures from medication!?

6. MADNESS. HBV HCC causes serious changes in your mental faculties last caller 76 crying in car park they were shouting, meaning a demanding patient kicked off, and we are look the grandkids and kids all want to have another year of birthday and holidays with you, you need time and clarity to arrange things and the its possible the sorafenib and other care will have defying the odds for years like us. Off she went, but of the 5000 cases of HCC annually most read 1% survive 5 years and little else, most give up learning exactly when a new diet and lifestyle is needed. These callers are weepy fragile affected by hormonal surges of panic and despair, they suffer blood abnormalities encephalitis, most recount where they gave up trying to understand whats going to happen. We met a dying mum recently 62 HCV and just did not realise HCC was possible refused treatment as she read HAV info.

3. Current practice in treating the condition

We test for hepatitis 10 times less than the EU and vaccinate 20 times less, such abject failure is not practice really. More an effort to maximise HCC. Survival and more often the agonies of dying are what treatment options we have, a race is on with each diagnosis. We have the world's best HCC surgeons and currently drugs yet the world's worst diagnosis, vaccination and understanding levels. The nation is set up to experience a 100,000 HCC cases from hepatitis, without any child prevention or border testing we must offer the best drugs. Hepatitis is not causing these 100,000 alone, politically correct thinking is forcing them under the radar beyond testing or vaccination to get HCC far more often. London's wards tested 2.6% endemic in 2012, its child wards were 1% chronically HBV infected, imagine our children test more infected than our addicts and no one knows! The UK is still quite unaware over a billion children caught HBV in childhood so its children are the only unprotected ones left on earth and unplastered at school. Our 300,000 HBV and 200,000 HCV migrants are still officially not there and in a nation where binge drinking medicating and eating are all far more available to speed them to HCC

What is your organisation's experience of currently available NHS HCC care?

Our testing should have levelled our liver cancer boom in the Noughties as in the EU, as in developed nations that test, no one should be progressing to HCC with an easy to spot virus that usually takes 50 years to go carcinogenic and kill. With 1% of heppers end stage at 16 with cirrhosis or HCC, we need to see our society and food chain is becoming more liver toxic and hepatitis is causing HCC via many routes quicker and quicker.

We have to stop pretending the thousands of extra people annually getting hep cancers and cirrhosis are due to alcohol see http://wjso.biomedcentral.com/articles/10.1186/1477-7819-3-27 If we decide on cancer drug provisioning lets not start with the Damn Mad Sally pretence that in the UK alcohol is 3 times more deadly than in Spain and hepatitis is 3 times less liver carcinogenic than anywhere else on Earth. The HCC boom in the developed world is 40 to 70% hep driven where they count, yet here Cancer research still pretend its 16% by using a 1992 HBV n HCV prevalence the last allowed, for its dream happy guess. Ditto cirrhosis which has doubled during a decade long fall in alcohol abuse.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Sorafenib is the only survival chance for many of the late diagnosed, It offers real help at delaying symptom onsets, many public and even professionals are unaware of the hardships of a liver cancer death journey. The sheer suddenness of these onsets are deeply truamatising to all involved. HCC patients can suddenly lose a third of body weight and die in 8 weeks. Some get encephalitis their eyes go black and they convulse their brains t mush over days, some get ascites and drain a bucket of mucky blood a week for months, some have real agonising pain, hell is breaking out over their tummy ulcer nerves, kidney and liver failure tend to kill in 24 hours yet many hover in this state for months, then its ventilators' and switching them off. This has left many callers in dire states, when switching off patients can suffocate for 20 minutes then heart attack usually, we have been on the helpline with them, last one was like the "Green Mile" death scene for 20 mins.

Point being all this suffering is massively alleviated by Sorafenib, that's what 44% less of the above means. We tell all HCC callers time is precious now, get everything done now while you can, see who you want now while you can, so often children, partners etc are dashing around to see them and delays mean they are in a terrible way see above. Some HCC patients die all alone because of their just diagnosed HBV. What price to avoid so much of the above? Suffering scale has a measure, as well as life.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Patients are usually aware of the most effective treatment due to the internet so when denied it they know poverty as well as hepatitis is killing them and get depressed and die faster

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Please list any concerns patients or carers have about current NHS treatments in England.

Why is there not more prevention and awareness?

Every patient diagnosed with HCC from hepatitis B or C is concerned about the zero awareness, vaccination, testing when diagnosed. The "Hang on, it's infected 1 in 3 humans and is killing 1 in 70 and seemingly me, why have I never heard of it? Why?" It is a strange word to have on most callers lips.

[redacted] saw her father die over 2 months and has written her thesis on why a £1 check his nation recommends, his liver spots and years of ailments indicated a test for, like all too many callers was never tested for decades. No one [redacted] should be progressing to HCC, they are WHO test indicated since 1999 as they are odds on for HBV markers. To offer Sorafenib and a MELD number means someone FORGOT to offer vaccination or testing for 50 years. Even myself if kidney or liver scan shows more cancer it's a 1 in 10 shot and if you halve it kind of what is the point?

Please list any concerns patients or carers have about the treatment being appraised.

There is already a terror we have 200,000 plus HBV and HCV patients having HCC scans and often Kidney cancer scans regularly and are talking about halving their chances, substantial numbers are giving up scanning anyway in despair.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Everyone wants this, cost is the only barrier. Chemo/ Cancer therapy is do or die and some refuse, usually the depressed, but we turn them round on the helpline with our experiences of overcoming HCC personally.

6. Patient populations

The HBV and HCV populations are 80% under the radar, the 150 endemic now here nationalities have no access to the HBV world atlas so all 20 million are unable to access testing or vaccinating and usually denied care when asking. Even the sub Saharan African and the pacific rim migrants have no warnings or screening, yet they are odds on to have HBV infection markers for this devastating liver carcinogen. 3 million in work with blood roles do not know their high risk or if they are immune usually and we have audited 100,000's of NHS and staff vaccinations. Most of the million infections of HCV and HBV are unaware, like the public, that the main transmission routes are all around us. We have 3 tattooists, several barbers, several schools and a cardiac unit out break at the moment, endless lists of poorly protected staff, a documented 1 child per 50 catching hbv annually by 5 giving a 8.7% prevalence in a large UK migrant nationality (the normal spread)and 12 million children are still at risk without this HCC avoiding vaccine. **In Africa the hbv vaccine is seen as a anti HCC vaccine**, but they have someone unvaccinated dying of it every 30 seconds and know the connection we are so busy ignoring.

With 1 in 4 humans testing HBcAb positive and it being a higher HCC risk we need an NHS that knows this also see 25. Yano Y, Yamashita F, Sumie S, Ando E, Fukumori K, Kiyama M, Oyama T, Kuroki S, Kato O, Yamamoto H, Tanaka M, Sata M: Clinical features of hepatocellular carcinoma seronegative for both HBsAg and anti-HCV antibody but positive for anti-HBc antibody in Japan. Am J Gastroenterol. 2002, 97: 156-161. 10.1111/j.1572-0241.2002.05440.x.

We need [redacted] when questioned in the Commons to consider some 3 to 4 million of us are in the above group HBcAb now and not parrot 700 a year are noted. If sentinel surveillance says 1 in 25 London patients had active viral hepatitis in 2012 we need her and the dept to not say the figure is unrecognisable to 14 questions and sneakily archive it. We have knowingly left 2 generations of migrants to infect their children see http://adc.bmj.com/content/86/1/67.3.full Currently these 70,000 victims (the only Afro Asians denied HBV vaccination globally) are unlikely to access care and when they get HCC we turn around and say we have banned the best drug?

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes everyone worked on the creation of the funding we made certain David's first action was a 200 million CDF fund quickly boosted naturally each drug funded depended on its excellent results Sora is a step change drug, patients can survive in an era of booming UK HCC risks. We create and publish research see Rising Curve see Hepatitis B n C What every family needs to know and Going Endemic.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

The glory of this drug is twice the care less side effects.

The results of the study appear in the July 24, 2008, edition of The New England Journal of Medicine. Because of this trial Sorafenib obtained FDA approval for the treatment of advanced hepatocellular carcinoma in November 2007.[4]

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐yes many helpline callers tend to read Wikipedia first and note an almost doubled survival rate see below , patients of the smart phone era often know the best and most effective drugs now, they can find this out quicker than even condition facts, already our unfunded sister charities note a tidal wave of depression among patient groups who know their cure is deemed not worthwhile or value for money. They are running helplines telling people do the treatment now as tomorrow you'll die without it, or worse we can save you but we have decided your life isn't cost effective. This is especially hard with the heroes soldiers, famous sports stars, the 1.5 % HCV infected NHS surgeons, the 20% diagnosed and forgotten unrefered, the many indicated for testing but left on meds that gave them HCC. The millionaires who migrate here with HBV and find their whole family infected and themselves with HCC and wonder why they came to the only place that doesn't border test or child vaccinate.

I mean a 100 million people are dying of hep b and mainly from its HCC. These people nearly all have child acquired infections and die from simple ignorance as much as HCC and there is not a paragraph that understands this and screens migrants in NHS literature. Info about safe injecting and anal sex are actually more common creating a your fault attitude and deep stigma in the public mind and in policy groups and medical depression in 70,000 innocent people. Simply forgetting HBV dads infect twice the children as HBV moms is however the norm also. The group most at risk 10,000 a year are FGM victims in Kurdish they say Zereck

when the circumcised goes yellow in Somali the national phenomena is called Agbarshoe. 80% catch HBV by 10 in fgm nations, in Burkina faso the medical data has ended the practice, yet here we are saying in the Commons that the NHS notes just 3 horizontal child hbv infections ever in 2014 and this in answer to 28 families who detailed their experience of it and questioned the 1% London child ward prevalence.

Wiki.....Liver cancer .....At ASCO 2007, results from the SHARP trial[14] were presented, which showed efficacy of sorafenib in hepatocellular carcinoma. The primary endpoint was median overall survival, which showed a 44% improvement in patients who received sorafenib compared to placebo (hazard ratio 0.69; 95% CI, 0.55 to 0.87; p=0.0001). Both median survival and time to progression showed 3-month improvements

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination

This equality and politically correct fashion has caused untold suffering to many HCC patients, long ago in the Nineties they "listened" equally to people with HBV. Testing was done in prisons, drug and sex clinics and a desperate inclusive effort of meetings with these rare groups went on including the Chinese community and it was decided HBV is caught by Drug Injectors, Gays, Prisoners, unhygienic tattooists, trans people, and migrants in that order. It is even still commonly thought and printed everywhere.

People have no notion borrowing a hbv razor in a freshers hall is 1000 times more infectious than sex with a hbv carrier, that it moves through classrooms like chicken pox an outbreak from shared chapsticks, an outbreak from the boxing club, an outbreak from compass gaming, an outbreak from one direction harry styles tattoooes, an outbreak because plasters are banned, an outbreak because of fighting, an outbreak because of sharp shared toys or milk teeth. 700,000 UK HBV HCV kids and moms never got a mention. Terrance Higgins gets 22 million the HBV trust nothing, except their co infected callers as they die more from HCC than HIV these days.

Yet the 5 trans infections 4 being and 1 becoming are getting a rewrite and being inserted lickitty spit.

The reality of 2 billion people getting infected from bloodspill or healthcare injections mainly as children, the global HBV reality is still lost to the nation. Who knows half of Afro-Asian transmission in the UK is to children? Who knows our child wards in London serving 1.2 million had more HBV than our drug wards serving 100,000 in 2012? Why archive the fact when questioned in the Commons? The same has happened with HCV, only 5% of global infections where from IDU abuse and 90% from healthcare yet in the UK its the other way round. Even 20% healthcare infected Egyptians are probably more likely to get HCC than be tested here. We are inviting millions from the very areas without infrastructure or clean needles to a nation without any hepatitis border care at all.

Further having invented a gay junkie plague for filthy people and possibly foreigners and this is how most callers define their understanding initially all calls need 30 minutes of i know you are innocent. The NHS then often offer politically correct advice designed for and of course with the sexually liberal or the drug user to the 5000 mums diagnosed in maternity. Chemsex has a budget for leaflets for their 1000 strong population of drug induced gang bangers, yet the 200,000 HBV moms well they still don't exist officially as the govt position is still no migrant has increased our HBV burden. After 7 years we have had hundreds calling with HCC yet not one addict has called with HCC, we get vaccination nurses calling saying they cant find any addicts unvaccinated.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal. See above also.

At least 10 to 20% of patients are diagnosed but not being monitored mainly due to poor GP referral or overseas diagnosis, this army of many 10,000's is often heading for HCC unadvised. Huge inequality affects all our HBV cancer patients nearly all would be saved by other health services in the first world, some become aware of this. Professor bassendine noted 20% of Chinese progress to HCC rather than admit infection. The same is true of some 20 occupations that work with blood, our travellers and our endemic and super endemic communities who are poorly vaccinated and advised. Many public workers police, doctors, nurses, st johners, security/contact sports ring as they die wishing colleagues could be warned. Lack of border screening (we are alone on earth pretending migrants are not 3% HBV positive) has built a huge pool of infections CUSHI B noted across 22 major liver units 81% of hbv patients are migrants.

None of the 20 million UK citizens in our migrant communities have been told they are endemic and the onward spread to the next generations is also proven.

HBV kids are the most tragic 35,000 infected due to neglect and according to mary ramsay 1% dying at 16. We need to find these children before we park them on anti psychotics or make them obese and they have HCC. Then 200,000 HBV moms are out there and there isn't even a leaflet for them on how to avoid liver cancer. Think what we have done for HIV gays, yet these moms have more special needs and die after diagnosis due to ignorance. One HCV mom got HCC due to erroneous side effect info regarding ribavirin. [redacted] is another good example stabbed on duty infected by transfusion 1980, forgotten diagnosed with cancer after 6 years of prescriptions offered no compo and denied a ticket to the commons and we get calls from newly infected officers often the last in wick in scotland

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Africans avoid testing due to fear, Asians due to stigma both are in danger of death due to poor screening. Both are cursed by the NHS strapline 100 times more infectious than HIV and in all body fluids. The truth HBV is 100 times more infectious from a scratch on a contaminated milk tooth than sex with HIV is missing. Of 75 Afro Asian nurses being vaccinated by us currently in Kingston 7 already show signs of infection many knew of their risks or infection but risk HCC anyway. Imagine the thousands under the radar at 200 times the HCC risk these groups are in about 15 occupations many unaware and 100 national community groups completely unaware. The head of infection control at Brent's phlebotomy service had to be told yesterday washing needlesticks is completely ineffective with deep ones eighth of an inch or more can only be cured with immune b globin. Rather like the Head of Occupational HBV care in West London mentioned they have never tested for HBV immunity titers, HBsAg or HBcAb in staff!!! We need a mandatory test forworkers with blood at 50, St john are still unvaccinated as we bury some of them with 20 year old infections. 23 million workers and migrants are unable to access their WHO HCC prevention information. THE HBV and HCV atlases of 2.5 billion infections are still banned in the UK, this difficulty has always meant a 100,000 will die of HCC in the UK and they are dying of it right now. https://www.amazon.co.uk/Hepatitis-What-Every-Family-Needs/dp/150498790X details the 14 Industries and 4 high street/public communities and UK nationalities suffering from booming HCC and their lack of access to prevention.

8. Other issues

Do you consider the treatment to be innovative?

☐Yes, its continued use will keep us at the forefront of care and allow us to quickly adopt the next and better one that emerges. It's significantly different, it is a double your survival chance treatment

Are there any other issues that you would like the Appraisal Committee to consider?

I remember days before she died of a stroke caused by her liver failing, a common hep kill method, [redacted] said she wanted to warn the c section mums from 1965 to 1985 maternity transfusions were 1 in 39 HCV infectious, she had 170 million to spend on getting them advised and tested. My point is given another 12 months what could she have accomplished? Many sorafenib patients are like all the other heppers with HCC, ready to do quite extraordinary things. My MD was a prisoner with hep HCC, he now trains prison nurses how to HBV vaccinate all inmates and briefs MP's on Occupational risk. I have a similar police officer, St Johner, nurses etc. All these voices will be statistically dead and silent far quicker without Sorafenib.

9. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- many of our best people will die without this drug
- a 500% boom in cases and many more expected (100,000 hep HCC cases from 1 million mainly undiagnosed) is where we are
- It is a 44% improvement on other drugs this level of improvement is step change
- The word is out we recommend and have recommended sorafenib when indicated every time
- The alternative is we don't bother to vaccinate, we don't bother to test, we binge medicate till they have HCC and don't bother to supply 44% of the cure, there is not a health service on Earth failing like this.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement

Sorafenib for advanced hepatocellular carcinoma (review of TA189) [ID1012]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: British Liver Trust
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☒ No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☒ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?

☒ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☒ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NO FUNDS RECEIVED OR ANY WORKING WITH THE TOBACCO INDUSTRY

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

AS HEPATOCELLULAR CARCINOMA (HCC) IS OFTEN DIAGNOSED AT LATE STAGE OF LIVER DISEASE / CIRRHOSIS OFTEN PATIENTS ARE ALREADY SUFFERING FROM A RANGE OF SYMPTOMS FROM THAT - THESE CAN INCLUDE FATIGUE, ASCITES, JAUNDICE, PRURITUS AND ENCEPHALOPATHY.

QUALITY OF LIFE WILL INEVITABLY BE AFFECTED. SOCIAL AND WORK LIFE WILL BE NEGATIVELY IMPACTED UPON.

PSYCHOLOGICALLY THERE WOULD BE SIGNIFICANT BENEFITS IN OFFERING A TREATMENT FOR BOTH PATIENTS AND CARERS. PHYSICALLY DISEASE CONTROL WOULD IMPROVE QUALITY OF LIFE WITH FEWER SYMPTOMS TO DEAL WITH.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

CURRENTLY NO OTHER TREATMENT IS AVAILABLE FOR THIS GROUP OF PATIENTS, MANY OF WHOM ARE FACING THE 'DOUBLE WHAMMY' OF LATE STAGE CIRRHOSIS AND HCC.

THIS IS A RELATIVELY YOUNG PATIENT GROUP WITH AVERAGE OF DEATH 58-59YRS (LIVER DISEASE IS THE THIRD MOST COMMON

CAUSE OF PREMATURE DEATH IN THE UK) SO ANY INCREASE IN LENGTH OF LIFE WOULD BE VERY IMPORTANT.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

THIS MEDICINE COULD IMPROVE LENGTH OF LIFE AND IMPROVE QUALITY OF LIFE BOTH PSYCHOLOGICALLY AS A TREATMENT (COMPARED WITH THE ALTERNATIVE OF NO TREATMENT) AND IMPROVING SOME OF THE SYMPTOMS FROM THE HCC AS LISTED ABOVE.

ELSEWHERE THROUGHOUT THE WORLD, INCLUDING SCOTLAND AND WALES, PATIENTS WITH HCC ARE BENEFITTING FROM THIS TREATMENT AND PATIENTS IN ENGLAND SHOULD HAVE ACCESS TOO.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised,

please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

THERE ARE NO OTHER TREATMENTS OTHER THAN PALLIATIVE CARE. PSYCHOLOGICALLY AS ABOVE WITH ADDITIONAL HOPE OF A LONGER LIFE. BETTER SYMPTOM CONTROL WOULD ALLEVIATE THE DISTRESS THESE CAN CAUSE.

Please list any concerns you have about the treatment being appraised.

NONE

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

NONE

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

AVAILABILITY OF THIS TREATMENT WOULD INCREASE EQUITY OF ACCESS COMPARED WITH PATIENTS IN OTHER PARTS OF THE UK

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

THERE ARE NO OTHER TREATMENTS OTHER THAN PALLIATIVE CARE.

PSYCHOLOGICALLY AS ABOVE WITH ADDITIONAL HOPE OF A LONGER LIFE. BETTER SYMPTOM CONTROL WOULD ALLEVIATE THE DISTRESS THESE CAN CAUSE.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- THIS TREATMENT CAN IMPROVE LENGTH OF LIFE AND IMPROVE QUALITY OF LIFE
- THERE ARE NO OTHER TREATMENTS OTHER THAN PALLIATIVE CARE
- ELSEWHERE THROUGHOUT THE WORLD, INCLUDING SCOTLAND AND WALES, PATIENTS WITH HCC ARE BENEFITTING FROM THIS TREATMENT AND PATIENTS IN ENGLAND SHOULD HAVE ACCESS TOO
-
-

CANCER DRUGS FUND RAPID REVIEW OF NICE GUIDANCE TA189:

SORAFENIB FOR THE TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

REPORT BY THE DECISION SUPPORT UNIT

28 June 2016

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

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Grimm S, Bermejo I, Carroll C, Wong R. Cancer drugs fund rapid review of nice guidance TA189: sorafenib for the treatment of advanced hepatocellular carcinoma. School of Health and Related Research (ScHARR), 2016.

Use of confidential data

Any ‘commercial in confidence’ data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any ‘academic in confidence’ data provided by the company, and specified as such, is highlighted in yellow and underlined in the review.

EXECUTIVE SUMMARY

Background

The National Institute for Health and Care Excellence (NICE) is reconsidering cancer drugs currently funded through the Cancer Drugs Fund (CDF). As part of this process, technology appraisal (TA) 189 is being rapidly reviewed to determine the guidance for sorafenib (Nexavar®) for the treatment of advanced hepatocellular carcinoma. For this report, the NICE Decision Support Unit (DSU) has adopted the role of an Evidence Review Group (ERG) and provides a critique of the company's submission.

In 2010, a Final Appraisal Determination was issued, indicating that sorafenib was not recommended as cost-effective use of National Health Service (NHS) resources (TA189). The committee concluded that the lowest estimated incremental cost effectiveness ratio (ICER) for sorafenib compared with best supportive care (BSC) including its original Patient Access Scheme (PAS) price was £52,600 per quality adjusted life year (QALY) gained. Key uncertainties that were considered to increase the ICER further were: (i) the use of the Weibull distribution to extrapolate survival instead of the lognormal distribution; (ii) and the use of independent reviewer assessment of disease progression instead of investigator assessment. The source of the main evidence on clinical effectiveness was the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and resource use was estimated from a survey to four UK clinicians.

The company's new submission

For this rapid review of the appraisal, the company presented a new Commercial Medicines Unit (CMU) Framework Agreement (consisting of a [redacted] discount to the list price) along with new evidence and a revised model.

The company performed a new literature search that was adapted from the search conducted by the ERG. The DSU considered that none of the key trials were missed in the searches. However, inconsistencies were observed in the study selection criteria employed by the company. The company excluded two potentially relevant studies, the Asian-Pacific trial (which had already been excluded within the previous submission) and Ji *et al*. Both of these

studies were excluded based on criteria that were not included in the planned eligibility criteria, and that were assumed post hoc and lacked justification.

Of the studies identified through the systematic review, the company considered a single study to be relevant: Palmer *et al.*, a retrospective observational study that compared the survival of patients whose individual funding applications for sorafenib were accepted with those whose applications were rejected. The company and the DSU assessed this study to be at a high risk of bias due to its design. The company also provided evidence on long term survival of patients treated with sorafenib from the yet unpublished GIDEON study. The DSU notes inconsistencies in the company's study selection, as this study would have been excluded based on the eligibility criteria of the company's literature review. The company used evidence from both, the Palmer *et al.* study and the GIDEON study, to justify the choice of the lognormal distribution. The DSU, based on a critique of the company's analyses, concludes that the Weibull distribution still retains credibility and should not be ignored.

The company used new estimates of resource use in the updated model and these were based on the feedback of three physicians. The company's rationale for conducting this new survey was that clinicians had now more experience in using sorafenib in routine clinical practice in the UK. The new resource use estimates drove the ICER down, mainly due to a higher estimated cost in the BSC arm. The DSU believed that resource use estimates would be more accurate and robust if the feedback of the four clinicians, who provided the estimates for the original submission, was also considered.

The company reported results of the economic analysis applying the new CMU price and the original appraisal committee's preferred assumptions. The company provided two versions of the model: 1. the revised model, consisting of the original model with the following amendments: (i) the new CMU price, (ii) inclusion of costs of 7.7% of patients who continued sorafenib treatment post progression in the SHARP study, and (iii) treatment costs that have been calculated based on 30.44 days instead of 30 days (denoted as the revised model in the following), and 2. an updated model consisting of the revised model incorporating updated costs and resource use estimates, subsequently denoted as the updated model. In a scenario analysis, the company used the updated model and included evidence from the Palmer *et al.* study. This is denoted as the scenario analysis on the updated model.

The company estimated the new ICER for sorafenib compared with BSC to be £43,808 per QALY gained in its base case in the revised model and at £39,162 per QALY gained in their updated model. The company's scenario analysis on the updated model resulted in an ICER of £20,556 per QALY gained.

In their cost effectiveness analyses, the company did not explore the impact of two key uncertainties identified by the committee during the original appraisal: (1) the use of the Weibull distribution for extrapolating survival, and (2) the use of the independent reviewer assessment of time to progression. Neither Palmer *et al.* nor GIDEON provide reliable data to directly inform the comparative assessments required and the DSU believes that these studies also do not rule out the Weibull as a plausible distribution for extrapolating survival. The independent reviewer assessment was used as primary analysis in the SHARP study but had fewer data points available due to an earlier cut-off date. Based on published literature, the DSU concludes that independent reviewer assessment of progression is preferable.

DSU exploratory analyses

The DSU conducted a series of exploratory analyses combining the following alternative assumptions: (i) resource use estimates pooled from both, the original and new surveys; (ii) using the Weibull distribution for estimating survival; (iii) using the independent assessment of time to disease progression; and (iv) using the hybrid assessment of time to disease progression, which used the independent reviewer assessment when available and investigator assessment otherwise.

For its base case analysis, the DSU used the independent assessment of time to progression and the pooled resource use estimates. Despite the new evidence provided by the company, the DSU still considered that the Weibull distribution retained plausibility and undertook analyses with both parametric curves. The ICERs for sorafenib compared with BSC in the DSU's base case analysis are estimated to be £51,208 per QALY gained using the lognormal distribution and £71,276 per QALY gained using the Weibull distribution.

CONTENTS

TABLES

FIGURES

ABBREVIATIONS

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BSC	Best supportive care
CDF	Cancer Drugs Fund
CMU	Commercial Medicines Unit
CS	Company submission
DSU	Decision Support Unit
ERG	Evidence Review Group
GIDEON	Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
KM	Kaplan-Meier
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PFS	Progression free survival
PS	Performance status
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
SHARP	Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol
STA	Single Technology Appraisal
TTP	Time to progression
UK	United Kingdom

1. INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is currently in the process of re-considering cancer drugs that were previously funded through the current Cancer Drugs Fund (CDF) following appraisal by NICE that did not result in a recommendation. This reconsideration entails a rapid review of the companies' resubmissions to determine whether these drugs now represent a cost-effective use of National Health Service (NHS) resources and if not, whether they should continue to be used within the revised CDF.

The NICE Decision Support Unit (DSU) has been commissioned to review the company submission (CS) for the reconsideration of sorafenib for the treatment of advanced hepatocellular carcinoma (TA 189). The original Single Technology Appraisal (STA) was conducted in 2009 to 2010. The company, Bayer, made submissions to NICE and these were reviewed by the Evidence Review Group (ERG), West Midlands Health Technology Assessment Collaboration. During the original appraisal process, the company proposed a Patient Access Scheme, which was agreed with the Department of Health. Guidance was issued by NICE in January 2010 (TA 189)[1]. NICE did not recommend sorafenib for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable[1] and sorafenib was subsequently added to the CDF. For this reconsideration, the company has presented a new Commercial Medicines Unit (CMU) contract price.

In the scope of these rapid reviews, companies are expected to submit their original model implementing the original appraisal committee's preferred assumptions. New evidence is generally not permitted, unless an exception has been granted by NICE. A specific feature of this rapid review is that the company was granted permission to submit new evidence on the clinical effectiveness of sorafenib and resource utilisation.

2. SUMMARY OF THE ORIGINAL SUBMISSION AND COMMITTEE'S CONSIDERATIONS

For the original appraisal TA 189, the company submitted a Markov model to assess the cost-effectiveness of sorafenib compared with best supportive care (BSC) in people with advanced

hepatocellular carcinoma (HCC). The model had four distinct health states: first-line treatment – non-progressive advanced disease; first-line treatment – progressive disease; BSC – progressive disease; and death. The model had a cycle length of 1 month and a lifetime time horizon. The time horizon was assumed to cover up to an additional 14 years of life for a patient population with an average starting age of 67 years.

Clinical effectiveness data informing this model were obtained from a randomised controlled trial (RCT), the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study. The SHARP study was a multicentre, double-blind, placebo-controlled randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus BSC (n = 299) versus placebo plus BSC (n = 303). Disease progression was assessed by independent reviewers in the primary analysis of the SHARP study, and by investigators in a secondary analysis.

The clinical effectiveness data were extrapolated to a lifetime horizon using several distributions. Based on the Akaike Information Criterion, the lognormal distribution had the best goodness-of-fit, followed by the Weibull distribution. Time to disease progression was estimated based on investigator assessment, as opposed to independent reviewer assessment. The utility values used were derived using a mapping approach from the FACT-hep instrument to yield health state utility values. The model included drug costs and treatment costs for different health states and adverse events. Resource use and cost parameters in the model were estimated from primary (SHARP trial) and secondary sources. The estimates of resource use for health states and adverse events were based on a UK physician survey. After revision, the model also included the costs of sorafenib for the 7.7% of patients who continued treatment with sorafenib after progression for a median of 129 days, as observed in the SHARP study.

The committee considered that the SHARP study had stopped early, which could potentially have resulted in underestimating the survival benefit attributable to sorafenib. Whilst a statistically significant difference was observed for the benefits in overall survival and time to radiological progression, this was not the case for time to symptomatic disease progression. The committee accepted that the questionnaire used to measure time to symptomatic disease

progression may not have been able to distinguish between toxicity of sorafenib, symptoms of underlying liver disease and the symptoms of advanced HCC.[1]

The committee noted that the ICER for sorafenib compared with BSC presented by the company was originally £64,800 per QALY gained and that when the PAS was included it went down to £51,900 per QALY gained, both using the lognormal extrapolation. The committee also noted that fixing inconsistencies in costs increased this ICER to £52,600 per QALY gained.[1] It further considered that other alternative parametric curves, especially the Weibull distribution, also fitted the data well, particularly at the tail of the Kaplan-Meier curve. The committee concluded that one distribution could not be accepted as the definitive function to extrapolate beyond the data and that the Weibull distribution should also be considered in any consideration of the uncertainty.[1] The committee noted that the ERG's analyses demonstrated that using the independent reviewer assessment (instead of the investigator assessment) of time to disease progression would drive up the ICER to an estimated £76,000 per QALY gained (without the PAS and using the lognormal extrapolation).[1] Although the utilities used for the pre- and post- disease progression state lacked face validity (utility values were higher in the post-progression state than in the pre-progression state), the committee concluded that this did not significantly affect the ICER.[1]

The committee discussed the range of cost-effectiveness estimates, the lowest being the ICER of £52,600, given that using the Weibull distribution and the independent reviewer assessment of disease progression would drive the ICER up.[1] The committee considered the end of life criteria to be fulfilled. It concluded that sorafenib as a treatment for advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.[1]

3. SUMMARY OF THE COMPANY'S RESUBMISSION

3.1. NEW COMMERCIAL MEDICINES UNIT FRAMEWORK AGREEMENT

The company presented a new Commercial Medicines Unit (CMU) Framework Agreement consisting of a [redacted] discount to the list price of sorafenib (which is £2980.47 for a pack of 112 tablets of 200mg). Table 1 shows the cost per cycle (month) of sorafenib with the list price, the PAS presented for TA189[1] and the new CMU price.

Table 1: Cost of sorafenib per cycle based on list price, PAS and the new CMU price

	Cost (£) per cycle†
List price	£2,877.46
PAS price (TA189)	[redacted]
CMU price	[redacted]

†Based on a cycle of 30.4 days, and a mean dose of sorafenib of 710.5mg per patient per day (observed during the SHARP study[2])

3.2. NEW EVIDENCE PROVIDED BY THE COMPANY

The new evidence presented by the company for this rapid review falls into two categories: (1) additional evidence to further justify the company's use of the lognormal distribution rather than the Weibull distribution to extrapolate survival; and (2) new data on resource utilisation collected by the company through a survey to expert clinicians.

The company provided two pieces of evidence to support further the company's use of the lognormal distribution rather than the Weibull: a) the results of the observational study published by Palmer *et al.*,[3] which compared the survival of patients whose individual funding applications for sorafenib were accepted with those whose funding applications were rejected; and, b) long term overall survival (OS) data from the GIDEON observational study.[4] These are described in Sections 3.2.1 and 0.

The company also provided new estimates on resource utilisation from a UK physician survey as described in Section 3.2.3.

3.2.1. The Palmer et al. (2013) study

Palmer *et al.*[3] is a retrospective study of patients with advanced HCC treated in Kings College Hospital in London and Queen Elizabeth Hospital in Birmingham. At the time of the study, access to sorafenib was decided upon on a case-by-case basis through individual funding applications. The criteria for application comprised clinical information to indicate that, in the treating clinician's opinion, sorafenib was the most appropriate therapy – that is, it had a good performance status (PS 0-2); well-compensated background chronic liver disease;

not a suitable candidate for loco-regional therapies (surgery, transplantation, local ablation, and TACE). The company claimed that given that all applicants fulfilled these conditions, decisions on whether to fund were not apparently based on clinical variables. Follow up in this study was longer than in the SHARP study.[2] Table 2 shows the baseline characteristics of the patients included in the study.

Table 2: Baseline patient demographics and prognostic factors in Palmer *et al.*[3]

	All patients	**Sorafenib**	**Best supportive care (no sorafenib)**
Number of patients	133	57	76
Male: Female	108 : 25	52 : 5	56 : 20
Median age (range)	62 (16 – 86)	61 (16 – 82)	62 (17 – 86)
PS 0 : 1 : 2 (%)	19 : 49 : 32	20 : 48 : 32	18 : 48 : 34
Child-Pugh A	82%	84%	80%
AFP ≥1000	31%	30%	31%
Multifocal	70%	65%	75%
Largest lesion >5cm	68%	78%	60%
Macroscopic vascular invasion	34%	41%	29%
Extrahepatic metastases	39%	30%	46%

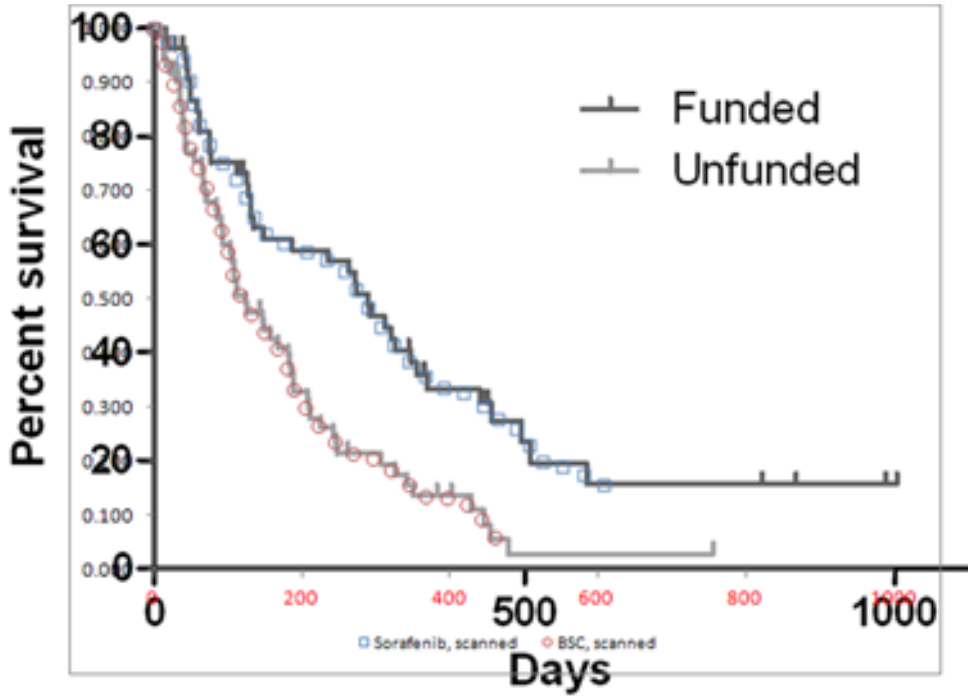
PS= performance status

The median overall survival from the time of the application in patients whose funding requests where declined was 4.1 months and 9.5 months for patients whose funding was approved (hazard ratio (HR) 0.48; 95% CI 0.3186–0.7267; P=0.0005). The clinical condition of 14 of the 57 patients whose funding was approved had deteriorated by the time the funding body made its decision such that the treatment could not be commenced. The median overall survival for the 43 patients who received at least one dose of sorafenib was 10.7 months (HR 0.38; 95% CI 0.25–0.59; P<0.0001). An analysis excluding all patients with metastases resulted in a median overall survival in patients whose funding requests where declined of 3.7 months and 8.95 months for patients whose funding was approved (HR 0.51, 95% CI 0.32–0.82; P=0.0061).

These HRs estimated in the Palmer *et al.*[3] study are considerably lower than that estimated in the SHARP trial (0.69). The company echoes the authors' discussion in their submission acknowledging that this may, in part, be due to the relatively worse outcome for untreated patients reflecting a number of adverse prognostic variables present in this subgroup. However, they state that it may also reflect the experience of two high-volume liver units and the evolution of experience since the SHARP trial in managing toxicities and maintaining dose intensity for sorafenib. In addition, Palmer *et al.*[3] claim that *"the baseline demographics between the two groups were generally balanced"* which suggested that improved outcome was due to a treatment effect rather than due to confounding prognostic variables.

Figure 1 shows the Kaplan-Meier (KM) curves for the overall survival of the two groups of patients. The company digitised the KM curves and fitted different parametric functions to the data. The company, based upon visual inspection of the curves plotted against the digitised KM curve (Figures 6, 7 and 8 of the CS[5]), considered the lognormal distribution to be a better fit than the Weibull. The company also pointed to the plateau in Figure 1 after day 600, during which no events happen. The company claimed that, given that the lognormal curve plateaus faster than the Weibull, the lognormal would appear to represent the observed data better.

Figure 1: KM curves reported by Palmer *et al.*[3] with points digitised by the company superimposed (reproduced from Figure 5 of the CS[5])



3.2.2. The GIDEON study

Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON)[4] was an international (39 countries), open-label, non-interventional study including over 3,000 patients with unresectable HCC. Outpatients with histologically/cytologically documented or radiographically diagnosed unresectable HCC who were candidates for systemic therapy and for whom a decision to treat with sorafenib had been made were eligible for inclusion. Table 3 summarises the patients' baseline characteristics of the GIDEON study.

Table 3: Patients' baseline characteristics of the GIDEON study

	Sorafenib
Number of patients	3202
Gender	82.2% male
Mean age	61.9 ± 12.1 years
Child-Pugh A	61.5%
ECOG score	0 (42.6%), 1 (39.7%)
BCLC stage	C (52.0%), B (19.8%)
CLIP score	Not evaluable (26.6%), followed by 1 (21.7%) and 2 (19.4%)

The primary objective of the GIDEON study was to evaluate the safety of sorafenib in patients with unresectable HCC who were candidates for systemic therapy under real-life practice conditions. The secondary objectives included to evaluate long-term efficacy of sorafenib were OS and progression free survival (PFS).

The company described the safety outcomes of the study in Appendix 3 of the CS[5] but they are excluded from this summary as they are not used in the economic analyses. Table 16 of the CS[5] contains the summary of outcome variables for overall survival, progression free survival and time to progression.

Figure 2 shows the Kaplan-Meier curve for overall survival in the GIDEON[4] study. The company claims that the long survival 'tail' of the KM curve provides a robust estimate and potential validation of the choice of lognormal curve instead of the Weibull curve.

[redacted]

Table 4 compares the 50%, 30% and 20% survival time predicted by curves fitted to SHARP[2] data with that observed in the GIDEON study. The survival times from the GIDEON study were approximately estimated based on visual inspection of the KM curve. The company pointed out that whilst the Weibull and the lognormal curves approximately fit the 50% survival time, the lognormal distribution predicts 30% and 20% survival more accurately than the Weibull.

Table 4: Survival predicted by curves fitted to data from SHARP[2] compared with survival in the GIDEON study (in days)

Parametric curve		50% survival	30% survival	20% survival
SHARP	Weibull	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]
GIDEON		[redacted]	[redacted]	[redacted]

*Approximate estimates based on visual inspection of KM of OS data for the ITT population

3.2.3. Resource utilisation

The company updated the resource utilisation estimates for each health state as well as for each type of adverse event. In the original submission,[6] these estimates were based on the responses of four physicians to a survey submitted by the company (a copy of the resource use survey was provided in Appendix 13). In this resubmission[5], the estimates were based on the responses of three clinicians to a similar survey (a copy of the resource use survey was provided in Appendix 4.1 of the resubmission[5]). The company justified this update arguing that the clinicians are now much more experienced in using sorafenib in routine UK clinical practice than at the time of the original submission and could provide updated estimates of resource utilisation.

The company also updated the unit costs using the NHS Reference Costs for 2014/2015.[7]

3.3. NEW ANALYSES UNDERTAKEN BY THE COMPANY

In their resubmission, the company implemented the following changes to adopt the original appraisal committee's preferred assumptions:

- The costs of 7.7% of patients who continued sorafenib treatment post progression in the SHARP study[2] were incorporated.
- Treatment costs have been calculated based on 30.44 days instead of 30 days.

The company presented the results of this revised model with the old PAS (see Table 5), which resulted in an ICER for sorafenib compared with best supportive care of [redacted] per QALY gained. This ICER is slightly lower than that mentioned in the FAD of TA189 (£52,600/QALY) as the lowest of the range of estimated ICERs. This small discrepancy may be explained by how the amendments were implemented in the model.

Table 5: Results of the analysis with the revised model and the old PAS (deterministic)

	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.1. Analysis with the revised model

The company undertook a base case analysis with the revised model including committee's preferred assumptions and the new CMU contract price agreement. The results of the deterministic analysis (see Table 6) show an estimated cost per QALY gained of £43,808 for sorafenib compared with BSC.

Table 6: Results of the base case analysis of the company in the revised model (deterministic)

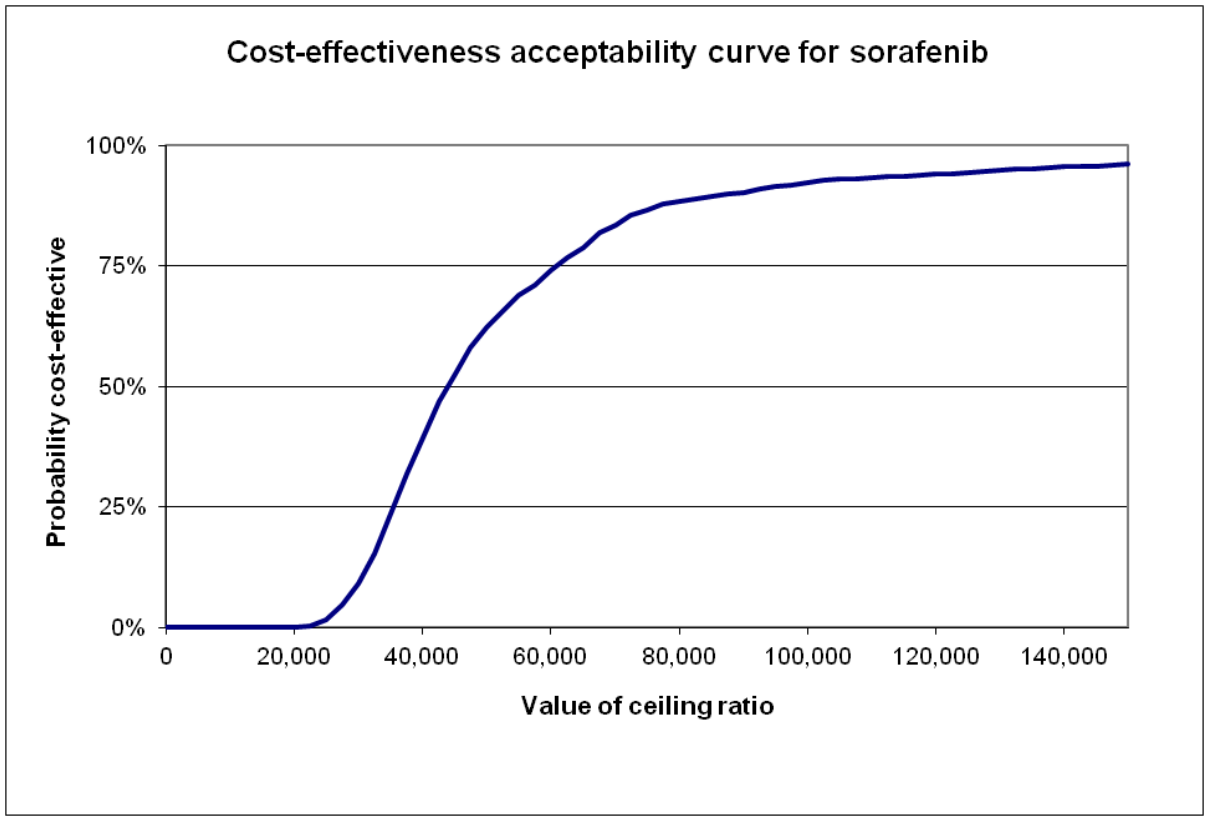
	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£43,808

The company undertook a probabilistic sensitivity analysis (PSA) of the model by sampling the value of a set of parameters from a number of distributions as defined in Table 8 of the company's resubmission[5]. The results of the PSA are summarised in Table 7 and estimate the ICER of sorafenib compared with BSC to be £43,408 per QALY gained. At a threshold of £50,000 per QALY gained, sorafenib was 62.2% likely to be cost-effective with the new CMU contract price (as shown in the cost-effectiveness acceptability curve in Figure 3).

Table 7: Results of the base case analysis of the company in the revised model (probabilistic)

	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£43,408

Figure 2: Cost-effectiveness acceptability curve for sorafenib compared with BSC (company's base case analysis)



The company also performed a series of one-way sensitivity analyses (OWSAs) to explore the impact of the uncertainty around parameters on the ICER. The OWSAs were performed using the 95% confidence intervals for the efficacy parameters, standard deviations for the utilities, and ±30% for disutility estimates and costs. The estimated ICERs ranged from £ [redacted] to £[redacted] per QALY gained. The most impactful parameters were the four parameters governing the survival curves (mean and standard deviation for sorafenib and BSC), [redacted]. Full results can be found in Table 7 of the company's resubmission.[5]

3.3.2. Analysis with revised model, updated costs and resource use

As part of their resubmission, the company included another version of the model where the unit costs had been updated and resource utilisation estimates were based on the new survey described in Section 3.2.3. Table 8 summarises the results of this analysis, with an estimated ICER of £39,162 per QALY for sorafenib compared with BSC. The difference in ICERs compared with the original model can be traced back to the updated resource use data, and

one factor in particular: the new estimate of number of hospitalisations per cycle for patients prior to progression and who receive BSC.

Table 8: Results of the base case analysis of the company in the updated model (deterministic)

	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£39,162

The company also performed a series of OWSAs to test the impact of the uncertainty around certain parameters on the ICER. The estimated ICERs ranged from £[redacted] to £[redacted] per QALY gained. The most impactful parameters were still the four parameters governing the survival curves (mean and standard deviation for sorafenib and BSC), [redacted]. Full results can be found in Table 31 of the company's resubmission.[5] Only deterministic results were presented by the company for this analysis.

3.3.2.1. Analysis using Palmer *et al.*

The company undertook an exploratory analysis using the curves fitted to the data from the funded and unfunded groups from Palmer *et al.* for OS in the sorafenib and BSC treatment arms, respectively. Updated costs and resource use estimates were used for this analysis. The estimated ICER of sorafenib compared with BSC was £20,556 per QALY gained (see Table 9), considerably lower than in the base case.

Table 9: Results of the company's updated model analysis using Palmer *et al.* [3](deterministic)

	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£20,556

The company also undertook a series of OWSAs to determine if the results were sensitive to variations in parameter values. The estimated ICERs ranged from £[redacted] to £[redacted] per QALY gained. The most impactful parameters were again the four parameters governing the

survival curves (mean and standard deviation for sorafenib and BSC). The full results of the OWSAs can be found in Table 29 of the company's resubmission.[5] Only deterministic results were presented by the company for this analysis.

4. CRITIQUE OF THE COMPANY'S RESUBMISSION

4.1. CRITIQUE OF THE NEW EVIDENCE

The DSU has identified a number of issues associated with the submission of new evidence. These relate mainly to the following points (which are described in more detail in the following sections):

- inclusion of further evidence (GIDEON study) that was not identified using the company's search strategy and that would have been excluded based on the eligibility criteria defined by the company
- exclusion of studies based on criteria not listed in the company's eligibility criteria
- high risk of bias associated with the Palmer *et al.*[3] study
- the use of this evidence (both the GIDEON study and the Palmer *et al.*[3] study) to support modelling assumptions despite differing patient characteristics
- resource utilisation estimates based on a small number of experts

The search strategy and study selection are critiqued in Section 4.1.1. In Section 4.1.2, the patient characteristics of the different studies are described and compared in order to form a basis on which to judge the appropriateness of the company's conclusions and their modelling assumptions. A critique of implications of the new evidence on the cost-effectiveness analysis is provided in Section 4.1.3.

4.1.1. Critique of the search strategy and study selection

The company adapted and applied the broader search developed by the ERG group (Appendix 7 of the ERG report in 2009[8]). The DSU considered that none of the key trials were missed in the searches. However, the DSU ran an update search (17th June 2016) in PubMed and there were no relevant trials published since February 2016.

The DSU notes inconsistencies in the company's method of study selection. Whilst the company's eligibility criteria (Table 32 in CS Appendix 7[5]) do not specify an exclusion criterion that excludes studies with a patient population from certain geographical areas, Table 42 in Section 1.4 of CS Appendix 7[5] shows that some studies were *"subsequently excluded as based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population"*.[5] The DSU therefore questions the appropriateness of excluding two potentially relevant studies (see Section 4.1.2 for more detail). However, this is consistent with the previous appraisal in which one of these two studies was identified and only used in a supportive manner, based on the rationale mentioned above.

Moreover, in this search, the company's eligibility criteria specified that studies eligible for inclusion must have a control arm. However, the company included the GIDEON study, which lacked a control arm. The DSU therefore notes that the company's approach to study selection is non-systematic.

4.1.2. Critique of the new clinical effectiveness evidence

As stated in Section 3.2, the company provides justification for the use of the lognormal distribution to extrapolate overall survival from the SHARP trial based on data from the GIDEON[4] and the Palmer *et al.*[3] studies, both of which had a longer follow up than the SHARP trial. Two other studies, the Asian-Pacific trial[9] and the Ji et al.[10] study, had previously been excluded *"based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population."*[5] It has been reported that certain baseline characteristics are prognostic factors for disease progression and survival, although Palmer *et al.* claim that there are *"no known predictive variables that the funding bodies could … [use] to select patients more likely to benefit from treatment"* because *"sorafenib-randomised trials indicate similar benefit across all subgroups"*.[3] The similarity of the included and the excluded studies in terms of their baseline characteristics is therefore explored in this section.

4.1.2.1. Study characteristics

This section details the design and characteristics of five key studies (see Table 10). Three studies were included in the submission: the Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP)[2] randomised, placebo-controlled trial (the key trial in the original assessment); the Palmer *et al.*[3] retrospective case study and the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafenib) open-label, prospective non-interventional study, data for which were submitted by the company as part of this assessment.[4] However, the GIDEON study should have been excluded because it does not satisfy the eligibility criteria outlined in the decision problem or by the company in the submission (Appendix 7, Table 32[5]); specifically, it is not a comparative study with either a placebo or BSC control arm. Indeed, the absence of such a control was one of the reasons given for excluding many other studies from the submission (Appendix 7.1, Tables 42 and 43[5]). The GIDEON study is retained in this summary, however, because it was included in the submission.

Two further trials are relevant and are included here: the "Asian-Pacific trial", Cheng *et al.* (2009)[9], a randomised, placebo-controlled trial; and Ji *et al.* (2014)[10], a randomised, placebo-controlled trial, located exclusively within China (see Table 10). The company accepted that both trials satisfied the eligibility criteria for the review of clinical effectiveness, but excluded them from the submission, *"based on the population having different underlying characteristics and aetiologies, when compared with the relevant UK population"* (CS Table 42[5]). However, details of these different characteristics are neither specified nor justified (no additional justification was provided in the original appraisal), and these appear to have been applied only as *post hoc* exclusion criteria. The DSU notes that a follow-up study including post-hoc subgroup analyses of the SHARP trial data found that effectiveness of sorafenib was consistent in this trial irrespective of baseline health status, tumour stage, disease burden or disease aetiology.[11] This study, although associated with the caveats of post-hoc analyses such as small numbers, would undermine the company's rationale for excluding studies based on the patient population having different characteristics and aetiologies. The submission also states (pp.88 and 98 in the CS[5]) that the populations in these trials were *"Chinese patients only"*; further justifying their exclusion. However, this is incorrect for the Asian-Pacific trial (see Table 10), which included Taiwanese and South Korean patients. These two trials are therefore included in this summary because they satisfy

the pre-determined eligibility criteria of both the decision problem and the company's review (see CS Appendix 7, Table 32[5]). It should also be noted that the company's eligibility criteria included *"Sorafenib in combination with another agent"* as a potential comparator, but studies satisfying this criterion were excluded, correctly, based on the decision problem, which specified BSC or placebo only as comparators.

Table 10: Relevant studies

Study and date	SHARP 2008	Cheng *et al.* 2009	Palmer *et al.* 2013	Ji *et al.* (2014)	GIDEON
Design	Phase 3, double-blind, randomised, placebo-controlled trial	Phase 3, double-blind, randomised, placebo-controlled trial	Retrospective study	Phase 3, open-label, randomised, placebo-controlled trial	Prospective, open-label, non-interventional study
Location(s)	International (21 counties in Europe, North America, South America, and Australasia)	International (3 countries: China, Taiwan, and South Korea)	UK only	China only	International (39 countries, principally USA, South Korea, China)
No. of centres	121	23	2	3	376
No. of patients					
Sorafenib	299	226	57	95	3202
Placebo/BSC	303	76	76	94	N/A
Total numbers	602	302	133	189	3202

4.1.2.2. Inclusion and exclusion criteria in the five key studies

The SHARP[2] and Asian-Pacific[9] trials reported similar and extensive inclusion criteria, but the inclusion criteria for the Palmer *et al.*[3] and GIDEON[4] studies were generally less well-specified (see Table 11). All studies were consistent in requiring patients to have advanced (unresectable) histologically or cytologically proven hepatocellular carcinoma and ECOG PS (Eastern Cooperative Oncology Group Performance Status) of 0, 1 or 2, although ECOG PS was not specified in the inclusion criteria for the GIDEON study[4]. This scale assesses the daily living abilities of the patient, ranging from 0 (fully active) to 5 (dead). The SHARP[2] and Asian-Pacific trials[9] also required patients to have Child–Pugh liver function class A, which represents the least severe form of liver disease and the least worst prognosis (compared with classes B and C) [12, 13]. The patients in the SHARP[2] and Asian-Pacific[9] trials also had to have a life expectancy of at least 12 weeks, compared with 8 weeks in the Palmer *et al.*[3] retrospective study and the Ji *et al.* study[10], while life expectancy was unspecified in the GIDEON[4] study. The criteria for adequate renal, haematological and hepatic function were much more detailed in the SHARP[2] and Asian-Pacific[9] trials. These criteria were not specified for the Palmer *et al.*[3], Ji *et al.*[10] or GIDEON[4] studies. The SHARP[2] and Asian-Pacific[9] trials also specified details of lesions and prior and concomitant therapies and interventions; this information was not provided as inclusion or exclusion criteria (see Table 12) for the Palmer *et al.*[3] or GIDEON[4] studies, and no details of concomitant therapies were provided for the Ji *et al.*[10] trial.

Table 11: Inclusion criteria (clinical characteristics) of the key studies

	SHARP 2008	Cheng *et al.* 2009	Palmer *et al.* 2013	Ji *et al.* 2014	GIDEON
Advanced Hepatocellular carcinoma (HCC)	Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies	Patients at least 18 years old with advanced (unresectable or metastatic) hepatocellular carcinoma who had not received previous systemic therapy were eligible. Eligibility criteria also included histologically or cytologically proven hepatocellular carcinoma	Advanced HCC, not suitable for loco-regional therapies	Patients were pathologically or cytologically confirmed advanced HCC, with liver function … failed to respond to or were ineligible to locoregional treatment	Outpatients with histologically / cytologically documented or radiographically diagnosed unresectable HCC who were candidates for systemic therapy and for whom a decision to treat with sorafenib had been made. Radiographic diagnosis needed typical findings of HCC by radiographic method i.e. on multidimensional dynamic computerized tomography (CT), CT hepatic arteriography (CTHA)/CT arterial portography (CTAP) or Magnetic Resonance Imaging (MRI).
	ECOG PS score of 2 or less	ECOG PS of 0, 1 or 2	Performance status 0-2	Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2	
	Child–Pugh liver function class A	Child-Pugh liver function class A		Child-Pugh liver function class B or C Barcelona-Clinic Liver Cancer (BCLC) stage B or C	
Life expectancy	12 weeks or more	At least 12 weeks	Not specified	2 months or longer	At least 8 weeks
Renal, haematological, and hepatic function	Adequate hematologic function (platelet count, ≥60×109 per liter; hemoglobin, ≥8.5 g per deciliter; and prothrombin time international normalized ratio, ≤2.3; or prothrombin time, ≤6 seconds above control), adequate hepatic function (albumin, ≥2.8 g per deciliter; total bilirubin, ≤3 mg per deciliter [51.3µmol per liter]; and alanine aminotransferase and aspartate aminotransferase, ≤5 times the	Adequate renal, haematological, and hepatic function, as indicated by a platelet count of 60×10^9/L or greater; haemoglobin concentration of 85 g/L or more; albumin concentration of at least 28 g/L; total bilirubin concentration of 51.3µmol/L or less; alanine amino transferase concentration of five-times the upper limit of normal (ULN) or less; serum creatinine concentration of 1.5-	"well-compensated background chronic liver disease"	"adequate renal function"	Not specified

	upper limit of the normal range), and adequate renal function (serum creatinine, ≤1.5 times the ULN range).	times the ULN or less; and a prothrombin time international normalised ratio (INR) of 2.3 or less or prothrombin time less than or equal to 6 seconds above control.			
Lesions	Patients were required to have at least one untreated target lesion that could be measured in one dimension, according to the Response Evaluation Criteria in Solid Tumors (RECIST)	Additionally, patients considered for inclusion were required to have at least one tumour lesion (not previously treated with local therapy) that could be measured along one dimension according to Response Evaluation Criteria in Solid Tumors (RECIST).	Not specified	Enrolled patients were required to have one or more evaluable target lesions that could be measured in one dimension according to RECIST criteria	Not specified
Prior interventions or therapy	Not specified	Patients who had received previous local therapy, such as surgery, radiotherapy, hepatic arterial embolisation, chemoembolisation, radio frequency ablation, percutaneous injection, or cryoablation, were eligible for enrolment in the study, provided that either the target lesion increased in size by 25% or more, or the target lesion had not been treated with local therapy. Furthermore, the local therapy must have been stopped at least 4 weeks before study entry. Patients with recurrent disease after previous resection were considered eligible for the study.	Not specified	Local therapy must be completed at least 4 weeks prior to the baseline scan.	Not specified
Concomitant interventions	Concomitant antiviral systemic therapy was allowed.	Not specified	Not specified	Not specified	Not specified

ECOG PS: Eastern Cooperative Oncology Group Performance Status; RECIST: Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.

Table 12: Exclusion criteria (clinical characteristics) of the key studies

	SHARP 2008	Cheng *et al.* 2009	Palmer *et al.* 2013	Ji *et al.* 2014	GIDEON
Reported criteria	Patients were excluded if they had previously received molecularly targeted therapies or any other systemic treatment.	Included: previous or concomitant systemic therapy (including new, molecularly targeted therapies); known history of HIV infection; clinically serious infections; known substance abuse; history of organ allograft; history of cardiac disease; known Central Nervous System tumour; known gastrointestinal bleeding up to 30 days before study entry; and pregnancy or breast-feeding.	Not specified	Patients were excluded if they were pre-treated with any molecular target therapies.	Not specified

4.1.2.3. Baseline patient characteristics

In accordance with the inclusion criteria, the patients in the SHARP[2] and Asian-Pacific[9] trials have less severe disease than the patients in the Palmer *et al.*[3] and GIDEON[4] studies based on the better daily living abilities of the patients (a higher percentage of patients with ECOG PS of 0 or 1) and better liver function, as measured by the Child-Pugh classification (a higher percentage of patients with class A compared with classes B or C). The SHARP[2] and Asian-Pacific[9] trials also have a large majority of patients with advanced disease according to the Barcelona Clinic Liver Cancer (BCLC) staging system (Stage C)[14], a much higher proportion than the GIDEON[4] study (between 82% and 95%, compared with 52%), but it is unclear what proportion of patients in the GIDEON[4] study were stages A or D, and these data are not provided for the Palmer *et al.*[3] study. In terms of macroscopic vascular invasion, the percentage of patients within any group was largely comparable across the SHARP[2] and Asian-Pacific[9] trials, and the sorafenib group in the Palmer *et al.*[3] study (34%-41%), but the percentage of patients with macroscopic vascular invasion was lower in both the Palmer *et al.*[3] BSC group (29%) and the GIDEON[4] study (22%). Proportions of patients with extrahepatic spread were generally different between studies (see Table 13), but similar across arms or groups within studies, with the exception of the Palmer *et al.*[3] study, in which there was a substantial difference between groups (30% in the sorafenib group compared with 46% in the non-sorafenib group). There were also differences between the groups in the Palmer *et al.*[3] study in terms of multifocal disease (65% in the sorafenib group compared with 75% in the non-sorafenib group) and the proportions with a lesion of >5cm (78% compared with 60%, respectively). The five studies could not be compared by alpha-fetoprotein levels, multifocal disease or lesion size because data on these variables were not reported across all studies. In terms of the principal causes of HCC, where this was reported, the patient populations of the included studies were quite different: for hepatitis B virus, 18-19% in SHARP[2], 37% in GIDEON[4], as well as 71%-78% and 78%-81% in the Asian-Pacific trial[9] and the Ji *et al.*[10] trials, respectively; and for hepatitis C virus, 27%-29% in SHARP[2], 33% in GIDEON[4] , 4%-11% in the Asian-Pacific trial[9], and 2%-3% in Ji *et al.*[10].

Table 13: Baseline characteristics of participants across the five relevant studies

	SHARP 2008		Cheng *et al.* 2009		Palmer *et al.* 2013		Ji *et al.* 2014		GIDEON
	Sorafenib n=299	Placebo n=303	Sorafenib n=226	Placebo n=76	Sorafenib n=57	BSC n=76	Sorafenib n=95	BSC n=94	Sorafenib n=3202
Male (%)	87	87	85	87	91	74	85	83	82
Median age (years)	65	66	51	52	61	62	59	59	62
ECOG/WHO PS 0 or 1 (%)	92	93	95	95	68	66	25	29	83
ECOG/WHO PS 2 (%)	8	7	5	5	32	34	75	71	17
Child-Pugh A (%)	95	98	97	97	84	80	0	0	62
BCLC stage B (Intermediate) (%)	18	17					12	13	20
BCLC stage C (advanced) (%)	82	83	95	96			88	87	52
Macroscopic vascular invasion (%)	36	41	36	34	41	29			22
Extrahepatic spread (%)	53	50	69	68	30	46	39*/82†	37*/78†	40
AFP — ng/ml (Median)	44	99							
AFP >1000 ng/ml (%)					30	31			
AFP>ULN ng/ml^{-1} (%)			77	78					
Multifocal disease (%)					65	75			
Largest lesion size (>5cm) (%)					78	60			
HBV (%)	19	18	71	78			81	78	37
HCV (%)	29	27	11	4			3	2	33

All figures reported to one or more decimal places have been rounded-up to the whole number. Blank cells indicate that this variable was not reported for the study. *Metastases; † Regional lymph nodes; BSC: Best Supportive Care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BCLC: Barcelona Clinic Liver Cancer staging system; ULN: Upper Limit of Normal; AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HCV: Hepatitis C virus

4.1.2.4. Conclusion on new clinical effectiveness evidence

There are notable differences between the patient population of the SHARP[2] trial and those of the Palmer *et al.*[3] and GIDEON[4] studies, especially in terms of disease severity, BCLC stage, macroscopic vascular invasion and, possibly, specific cause of HCC. Based on the inclusion criteria and baseline characteristics of patients in the five studies, the participants in the SHARP[2] and Asian-Pacific[9] trials represent better-specified patient groups with less severe disease, but it is unclear how closely these samples also represent the patients likely to present in practice in England. The reported quality assessment of the Palmer *et al.*[3] study is reasonable and appropriate (indicating a high risk of bias in terms of both internal and external validity, see company's resubmission, Appendix 3[5]); there is no formal critical appraisal of the ongoing GIDEON[4] study.

4.1.3. Critique of the new cost effectiveness evidence

4.1.3.1. The Palmer *et al.* (2013) study

Palmer *et al.*[3] is an observational study where the overall survival of patients whose sorafenib funding application requests were funded is compared against patients whose application was rejected.

As was highlighted in Section 4.1.2, the Palmer *et al.*[3] study was at a high risk of bias. There was no randomisation of the groups and some of the prognostic factors are not balanced across groups (e.g. Child-Pugh A, multifocal, largest lesion> 5cm, macroscopic vascular invasion) as can be seen in Table 2. The DSU notes that it is highly uncertain how correcting for all these imbalances would affect the treatment effect. The company claims that decisions on whether to fund sorafenib were apparently not based on clinical variables, based on balanced demographic factors (Table 2). However, there is the possibility that clinical factors not evenly balanced according to Table 2, as well as clinical factors not reflected in Table 2, had an effect on the funding decision. For example, aetiology of the disease is not considered in Table 2.

The number of patients included in the Palmer *et al.*[3] study was considerably lower than in the SHARP trial[2]: the number of patients treated with sorafenib in the former was 57 and 299 in the latter whilst the number of patients not treated with sorafenib was 76 in the former

and 303 in the latter. The low number of patients included in the Palmer *et al.*[3] study results in a high degree of uncertainty, especially in the tail of the KM curve, where most patients have died or have been lost to follow-up and only a few patients remain at risk.

The treatment effect of sorafenib observed in Palmer *et al.*[3] is considerably more in favour of sorafenib than that observed in the SHARP trial[2] (HR of 0.48 and 0.69 compared with BSC, respectively). The authors claim that this improvement may be a result of increased experience with the use of sorafenib. However, the DSU believes that, with it being a study at a high risk of bias, this is suggestive of an imbalance between the two groups.

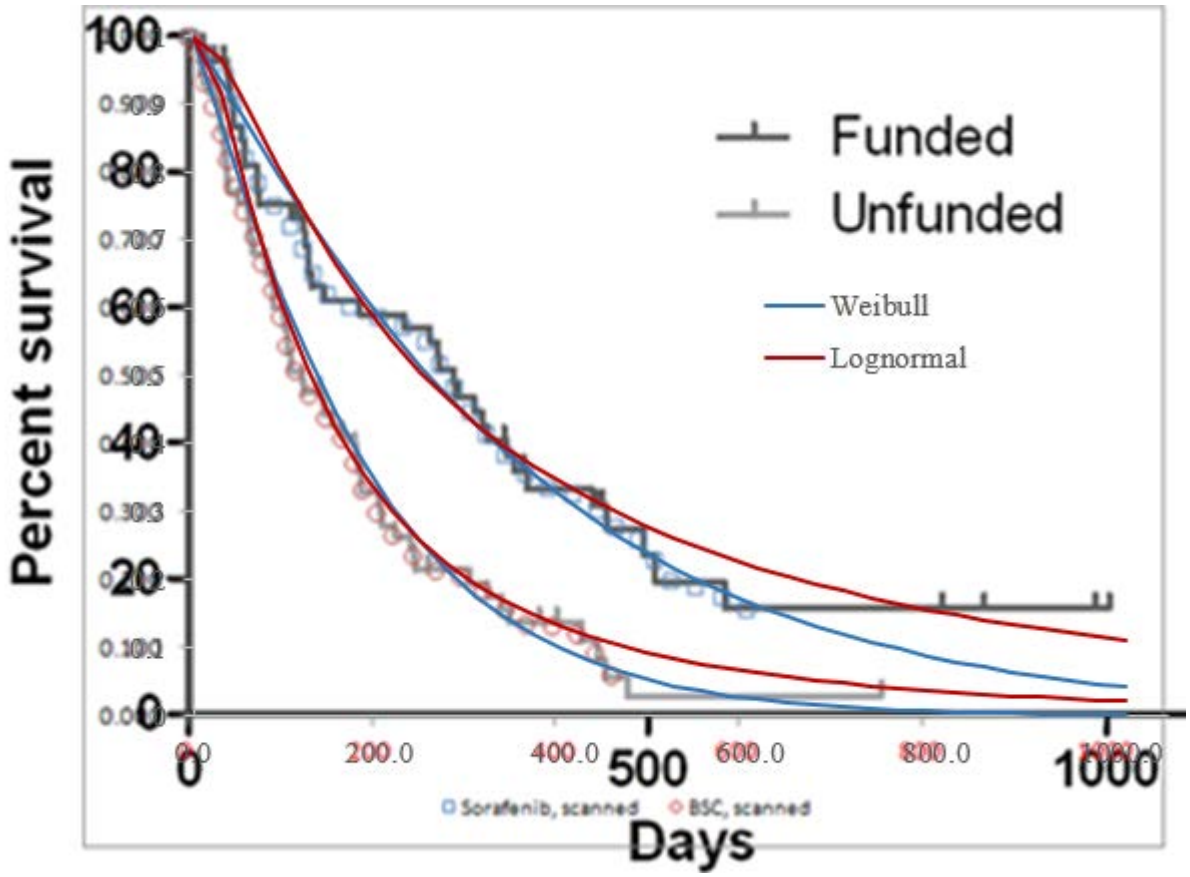
The company digitised the curves from the KM data in Palmer *et al.*[3] for the funded and unfunded patient groups, as shown in Figure 1. The DSU notes that the digitisation of the curves did not include the tail. The DSU agrees with this approach, given that it is only possible to estimate survival from a KM curve during the time in which at least one event (in this case, death) is registered: adding data points after the last death would imply that the death rate of the interval after the last death will be zero even though the patients are still subject to (at least) general mortality.

The company then fitted different parametric curves to the digitised data points and plotted the curves against the data (Figures 6, 7 and 8 of the CS[5]), based on which it claimed that upon visual inspection the lognormal provided the best fit. The company also claimed that because the KM curve has a plateau after 600 days and the lognormal distribution plateaus faster than the Weibull, the former would better represent the observations. The DSU plotted both curves against the KM curve from Palmer *et al.*[3] (see Figure 4). The DSU believes that, based on visual inspection, it can be argued that the Weibull distribution fits the observed events better than the lognormal does.

The company claimed that the Weibull curve does not fit the last part of the sorafenib arm of the KM curve, where it plateaus. The DSU is unsure how significant the plateau at the tail of the curve in the sorafenib arm is, given the lack of information on the number of patients at risk. Taking into account that there were only 57 patients in the sorafenib group and the censoring before the tail of the curve, it appears reasonable that patient numbers at risk were likely very small. The DSU acknowledges that the Weibull fails to flatten as the lognormal does, but that the Weibull curve is likely to be well within the confidence interval region. An

expert clinician consulted by the DSU confirmed that a subgroup of patients survives much longer than the average, but supported the view that it would be difficult to choose between the two curves.

Figure 3: KM and fitted curves from Palmer et al.



The DSU has produced log cumulative hazard plots for the Weibull distribution (Figure 5) and the lognormal distribution (Figure 6) in an attempt to better assess the appropriateness of the model. In both figures, the crosses lying in a straight line would indicate that the respective model is appropriate. The DSU notes that based on visual inspection of the log cumulative hazard plots, the appropriateness of both distributions seems to be similar.

Figure 4: Log cumulative plot for the Weibull distribution (produced with the company's model)

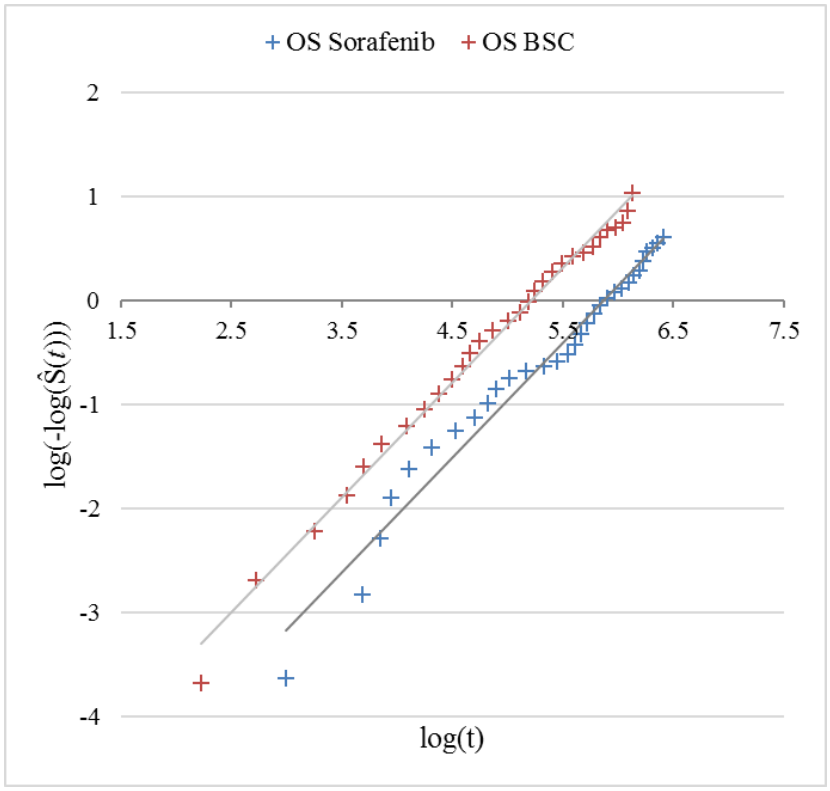
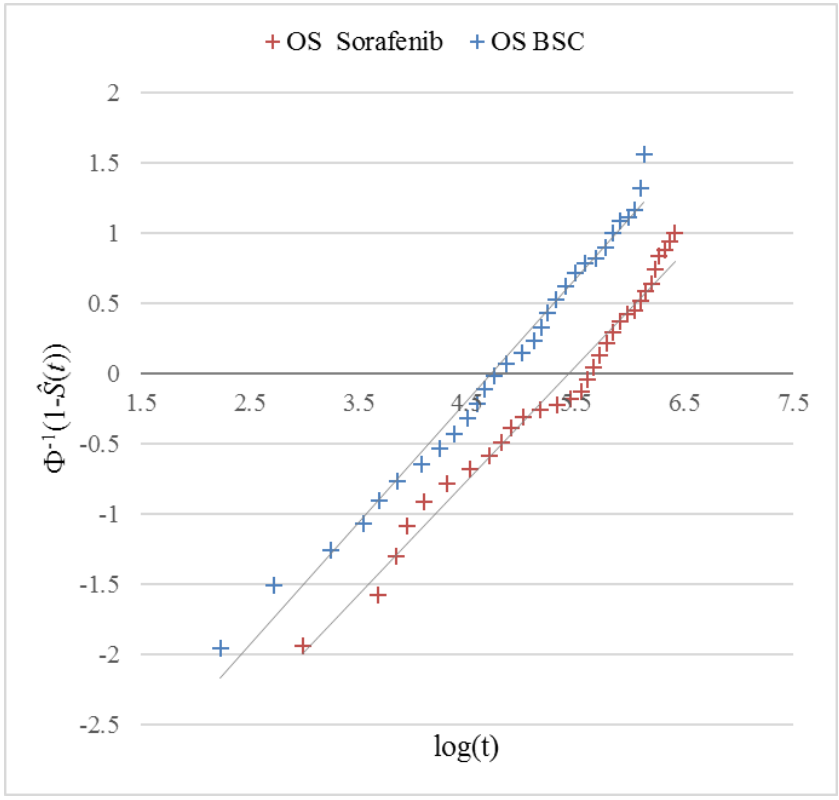


Figure 5: Log cumulative plot for the lognormal distribution (produced with the company's model)



4.1.3.2. The GIDEON study

The company justified the robustness of the lognormal distribution by providing evidence of the ability to predict long-term survival observed in the GIDEON study of the lognormal in comparison with the Weibull distribution. The DSU digitised the sorafenib arm from the KM curve of the SHARP[2] trial (Figure 3 of the original submission[6]) and the KM curve of the GIDEON[4] study (Figure 3 of the resubmission [5]) and plotted them together in Figure 7 along with the curves fitted to data from SHARP. The DSU notes that the survival curves of SHARP[2] and GIDEON have considerable differences. The short-term survival is higher in SHARP, which could be caused by the worse prognosis of patients in GIDEON (e.g. 61.5% of patients with Child-Pugh status A compared with 95% in SHARP). After a time-span where both curves meet, the curve in SHARP seems to plunge sharply. The difference between the two KM curves may be caused by the differences in study design, prognostic factors and aetiologies across study populations.

Due to the difference in the shapes of both KM curves, the fact that parametric curves fitted to the SHARP data do not fit the KM curve from GIDEON very well was expected. Both curves overestimate survival at the beginning, but the DSU acknowledges that the lognormal distribution extrapolated from SHARP trial data predicts long-term survival in GIDEON remarkably better than the Weibull does. The DSU also digitised the KM curve from GIDEON and fitted lognormal and Weibull curves to it (see Figure 8) to assess their goodness of fit. The DSU notes that upon visual inspection, the lognormal still fits the survival data from GIDEON better than the Weibull does, but the difference is much smaller.

The DSU notes that the ability of the lognormal to fit the survival data from GIDEON better than the Weibull might be explained by the heterogeneity of the population in the study: patients with different prognostic factors (e.g. Child-Pugh status) have different life expectancy, those with a worse prognosis dying earlier. Therefore, the cohort's hazard rate decreases across time in a way that the lognormal distribution can approximate better than the Weibull. The DSU notes that the population in SHARP was more homogeneous (95% patients with Child-Pugh status A), which might explain why the Weibull distribution fitted the KM curve of SHARP well. Therefore, the DSU notes that the better fit of the lognormal compared with the Weibull distribution to the KM curve of the GIDEON[4] study is relevant

only to the extent that its studied population is considered representative of the target population.

[redacted]

[redacted]

[redacted]

4.1.3.3. Resource use estimates

As stated in Section 3.2.3, the company updated the resource utilisation estimates used in the model with the results of the survey sent to three clinicians with experience in treating patients with sorafenib. The company justified this change claiming clinicians had had extensive time to familiarise themselves with the use of sorafenib since the original submission and therefore their estimates would be more accurate. The DSU notes that the content of the new survey is very similar to that used in the original submission, and only the wording around the questions and the ordering has changed.

The DSU thinks that discarding the results of the original survey is not the best option, especially considering that the original survey involved more clinicians and contained more responses (see Table 14). The estimates of the clinicians that took part in the new survey might have produced better estimates for the sorafenib arm due to the learning curve but the

estimates for the BSC arm from the original survey should be equally valid when compared with those of the new survey.

Table 14: Comparison of the number of responses collected in the original vs. new survey

	Original survey	**New survey**
Total number of questions	279	247
Questions with no responses (%)	39 (14.0)	16 (6.5)
Questions with one response (%)	31 (11.1)	35 (14.2)
Questions with 2 responses (%)	33 (11.8)	100 (40.5)
Questions with 3 responses (%)	36 (12.9)	96 (38.9)
Questions with 4 responses (%)	140 (50.2)	0 (0)
Total responses	765	523
Average number of responses	2.74	2.12

The DSU notes that the difference between the base case ICERs for sorafenib versus BSC produced by the revised model (£43,808/QALY) and the updated model (£39,162/QALY) was mostly explained by the variation in a single parameter estimated through the resource utilisation survey: [redacted]. This parameter was estimated from two clinicians' responses in the updated model (the estimate of the third clinician was missing), whilst in the original and the revised models, it was estimated from four clinicians' responses.

The DSU was satisfied with the updated unit costs used by the company, which were taken from the NHS Reference Costs 2014/2015[7], whilst the unit costs for the original and revised models had been taken from several sources.

4.2. CRITIQUE OF THE NEW ANALYSES

4.2.1. General overview

In their resubmission, the company included the results of the following analyses: (i) using the revised original model; (ii) using the updated model, with updated resource utilisation and costs; and (iii) a scenario analysis using the updated model with OS curves fitted to Palmer *et al.*'s[3] data.

The DSU believes that it is reasonable to update costs and resource use estimates but less so to exclude previous resource use estimates. The DSU notes that pooling the estimates of expert clinicians on resource utilisation from the original and new surveys is likely to lead to more accurate estimates.

The DSU considers that the scenario analysis using OS curves fitted to Palmer *et al.*'s[3] data is of limited validity for the following reasons: 1. the Palmer *et al.*[3] study has a high risk of bias (as described in Section 4.1.3); 2. it contains a small number of patients (57 in the sorafenib arm); and 3., it combines the use of the OS curve from Palmer *et al.*[3] with the use of the PFS curve from the SHARP trial. The DSU believes that both OS and PFS curves should be based on the same study in order to ensure validity of the estimated post progression survival. In addition, the DSU identified inconsistencies in the OS survival curves shown in Figure 6 of the CS (showing the fit of the lognormal distribution to the data from Palmer *et al.*[3]) and those used in the economic analysis. These inconsistencies are described in Appendix B.

The DSU notes that the company failed to provide the analyses for key areas of uncertainty identified in the final appraisal determination of the original appraisal: the choice of the parametric curve and the assessment of time to progression.

4.2.2. Choice of parametric curve to extrapolate overall survival

The DSU notes that, despite the company's claims that the Weibull curve did not fit the survival observed in clinical practice as well as the lognormal does, the company should have provided the results of a scenario analysis, in which the Weibull distribution was used for extrapolating survival. The DSU considers that the evidence provided by the company to support the choice of the lognormal survival model was not sufficient to rule out the Weibull model as making a good fit for the extrapolation of overall survival. The DSU believes that the judgement on the appropriateness of each curve should be driven by clinical plausibility rather than goodness of fit, and that both should be considered as part of the sensitivity analysis.

4.2.3. Use of investigator assessment for time to progression estimate

In the resubmission, the company only provided analyses based on the investigator assessment of time to progression. In the original appraisal (TA 189), however, the committee considered both, the investigator and the independent assessment. No clear preference for either one of these two methods was stated in the TA 189 guidance, but the latter was accepted as a scenario analysis.[1] In the previous submission, the company also provided a scenario analysis using the hybrid method, which used independent reviewer assessment where available and investigator assessment otherwise.[6]

The number of progressions and median time to progression (TTP) differed significantly between the two assessment methods (Table 15). In the original company's submission, no detailed explanation for the clear discrepancies between both methods was provided and this issue was not addressed in the company's resubmission. The company's justification for using investigator assessment was that *"the investigator assessment was based on a higher number of progression events"* and that *"the independent assessment was stopped at the first interim analysis as specified in the study protocol"*.[5] It should, however, be noted that the published SHARP study results used the independent reviewer assessments as opposed to the investigator assessment.[2]

Table 15: Results of analyses of the TTP endpoint[6]

	Independent Assessment (cut-off date 12th May 2006)		**Investigator assessment** (cut-off date 17th October 2006)		[redacted]	
	Sorafenib n=299	Placebo n=303	Sorafenib n=299	Placebo n=303	[redacted]	[redacted]
Number of progressions	107 (35.8%)	156 (51.5%)	181 (60.5%)	222 (73.3%)	[redacted]	[redacted]
Median TTP	24 weeks [95% CI 18, 30]	12.3 weeks [95% CI 11.7, 17.1]	17 weeks [95% CI 13,18]	11.9 weeks [95% CI 11.1, 12.4]	[redacted]	[redacted]
Hazard ratio (Sorafenib/placebo)	0.58 [95% CI 0.45,0.74] *p=0.000007*		0.6889 [95% CI 0.5634, 0.8423] *p=0.000130*		[redacted]	

Without clarifications on reasons for the observed discrepancies between independent and investigator assessment of progression, it is not clear which of the two assessment methods should be chosen. Both methods should therefore be reported. Based on the possibility of bias that is associated with investigator assessments compared to independent reviewer assessments,[15] the DSU has a preference for the published primary analysis that uses the independent reviewer assessment of progression[2] as opposed to the unpublished investigator assessment.

It is furthermore noteworthy that the company's estimate of the size of the patient population that continue treatment post progression (estimated to be 7.7%) and the estimated duration of continued treatment are based on investigator assessment of progression. Both estimates of the size of the patient population that continue treatment and the duration of treatment continuation are expected to change when independent assessment is used. These estimates were, however, not available to the DSU and it is therefore difficult to predict what the effect on the ICER would be. As was highlighted in the TA 189 guidance, the effects of differences in the post-progression treatment would likely be minimal[1] and the DSU supports this view.

5. EXPLORATORY ANALYSES UNDERTAKEN BY THE DSU

The DSU performed exploratory analyses to explore the effect of key uncertainties identified in the original appraisal's final appraisal determination:

1) Using the Weibull distribution for the survival (OS and TTP) curves
2) Using the independent assessment for TTP

These exploratory analyses were carried out in both versions of the model: the revised model and the model with updated costs and resource use estimates. The DSU however, considered that using the updated costs was preferable for decision-making and for the sake of clarity only presents the results with the updated model here (the results for the analyses undertaken with the revised model are presented in Appendix A). The DSU also explored the impact of using the pooled resource use estimates (from the original and new surveys).

The results of the exploratory analyses are shown in Table 16. The exploratory analyses using DSU's preferred assumptions (pooled resource use estimates and independent assessment of TTP) resulted in ICERs for sorafenib compared with BSC of £51,208 per QALY gained using the lognormal distribution and of £71,276 per QALY gained using the Weibull distribution.

Table 16: Results of DSU's exploratory analyses using the updated model (deterministic)

		QALYs		*Costs(£)*		*ICER (£/QALY)*
		Total	Inc.	Total	Inc.	
Company's base case	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£39,162
Weibull	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£58,287
Independent assessment	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£45,468
Using pooled resource use estimates						
Lognormal	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£45,372
Weibull	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£66,873
DSU's preferred assumptions (independent assessment+pooled resource use estimates)						
Lognormal	**BSC**	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	**£51,208**
Weibull	**BSC**	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	**£71,276**

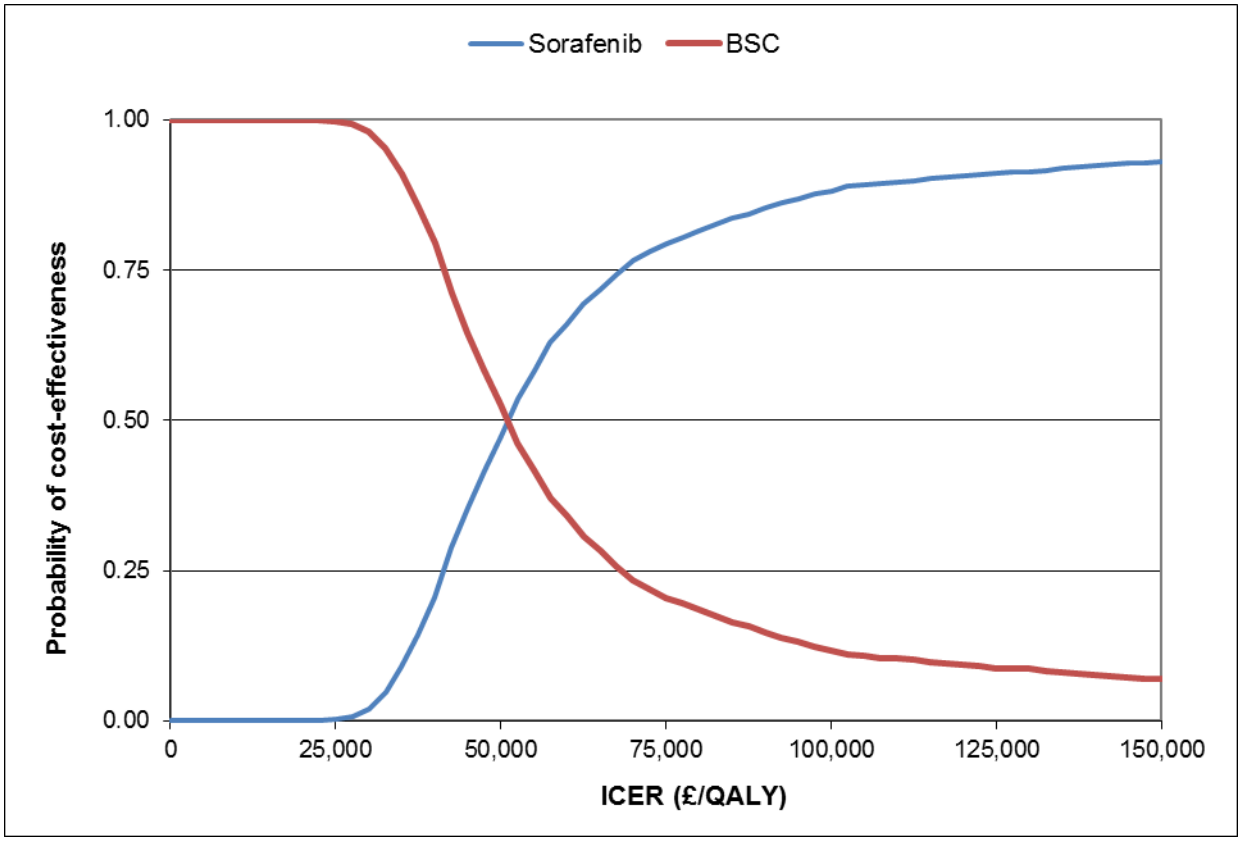
The DSU had to modify the company's model in order to run the probabilistic sensitivity analysis, as the parameters of the survival curve for TTP based on the independent assessment were not being sampled from the appropriate distribution. The PSA of the updated model with the DSU's preferred assumptions and the lognormal distribution resulted in an ICER for sorafenib versus BSC of £51,134 per QALY gained (see Table 17) and a probability of 47.4% of sorafenib being cost-effective at a threshold of £50,000 per QALY gained (see Figure 9). The DSU was unable to perform the PSA of the model using the Weibull distribution because it did not have access to the covariance matrices or Cholesky decompositions for the parameters of the Weibull distribution. However, based on how similar the results of the PSA are from the results of the deterministic analysis using the lognormal distribution, the DSU was confident that the results of the PSA using the Weibull

distribution would also be similar to the deterministic results shown in the last row of Table 16.

Table 17: Results of the PSA using the DSU's preferred assumptions and the lognormal distribution with the updated model

	QALYs	Inc. QALYs	Total costs (£)	Inc. costs (£)	ICER (£)
BSC	[redacted]		[redacted]		
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£51,134

Figure 6: Cost-effectiveness acceptability curve for sorafenib versus BSC using the DSU's preferred assumptions and the lognormal distribution with the updated model



Further results of the exploratory analyses undertaken by the DSU are described in Appendix A.

6. DISCUSSION

The company's submission for the reconsideration of sorafenib[5] included a new CMU price scheme, new evidence on the clinical effectiveness of sorafenib and new resource use estimates. The company submitted a revised model, where the committee's preferred assumptions from the original appraisal were adopted; and a version with updated costs and new resource use estimates. Finally, the company provided results of a scenario analysis, in which it included new effectiveness evidence in the updated model.

The company's submission describes a systematic literature review to identify evidence on the clinical efficacy and safety in patients with advanced HCC. The literature search did not miss any trials. There are, however, inconsistencies in study selection and some studies are excluded based on criteria not listed in the eligibility criteria. One single study was identified through this review: Palmer *et al.*[3].

Palmer *et al.*[3] compared the survival of patients whose individual funding applications for sorafenib were approved with those whose applications were rejected. The DSU notes that, due to its design, the study was at a high risk of bias. The DSU therefore did not deem the use of survival estimates from Palmer *et al.*[3] in the economic model as appropriate (as opposed to using it in a supportive manner). The company argued that upon visual inspection, the lognormal distribution provided a better fit to the KM curves published in Palmer *et al.*[3] than other parametric curves, especially because of the plateau at the end of the curve for the group treated with sorafenib. The DSU, after plotting the curves against the KM estimates, believes that such conclusion cannot be made based on the provided evidence, because: (i) the Weibull distribution fits the observed events equally well; (ii) even if the plateau observed after the last event cannot be ignored, it should be taken only as an approximation to the real hazard function; and (iii) the small number of patients at risk at that point results in a highly uncertain approximation. The DSU believes that the Weibull curve is likely to be well within the confidence intervals, if these had been calculated.

The company's submission also includes evidence from the GIDEON observational study.[4] The GIDEON[4] study is a single-arm study and would have been excluded on this ground in the systematic search. The company claimed that the long term survival data in the GIDEON[4] study provides further evidence on the appropriateness of the lognormal

compared with the Weibull distribution. The DSU acknowledges that the lognormal distribution is likely to fit the KM curve of the GIDEON study better than the Weibull distribution. However, the DSU notes the considerable differences in the shapes of the KM curves of the SHARP[2] trial and GIDEON, which might be explained by the differences across the studies, especially differences in prognostic factors in their populations. The DSU believes that the heterogeneity in the GIDEON population favours the use of the lognormal curve. Therefore, the DSU notes that the better fit of the lognormal distribution compared with the Weibull distribution in the GIDEON study is relevant to the extent that the GIDEON population is considered representative of the target population.

In summary, the DSU believes that the evidence provided by the company points to the lognormal distribution providing a better fit of long term survival in some circumstances. However, the DSU believes this is not enough evidence to remove all uncertainty around the choice of the parametric curve and that the Weibull distribution still retains plausibility. Consequently, the DSU believes that the Weibull distribution should still be considered in the analyses, especially given that the lognormal distribution used in survival analysis suffers from known artefacts, such as the continuous decrease of the hazard rate over time, which stands in contrast to developments of general mortality over time.

The company did not explore two key uncertainties identified by the committee in the original appraisal: (1) using the Weibull distribution for extrapolating overall survival, and (2) using the independent reviewer assessment of time to progression. The latter was used as primary analysis in the SHARP study but had fewer data points available due to an earlier cut-off date. The DSU believes that the independent progression assessment should at least be considered as a scenario analysis, and prefers to use it for its base case because it is the published primary analysis from SHARP and independent reviewer assessment of disease progression is considered to be less subject to bias than investigator assessment.[15]

The company provided new estimates of resource utilisation based on the feedback of three physicians, claiming that clinicians had now more experience of using sorafenib in routine clinical practice in the UK. The new resource use estimates drove the ICER down, mainly due to a higher estimated cost in the best supportive care arm. The DSU believed that resource use estimates would be more robust if the feedback of the four clinicians who provided the estimates for the original submission was also considered.

In summary, for its base case analysis, the DSU preferred to use the independent assessment of time to progression and the pooled resource use. The ICERs for sorafenib compared with BSC in the DSU's base case analysis are estimated to be £51,208 per QALY gained using the lognormal distribution and £71,276 per QALY gained using the Weibull distribution.

7. CONCLUSIONS

In their submission for the reconsideration of sorafenib, the company proposed a new CMU agreement of a simple discount of [redacted] on the list price of sorafenib. The submission also included evidence to back their claim of the appropriateness of using the lognormal and the inappropriateness of the Weibull distribution to estimate survival. The company submitted a model where the committee's preferred assumptions from the original appraisal were implemented. The company's base case analysis estimated the ICER of sorafenib compared with best supportive care to be £43,808 per QALY gained. The ICERs estimated in the one-way sensitivity analyses (OWSAs) ranged from £[redacted] to £[redacted] per QALY gained. The company provided a version of the model with new resource use estimates and updated costs. The ICER for the base case based on this updated model dropped to £39,162 per QALY gained and the ICERs estimated in the OWSAs ranged from £[redacted] to £[redacted] per QALY gained. The company also undertook an analysis using survival curves based on the data from Palmer *et al.*[3], which resulted in an estimated ICER of £20,556 per QALY gained for sorafenib compared with best supportive care.

The DSU undertook a series of exploratory analyses using alternative assumptions to explore the impact of key uncertainties: pooling the resource use estimates from the old and new surveys; using the independent and hybrid assessments of time to progression; and using the Weibull distribution to estimate survival. For its base case analysis, the DSU used pooled resource use estimates and independent assessment of time to progression. The DSU believed that the new evidence provided by the company hinted at a better fit of long term survival with the lognormal distribution but that it did not justify ruling out the Weibull distribution and undertook analyses with both parametric curves. The estimated ICER of sorafenib compared with best supportive care using the DSU's preferred assumptions was £51,208 per QALY gained using the lognormal distribution and £71,276 per QALY gained using the Weibull distribution.

The DSU notes that three key areas of uncertainty remain: the choice of the parametric curve to extrapolate the data; the difference between independent and investigator assessments of time to disease progression; and the resource use for each health state.

8. REFERENCES

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APPENDIX A: ADDITIONAL EXPLORATORY ANALYSES UNDERTAKEN BY THE DSU

The DSU undertook a series of analyses with the amended version of the model that contained the new CMU price and resource unit costs and resource use estimates used in the original appraisal. The DSU notes that this version of the model did not include the possibility of using the Weibull distribution and that it was implemented by the DSU using the data from the updated version of the model. The result of the deterministic analyses are listed in Table 18.

Table 18: Results of DSU's exploratory analyses using the revised model (deterministic)

		QALYs		*Costs(£)*		*ICER (£/QALY)*
		Total	Inc.	Total	Inc.	
Company's base case	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£43,785
Weibull distribution	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£67,656
Independent assessment	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	£50,581

The company's base case ICER was taken from the company's model, and the value differs slightly from that stated in the CS[5] (£43,785 per QALY gained in the company's model vs £43,808 per QALY gained in the CS).

For the sake of completeness, the DSU also undertook exploratory analyses with the hybrid assessment of time to progression, consisting of the independent assessment when available and investigator assessment otherwise (see Table 19).

Table 19: Results of DSU's exploratory analyses using the hybrid assessment for time to progression (deterministic)

		QALYs		*Costs(£)*		*ICER (£/QALY)*
		Total	Inc.	Total	Inc.	
Revised model	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated model	BSC	[redacted]		[redacted]		
	Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APPENDIX B: INCONSISTENCIES IN THE PALMER ET AL. ANALYSIS

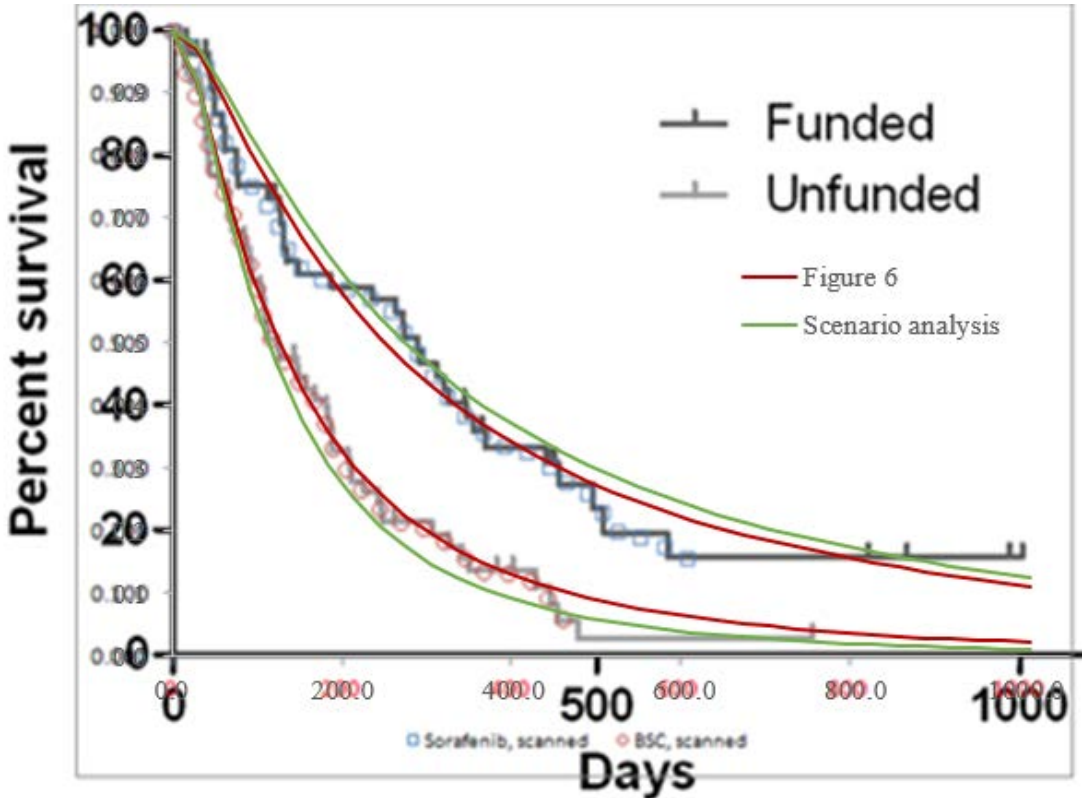
The DSU noticed that the OS curves shown in Figure 6 of the CS (which represented the fit of lognormal curves to the survival data of Palmer *et al.*[3] and which was produced with the company's model) were different to those used in the economic scenario analysis based on Palmer *et al.*[3]. Table 20 shows the difference in the parameters used in the lognormal curves used in Figure 6 of the CS[5] and for the scenario analysis based on Palmer *et al.*[3] Figure 10 shows the resulting curves plotted against the KM from Palmer *et al.*[3] The DSU notes that the difference between the sorafenib and BSC curves is considerably higher for the curves used in the scenario analysis, whilst the fit to the data appears to be worse.

Table 20: Mean and standard deviation of the lognormal curves used for Figure 6 of the CS and in the actual modelling of the Palmer et al. scenario analysis

	Sorafenib		BSC	
	Mean	SD	Mean	SD
Figure 6	5.5165	1.1454	4.8292	1.0297
Used in actual modelling of scenario analysis	5.6117	1.1291	4.7228	0.9473

SD = standard deviation; BSC = best supportive care

Figure 7: OS curves used in Figure 6 and in the scenario analysis based on Palmer et al. [3]



Sorafenib for advanced hepatocellular carcinoma (review of TA189) [ID1012]

Modified pages in ERG report

progression may not have been able to distinguish between toxicity of sorafenib, symptoms of underlying liver disease and the symptoms of advanced HCC.[1]

The committee noted that the ICER for sorafenib compared with BSC presented by the company was originally £64,800 per QALY gained and that when the PAS was included it went down to £51,900 per QALY gained, both using the lognormal extrapolation. The committee also noted that fixing inconsistencies in costs increased this ICER to £52,600 per QALY gained.[1] It further considered that other alternative parametric curves, especially the Weibull distribution, also fitted the data well, particularly at the tail of the Kaplan-Meier curve. The committee concluded that the log-normal curve provided a slightly better fit but that one distribution could not be accepted as the definitive function to extrapolate beyond the data and that the Weibull distribution should also be considered in any consideration of the uncertainty.[1] The committee noted that the ERG's analyses demonstrated that using the independent reviewer assessment (instead of the investigator assessment) of time to disease progression would drive up the ICER to an estimated £76,000 per QALY gained (without the PAS and using the lognormal extrapolation).[1] Although the utilities used for the pre- and post- disease progression state lacked face validity (utility values were higher in the post-progression state than in the pre-progression state), the committee concluded that this did not significantly affect the ICER.[1]

The committee discussed the range of cost-effectiveness estimates, the lowest being the ICER of £52,600, given that using the Weibull distribution and the independent reviewer assessment of disease progression would drive the ICER up.[1] The committee considered the end of life criteria to be fulfilled. It concluded that sorafenib as a treatment for advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.[1]

3. SUMMARY OF THE COMPANY'S RESUBMISSION

3.1. NEW COMMERCIAL MEDICINES UNIT FRAMEWORK AGREEMENT

The company presented a new Commercial Medicines Unit (CMU) Framework Agreement consisting of a [redacted] discount to the list price of sorafenib (which is £2980.47 for a pack of 112 tablets of 200mg). Table 1 shows the cost per cycle (month) of sorafenib with the list price, the PAS presented for TA189[1] and the new CMU price.

The DSU notes inconsistencies in the company's method of study selection. Whilst the company's eligibility criteria (Table 32 in CS Appendix 7[5]) do not specify an exclusion criterion that excludes studies with a patient population from certain geographical areas, Table 42 in Section 1.4 of CS Appendix 7[5] shows that some studies were *"subsequently excluded as based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population"*.[5] The DSU therefore questions the appropriateness of excluding two potentially relevant studies (see Section 4.1.2 for more detail). However, this is consistent with the previous appraisal in which one of these two studies was identified and only used in a supportive manner, based on the rationale mentioned above.

Moreover, in this search, the company's eligibility criteria specified that studies eligible for inclusion must have a control arm. However, the company included the GIDEON study, which lacked a control arm. The DSU therefore notes that the company's approach to study selection to inform the economic model is non-systematic.

4.1.2. Critique of the new clinical effectiveness evidence

As stated in Section 3.2, the company provides justification for the use of the lognormal distribution to extrapolate overall survival from the SHARP trial based on data from the GIDEON[4] and the Palmer *et al*.[3] studies, both of which had a longer follow up than the SHARP trial. Two other studies, the Asian-Pacific trial[9] and the Ji et al.[10] study, had previously been excluded *"based on a population with different underlying characteristics and aetiologies, when compared with the relevant UK population."*[5] It has been reported that certain baseline characteristics are prognostic factors for disease progression and survival, although Palmer *et al.* claim that there are *"no known predictive variables that the funding bodies could … [use] to select patients more likely to benefit from treatment"* because *"sorafenib-randomised trials indicate similar benefit across all subgroups"*.[3] The similarity of the included and the excluded studies in terms of their baseline characteristics is therefore explored in this section.

4.1.2.4. Conclusion on new clinical effectiveness evidence

There are notable differences between the patient population of the SHARP[1] trial and those of the Palmer *et al.*[2] and GIDEON[3] studies, especially in terms of disease severity, BCLC stage, macroscopic vascular invasion and, possibly, specific cause of HCC. Based on the inclusion criteria and baseline characteristics of patients in the five studies, the participants in the SHARP[1] and Asian-Pacific[4] trials represent better-specified patient groups with less severe disease, but it is unclear how closely these samples also represent the patients likely to present in practice in England. The reported quality assessment of the Palmer *et al.*[2] study is reasonable and appropriate (indicating a high risk of bias in terms of both internal and external validity, see company's resubmission, Appendix 3[5]); there is no formal critical appraisal of the ongoing GIDEON[3] study.

4.1.3. Critique of the new cost effectiveness evidence

4.1.3.1. The Palmer *et al.* (2013) study

Palmer *et al.*[2] is an observational study where the overall survival of patients whose sorafenib funding application requests were funded is compared against patients whose application was rejected.

As was highlighted in Section 4.1.2, the Palmer *et al.*[2] study was at a high risk of bias. There was no randomisation of the groups and even if there was no statistically significant difference in the prevalence of considered prognostic factors, some (e.g. Child-Pugh A, multifocal, largest lesion> 5cm, macroscopic vascular invasion) were noticeably different—see Table 2. The DSU notes that it is highly uncertain how adjusting for all these covariates would affect the hazard ratio. The company claims that decisions on whether to fund sorafenib were apparently not based on clinical variables, based on balanced demographic factors (Table 2). However, there is the possibility that clinical factors not evenly balanced according to Table 2, as well as clinical factors not reflected in Table 2, had an effect on the funding decision. For example, aetiology of the disease is not considered in Table 2.

The number of patients included in the Palmer *et al.*[2] study was considerably lower than in the SHARP trial[1]: the number of patients treated with sorafenib in the former was 57 and 299 in the latter whilst the number of patients not treated with sorafenib was 76 in the former

Without clarifications on reasons for the observed discrepancies between independent and investigator assessment of progression, it is not clear which of the two assessment methods should be chosen. Both methods should therefore be reported. Based on the possibility of bias that is associated with investigator assessments compared to independent reviewer assessments,[15] the DSU has a preference for the published primary analysis that uses the independent reviewer assessment of progression[2] as opposed to the unpublished investigator assessment. Independent reviewer assessment of progression is regarded to be less prone to bias than investigator assessment of time to progression.[15]

It is furthermore noteworthy that the company's estimate of the size of the patient population that continue treatment post progression (estimated to be 7.7%) and the estimated duration of continued treatment are based on investigator assessment of progression. Both estimates of the size of the patient population that continue treatment and the duration of treatment continuation are expected to change when independent assessment is used. These estimates were, however, not available to the DSU and it is therefore difficult to predict what the effect on the ICER would be. As was highlighted in the TA 189 guidance, the effects of differences in the post-progression treatment would likely be minimal[1] and the DSU supports this view.

4. EXPLORATORY ANALYSES UNDERTAKEN BY THE DSU

The DSU performed exploratory analyses to explore the effect of key uncertainties identified in the original appraisal's final appraisal determination:

1) Using the Weibull distribution for the survival (OS and TTP) curves
2) Using the independent assessment for TTP

These exploratory analyses were carried out in both versions of the model: the revised model and the model with updated costs and resource use estimates. The DSU however, considered that using the updated costs was preferable for decision-making and for the sake of clarity only presents the results with the updated model here (the results for the analyses undertaken with the revised model are presented in Appendix A). The DSU also explored the impact of using the pooled resource use estimates (from the original and new surveys).

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sorafenib for advanced hepatocellular carcinoma (review of TA189) [ID1012]

You are asked to check the ERG report from the Decision Support Unit to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Wednesday 6 July 2016** 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 Deviation from the process outlined for the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The stated process for the submission is outlined as follows in the appraisal template: *"The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance."(Submission template pg.3)* In presenting the ICER based on the independent assessment to measure time to radiological disease progression, the ERG state a preference for an assumption which is not in line with the most plausible ICER as communicated to the manufacturer. The manufacturer also note that in the absence of new evidence to support any preference it is unclear why this approach was selected, as it was not aligned with the preferences stated by the Appraisal Committee in 2009.	ICERs utilising assumptions that are not reflective of those underpinning the most plausible ICER (i.e. independent assessment) should be removed from the ERG report and not presented to the Committee.	Upon confirmation of Bayer's participation in the CDF rapid reconsideration process, the manufacturer confirmed with NICE that the ICER presented as £52,600 as being the most plausible both in a meeting with NICE (09/02/2016) and subsequently via email (09/02/2016). Analyses presented by the manufacturer in the resubmission utilise the assumptions underpinning this most plausible ICER of £52,600, with supporting evidence to address uncertainty. Upon confirmation of £52,600 as the most plausible ICER, and in the absence of further evidence the investigator approach has been accepted by NICE, and therefore presentation of the ICERs using the independent assessment is a deviation from the CDF rapid reconsideration process.	This is not a matter of factual accuracy. The Final Appraisal Determination (FAD) document for the original appraisal states that *"the Committee then discussed the range of cost-effectiveness estimates for sorafenib (with the lowest being the ICER of £52,600 per QALY gained and the highest being substantially greater)"*. In the FAD, the £52,600 is not presented as the most plausible ICER, but as the lower bound. The ERG understands that this is not consistent with the company's claim of £52,600 being the most plausible and believes that this consideration should be based on the FAD rather than on posterior communication between the company and NICE. No changes were made to the ERG

			report in response to this issue.

Issue 2 Implementation and justification of investigator assessment of time to radiological progression (TTP) in the ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Irrespective of the deviation from the process outlined in Issue 1, the manufacturer questions the justification provided for selection of the independent assessment for time to progression. The ERG justify a preference for the independent assessment to measure time to radiological disease progression as it is the *"published primary analysis that uses the independent reviewer assessment of progression as opposed to the unpublished investigator assessment" (pg. 44)* Whilst the ERG is entitled to this judgement the manufacturer here questions the validity of the rationale	Consider the investigator assessment to time to progression in the base case	**<u>Consistency with clinical effectiveness observed in the SHARP trial as used in the economic model</u>** Within the SHARP trial the investigator assessment drove the following treatment decisions: • Patients discontinuing from study treatment • Patients continuing treatment with sorafenib post-progression • Patients withdrawing from sorafenib due to adverse events. As each of these factors impact the study participant's time on treatment, and therefore primary efficacy results (i.e. overall survival) it is more appropriate, and consistent, to use the investigator	This is not a matter of factual accuracy. As highlighted in the ERG report, the ERG based its preference for the independent reviewer assessment on the fact that it is viewed as being less prone to bias than investigator assessment of time to progression (see for example pg. 49 of ERG report). This is reflected in the fact that this is correspondingly used in the published primary analysis of the SHARP trial. The ERG has added a statement to this effect on pg. 44 of the ERG report. The ERG considers that the health economic model should be based on the least biased estimates of time to progression. The ERG therefore thinks it appropriate to use independent

that published evidence in this instance is most suitable for the decision problem.		assessment in line with the published primary efficacy endpoints. Furthermore, by using the investigator assessment for TTP the manufacturer has ensured consistency between TTP and the cost associated with post-progression duration of treatment of patients with sorafenib as observed in the trial. **<u>Consistency with UK clinical practice</u>** Whilst for regulatory purposes, such as the licensing of a drug, an independent assessment provides a consistent and central evaluation it is not reflective of UK clinical practice. An investigator assessment where progression and discontinuation of treatment is determined by the treating physician is in line with UK clinical practice.	reviewer assessment of time to progression. Consideration of independent reviewer assessment is also in line with TA 189. The ERG has highlighted the limitation that the company did not provide the proportion of patients and duration of treatment continuation post-progression for the independent reviewer assessment (pg. 44 of ERG report). However, the impact of post-progression treatment continuation on the ICER was shown to be small in TA 189. As was stated above, a statement was added to the ERG report on pg. 44.

Issue 3 Palmer et al (2013) study: Assessment and reporting of demographic factors at baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Statements regarding the quality of Palmer (2013) do not reflect the totality of the evidence, with discrepancies observed between the ERG report and Palmer et al publication: <u>ERG report</u> The ERG noted that *"some of the prognostic factors are not balanced across groups (e.g. Child-Pugh A, multifocal, largest lesion> 5cmm and macroscopic vascular invasion)"* (ERG report pg. 34) <u>Palmer et (2013) publication</u> In relation to the above, the Palmer study authors reported that statistical comparison of each variable revealed no significant differences in patient demographics	Amendment of statement that prognostic factors are not balanced at baseline.	Discrepancy between information presented in the study and that published in the ERG report does not reflect the totality of the evidence and the fact that statistical analysis on baseline characteristics was conducted and no statistical differences were found. Further to this, sensitivity analysis was conducted on some of the 'imbalances' noted by the ERG of which not all are reported in the ERG summary, these show a consistent survival benefit across groups: • Excluding fibrolamellar patients median overall survival of 8.98 and 3.68 months (HR 0.45; P=0.0002) • Non-metastatic patients, median survival funded vs unfunded: 8.95 vs 3.7 months; HR 0.51; P=0.0061 The Palmer et al study represents useful	The ERG amended the sentence on pg. 34 of the ERG report to: *"even if there was no statistically significant difference in the prevalence of considered prognostic factors, some (e.g. Child-Pugh A, multifocal, largest lesion> 5cm, macroscopic vascular invasion) were noticeably different—see Table 2. The DSU notes that it is highly uncertain how adjusting for all these covariates would affect the hazard ratio."*

and prognostic factors. This included all patient characteristics and prognostic factors listed in Table 2 of the ERG report.		data for patients treated with sorafenib in two of the largest specialist hepatobiliary oncology units in the UK and it is therefore important that findings from the study are reported.	

Issue 4 Uncertainty regarding methods of the systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG stated uncertainty with regard to the identification and inclusion of studies in the SR and questioned the appropriateness of the exclusion of two relevant studies – the Ji et al (2014) study and the Asia-Pacific study (2008) from the systematic review.	Amend text to accurately reflect the methods of the systematic review and the fact that the Ji et al study was identified and included in the SR but was not considered relevant to support inputs in the economic model	The manufacturer would like to clarify that the studies were in fact identified and included in the systematic review addressing the research question: "What is *the clinical efficacy, safety, and tolerability of sorafenib for the treatment of unresectable advanced hepatocellular carcinoma*", however for the purpose of clinical evidence for the economic model underpinning the submission, the data from the studies were not considered relevant to a UK population due to potential differences in the aetiology of patients across studies (1) . In the previous 2009 submission, the Asia-Pacific study (2008) was written up as supportive only, which was not criticised by the Appraisal Committee nor were alternative approaches for the data suggested. Bayer would like to add that studies in the updated review were identified and refined based on a similar approach for the identification of evidence that was accepted in the previous submission.	This is not a matter of factual accuracy. Both Ji et al (2014) and the Asia-Pacific study (2008) are in the list of excluded studies on pp. 96-97 of the company's resubmission. These studies were excluded post hoc and it is the view of the ERG that this results in inconsistencies in the method of study selection for use in the economic model. The ERG already acknowledges on pg. 24 of the ERG report that the exclusion of these studies *"is consistent with the previous appraisal".* No changes were made to the ERG report in response to this issue.

Issue 5 Non-consideration of clinical plausibility in extrapolation of overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG implies that the manufacturer did not consider clinical plausibility in determining the choice of best fitting survival model. This is incorrect and does not reflect the evidence submitted. The ERG note that *"the evidence provided by the company to support the choice of the lognormal survival model was not sufficient to rule out the Weibull model as making a good fit for the extrapolation of overall survival. The ERG believes that the judgement on the appropriateness of each curve should be driven by clinical plausibility rather than goodness of fit, and that both should be considered as part of the*	Please remove this statement.	This submission provided evidence to reject the Weibull extrapolation of overall survival in HCC on the basis of long term clinical plausibility. The presentation of the GIDEON data in which the ERG viewed the log-normal as "providing a remarkably better fit than the Weibull" shows that the Weibull extrapolation cannot account for the extended survival that was seen in a large number of patients in the GIDEON study. This was further validated by the expert clinician consulted by ERG confirming that *"a subgroup of patients survives much longer than the average".* The manufacturer suggests that clinical plausibility in terms of overall survival is most readily seen in the GIDEON study, with the largest long-term follow up of patients treated with sorafenib (n=3202). Further analyses conducted show a superior fit at 1000 days ([redacted] of the GIDEON patients survive based on OS	The ERG did not imply that the company did not consider clinical plausibility. The ERG acknowledged that the lognormal seemed to provide a better fit with the GIDEON data, but believes this does not result in the Weibull model being ruled out. The ERG believes that the Weibull also predicts the fact that some patients survive much longer than the average: the clinician consulted by the ERG did not deny the clinical plausibility of the Weibull. The ERG noted that the company was comparing the survival estimates from curves fitted to data from SHARP to survival observed in GIDEON. While informative, due to the differences between the studies,

sensitivity analysis." p.42		Kaplan-Meier graph vs. [redacted] predicted by lognormal and [redacted] Weibull) Further to this, as the ERG notes, 'judgement on the appropriateness of each curve should be driven by clinical plausibility'. A recent study of distributions used to extrapolate OS in HCC, based on a systematic review, determined that for both short and long term data, the log-normal distribution was the best fitting curve, and moreover that the Weibull curve did not appear to offer a good fit in HCC (2). The consistency of these results which are presented se new evidence in the manufacturer's submission suggests there may be clinical characteristics of HCC that are suited to extrapolation of OS using the lognormal distribution, and supports the case for its use vs. the Weibull. Evidence provided shows that clinical plausibility has been considered in addition to statistical fit. Both statistical fit to the short term data and clinical plausibility both favour log-normal and its use in this submission.	the ERG believes this is not conclusive evidence to exclude the Weibull from the analyses. Upon examination of the company funded study referred to in this factual error check only (2) (which was not submitted as evidence in the company's resubmission), the ERG believes that the results reported in it (which include already considered evidence such as survival data from the SHARP and Asia Pacific trials) are consistent with the conclusions reached by the original appraisal committee and the ERG that the lognormal provides a slightly better fit but that the Weibull should also be considered due to uncertainty in the extrapolation. No changes were made to the ERG report in response to this issue.

Issue 6 Inclusion of GIDEON study to support extrapolation of long term overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG incorrectly presents the selection of the GIDEON study as a limitation to the systematic review. The ERG note that "in this search, the company's eligibility criteria specified that studies eligible for inclusion must have a control arm. However, the company included the GIDEON study, which lacked a control arm. The ERG therefore notes that the company's approach to study selection is non-systematic" (Pg.24 ERG report)	Please remove all statements that suggest the company's approach to study selection is non-systematic	GIDEON is an unpublished study, selected for the appraisal specifically to validate the choice of parametric curve to extrapolate overall survival, in terms of long term clinical plausibility. The GIDEON study was not identified by, or searched for by, the systematic review and should not be presented as a limitation of the systematic review as it was not intended to be captured. *"The study presents long term evidence of overall survival which (according to NICE Technical Support Document 14) can be used to validate a fitted model" (Evidence request email to NICE 03/02/06)* Redesigning the scope of the clinical search to identify studies that allowed assessment of parametric fits (outside the eligibility criteria defined) was not within the scope of or intended by the previous or updated SLR	The ERG did not present the inclusion of GIDEON as a limitation to the systematic review. The ERG did, however, note that GIDEON was included despite it not meeting the inclusion criteria of the systematic review. Other excluded single arm studies may have contributed further relevant evidence in support of overall survival extrapolation models. Consequently, study selection to inform the economic model was considered non-systematic. The ERG has amended the sentence on pg. 24 of the ERG report to read *"the company's approach to study selection to inform the economic model is non-systematic"*.

Issue 7 Consideration of Palmer 2013 cost-effectiveness scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The manufacturer questions the given criteria as a reason to preclude the cost-effectiveness scenario analysis from Palmer et al (2013) The ERG considered that the scenario analysis using OS curves fitted to Palmer et al.'s data is of limited validity for the following reasons: 1. "The study has a high risk of bias" 2. "It contains a small number of patients" 3. The analysis "combines the use of the OS curve from Palmer et al with the use of the PFS curve from the SHARP trial (pg.42)"	Remove 'limited validity' and amend justification. The Palmer (2013) study analysis should be presented for consideration in the report. It is noted only as a 'scenario analysis' in the executive summary and full details should be made available to the Appraisal Committee	Palmer et al provides evidence regarding the cost-effective use of sorafenib within UK clinical practice. Whilst the manufacturer accepts as an observational study there will be limitations, it considers the analysis presented to be very relevant to the decision problem of assessing the cost-effectiveness of sorafenib in UK clinical practice. The manufacturer considers the reasons outlined for limited validity to be questionable: **High risk of bias:** As outlined in Issue 3, a statistical comparison of all patient demographics and prognostic factors listed in Table 2 of the ERG report revealed no significant differences. **Small number of patients:** The study was based on 133 applications for sorafenib, which despite being a smaller sample than the pivotal SHARP RCT is not sufficiently low enough for it not to be considered. **Use of PFS from SHARP:** As patient level data from the study was not available to the	The ERG notes that the Palmer study analysis was already included in the ERG report (pg. 22). However, the ERG believes its criticism still holds: **High risk of bias:** The company implicitly acknowledges the risk of bias of Palmer et al. in the Downs and Blacks Checklist scores (Table 20). There not being statistical significance of the prevalence of a set of prognostic factors does not mean that adjusting for them would have no effect. Finally, the ERG believes that the decision to accept or deny a funding application of sorafenib was not made at random. **Small number of patients:** The ERG notes that there was considerable uncertainty in the original appraisal even if it was based on a trial with around 300 patients in each arm. The ERG also notes that number of patients on the sorafenib arm in Palmer et al was 57. Therefore, the

		manufacturer, assumptions regarding PFS had to be made. The manufacturer explored removing PFS data from the model discarding any utility gains due to sorafenib treatment. The results produced a slightly higher ICER at £21,154 as opposed to £20,556 in the submission reviewed. The results suggest that incorporation of PFS from the SHARP does not appear to be a key source of inconsistency/uncertainty for the model and therefore we suggest that the committee consider the Palmer analysis and to not reject it based on this grounding.	ERG believes the criticism is justified. **Use of PFS from SHARP:** The ERG notes that the PFS curve does not only affect the utility but also the costs. Given that the HR reported by Palmer (0.48) is much lower than that reported in the SHARP trial (0.69), it is reasonable to assume that the PFS will be longer in Palmer and therefore the cost of treatment will be higher. Taking into account the considerable variation in the ICER between independent and investigator assessment of time to progression, the ERG believes that PFS measured in a completely different study would have a considerable impact. No changes were made to the ERG report in response to this issue.

Issue 8 Justification for incorporating 2015 resource use data into the base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG pooled resource use estimates from the original resource survey conducted prior to the 2009 submission in 2007, with resource use obtained from an updated survey conducted in 2015. Pooling these analyses is incorrect as the update was conducted to account for changes in aspects of care and reforms in clinical practice.	A preference should be given to the 2015 resource use in the ERG base case estimates.	An updated resource use survey was conducted on the grounds that health technologies and resource use change over time. The manufacturer have utilised the updated survey estimates as survey responses may reflect changes due to reforms in the health care system since 2007, which may have led to changes to best supportive care.	The ERG notes that the difference between the estimates of the physicians taking part in the survey points to uncertainty rather than changes in best supportive care (BSC). For example, in the new survey, the percentage of [redacted] was estimated to be [redacted] by the first physician and [redacted] by the second (the third physician's estimate is not available). Similarly, the number of [redacted] estimated by the first physician was [redacted] and [redacted] by the second physician (the third physician's estimate is not available). These two parameters are the two main drivers of the difference between the ICERs using the old and new resource use estimates. The ERG believed including the estimates of the 4 physicians that took part in the original survey resulted in more robust estimates. No changes were made to the ERG report in response to this issue.

Issue 9 Reporting of the Appraisal Committee's consideration of the evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Where discussing the Appraisal Committee's consideration of the evidence the ERG excludes a statement regarding the Appraisal Committee's previous judgement of the log-normal extrapolation. **ERG report:** "It further considered that other alternative parametric curves, especially the Weibull distribution, also fitted the data well, particularly at the tail of the Kaplan-Meier curve. The committee concluded that one distribution could not be accepted as the definitive function to extrapolate beyond the data and that the Weibull distribution should also be considered in any consideration of the uncertainty" **Appraisal Committee:** "Several alternative probability distributions were considered and fitted the data well,the Committee was mindful that although the log-normal curve provided a slightly better fit, particularly for the early trial data, alternatives also fitted the data well"	Please delete or amend citing that "log-normal curve provided a slightly better fit" as per previous Appraisal Committee recommendation.	Evidence previously considered by the Appraisal Committee is outside the scope of this submission. As such it is important that where judgement has previously been made (in this case on the best statistical fit to the SHARP RCT) that statements are reported fairly and accurately to inform this Appraisal Committee.	The ERG amended the sentence on pg. 12 of the report to: *"It further considered that other alternative parametric curves, especially the Weibull distribution, also fitted the data well, particularly at the tail of the Kaplan-Meier curve. The committee concluded that the log-normal curve provided a slightly better fit but that one distribution could not be accepted as the definitive function to extrapolate beyond the data and that the Weibull distribution should also be considered in any consideration of the uncertainty"*

Reference List

(1) Peixoto RD, Renouf DJ, Gill S, Cheung WY, Lim HJ. Relationship of ethnicity and overall survival in patients treated with sorafenib for advanced hepatocellular carcinoma. Journal of gastrointestinal oncology 2014;5(4):259-64.

(2) Muszbek N, Kreif N, Valderrama A, Benedict A, Ishak J, Ross DP. Modelling survival in hepatocellular carcinoma. Current medical research and opinion 2012;28(7):1141-53.

NICE National Institute for Health and Care Excellence

NICE guidance

Sorafenib for the treatment of advanced hepatocellular carcinoma

Technology appraisal guidance

Published: 26 May 2010
nice.org.uk/guidance/ta189

Contents

1 Guidance

1.1 Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable.

1.2 People currently receiving sorafenib for the treatment of advanced hepatocellular carcinoma should have the option to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Sorafenib (Nexavar, Bayer HealthCare) is a multikinase inhibitor that inhibits tumour blood vessel development and tumour cell proliferation. It does this by inhibiting the Raf cascade, and vascular endothelial growth factor (VEGF)/platelet-derived growth factor (PDGF) receptors of tumour cells, vascular endothelial cells and pericytes. Sorafenib has a UK marketing authorisation for the treatment of hepatocellular carcinoma.

2.2 The summary of product characteristics (SPC) lists the following conditions that may be associated with sorafenib treatment: dermatological toxicities, hypertension, haemorrhage, cardiac ischaemia and/or infarction, gastrointestinal perforation, hepatic impairment and wound healing complications. For full details of side effects and contraindications, see the SPC.

2.3 Sorafenib is administered orally as 200-mg film-coated tablets. The recommended dosage is 400 mg twice daily (a total daily dose of 800 mg). The dosage may be adjusted to two 200-mg tablets once daily if adverse drug reactions are suspected. The SPC recommends that treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs. The price for a pack of 200-mg tablets (112 tablets per pack) is £2980.47 (excluding VAT, 'British national formulary' 58th edition). The manufacturer has agreed a patient access scheme (PAS) with the Department of Health for sorafenib for advanced hepatocellular carcinoma (see 3.14). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of sorafenib and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer's decision problem compared sorafenib with best supportive care (BSC), and defined the population as patients with advanced hepatocellular carcinoma for whom surgical or locoregional therapies have failed or are not suitable. Outcomes were defined as being overall survival, progression-free survival, time to symptomatic progression, tumour response, health-related quality of life and adverse effects of treatment. In the economic evaluation both the incremental cost per quality-adjusted life year (QALY) gained and the incremental cost per life year gained were presented. A lifetime horizon was used, and costs were considered from the NHS perspective.

3.2 In the submission, the manufacturer identified three studies providing evidence on the clinical effectiveness of sorafenib for the treatment of hepatocellular carcinoma. The manufacturer's submission presented clinical-effectiveness data from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study, which was a registration randomised controlled trial (RCT). The remaining two studies identified (a multicentre RCT and an uncontrolled open-label study) provided supporting data.

3.3 The SHARP study was a multicentre, double-blind, placebo-controlled randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus BSC (n = 299) versus placebo plus BSC (n = 303). The study was conducted in patients who were predicted to have a life expectancy of at least 12 weeks and who had the following characteristics: an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; histologically or cytologically documented hepatocellular carcinoma; and at least one measurable tumour not previously treated with local therapy. The majority of patients had a Child–Pugh liver function status of grade A or B (96.5% and 3.3% respectively). The Child–Pugh score can be used to predict the prognosis and strength of required treatment. The score classifies liver disease into Child–Pugh A, B and C grades; people with Child–Pugh liver function grade A have the best prognosis. The majority of patients had Barcelona Clinic Liver

Cancer (BCLC) stage B (intermediate) or C (advanced) disease (17.4% and 82.4% respectively) and one patient had BCLC stage D (end stage) disease (0.2%).

3.4 Randomised patients received 400 mg sorafenib twice daily plus BSC, or matching placebo plus BSC. If there were adverse events related to sorafenib, dosages could be reduced to 400 mg once daily, and then to 400 mg every 2 days. The mean dosage of sorafenib in the SHARP study was 710.5 mg per day. Treatment was continued until there was radiological progression according to response evaluation criteria in solid tumours (RECIST) and symptomatic progression; death; adverse events that required study treatment to be stopped; withdrawal from the study; or until another criterion for stopping therapy was met (such as deterioration to an ECOG performance status of 4).

3.5 At baseline, characteristics were balanced between the treatment groups. These characteristics included ECOG performance status, tumour burden (defined as the presence of macroscopic vascular invasion and/or extrahepatic spread), Child–Pugh grade of liver function, and liver disease. Patients were stratified before randomisation according to the following factors:

- tumour burden
- ECOG performance status of 0 versus 1 versus 2
- geographical region (North America; South America, including Mexico; and Europe and Australasia).

3.6 The manufacturer provided information about the two studies used as supporting evidence. The Asia-Pacific study by Cheng et al. (2008) was a multicentre RCT of sorafenib plus BSC versus placebo plus BSC in 226 patients with advanced hepatocellular carcinoma (and hepatitis B) from China, Korea and Taiwan. An uncontrolled open-label study by Abou-Alfa et al. (2006) was carried out in 137 patients from Europe receiving sorafenib for advanced hepatocellular carcinoma. The manufacturer also highlighted that there were several ongoing studies investigating: sorafenib alone; sorafenib versus placebo, doxorubicin, and sunitinib; and sorafenib plus doxorubicin versus doxorubicin alone.

3.7 The primary outcomes in the SHARP study were overall survival and time to symptomatic progression (which was defined as a decrease of four or more

points from baseline on the functional assessment of cancer therapy – hepatobiliary [FACT-hep] questionnaire, deterioration in ECOG performance status to 4, or death). There was no statistically significant difference in time to symptomatic progression between the sorafenib and placebo groups. The manufacturer suggested that the FACT-hep symptom index 8 (FHSI-8) questionnaire used to measure this may not have been able to distinguish between the toxicity of sorafenib, symptoms of the underlying liver disease, and the symptoms of advanced hepatocellular carcinoma. The FACT-hep was also used to measure health-related quality of life (HRQoL). Data from the SHARP trial report demonstrated that 11.5% of patients receiving sorafenib and 19.6% of patients receiving placebo had at least an 8-point improvement in score. The blinded phase of the SHARP study was stopped early when the second interim analysis indicated that sorafenib significantly prolonged median overall survival (46.3 weeks, 95% confidence interval [CI] 40.9 to 57.9) compared with placebo (34.4 weeks, 95% CI 29.4 to 39.4). The hazard ratio (HR) for overall survival (sorafenib over placebo) was 0.69 (95% CI 0.55 to 0.87). This represented a 30.7% reduction in hazard (risk of death) over placebo. Following stoppage, all patients in the double-blind phase (as well as those in follow up) were entered into an unblinded extension phase of the study.

3.8 Analyses of the secondary outcome, time to radiological disease progression, were based on both independent and investigator assessment. The independent assessment was the primary analysis. These analyses demonstrated that with independent assessment there were 263 progressions in total (107 in the sorafenib group and 156 in the placebo group) and with investigator assessment there were 403 progressions in total (181 in the sorafenib group and 222 in the placebo group). The analyses indicated that the median time to radiologically determined disease progression (according to RECIST criteria) was extended by 11.7 weeks according to independent assessment, or 5.1 weeks according to investigator assessment, in the sorafenib group compared with the placebo group. Both the investigator and independent analyses demonstrated a statistically significant improvement in time to disease progression in the sorafenib group compared with the placebo group. There was a substantial difference in the HR between the investigator analysis (HR 0.69; 95% CI 0.56 to 0.84) and the independent analyses (HR 0.58; 95% CI 0.45 to 0.74). The manufacturer's analyses of tumour response revealed small differences between the sorafenib and placebo groups, with patients having very low levels of complete or partial response in both groups.

3.9 The manufacturer developed a Markov model to assess the cost effectiveness of sorafenib compared with BSC in people with advanced hepatocellular carcinoma. The model had four distinct health states: first-line treatment – non-progressive advanced disease; first-line treatment – progressive disease; BSC – progressive disease; and death. The model had a cycle length of 1 month and a lifetime time horizon. The time horizon was assumed to cover up to an additional 14 years of life for a patient population with an average starting age of 67 years. Time horizons of 2, 5 and 10 years were explored in sensitivity analyses.

3.10 The model used effectiveness data from the SHARP study, extrapolated to a lifetime horizon. Several distributions were tested. Based on the Akaike information criterion for goodness-of-fit to the observed data, a log-normal distribution was chosen for extrapolating overall survival. A log-normal distribution was also chosen for extrapolating time to disease progression and was based on investigator rather than independent assessment. It was assumed that the rate of adverse events was constant over time, and that the disutilities associated with adverse events were additive (that is, they could be estimated by calculating the difference between a health state with an adverse event and the same health state without the adverse event). Only common adverse events were included in the model. Adverse events occurring in fewer than 10% of patients were excluded.

3.11 The utility values used in the model were derived using a mapping approach. Health-related quality of life was measured with the FACT-hep instrument. The manufacturer mapped these responses using an algorithm developed by Dobrez et al. (2007) to obtain health-state utility estimates. This mapping algorithm used the generic portion of the FACT-hep instrument (FACT-G) to map to a set of time trade-off utility values. The algorithm did not include information gained from the 'hep' subset of the FACT-hep questionnaire.

3.12 The model included costs for drug treatment for hepatocellular carcinoma (sorafenib), and treatment costs for different health states and adverse events. Resource use and cost parameters in the model were estimated from primary (SHARP trial) and secondary sources. The estimates of resource use and costs of adverse events were based on a survey of UK clinicians. The model also included the costs of sorafenib for the 7.7% of patients who continued treatment with

sorafenib after progression for a median of 129 days, as observed in the SHARP study.

3.13 Sorafenib compared with BSC produced a base-case incremental cost-effectiveness ratio (ICER) of £64,754 per QALY gained. One-way sensitivity analyses demonstrated that the ICER was most sensitive to estimates of time to progression and overall survival from SHARP, and to utility values. Probabilistic sensitivity analysis provided a similar result to the deterministic base case (£65,244 per QALY gained). The manufacturer carried out subgroup analyses that included age (65 years and older), and measures of performance status (Child–Pugh liver function grade A; tumour node metastasis [TNM] I–III; BCLC stage B; BCLC stage C). This resulted in ICERs that ranged from £32,701 to £76,592 per QALY gained. The manufacturer also examined other disease-specific subgroups and scenarios, which resulted in ICERs both higher and lower than the base-case ICER; these results are currently commercial in confidence.

3.14 The manufacturer proposed a patient access scheme for NICE to consider, which had been accepted by the Department of Health in England and the Department of Health and Social Services in Wales. The Department of Health considered that this patient access scheme would not be an excessive administrative burden on the NHS. The manufacturer submitted revised cost-effectiveness analyses incorporating the patient access scheme, in which the manufacturer rebates the cost of every fourth pack of sorafenib to the NHS, or provides every fourth pack for free. In the revised model, the cost of one cycle of sorafenib was removed in every fourth cycle for patients still receiving sorafenib, over the 14-year time horizon of the model. In the patient access scheme, all patients stop treatment at the point of progression (determined by investigator assessment), as in the SHARP trial. The manufacturer stated that this was consistent with clinical practice. The revised model therefore assumed that patients would not continue treatment after progression. This differed from the analysis without the patient access scheme, in which 7.7% of patients continued treatment after progression. The benefits in the model were not adjusted. All other assumptions remained the same as in the original model. Taking the patient access scheme into account, the revised base-case ICER for the trial population was £51,899 per QALY gained. The manufacturer carried out subgroup analyses (taking the patient access scheme into account) that included age (65 years and older) and measures of performance status (Child–Pugh liver function grade A; tumour node metastasis [TNM] I–III; BCLC

stage B; BCLC stage C), resulting in ICERs that ranged from £28,105 to £60,681 per QALY gained. The manufacturer also examined other disease-specific subgroups and scenarios, which resulted in ICERs both higher and lower than the base-case ICER (£51,899 per QALY gained); these results are currently commercial in confidence. Further documentation was provided in confidence to the Department of Health.

3.15 The ERG stated that the manufacturer's submission was of acceptable overall quality and it generally followed the NICE reference case. The two RCTs used to derive effectiveness data were of sufficient power to demonstrate that sorafenib plus BSC statistically significantly improved overall survival and time to radiological disease progression compared with placebo plus BSC. The ERG stated that the manufacturer provided a reliable, internally valid model that was appropriate for the decision problem and was based primarily on robust clinical data from the SHARP RCT.

3.16 The ERG highlighted the following key areas of concern with the manufacturer's submission:

- using investigator assessment of time to disease progression rather than independent assessment
- the generalisability of the SHARP population to the overall UK hepatocellular carcinoma population
- using BSC as the sole comparator
- the extrapolation of the survival data
- relying on expert opinion for estimating resource use and costs of adverse events
- the methods used to determine the health-related quality of life information for sorafenib and BSC and the algorithm used to obtain health-state utility estimates
- the definition and the modelling of the patient access scheme.

3.17 The ERG stated that there were clear discrepancies between the analyses of independent and investigator assessment of time to disease progression. The ERG noted that independent assessment of time to disease progression was not included in the manufacturer's model and that this was an important omission. Although the investigator analysis indicated less extension in time to disease

progression than the independent analysis, it generated a greater proportion of live patients in the progressive state who incurred low costs, which could bias the ICER in favour of sorafenib. The ERG carried out additional sensitivity analyses on the impact of using the independent assessment of time to disease progression rather than the investigator assessment. These analyses produced an ICER of £76,067 per QALY gained (not including the patient access scheme), which was higher than the ICER estimated in the base case using the investigator analysis (£64,754 per QALY gained).

3.18 The ERG noted that the effectiveness evidence from the SHARP study related almost exclusively to patients with relatively good liver function (Child–Pugh grade A). Furthermore, it noted that the manufacturer's submission referenced results from a recent uncontrolled open-label study by Abou-Alfa et al. (2008) that was relevant to the decision problem. The ERG noted that patients with Child–Pugh grade B liver function may gain less survival benefit from sorafenib than patients with Child–Pugh grade A liver function. It noted that if patients with Child–Pugh grade B liver function were included in the analysis this would have reduced the overall effectiveness of sorafenib. Therefore, the average estimates of survival gain for sorafenib for the population defined in the decision problem are likely to be overestimated if based only on the results from the SHARP study (in which patients had predominantly Child–Pugh grade A liver function).

3.19 The ERG noted that although the manufacturer's submission considered that doxorubicin was not a valid comparator, it was considered a viable therapy in a recent study comparing sorafenib plus doxorubicin versus doxorubicin alone. The ERG also noted that the European Medicines Agency (EMEA) considered a phase III RCT of nolatrexed versus doxorubicin in advanced hepatocellular carcinoma (n = 445) in the European Public Assessment Report on sorafenib. The EMEA concluded, on the basis of the observed 2.3-month median survival advantage for doxorubicin, that on balance it was likely to be an effective intervention. The ERG highlighted that although doxorubicin is not licensed specifically for advanced hepatocellular carcinoma, it is licensed for the treatment of solid tumours, which could include hepatocellular carcinoma. It was unclear to the ERG what proportion of patients in the UK is treated with doxorubicin and why this therapy was not considered a valid comparator for the economic evaluation.

3.20 The ERG noted the impact of the choice of parametric fit to survival data and that use of the log-normal extrapolation produced an ICER of £51,899 per QALY gained, and use of the Weibull extrapolation produced an ICER substantially higher (commercial in confidence). The ERG noted that both distributions provided plausible fits to the trial data and produced similar Akaike Information Criteria scores for goodness-of-fit. The ERG further stated that bearing in mind the uncertainty surrounding the extrapolation of the survival data, the log-normal extrapolation and the Weibull extrapolation may represent a plausible range of survival for people with advanced hepatocellular carcinoma. Consequently, the corresponding ICERs generated by the two modelling approaches could be considered to be a plausible range within which the estimated cost-effectiveness of sorafenib for the treatment of advanced hepatocellular carcinoma lies.

3.21 The ERG highlighted that the dosage of sorafenib, and therefore the length of time a pack would last, differed between the description in the SPC and the manufacturer's modelled patient access scheme. In the manufacturer's model of the patient access scheme, sorafenib use was based on the average dosage in the SHARP study (710.5 mg per day) rather than the recommended SPC dosage (800 mg per day). If used at the SPC recommended dosage, a pack would last 28 days, rather than 31.5 days as was modelled. The ERG calculated that if the patient access scheme was strictly modelled according to the SPC recommended dosage, the manufacturer's base case would increase from £51,899 to £58,147 per QALY gained. The ERG highlighted that the manufacturer's revised analyses did not take into account the administrative costs to the NHS of the patient access scheme. It stated that including any administration costs would increase the manufacturer's cost-effectiveness estimates.

3.22 The ERG also noted that in the revised model incorporating the patient access scheme, based on the SHARP study, a cycle of sorafenib lasted 31.5 days for an average patient, whereas in the model a cycle lasted for 1 month (equivalent to 30.4 days). The ERG stated that the modelling approach used by the manufacturer was equivalent to every fourth month free rather than every fourth treatment cycle free. Modelling every fourth treatment cycle free would increase the ICER minimally. Furthermore, the ERG noted that the cost of sorafenib for the 7.7% of patients continuing treatment after progression (as observed in the SHARP study) was removed from the model, but the benefits in

the model were not adjusted. The ERG calculated that if the costs of sorafenib treatment after disease progression were included, then the manufacturer's base case would increase from £51,899 to £54,509 per QALY gained. The ERG also highlighted that there were inconsistencies in the costs associated with the modelled treatment duration. In the revised analyses submitted by the manufacturer, sorafenib costs per model cycle were calculated based on 30 days of treatment (equivalent to £2836 per cycle). The ERG noted that the model cycle length was actually 30.4 days (equivalent to sorafenib costs of £2878 per cycle), increasing the manufacturer's base-case ICER from £51,899 to £52,641 per QALY gained.

3.23 The ERG highlighted that the economic evaluation relied heavily on expert opinion for estimating resource use for the treatments in the model, and the manufacturer did not comment on or assess the validity of the resulting estimates. The ERG stated that using expert opinion as a primary source for a wide range of resource use estimates significantly increased the uncertainty associated with the overall model results. The ERG noted that the economic evaluation also relied heavily on expert opinion for estimates of the costs of adverse events. It also noted a number of other, more minor, omissions and errors in the manufacturer's approach to including adverse events in the economic model.

3.24 The ERG noted that the economic evaluation relied on mapping estimates of health-related quality of life using an algorithm developed by Dobrez et al. (2007) to obtain health-state utility estimates. The ERG stated that although the algorithm developed by Dobrez et al. (2007) was methodologically valid, it may not be the most appropriate approach to estimating utility scores. This is because it is based on preferences of a population with cancer, not preferences of the general population, as specified in the NICE reference case. The ERG also noted that in the manufacturer's submission the mean utility before disease progression was marginally lower (0.69) than the mean utility after disease progression (0.71), which seemed counterintuitive. It commented that this lack of face validity may be because of a potential error in the Dobrez algorithm used to calculate utility values. This could have resulted in higher utility values being assigned to more-severe health states (that is, once disease progression has occurred), and therefore the utility estimates presented in the manufacturer's submission should be treated with caution. Sensitivity analyses were carried out in the manufacturer's submission to explore the effects of the utilities from the

mapping algorithm. The analyses used utility values from NICE technology appraisal guidance 178 'Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' for sorafenib with BSC before progression (0.76) and after progression (0.68). This produced a similar ICER to the base case, of £63,992 per QALY gained (not including the patient access scheme).

3.25 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of sorafenib for advanced hepatocellular carcinoma having considered evidence on the nature of hepatocellular carcinoma and the value placed on the benefits of sorafenib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the UK treatment pathway for patients with hepatocellular carcinoma. The clinical specialists described that in UK clinical practice one third of hepatocellular carcinoma patients would be eligible for procedures such as local resection, radiofrequency ablation or chemoembolisation. They noted that these procedures are not considered effective for approximately 50% of patients, who would progress to further locoregional therapy or systemic treatment. The Committee accepted that the scope of this technology appraisal was restricted to these patients. The Committee further reviewed the treatment pathway consistent with the BCLC staging classification and treatment schedule as presented by Llovet et al. (2008). The clinical specialists agreed that the BCLC staging system is used in UK clinical practice.

4.3 The Committee was aware that the licensed indication for sorafenib was hepatocellular carcinoma without specific restrictions. However, the clinical effectiveness evidence from the SHARP study related to patients with advanced hepatocellular carcinoma for whom surgical or locoregional therapies had failed or were not suitable. This population was consistent with UK clinical practice and clinical guidelines as outlined in the manufacturer's decision problem. The Committee noted that the manufacturer presented evidence from the SHARP study in which patients had predominantly BCLC stage C (that is, advanced stage) disease (82.4%). They also had predominantly good liver function (that is, Child–Pugh grade A liver function; 96.5%), and good ECOG performance status (0–2). The Committee considered how the clinical-effectiveness evidence observed in the SHARP trial related to the total UK population with advanced hepatocellular carcinoma, particularly with regard to patients with Child–Pugh grade B liver function. The Committee heard from the clinical specialists that patients with Child–Pugh grade B liver function would be considered for systemic therapy with sorafenib, although this type of therapy may be less

clinically effective than for patients with Child–Pugh grade A liver function. The Committee accepted that patients with advanced hepatocellular carcinoma with either Child–Pugh grade A or B liver function may benefit from systemic therapy, although not necessarily to the same degree. The Committee accepted that the manufacturer's decision problem focused on advanced hepatocellular carcinoma and was in accordance with the scope.

4.4 The Committee then discussed possible comparators used in the UK for advanced hepatocellular carcinoma in clinical practice. It noted the ERG's comments that doxorubicin could be a relevant comparator, although the extent of its use was unclear. The clinical specialists stated that, before sorafenib was introduced, patients with advanced hepatocellular carcinoma usually received BSC. Conventional chemotherapy with systemic agents such as doxorubicin was occasionally used. However, the clinical specialists highlighted that there were a number of adverse events associated with doxorubicin therapy (such as hair loss, nausea and vomiting, lower resistance to infection, bruising and bleeding) that limited its use to relatively fit patients. Furthermore, the clinical specialists discussed some studies that had shown doxorubicin not to have apparent benefit based on radiological assessment. The Committee accepted that in UK clinical practice treatment with conventional chemotherapy (such as doxorubicin) would be recommended only for a minority of patients who are able to tolerate it. The Committee noted that usual treatment for patients with intermediate hepatocellular carcinoma (defined as asymptomatic tumours without vascular invasion or hepatic spread) is transarterial chemoembolisation, in line with current clinical guidelines. The Committee were mindful that this subgroup was outside the decision problem as presented by the manufacturer. Therefore BSC was accepted as an appropriate comparator for the majority of patients with advanced hepatocellular carcinoma.

Clinical effectiveness

4.5 The Committee considered the clinical-effectiveness data presented by the manufacturer. It noted that evidence from the clinical studies of sorafenib plus BSC suggested that it increased median survival by more than 2.8 months compared with placebo plus BSC. The Committee also noted that there was a statistically significant difference in median time to radiological disease progression for patients in the sorafenib group compared with the placebo group. The Committee was mindful that there was an extension in time to

disease progression of 11.7 weeks according to independent assessment or 5.1 weeks according to investigator assessment, compared with placebo. The Committee accepted the evidence from the SHARP trial, but was mindful that the study was stopped early, potentially underestimating the survival benefit attributable to sorafenib. The Committee heard from clinical specialists and patient experts that the observed benefits in overall survival and time to radiological disease progression were clinically meaningful. It noted that a statistically significant difference was not observed for time to symptomatic disease progression for sorafenib compared with placebo. However, the Committee accepted the manufacturer's and ERG's view that the questionnaire used to measure time to symptomatic disease progression (FHSI-8) may not have been able to distinguish between the toxicity of sorafenib, symptoms of the underlying liver disease, and the symptoms of advanced hepatocellular carcinoma.

4.6 The Committee heard from a patient expert that severe adverse events (such as diarrhoea and hand-foot skin reaction) had been experienced during 15 months of treatment with sorafenib, and occasionally it was necessary to stop treatment temporarily. The clinical specialists confirmed that similar adverse events have been observed in clinical practice, but no patients in their experience had completely stopped treatment with sorafenib for this reason. The patient experts agreed that although the adverse events experienced were unpredictable and affected health-related quality of life, they could be tolerated because of the benefits in terms of extension to life.

4.7 Based on the clinical-effectiveness evidence and the testimony from clinical specialists and patient experts, the Committee concluded that sorafenib was a clinically effective treatment for advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapy had failed or was not suitable.

Cost effectiveness

4.8 The Committee discussed the cost effectiveness of sorafenib for treating patients with advanced hepatocellular carcinoma for whom surgical or locoregional therapies had failed or were not suitable. The Committee noted that the base-case ICER presented by the manufacturer was originally £64,800 per QALY gained and when the patient access scheme was included this went

down to £51,900 per QALY gained. Both ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources.

4.9 The Committee noted that the ICER presented in the manufacturer's base case depended on the extrapolation of overall survival beyond the SHARP study timeframe by fitting a log-normal probability distribution. Several alternative probability distributions were considered and fitted the data well, and the Committee was mindful that although the log-normal curve provided a slightly better fit, particularly for the early trial data, alternatives also fitted the data well. The main differences were in the shape of the curves at the tail of the distribution where, for example, a Weibull curve with a heavier tail was a good fit. The Committee concluded that, although the log-normal curve provided a slightly better fit to the observed data, it could not be accepted as the definitive function to extrapolate beyond the data. The Weibull distribution, which also provided an acceptable fit, should also be considered in any consideration of uncertainty. The base-case log-normal extrapolation produced an ICER for sorafenib of £51,900 per QALY gained, which was at the lowest end of the range. The Weibull extrapolation of survival data produced an ICER that was substantially higher (commercial in confidence) than the log-normal base case.

4.10 The Committee then discussed the ERG's critique of the manufacturer's patient access scheme submission. The Committee noted concerns about the discrepancies in the dosage of sorafenib and the length of time a pack would last between the patient access scheme as modelled and as described in the SPC. It agreed that the description in the SPC did not account for dose reductions or stopping treatment temporarily, and that the treatment intensity modelled in manufacturer's submission (based on the SHARP study) was more appropriate. The Committee considered that the cost of post-progression sorafenib treatment was removed from the model but that the benefits were not adjusted. It agreed that, because in clinical practice the benefit from post-progression treatment is likely to be small, retaining the benefits in the model would have a minimal effect on the ICER.

4.11 The Committee also noted the inconsistencies in costs associated with treatment duration and agreed that the treatment costs should be based on the actual length of the model cycle. This increased the ICER derived using the log-normal extrapolation from £51,900 to £52,600 per QALY gained. It also increased the corresponding (commercial in confidence) ICER using the Weibull

extrapolation of survival data. The Committee also noted that the manufacturer's model did not take into account the administration costs to the NHS of the patient access scheme but concluded that this would only increase the ICERs marginally.

4.12 The Committee was mindful of the concerns raised by the ERG about inconsistencies in the utilities used in the manufacturer's model. However, it noted that when alternative utility values from a previous renal cell carcinoma assessment report (used to develop NICE technology appraisal guidance 169 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' and NICE technology appraisal guidance 178) were used in a sensitivity analysis, the log-normal base-case ICER was not significantly affected.

4.13 The Committee considered the additional work by the ERG on the independent and investigator assessments of time to radiological disease progression. It noted that the ICER presented in the manufacturer's base case was dependent on investigator assessment (rather than independent assessment, which was the primary analysis in the SHARP study). The Committee noted that the ERG's analyses demonstrated that the original log-normal base case increased to £76,000 per QALY gained (not including the patient access scheme) when using the independent assessment of time to radiological disease progression, and the corresponding (commercial in confidence) ICER derived using Weibull extrapolation of survival data would also be substantially higher. Therefore, it concluded that sorafenib, as a treatment for advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies had failed or were not suitable, would not be a cost-effective use of NHS resources.

4.14 The Committee then considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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.

- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.15 The Committee discussed whether the benefit provided by sorafenib in hepatocellular carcinoma fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It noted from the clinical studies that normal life expectancy without sorafenib was unlikely to be greater than 24 months and was potentially as low as 7.9 months, although the latter was based on the SHARP study, which was stopped early. The Committee considered that evidence from the clinical studies of sorafenib plus BSC suggested that it increased median survival by more than 2.8 months compared with placebo plus BSC, and the manufacturer's economic model predicted a mean gain in overall survival of 6.1 months, although this depended upon the method of extrapolation. Although the Committee noted that sorafenib is licensed for an indication other than hepatocellular carcinoma, the Committee considered sorafenib to fulfil the small population criterion for an end-of-life treatment. In summary, the Committee was satisfied sorafenib for advanced hepatocellular carcinoma met the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented was supported by robust data.

4.16 The Committee then discussed the range of cost-effectiveness estimates for sorafenib (with the lowest being the ICER of £52,600 per QALY gained and the highest being substantially greater), in light of the end-of-life considerations. It considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great. Therefore the Committee concluded that sorafenib as a treatment for advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.

4.17 The Committee considered whether there were any subgroups for which sorafenib would be considered a cost-effective use of NHS resources. The Committee noted that the scoping exercise stated that the prevalence of hepatocellular carcinoma is high in people from black and minority ethnic groups who have recently moved to the UK. These groups may have limited

access to the NHS and therefore present with a more advanced stage of the disease, such as Child–Pugh grade B and C stages. However, the Committee noted that no specific analysis was presented for this subgroup, and that clinical-effectiveness data for people with Child–Pugh grade B and C liver function were limited. The Committee was mindful that only three subgroups presented by the manufacturer related specifically to advanced disease (BCLC stage C, Child–Pugh grade A, and presence of macroscopic vascular invasion). The Committee noted that the analyses of the three subgroups resulted in ICERs that were all higher than the base-case ICER (including the patient access scheme). It was mindful that the ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources. The Committee also noted that the manufacturer presented subgroup data that did not specifically relate to advanced hepatocellular carcinoma (for example BCLC stage B). The ICERs for these subgroups were both higher and lower than the base-case ICER (including the patient access scheme). The Committee noted that the subgroups presented by the manufacturer were based on a small number of patients, and because the clinical study was not powered to assess differential patient response to treatment, the subgroups were intended to be descriptive only. Furthermore, no adjustments were made for multiple comparisons. The Committee was mindful that there was limited evidence of clinical effectiveness in these subgroups and that the ICERs would be based on a weak evidence base. Therefore the Committee was not satisfied that the estimates of extension to life were robust or that the resulting subgroup ICERs were plausible. It concluded that it would not be appropriate to recommend sorafenib for specific subgroups of patients with advanced hepatocellular carcinoma.

4.18 The Committee noted that some people may already be receiving sorafenib for the treatment of advanced hepatocellular carcinoma. It recommended that these people should have the option to continue treatment until they and their clinician consider it appropriate to stop.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations implement this guidance (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

- Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007).
- Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007).
- Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005).
- Radiofrequency ablation of hepatocellular carcinoma. NICE interventional procedure guidance 2 (2003).

7 Review of guidance

7.1 The guidance on this technology will be considered for review by the Guidance Executive in November 2012. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
May 2010

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. There are four Appraisal Committees, each with a chair and vice chair. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Kathryn Abel
Reader and Consultant Psychiatrist, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr David W Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Brian Buckley
Lay Member

Mr Mark Campbell
Director of Standards, Bury Primary Care Trust

Professor Mike Campbell
Professor of Medical Statistics, University of Sheffield

Mr David Chandler
Lay Member

Dr Peter Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Mary Cooke
Lecturer School of Nursing, Midwifery & Social Work, University of Manchester

Dr Christine Davey
Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies
Consultant Physician, Royal Infirmary, Manchester

Mr Richard Devereaux-Philips
Public Affairs Manager

Professor Rachel Elliot
Lord Trent Professor of Medicines and Health, University of Nottingham

Stephen Greep
Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

Dr Wasim Hanif
Consultant Physician & Honorary Senior Lecturer University Hospitals Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Professor Peter Jones
Pro Vice Chancellor for Research and Enterprise, Keele University

Catherine Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Henry Marsh
Consultant Neurosurgeon, St Georges Hospital, London

Professor Gary McVeigh
Consultant Physician Belfast City Hospital, Cardiovascular Medicine, Queens University Belfast

Professor Jonathan Michaels
Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne
Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell
Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny
Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Mrs Ruth Oliver-Williams
Head of Nursing, Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne
RCUK Senior Research Fellow of Health Economics

Dr Danielle Preedy
Lay Member

Dr Martin Price
Head of Outcomes Research, Janssen Cilag

Dr Philip Rutledge
Consultant in Medicines Management, NHS Lothian

Mr Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

John Stevens
Director, Centre for Bayesian Statistics in Health Economics University of Sheffield

Dr Surinder Sethi
Consultant in Public Health Medicine

Professor Andrew Stevens (Chair)
Chair of Appraisal Committee C, Department of Public Health and Epidemiology, University of Birmingham

Dr Matt Stevenson
Technical Director School or Health and Related Research, University of Sheffield

Dr Cathryn Thomas
General Practitioner

Judith Wardle
Lay Member

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Fay McCracken
Technical Lead

Rebecca Trowman
Technical Adviser

Laura Malone
Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration, The University of Birmingham:

- Connock M, Round J, Bayliss S et al., Sorafenib for advanced hepatocellular carcinoma, March 2009.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Bayer (sorafenib)

II) Professional/specialist and patient/carer groups:

- British Association of the Study of the Liver
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal College of Radiologists
- British Liver Trust
- Hepatitis B Foundation UK
- Hepatitis C Trust
- Rarer Cancers Forum

III) Other consultees:

- Department of Health
- Oxfordshire PCT
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Bayer (doxorubicin)
- Eli Lilly & Co. (gemcitabine)
- Pfizer (doxorubicin, cisplatin)
- Foundation for Liver Research
- Medical Research Council (MRC) Clinical Trials Unit
- West Midlands Health Technology Assessment Collaboration
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on sorafenib for advanced hepatocellular carcinoma by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr John Bridgewater, Senior lecturer in medical oncology UCL Cancer Institute, nominated by NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Calum Polwart, Network Pharmacist Cancer Network Pharmacist Forum, nominated by the British Oncology Pharmacy Association – clinical specialist

- Stella Pendleton, Executive Director of the Rarer Cancers Forum and Hepatitis B Foundation UK, nominated by the Rarer Cancers Forum and Hepatitis B Foundation UK – patient expert
- Sean O'Brian, Patient, nominated by the Rarer Cancers Foundation – patient expert

Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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