NICE National Institute for Health and Care Excellence

For public (all confidential data redacted)

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma (ID1276)

Multiple technology appraisal

Second appraisal committee meeting

Assessment Group: York CRD and York CHE

Technical team: Stephen O'Brien (chair), Verena Wolfram, Chris Griffiths, Jasdeep Hayre

Companies: BTG, SIRTEX, Terumo Europe

22 January 2020

Key issues from consultation

Evidence	Not all non-randomised evidence was considered
	Real-world UK evidence and UK clinical experience were not considered enough
Quality of life	Patient expert testimonies were not considered enough
	Impact on QoL was not considered enough
Subgroups	Stakeholders identified 4 subgroups that might benefit most from SIRTs
AG model	Stakeholders identified possible factual inaccuracies and errors in model
	Downstaging should be included in base-case analysis
Price	BTG proposed PAS for TheraSphere
Coverage with evidence	Stakeholders proposed coverage with evidence generation for subgroups

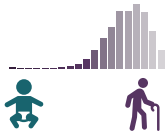
Background

Disease background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer

2,700 new cases of HCC in the England in 2017

Incidence is higher in men than women



Incidence increases with age

50% of people with HCC are diagnosed with advanced stage HCC and have poor prognosis with median survival of **less than 12 months**

HCC is commonly associated with cirrhosis

Common symptoms are:

- Pain in the upper right part of your belly
- A lump or feeling of heaviness in your upper belly
- Bloating or swelling in your belly

Selective internal radiation therapy (SIRT)

SIRT is a way of using radiotherapy to control cancers in the liver that can't be removed with surgery

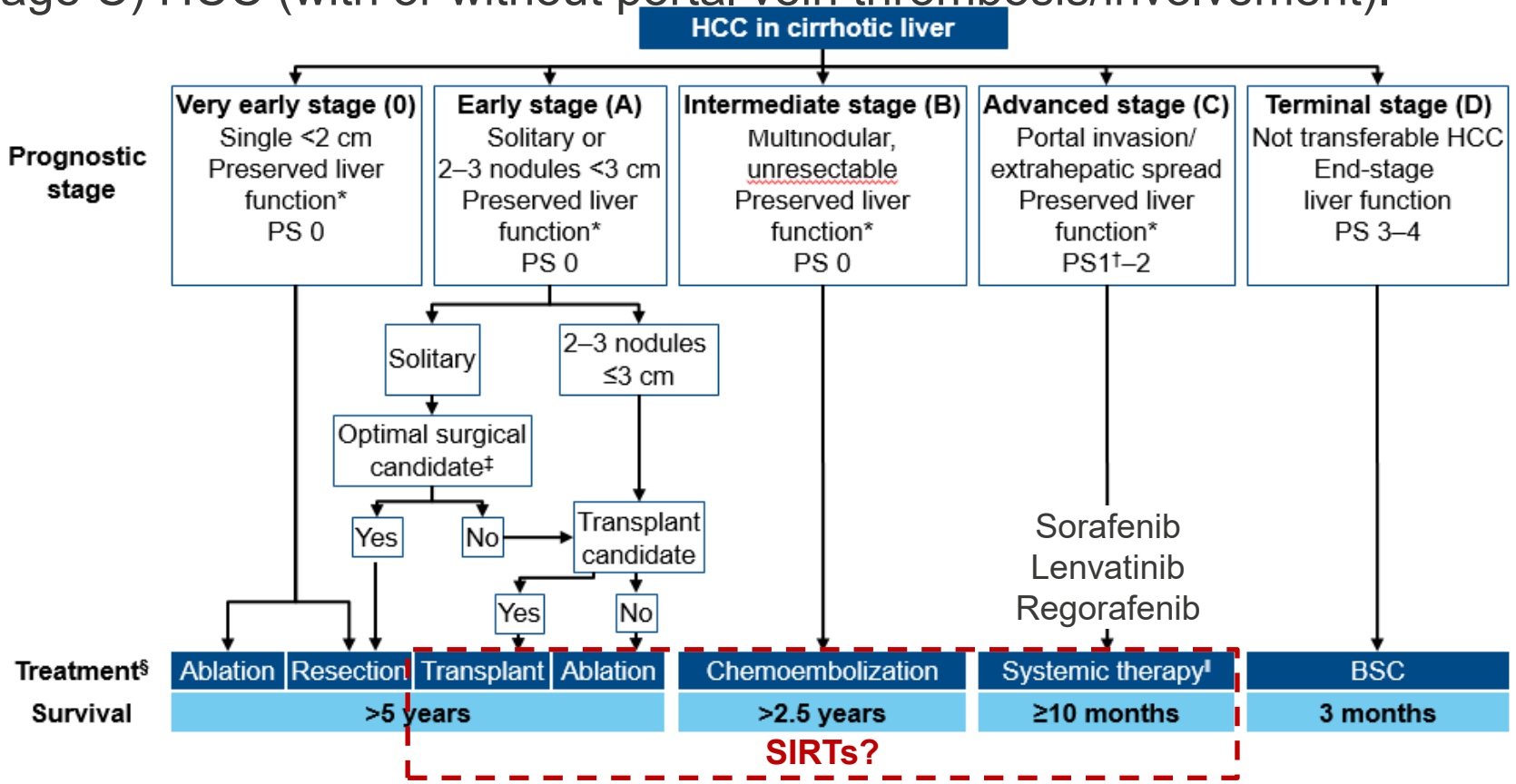
Internal radiotherapy using small radioactive beads that are injected into the tumour's blood supply and damage the tumour and the blood vessels it needs to survive

A work-up procedure including an angiogram is used to assess suitability for SIRT

SIRT is also called radioembolisation or transarterial radioembolisation (TARE)

Current UK treatment pathway

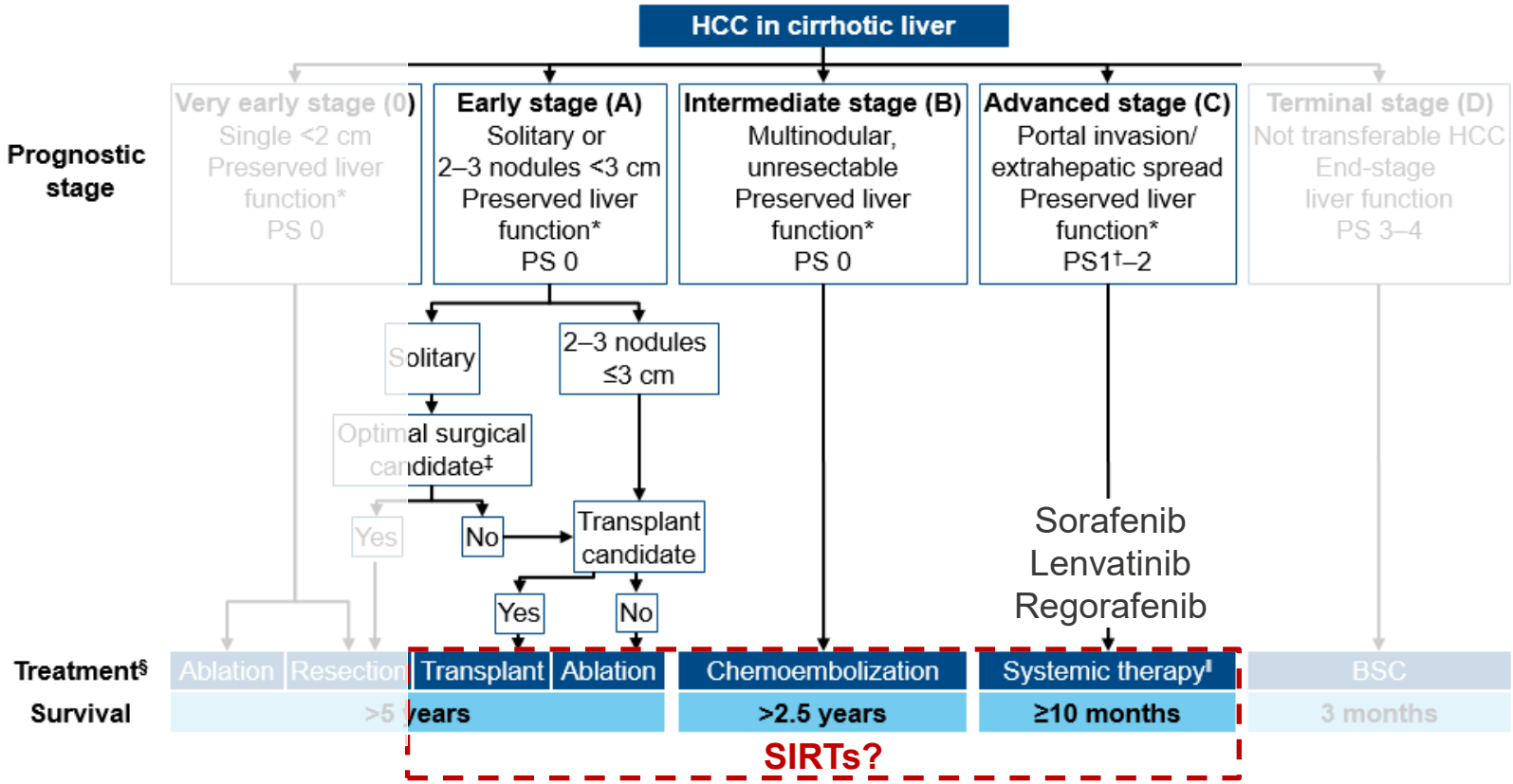
This appraisal considers selective internal radiation therapies for people with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).



Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies (CTT)	Ineligible for conventional transarterial therapies (CTT)

NICE *HCC EASL clinical practice guideline*
BCLC: Barcelona Clinical Liver Cancer

Committee considered 3 subgroups for the potential treatment with SIRTs



Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies (CTT)	Ineligible for conventional transarterial therapies (CTT)

Interventions: 3 SIRTs are being appraised

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
License	CE-marked class III active medical device	CE-marked class III active medical device	CE-marked class III active medical device
Indication	Treatment of inoperable liver tumours	Treatment of hepatic neoplasia	Treatment of unresectable liver tumours
Design	Resin microspheres	Glass microspheres	Poly-L-lactic acid (PLLA) microspheres
Active substance	Yttrium-90	Yttrium-90	Holmium-166
List price	£8,000	£8,000 (excluding PAS)	£9,896 (excluding PAS)

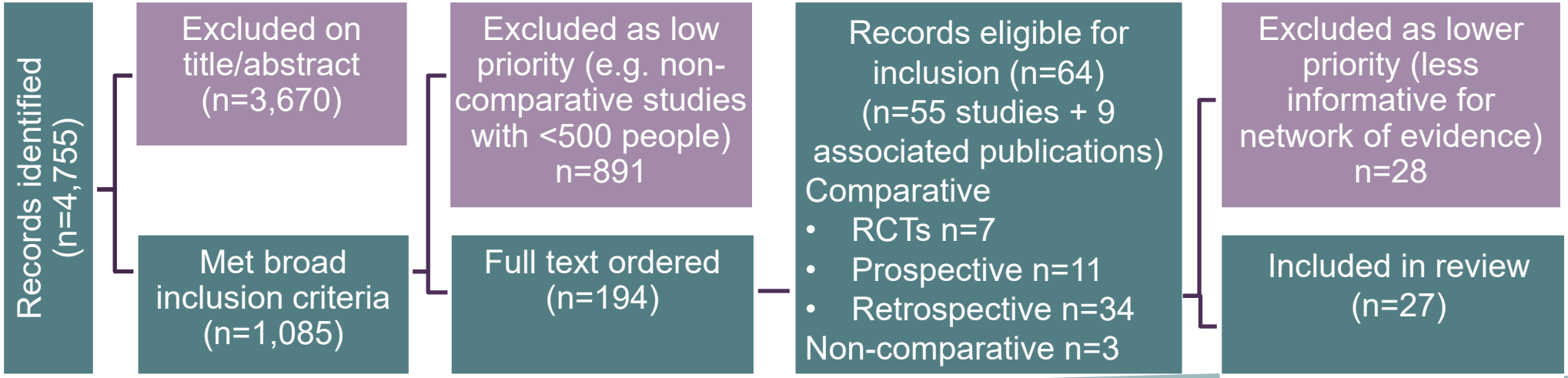
Summary

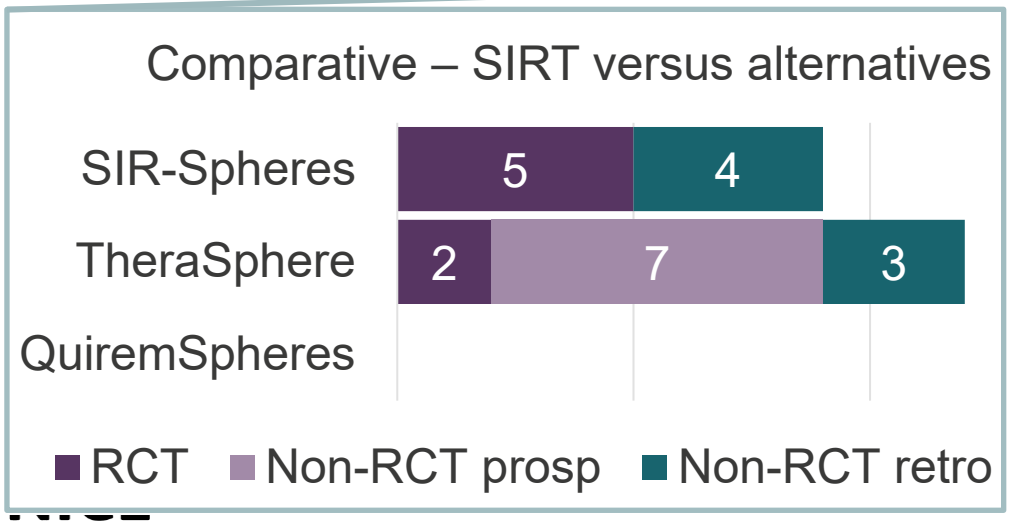
Appraisal Committee Meeting 1

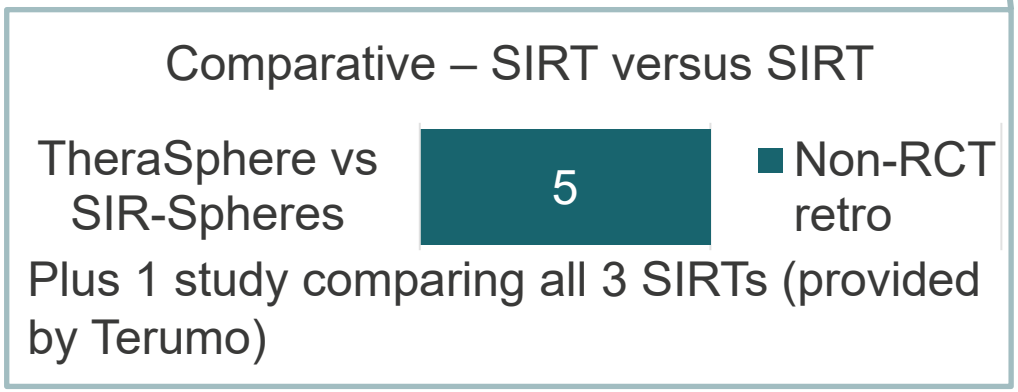
November 2019

Systematic review identified many studies – only the most relevant were included in the evidence synthesis

- AG identified all publications included in the company submissions
- Included non-randomised studies where comparative evidence was not sufficient







1 non-comparative study for QuiremSpheres

27 studies were included in the review or considered for the network meta-analysis

Type of evidence	SIR-Spheres	TheraSphere	QuiremSpheres
Comparative studies versus conventional transarterial therapies			
RCTs	5 • 2 vs. sorafenib (SARAH n=459; SIRveNIB n=360) • 2 vs. TACE/DEB-TACE (n=18 and n=24) • 1 SIR-Spheres followed by sorafenib vs. sorafenib (n=40)	2 • 1 vs. TACE (PREMIERE n=45) • 1 vs. TheraSphere with sorafenib (n=20)	0
Non-RCTs – prospective	0	7* (n=765, 96, 94, 86, 56, 52, 45)	0
Non-RCTs – retrospective	4* (n=137, 80, 73, 63)	3* (n=116, 96, 45)	0
Comparative studies SIRT versus SIRT			
Non-RCTS - retrospective	5* (n=97, 90, 77, 58, 17) SIR-Spheres versus TheraSphere		0
Non-comparative studies			
Non-comparative studies	0	0	1 (n=9)

NICE *not all were suitable for inclusion in NMA (e.g. did not report results for subgroups)
For details on included studies see Table 3 AG report

Companies reported ongoing studies for SIRT products

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
RCTs	None	STOP-HCC phase 3 trial comparing TheraSphere plus sorafenib and sorafenib alone	None
Non-RCTs	• The Austrian CIRSE Registry for SIR-Spheres Therapy (CIRT) • RESIN tumour registry in the USA • RESIN tumour registry in Taiwan • VESPRO patient data retrospective meta-analysis of patients from the SIRveNIB and SARAH trials	BTG sponsored studies • LEGACY – retrospective study • TARGETA – retrospective study BTG supported studies • 10 prospective or retrospective studies	• HORA EST HCC • HEPAR primary – interventional phase 2 • Hope166 – observational

Committee concluded there is enough robust evidence for clinical effectiveness in the ineligible for CTT population

	Eligible for transplant	Eligible for CTT	Ineligible for CTT
Clinical evidence	QuiremSpheres – no evidence	QuiremSpheres – no evidence	QuiremSpheres – no evidence
	SIR-Spheres – no evidence	SIR-Spheres – RCT evidence (limited; 1 RCT n=24)	SIR-Spheres – RCT evidence (SARAH n=459 and SIRveNIB n=360, might not be generalisable), retrospective evidence
	TheraSphere – RCT evidence (limited; 2 RCTs n=45, 20), non-comparative evidence low quality and high risk of bias	TheraSphere – evidence (limited; 1 retrospective n=35), prospective comparative evidence low quality and high risk of bias	TheraSphere – evidence (limited; 2 retrospective n=90, 42)
Network meta-analysis	Not enough data available	Comparative effectiveness is very uncertain (weak link for SIR-Spheres; weak link for TheraSphere) – Not suitable for decision making	Comparative effectiveness is uncertain – BUT suitable for decision making

This evidence was included to calculate cost effectiveness for this subgroup

	Eligible for transplant	Eligible for CTT	Ineligible for CTT
ICERs	Not performed	Not performed	Sorafenib dominated SIRTs in plausible scenarios SIRTs had fewer QALYs and were more expensive in plausible scenarios
End of life criteria	Not met – life expectancy criteria not met	Not met – life expectancy criteria not met	Not met – extension of life ≥3 months not met

ACD: preliminary recommendation

The selective internal radiation therapies (SIRTs) QuiremSpheres, SIR-Spheres and TheraSphere are **not** recommended, within their CE marking, for treating hepatocellular carcinoma in adults.

Comments from consultation

ACD consultation responses – overview

Companies

- BTG
- Sirtex
- Terumo

Experts

- 2 clinical experts
- Patient expert

Patient & Professional

- British Liver Trust
- British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres
- National cancer research institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists

There was no new evidence requested by the committee
BTG submitted results of dosimetry study
BTG proposed patient access scheme for TheraShere

There were some equality issues raised during consultation

Comments from stakeholders covered 4 themes

Theme	Discussed by	Issues highlighted
Evidence	Experts, Patient and Professional groups Companies	• Not all non-randomised evidence was considered • Real-world UK evidence and UK clinical experience were not considered enough
Quality of life	Experts, Patient and Professional groups	• Patient expert testimonies were not considered enough • Impact on QoL was not captured
Subgroups	Experts, Professional groups, Companies	• Stakeholders identified subgroups that might benefit most from treatment with SIRTs
Coverage with evidence generation	Experts, Professional groups	• Stakeholders discussed possibilities of coverage with evidence generation for subgroups

Evidence – Companies suggested that not all non-randomised evidence was presented

Background
- 3 companies submitted clinical evidence
- AG undertook evidence synthesis of published literature
- There is a large volume of evidence for SIRTs
  - Only few RCTs
  - Large volume of non-randomised studies

Stakeholder comments
- Companies suggest that not all published evidence was considered
- SIRTs are medical devices and evidence is of lower quality than for drugs and from small non-randomised studies with mixed population

AG
- Identified all publications included in the company submissions
- Included non-randomised studies where comparative evidence was judged not to be sufficient (size or quality)
- Included studies for relevant subgroups
- Assessed risk of bias of included evidence and provided rationale

ACD
- Agreed with AG to include non-randomised evidence only where relevant
- Considered presented non-randomised evidence and agreed that most had high risk of bias
- Concluded that non-randomised evidence was not robust enough to support routine commissioning

Evidence – NHS clinicians have experience treating people with HCC with SIRTs

Background

- SIRTs are available for metastatic colorectal cancer in 10 specialist centres in England
- Clinicians use SIRT as an option to treat people with HCC through compassionate schemes

Stakeholder comments

- NHS clinicians have experience with SIRTs in HCC and can provide testimonies of benefit for selected patients
- Patient testimonies highlight the benefit of SIRTs in HCC over other treatments
- Data from European real-world studies (CIRSE registry and French patient series) suggest benefit for SIRTs in HCC

ACD

- Committee was aware of the use of SIRT for HCC within the specialised centres
- Considered clinical expert statements and patient testimonies
- Understood that there are no published UK data that support routine commissioning

Health-related quality of life and side effects – Was this considered sufficiently?

Background

- Utility values presented at committee meeting 1

Health State	Utility values		
	SIRT	Systemic therapy	Work-up no SIRT
Progression-free survival	0.71	0.70	0.70
Progressive disease	0.67	0.66	0.66
Post-transplant*	0.71	0.71	0.71

*AG Scenarios 6 & 10 only

Stakeholder comments

- Quality of life data from the SARAH trial were favourable for SIRT (group effect p=0.0048)
- Fewer and less severe side effects than other treatment options*
- One-off treatment with short lasting side effects*
- Sorafenib is long-term treatment with side effects; clinical experience suggest high discontinuation with sorafenib*
- Faster recovery time after SIRT when compared with TACE†

ACD:

- Committee noted that utility values were similar for SIRT and sorafenib
- Acknowledged that SIRTs are one-off options with short lasting side effects
- Committee was not presented with evidence comparing this benefit with relevant comparator

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*Included in model via adverse event rate or HRQoL data; †Not included in model as TACE is not included

Subgroups – People with portal vein thrombosis (PVT) could benefit from SIRT

Stakeholder comments

- *Rationale*
  - People with PVT have poor prognosis
  - People with PVT have limited treatment options; TACE not used
- *Evidence*
  - Clinical experience that shows benefit in this group
  - Limited evidence comparing SIRTs with TACE
  - Limited evidence comparing different SIRTs

ACD

- Committee saw limited evidence, with contradictory results, comparing different SIRTs
- Considered PVT subgroup and concluded there was not enough evidence

Clinical expert after consultation

- Agreed with stakeholder comments
- Sorafenib used in this group but not well tolerated
- Usually older people
- Small number fit enough to be treated

AG evidence (presented previously)

- SIRveNIB subgroup analysis no difference in OS
- SARAH no subgroup analysis for PVT but subgroup analysis of people with complete occlusion of main portal vein (n=28) favouring sorafenib

Company evidence

- 2 comparative studies TheraSphere versus TACE no difference in OS (in company submission)
- French registry study currently ongoing
- Prognostic retrospective comparative study

Subgroups – People with large tumour could benefit from treatment with SIRT

Identified subgroup
People with 1 or more large tumour (≥5 or 7cm) with or without PVT

Stakeholder comments
- Rationale
  - TACE is not well tolerated
  - Some tumours might downstage to resection and cure
- Evidence
  - Clinical experience
  - DOSISPHERE study (see next slide)
  - Lack of comparative evidence

ACD
- DOSISPHERE interim data were available to committee but dosimetry was not included in model
- Subgroup was not identified at this stage

Clinical expert after consultation
- Can be treated with TACE or sorafenib variation across the UK
- TACE not very effective
- SIRT are well tolerated

AG evidence
- DOSISPHERE was identified
- Dosimetry was not included in model

Company evidence
- DOSISPHERE
- Prognostic retrospective comparative study, non-comparative studies

New evidence – DOSISPHERE suggests improved outcome in people with large tumours

- BTG submitted results of dosimetry study (interim results were available previously)
- Study included only people with one or more large (≥7cm) tumour

	Personalised dosimetry	Standard dosimetry
Number of people randomised	[redacted]	[redacted]
Number of people treated	[redacted]	[redacted]
Response rate	[redacted]	[redacted]
Median OS (95% CI) in months	[redacted]	[redacted]
People with hepatic AEs (≥grade 3)	[redacted]	[redacted]

AG

- Details of study design unclear (only available as conference abstract and conference presentation video)
- Some evidence of base-line imbalances
- Study is not a direct comparison of SIRT and sorafenib
- NMA would be needed to connect the results and results might be highly uncertain or misleading

Subgroups – People with ALBI grade 1 and ≤25% tumour burden could benefit from treatment with SIRT

Identified subgroup
ALBI grade 1 and tumour burden ≤25% as an alternative to TACE

Stakeholder comments
- Rationale
  - These people were identified as best responders in SARAH
  - ALBI is an easy tool and less subjective than Child-Pugh
- Evidence
  - Post-hoc analysis of SARAH

ACD
- Considered subgroup and concluded there was not enough robust evidence

Clinical expert after consultation
- Agreed with stakeholder comments
- ALBI currently not widely used in NHS; tumour burden not reported on scans as %
- Both could be measured using current technologies so identifying this group is possible
- From experience there are few people with cirrhosis in clinical practice, if they have good ALBI then tumour burden is irrelevant for treatment choice and people would be treated with sorafenib

AG evidence
- No additional evidence

Company evidence
- Post-hoc of SARAH

Subgroups – People who are unable to tolerate sorafenib could benefit from treatment with SIRT

Stakeholder comments

Rationale
- Lack of treatment options
- Recommended in ESMO HCC guideline

Evidence
- Clinical experience
- SARAH indicated that sorafenib and SIRT had similar outcome

ACD
- Subgroup was not identified at this stage
- There was no evidence presented specific to this subgroup

Clinical expert after consultation
- This group includes older people who currently receive palliative care
- People who are fit for treatment but cannot tolerate sorafenib because of comorbidities such as cardiac impairment, renal impairment, low platelet count
- People with poor mobility for whom sorafenib side effects such as diarrhoea would be an issue
- Subgroup not included in clinical trials
- Representative group in clinical practice; good outcomes in OS and downstaging

AG evidence
- No evidence

Company evidence
- No evidence

Coverage with evidence generation – Is this an option for SIRTs in HCC?

Background

- In England SIRTs are used for HCC on compassionate scheme (not covered by NHS) in 10 specialist centres
- SIRTs are covered by NHS for metastatic colorectal cancer based on the outcome of a commissioning through evaluation (CtE) program

Stakeholder comments

- Stakeholders identified subgroups with unmet need
- Limited evidence available for these subgroups
- Evidence gap could be addressed through coverage with evidence generation such as the CtE program for metastatic colorectal cancer

Coverage with evidence generation

CDF	Only in research (OiR)	Evaluative commissioning (specialised services)
• Available for anti-cancer drugs (***not devices***) where uncertainties exist • Uncertainties could be addressed through data collection during a defined period of time	• Available for all technologies with weak evidence or uncertainties and unmet need or value to the NHS • Evidence gap addressed through newly commissioned research • Committee could make OiR recommendations	• CtE was a pilot with 8 schemes now completed • There are ongoing schemes at discretion of the NHS • ***Committee can NOT make a recommendation on evaluative commissioning***

Downstaging – Downstaging should be included in base-case analysis

Background
- Downstaging might be a treatment aim for some people who have SIRT
- Limited data available for these people

Stakeholder comments
- Sirtex suggest that downstaging should be included in base-case analysis based on ACD

AG
- Limited date available for people whose tumour downstages
- Downstaging is rare; unclear what is the proportion of people whose tumour downstages
- Unclear whether people whose tumour downstages get curative treatment
- Highly uncertain whether SIRT technologies increase the proportion of patients who are downstaged
- Provided scenario analysis for downstaging

ACD:
- Considered downstaging and agreed that this should be included in the base-case analysis if possible
- Proportion of people who have tumours that downstage and subsequent outcomes are uncertain

Factual inaccuracies – Sirtex highlighted 2 possible factual inaccuracies in the AG model

Proposed factual error	Company	AG
The cost of SIR-Spheres is overestimated	Suggest that AG remove extra procedural costs for SIR-Spheres	• Used information from company submissions and packaging insert and included costs for contrast fluoroscopy procedure (£209) for SIR-Spheres • Addressing this point had no net effect on the costs
The cost of sorafenib is underestimated	• Suggest that treatment duration of sorafenib should be based on SARAH individual participant data (IPD) • Currently duration of sorafenib is underestimated which affects costs	• AG used median duration from SARAH in original model • AG agreed that using IPD is an appropriate approach • AG provided a scenario analysis with IPD after consultation (analysis contains comparator PAS and will be discussed in part 2)

Error in model – BTG suggested an error in the AG model

Company	AG
Suggest that in model people who underwent the work-up procedure but didn't receive SIRT were assumed to accrue no benefit	• SARAH was main data source, data were provided in confidence they were highlighted in the model and redacted before release • Full model was validated and results presented to committee were accurate • Company used the redacted version which has a disclaimer that results can't be reproduced accurately

Results of the cost-effectiveness analyses contain comparator PAS and will be presented in part 2

Innovation and equality

Innovation

Companies

- SIR-Spheres can alter treatment paradigm
- SIR-Spheres can offer chance of potentially curative therapy to people who would not otherwise have this option
- QuiremScout and QuiremSpheres enable more personalised procedure by improved patient selection

Patient organisation

- Targeted treatment option delivering small beads directly to tumours

Equality

Patient organisation

- Concerned about equality to access; needs clear referral pathway

Clinical expert (during consultation)

- People with intermediate or advanced stage HCC will be disadvantaged if SIRT is not recommended

Key issues from consultation

Evidence	Not all non-randomised evidence was considered
	Real-world UK evidence and UK clinical experience were not considered enough
Quality of life	Patient expert testimonies were not considered enough
	Impact on QoL was not considered enough
Subgroups	Stakeholders identified 4 subgroups that might benefit most from SIRTs
AG model	Stakeholders identified possible factual inaccuracies and errors in model
	Downstaging should be included in base-case analysis
Price	BTG proposed PAS for TheraSphere
Coverage with evidence	Stakeholders proposed coverage with evidence generation for subgroups

Research recommendations – process guide section 6.4

6.4.1 When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted. Before issuing such recommendations the Committee will consider the following factors:

- the need for and potential value to the NHS of additional evidence that can inform the development of NICE guidance and clinical practice on the use of the technology
- the uncertainty in the analysis and what could be gained by reconsidering the decision in the light of research findings
- whether the research is feasible in circumstances when the Appraisal Committee recommends the intervention for NHS use outside the context of research
- irrecoverable costs incurred from introducing the technology
- the likely net benefits for all NHS patients of use only in a research setting during the time that the recommended research is being conducted.
- In considering these factors the Committee will balance the potential net benefits to current NHS patients of a recommendation not restricted to research with the potential net benefits to both current and future NHS patients of being able to produce guidance and base clinical practice on a more secure evidence base.

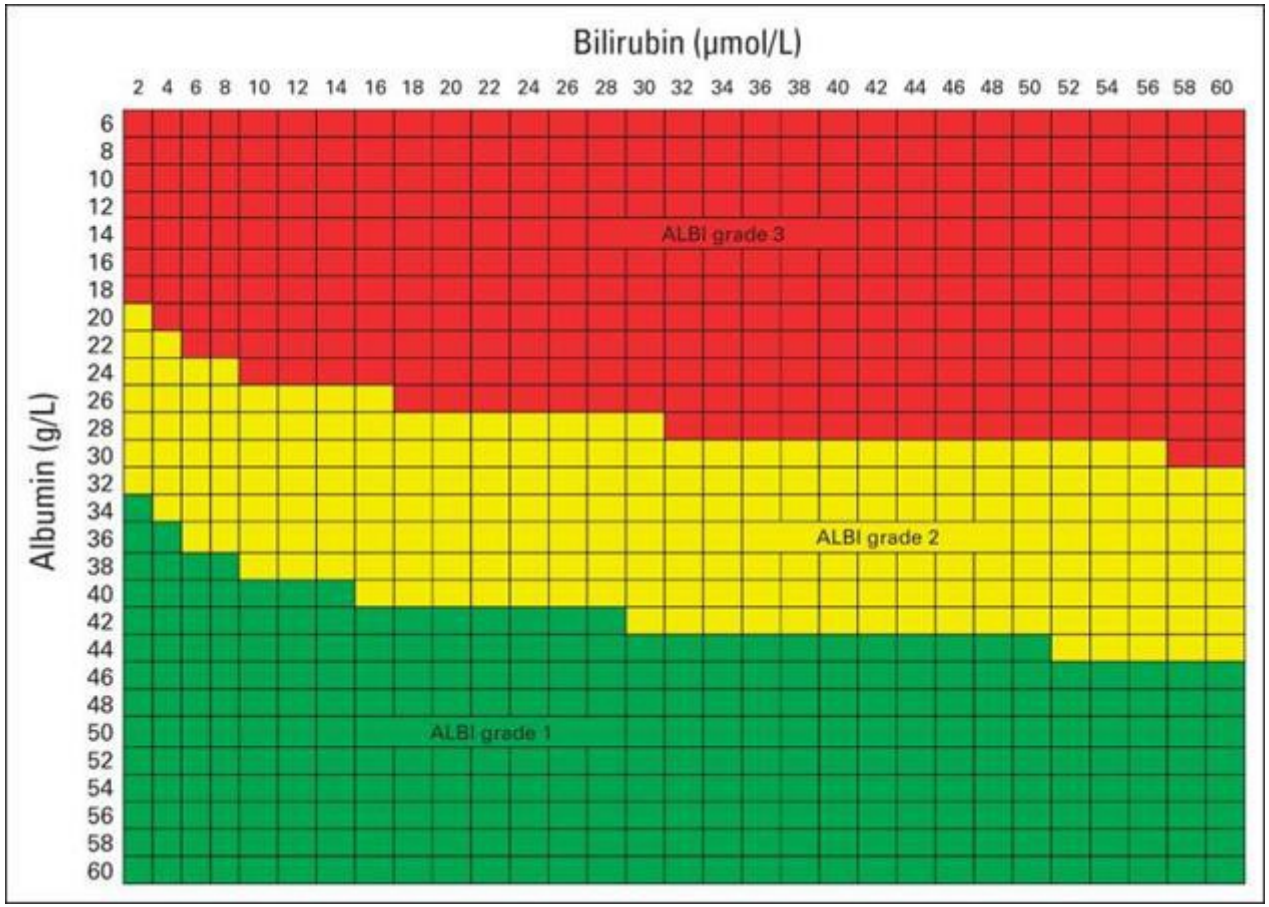
Research recommendations – process guide section 6.4

6.4.2 Recommendations on the use of technologies only in the context of research will not include consideration of which organisation (public or private) will fund the research. The Appraisal Committee will consider:

- the likelihood that the research needed will be commissioned and successfully report
- the time it is likely to take for research findings to be available to inform subsequent NICE guidance and clinical practice
- other factors which may impact on the value of evidence generation, such as other research that is underway or likely to be commissioned and completed.
- In considering these factors the Committee may seek advice from research commissioners, the wider research and clinical communities and consultees.

ALBI tool

- Simple & objective measure of liver function
- Grades A, B and C distinguish survival in patients with HCC of all aetiologies, in different treatment categories
- Distinguishes patients within Childs Pugh Grade A
- Useful in patients without cirrhosis



NICE

Child-Pugh score

Childs Pugh Score and Stage

Score	1	2	3
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Mild	Moderate
Bilirubin (μmol/l)	17-34	35-49	>50
Albumin (g/l)	>35	28-35	<28
PT (seconds ↑)	1-4	5-10	>10
CP Stage	A = 5-6	B = 7-9	C>9

Clinical expert highlighted that HCC aetiology might be important for sorafenib effectiveness

- HCC caused by hepatitis C virus is more responsive to sorafenib than HCC of other causes
- In UK people with HCC seldom have hepatitis C virus therefore sorafenib might not be the most appropriate treatment

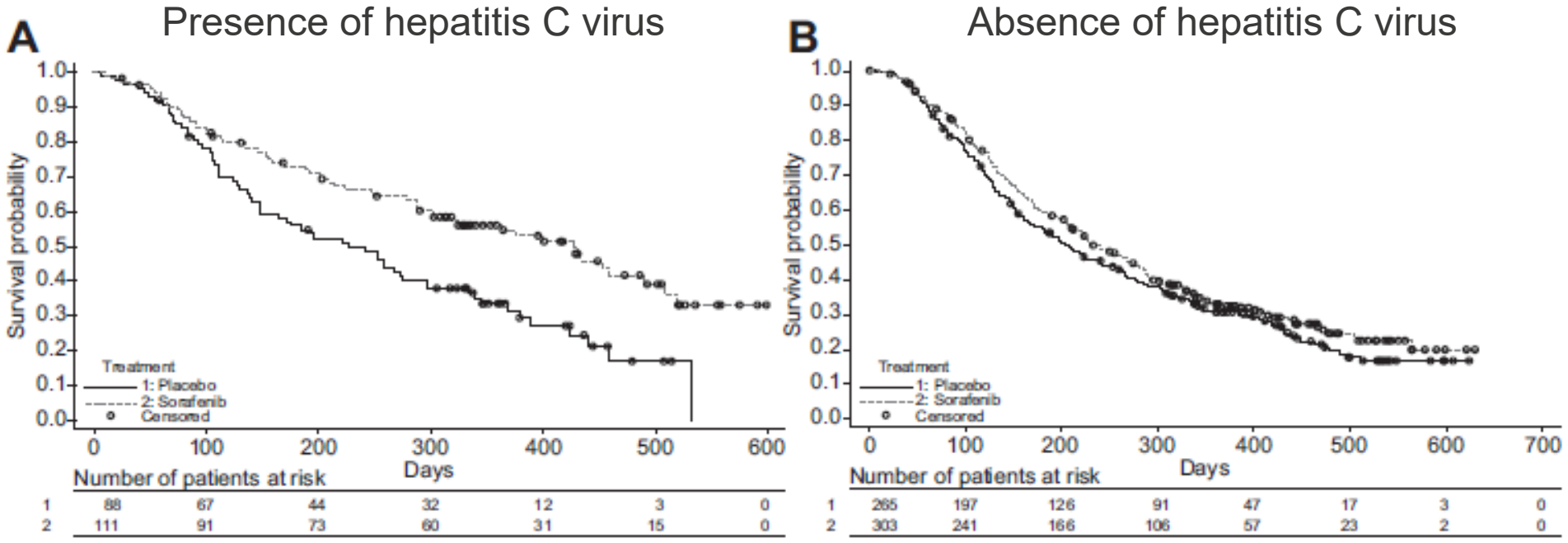


Fig. 2. Kaplan-Meier plots of overall survival by hepatitis C virus (HCV) status for sorafenib vs. placebo. Patients with (A) presence of HCV and (B) absence of HCV.