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

Lead team presentation

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Assessment Group: York CRD and York CHE

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Key issues for consideration – clinical

Positioning of SIRT in treatment pathway	Are there clinically identifiable subgroups that might benefit from SIRT more than others for example people with intermediate disease?
Clinical effectiveness of SIRT	Are the results for SIR-Spheres generalisable to the UK population?
	Is it appropriate to assume that SIRTs have equal effectiveness?
	Is there enough evidence for clinical effectiveness of QuiremSpheres?
	What proportion of people fail work-up and do not have SIRT?
Systemic therapies	Is it appropriate to assume that sorafenib and lenvatinib have equal effectiveness?
	Which systemic treatment is the current standard of care? Is it appropriate to use this treatment as the sole comparator in people who are not eligible for CTT?
NMA analysis for comparative clinical effectiveness	Does the available evidence support NMA analyses?

[redacted]

Key issues for consideration – cost effectiveness

Cost-effectiveness model	What is the most appropriate model to extrapolate OS and PFS?
	Should the base-case model allow for downstaging of disease?
	What is the most appropriate comparator, lenvatinib or sorafenib, in people who are not eligible for CTT?
Model suitability	Are the models suitable for decision-making?
ICER plausibility	What are the most plausible ICERs?
End of life	Are End of life criteria met?
Innovation	Are SIRTs innovative?
Equality	Are there any equality issues?

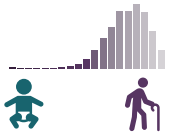
Background

Disease background

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

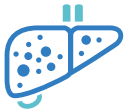
2,700 new cases of HCC in the England in 2017

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

Related NICE guidance for treating HCC

TA474 (2017)

Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma:

- only for people with Child-Pugh grade A liver impairment
- only if the company provides sorafenib within the agreed commercial access arrangement.

TA551 (2018)

Lenvatinib is recommended as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults, only if:

- they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
- the company provides it according to the commercial arrangement.

TA555 (2019)

Regorafenib is recommended as an option for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib, only if:

- they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
- the company provides it according to the commercial arrangement.

Others

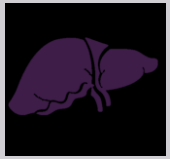
Medtech innovation briefings

- MB62 TheraSphere for treating operable and inoperable hepatocellular carcinoma
- MB63 SIR-Spheres for treating inoperable hepatocellular carcinoma

Interventional procedures

- SIRT for primary HCC
- Microwave ablation of HCC
- Radiofrequency ablation of HCC

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

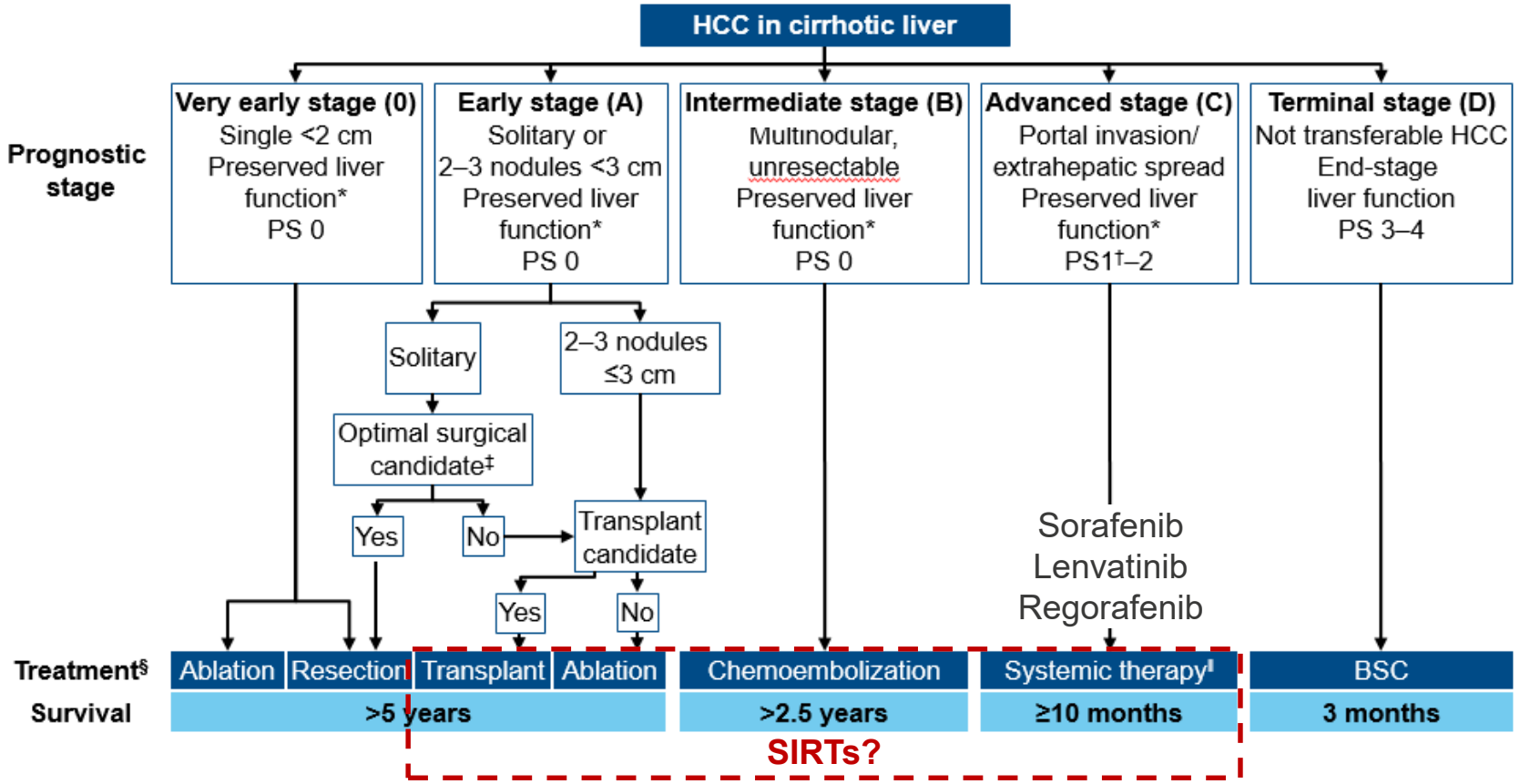
Internal radiotherapy using small radioactive beads that are injected into the tumour's blood supply and damage the tumour and the blood vessels it needs to survive

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)

Interventions: MTA will appraise 3 SIRTs

	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	£9,896

[redacted]

MTA flowchart

Company submissions

All companies submitted their clinical evidence

2 companies submitted a cost-effectiveness model

Assessment group report

Assessment group (AG)

- Reviewed the company submissions and models
- Undertook own evidence review and synthesis
- Developed cost-effectiveness model that included data provided by the companies and from other sources
- AG report consulted on for 4 weeks
- *AG can respond to consultation comments but is not compelled to do so*

Committee decision making

Will be informed by AG report & model, company submissions and expert testimonies

[redacted]

Decision problem

	NICE	Assessment group
Population	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).	Looked at full population **BUT** available evidence restricted analysis to people who are ineligible for conventional transarterial therapies
Comparator	Unresectable HCC • Other SIRTs • Transarterial embolisation (TAE) • Transarterial chemoembolisation (TACE) • Drug-eluting bead transarterial chemoembolisation (DEB-TACE) For people for whom any transarterial embolisation is inappropriate • Established clinical management without SIRT including systemic therapies and best supportive care	
Intervention & outcomes	Intervention and outcomes align with scope	

Expert submissions

Comments from patient experts

Patient expert submissions provided by 1 patient expert and British Liver Trust

	Patient experts comments
Unmet need	• Diagnosis often at later stages; few symptoms in early disease • Poor prognosis for advanced HCC • Few treatment options for advanced HC • Treatment options for advanced are non curative • Liver disease often complicates treatment • High incidence of recurrence
Quality of life	• People with HCC and their carers feel emotionally overwhelmed by diagnosis • People with HCC and carers live with uncertainty, hopelessness and often stigma and isolation
Advantages	• Life prolonging with less side effects and fast recovery • Might downstage tumour to allow transplant
Side effects	• Fewer side effects than TACE • Manageable side effects • Side effects less severe than for TACE or liver resection surgery

Comments from clinical experts – current management

Clinical expert submissions provided by 1 clinical expert and British Society of Interventional Radiology

	Clinical expert
Current disease management	• HCC is managed by multidisciplinary team • Treatment options include: – Transplantation – Resection – Loco-regional therapies (such as ablative techniques, transarterial chemo-embolisation or embolisation – TACE/TAE) – Sorafenib or immune mediated approaches – Best supportive care – Sometimes stereotactic body radiotherapy
Possible position in treatment pathway	• In early and intermediate stage HCC as an alternative to TACE to prolong survival or downstage to curative therapies such as resection or transplantation • In advanced BCLC stages as an alternative to sorafenib with similar outcomes but better side effect profile to palliate those without metastatic disease and offer prolonged survival comparable to sorafenib • Unmet need in patients who are not good TACE candidates (lesion size ≥7cm) who have unilobar disease within the intermediate stage of BCLC

[redacted]

Comments from clinical experts – experience with SIRT

Clinical expert submissions provided by 1 clinical expert and British Society of Interventional Radiology

	Clinical expert

Availability of SIRTs	• Not routinely funded, access is limited and managed locally
	• Might be available to:
	  • People whose tumour might be 'downstaged to resection'
	  • People whose disease is too advanced for standard TACE, and for whom sorafenib is not suitable (because of presence of a portal vein thrombosis)
	  • People after unsuccessful loco-regional therapies
	• Work-up procedure is required
	• 10 centres in England are commissioned to provide SIRT for metastatic colorectal cancer

Advantages	Survival benefit for younger people
Side effects	• Non-target radio-isotope delivery and radiation induced liver disease can be minimised by careful planning, dosimetry and delivery • Better tolerated than sorafenib, manageable side effects

[redacted]

Clinical evidence

There is RCT evidence for SIR-Spheres and TheraSphere, but limited evidence for QuiremSpheres

- Table shows only evidence included in the AG report
- Identified non-comparative evidence only included when there was no other evidence

Type of evidence	SIR-Spheres	TheraSphere	QuiremSpheres
Comparative studies versus conventional transarterial therapies			
RCTs	5 • 2 vs. sorafenib • 2 vs. TACE/DEB-TACE • 1 SIR-Spheres followed by sorafenib vs. sorafenib	2 • 1 vs. TACE • 1 vs. TheraSphere with sorafenib	0
Non-RCTs – prospective	0	7	0
Non-RCTs – retrospective	4	3	0
Comparative studies SIRT versus SIRT			
Non-RCTS - retrospective	5 – Compare SIR-Spheres with TheraSphere		0
	1 – Compares all 3		
Non-comparative studies			
Non-comparative studies	0	0	1

Clinical evidence

SIR-spheres

SIR-Spheres – 2 large RCTs compared SIR-Spheres with established therapies

	SARAH*	SIRveNIB*
Trial characteristics		
Location	France (25 centres)	Asia-Pacific region (11 countries)
Inclusion criteria	Locally advanced HCC (BCLC stage C), or new HCC not eligible for surgery/ablation after previously cured HCC, or HCC with 2 unsuccessful rounds of TACE. Life expectancy >3 months, ECOG PS 0 or 1, Child-Pugh class A or B score ≤7.	Locally advanced HCC (BCLC stage B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities.
Intervention	SIR-Spheres (n=237) Second SIRT possible. 53/237 (22%) did not get SIRT.	SIR-Spheres (n=182) Single SIRT. 52/182 (29%) did not get SIRT.
Comparator	Sorafenib (n=222)	Sorafenib (n=178)
Primary outcome	Overall survival	Overall survival

*designed as superiority studies

SIR-Spheres – Baseline characteristics between groups in SARAH and SIRveNIB were similar

	SARAH		SIRveNIB	
Baseline patient characteristics (ITT population)				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Number of patients	237 (ITT) 174 (per protocol)	222 (ITT) 206 (per protocol)	182 (ITT) 130 (per protocol)	178 (ITT) 162 (per protocol)
Median/Mean age	66 (IQR: 60-72)	65 (IQR: 58-73)	59.5 (SD: 12.9)	57.7 (SD: 10.6)
Proportion male	89%	91%	81%	85%
Cirrhosis present	211 (89%)	201 (91%)	NR	NR
HCC caused by alcohol*	147 (62%)	124 (56%)	NR	NR
Non-alcoholic steatohepatitis*	49 (21%)	60 (27%)	NR	NR
Hepatitis B*	13 (5%)	15 (7%)	93 (51%)	104 (58%)
Hepatitis C*	55 (23%)	49 (22%)	26 (14%)	19 (11%)
Hepatitis B & C*	NR	NR	4 (2%)	5 (3%)
Other/unknown*	45 (19%)	41 (18%)	NR	NR

* aetiology of HCC is different in Europe and Asia

SIR-Spheres – Baseline characteristics between groups in SARAH and SIRveNIB were similar

	SARAH		SIRveNIB	
Baseline patient characteristics (ITT population)				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
BCLC				
Stage A	9 (4%)	12 (5%)	0	1 (<1%)
Stage B	66 (28%)	61 (27%)	93 (51%)	97 (55%)
Stage C	162 (68%)	149 (67%)	88 (48%)	80 (45%)
Child-Pugh classification	A: 196 (83%) B7: 39 (16%) Unknown: 2 (1%)	A: 187 (84%) B7: 35 (16%) Unknown: 0 (0%)	A: 165 (91%) B: 14 (8%)	A: 160 (90%) B: 16 (9%)
Previously received TACE	106/237 (45%)	94/222 (42%)	NR	NR

SIR-Spheres – No evidence of differences in OS or PFS

	SARAH		SIRveNIB	
Trial results with 95% CIs				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Median overall survival (months)	8.0 (6.7-9.9)	9.9 (8.7-11.4)	8.8	10.0
	HR: 1.15 (0.94-1.41) **ITT** HR: 0.99 (0.79-1.24) **Per protocol**		HR: 1.12 (0.9-1.4) **ITT** HR: 0.86 (0.7-1.1) **Per protocol**	
Median progression-free survival (months)	4.1 (3.8-4.6)	3.7 (3.3-5.4)	5.8	5.1
	HR: 1.03 (0.85-1.25) **ITT**		HR: 0.89 (0.7-1.1) **ITT** HR: 0.73 (0.6-0.9) **Per protocol**	
Time to progression	Not reported		6.1 **ITT**	5.4 **ITT**
Tumour response rate	36/190 (19%) n=5 complete n=31 partial	23/198 (12%) n=2 complete n=21 partial	17% **ITT**	2% **ITT**

SIR-Spheres – Mixed HRQoL results, but more adverse events with sorafenib

	SARAH		SIRveNIB	
Trial results				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Rates of subsequent liver transplantation or resection	6/237 (3%) ablation 3/237 (1%) surgery 2/237 (1%) transplant	2/222 (1%) ablation 1/222 (<1%) transplant	1/182 (<1%) ablation 2/182 (1%) surgery	2/178 (1%) ablation 1/178 (1%) surgery
Health-related quality of life*	Global health status sub-score better in SIRT than sorafenib group (group effect p=0.0048; time effect p<0.0001)		No statistically significant differences in EQ-5D between the SIRT and sorafenib groups	
# patients with TRAE	173/226 (77%)	203/216 (94%)	78/130 (60%)	137/162 (85%)
# patients with Grade 3 or worse AE	92/226 (41%)	136/216 (63%)	36/130 (28%)	82/162 (51%)

[redacted]

*proportion of people completing the questionnaires was low
AE: adverse events; TRAE: treatment-related adverse events,

SIR-Spheres – The company provided a subgroup analysis which was included in their base-case model

Company:
- Selected subgroup of patients from the SARAH trial with ≤25% tumour burden and Albumin-Bilirubin (ALBI) grade 1 for their base-case analysis in the economic model

	SIR-Spheres (n=48)	Sorafenib (n=37)
Results for subgroup with 95% CI		
Median overall survival (months)	21.9 (15.2-32.5)	17.0 (11.6-20.8)
	HR 0.73 (0.44-1.21)	
Median progression free survival (months)	HR 0.65 (0.41-1.02)	

Assessment Group:
- Not a clinically recognised subgroup
- Based on a post-hoc analysis, breaks randomisation
- Explored in AG scenario analysis

Stakeholder comments:
- ALBI classification not routinely used
- People with ALBI 1 have good liver function – would be Child Pugh A
- People with tumour burden ≤25% and Child Pugh A are a recognisable groups
- Evidence in this group is emerging
- Group relevant to SIRTs in particular

[redacted]

SIR-Spheres – 2 small RCTs compared SIR-Spheres with TACE or DEB-TACE

	SIR-TACE		Pitton et al.	
Population	people with unresectable HCC without portal vein occlusion		people with unresectable intermediate (BCLC stage B) HCC with preserved liver function (Child-Pugh A-B7)	
Comparator	TACE		DEB-TACE	
Trial results				
	SIR-Spheres (n=13)	**TACE** (n=15)	**SIR-Sphere** (n=12)	**DEB-TACE** (n=12)
OS	46% (1 yr)	67% (1 yr)	No difference (medians)	
PFS	No difference		No difference (medians)	
Partial response	31%	13%	Not available	
HRQoL*	No difference		Not available	
TRAE	23%	33%	No AEs reported	
# patients with Grade 3 or worse AE	3	2		
# patients with serious AE	7	5		

[redacted]

*proportion of people completing the questionnaires was low; 10/28 had missing baseline data
AE: adverse events; TRAE: treatment-related adverse events,

SIR-Spheres summary – no evidence of difference to sorafenib or (DEB)-TACE, and evidence has limitations

Evidence

- No evidence of difference in OS/PFS versus:
  - Sorafenib: 2 RCTs (SARAH and SIRveNIB)
  - (DEB)-TACE: 2 small RCTs

Assessment group

- Results might not be generalisable to UK
  - Trials in France and Asia
  - People in trial might have poorer prognosis than those considered for SIRT in UK

Stakeholder comments

- SARAH and SIRveNIB conducted outside UK
  - included different patient groups that might not be comparable to UK patients
- In NHS current patient selection is more targeted using dosimetry allowing for personalised treatment

Are the results from SARAH and SIRveNIB generalisable to the UK population?

[redacted]

Clinical evidence

TheraSphere

TheraSphere – 2 small RCTs compared TheraSphere with TACE or combination treatment to prepare for transplant

	PREMIERE	RCT by Kulik et al.
Trial characteristics		
Study design	Single centre open-label RCT	Single centre open-label RCT pilot study
Location	US	US
Inclusion criteria	Adults with BCLC stage A/B unablatable/unresectable HCC with no vascular invasion, Child-Pugh A/B	Adults with Child-Pugh ≤B8 and potential candidates for orthotopic liver transplant
Intervention	TheraSphere	TheraSphere
Comparator	TACE	TheraSphere with sorafenib*
Outcomes	Overall survival Time to progression Rate of liver transplant/resection Time to transplant/resection	Rate of liver transplant/resection Adverse events

*combination therapy is off label for sorafenib or CE mark for TheraSphere

TheraSphere – Baseline characteristics in RCTs

	PREMIERE		RCT by Kulik et al.	
Baseline patient characteristics				
	TheraSphere (n=24)	**TACE (n=21)**	**TheraSphere (n=10)**	**TheraSphere with sorafenib (n=10)**
# of patients	24	21	10	10
Median age	62 (95% CI 58-65)	64 (95% CI 62-70)	60 (range 54-67)	58 (range 53-63)
Proportion male	71%	76%	50%	80%
Cirrhosis present	100%	95%		
HCC caused by				
Alcohol	5	3	2	1
Non-alcoholic steatohepatitis	1	1	1	1
Hepatitis B	3	2		
Hepatitis C	13	13	6	8
Other/unknown	2	4	2	0
BCLC				
Stage A	18 (75%)	17 (81%)	5 (50%)	7 (70%)
Stage B	6 (25%)	4 (19%)	1 (10%)	1 (10%)
Stage C			4 (40%)	2 (20%)
Child-Pugh classification	A: 12 (50%) B: 12 (50%)	A: 15 (71%) B: 6 (29%)	A: 6 B: 4	A: 8 B: 2

TheraSphere – Results of RCTs

	PREMIERE		RCT by Kulik et al.	
Results				
	TheraSphere (n=24)	**TACE (n=21)**	**TheraSphere (n=10)**	**TheraSphere with sorafenib (n=10)**
Median overall survival (months)	18.6* (95% CI: 7.4-32.5)	17.7* (95% CI: 7.4-32.5)	3 deaths	2 deaths
Time to progression	Not reached (>26 months)	6.8 months	Not reported	
Rate of liver transplant/ resection	87%	70%	90%	90%
Time to transplant/ resection	8.8 months	7.6 months		
HRQoL	Not reported		Not reported	
Adverse events	Not reported		More common in TheraSphere than TheraSphere with sorafenib arm	

[redacted]

*censored to liver transplant

TheraSphere – 5 prospective studies compared

TheraSphere with current therapies reporting OS/PFS

	Comparator	Location	#	Population	Results	
					Thera	Compar.
El Fouly 2015	TACE	Germany and Egypt	86	Adults with intermediate stage (BCLC B) un-resectable HCC & good liver function (Child-Pugh B<7)	OS 16.4 (7.9-25.3) TtP 13.3 (3.4-23.1)	OS 18 (12.1-25.5) TtP 6.8 (3.9-8.8)
Memon 2013	TACE	USA	96	Adults with HCC that progressed after intra-arterial loco-regional therapies (TACE and SIRT)	OS NR TtP 13.3 (9.3-25.0)*	OS NR TtP 8.4 (7.3-10.6)*
Hickey 2016	TACE	USA	765	Adults with unresectable HCC and bilirubin ≤3.0 mg/dL	OS reported for subgroups (BCLC and C-P): no diff.	
Maccaur 2014	TheraSphere + sorafenib	Italy	45	Adults with unresectable HCC (Child-Pugh A)	OS 10 PFS 7	OS 10 PFS 6
Woodall 2009	Best supportive care	USA	52	Adults with unresectable HCC (with and without portal vein thrombosis)	-PVT OS 13.9 +PVT OS 3.2	OS 5.2

*range

TheraSphere summary – no evidence of difference to comparators, and evidence has limitations

Evidence

- RCTs – no difference in transplant rate and OS versus:
  - TheraSphere with sorafenib
  - TACE
- Retrospective studies
  - No difference in OS versus:
    - TheraSphere with sorafenib
    - TACE
  - TheraSphere increased OS in people with PVT compared with people without PVT or people who got BSC
  - Longer TtP versus TACE

Assessment group

RCTs were small trials (n = 45 & 20)

- Imbalance in baseline characteristics
- Kulik et al. only includes people eligible for curative treatment

Identified some retrospective studies but these are not included because of low quality

NICE technical team comments

- RCT and prospective studies
  - Use of sorafenib in combination with TheraSphere is off label

Stakeholder comments

- Retrospective studies should be included for clinical effectiveness

Are the results generalisable to the UK population?

Should retrospective evidence be taken into consideration when estimating clinical effectiveness for TheraSphere?

Clinical evidence

QuiremSpheres

QuiremSpheres summary – very small evidence base for non-comparative effectiveness and safety

Evidence

- Retrospective case series
  - Conducted in Germany in 1 centre (n=9)
  - Response rate 56% (complete or partial response)

Assessment group

- Available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres

Is there enough evidence for clinical effectiveness of QuiremSpheres?

[redacted]

Clinical evidence

Comparative data

Comparisons of SIRT options – 5 studies compared SIR-Spheres and TheraSphere

	Biederman 2015		Biederman 2016		Van der Gucht 2017		Bhangoo 2015		D'Abadie 2018	
Population	BCLC stage C HCC with PVT		Unresectable HCC with main or lobar PVT		Unresectable HCC, ECOG PS <2 & life expectancy >3 months		Unresectable HCC; failed or unsuitable for alternatives ECOG PS <2		HCC imaged by 90Y TOF-PET	
	Thera	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**
# people	72	25	69	21	36	41	11	6	33†	25†
Median OS, months	15 (8.6-19.5)	4.1 (2.7-6.6)	9.5 (7.6-15.0)	3.7 (2.3-6.0)	7.0 (1.6-12.4)	7.7 (7.2-8.2)	8.4 (1.3-21.1)	7.8 (2.3-12.5)	Not reported¶	
Median TTP/PFS, months	9.1 (5.4-11.7)‡		5.9§ (4.2-9.1)	2.8 § (1.9-4.3)	5.0‖ (0.9-9.2)	6.1‖ (4.7-7.4)	Not reported		Not reported	
HRQoL	Not reported		Not reported		Not reported		Not reported		Not reported	
AE	Not reported for arms		No significant difference		Not reported		More frequent in Thera arm		Not reported	

[redacted]

†procedures; ‡not reported for single arms; ¶Kaplan-Meier curves for different equivalent uniform doses presented; §time to progression; ‖progression-free survival

Most of these studies have high risk of bias

Trial	Biederman 2015	Biederman 2016	Van Der Gucht 2017	Bhangoo 2015	d'Abadie 2018
Inclusion criteria clearly defined	No	Yes	Yes	Yes	No
Population	Adults with unresectable HCC with PVT	Patients with unresectable HCC and main or lobar PVT	Subgroup of advanced stage HCC patients	Mixed pop.: unresectable HCC, either failed or not amenable to other loco-regional therapies	Appears to include both pts. eligible and ineligible for TACE
Representative sample from relevant population	Unclear	Yes	Yes	Yes	Unclear
Groups similar at baseline	Unclear	No	No Pts. with small tumour more likely to get TheraSphere	Unclear	No
Overall judgement of risk of bias	**High**	**High**	**High**	**Unclear**	**High**

Evidence on comparison of SIRTs is limited with some studies favouring TheraSphere over SIR-Spheres

Evidence

- 5 retrospective studies compared TheraSphere and SIR-Spheres
  - In 2 studies TheraSphere showed longer OS for people with PVT
  - Conflicting results from other studies
- 1 small retrospective study compared all 3 SIRTs (submitted as addendum)
  - No difference in OS at 6 and 12 months

Assessment group

- All studies are retrospective with high or unclear risk of bias
- Studies were generally small with less than 100 people

Stakeholder comments

- Conflicting opinion of whether SIRTs show similar effectiveness
- Conflicting opinion of whether non-RCT studies should be included in analysis

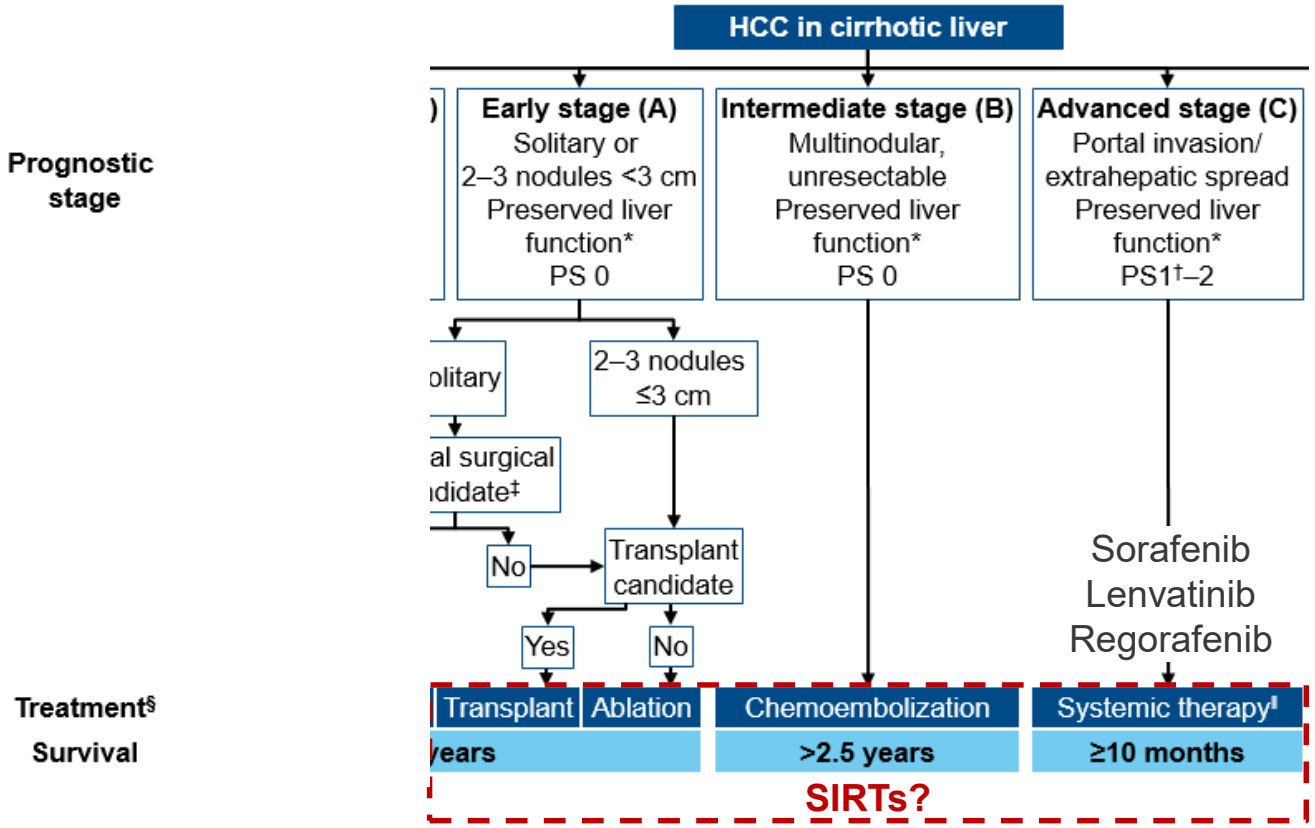
Is it appropriate to consider non-RCTs?

Is there sufficient evidence to show that TheraSphere is more effective than SIR-Spheres?

Is it reasonable to assume SIRTs are all similarly effective?

Network meta-analyses

3 subpopulations could potentially benefit from SIRT treatment



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

The AG planned 3 NMAs to estimate comparative effects

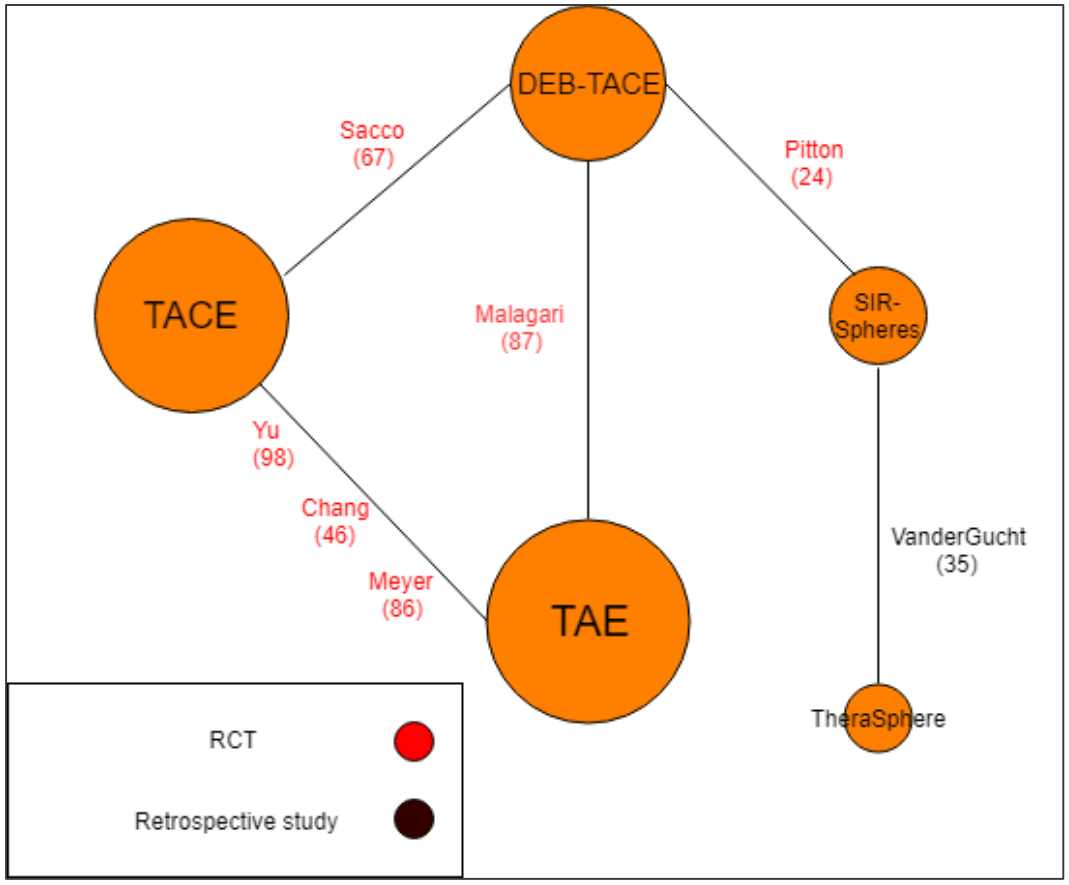
Aim of NMA is to compare effectiveness of two or more treatment options

Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies (CTT)	Ineligible for conventional transarterial therapies (CTT)
Network 1 • 2 small non-UK RCTs • Results might not be generalisable to UK population: transplant waiting times in studies longer than NHS • In UK, TACE rather than SIRT is often used during transplant waiting • **Not performed**	**Network 2** • 6 RCTs (5 compare CTTs with each other, 1 small trial of 24 people compares DEB-TACE and SIR-Spheres) • 1 retrospective comparative study • Weak link in network between CTTs and SIRTs • Results are uncertain • No evidence for downstaging identified	**Network 3** • 3 RCTs and 2 retrospective comparative studies • Most robust evidence • Complete network • Scenario analyses and sensitivity analyses provided

[redacted]

Network 2 – treatment effectiveness in adults with unresectable HCC who are eligible for CTT

- NMA performed following consultation
- CTT-eligible population includes:
  - people with intermediate stage HCC (BCLC B)
  - people with advanced stage HCC (BCLC C) if they do not have portal vein thrombosis (PVT)/portal vein involvement (PVI) or extra-hepatic spread
- SIR-Spheres connected by 1 trial (n=24)
- Base case analysis for OS and PFS
- No scenario or sensitivity analyses were performed



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Base case results – Hazard ratios show in OS and PFS between treatment options

- Mean HR for OS are uncertain BUT effect is similar across treatments

vs		*Comparator*				
		TACE	SIR-Spheres	TheraSphere	DEB-TACE	TAE
Treatment	TACE		-	-	-	-
	SIR-Spheres	1.06 (0.21-3.31)		-	-	-
	TheraSphere	1.02 (0.13-3.77)	0.96 (0.34-2.18)		-	-
	DEB-TACE	0.88 (0.29-2.09)	0.95 (0.35-2.56)	1.41 (0.28-4.34)		-
	TAE	0.98 (0.61-1.57)	1.60 (0.27-5.25)	2.08 (0.24-8.01)	1.48 (0.42-3.77)	

- Mean HR for PFS are uncertain BUT effect is similar across treatments

vs		*Comparator*				
		TACE	SIR-Spheres	TheraSphere	DEB-TACE	TAE
Treatment	TACE		-	-	-	-
	SIR-Spheres	1.20 (0.22-3.82)		-	-	-
	TheraSphere	1.14 (0.15-4.20)	0.95 (0.36-2.05)		-	-
	DEB-TACE	0.86 (0.26-2.15)	0.92 (0.31-2.12)	0.94 (0.26-3.44)		-
	TAE	0.87 (0.61-1.20)	0.93 (0.21-4.05)	1.58 (0.20-5.97)	1.35 (0.38-3.50)	

[redacted]

HR <1 indicates better OS/PFS

Network 2 – results show no difference between treatment options and are uncertain

Stakeholder comments

- NMA for CTT-eligible population should be done
- Network is complete if all evidence is considered
- Non-randomised and non-comparative evidence should be included

AG's NMA results for network 2 following consultation

Included evidence

- Weak evidence to connect SIRTs in the network
- Non-comparative evidence was not used because of low quality
- No evidence on downstaging identified

Results

- No difference between the treatment options
- Results are uncertain because of wide credible intervals

Is this network informative for decision making?

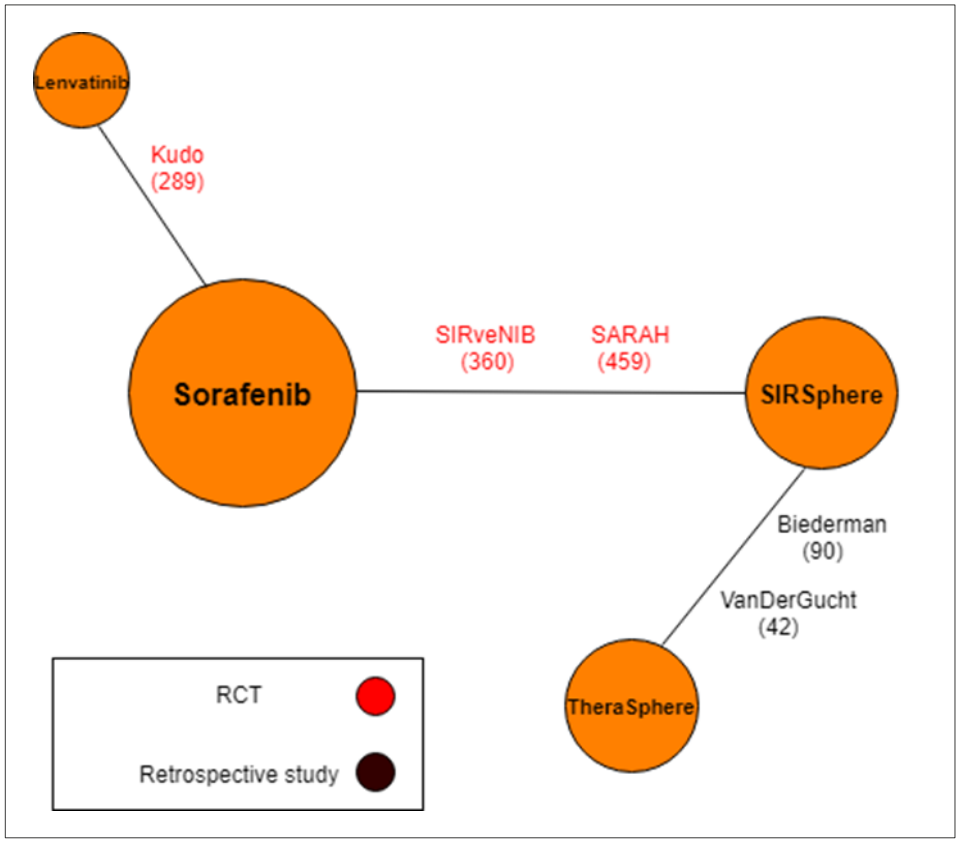
[redacted]

Network 3 – treatment effectiveness in adults with unresectable HCC who are ineligible for CTT

Base-case NMA – adults with Child-Pugh A

- SARAH and SIRveNIB trials (SIR-Spheres) included
- Per-protocol and intention-to-treat population

- Sensitivity analysis
  - SARAH trial only
  - Per-protocol and intention-to-treat population
- Scenario analysis 1
  - Includes Biederman et al. 2016 to add TheraSphere



Alternative NMA – all adults

- Intention-to-treat population
- Scenario analysis
  - Includes Biederman et al. 2016, and van der Gucht to add TheraSphere

[redacted]

Base case NMA – adults with Child-Pugh A per-protocol and ITT population

- Treatment effect estimates for OS are uncertain
- Treatment effect similar for the 3 treatment options
- PFS could not be assessed because it was not reported in SIRveNIB for people with Child-Pugh A

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

	vs	*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib		-	-
	SIR-Spheres	0.94 (0.77-1.14)		-
	Lenvatinib	1.06 (0.79-1.40)	1.14 (0.79-1.58)	

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

	vs	*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib		-	-
	SIR-Spheres	1.13 (0.96-1.32)		-
	Lenvatinib	1.06 (0.79-1.40)	0.92 (0.67-1.29)	

[redacted]

Mean HR <1 indicates better OS/PFS

Sensitivity analysis – excluding SIRveNIB study from base case NMA; PP and ITT population

- SIRveNIB was conducted in Asia
- Exclusion had some impact on the results for OS in the PP population
  - HRs got numerically higher (worse) for SIR-Spheres
- Exclusion had very little impact on the results for OS in the ITT population

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

	vs	*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib			
	SIR-Spheres	1.02 (0.79-1.29)*		-
	Lenvatinib	1.06 (0.79-1.40)	1.06 (0.71-1.52)	

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

	vs	*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib			
	SIR-Spheres	1.14 (0.90-1.4)		-
	Lenvatinib	1.06 (0.79-1.40)	0.94 (0.65-1.34)	

[redacted]

* Higher than base case Mean HR <1 indicates better OS/PFS

Scenario analysis 1 – adults with Child-Pugh A inclusion of Biederman *et al*. study; PP and ITT population

- Biederman et al. 2016 is a retrospective, poor quality study, adds TheraSphere to the network
  - All people have portal vein thrombosis
- TheraSphere showed significant improvement in OS compared to SIR-Spheres, sorafenib and lenvatinib in both per protocol and ITT population

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

vs		*Comparator*			
		Sorafenib	SIR-Spheres	Lenvatinib	TheraSphere
Treatment	Sorafenib		-	-	-
	SIR-Spheres	0.94 (0.77-1.13)		-	-
	Lenvatinib	1.06 (0.79-1.40)	1.13 (0.79-1.57)		-
	TheraSphere	**0.41 (0.20-0.77)**	**0.44 (0.20-0.84)**	**0.40 (0.18-0.78)**	

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for ITT population

vs		*Comparator*			
		Sorafenib	SIR-Spheres	Lenvatinib	TheraSphere
Treatment	Sorafenib		-	-	-
	SIR-Spheres	1.13 (0.96-1.32)		-	-
	Lenvatinib	1.06 (0.79-1.40)	0.95 (0.67-1.29)		-
	TheraSphere	**0.47 (0.21-0.88)**	**0.41 (0.20-0.77)**	**0.45 (0.20-0.89)**	

Alternative NMA – all adults ITT population, no restriction to Child Pugh A

- SIR-Spheres showed significant reduction in OS compared with sorafenib

Base case (Child Pugh A) – Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients ITT population

vs		*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib			
	SIR-Spheres	1.13 (0.96-1.32)		-
	Lenvatinib	1.06 (0.79-1.40)	0.92 (0.67-1.29)	

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients in ITT population

vs		*Comparator*		
		Sorafenib	SIR-Spheres	Lenvatinib
Treatment	Sorafenib			
	SIR-Spheres	**1.14 (1.01-1.28)**		-
	Lenvatinib	1.06 (0.79-1.40)	0.93 (0.67-1.25)	

[redacted]

Mean HR <1 indicates better OS/PFS

Scenario analysis 2 – all adults ITT population, no restriction to Child Pugh A

- Inclusion of Biederman et al. 2016 and Van der Gucht et al. showed significant improvement in OS with TheraSphere when compared to sorafenib, SIR-Spheres and lenvatinib

Mean hazard ratio estimates (95% CrI) for OS for each treatment comparison for ITT population

vs		*Comparator*			
		Sorafenib	SIR-Spheres	Lenvatinib	TheraSphere
Treatment	Sorafenib		-	-	-
	SIR-Spheres	**1.14 (1.01-1.28)**		-	-
	Lenvatinib	1.06 (0.79-1.40)	0.93 (0.67-1.25)		-
	TheraSphere	**0.53 (0.31-0.84)**	**0.46 (0.28-0.72)**	**0.51 (0.28-0.86)**	

[redacted]

Mean HR <1 indicates better OS/PFS

Network 3 – no difference between systemic treatments and SIR-Spheres if only high quality evidence is used

AG's NMA results for network 3

- *Child-Pugh A*
  - No difference between SIR-Spheres, sorafenib & lenvatinib in base case
  - Similar results when SIRveNIB is excluded
  - TheraSphere longer OS than SIR-Spheres, sorafenib and lenvatinib if retrospective evidence is included
- *All adults*
  - SIR-Spheres reduced OS than sorafenib in base case network
  - TheraSphere longer OS than SIR-Spheres, sorafenib and lenvatinib if retrospective evidence is included

Stakeholder comments

- Non-randomised and non-comparative evidence should be included in analysis; TheraSphere should be included in base-case network
- Comparison should consider similar populations from REFLECT and SARAH
- No relevant evidence comparing TheraSphere or QuiremSpheres with comparators for CTT-ineligible patients
- SIRTs are not equally effective

Should non-randomised and non-comparative evidence be included?

Are SIRTs similarly effective?

Cost-effectiveness evidence

2 companies included cost-effectiveness evidence in their submission

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
Economic evidence	Model 1 CTT-eligible population – cost minimisation analysis to compare SIR-Spheres, TheraSphere, TACE and DEB-TACE	Model 1 CTT-eligible population – cost-utility analysis to compare TheraSphere, SIR-Spheres and QuiremSpheres with TACE, DEB-TACE and TAE	Budget impact model
	Model 2 CTT-ineligible population – cost-utility analysis to compare SIR-Spheres with sorafenib (and lenvatinib)	Model 2 CTT-ineligible population – cost-utility analysis to compare SIRTs with systemic therapies	

[redacted]

SIR-Spheres models and AG critique

Model 1 – CTT-eligible population; cost-minimisation analysis

Company

- Comparison of SIR-Spheres, TheraSphere, TACE and DEB-TACE
- Costs included for initial treatment, hospitalisation and management of adverse events
- Scenarios presented using different assumptions and cost sources
- Ranges of costs associated with CTT, TheraSphere, and SIR-Spheres overlapped

	Cost (range)
TACE	£9,257 to £14,167
SIR-Spheres	£11,185 to [redacted]
TheraSphere	£12,026 to [redacted]

- No cost-utility analysis because of lack of comparative evidence

AG critique

- Choice of approach inappropriate and potentially misleading
- Insufficient evidence to demonstrate equivalence of treatments
- Excludes important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or receive subsequent therapy after progression of disease
- Cost analysis of CTT highlighted significant uncertainties in the number of CTT treatments that are typically given, and the impact on the total costs

[redacted]

SIR-Spheres models and AG critique

Model 2 – CTT-ineligible population; cost-utility analysis

Company

- Comparison of SIR-Spheres versus sorafenib
- Base case was restricted to low tumour burden/ALBI 1 subgroup
- Downstaging was permitted
- Scenario analysis for broader population
- SIR-Spheres dominated sorafenib, producing more QALYs at a lower cost

	Incremental		
	QALYs	Costs (£)	ICER (£)
Probabilistic model			
SIR	0.682	-£1,979	Dominant
Sorafenib			
Deterministic model			
SIR	0.601	-£1,784	Dominant
Sorafenib			

AG critique

- Low tumour burden/ALBI 1 subgroup might not be clinical relevant
- Downstaging to curative therapies might not be clinical relevant in UK setting
- Modelling of OS and use of data which was not censored for downstaging to curative therapy
- Assumptions regarding the modelling of patients who underwent work-up but did not receive SIR-Spheres
- Number of SIRT treatments received; assumption bilobar tumours will be treated in one session
- Duration of subsequent treatments
- ICER very uncertain and company's estimate is probably optimistic

[redacted]

TheraSphere models and AG critique

Model 1 – CTT-eligible population; cost-utility analysis;

Company

- Comparison of TheraSphere with SIR-Spheres, QuiremSpheres, TAE, TACE and DEB-TACE
- Same efficacy of TheraSphere, SIR-Spheres and QuiremSpheres
- Same efficacy of TAE, DEB-TACE and TACE
- Key benefit of SIRT was increased proportion of patients who achieved downstaging after treatment and therefore receive curative treatment
- Cheapest strategy was DEB-TACE, which dominated TAE and TACE
- TheraSphere, QuiremSpheres and SIR-Spheres had a probabilistic ICER of **£25,052** per QALY gained, compared to DEB-TACE

AG critique

- Downstaging to curative therapies might not be clinical relevant in UK setting
- Use of a non-HCC specific dataset
- Failure to correctly account for patients who do not get SIRT after work-up
- Limitations in clinical evidence used to assume relative effectiveness
- Inappropriate implementation of age-adjusted utility values
- Inaccurate representation of patients in the pharmacological management health state
- ICER is uncertain; overall direction of uncertainty is not clear

[redacted]

TheraSphere models and AG critique

Model 2 – CTT-ineligible population; cost–utility analysis

Company

- Comparison of TheraSphere with SIR-Spheres, QuiremSpheres, and systemic therapies

	Incremental (to regorafenib)		
	QALYs	Costs (£)	ICER (£)
Probabilistic model (calculated by AG)			
Thera	0.185	£12,778	£69,070
Quirem	-0.030	£650	Dominated
SIR	-0.031	£610	Dominated
Sorafenib	0.000	£2,181	Dominated
Lenvatinib	0.030	£24,486	Dominated

- In response to AG critique BTG provided updated analysis without regorafenib and updated costs: TheraSphere ICER **£66,854** per QALY gained compared with sorafenib

AG critique

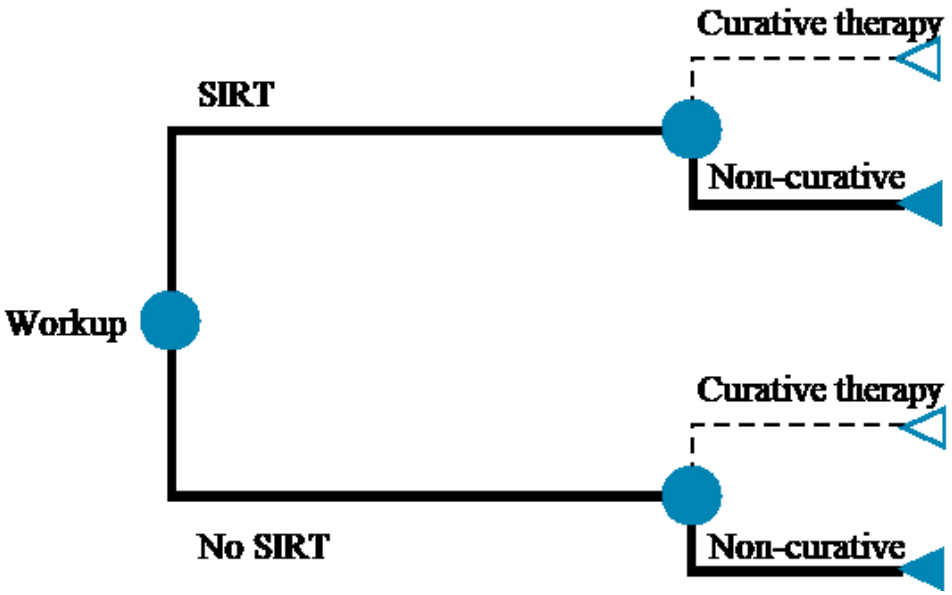
- Inclusion of regorafenib as direct comparator is not appropriate
- Failure to correctly account for patients who do not get SIRT after work-up
- Limitations in clinical evidence used to model the relative effectiveness
- Inappropriate and incorrect implementation of age-adjusted utility values
- Assumptions about time on treatment for systemic therapies
- Assumptions about subsequent therapies received following SIRT therapy
- ICER is uncertain; net effect on ICER is unclear because issues have opposite effects

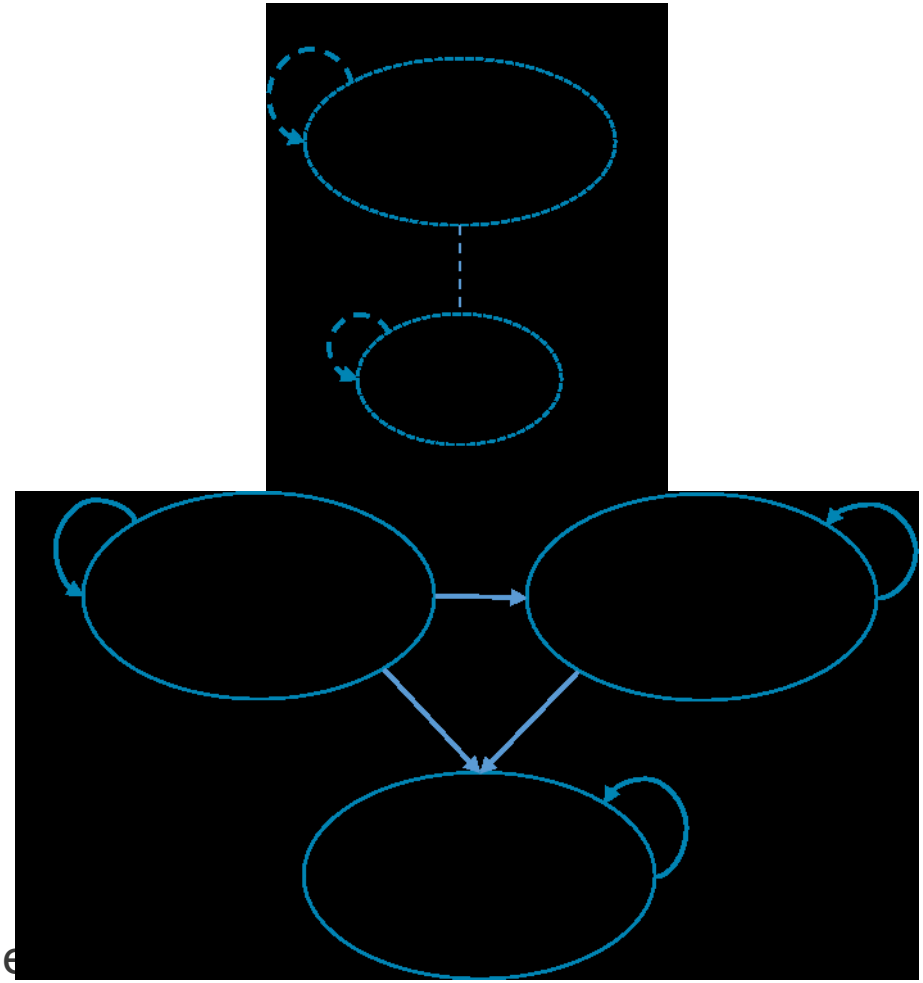
AG proposed model for CTT-ineligible population

Model Component	Description
Population	Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • for whom any conventional transarterial therapy (TAE, TACE, DEB-TACE) is inappropriate • with or without macroscopic vascular invasion • without extrahepatic disease.
Intervention	• SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres Ho-166 PLLA microspheres
Comparator	Established clinical management without SIRT: • Sorafenib • Lenvatinib
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained, incremental net monetary benefit
Perspective	NHS and PSS
Time horizon	Lifetime (10 years)
Discount rate	Annual rate of 3.5% applied to costs and QALYs

[redacted]

The AG model is a hybrid decision tree & partitioned survival model with 3 health states





- Decision tree model enables separate outcome
  people who do not get SIRT after work-up procedure
- Curative therapy is considered in scenario analyses not base case
- Structure of partitioned survival model is similar to the company models

AG model input parameters

Model parameter	Evidence source
OS	• SIR-Spheres and sorafenib – parametric survival models fitted to pooled OS data (per protocol or intention to treat depending on trial arm) from the SARAH and SIRveNIB trials • TheraSphere and QuiremSpheres assumed to have same OS as SIR-Spheres (scenario analysis for alternative TheraSphere OS estimates) • Lenvatinib – hazard ratio to sorafenib OS curve from the NMA • Patients who received work-up but were ineligible to receive SIRT – observed KM data from SARAH
PFS	• SIR-Spheres and sorafenib – parametric survival models fitted to pooled PFS data (per protocol or intention to treat) from the SARAH and SIRveNIB trials • Lenvatinib – hazard ratio to sorafenib PFS curve from the NMA
Proportion receiving SIRT	• Based on the full SARAH trial population • Number of administrations of SIRT was based on the SARAH trial

[redacted]

AG model input parameters

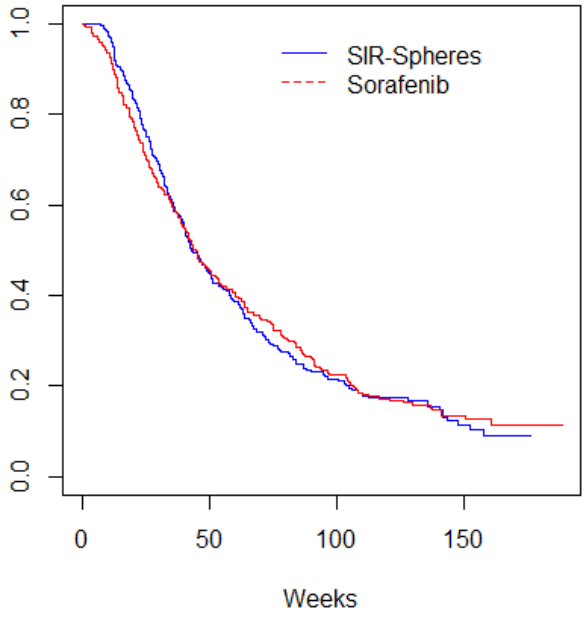
Model parameter	Evidence source
SIRT costs	Acquisition costs: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference Costs 2017-18
Systemic therapy costs	Sorafenib and lenvatinib: BNF Dosing of sorafenib: SARAH trial Dosing of lenvatinib: REFLECT Western subgroup Duration of sorafenib: SARAH trial Duration of lenvatinib: PFS HR from REFLECT applied to SARAH, sorafenib ToT
Subsequent treatment costs	BNF, eMIT, TA555 (regorafenib)
AE costs	AEs ≥5% of the population were modelled with rates drawn from the SARAH and REFLECT trials. Unit costs based on TA474 and TA551.
Health state costs	Sirtex survey of clinical experts and NHS reference costs 2017/2018

Effectiveness – OS and PFS evidence

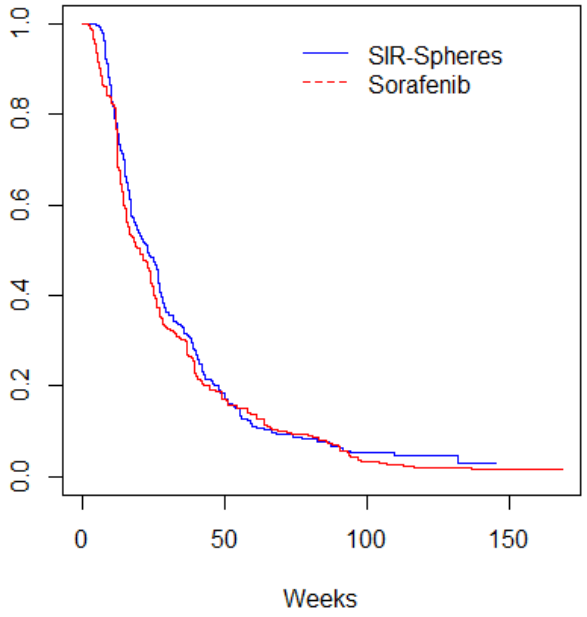
- Summary of observed survival estimates for SIR-Spheres and sorafenib, SARAH and SIRveNIB pooled dataset

	SIR-Spheres	Sorafenib
Overall survival		
Median (weeks)	42.9 (95% CI 39.9 – 51.1)	44.4 (95% CI 40.7 – 50.8)
Interquartile range	26.4 – 84.0	22.0 – 91.0
Progression-free survival		
Median (weeks)	23.0 (95% CI 19.0 – 26.8)	20.5 (95% CI 16.3 – 23.7)
Interquartile range	12.8 – 41.1	12.1 – 39.5

Overall survival



Progression-free survival



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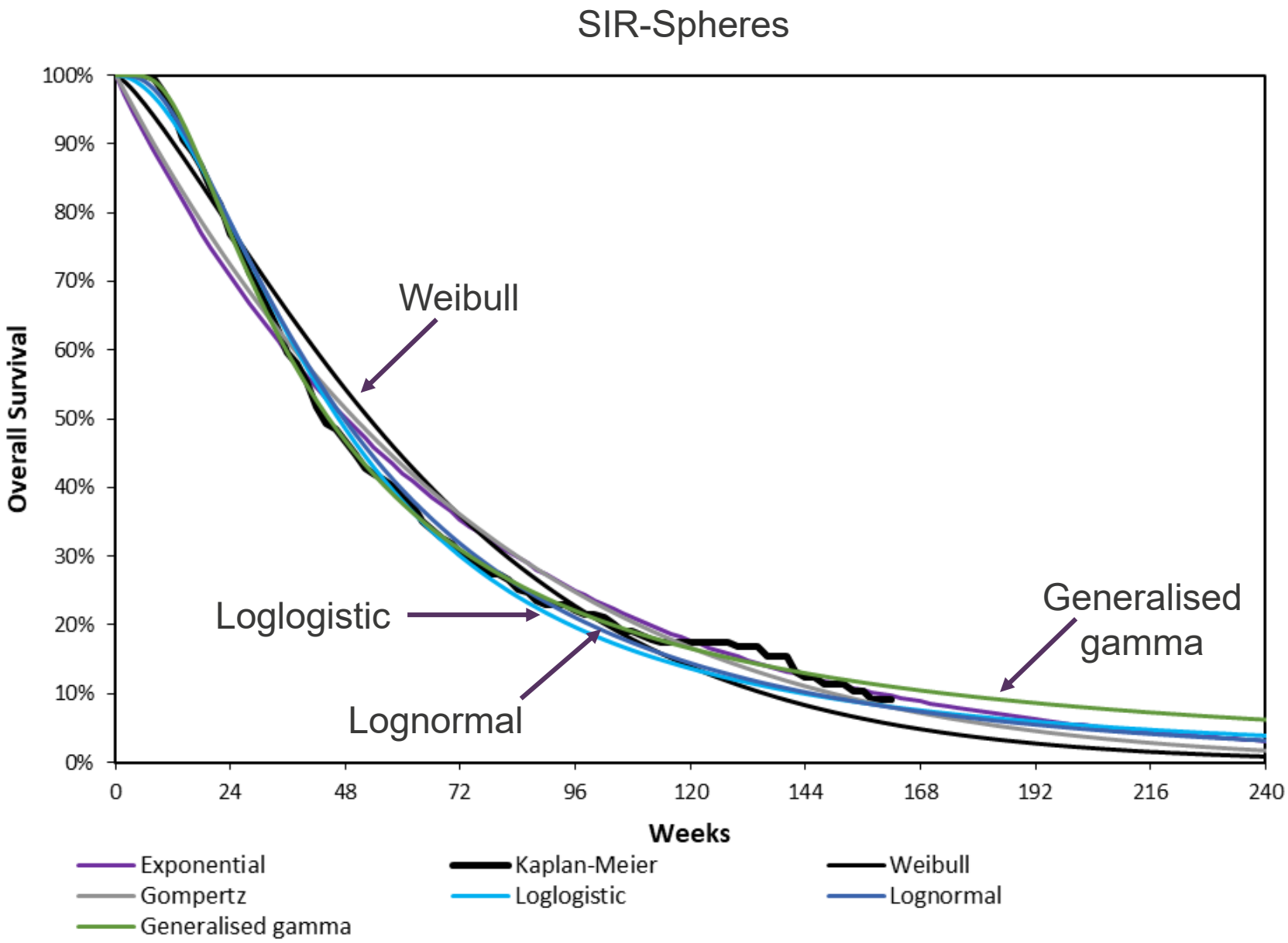
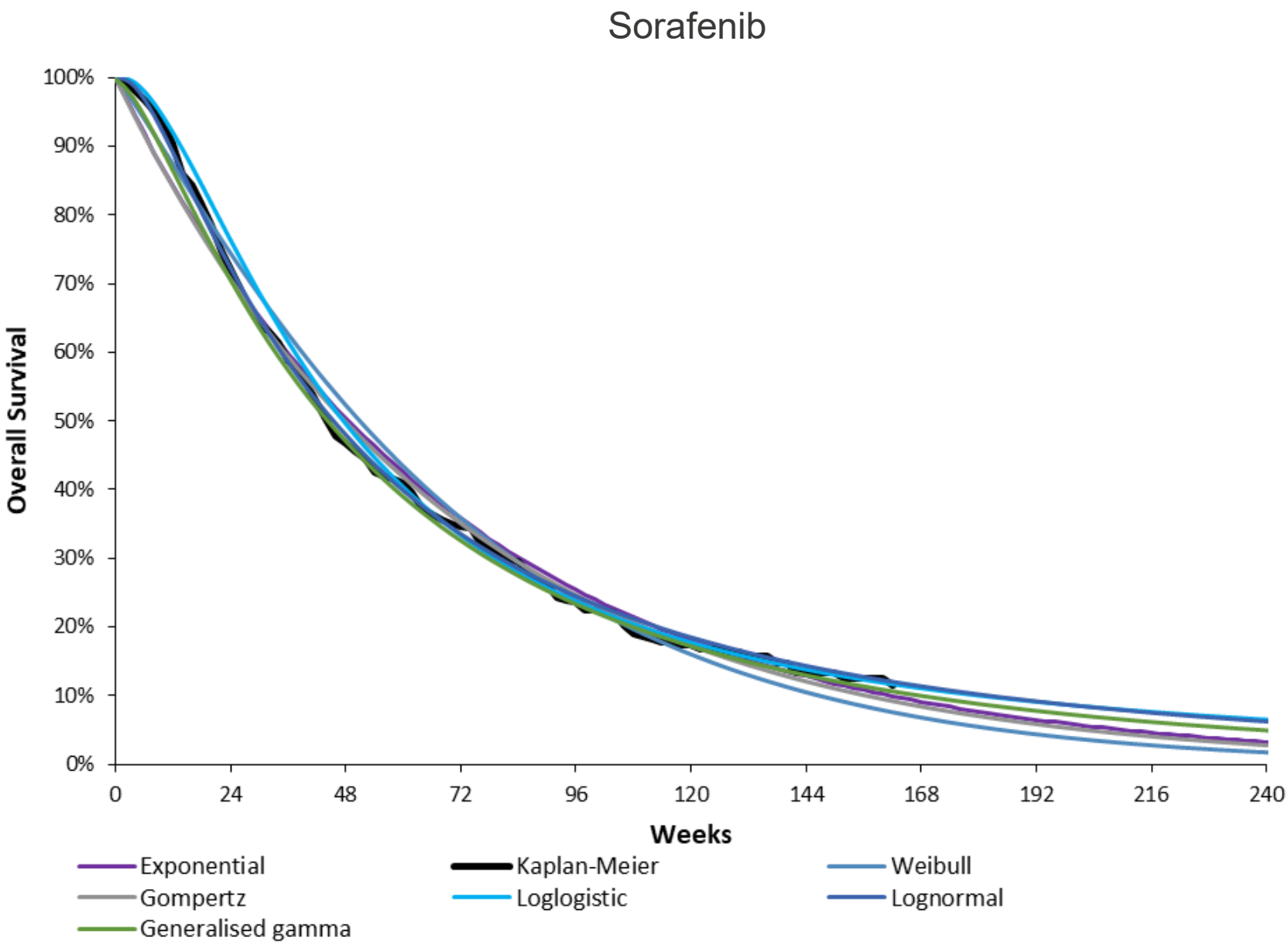
SIR-Spheres OS model fits

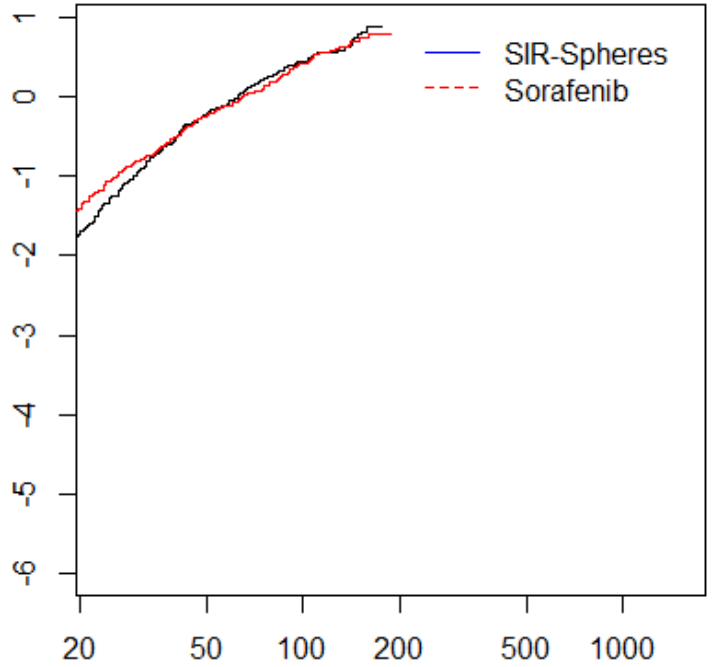


Sorafenib OS model fits



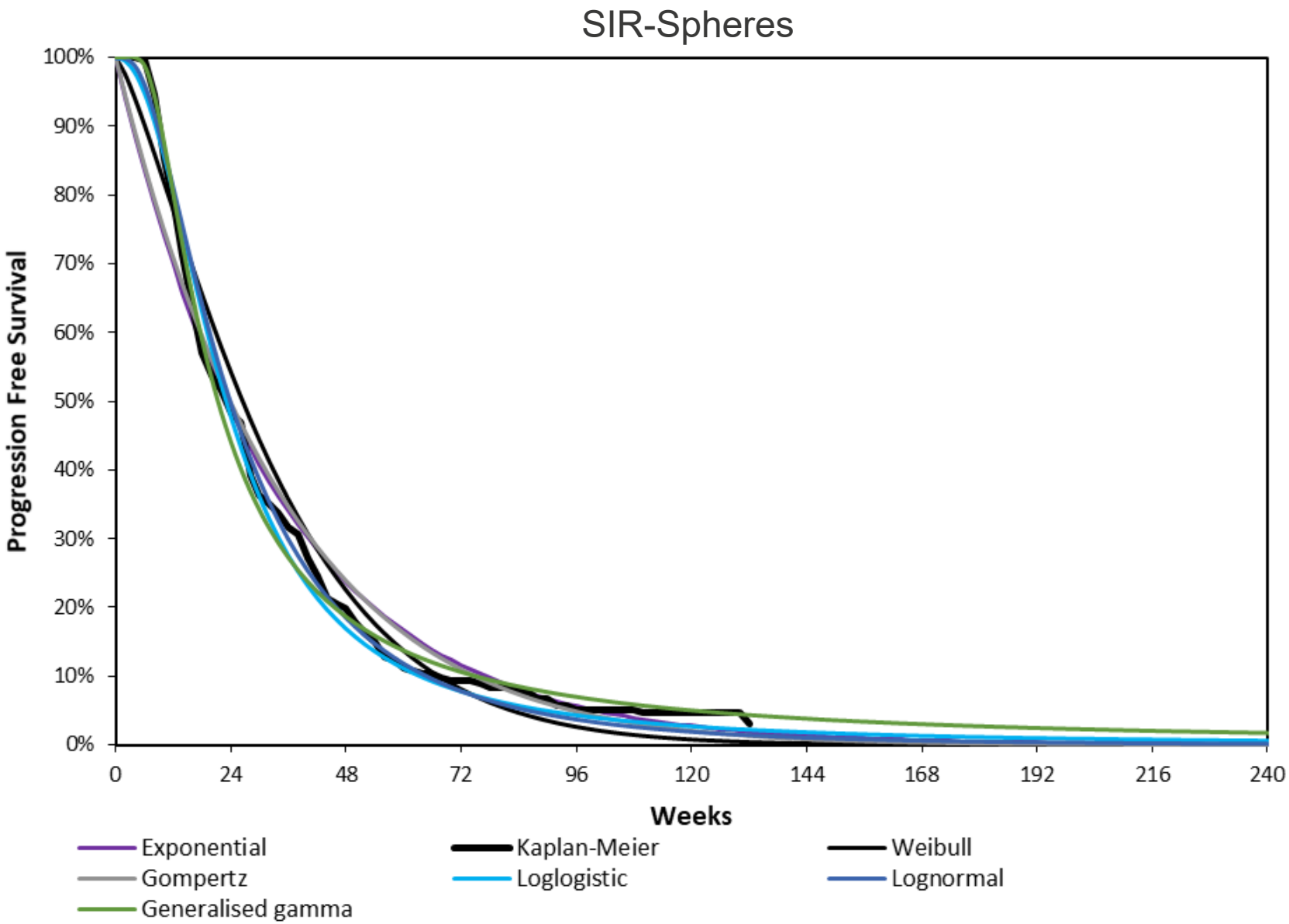
OS model choice for base case depended on model fit and model properties to allow HR use for lenvatinib

- Log-cumulative hazard plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset
  - Plot suggests that proportional hazard can be assumed and therefore HRs can be used
- AG used Weibull to fit OS and PFS curves in base case
  - Three better fitting curves not used because single HRs required to include lenvatinib and non-RCT TheraSphere studies
  - All 3 curve fits included in scenario analysis

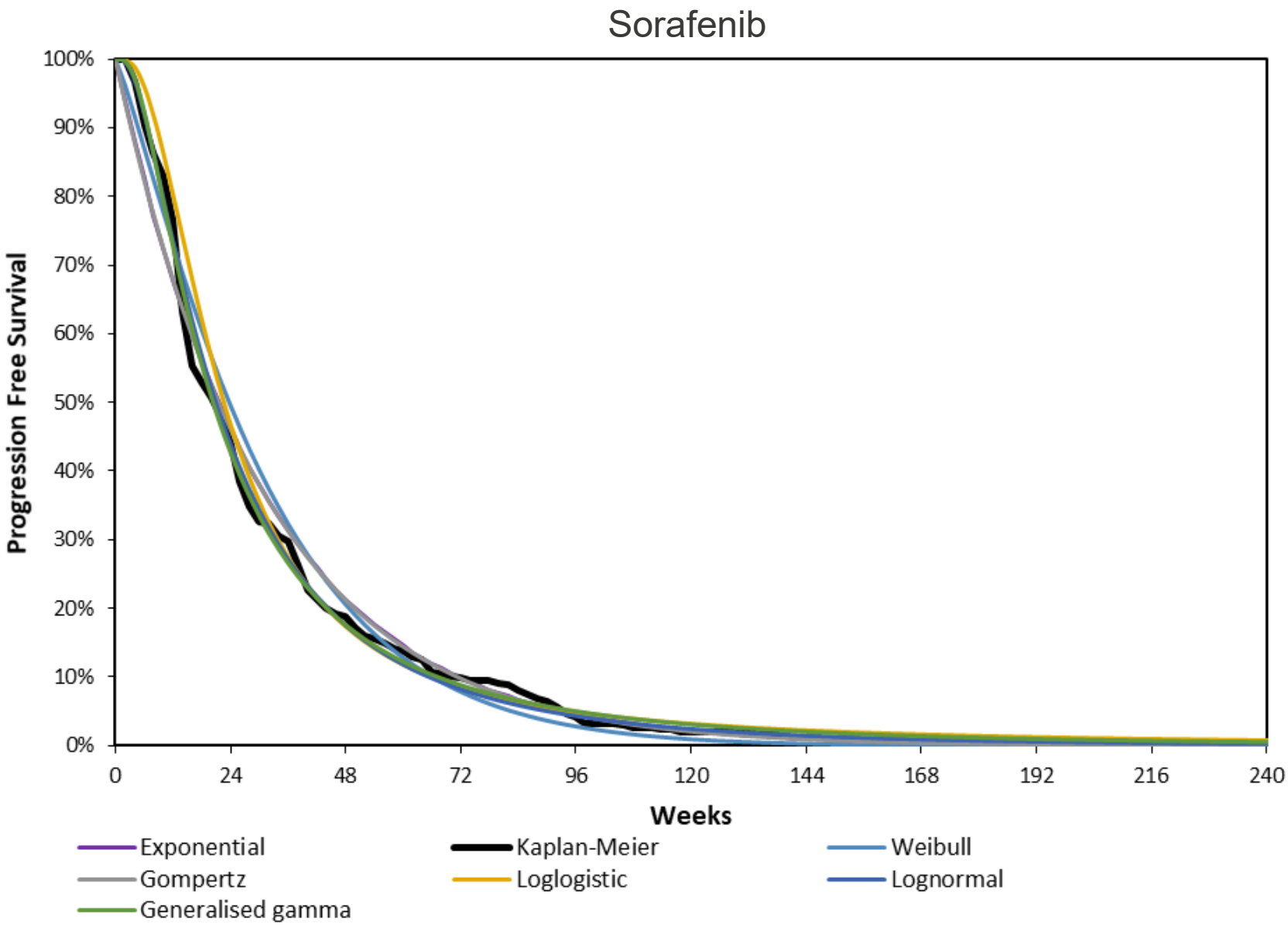


	SIR-Spheres		Sorafenib	
	AIC	BIC	AIC	BIC
Log-normal	2350	2358	3146	3154
Generalised gamma	2344	2355	3147	3159
Log-logistic	2358	2365	3144	3152
Weibull	2394	2401	3168	3176
Exponential	2412	2416	3173	3177
Gompertz	2413	2420	3175	3183

SIR-Spheres PFS model fits

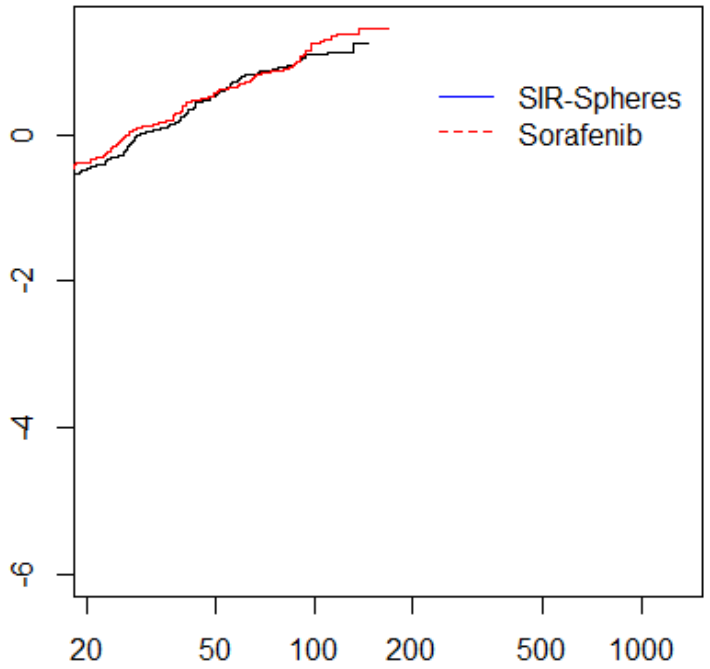


Sorafenib PFS model fits



PFS model choice for base case depended on model fit and model properties to allow HR use for lenvatinib

- Log-cumulative hazard plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset
  - Plot suggests that proportional hazard can be assumed and therefore HRs can be used
- AG used Weibull to fit OS and PFS curves in base case
  - Three better fitting curves not used because HRs are required to include lenvatinib and non-RCT TheraSphere studies
  - All 3 curve fits included in scenario analysis



	SIR-Spheres		Sorafenib	
	AIC	BIC	AIC	BIC
Generalised gamma	2226	2237	3120	3132
Log-normal	2246	2253	3120	3128
Log-logistic	2255	2262	3130	3138
Weibull	2313	2320	3182	3190
Exponential	2337	2341	3195	3199
Gompertz	2339	2346	3197	3205

Utility values and costs used in AG base case

Utility values

- Based on per-protocol population of SARAH, calculated by company (mapping EORTC-QLQ-C30 summary scores to EQ-5D using Longworth et al. algorithm)

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

Costs

- Derived from literature searches, previous NICE TAs, and company submissions
- Include:
  - treatment costs† (acquisition, procedures, and monitoring)
  - health service utilisation driven by disease status
  - adverse event management
- Cost for work-up procedure
  - £860.32 for SIR-Spheres and TheraSphere
  - [redacted] for QuiremSpheres (list price of QuiremScout unpublished)
- Disease management costs from company submission (resource survey 11 clinicians)

AG also explored sensitivity of using values from TA511

[redacted]

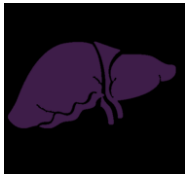
†list price; results with PAS included are presented in part 2

Other base case assumptions

Downstaging to curative therapy not permitted

People who fail workup are modelled separately

SIRTs have similar efficacy



Bilobar treatments performed in two separate procedures

AG base case results all treatment options (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
Lenvatinib	£30,005	1.183	0.805	£117	0.04	£2,911	£1,090	£2,911
SIR-Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£57,488
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	Dominated	-£6,614	Dominated
AG Probabilistic base case								
Lenvatinib	£29,658	1.202	0.825					
TheraSphere	£30,014	1.111	0.765	£356	-0.060	Dominated	-£2,154	Dominated
SIR Spheres	£30,196	1.111	0.765	£538	-0.060	Dominated	-£2,323	Dominated
Sorafenib	£32,444	1.244	0.841	£2,786	0.016	£174,320	-£2,306	£174,320
QuiremSpheres	£36,613	1.111	0.765	£6,955	-0.060	Dominated	-£8,741	Dominated

NMB, net monetary benefit; *threshold of £30,000

[redacted]

AG performed several scenario analyses (1/2)

Scenario 1*	**Efficacy data from SARAH only** • Only data from SARAH included, might be more similar to UK population • SIRveNIB excluded (conducted in Asia)
Scenario 2*	**Low tumour burden/ALBI grade 1 subgroup** • Company's preferred post-hoc grouping of patients from the SARAH trial • Use of the higher low tumour burden/ALBI 1 subgroup utilities from the SARAH trial • Lower proportion of patients who receive work-up but not SIRT (8.1% vs 18.6%).
Scenario 3*	**No macroscopic vascular invasion (SARAH)** • Subgroup analysis – people who had no macroscopic vascular invasion (MVI) or portal vein invasion • Subgroup might benefit more from SIRT technologies because of more favourable positioning and spread of tumour • Subgroup identified in NICE's scope
Scenario 4*	**TheraSphere HR from Biederman and Van Der Gucht NMA scenario** • Hazard ratio derived from the AG's NMA scenario, inclusion of retrospective studies • Biederman et al. 2016 included only patients with MVI

[redacted]

*AG provided deterministic and probabilistic sensitivity analyses

AG performed several scenario analyses (2/2)

Scenario 5	Utilities from lenvatinib TA511
Scenario 6	Downstaging to curative therapy possible (SARAH ITT proportions)
Scenario 7	Bilobar disease treated in same procedure
Scenario 8	Work-up costs from NHS Reference Costs (Sirtex assumption)
Scenario 9	Disease management costs taken from TA551
Scenario 10	Low tumour burden/ALBI 1 subgroup including possibility of downstaging
Scenario 11	Gompertz OS
Scenario 12	Exponential OS
Scenario 13	Generalised gamma OS (lenvatinib OS equal to sorafenib)
Scenario 14	Log-normal OS (lenvatinib OS equal to sorafenib)
Scenario 15	Log-logistic OS (lenvatinib OS equal to sorafenib)
Scenario 16	5% work-up/no SIRT
Scenario 17	SIRveNIB work-up/no SIRT (28.57%)

[redacted] AG provided deterministic sensitivity analyses for these scenarios

Incremental net monetary benefit at £30K WTP – lenvatinib almost always ranked first (list price analysis)

Intervention	Incremental NMB Rank																	
	Base case*	S1*	S2*	S3*	S4*	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
SIR-Spheres	4	4	2	4	4	4	2	3	4	3	2	4	4	3	4	4	4	3
TheraSphere	2	3	**1**	3	**1**	3	**1**	2	3	2	**1**	3	3	2	3	3	3	2
QuiremSpheres	5	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	5
Lenvatinib	**1**	**1**	3	**1**	2	**1**	3	**1**	**1**	**1**	4	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Sorafenib	3	2	4	2	3	2	4	4	2	4	5	2	2	4	2	2	2	4

[redacted]

*probabilistic analysis

Scenario analyses (list price analysis) (1/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
Probabilistic scenario 1 – Efficacy data from SARAH only								
Lenvatinib	£29,413	1.171	0.805					
TheraSphere	£29,476	0.978	0.672	£62	-0.133	Dominated	-£4,044	Dominated
SIR Spheres	£29,660	0.977	0.671	£246	-0.134	Dominated	-£4,267	Dominated
Sorafenib	£32,300	1.213	0.818	£2,887	0.014	£212,505	-£2,479	£212,505
QuiremSpheres	£36,064	0.977	0.670	£6,650	-0.134	Dominated	-£10,684	Dominated
Probabilistic scenario 2 – Low tumour burden/ALBI grade 1 subgroup								
Lenvatinib	£31,233	1.397	1.024					
Sorafenib	£33,834	1.436	1.048	£2,601	0.024	£109,709	-£1,890	Dominated
TheraSphere	£34,086	1.552	1.161	£2,854	0.136	£20,926	£1,237	£20,926
SIR Spheres	£34,389	1.553	1.163	£3,156	0.139	£22,725	£1,010	£119,562
QuiremSpheres	£41,088	1.552	1.162	£9,855	0.138	£71,372	-£5,712	Dominated

NMB, net monetary benefit; *threshold of £30,000

[redacted]

Scenario analyses (list price analysis) (2/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
Probabilistic scenario 3 – No macroscopic vascular invasion (SARAH)								
Lenvatinib	£29,983	1.296	0.893					
TheraSphere	£30,093	1.335	0.743	£110	-0.149	Dominated	-£4,585	Dominated
SIR Spheres	£30,287	1.083	0.744	£304	-0.149	Dominated	-£4,765	Dominated
Sorafenib	£32,852	1.082	0.905	£2,868	0.012	£23,195	-£2,507	£238,195
QuiremSpheres	£36,683	1.081	0.745	£6,699	-0.148	Dominated	-£11,134	Dominated
Probabilistic scenario 4 – TheraSphere HR from Biederman and Van Der Gucht NMA								
Lenvatinib	£29,601	1.197	0.822					
SIR Spheres	£30,242	1.110	0.764	£641	-0.058	Dominated	-£2,387	Dominated
Sorafenib	£32,477	1.244	0.843	£2,876	0.021	£140,205	-£2,260	Dominated
TheraSphere	£33,670	1.931	1.330	£4,068	0.507	£8,017	£11,156	£8,017
QuiremSpheres	£36,616	1.111	0.765	£7,014	-0.058	Dominated	-£8,746	Dominated

NMB, net monetary benefit; *threshold of £30,000

[redacted]

Scenario analyses (list price analysis) (3/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
Deterministic scenario 10 – Low tumour burden/ALBI 1 subgroup and downstaging								
Lenvatinib	£31,072	1.404	1.029					
TheraSphere	£31,255	1.752	1.316	£183	0.286	£639	£8,407	£639
SIR Spheres	£31,501	1.752	1.316	£429	0.286	£1,499	£8,160	Dominated
Sorafenib	£33,007	1.457	1.066	£1,935	0.037	£52,685	-£833	Dominated
QuiremSpheres	£38,166	1.752	1.316	£7,094	0.286	£24,775	£1,496	Dominated

NMB, net monetary benefit; *threshold of £30,000

Assessment Group comments on scenario 10:

- Low tumour burden/ALBI 1 is not a clinically recognised subgroup
- Based on a post-hoc analysis → breaks randomisation
- Downstaging is rare and is currently largely experimental

[redacted]

Responding to stakeholder comments AG conducted analysis with same work-up costs (list price analysis)

- Incremental net monetary benefit at £30K WTP
  - QuiremSpheres ranks 5th in 4 out of the 6 scenarios

Intervention	Incremental NMB Rank					
	Base case	S1	S2	S3	S4	S10
SIR-Spheres	4	4	2	4	4	2
TheraSphere	3	3	**1**	3	**1**	**1**
QuiremSpheres	5	5	4	5	5	3
Lenvatinib	**1**	**1**	3	**1**	2	4
Sorafenib	2	2	5	2	3	5

[redacted]

Base case results with same work-up costs (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
Lenvatinib	£30,005	1.183	0.805	£117	0.040	£2,911	£1,090	£2,911
SIR Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
QuiremSpheres	£31,868	1.110	0.764	£1,980	0.000	Dominated	-£1,980	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£57,488

NMB, net monetary benefit; *threshold of £30,000

- Cost-effectiveness results in scenario analyses are consistent with results from main analysis

[redacted]

Responding to stakeholder comments AG conducted analysis without lenvatinib (list price analysis)

- Incremental net monetary benefit at £30K WTP – Sorafenib ranks 1st in base case while TheraSphere ranks 1st in 3 out of 5 scenarios

Intervention	Incremental NMB Rank					
	Base case	S1	S2	S3	S4	S10
SIR-Spheres	3	3	2	3	3	2
TheraSphere	2	2	**1**	2	**1**	**1**
QuiremSpheres	4	4	4	4	4	3
Sorafenib	**1**	**1**	3	**1**	2	4

[redacted]

Base case results excl. lenvatinib (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
SIR Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£28,728
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	Dominated	-£6,614	Dominated
AG Probabilistic base case								
TheraSphere	£30,017	1.111	0.765					
SIR Spheres	£30,230	1.111	0.765	£213	0.000	Dominated	-£217	Dominated
Sorafenib	£32,495	1.244	0.841	£2,478	0.077	£32,302	-£177	£32,302
QuiremSpheres	£36,618	1.111	0.765	£6,600	0.000	Dominated	-£6,604	Dominated
AG Deterministic base case with generalised gamma								
TheraSphere	£30,992	1.277	0.875					
SIR Spheres	£31,211	1.277	0.875	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,854	1.357	0.916	£1,862	0.040	£46,103	-£650	£46,103
QuiremSpheres	£37,607	1.277	0.875	£6,614	0.000	Dominated	-£6,614	Dominated

NMB, net monetary benefit; *threshold of £30,000

- AG used Weibull and generalised gamma for base case analysis
- AG used Weibull in all scenarios

Scenarios excl. lenvatinib – deterministic analyses (1/2)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
Deterministic scenario 1 – Efficacy data from SARAH only								
TheraSphere	£29,395	0.976	0.671					
SIR Spheres	£29,614	0.976	0.671	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£31,951	1.209	0.817	£2,556	0.147	£17,424	£1,845	£17,424
QuiremSpheres	£36,010	0.976	0.671	£6,614	0.000	Dominated	-£6,614	Dominated
Deterministic scenario 2 – Low tumour burden/ALBI grade 1 subgroup								
Sorafenib	£33,388	1.420	1.037					
TheraSphere	£34,021	1.542	1.153	£633	0.116	£5,466	£2,841	£5,466
SIR Spheres	£34,267	1.542	1.153	£879	0.116	£7,594	£2,594	Dominated
QuiremSpheres	£40,931	1.542	1.153	£7,544	0.116	£65,152	-£4,070	Dominated
Deterministic scenario 3 – No macroscopic vascular invasion (SARAH)								
TheraSphere	£29,949	1.078	0.740					
SIR Spheres	£30,167	1.078	0.740	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,452	1.326	0.897	£2,503	0.157	£15,923	£2,213	£15,923
QuiremSpheres	£36,563	1.078	0.740	£6,614	0.000	Dominated	-£6,614	Dominated

NMB, net monetary benefit; *threshold of £30,000

Scenarios excl. lenvatinib – deterministic analyses (2/2)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB*	
Deterministic scenario 4 – TheraSphere HR from Biederman and Van Der Gucht NMA								
SIR Spheres	£30,107	1.110	0.764					
Sorafenib	£32,082	1.243	0.841	£1,976	0.076	£25,870	£315	Dominated
TheraSphere	£33,373	1.883	1.297	£3,267	0.533	£6,130	£12,722	£6,130
QuiremSpheres	£36,503	1.110	0.764	£6,396	0.000	Dominated	-£6,396	Dominated
Deterministic scenario 10 – Low tumour burden/ALBI 1 subgroup with downstaging								
TheraSphere	£31,255	1.752	1.316					
SIR Spheres	£31,501	1.752	1.316	£246	0.000	Dominated	-£246	Dominated
Sorafenib	£33,007	1.457	1.066	£1,752	-0.250	Dominated	-£9,240	Dominated
QuiremSpheres	£38,166	1.752	1.316	£6,911	0.000	Dominated	-£6,911	Dominated

NMB, net monetary benefit; *threshold of £30,000

Assessment Group comments on scenario 10:

- Low tumour burden/ALBI 1 is not a clinically recognised subgroup
- Based on a post-hoc analysis → breaks randomisation
- Downstaging is rare and is currently largely experimental

AG model for CTT-ineligible population (1/2)

Cost-effectiveness results (AG model – list price analysis)

- AG produced model for CTT-ineligible population only
- When all treatment options are included:
  - Lenvatinib is the least costly treatment and ranks first in most scenarios at a WTP of £30K
  - In probabilistic base case (Child-Pugh A population) SIRTs are more costly and less effective than lenvatinib
  - In low tumour burden and good liver function population (scenario 2) ICERs for TheraSphere and SIR-Spheres were £17,175 and £18,783 per QALY gained versus lenvatinib
  - In narrower population and downstaging (scenario 10) ICERs for TheraSphere, SIR-Spheres and QuiremSpheres were to £639, £1,499 and £24,775 per QALY gained versus lenvatinib
- When lenvatinib is excluded:
  - TheraSphere is the least costly treatment and ranks first in most scenarios undertaken

Stakeholder comments – base case assumptions

- Lenvatinib is not widely used in NHS; comparison to lenvatinib not relevant to UK
- Clinical evidence does not support equivalent effectiveness for SIRTs
- Downstaging should be included in base case; there is evidence that SIRTs increases use of curative treatments
- Bilobar disease can be treated with SIR-Spheres in single procedure

AG model for CTT-ineligible population (2/2)

Stakeholder comments

Structure/modelling

- State occupancy is incorrectly modelled; some are modelled independently and others via relative effects
- Sorafenib OS data pooling is misleading as no detail is provided
- In base case OS and PFS should be modelled with lognormal
- Time to treatment should be fitted with lognormal function to patient level data

Inputs

- *Costs*
  - There are no additional imaging costs for SIR-Spheres
  - Similar work-up costs for all SIRTs should be assumed
- *Population*
  - Scenario analysis needed that aligns SARAH and REFLECT population (see NMA comment)

What is the most appropriate comparator for CTT-ineligible population?

Is it appropriate to assume that SIRTs have equal effectiveness?

Is it appropriate to include downstaging in base-case model (ineligible for CTT)?

Can bilobar disease be treated in a single procedure?

What is the most appropriate model to extrapolate OS and PFS?

Critique on missing AG models for population eligible for transplant and CTT-eligible population

Adults with unresectable HCC	
Eligible for transplant	Eligible for conventional transarterial therapies
AG • Did not conduct NMA because of lack of evidence in this population • Did not conduct cost-effectiveness analysis	**AG** • NMA results very uncertain • Weak link between CTTs and SIRTs • No evidence for downstaging in this population • Did not conduct cost-effectiveness analysis
Stakeholder comments • Agree with limited evidence • ESMO guidelines suggest SIRT as alternative • SIRT could be a potential treatment option in this population • Non-comparative evidence supports benefit in specific groups in this population	**Stakeholder comment** • Proportion of people might be unsuitable for CTT and this group is likely to benefit from SIRT • NMA and cost-effectiveness analysis provided by companies should be considered for decision making

Is there enough evidence to perform robust NMAs and cost-effectiveness analyses in these populations?
Should the company models be considered for the CTT-eligible population?

End of life criteria extension of life ≥3 months a not satisfied in most scenarios

Criterion		Evaluation
Life expectancy <24 months	✓	• Life expectancy for people ineligible for CTT is less than 24 months • Expected mean survival lenvatinib 14.72 months • Expected mean survival sorafenib 15.49 months
Extension of life ≥3 months	?	• Base case: SIRTs inferior to systemic therapies

Subgroup	Incremental undiscounted LYGs (months)	
	SIRT vs lenvatinib	SIRT vs sorafenib
AG base-case (no downstaging)	-0.95	-1.73
AG base-case (with downstaging)	0.11	-0.65
Low tumour/ALBI 1 subgroup (no downstaging)	2.80	2.11
Low tumour/ALBI 1 subgroup (with downstaging)	5.30	4.61
MVI subgroup (no downstaging)	-2.49	-3.18
MVI subgroup (with downstaging)	-1.51	-2.19

[redacted]

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