



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1493 - Transarterial radioembolisation using yttrium-90 (TARE-Y) for the treatment of unresectable hepatocellular carcinoma (HCC)

Applicant: BTG International Asia Ltd

Date of MSAC consideration: MSAC 73rd Meeting, 26-27 July 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing for transarterial radioembolisation with yttrium-90 (TARE-Y) for the treatment of unresectable hepatocellular carcinoma (HCC) was received from BTG International Asia by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC deferred its advice for MBS funding of transarterial radioembolisation with yttrium-90 (TARE-Y) for the treatment of unresectable hepatocellular carcinoma (HCC).

MSAC accepted there was a clinical need in this small population with poor treatment options. However, MSAC considered that the clinical evidence base was limited and weak, which flowed on to uncertainties with the modelled economic evaluation.

MSAC deferred its advice to request a revised economic evaluation. MSAC considered there were two potential options:

- Option 1 is a comparison against sorafenib only (for advanced HCC), based on clinical noninferiority and likely better safety profile in the subgroup currently eligible for sorafenib. This would take a cost-minimisation approach using the SARAH trial data and include the different costs of different adverse event profiles. MSAC advised that if the applicant chose this option then the additional information could be provided back to the next suitable MSAC meeting.
- Option 2 is a comparison against sorafenib and TACE across the overall proposed population (ie advanced and intermediate HCC) with a cost-utility analysis, based on stronger clinical evidence of clinical superiority over mixed comparators (TACE, sorafenib or best supportive care [BSC]), resulting in overall net safety and utility gains. MSAC advised that should the applicant elect to proceed with option 2 then further information would need to be considered by ESC.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that there are two types of microspheres used for TARE-Y: resin and glass. TARE-Y using resin beads has interim MBS funding (since 2006) for colorectal cancer metastases. MSAC noted that the current application includes TARE-Y via both glass and resin beads.

MSAC noted that the PICO in this submission included two populations:

- population 1: people with advanced HCC (stage Barcelona Liver Clinic-C [BCLC-C]); the comparator for this group is sorafenib or BSC
- population 2: people with intermediate HCC (stage BCLC-B) who are contraindicated to, intolerant of, or who have failed first-line treatment with transarterial chemoembolisation (TACE); the comparator for this group is BSC.

MSAC noted that these populations are different to those in the PASC-ratified PICO. MSAC also noted that in the current PICO, TACE has been removed as a comparator for population 2. MSAC acknowledged the applicant's response that this change was made on the basis of expert advice that it reflected best practice. However, MSAC considered this to be inappropriate as TACE is still used in practice.

MSAC acknowledged that, for patients with advanced HCC, there is currently no alternative to sorafenib, a medicine that has major side effects. MSAC noted that TARE-Y is a one-off treatment (compared with daily doses of sorafenib). MSAC also noted that TARE-Y is the only treatment option when first-line TACE is contraindicated or fails, and when the patient is intolerant to second-line treatment with sorafenib (e.g. due adverse events relating to the skin, gut or heart).

MSAC noted that TARE-Y is intended to replace some use of sorafenib (PBS item) for patients with advanced HCC, and replace some TACE (MBS item) for patients with intermediate HCC. MSAC noted that TARE-Y may reduce the size of lesions in some patients and so provide a bridge to liver transplant.

MSAC noted that TARE-Y is intended for use in patients with HCC that is unresectable and unablatable (on the basis of the number and size of lesions) after referral by a multidisciplinary team. Pre-intervention work-up involves detailed staging and calculations (requiring nuclear medicine imaging of arterial anatomy) to determine the extent of possible shunting to the lungs and gastrointestinal system. The intervention is performed by a nuclear physician and interventional radiologist. MSAC noted that TARE-Y is contraindicated where the hepatic artery is not accessible, there is a risk of extrahepatic delivery, or the lung shunt is greater than 20%.

MSAC recommended that the item descriptor be amended to specify that TARE-Y should be delivered by a 'specialist interventional radiologist'. MSAC recommended that the descriptor should include both glass and resin microspheres. MSAC also recommended that the descriptor should specify that TARE-Y should not be performed concurrently with sorafenib, as randomised controlled trials (RCTs) assessing the safety of this combination are currently ongoing. MSAC concluded that it is not necessary for the descriptor to include a limit on the number of times the item can be claimed. Although TARE-Y may be repeated if there are no other treatment options, this is done with extreme caution due to the risk of radiation-induced liver damage and gastrointestinal adverse events, and an associated major reduction in quality of life.

MSAC recommended that the procedure should be classified as day surgery (Type B); this could be certified up to type A if the patient needs to stay overnight due to post-intervention pain.

MSAC noted that evidence for safety and clinical effectiveness of TARE-Y versus sorafenib was obtained from two RCTs and a number of small observational studies. Evidence for safety and clinical effectiveness of TARE-Y versus BSC and of glass versus resin microspheres was obtained from a number of observational studies. MSAC identified issues with the available studies due to variations in disease stages and controls, and changes in treatments.

MSAC noted that safety of TARE-Y is claimed to be superior to sorafenib for patients with advanced HCC; however, this is based on only one RCT (the SARAH trial). MSAC noted the substantially different adverse event profiles of TARE-Y and sorafenib. Adverse events for TARE-Y include one-off events such as REILD (radioembolisation-induced liver disease) and lung toxicity, whereas adverse events for sorafenib include daily systemic effects. MSAC noted that available evidence shows TARE-Y to be inferior to BSC in terms of safety in patients with intermediate or advanced unresectable HCC. Adverse events include pain and REILD.

MSAC noted that there was no apparent difference in the safety of glass and resin microspheres, with REILD in approximately 4% of patients.

MSAC noted that TARE-Y is claimed to be noninferior to sorafenib in terms of overall survival and recurrence-free survival. However, MSAC noted that this is based on the SARAH trial, which was designed as a superiority trial and may be underpowered to assess noninferiority, or may have measured different time points, making it difficult to assess any differences in the minimum clinically important difference. MSAC noted that TARE-Y appears to be superior to sorafenib in patients with advanced HCC and portal vein invasion or thrombosis (PVI; PVT), and glass microspheres appear superior to resin microspheres in patients with advanced HCC and PVI (based on observational studies).

MSAC noted that the comparison of TARE-Y to sorafenib included an estimate of the equi-effective dose of TARE-Y in terms of duration. MSAC recommended that equi-effective doses in terms of dose frequency, dose intensity and compliance are also required. MSAC noted that TARE-Y appears to be significantly more effective than BSC in patients with unresectable HCC (based on observational studies).

MSAC noted that the submission did not include a comparison of TARE-Y with TACE. MSAC considered this a major omission because TARE-Y would be an alternative to TACE for patients with intermediate HCC, who currently incur high out-of-pocket costs. MSAC recommended further analysis by the applicant to establish the safety and efficacy of TARE-Y following failed TACE, and the safety of repeat TARE-Y.

MSAC noted that a cost-utility analysis should have been done to compare TARE-Y and sorafenib because of the difference in adverse event profiles. MSAC considered that the cost-minimisation analysis undertaken was inadequate. The cost of adverse events was not adequately included, so it is unclear what the cost implications of adverse events would be (e.g. TARE-Y may have fewer adverse events than sorafenib, but they may have greater cost implications).

MSAC noted that the ICER for TARE-Y versus BSC was calculated as just over \$43,000 per quality adjusted life year gained. The key drivers of the ICER were costs and mortality

estimates. MSAC considered that, although the ICER is not high, it is potentially unreliable due to major limitations in the economic model, including:

- inadequacy of the model structure to capture disease states
- extrapolation of 5-year survival data to 10 years, which is inappropriate for patients with advanced disease
- exclusion of adverse events other than REILD
- use of an inappropriate control group
- incorrect assumption of zero cost for BSC.

MSAC suggested that the cost-effectiveness analysis by Rognoni et al may be a more suitable model for comparing TARE-Y with BSC.

MSAC noted that the number of patients predicted to access TARE-Y is low, approximately 60 per year. However, this may be an underestimate due to uncertainty regarding the number of eligible patients and the potential underestimation of repeat treatments.

MSAC noted the proposed fees for the procedure are \$346.50 for handling and \$813.50 for delivery. The cost of the spheres themselves is \$8230. MSAC noted that other associated costs would include the cost of work-up and follow-up (as for current practice) and the cost of REILD as an adverse event (\$13,670–\$15,487 per year in the first 5 years). MSAC noted that the estimated total cost over the first 5 years is \$352,616–\$398,798.

MSAC noted potential savings from reduced use of sorafenib of approximately \$811,762–\$919,644 per year in the first 5 years. However, this was calculated on the assumption that 40% of patients would switch from sorafenib to TARE-Y, which may be an overestimate. MSAC noted that the cost of sorafenib is based on a special PBS pricing arrangement, so may overestimate the true cost of sorafenib. MSAC noted that there would also be savings from reduced use of TACE, but this was not quantified. MSAC noted net annual savings over the first 5 years of \$445,476–\$505,359; however, this would depend on the extent of use of sorafenib.

4. Background

MSAC has previously considered TARE-Y for HCC in 2005 (App 1082) through an application for SIR-Spheres (resin microspheres), and did not support public funding at that time.

TARE-Y using SIR-Spheres (resin microspheres) is currently subsidised by the MBS on an interim basis (commenced in May 2006) for the treatment of hepatic metastases that are secondary to colorectal cancer. SIR-Spheres are currently funded via the Prostheses List (SE001).

5. Prerequisites to implementation of any funding advice

There are two types of Y-90 microspheres currently commercially available: TheraSphere (glass; BTG International) and SIR-Spheres (resin; Sirtex Medical). Both types of microspheres are registered by the Therapeutic Goods Administration.

6. Proposal for public funding

The proposed MBS listings of TARE-Y are based on the items available for the treatment of colorectal liver metastases using SIR-Spheres. The two item numbers cover: (i) dosimetry, handling and injection of the microspheres and (ii) transfemoral catheterisation of the hepatic

artery to administer the microspheres, and are not limited to a specific microsphere type (i.e. resin or glass).

Table 1 Proposed MBS item descriptors

Category 3 – THERAPEUTIC PROCEDURES	
Group	T8 – SURGICAL OPERATIONS
Subgroup	3 - VASCULAR
Subheading	13 – INTERVENTIONAL RADIOLOGY PROCEDURES
<p>DOSIMETRY, HANDLING AND INJECTION OF yttrium-90-emitting microspheres for selective internal radiation therapy of <i>hepatocellular carcinoma that is not suitable for resection or ablation including (i) advanced hepatocellular carcinoma, or (ii) intermediate hepatocellular carcinoma where transarterial chemoembolisation is contraindicated, unable to be tolerated or has failed</i>, not being a service to which item 35317, 35319, 35320 or 35321 applies</p> <p>The procedure must be performed by a specialist or consultant physician recognised in the specialties of nuclear medicine or radiation oncology on an admitted patient in a hospital.</p> <p>Fee: \$346.50 Benefit: 75% = \$259.95</p>	
Category 3 – THERAPEUTIC PROCEDURES	
Group	T8 – SURGICAL OPERATIONS
Subgroup	3 - VASCULAR
Subheading	13 – INTERVENTIONAL RADIOLOGY PROCEDURES
<p>Transfemoral catheterisation of the hepatic artery to administer yttrium-90-emitting microspheres for selective internal radiation therapy to embolise the microvasculature of <i>hepatocellular carcinoma that is not suitable for resection or ablation including (i) advanced hepatocellular carcinoma, or (ii) intermediate hepatocellular carcinoma where transarterial chemoembolisation is contraindicated, unable to be tolerated or has failed</i>, not being a service to which item 35317, 35319, 35320 or 35321 applies</p> <p>Excluding associated radiological services or preparation, and excluding aftercare</p> <p>Fee: \$813.50 Benefit: 75% = \$610.00</p>	

7. Summary of Public Consultation Feedback/Consumer Issues

Six responses were received following the Public Consultation period: five of the six organisations who responded noted the benefit of having an efficacious treatment such as TARE-Y available in a patient population that has few treatment options. In terms of disadvantages, the main one noted is that the treatment is not currently reimbursed, which makes it prohibitive to the majority of eligible patients. The final response requested that the item number relating to transfemoral catheterisation be limited to specialist interventional radiologists.

8. Proposed intervention's place in clinical management

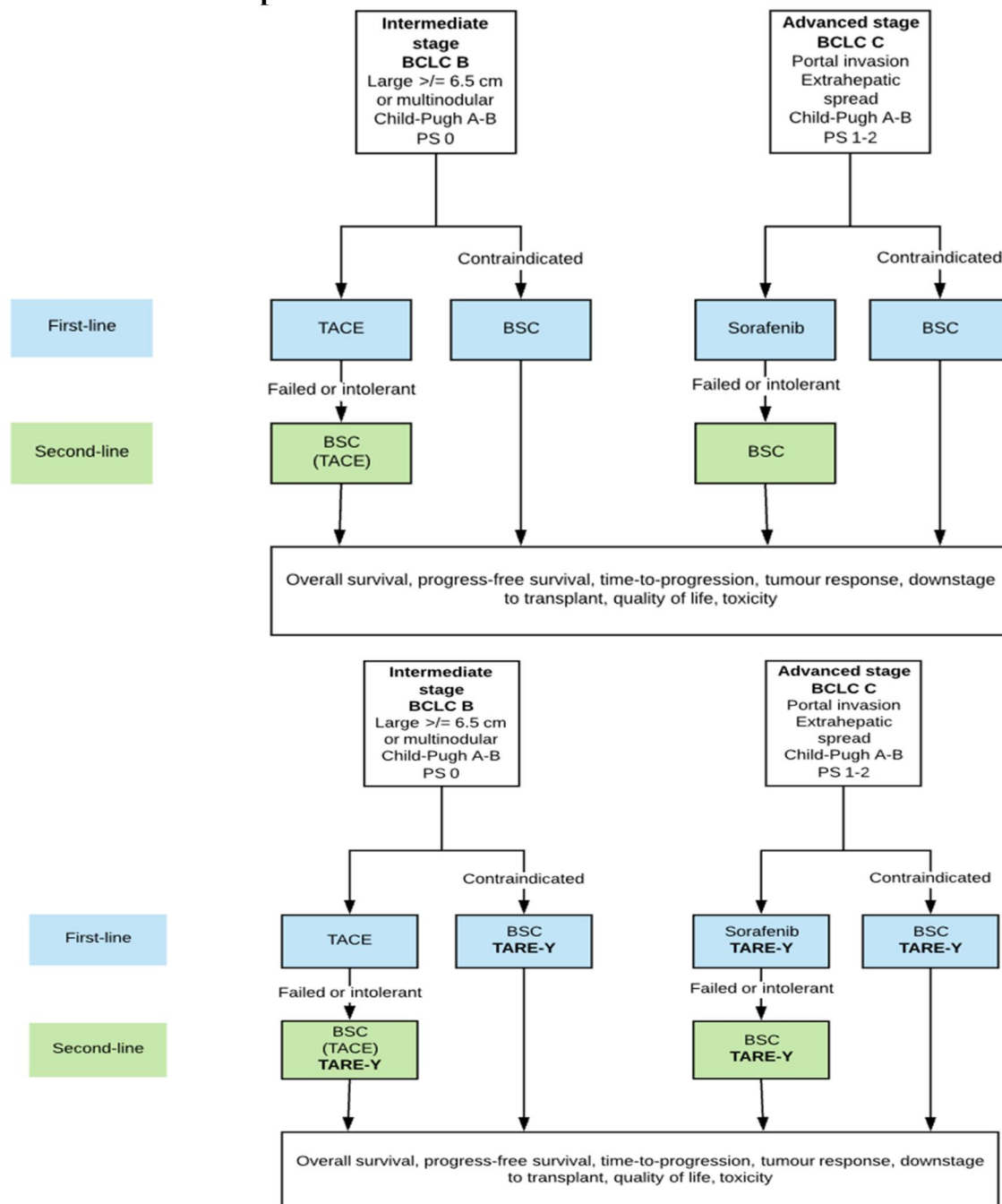
Hepatocellular carcinoma is a type of primary liver cancer arising from hepatocytes, the main cell type found in the liver. This intervention targets patients with intermediate and advanced HCC.

The procedure involves delivery of microspheres containing yttrium-90 to the liver via transfemoral catheterisation of the hepatic artery.

TARE-Y, also known as selective internal radiation therapy (SIRT), is currently listed on the MBS for the treatment of unresectable and unablatable hepatic metastases secondary to colorectal cancer (items 35404 to 35408). However, currently there is no public funding for TARE-Y for the treatment of unresectable HCC.

The clinical management algorithms presented in the submission based assessment (Figure 1) are slightly modified from those ratified by PASC. It is expected that TARE-Y would be a direct substitution for sorafenib and BSC in advanced HCC (Population 1) and a direct substitution for BSC in intermediate HCC (Population 2).

Figure 1 Clinical management algorithm for including TARE-Y relative to current clinical practice



Abbreviations: BCLC=Barcelona Clinic Liver Cancer; BSC=best supportive care; PS=performance status; TACE=transarterial chemoembolisation; TARE-Y=transarterial radioembolisation using yttrium-90.

9. Comparator

According to the BCLC management pathway, the recommended active treatments for intermediate and advanced HCC are TACE and sorafenib, respectively. However, sorafenib is not registered or reimbursed in this population in Australia. Table 2 summarises the comparator for different patient populations.

Table 2 Summary of populations and comparators for TARE-Y

Population		BCLC Stage	Line of therapy	Comparator
1	Patients with advanced HCC as an alternative to sorafenib	C/advanced	First	Sorafenib
	Patients with advanced HCC in whom sorafenib is contraindicated		First	BSC
	Patients with advanced HCC who have failed or are intolerant to first-line treatment with sorafenib		Second	BSC
2	Patients with intermediate HCC in whom TACE is contraindicated	B/intermediate	First	BSC ¹
	Patients with intermediate HCC who have failed treatment of are intolerant to first-line treatment with TACE		Second	BSC ²

Abbreviations: BCLC=Barcelona Clinic Liver Cancer; BSC=best supportive care; HCC=hepatocellular carcinoma; TACE=transarterial chemoembolisation.

It should be noted that TACE has been removed as a main comparator for intermediate HCC in the second-line setting, despite being ratified by PASC.

10. Comparative safety

TARE-Y versus sorafenib

Five studies were included in the SBA for this comparison: one RCT (SARAH; Vilgrain 2017), and four retrospective observational studies (Cho 2016, de la Torre 2016, Edeline 2016 and Gramenzi 2015).

Results from these studies suggest that TARE-Y is superior to sorafenib in terms of safety in patients with advanced HCC.

The critique noted that in the SARAH trial there were 19/226 treatment-related deaths in the TARE-Y group (of which 13 were TARE-Y-related and 6 sorafenib-related), and 12/216 sorafenib-related deaths in the sorafenib group.

TARE-Y versus BSC

Three studies were included in the SBA for this comparison: two comparative observational studies (Kwok 2014 and D'Avola 2009) and one systematic review (Braat 2017).

Summary of results from these studies show that REILD and epigastric pain occur more frequently following TARE-Y than BSC.

Results from these studies suggest that TARE-Y is inferior to BSC in terms of radiation-related safety in patients with unresectable HCC.

¹ While the clinician survey conducted for this submission suggests some patients in this population receive sorafenib, and the BCLC algorithm suggests sorafenib as an alternative for these patients, sorafenib is not registered or reimbursed for the treatment of intermediate HCC in Australia.

TARE-Y (glass) versus TARE-Y (resin)

Three studies were included in the SBA for this comparison: two comparative observational studies (Van der Gucht 2017 and Biederman 2016) and one systematic review (Kallini 2017).

In terms of safety, for most outcomes there was no difference between glass and resin microspheres.

11. Comparative effectiveness

TARE-Y versus sorafenib

The SBA stated that the results of the systematic literature review of RCT and observational study evidence show that in patients with advanced HCC, treatment with TARE-Y is at least non-inferior to treatment with sorafenib.

A summary of the efficacy results from the SARAH trial and the included observational studies is presented in Table 3.

Table 3 Efficacy outcomes of interest from the RCT and observational studies: TARE-Y versus sorafenib

Efficacy outcome	RCT	Observational studies					Interpretation ³	
	Vilgrain 2017 RE (95% CI) P value	Cho 2016 RE (95%CI) P value	De la Torre 2016 RE (95%CI) P value	Edeline 2016 RE (95%CI) P value	Gramenzi 2015 RE (95%CI) P value	Pooled RE (95%CI) P value		
Overall survival (unresectable HCC)	ITT: HR 1.15 (0.94, 1.41); P=0.18 PP: HR 0.99 (0.79, 1.24); 0.92	-	-	-	-	HR 1.27 (0.82, 1.98); P=0.29 ⁴	-	No difference
Overall survival (advanced HCC)	ITT: HR 1.22 (0.95, 1.56); NR PP: HR 1.06 (0.81, 1.39); NR	-	-	-	-	-	-	No difference
Overall survival (HCC + PVI/PVT) ⁵	ITT: HR 1.19 (0.75, 1.42); NR PP: HR 1.02 (0.77, 1.36); NR	HR NR P=0.97	HR 0.45 (0.28, 0.80) P<0.05 ⁶	HR 0.40 (0.19, 0.82) NR ⁷	-	HR 0.36 (0.21, 0.63) P<0.001 ⁸	-	Higher for TARE-Y than SOF

³ Results were interpreted as follows: (i) if there was one or more P value < 0.05, the outcome was considered to be higher in one treatment than the other; (ii) if there was a single P value < 0.05, and other results were supportive (i.e. P value < 0.1 or magnitude of RR), this was considered to be higher in one treatment than the other; (iii) if there was a single P value < 0.1 but ≥ 0.05, but no additional supportive results, this was considered to show no difference; and (iv) if the RRs were in opposite directions, and the P values were < 0.1, the evidence was considered to be inconsistent.

⁴ Includes patients with intermediate and advanced HCC only. Result shown is that for the whole population, adjusted for confounding. When a matched population was used, the P value was 0.39.

⁵ Macrovascular invasion for Vilgrain 2017.

⁶ When censored at subsequent use of sorafenib, the HR is 0.32 (95% CI 0.14, 0.73); P<0.05.

⁷ Matched and adjusted result. When adjusted (but not matched) the HR was 0.62 (0.39, 0.97); P=0.04.

⁸ Includes de la Torre 2016 and Edeline 2016 studies only.

Efficacy outcome	RCT	Observational studies					Interpretation ³
	Vilgrain 2017 RE (95% CI) P value	Cho 2016 RE (95%CI) P value	De la Torre 2016 RE (95%CI) P value	Edeline 2016 RE (95%CI) P value	Gramenzi 2015 RE (95%CI) P value	Pooled RE (95%CI) P value	
Progression-free survival (unresectable HCC)	ITT: HR 1.03 (0.85, 1.25); P=0.76 ⁹ PP: HR 0.97 (0.79, 1.20); P=0.77	-	-	-	-	-	No difference
Time to progression (unresectable HCC)	-	-	-	-	HR NR; P=0.08	-	No difference
Time to progression (unresectable HCC)	-	HR NR; P=0.34	-	-	-	-	No difference
Objective response (unresectable HCC)	ITT: RR 1.63 (1.01, 2.65); P=0.05 PP: RR 1.59 (0.97, 2.61); P=0.06	-	-	-	RR 6.67 (2.20, 20.2) P<0.001	-	Higher for TARE-Y than SOF
Disease control (unresectable HCC)	ITT: 0.87 (0.77, 0.99) ; P=0.03 PP: 0.89 (0.79, 1.01); P=0.07	-	-	-	RR 1.86 (1.21, 2.85) P=0.004	-	Inconsistent
Complete response (unresectable HCC)	ITT: RR 2.61 (0.51, 13.3); P=0.25 PP: RR 2.29 (0.43, 12.4); P=0.33	-	-	-	RR 9.00 (0.50, 1.09) P=0.14	-	No difference
Tumour progression (unresectable HCC)	ITT: RR 1.42 (1.02, 1.99) ; P=0.04 PP: RR 1.40 (0.98, 2.02); P=0.07	-	-	-	RR 0.73 (0.49, 1.09); P=0.45 ¹⁰	-	Inconsistent

Abbreviations: CI=confidence interval; HCC=hepatocellular carcinoma; HR=hazard ratio; ITT=intention-to-treat; NR=not reported; PP=per-protocol; PVI=portal vein invasion; PVT=portal vein thrombosis; RE=risk estimate; RR=relative risk; SOF=sorafenib; TARE-Y=transarterial radioembolisation using yttrium-90.

Notes: Results shown in black bold are statistically significant in favour of TARE-Y.

TARE-Y versus BSC

The SBA stated that the results of the systematic literature review show that in patients with intermediate or advanced HCC, treatment with TARE-Y is associated with significantly increased survival compared with BSC.

⁹ The subdistribution HR for liver-specific progression when death and progression outside the liver considered as competing risks is 0.72 (0.56, 0.93); P=0.01.

¹⁰ P value reported in publication does not match P value calculated in post hoc analysis (P=0.12).

A summary of the efficacy results from the included observational studies is presented in Table 4.

Table 4 TARE-Y vs. BSC: efficacy outcomes from the observational studies: TARE-Y versus BSC

Efficacy outcome	Observational studies		Interpretation
	Kwok 2014 RE (95% CI); P value	D'Avola 2009 RE (95% CI); P value	
Overall survival (unresectable HCC)	HR 2.24 (1.05, 4.79); P=0.037	-	Higher for TARE-Y than BSC
Overall survival (unresectable HCC and poor candidates for TACE)	-	OR 3.53 (1.91, 6.52); P<0.001	Higher for TARE-Y than BSC
Objective response – 3 months RECIST (intermediate HCC)	RR 2.50 (0.14, 45.3) RD 0.15 (-0.125, 0.43)	-	No difference
Objective response – 3 months RECIST (advanced HCC)	RR 3.57 (0.19, 66.6) RD 0.15 (-0.09, 0.40)	-	No difference
Objective response – 3 months RECIST (intermediate and advanced HCC)	RR 5.33 (0.31, 92.7) RD 0.15 (-0.01, 0.32)	-	No difference
Objective response – 3 months EASL (intermediate HCC)	RR 5.50 (0.35, 86.0) RD 0.38 (0.07, 0.70)	-	Higher for TARE-Y than BSC
Objective response – 3 months EASL (advanced HCC)	RR 7.86 (0.49, 127) RD 0.38 (0.10, 0.67)	-	Higher for TARE-Y than BSC
Objective response – 3 months EASL (intermediate and advanced HCC)	RR 12.4 (0.78, 198) RD 0.38 (0.18, 0.59)	-	Higher for TARE-Y than BSC
Objective response – 6 months RECIST (intermediate HCC)	RR 2.50 (0.14, 45.3) RD 0.15 (-0.12, 0.43)	-	No difference
Objective response – 6 months RECIST (advanced HCC)	RR 5.00 (0.29, 86.4) RD 0.23 (-0.36, 0.49)	-	No difference
Objective response – 6 months RECIST (intermediate and advanced HCC)	RR 6.52 (0.39, 110) RD 0.19 (0.02, 0.37)	-	Higher for TARE-Y than BSC
Objective response – 6 months EASL (intermediate HCC)	RR 6.50 (0.42, 99.6) RD 0.46 (0.14, 0.79)	-	Higher for TARE-Y than BSC
Objective response – 6 months EASL (advanced HCC)	RR 5.00 (0.29, 86.4) RD 0.23 (-0.03, 0.49)	-	No difference
Objective response – 6 months EASL (intermediate and advanced HCC)	RR 11.3. (0.70, 181) RD 0.35 (0.15, 0.55)	-	Higher for TARE-Y than BSC

Abbreviations: BSC=best supportive care; CI=confidence interval; HCC=hepatocellular carcinoma; HR=hazard ratio; RD=risk difference; RE=risk estimate; RR=relative risk; TARE-Y=transarterial radioembolisation using yttrium-90.

Note: Results shown in black bold are statistically significant in favour of TARE-Y.

TAREY-Y (glass) versus TARE-Y (resin)

The SBA stated that the results suggest that TARE-Y (glass) is more effective in terms of overall survival than TARE-Y (resin) in patients with unresectable HCC and portal vein invasion (PVI). There was also evidence that TARE-Y (glass) is more effective than TARE-Y (resin) in terms of time to progression (TTP) in patients specifically with main portal vein thrombosis (PVT), and in terms of overall response. However, these findings are based on unadjusted analyses.

Clinical Claim

Two clinical claims were made in the SBA:

1. TARE-Y has at least non-inferior effectiveness and superior safety in patients with advanced HCC compared with sorafenib.
2. TARE-Y has superior effectiveness and inferior safety in patients with intermediate or advanced HCC compared with BSC.

12. Economic evaluation

TARE-Y versus sorafenib

A cost-minimisation analysis was presented where TARE-Y likely dominates sorafenib in advanced HCC as it is cheaper and may be superior in terms of safety, as well as effectiveness in the subgroup of patients with PVI/PVT.

The critique noted that the appropriate economic analysis for this evaluation should have been a cost-effectiveness or cost-utility analysis.

TARE-Y versus BSC

A cost-utility analysis was presented in patients with intermediate or advanced HCC. The economic model is a pure mortality model that does not model progression. The base case ICERs are \$21,785/YOL gained and \$43,129/QALY gained with a base case time horizon of 10 years.

The economic model is most sensitive to price and mortality inputs.

13. Financial/budgetary impacts

An epidemiological approach was used to generate the utilisation and financial estimates of introducing TARE-Y to the MBS, which are summarised in Table 5.

Table 5 Total costs to the MBS associated with TARE-Y

	2018	2019	2020	2021	2022
Expected number of patients receiving TARE-Y	56	58	60	62	64
Costs to the MBS - per patient	\$6,250	\$6,250	\$6,250	\$6,250	\$6,250
Total MBS Costs	\$352,016	\$363,279	\$374,826	\$386,664	\$398,798

Abbreviations: MBS=Medicare Benefits Schedule; TARE-Y=transarterial radioembolisation using yttrium-90.

The anticipated number of patients receiving treatment with TARE-Y is 56 in Year 1, increasing to 64 in Year 5. The MBS costs are approximately \$0.4m for each year of the financial estimates.

14. Key issues from ESC for MSAC

Key Issues from ESC to MSAC

ESC Key ISSUES	ESC ADVICE
PICO	SBA PICO differs to ratified PICO. Should the applicant Resubmit or should PASC amend the PICO.
Evidence based	<ul style="list-style-type: none"> 1 RCT, cannot conclude non-inferiority SBA reliance on observation studies with high bias Lack of confirmatory studies. RNo analysis of repeat TACE vs TARE-Y comparison Resubmission with more data , particularly results of other RCTs.
Comparative effectiveness	No OS difference compared to sorafenib: has lesser toxicity, better QOL and better tumour response enough to support approval (cost effectiveness needed) Patients may still be prescribed sorafenib after failed TARE-Y (cost)
Item Descriptor	Specify 'specialist interventional radiologist' in descriptor Allow Glass and Resin: (PASC ratified & limited data) Specify TARE-Y not concurrent with sorafenib (RCTs currently assessing this)

Safety	Require analysis of safety & efficacy for patients who have TARE-Y following failed TACE Require more information on safety of repeat TARE-Y (limit no?)
TARE-Y versus sorafenib Health economic evaluation	Cost-minimisation analysis undertaken is not adequate: 1. Intervention have a considerably different safety profile) 2. Cost of AEs NOT included in the CMA provided. Note that the Pre-ESC response reports an abbreviated CUA, it is really a costing analysis
TARE-Y versus BSC Health economic evaluation	Major limitations in the model – makes the ICER unreliable (highly) The model structure is inadequate to capture disease states. Use of Kwok 2014 – inappropriate as control group not BSC Extrapolation issues as detailed in ESC slides and discussion)
Estimation of financial implications	Does not include the associated interventions described in Section A6, and potentially underestimates the total costs of TARE-Y to the MBS.

ESC Discussion

ESC noted that the submission is a new application to support the listing of transarterial radioembolisation using yttrium-90 (TARE-Y) for the treatment of unresectable hepatocellular carcinoma (HCC). The application was for two populations:

- population 1: people with advanced HCC (stage Barcelona Liver Clinic-C [BCLC-C]). The comparator for this group is sorafenib or best supportive care (BSC); and
- population 2: people with intermediate HCC (stage BCLC-B) who are contraindicated to, intolerant of, or who have failed first line treatment with transarterial chemoembolisation (TACE). The comparator for this group is repeat TACE or BSC.

TARE-Y involves the delivery of microspheres containing yttrium-90 to the liver via the hepatic artery. Yttrium-90 emits high energy beta radiation which causes tumour necrosis. Almost all the blood supply to liver tumours is through the hepatic artery and thus the microspheres deliver the radiation dose to cancer cells with minimal irradiation of normal liver tissue.

ESC noted that there are two commercially available types of yttrium-90 microspheres, glass microspheres (TheraSphere) and resin microspheres (SIR-spheres). ESC noted that the ratified PICO is for both types of yttrium-90 microspheres. ESC noted that TARE-Y using SIR-Spheres has had interim funding for unresectable liver metastases from colorectal cancer since 2006 and that this interim funding was supported on the basis of a single small randomised controlled trial. ESC considered that the evidence base has changed significantly since this decision.

ESC noted that three comparisons were conducted in the submission: TARE-Y compared with sorafenib; TARE-Y compared with best supportive care; and glass microspheres compared with resin microspheres.

ESC noted that despite TACE being listed as a comparator for population 2 in the ratified PICO, TACE had been removed as a comparator in the submission, and only included as an Appendix. ESC queried the justification for changing the PICO as a survey of 30 clinicians (Attachment 1 of SBA) conducted for the submission indicated that repeat TACE is used in practice. ESC queried the applicant's claim that repeat TACE treatment after treatment failure or intolerance was not appropriate (Facciorusso A et al 2015) and queried the applicants' claim that repeat TACE most likely occurs due to lack of other available active treatments.

ESC noted that some evidence of effectiveness (overall survival, progression free survival, time to progression, tumour response, quality of life) and safety (adverse events) between TARE-Y and TACE was provided in Appendix G of the submission but considered this to be inadequate. ESC noted that there was no comparative safety data or economic evaluation of TARE-Y and TACE. ESC considered that this information should be provided.

ESC noted that there was one randomised control trial, the SARAH trial (Vilgrain VH et al 2017), and five observational studies comparing TARE-Y with sorafenib (Cho YY et al 2016; De La Torre MA et al 2016; Edeline JL et al 2016; Gramenzi AR et al 2015). ESC considered that all observational studies used to compare TARE-Y with sorafenib were small and at a high risk of bias.

ESC noted that the studies used to compare TARE-Y with BSC, and glass microspheres with resin microspheres, were also small observational studies at a high risk of bias or with inadequate control of confounders.

Furthermore, ESC considered that there were issues with drawing conclusions from the studies because:

- there were difficulties with accurately identifying the specific intervention that the patients in the control arms received;
- most of the studies included a mix of BCLC-B and BCLC-C stage patients in the same study; and
- of treatment migration where some patients may not be given the treatment protocol specific to their cancer stage (BCLC-B or BCLC-C) but instead receive a mix of treatments that would otherwise be allocated for another cancer stage (e.g. a patient with BCLC-B receives sorafenib after failed TACE even though sorafenib is generally reserved for patients with BCLC-C).

ESC noted that the SARAH trial showed TARE-Y had a better safety profile when compared with sorafenib as it had less, albeit different, adverse effects and better quality of life. ESC considered that this is because TARE-Y adverse effects are localised to the tumour and mainly a single treatment whereas sorafenib is an oral medicine, which is given as an ongoing treatment with systemic effects.

ESC considered the sponsor's claim of non-inferiority for TARE-Y compared with sorafenib, based on the SARAH trial, was inappropriate. While ESC noted the SARAH trial had showed no difference in overall survival or progression-free survival for TARE-Y compared with sorafenib, it noted that the trial had been designed as a superiority trial and was underpowered to demonstrate non-inferiority.

ESC considered the claim that TARE-Y had superior effectiveness and inferior safety when compared with BSC to be highly uncertain as it was based upon small, retrospective studies at a high risk of bias (D'avola DM et al 2009; Kwok PC et al 2014) and a systematic review of single armed studies (Braat MN et al 2017). ESC noted that TARE-Y was associated with an increased risk in radioembolisation induced liver disease (REILD) when compared with BSC (Braat MN et al 2017).

ESC considered the cost minimisation analysis undertaken comparing TARE-Y and sorafenib to be inappropriate as the MSAC guidelines recommend a cost utility analysis when the intervention is non-inferior in efficacy and superior in safety. ESC also noted that the adverse effects profiles of sorafenib and TARE-Y had considerable differences and noted that PBAC guidelines state that in this situation 'it is unlikely that a cost minimisation analysis will suffice'. ESC acknowledged that the sponsor provided further information on the cost of adverse effects in their pre-ESC response and provided an 'abbreviated cost utility analysis',

However, ESC considered this information to be closer to a cost analysis than a cost utility analysis.

ESC queried whether TARE-Y delays, rather than replaces, the use of sorafenib as there is significant migration of patients between treatment groups since their health state would guide the treatment they receive. ESC also noted that trials of TARE-Y in conjunction with sorafenib create additional uncertainty in the economic evaluation.

ESC considered that there were major limitations in the modelling used to establish the cost-effectiveness of TARE-Y compared with BSC and considered that the incremental cost-effectiveness ratio (ICER) presented to be highly unreliable. ESC noted that the model:

- relied upon the Kwok study in which it was unclear if the treatment received by the control group really was BSC;
- oversimplified the treatment algorithm;
- only used two health states of alive or dead, and did not including progression states, which was overly simplistic;
- used a zero cost for BSC which ESC considered to be unrealistic as it does not account for the costs of hospitalisation, medical staff, pathology tests and radiological tests;
- further increased uncertainty by extrapolating 5 year data from the Kwok study to 10 years; and
- only included REILD adverse events in the model despite other serious adverse events being reported in the SARAH trial.

ESC noted the model structure provided in a cost effectiveness analysis by Rognoni et al may be a more suitable model for comparing TARE-Y with BSC as it takes into account multiple health states (Rognoni CO et al 2017). ESC recommended this model to be adapted to the Australian setting using appropriate costs and utilities.

ESC considered the estimates of financial and budgetary impacts to be highly uncertain. ESC queried the use of UK cancer registry data which may not accurately reflect the Australian population. Furthermore, ESC considered that the costs of associated interventions have not been completely accounted for which could potentially underestimate the total cost of TARE-Y to the MBS. ESC also considered any potential cost savings to the PBS resulting from a reduction in sorafenib use if TARE-Y is available on the MBS to be uncertain.

ESC noted that there is no limit on the number of times the comparative MBS item for the treatment of colorectal cancer with yttrium-90 microspheres can be claimed (MBS items 35404, 35406, 35408). ESC noted that the evidence on the safety of repeat TARE-Y was limited and suggested a limit on TARE-Y claims for HCC to prevent the risk of unacceptable liver damage from repeat treatments of TARE-Y, particularly as patients with HCC frequently have pre-existing liver damage from cirrhosis (unlike patients with metastatic colorectal cancer).

ESC noted that there are ongoing randomised trials of TARE-Y against sorafenib, some which were published/presented following the SBA, and that these studies have the potential to provide more data for decision makers.

ESC noted that the application was for both types of microspheres (glass and resin) and considered that there was no reason to treat them differently.

ESC queried whether the proposed item descriptor should restrict TARE-Y from being used concurrently with sorafenib, as there are trials assessing efficacy of safety of this combination.

ESC queried whether the proposed procedure should be classified as day surgery given patients often leave the hospital on the same day they have the procedure. ESC noted that the comparable procedure for liver metastases from colorectal cancer is classified as an overnight stay (type A). ESC queried if Australian guidelines from organisations such as the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) may provide direction on whether patients need to stay overnight for observation.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)