Australian Government

Medical Services Advisory Committee

Public Summary Document

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

Applicant: **BTG International Asia Ltd**

Date of MSAC consideration: **MSAC 75th Meeting, 28-29 March 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A submission based application (SBA, comprising a revised economic evaluation) for Medicare Benefit Schedule (MBS) listing for transarterial radioembolisation with yttrium-90 (TARE-Y) for the treatment of advanced hepatocellular carcinoma (HCC) was received from BTG International Asia by the Department of Health.

This SBA was made in response to the MSAC deferral of the same MBS listing request in July 2018.

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 supported MBS listing of transarterial radioembolisation with yttrium-90 (TARE-Y) for the treatment of unresectable advanced hepatocellular carcinoma. MSAC advised that the cost per patient of TARE-Y should be no greater than that of sorafenib after incorporating cost off-sets due to accepted reduced rates of adverse events.

Before implementation, MSAC requested that, based on this advice, further information on the calculated price for TARE-Y in the treatment of unresectable advanced hepatocellular carcinoma be provided to the MSAC Executive for review.

MSAC accepted there was a clinical need in this small population with poor treatment options. MSAC considered that TARE-Y offered patients a better quality of life and safety advantages compared with sorafenib.

MSAC advised that the MBS listing should be confined to inpatient use of the service and that the 85% rebate applicable to non-inpatient use not be available. The MSAC noted the current listing of yttrium-90 on the Prostheses List will need to be amended to allow funding through private health insurance for use in conjunction with the new MBS listing.

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

At its July 2018 meeting, MSAC deferred its advice to request a revised economic evaluation. At that time, MSAC considered there were two potential options for progressing this matter. The applicant chose option 1, which was:

- A comparison against sorafenib only (for advanced hepatocellular carcinoma (HCC); i.e. Barcelona Clinic Liver Cancer (BCLC) stage C), based on clinical non-inferiority 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 (AE) profiles.

This application again requests listing of transarterial radioembolisation using yttrium-90 (TARE-Y) for the treatment of advanced HCC. TARE-Y involves the delivery of yttrium-90-containing microspheres (Y-90 microspheres) to liver tumours via a catheter inserted in the hepatic artery. MSAC noted the high clinical need for this group of patients.

Overall, MSAC was satisfied that the available evidence supports conclusions that TARE-Y and sorafenib have no significant differences in efficacy, and that TARE-Y has superior safety compared with sorafenib.

The MSAC noted that the submission to the March 2019 MSAC meeting presented an economic evaluation based on the assumption of the non-inferiority of TARE-Y over sorafenib for overall survival in patients with advanced HCC with cost-offsets for the different rates of adverse events (AE).

The type of analysis was a cost-minimisation analysis (CMA) using multiple data sources for costing inputs, as follows:

- The equi-effective doses were assumed to be **redacted** TARE-Y doses versus sorafenib **redacted**;
- AE rates from SARAH per protocol population were used in the base-case analysis and AE rates from the SARAH safety population and the SIRveNIB trial were used in a sensitivity analyses;
- Hospital and Australian Refined-Diagnosis related Groups' (AR-DRG) costs that were not up to date.

The MSAC did not accept the submission's approach to the CMA and requested the Department undertake further work to establish the most appropriate basis for a CMA analysis.

The MSAC's specific concerns were that:

- The use of the per protocol population from the SARAH trial had the potential to incorrectly estimate the costs of adverse events;
- The equi-effective doses were not derived from the trials used to support the clinical claim;
- Many of the cost inputs into the CMA were not current.

The MSAC noted the cost of managing adverse events was based on the SARAH trial. The base case for the CMA included AEs from the per-protocol population, and only grade ≥3 AEs were considered. The MSAC noted the Critique queried this approach, because all AEs would affect resource use and costs. MSAC noted the Critique's view that the per-protocol analysis can substantially bias the results in either direction. The MSAC considered the safety population to be most appropriate for informing cost offsets from AE data as this

population had fewer randomised patients excluded from analysis compared with the per-protocol population (4% vs. 17%, respectively).

The MSAC noted that the applicant had sourced the equi-effective dose for TARE-Y (**redacted** treatments) from an observational study (**redacted**) in population with advanced HCC with portal vein thrombosis (100% stage C); and for sorafenib from a trial arm of an RCT (**redacted**) in patients with advanced HCC (83% stage C). The sorafenib treatment duration was assumed to be **redacted**.

The MSAC considered that a **redacted** TARE-Y treatments based on the SARAH trial is likely realistic of what will occur in clinical practice.

The MSAC further noted that the median duration of sorafenib treatment was 2.8 months in SARAH with a dose intensity of 800 mg/day, compared with ~3.2 months and 644.5 mg/day in the SIRveNIB trial.

However, the MSAC accepted, as argued in the pre-Applicant response, the median estimates of dose and duration for sorafenib might underestimate the average duration of treatment with sorafenib. Due to the poor tolerability of sorafenib, a large proportion of patients will cease treatment in the first month, whilst others remain on treatment for a longer duration (i.e. right skewed distribution). MSAC acknowledged the limitation of using the median duration of treatment of sorafenib from SARAH (rather than the truncated mean) to inform the CMA, and agreed that an estimate of the cost of treatment of sorafenib will be better captured by using the mean dose and duration of treatment.

As noted above, the MSAC requested the revised economic analyses be presented to the MSAC Executive.

The MSAC advised that this is an inpatient procedure, a revision of its earlier advice 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.

4. Background

MSAC has previously considered TARE-Y for the treatment of unresectable HCC (ie advanced and intermediate HCC) in 2018 (App 1493) and deferred its advice to request a revised economic evaluation.

Refer to Public Summary Document (PSD), Application No.1493 2018 for further information.

Previously, MSAC had 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

Refer to PSD, Application No.1493 2018.

6. Proposal for public funding

Refer to PSD, Application No.1493 2018.

However, the Critique stated the SBA should have included an updated item descriptor which specified the patient population to be advanced HCC (rather than advanced and intermediate HCC from previous application); and included the proposals made by MSAC which requested that TARE-Y should be delivered by a specialist interventional radiologist [PSD, Application No. 1493, p2]. The Critique's item descriptor is presented in Table 1.

Table 1 Proposed MBS item descriptors

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

The Critique also highlighted the advice from ESC that recommended the proposed item descriptor should restrict TARE-Y from being administered concurrent with sorafenib, as trials assessing efficacy and safety of this combination are currently underway.

7. Summary of Public Consultation Feedback/Consumer Issues

Refer to PSD, Application No.1493 2018.

8. Proposed intervention's place in clinical management

Refer to PSD, Application No.1493 2018, noting that this application relates only to the population with advanced HCC treated with TARE-Y or sorafenib (highlighted in red below in Figure 1).

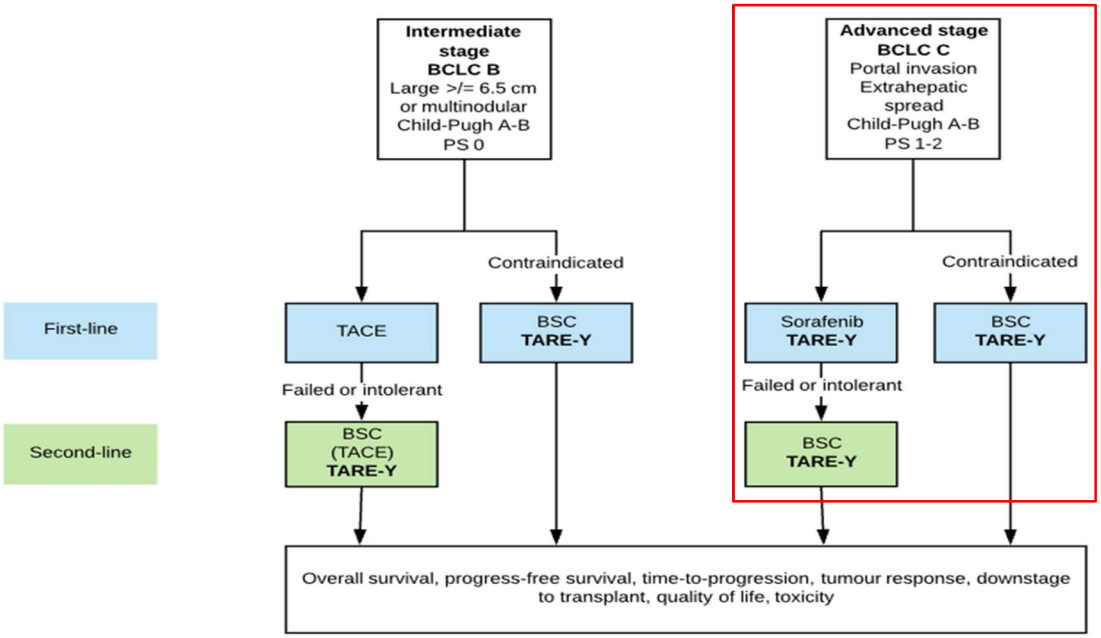

Figure 1 Clinical management algorithm for including TARE-Y relative to current clinical practice

Source: PSD, Application No.1493 2018
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

Refer to PSD, Application No.1493 2018, noting that the recommended active treatment for advanced HCC is sorafenib.

10. Comparative safety

Refer to PSD, Application No.1493 2018.

In addition to the previously seen adverse event (AE) profile from SARAH trial, the SBA included a summary of adverse events from the SIRveNIB trial (Chow et al. 2018). Similar to SARAH, this was a randomised controlled trial with an open label design (safety population n=292).

The SBA stated that a total of 1,468 treatment-emergent adverse events occurred: 437 in patients treated with TARE-Y and 1,031 in patients treated with sorafenib. This equated to:

- 60% of patients treated with TARE-Y and 85% of patients treated with sorafenib experiencing at least one adverse event of any severity;
- 28% of patients treated with TARE-Y and 51% of patients treated with sorafenib experiencing at least one grade ≥ 3 adverse event; and
- 21% of patients treated with TARE-Y and 35% of patients treated with sorafenib experience at least one serious adverse event.

The Critique stated that neither trial disaggregated the AEs by disease stage, therefore they may not be truly representative of the AEs occurring in patients with advanced HCC Barcelona Clinic Liver Cancer (BCLS) stage C (stage C patients made up 68% of the total sample size in the SARAH trial and 47% in the SIRveNIB trial).

11. Comparative effectiveness

Refer to PSD, Application No.1493 2018.

In addition, the SBA also presented overall survival results from the previously seen SARAH trial and a new trial: the Selective Internal Radiation Therapy Versus Sorafenib (SIRveNIB) trial (Table 2).

Table 2 Overall survival results of the SARAH and SIRveNIB RCTs

Outcome	Study	ITT analysis			PP/treated analysis		
		N	TARE-Y vs. SOF Median or %	TARE-Y vs. SOF Risk estimate (95% CI)	N	TARE-Y vs. SOF Median or %	TARE-Y vs. SOF Risk estimate (95% CI)
All patients	SARAH SIRveNIB	459 360	8.0 m vs. 9.9 m 8.8 m vs. 10.0 m	HR 1.15 (0.94, 1.41) HR 1.12 (0.9, 1.4)	380 292	9.9 m vs. 9.9 m 11.3 m vs. 10.4 m	HR 0.99 (0.79, 1.24) HR 0.86 (0.7, 1.1)
BCLC A+B	SARAH	148	NR	HR 1.00 (0.69, 1.44)	123	NR	HR 0.89 (0.59, 1.33)
BCLC B	SIRveNIB	190	11.8 vs. 14.4	HR 1.14 (0.8, 1.6)	167	13.5 vs. 14.8	HR 1.01 (0.7, 1.5)
BCLC C	SARAH SIRveNIB	311 168	NR 6.8 m vs. 5.8 m	HR 1.22 (0.95, 1.56) HR 1.00 (0.7, 1.4)	257 123	NR 9.2 m vs. 5.8 m	HR 1.06 (0.81, 1.39) **HR 0.67 (0.4, 1.0)**

Source: SBA for TARE-Y for SARAH trial and Chow 2018 (Figure 2, Figure 3, Table 3) and Supplementary Appendix (Figure A1, Figure A2, Table A7) for SIRveNIB. (Table 9, p20 of the Critique)
Abbreviations: BCLC=Barcelona Clinic Liver Cancer; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; m=months; NR=not reported; PP=per protocol; SOF = sorafenib; TARE-Y= transarterial radioembolisation using yttrium-90.
Note: Results shown in black bold are statistically significantly in favour of TARE-Y over sorafenib; no findings are statistically significantly in favour of sorafenib over TARE-Y.

SARAH and SIRveNIB trials were open label randomised controlled trials (RCT)s included as the pivotal evidence for the submission's revised economic evaluation. The main characteristics of the SARAH and SIRveNIB studies are summarised in Table 3, noting that the SARAH trial had a closer match to the proposed MBS population with advanced HCC (Barcelona Clinic Liver Cancer (BCLC) stage C patients: 68% in SARAH trial *vs*. 47% in SIRveNIB trial).

Table 3 Key characteristics of the submission's pivotal RCT evidence: SARAH and SIRveNIB trials

Parameter	SARAH trial	SIRveNIB trial
Location	France	Asia-Pacific
Efficacy population	ITT (N=459) Patients randomised to treatment who did not withdraw consent[a] PP (N=380) Patients who received treatment with no major protocol deviations[b]	ITT (N=360) All randomised patients Treated (N=292) All patients who received treatment[c]
Safety population	Patients who underwent workup (TARE-Y) or received sorafenib[d] (N=442)	All patients who received treatment[c] (N=292)
Exclusion criteria Serum bilorubin	32 mmol/L	≤50 mmol/L
Age, years, mean (SD)	TARE-Y arm: 66 (60-72)[a]	TARE-Y arm: 60 (12.9)
Advanced HCC (BCLC stage C)	68%	47%
Aetiology Alcohol Hep B Hep C Steatohepatitis	 59% 6% 23% 9%	 NR 55% 13% NR
ECOG 0 1	 63% 38%	 77% 23%
Previous treatment TACE	 44%	 NR

Source: Table 8, pp17-18 of the Critique

Abbreviations: BCLC=Barcelona Clinic Liver Cancer; HCC=hepatocellular carcinoma; ITT=intention-to-treat; NR=not reported; PP=per-protocol; RCT=randomised controlled trial; SD = standard deviation; SIRveNIB = Selective Internal Radiation Therapy Versus Sorafenib; TACE= transarterial chemoembolisation; TARE-Y= transarterial radioembolisation using yttrium-90.

[a] Eight randomised patients excluded from intention-to-treat population (2 in TARE-Y group; 6 in sorafenib group).

[b] 79 randomised patients excluded from per-protocol population (63 in TARE-Y group; 16 in sorafenib group).

[c] 68 randomised patients excluded from treated population (52 in TARE-Y group; 16 in sorafenib group).

[d] 17 randomised patients excluded from safety population (11 in TARE-Y group; 6 in sorafenib group).

One major difference in the conduct of the two trials was the number of treatments of TARE-Y allowed. In the SARAH trial, patients could have more than one treatment with TARE-Y (63% of patients received one TARE-Y treatment, 31% received two treatments and 6% received three treatments) compared with in the SIRveNIB trial where patients were allowed only one treatment with TARE-Y.

Intention-to-treat (ITT) analyses and per protocol/treated analysis for overall survival were presented for both trials (Table 2). However, the submission argued that using the ITT analysis to determine the non-inferiority of TARE-Y over sorafenib is problematic due to the large proportion of patients randomised to TARE-Y who subsequently did not receive treatment, largely due to the results of a pre-treatment lung shunting study. For the ITT analyses in both the SARAH and SIRveNIB studies, there was no significant difference in overall survival. However, in the subgroup population with advanced HCC, there was a statistically significant overall survival benefit for TARE-Y over sorafenib for in SIRveNIB trial (hazard ratio (HR) 0.67; 95% CI 0.4, 1.0; P=0.0475). The submission stated this supports a finding of non-inferiority of TARE-Y over sorafenib.

However, the Critique noted that the per-protocol analysis can be subject to significant bias (in either direction). The Critique noted that TARE-Y achieved a marginally statistically significant result in the per-protocol analysis that was not confirmed in the ITT analysis, and in one subgroup only. The sample size of this subgroup was small (n=123) and the analysis was not adjusted for the multiplicity correction. The authors of the SIRveNIB study (Chow et al. 2018) themselves advise that this finding should be considered exploratory, requiring further confirmation in a sufficiently powered study [Critique 1493 p20].

Clinical Claim

This was unchanged; refer to PSD, Application No.1493 2018.

12. Economic evaluation

The SBAs revised economic evaluation was a cost-minimisation analysis comparing TARE-Y and sorafenib in patients with advanced HCC (Table 4; as presented by the Critique).

Table 4 Summary of the economic evaluation: CMA

	Previous SBA (Application 1493)	**Revised economic evaluation**
Perspective	Health system	Health system
Population	Intermediate and advanced HCC (BCLC stage B and C)	Advanced HCC (BCLC stage C)
Comparator	Sorafenib	Sorafenib
Type of economic evaluation	Cost-minimisation	Cost-minimisation
Sources of evidence	Equi-effective dose: TARE-Y: **redacted** Sorafenib: **redacted** Adverse events: none	Equi-effective dose: TARE-Y: not provided Sorafenib: not provided Adverse events: SARAH subgroup (per-protocol population, n=380) SIRveNIB subgroup (as-treated population, n=292)
Outcomes	Incremental cost	Incremental cost
Methods used to generate results	Cost comparison	Cost comparison
Discount rate	Not applied	Not applied
Software packages used	Microsof Excel	Microsoft Excel

Source: Compiled during evaluation

Abbreviations: BCLC=Barcelona Clinic Liver Cancer; CMA=cost-minimisation analysis; HCC=hepatocellular carcinoma; SBA=submission-based assessment; TARE-Y=transarterial radioembolisation using yttrium-90

The results from the SBAs revised economic evaluation are presented in Table 5.

Table 5 SBAs revised economic analysis (CMA)

Analysis	Efficacy	Safety	Quality of life	Cost of treatment	Cost of AEs	Interpretation
Original in SBA	Non-inferior	Superior	Superior	Lower	Not included ($0.00)	TARE- Y dominant
Requested revised economic evaluation – SARAH study						
+ AE costing (base case)[1]	Non-inferior	Superior	Superior	Lower	Lower (-$1,664.51)	TARE- Y remains dominant
+ AE costing (base case) + AE costing (sensitivity analysis a)[2]	Non-inferior	Superior	Superior	Lower	Lower (-$1,370.65)	TARE- Y remains dominant
+ AE costing (base case) + AE costing (sensitivity analysis a) + REILD	Non-inferior	Superior	Superior	Lower	Lower (-$1,127.95)	TARE- Y remains dominant
+ AE costing (sensitivity analysis b)[3]	Non-inferior	Superior	Superior	Lower	Lower (-$312.57)	TARE- Y remains dominant
+ AE costing (sensitivity analysis b) + REILD	Non-inferior	Superior	Superior	Lower	Lower (-$69.87)	TARE- Y remains dominant
Additional economic evaluation – SIRveNIB study						
+ AE costing (base case)[4]	Non-inferior	Superior	Similar	Lower	Lower (-$418.60)	TARE- Y remains dominant
+ AE costing (base case) + AE costing (sensitivity analysis)[4]	Non-inferior	Superior	Similar	Lower	Lower (-$1,370.65)	TARE- Y remains dominant
+ AE costing (base case) + AE costing (sensitivity analysis) + REILD	Non-inferior	Superior	Similar	Lower	Lower (-$191.78)	TARE-Y remains dominant

Abbreviations: AE, adverse event; REILD, radioembolisation-induced liver disease; SBA, submission-based assessment; TARE-Y, transarterial radioembolisation using yttrium-90.

[1] Any ≥ grade 3 adverse events in the *per-protocol* population that show a statistically significant difference between TARE-Y and sorafenib

[2] Non-significant treatment-related TARE-Y grade ≥ 3 adverse events of interest (gastrointestinal bleeding and liver dysfunction) in the *per-protocol population*.

[3] Any ≥ grade 3 adverse events, according to MedDRA coding that occurred in at least 10% of patients in the *safety* population, that showed a significant difference between TARE-Y and sorafenib.

[4] Any ≥ grade 3 adverse events in the *treated* population that show a statistically significant difference between TARE-Y and sorafenib

[5] Non-significant TARE-Y-associated adverse events (as defined by the study authors) from the *treated* population.

The SBA also presented two sensitivity analyses, which looked at:

1. non-significant treatment-related TARE-Y grade ≥3 AEs of interest (gastrointestinal [GI] bleeding and liver dysfunction) from the per-protocol population and inclusion of radioembolisation-induced liver disease (REILD)
2. any grade ≥3 AEs, according to MedDRA coding that occurred in at least 10% of patients in the safety population of the SARAH trial, considering only statistically significant events, and inclusion of REILD cost.

The Critique queried the applicant's reasoning behind the addition of GI bleeding and liver dysfunction AEs to the first sensitivity analysis; considering that including both trial-reported AEs and REILD in the sensitivity analyses is likely causing some AEs to be double-counted. Also, at least part of the liver dysfunction or GI bleeding cases could have been due to

REILD. In the second sensitivity analysis, the applicant intended to only use AEs occurring in at least 10% of patients in the safety population, but since it only included grade ≥3 AEs, this is not actually what is represented in the calculations. In addition, the Critique noted the base-case analysis and first sensitivity analysis relate to the treatment-related AEs, while the second sensitivity analysis uses data on all-cause AEs, both treatment-related and not.

The applicant conducted an additional economic analysis based on the SIRveNIB trial, but the Critique identified similar issues with this analysis as for the one based on the SARAH trial.

13. Financial/budgetary impacts

Refer to PSD, Application No.1493 2018.

14. Key issues from ESC for MSAC

Refer to PSD, Application No.1493 2018.

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