



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1525 - Low dose-rate (LDR) brachytherapy for intermediate and high-risk prostate cancer

Applicant: BXTAccelyon Australia Pty Ltd

Date of MSAC consideration: MSAC 76th Meeting, 1-2 August 2019

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 Benefits Schedule (MBS) listing of LDR Brachytherapy (LDR-BT) for intermediate and high-risk prostate cancer was received from MedTechnique on behalf of BXTAccelyon Australia Pty Ltd 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 did not support public funding for LDR-BT boost (following primary external beam radiotherapy [EBRT]) for intermediate and high-risk prostate cancer. MSAC considered that the limited comparative safety and effectiveness evidence was too uncertain relative to dose escalated (DE-EBRT), and no evidence was presented relative to treatment with high dose-rate brachytherapy (HDR-BT) boost following EBRT or radical prostatectomy (RP).

Consumer summary

BXTAccelyon Australia applied for public funding for low dose-rate brachytherapy (LDR-BT) in the treatment of prostate cancer.

In LDR-BT, small radioactive “seeds” are placed into the prostate gland and stay there permanently to deliver radiation close to the tumour. This is done to boost the radiation dose after a patient has already had radiation directed at the tumour from outside the body (called external beam radiotherapy, or EBRT). Other options for patients who have already had EBRT are more doses of EBRT (called dose-escalated EBRT) or temporary radiation given through a small tube into the prostate (called high dose-rate brachytherapy, or HDR-BT).

LDR-BT is already listed on the MBS for use in patients who have low-risk prostate cancer. This application is requesting MBS listing for LDR-BT to be used as a radiation boost after EBRT in patients with intermediate- to high-risk prostate cancer.

Consumer summary

MSAC's recommendation to the Commonwealth Health Minister

MSAC did not support public funding of LDR-BT for this use because there is not enough evidence to be certain of its safety and effectiveness compared with other treatment options.

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

Application 1525 proposes that LDR-BT would be used as a radiation boost after primary EBRT, as an alternative to RP, DE-EBRT or HDR-BT boost following EBRT. MSAC noted that LDR-BT for use in low-intermediate/low-risk prostate cancer has been listed on the MBS since 2001 (MBS items 37220 and 15338). MSAC also noted that international clinical guidelines recommend LDR-BT in combination with EBRT as a treatment option for intermediate- and high-risk prostate cancer.

MSAC noted two new MBS items were proposed for the urological component of the procedure and the radiation oncology component. MSAC confirmed that the item descriptor should specify that LDR-BT is intended for use as a boost following EBRT and in association with androgen blockade.

MSAC confirmed that the comparators – RP, DE-EBRT and HDR-BT boost following EBRT – were appropriate. MSAC noted that these comparators are currently funded under the MBS and match those in the ratified PICO. MSAC noted consultation feedback suggesting that comparators should also include intensity modulated radiation therapy.

MSAC noted that very limited evidence was presented on the comparative safety and clinical effectiveness of LDR-BT. In the ASCENDE-RT trial, adverse effects (acute genitourinary (GU) toxicity, and late gastrointestinal (GI) and GU morbidity) were more frequent in the EBRT+LDR-BT boost arm than the DE-EBRT arm, and health-related quality of life scores were lower. No statistically significant differences were reported for serious adverse events (AEs) or the frequency of erectile dysfunction. Given that this application is for radiation therapy and the importance of certainty regarding radiation safety, MSAC concluded that EBRT plus LDR-BT has inferior safety relative to DE-EBRT.

However, no safety data were provided comparing EBRT+LDR-BT boost with RP or EBRT+HDR-BT boost. MSAC therefore concluded that EBRT+LDR-BT boost has uncertain safety relative to RP and EBRT+HDR-BT boost.

MSAC noted that it is possible that the AEs observed in the trial may be avoidable with improvements in planning and modern imaging techniques that have occurred since the trial was conducted. However, without evidence, this remains uncertain.

MSAC noted that evidence for clinical effectiveness was from the ASCENDE-RT trial and a retrospective cohort study. The ASCENDE-RT trial suggested superior effectiveness of EBRT+LDR-BT boost versus DE-EBRT for biochemical progression-free survival. However, there was no difference in overall survival, metastasis-free survival or prostate cancer-specific survival, and the study was not powered or long enough to assess survival outcomes. The retrospective cohort study suggested better overall survival for EBRT+LDR-BT boost than for DE-EBRT. However, this study was at a high risk of bias and, potentially, low applicability. MSAC therefore concluded that EBRT+LDR-BT boost has superior effectiveness for biochemical progression-free survival, but uncertain effectiveness for

overall survival, metastasis-free survival or prostate cancer-specific survival, relative to DE-EBRT.

No data were provided comparing effectiveness of EBRT+LDR-BT boost with either RP or EBRT+HDR-BT boost. MSAC therefore concluded that EBRT+LDR-BT boost has uncertain effectiveness relative to EBRT+HDR-BT boost and RP.

MSAC noted that the economic model was modified to address concerns raised by ESC. MSAC accepted that the revised model is likely to be appropriate and now shows that use of LDR-BT as a boost following EBRT appears to be cost-effective based on the revised inputs used. MSAC noted that cost-effectiveness is sustained or increased over a 20–30-year time horizon based on life year and quality-adjusted life year (QALY) outcomes.

MSAC noted that the amended financial model estimates a cost to the MBS of approximately \$400,000 in Year 5.

MSAC advised that any future resubmission should include:

- comparative safety data based on up-to date practice, ideally for all three comparators;
- effectiveness data for the other two comparators (RP and EBRT+HDR-BT boost); and
- cost-effectiveness analyses should be updated to reflect any newly relevant comparative safety and effectiveness data.

MSAC suggested that the Medical Research Future Fund may be a suitable vehicle for providing more evidence.

MSAC considered that States, Territories and others paying for the seeds should be made aware of the lack of evidence for comparative safety and effectiveness of LDR-BT boost (following EBRT) for patients with intermediate and high-risk prostate cancer.

4. Background

This is the first submission for LDR Brachytherapy for intermediate and high-risk prostate cancer. MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

The intervention does not require a new device, a number of brachytherapy-related items are already listed on the ARTG (Australian Register of Therapeutic Goods).

6. Proposal for public funding

The applicant proposed two new MBS items to cover the urological component and radiation oncology component of LDR-BT for use as a boost to EBRT in patients with high-intermediate and high-risk prostate cancer. The proposed MBS item descriptors are summarised in Table 1.

Table 1 Applicant proposed MBS item descriptor

Category 3 – Therapeutic procedures
PROSTATE, radioactive seed implantation (radiation oncology component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as high-intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and a Gleason score of 7 and a tumour classified as T2b-c) or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 and/or a tumour classified as T3). It is recommended the procedure only be performed as 'boost' treatment, in addition to external beam radiotherapy, at an approved site in association with a urologist. Fee: \$935.60
PROSTATE, radioactive seed implantation (urological component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as high-intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and a Gleason score of 7 and a tumour classified as T2b-c) or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 and/or a tumour classified as T3). It is recommended the procedure only be performed as 'boost' treatment, in addition to external beam radiotherapy, at an approved site in association with a radiation oncologist. Fee: \$1,044.20

Source: Table 1, pp20-21 of the CA

The Department proposed the following item descriptors in Table 2.

Table 2 Department proposed MBS item descriptor

Category 3 – Therapeutic Procedures
PROSTATE, radioactive seed implantation (radiation oncology component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as high-intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and a Gleason score of 7 and a tumour classified as T2b-c) or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 and/or a tumour classified as T3). For the population above this procedure will be rebated if it is performed at an approved site as a boost treatment in addition to external beam radiotherapy and in association with androgen blockade, in association with an urologist. MBS Fee: \$935.60 MBS Benefit (Rebate): 75% = \$701.70 (in-hospital / admitted patient) AND 85% = \$853.90 (out-of-hospital / outpatient) = higher than 85% because of the provision of higher rebates for outpatient services when MBS fee is higher
Category 3 – Therapeutic Procedures
PROSTATE, radioactive seed implantation (urological component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as high-intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and a Gleason score of 7 and a tumour classified as T2b-c) or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 and/or a tumour classified as T3). For the population above this procedure will be rebated if it is performed at an approved site as a boost treatment in addition to external beam radiotherapy and in association with androgen blockade, in association with a radiation oncologist MBS Fee: \$1,044.20 MBS Benefit (Rebate): 75% = \$783.15 (in-hospital / admitted patient only)

7. Summary of Public Consultation Feedback/Consumer Issues

Targeted consultation feedback was received from three organisations which supported the listing of LDR-BT boost on the MBS, citing superior biochemical progression-free survival (b-PFS) and freedom from failure of LDR-BT boost compared to DE-EBRT treatment in the ASCENDE-RT trial (Morris, Tyldesley et al. 2017).

8. Proposed intervention's place in clinical management

The current and proposed algorithms are depicted in Figure 1 and Figure 2. The difference between the current clinical management algorithm and the proposed clinical management algorithm for high-intermediate and high-risk prostate cancer is that there would be an option for patients to receive LDR-BT boost following primary EBRT treatment.

LDR-BT can be provided in both the public and private hospital sector, performed at an approved site where radiation oncology services may be performed lawfully under the law of the State or Territory in which the site is located. The applicant advised, at present, LDR-BT is only available in a limited number (25) of centres in Australia. The proposed clinical algorithm is identical to that in the ratified PICO.

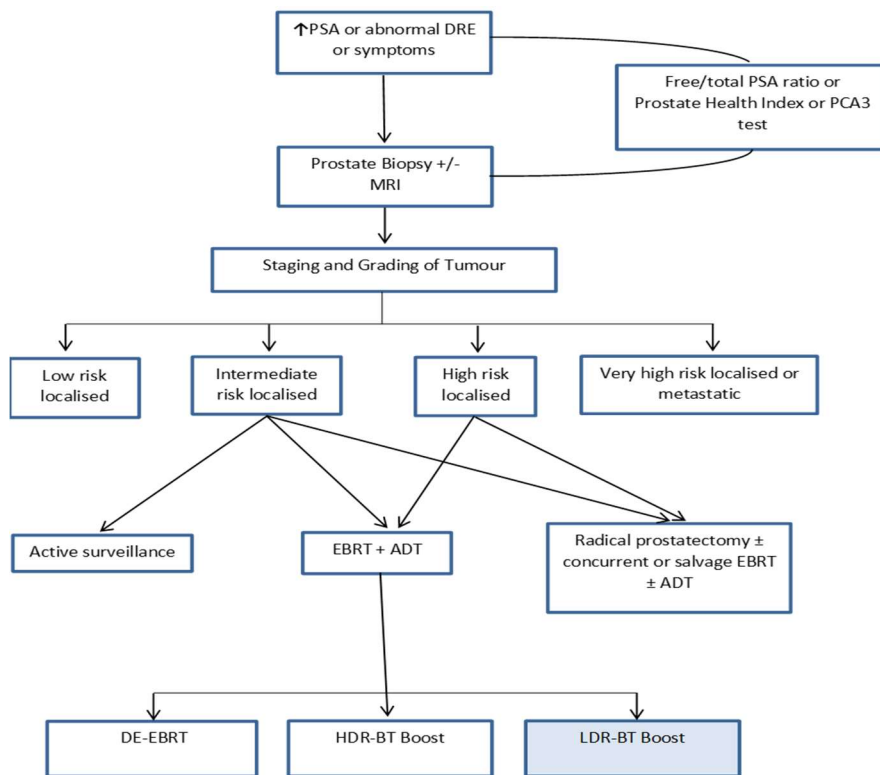


Figure 1 Current and proposed (shaded) clinical treatment algorithm for patients with intermediate and high-risk prostate cancer – part 1 (continued in Figure 2)

Abbreviations: ADT=androgen deprivation therapy; DRE=digital rectal examination; EBRT=external beam radiation therapy; DE-EBRT=dose-escalated external beam radiation therapy; HDR-BT=high-dose rate brachytherapy; LDR-BT=low-dose rate brachytherapy; MRI=magnetic resonance imaging; PSA=Prostate Specific Antigen

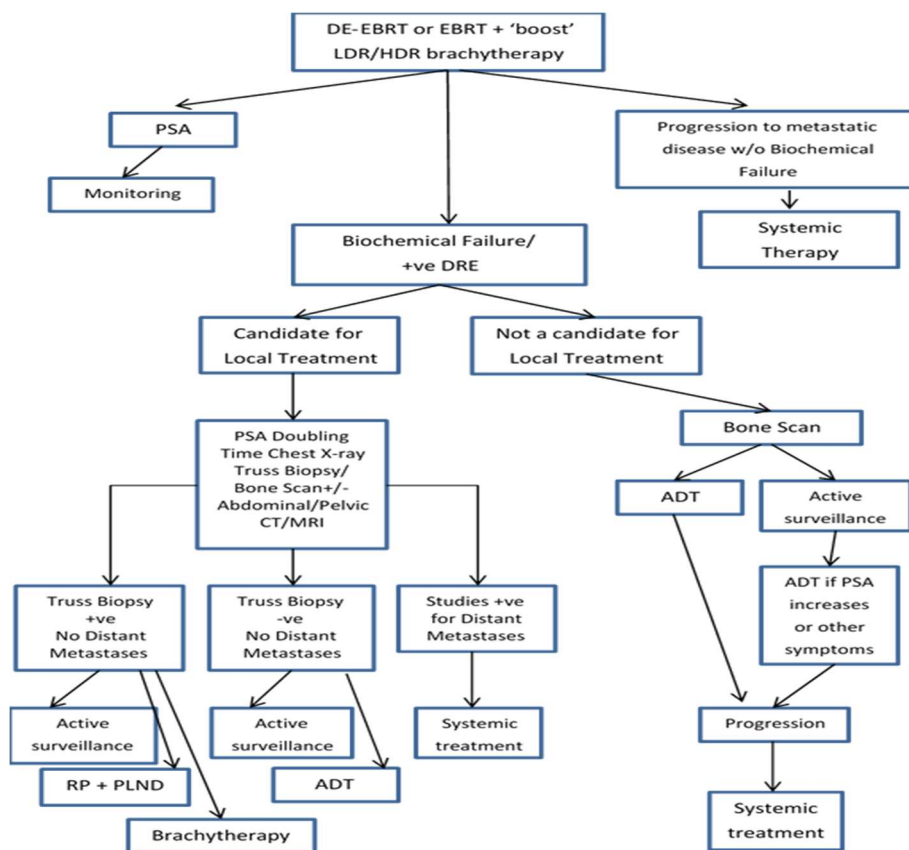


Figure 2 Current and proposed clinical treatment algorithm for patients with intermediate and high-risk prostate cancer – part 2 (continued from Figure 1)

Abbreviations: ADT=androgen deprivation therapy; CT=computed tomography; DRE=digital rectal examination; MRI=magnetic resonance imaging; PLND=pelvic lymph node dissection; PSA=Prostate Specific Antigen; RP=radical prostatectomy

9. Comparator

Three comparators have been identified for LDR-BT boost for high-intermediate and high-risk prostate cancer treatment:

1. Radical prostatectomy (RP) (i.e. a surgical treatment);
2. Dose escalated (DE)–EBRT; and
3. High-dose-rate brachytherapy (HDR-BT) boost, following EBRT; referred to as EBRT+HDR-BT in application).

The intervention and the two radiotherapy comparators all involve initial EBRT treatment, but the difference lies in the type of additional radiation delivered as a ‘boost’. Subsequent ‘boost’ may be delivered as additional doses of the same procedure (DE-EBRT), through permanent implantation of LDR-BT seeds, or through temporary HDR-BT (Duchesne 2011). The comparators are currently funded by the MBS, and match those in the ratified PICO.

In Australia, the CA stated that the most commonly used treatment modalities for localised prostate cancer include surgery, radiotherapy (external beam or interstitial brachytherapy) and hormonal therapy (Miller 2012, VIC-PCR 2015). Currently, primary treatment options for patients with intermediate and high-risk prostate cancer include EBRT +/- boost or RP with concurrent or salvage EBRT.

10. Comparative safety

1. *Vs. RP*

No data were identified comparing the safety of EBRT+LDR-BT boost to RP in people with high-intermediate and high-risk prostate cancer.

2. *Vs. DE-EBRT*

One randomised controlled trial (RCT) (ASDENDE-RT; Rodda, Tyldesley et al. 2017) was included in the assessment of safety of EBRT+LDR-BT boost compared with DE-EBRT in patients with intermediate- and high-risk prostate cancer was found. (n=383 for assessing adverse events). The application stated that EBRT+LDR-BT boost arm had a higher number of adverse effects (acute GU toxicity, late GI and GU morbidity) compared to DE-EBRT arm. No statistically significant differences were reported for erectile dysfunction, acute grade 3 GU toxicity or acute grade 0-2 GI toxicity.

3. *Vs. EBRT+HDT-BT boost*

No data were identified comparing the safety of EBRT+LDR-BT boost to EBRT+HDR-BT boost in people with high-intermediate and high-risk prostate cancer.

11. Comparative effectiveness

1. *Vs. RP*

No data were identified comparing the effectiveness of EBRT+LDR-BT boost to RP in people with high-intermediate and high-risk prostate cancer.

2. *Vs. DE-EBRT*

One RCT (3 publications (Morris, Tyldesley et al. 2017, Rodda, Morris et al. 2017, Rodda, Tyldesley et al. 2017) and one retrospective cohort study (Johnson, Lester-Coll et al. 2017) were included in the evidence base for effectiveness of EBRT plus LDR-BT boost.

The single RCT (Morris, Tyldesley et al. 2017, Rodda, Morris et al. 2017, Rodda, Tyldesley et al. 2017) was assessed to be at low risk of bias for survival outcomes (Table 3). The retrospective cohort study (Johnson, Lester-Coll et al. 2017) was assessed to be at high risk of bias overall. Further, the CA also highlighted the applicability issues associated with the pivotal RCT (ASDENDE-RT) which included around half of the population with low-intermediate risk prostate cancer. The Critique also highlighted that the CA adopted a modified version of the NCCN Prostate Cancer Risk Group, Intermediate-Risk, to represent the high-intermediate risk group considered in the application (without a clear statement explaining why this modified version was used). However, the Critique deduced that the requirement for Gleason 7 and T2bc (in the CA definition) rather than the option for Gleason 7 and T2bc (in the NCCN definition), indicates that patients with these clinical characteristics represent patients who are of higher risk in the intermediate group, thereby moving them into the high-intermediate risk group.

Table 3 Balance of clinical benefits and harms of EBRT plus LDR-BT boost, relative to DE-EBRT, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Hazard ratio (95%CI; p-value)	Comments
b-PFS Median follow-up 6.5 years	1 RCT N=398	⊕⊕⊕⊖ MODERATE	HR = 0.49 (0.30-0.80; p=0.004)	RCTs start at high quality in GRADE. Downgraded for serious indirectness as around half the population comprises low intermediate risk patients (which does not align with the intended target population).
OS (for RCT) Median follow-up 6.5 years	1 RCT N=398	⊕⊕⊖⊖ LOW	HR = 0.88 (0.54-1.45; p=0.62)	Downgraded for serious imprecision due to wide confidence intervals and as the trial was small and was not powered to measure the outcome. Downgraded for indirectness as around half the population comprises low intermediate risk patients.
OS (for observational study) Median follow-up of 63 months	1 Cohort N=25,436	⊕⊖⊖⊖ VERY LOW	HR=0.74, (0.66–0.89)	Observational studies start at low quality in grade. Downgraded for very serious risk of bias. Downgraded for serious indirectness due to lack of detailed reporting of interventions delivered.
MFS Median follow-up 6.5 years	1 RCT N=398	⊕⊕⊖⊖ LOW	HR = 0.99 (0.51–1.96; p=0.99)	Downgraded for serious imprecision due to wide confidence intervals and as the trial was small and was not powered to measure the outcome. Downgraded for serious indirectness as around half the population comprises low intermediate risk patients.
PCSS Median follow-up 6.5 years	1 RCT N=398	⊕⊕⊖⊖ LOW	HR = 0.71 (0.27 – 1.88; p=0.49)	Downgraded for serious imprecision due to wide confidence intervals and as the trial was small and was not powered to measure the outcome. Downgraded for serious indirectness as around half the population comprises low intermediate risk patients.
Adverse effects Median follow-up 6.5 years	1 RCT N=383	⊕⊕⊖⊖ LOW	LDR-BT boost arm had a higher number of adverse effects (GI and GU morbidity and erectile dysfunction) compared to DE-EBRT boost arm.	Downgraded for unclear risk of reporting bias (because adverse data were not reported in the format as specified). Downgraded for serious imprecision as the trial was small and was not powered to measure the outcome. Although around half the population comprises low intermediate risk patients, treatment-related adverse events would be experienced across all risk groups and therefore indirectness was not considered to be a serious concern (therefore evidence was not downgraded for this outcome)
HRQoL Median follow-up was 6 years	1 RCT N=357	⊕⊕⊖⊖ LOW	Significantly larger drop in mean HRQoL scores (compared with baseline) in the LDR-BT boost arm compared to DE-EBRT boost arm for	Downgraded for unclear risk of detection bias (because a lack of blinding is likely to influence patient-reported outcomes). Downgraded for serious imprecision as the trial was small and was not powered to measure the outcome.

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Hazard ratio (95%CI; p-value)	Comments
			some SF36v2 measures.	Although the population was indirect, as around half the population comprises low intermediate risk patients, this outcome was not downgraded for indirectness, as it is unlikely to seriously affect this outcome.

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: b-PFS=biochemical progression-free survival; EBRT=external beam radiation therapy; GS=Gleason sum; HRQoL=health-related quality of life; LDR-BT=low-dose rate brachytherapy; MFS=metastasis-free survival; OS=overall survival; PCSS=prostate cancer-specific survival; RCT=randomised controlled trial; GI=gastrointestinal; GU=genitourinary; SF36v2= Short Form 36 version 2; **Bold** = statistically significant

3. *Vs. EBRT+HDT-BT boost*

No data were identified comparing the effectiveness of EBRT+LDR-BT boost to EBRT+HDR-BT boost in people with high-intermediate and high-risk prostate cancer.

Clinical Claim

It is suggested that, relative to DE-EBRT, EBRT plus LDR-BT boost has inferior safety and superior effectiveness for biochemical progression-free survival (b-PFS), and uncertain effectiveness for overall survival (OS), metastasis-free survival (MFS) and prostate cancer-specific survival (PCSS) in men with high-intermediate and high-risk prostate cancer.

Given the paucity of evidence for the population of men with high-intermediate or high-risk prostate cancer, it is suggested that, relative to EBRT plus HDR-BT boost and RP, EBRT plus LDR-BT boost has uncertain safety.

Post-ESC Addendum

For clarification on the population included in the ASCENDE-RT trial, a table (Table 4) of the relevant baseline characteristics (iPSA, Gleason sum and clinical T stages) applicable to the population definitions of this application (high-intermediate and high risk) was provided.

Table 4 Baseline characteristics in ASCENDE-RT

Baseline characteristic	Baseline proportion
iPSA (ng/mL)	
10 - 20	33.2%
>20	18.2%
Gleason sum	
7	53.8%
8-10	40.7%
Clinical T stage	
T1c-T2c	70.9%
T3a	29.1%

Table 4 shows that for high-intermediate risk, defined as PSA>10.0-<20.0 ng/mL and Gleason score 7 and stage T2b-c, it cannot be determined exactly the proportion of patients that would have all three of these criteria. PSA>10.0-<20.0 ng/mL is 33.2%, Gleason sum of 7 is 53.8% and clinical T stages T2b-c is not reported separately and only reported as 70.9%. Therefore if all three criteria are to be fulfilled, then the proportion of patients can be assumed to be ≤33.2%.

High risk is defined as PSA>20.0 ng/mL and/or Gleason score 8-10 and/or stage T3a. PSA>20.0 ng/mL is 18.2%, Gleason sum of 8-10 is 40.7% and clinical T stage T3a is 29.1%. As this is and/or criteria, the proportion of patients can be assumed to be ≥40.7%.

In total, it can be assumed that approximately 73.9% of the ASCENDE trial is applicable to the population of the current application, however the exact percentage is uncertain.

12. Economic evaluation

Pre-ESC model

A cost-utility analysis was presented comparing EBRT+LDR-BT boost with DE-EBRT (Table 5).

Table 5 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Dose-escalated external beam radiation therapy (DE-EBRT)
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RCT, observational studies
Time horizon	10 years
Outcomes	LYG and QALYs gained
Methods used to generate results	Decision analytic Markov model
Health states	Eight health states: Remission, acute toxicity GI/GU all grades (first 6 months), late toxicity (GI/GU) grade ≥3, biochemical failure without late toxicity, biochemical failure with late toxicity, metastases, prostate cancer death, all-cause death (other causes)
Cycle length	12 months
Discount rate	5%
Software packages used	TreeAge Pro 2018, 18.2.1-v20180828

The model structure was based on a published Markov model by Carter, Martin et al. (2014), which was considered appropriate by the Critique. Key structural assumptions of the CAs model included grouping acute GI and GU toxicities together as a single health state; excluding the probability of transiting to metastatic disease without biochemical failure and that prostate cancer death would be preceded by the metastases health state regardless of the proximate cause of death. The Critique stated that these assumptions were reasonable. However, the Pre-ESC response highlighted potential structural modelling errors (e.g. no option to progress from late toxicity to remission without toxicity or to biochemical failure without toxicity) and errors estimating model transitional probabilities (e.g. substantially higher transitional probability of biochemical failure to metastases was applied to intervention arm compared with comparator arm (0.043 vs. 0.108, respectively), which it claimed made no clinical sense. The Pre-ESC Response noted both potential errors favoured the comparator.

The overall costs and outcomes, and incremental costs and outcomes (QALYs and life years [LYs]) as calculated for the intervention and comparator in the model, and using the base

case assumptions, are shown in Table 6 and Table 7, respectively. The CA explained that incremental LYs was higher as overall survival (both prostate cancer- and noncancer-related) was higher for the LDR-BT boost (relative to DE-EBRT). However, incremental QALYs was lower due to higher toxicity experienced by patients undergoing LDR-BT (relative to DE-EBRT).

Table 6 Base case incremental cost effectiveness ratio – high-intermediate and high risk: QALY outcomes

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
LDR-BT boost	\$27,866.37	\$8,072.40	7.01	-0.04	Dominated (more expensive, less effective)
DE-EBRT	\$19,793.97	-	7.05	-	-

Abbreviations: DE-EBRT=dose-escalated external beam radiation therapy; ICER=Incremental Cost Effectiveness Ratio; LDR-BT=low-dose rate brachytherapy; QALYs=quality-adjusted life years

Table 7 Base case Incremental costs and effectiveness – high-intermediate risk and high risk: LY outcomes

	Cost	Incremental cost	Effectiveness (LYs)	Incremental effectiveness	ICER
LDR-BT boost	\$27,866.37	\$8,072.40	7.48	0.03	\$237,027.21
DE-EBRT	\$19,793.97	-	7.45	-	-

Abbreviations: DE-EBRT=dose-escalated external beam radiation therapy; ICER=Incremental Cost Effectiveness Ratio; LDR-BT=low-dose rate brachytherapy; LYs = Life years

The CA stated that the economic model conclusions were robust across a range of plausible estimates (Figure 3). In addition, LDR-BT boost was also unlikely to be cost-effective compared with DE-EBRT over a 20 or 30 year time horizon. The Critique stated there were several minor errors within the economic evaluation, but these did not impact on the results.

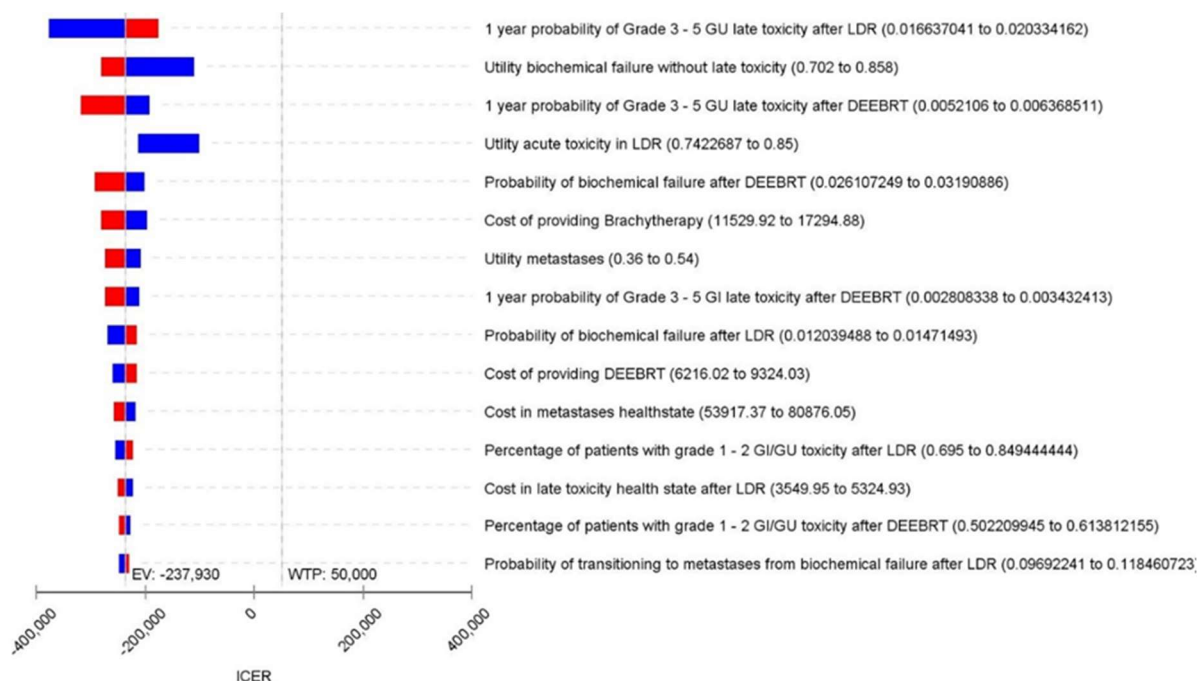


Figure 3 Tornado diagram. One-way sensitivity analysis LDR-BT boost versus DE-EBRT

The CA validated the ICER by comparing the modelled 10-year survival curve estimates with overall survival estimates from the ASCENDE-RT trial and study by Johnson, Lester Coll et al. 2017. The CA stated that the model provided a similar overall survival curve for the LDR-

BT boost arm; however, it was overestimated for the DE-EBRT arm (0.87 vs. 0.7 and 0.78, respectively).

Post-ESC model: Addendum

The CA addressed several modelling issues raised during ESC (and raised by the applicant):

- The model structure was amended to allow patients to enter biochemical failure with without late toxicity following GU/GI late toxicity grade3+;
- The transitional probability from biochemical failure to metastases was adjusted to align with clinical data inputs (ASCENDE-RT); and
- The transitional probability from remission without toxicity to biochemical failure without late toxicity was corrected for a coding error.

In addition, the CA group confirmed with a local expert that the derivation of utility weights in the pre-ESC model was correct and thus no changes were made to the Post-ESC model.

The results of the revised model is summarised for QALY outcomes (Table 8) and LYs (Table 9).

Table 8 Base case incremental costs and effectiveness – high-intermediate risk and high-risk prostate cancer: QALY outcomes

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
LDR-BT boost (over 10 years)	\$21,840.00	\$2,886.00	7.05	0.17	\$16,976/QALY
DE-EBRT (over 10 years)	\$18,954.00	-	6.88	-	

Abbreviations: DE-EBRT=Dose-escalated external beam radiotherapy; ICER=Incremental Cost Effectiveness Ratio; LDR-Brachytherapy=Low-dose rate Brachytherapy; QALY=quality-adjusted life-years

Table 9 Base case incremental costs and effectiveness – high-intermediate risk and high-risk prostate cancer: LY outcomes

	Cost	Incremental cost	Effectiveness (LYs)	Incremental effectiveness	ICER
LDR-BT boost (over 10 years)	\$21,840.00	\$2,886.00	7.49	0.04	\$80,5444/LY
DE-EBRT (over 10 years)	\$18,954.00	-	7.46	-	

Abbreviations: DE-EBRT=Dose-escalated external beam radiotherapy; ICER=Incremental Cost Effectiveness Ratio; LDR-Brachytherapy=Low-dose rate Brachytherapy; LY=Life-years

The CA stated that the economic model was most sensitive to the utility gained in the health state for biochemical failure with late toxicity (Figure 4).

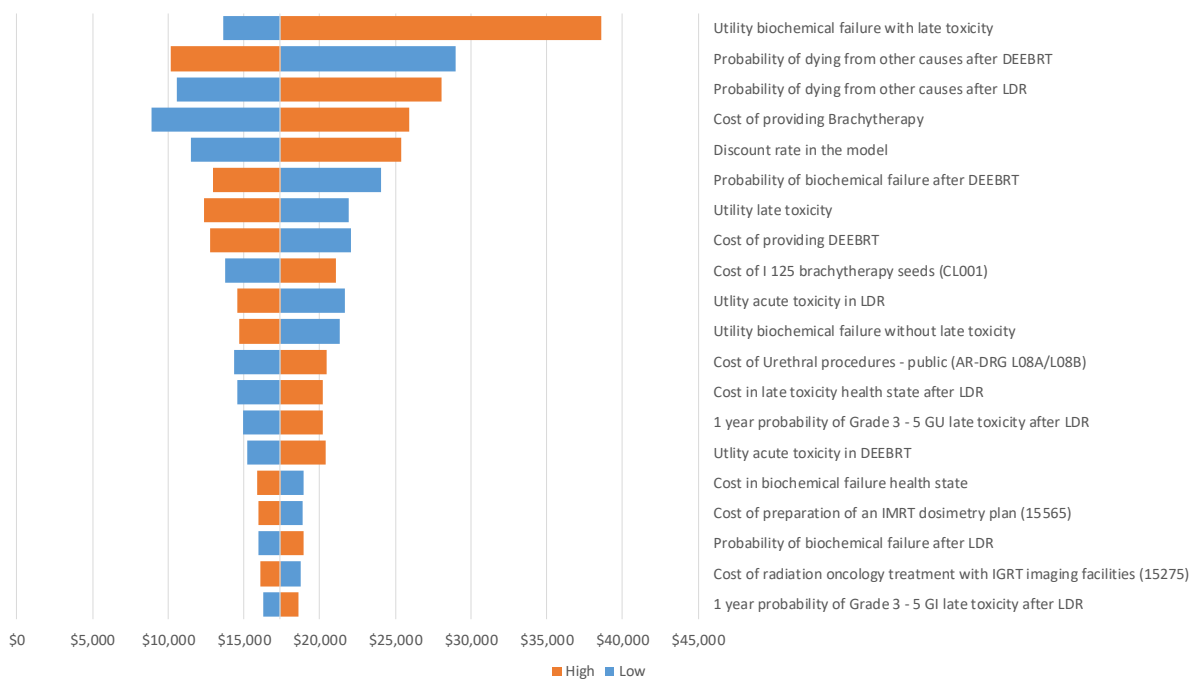


Figure 4 Tornado diagram. One-way sensitivity analysis LDR-BT boost versus DE-EBRT

13. Financial/budgetary impacts

Pre-ESC financials

An epidemiological approach has been used to estimate the financial implications to the MBS of introducing LDR-BT boost for patients with high-intermediate and high-risk prostate cancer (Table 10).

The proposed item costs of LDR-BT boost are \$935.60 for the radiation oncology component and \$1,044.20 for the urological component of radioactive seed implantation. The direct cost of LDR-BT boost items (five items including seed implantation, brachytherapy planning, transrectal ultrasound and radiation source localisation) is \$2,521.70, considering 75% rebate for urological component of seed implantation and transrectal ultrasound and 85% rebate for radiation oncology items.

Table 10 Total costs to the MBS associated with LDR-BT boost

Description	2020	2021	2022	2023	2024
LDR-BT boost					
Number of services	106.70	110.69	115.57	119.60	123.62
Sub-total cost*	\$269,059.35	\$279,127.37	\$291,431.27	\$301,582.96	\$311,734.65
Increased usage services currently MBS listed (co-administered and adverse-effect treatment-related)					
Number of services	106.70	110.69	115.57	119.60	123.62
Sub-total cost*	\$96,439.00	\$100,047.68	\$104,457.77	\$108,096.44	\$111,735.12
<i>Critique's values</i>	\$96,670.67	\$100,288.02	\$104,708.70	\$108,356.12	\$112,003.53
Decreased usage services currently MBS listed (HDR-BT boost)					
Number of services	106.70	110.69	115.57	119.60	123.62
Sub-total cost*	-\$313,951.47	-\$325,699.34	-\$340,056.12	-\$351,901.60	-\$363,747.09
Total cost	\$51,546.87	\$53,475.72	\$55,832.92	\$57,777.80	\$59,722.68
<i>Critique's values</i>	\$51,778.54	\$53,716.06	\$56,038.86	\$58,037.48	\$59,991.10

* Medical services delivered in inpatient settings were calculated at 75% of MBS fee. If it was deemed feasible to deliver a service in outpatient settings, 85% of total fee was used.

Abbreviations: HDR-BT=high-dose rate brachytherapy; LDR-BT=low-dose rate brachytherapy

The Critique stated consideration should have been given to the impact on PBS of funding LDR-BT boost, at a minimum, the cost of hormone therapy (leuprorelin) when used to treat patients who progress to biochemical failure. For MBS impacts (with the exception of higher uptake for LDR-BT boost), there is potential for the net cost per year to be less than estimated in the CA.

Post- ESC financials: Addendum

An additional analysis was conducted to account for the overall financial impact of LDR-BT boost compared with DE-EBRT, using the inputs from the cost-effectiveness model (Markov traces). Specifically, costs in the CEA model were grouped into four categories: MBS costs, PBS costs, hospital costs, and prosthesis costs. The CA presented the results as per the base case model presented to ESC (Table 11) and revised model presented post ESC, in the Addendum (Table 12).

Table 11 Revised Pre-ESC model: Total forecasted services, overall deconstructed costs for each treatment arm and the difference between the treatment arms between 2020 and 2024 using outputs from the base case model.

Description	2020	2021	2022	2023	2024
Total services	107	111	116	120	124
LDR-BT boost					
PBS Costs	\$10,447	\$17,060	\$33,570	\$62,267	\$104,753
MBS	\$177,882	\$208,730	\$246,676	\$289,140	\$337,354
Hospital	\$272,719	\$309,632	\$377,084	\$471,599	\$595,465
Prosthesis	\$329,436	\$341,755	\$356,822	\$369,265	\$381,677
TOTAL COST	\$790,485	\$877,178	\$1,014,153	\$1,192,271	\$1,419,250
DE-EBRT					
PBS Costs	\$6,961	\$13,434	\$27,046	\$47,764	\$75,567
MBS	\$433,579	\$475,952	\$526,388	\$577,784	\$633,126
Hospital	\$0	\$23,828	\$72,941	\$146,384	\$243,019
Prosthesis	\$0	\$0	\$0	\$0	\$0
TOTAL COST	\$440,540	\$513,214	\$626,375	\$771,932	\$951,712
Difference					
PBS Costs	\$3,486	\$3,626	\$6,524	\$14,502	\$29,187
MBS	-\$255,696	-\$267,222	-\$279,712	-\$288,643	-\$295,772
Hospital	\$272,719	\$285,804	\$304,143	\$325,215	\$352,446
Prosthesis	\$329,436	\$341,755	\$356,822	\$369,265	\$381,677
TOTAL COST	\$349,945	\$363,964	\$387,777	\$420,339	\$467,537

Table 12 Revised Post-ESC model: Total forecasted services, overall deconstructed costs for each treatment arm and the difference between the treatment arms between 2020 and 2024 using outputs from the amended model.

Description	2020	2021	2022	2023	2024
Total services	107	111	116	120	124
LDR-BT boost					
PBS Costs	\$790,485	\$877,178	\$1,006,112	\$1,162,435	\$1,349,915
MBS	\$10,447	\$17,060	\$29,706	\$47,985	\$71,701
Hospital	\$177,882	\$208,730	\$246,014	\$286,687	\$331,667
Prosthesis	\$272,719	\$309,632	\$373,570	\$458,497	\$564,871
TOTAL COST	\$329,436	\$341,755	\$356,822	\$369,265	\$381,677
DE-EBRT					
PBS Costs	\$440,540	\$513,214	\$625,228	\$768,154	\$943,556
MBS	\$6,961	\$13,434	\$26,304	\$45,511	\$71,019
Hospital	\$433,579	\$475,952	\$528,637	\$584,232	\$645,478
Prosthesis	\$0	\$23,828	\$70,287	\$138,410	\$227,059
TOTAL COST	\$0	\$0	\$0	\$0	\$0
Difference					
PBS Costs	\$349,945	\$363,964	\$380,884	\$394,281	\$406,360
MBS	\$3,486	\$3,626	\$3,402	\$2,474	\$682
Hospital	-\$255,696	-\$267,222	-\$282,623	-\$297,545	-\$313,812
Prosthesis	\$272,719	\$285,804	\$303,283	\$320,087	\$337,812
TOTAL COST	\$329,436	\$341,755	\$356,822	\$369,265	\$381,677

14. Key issues from ESC for MSAC

Key Issues from ESC to MSAC	ESC advice to MSAC
Is the data from the RCT of high enough quality? Does effectiveness (biochemical progression-free survival) balance adverse effects and their QoL effect?	The ASCENDE-RT trial showed superior effectiveness of EBRT + LDR-BT compared with dose escalated (DE)–EBRT, but with inferior safety and lower health-related QoL scores. The Critique downgraded the evidence from the trial, but this may not be appropriate.
Are the adverse events reported in the trial still representative?	Adverse events observed in the trial may be avoidable with improvements in planning and imaging techniques since the trial was conducted.
Item descriptor needs to be refined	Avoid use of ‘recommended’ in statement specifying that LDR-BT is to be used only as a ‘boost’ treatment after EBRT. Retain ‘in association with [a radiation oncologist/urologist]’ to ensure the radiology oncology and urology components of the procedure are done together. Stipulate that LDR-BT would also be in addition to androgen blockade.
Issues with model: <ul style="list-style-type: none"> • transition between remission and late GU/GI toxicity should be two-way • incorrect transition probability from biochemical failure to metastases • utility decrement for acute and late adverse events derived using EQ-5D 3L rather than EQ-5D 5L • query whether utility decrement for acute grade toxicity has been carried through 	Model should be checked and verified, and the analysis re-run. Corrections will affect the ICER significantly and likely favour the intervention.
Corrected model should use Australian utility weights	Mapping from SF-36 using Australian SF-6D algorithms will require data for individual item levels. Check whether applicant has access to study item data.
Net cost per year may be lower than that estimated in the Contracted Assessment	Further cost offsets should be considered: <ul style="list-style-type: none"> • cost of treating adverse events after HDR-BT • PBS cost of hormone therapy to treat patients who progress to biochemical failure.

ESC discussion

Application 1525 requests Medicare Benefits Schedule (MBS) listing of low dose-rate brachytherapy (LDR-BT) as a boost following external beam radiation therapy (EBRT) in the treatment of high-intermediate and high-risk prostate cancer. ESC recalled that LDR-BT is already included on the MBS for low-risk prostate cancer.

For the purposes of this application, high-intermediate risk is defined as PSA>10.0–<20.0 ng/mL **and** Gleason score 7 **and** stage T2b–c, while high risk is defined as PSA>20.0 ng/mL **and/or** Gleason score 8–10 **and/or** stage T3a. ESC noted the importance of the differentiation between ‘and’ and ‘and/or’ in these definitions. A patient does not need to meet all three criteria in the high risk definition to be considered high risk.

ESC noted the Critique’s comment that the populations included in the primary sources of evidence – the ASCENDE-RT randomised controlled trial (RCT) and a retrospective cohort study (Johnson et al., 2017) – were more extensive than those proposed in the PICO.

Definitions of intermediate and high risk in these studies were based on National Comprehensive Cancer Network (NCCN) risk strata. ESC noted that the designation of intermediate and high risk is arbitrary from a clinical point of view and queried which definition of intermediate risk should be used (NCCN or PICO).

ESC considered that the proposed fees for the radiology oncology and urology components of the procedure are appropriate and in line with existing brachytherapy items.

ESC noted that the item descriptor needs to be reworded to avoid the use of ‘recommended’ with regard to LDR-BT being used only as a ‘boost’ treatment after EBRT. ESC noted the Department’s proposed wording: ‘For the populations this procedure will be rebated if it is performed as a “boost” treatment, in addition to external beam radiotherapy, at an approved site.’ And that [a radiation oncologist/urologist]’ should be retained in the descriptor to ensure the radiology oncology and urology components of the procedure are done together.

ESC also noted that the item descriptor should be further refined to stipulate that LDR-BT would also be in addition to androgen blockade, which is standard practice in Australia and consistent with the ASCENDE-RT trial.

ESC noted that the one of the comparators in practice would be surgery. However, the item descriptor does not indicate when to use LDR-BT instead of surgery. There is no direct evidence comparing LDR-BT boost with surgery; the comparator in the trial was dose escalated (DE)–EBRT.

ESC noted that, although the ASCENDE-RT trial was well designed and had a low risk of bias, the Critique applied a low certainty rating to the data because ‘around half the population comprises low intermediate risk patients’. However, the applicant disputed this, claiming that the Critique based this judgement on a misinterpretation of the definition of high risk. The applicant reiterated that the baseline characteristics of the ASCENDE-RT trial population were based on NCCN risk strata and the majority of patients in the trial were at high risk. ESC noted that the conclusions in the Critique and Contracted Assessment about the quality of the trial are difficult to reconcile, and downgrading may not have been appropriate.

ESC noted that the ASCENDE-RT trial showed late genitourinary (GU) and gastrointestinal (GI) adverse effects were more frequent in the EBRT + LDR-BT boost arm than in the DE-EBRT arm, and health-related quality of life (QoL) scores were lower. However, there was no significant difference in serious adverse events. ESC noted that, importantly, there were no differences in the frequency of erectile dysfunction. ESC commented that although GU and GI side-effects affect patients’ QoL, they pass and are treatable; consumer feedback indicates that irreversible erectile dysfunction is of more importance to patients. ESC considered that adverse events observed in the trial may be avoidable with improvements in planning and modern imaging techniques that have occurred since the trial was conducted.

ESC noted that adverse events in the ASCENDE-RT trial were balanced by superior effectiveness for biochemical progression-free survival (b-PFS), the primary outcome, for those receiving LDR-BT boost compared with DE-EBRT; however, there was no difference in overall survival, metastasis-free survival or prostate cancer-specific survival.

ESC noted that the differences between the two arms of the ASCENDE-RT trial were well accounted for, but the study was not powered or long enough to assess survival outcomes.

ESC noted that the retrospective cohort study showed better overall survival for EBRT + LDR-BT boost than for DE-EBRT. However, ESC agreed with the Critique that this study is at a high risk of bias and low applicability because the majority of patients were at low-intermediate risk. ESC noted that survival data from this study were not used in the economic model.

ESC noted that cost utility analysis was appropriate, and the 10-year time horizon is consistent with the RCT and appropriate for the target population.

ESC noted a structural issue with the model (raised by the applicant) in that it does not allow for remission of patients with late GU/GI toxicity. ESC noted that some of these late events may resolve with treatment, and there is evidence from the RCT that some of these events are transitory. The applicant claimed that the model should have included options to progress from late toxicity to remission without toxicity or to biochemical failure without toxicity. Not allowing for this in the model would overestimate the QoL detriment of adverse events, as patients enter the late toxicity state and remain there, accruing costs but with lower utility.

ESC agreed with the submission that this would have a significant effect on the incremental cost-effectiveness ratio (ICER). ESC suggested a sensitivity analysis should be done on the proportions of patients with transitory events.

ESC noted that the transition probabilities from acute toxicity to late toxicity make clinical sense. However, the transition probability from biochemical failure to metastases seems to be incorrect. The model gives a transition probability for LDR-BT boost that is 2.5-times higher than for DE-EBRT. This is a key driver in the model (with high cost and low utility) so will have a significant effect on the ICER. ESC agreed with the applicant that there is no reason for probability in the two arms to be different; there is no evidence from the trial that this is the case. ESC queried whether this may be a coding error in the model.

ESC noted that a conditional probability (using the number of patients who progressed as a denominator) would be more appropriate than a transition probability. A corrected calculation resulted in a conditional probability of 0.085 ($17/25 \times 25/198$ or $17/198$) for LDR-BT boost versus 0.09 ($18/51 \times 51/200$ or $18/200$) for DE-EBRT. ESC recommended that probabilities be verified and corrected.

ESC noted that changing the model structure and transitional probabilities will reduce costs, as acute GU/GI toxicity (all grades), late GU/GI toxicity (grade ≥ 3) and metastases make up the highest proportions of total incremental costs.

ESC noted that changes in the model will also change QoL outcomes. ESC queried why there is no QoL included for acute GU/GI toxicity (all grades). ESC noted that the Contracted Assessment assumes that the utility decrement for acute grade toxicity symptoms starts at 12 months, but the model has no-one left in that health state beyond 12 months. ESC recommended that the model is checked to ensure that utilities are carried through in that state.

ESC noted an issue with utility weights used in the model. SF-36 scores from the ASCENDE-RT trial were mapped to the EQ-5D index using the method by Ara and Brazier (2008), which ESC considered to be appropriate if only mean values were available from the trial. However, the EQ-5D 3L instrument that was used in this method has been largely replaced by the EQ-5D 5L. The utility decrement when a patient moves from one level to another (i.e. no problems to some problems) is likely to be lower with the 5L instrument, which would favour the intervention.

ESC agreed with the applicant that Australian utility weights should be used in the model. It is possible to map from SF-36 using SF-6D algorithms available for Australia. However, this would require data for individual item levels. ESC recommended checking whether the applicant has access to study item data to allow mapping to actual Australian utilities rather than EQ-5D.

ESC noted the applicant's claim that the utility weight used in the model for the remission without toxicity health state is too high and is inconsistent with other derived Australian utility scores. QoL values suggested by the applicant based on Australian algorithms were lower and would favour the intervention. ESC considered that using an Australian derived utility measure for remission may not be possible without changing the relative utility values. Other utility weights were derived from another paper, which ESC considered appropriate.

ESC recommended that, to be able to draw any conclusions, the model should be verified and corrected before going to MSAC, to ensure it is consistent with the clinical pathway with regard to remission following late toxicity. Analysis should be re-run using:

- corrected metastasis transition probabilities
- lower decrement for acute and late adverse events (using EQ-5D 5L instrument)
- Australian utility weights.

ESC noted that these corrections will all likely favour the intervention, and will affect the ICER significantly.

ESC considered that the epidemiological approach used to estimate financial implications is appropriate.

ESC noted the potential for the net cost per year to be lower than that estimated in the Contracted Assessment. Cost offsets would be greater if the cost of treating adverse events after high dose-rate (HDR)-BT was included. The impact on the PBS should also have been considered (at least the cost of hormone therapy to treat patients who progress to biochemical failure).

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](#)