Technology Guidance

Talazoparib in combination with enzalutamide

for treating HRR gene-mutated metastatic castration-resistant prostate cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended talazoparib in combination with enzalutamide for inclusion on the MOH List of Subsidised Drugs for treating homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer. The decision was based on the low clinical need, uncertain or unfavourable cost-effectiveness compared with treatment alternatives, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for talazoparib plus enzalutamide are provided in the Annex.

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Company-led submission

1.1. At the June 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of talazoparib in combination with enzalutamide for treating patients with homologous recombination repair gene-mutated (HRRm) metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. The evaluation included the company's evidence submission and a review by one of ACE's evidence review centres.

1.2. Expert opinion, obtained from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations, assisted ACE in ascertaining the clinical value of talazoparib in combination with enzalutamide.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. In Singapore, approximately 25 patients are diagnosed with HRRm mCRPC each year, of whom chemotherapy is not clinically indicated in about 15 of them. The Committee noted that BRCA1/2 and ATM alterations are the most frequently detected HRR gene mutations. For patients with these alterations, olaparib monotherapy is the current standard of care. The Committee also noted that most patients with mCRPC would have previously received novel hormonal agents (NHAs) and rechallenge with these agents is generally avoided following disease progression, due to cross-resistance. Hence, the Committee considered that there is low clinical need for adding enzalutamide, an NHA, to talazoparib, in this setting. The Committee noted that the submission excluded olaparib monotherapy as a comparator, citing the absence of direct comparative evidence and limitations in conducting indirect comparisons given the different patient populations enrolled in the respective trials.

2.2. For patients who have not received prior NHA treatment, the current subsidised treatment options are abiraterone acetate in combination with prednisolone ("AAP") and enzalutamide monotherapy. In addition, olaparib in combination with AAP is HSA-approved for treating mCRPC. Therefore, the Committee considered that the

submission appropriately nominated AAP and enzalutamide as comparators, and olaparib in combination with AAP as a near-market comparator.

2.3. The Committee considered seven testimonials from local patient experts about their experiences living with prostate cancer and the treatments they had received. They heard that treatment side effects such as hot flashes, fatigue, gynaecomastia, and insomnia, as well as post-surgery complications such as incontinence, erectile dysfunction and burning sensation while urinating, had negatively impacted their lives. The Committee also noted these side effects affected patients' ability to work and caused significant emotional and mental burden, particularly due to concerns about disease progression and relapse. While patients found their various treatments (including surgery, chemotherapy, and radiotherapy) to be effective, they welcomed new treatment options. Although not familiar with talazoparib and enzalutamide combination treatment, the patient experts considered that any new treatment options for prostate cancer should stop their cancer from worsening, prolong their time living with cancer, cause fewer side effects and improve quality of life.

Clinical effectiveness and safety

3.1. The company requested a listing for patients with HRRm mCRPC in whom chemotherapy is not clinically indicated. The Committee noted that the requested listing is a subset of the HSA-approved indication, which is not restricted by HRR gene mutation status, but is broader than the TALAPRO-2 trial population, which was primarily NHA naïve. The Committee noted that local clinicians considered the requested listing reasonable, as talazoparib plus enzalutamide may be offered to some patients with prior exposure to AAP.

3.2. The Committee reviewed the clinical evidence in the company's submission from an ongoing phase III, double-blind, randomised controlled trial (Cohort 2 of TALAPRO-2). The trial compared talazoparib plus enzalutamide with enzalutamide monotherapy in patients with HRRm mCRPC.

<u>Talazoparib plus enzalutamide versus enzalutamide monotherapy</u>

3.3. The Committee noted that only 8.6% of the TALAPRO-2 participants had prior NHA treatment, which differs significantly from local clinical practice, where NHA use in earlier disease stages is common. Hence, the Committee considered that the trial results have limited generalisability to the local setting.

3.4. At a median follow-up of 44 months (September 2024 data cut-off), talazoparib plus enzalutamide led to statistically significant improvements in radiographic progression-free survival (rPFS) and overall survival (OS) compared with enzalutamide (Table 1).

Table 1: Results of rPFS and OS in Cohort 2 of TALAPRO-2 trial

September 2024 data cut-off	TAL+ENZ (N=200)	PBO+ENZ (N=199)	Absolute difference	HR (95% CI), p value
rPFS based on blinded independent central review				
Patients with event, n (%) Progression Death	99 (49.5) 85 (42.5) 14 (7.0)	127 (63.8) 116 (58.3) 11 (5.5)	-14.3%	-
Median rPFS, months (95% CI)	30.7 (24.3 to 38.5)	12.3 (11.0 to 16.5)	18.4	**0.47 (0.36 to 0.61), p<0.0001**
rPFS based on investigator assessment				
Patients with event, n (%) Progression Death	82 (41.0) 64 (32.0) 18 (9.0)	106 (53.3) 96 (48.2) 10 (5.0)	-12.3%	-
Median rPFS, months (95% CI)	38.8 (30.7 to 46.2)	17.0 (13.9 to 22.1)	21.8	**0.50 (0.37 to 0.67), p<0.0001**
OS				
Patients with event, n (%)	93 (46.5)	126 (63.3)	-16.8%	-
Median OS, months (95% CI)	45.1 (35.4 to NE)	31.1 (27.3 to 35.4)	14.0	**0.62 (0.48 to 0.81), p=0.0002**

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival; PBO+ENZ, placebo plus enzalutamide; rPFS, radiographic progression-free survival; TAL+ENZ, talazoparib plus enzalutamide.
Bold indicates statistically significant result.

3.5. In terms of safety, the Committee noted that talazoparib plus enzalutamide was associated with higher incidences of grade 3 or 4 treatment-emergent adverse events (TEAEs; 53.0% versus 14.1%) and serious TEAEs of any grade (13.6% versus 0%) compared with enzalutamide monotherapy. Anaemia, neutropenia, and thrombocytopenia were the most frequently reported adverse events leading to a dose modification of talazoparib.

3.6. The submission described talazoparib plus enzalutamide as superior in terms of effectiveness and manageable in terms of safety compared with enzalutamide monotherapy for patients with HRRm mCRPC. While the Committee agreed that the claim of superior effectiveness was reasonable within the trial population, they had concerns about the applicability of the evidence to the local setting. In terms of safety, the Committee considered talazoparib plus enzalutamide to be inferior to enzalutamide monotherapy.

<u>Talazoparib plus enzalutamide versus AAP and olaparib plus AAP</u>

3.7. In the absence of head-to-head trials comparing talazoparib plus enzalutamide with AAP and olaparib plus AAP, the Committee reviewed unanchored matching-adjusted indirect comparisons (MAICs) included in the submission. The MAICs were informed by trial data from TALAPRO-2 (talazoparib plus enzalutamide), MAGNITUDE (AAP), and PROpel (olaparib plus AAP).

3.8. The Committee noted several limitations with the MAICs. For example, the reduced sample size of the TALAPRO-2 matched cohort led to imprecise estimates. In

addition, several important prognostic factors could not be adjusted for in the analyses, including time to mCRPC while on continuous androgen deprivation therapy.

3.9. Results from the MAICs showed that talazoparib plus enzalutamide significantly improved OS (HR 0.55; 95% CI 0.34 to 0.87) and rPFS (HR 0.40; 95% CI 0.28 to 0.57) compared with AAP. No significant differences in rPFS and OS were observed between talazoparib plus enzalutamide and olaparib plus AAP. However, limitations of the MAICs precluded robust clinical conclusions.

3.10. Regarding safety, the submission did not provide any indirect treatment comparisons. Instead, it referenced published literature showing comparable safety profiles between AAP and enzalutamide, and suggested that talazoparib plus enzalutamide is inferior to AAP in safety. The Committee considered these reasonable and also noted that in previous deliberations, they had considered the safety profiles of AAP and enzalutamide to be clinically comparable in mCRPC treatment.

3.11. The submission claimed that talazoparib plus enzalutamide had a comparable safety profile to olaparib plus AAP, based on both combinations sharing class effects. The Committee agreed with the claim and noted that this safety assessment is aligned with the conclusions made by the Australian Pharmaceutical Benefits Advisory Committee.

Cost effectiveness

4.1. The Committee noted that the submission included cost-utility analyses (CUAs) comparing talazoparib plus enzalutamide with (1) enzalutamide monotherapy; (2) AAP; and (3) olaparib plus AAP. The Committee considered that the comparison with AAP was highly uncertain, as the extrapolations for AAP solely relied on hazard ratios based on an unanchored MAIC, which had unresolved issues as mentioned in para 3.8. Moreover, the Committee considered that the use of CUA for the comparison with olaparib plus AAP was inappropriate given the submission's claim of comparable effectiveness and safety.

4.2. The Committee considered the results of the submission's CUA that compared talazoparib plus enzalutamide with enzalutamide monotherapy based on the TALAPRO-2 trial. Key components of the base-case economic evaluation provided in the submission are summarised in Table 2.

Table 2: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with HRRm mCRPC in whom chemotherapy is not clinically indicated
Outcomes	1. Total and incremental LYs 2. LYs by health state 3. Total and incremental QALYs 4. QALYs by health state 5. Total and incremental costs 6. Costs by health state 7. Cost breakdowns by resource type, including drug acquisition, administration costs and premedication costs, drug monitoring costs, AE management costs, disease monitoring costs for both 1L and 2L treatments and palliative care costs
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	7 years in the model base case, based on a follow-up period of 42.0 months for rPFS (median for TAL+ENZ was 17.5 months; median for PBO+ENZ arm was 16.8 months) and 49.0 months for OS (median for TAL+ENZ was 44.2 months; median for PBO+ENZ was 44.4 months) in the TALAPRO-2 trial.
Health states	PF, PD, death
Cycle length	Monthly
Extrapolation methods used to generate results	Extrapolated curves estimated using parametric functions from KM data for rPFS, OS and TTD were used. For rPFS, OS, and enzalutamide TTD curves, a joint fitting was used. Independent fitting was used for talazoparib TTD curve. • rPFS for both treatment arms = Gamma • OS for both arms = Gamma • TTD for enzalutamide for both arms = Log-logistic • TTD for talazoparib = Log-logistic No treatment waning was applied in the base case.
Health-related quality of life	EQ-5D-5L based utilities from TALAPRO-2 mapped to EQ-5D-3L values for rPFS and literature values (based on NICE technology appraisal 377) for PD health state were used. In the base case: • PF health state: 0.811 • PD (on treatment) health state: 0.658 • PD (on palliative care) health state: 0.500
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; EQ-5D-3L, EuroQoL-5 Dimension-3 Level; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; ICERs, incremental cost-effectiveness ratio; HRRm, homologous recombination repair gene mutation; KM, Kaplan-Meier; LY, life-year; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PBO+ENZ, placebo plus enzalutamide; PD, progressed disease; PF, progression-free; QALY, quality-adjusted life year; rPFS, radiographic progression-free survival; TAL+ENZ, talazoparib plus enzalutamide; TTD, time to treatment discontinuation.

4.3. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$135,000 and SG$165,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, given:

- The submission's modelled incremental benefits for the talazoparib plus enzalutamide arm relied heavily on a higher proportion of those patients remaining in the progression-free (PF) health state compared to patients receiving enzalutamide monotherapy. However, the Committee noted that rPFS data were immature, with the median not reached in the talazoparib plus enzalutamide arm at 17 months of median follow-up. These data were extrapolated to seven years without any treatment effect waning assumed.

- The submission's extrapolated time to treatment discontinuation (TTD) curve for talazoparib was substantially lower compared to the extrapolated rPFS curve, suggesting that a considerable proportion of patients discontinued talazoparib before progression. The Committee considered that this may not align with clinical practice and may underestimate treatment cost of talazoparib in the PF health state.

- The submission used different sources for health-state utility values (HSUVs). Pooled EQ-5D-5L data from TALAPRO-2 (mapped to EQ-5D-3L values) were used for PF health state, and literature-based values were used for the progressed disease (PD) health states. The Committee had concerns with using different sources of data for HSUVs. The PF HSUVs derived from TALAPRO-2 were higher than those reported in the literature, suggesting that using TALAPRO-2 values alongside literature-based values likely overestimated the utility difference between PF and PD health states.

- The submission used cost price of talazoparib instead of selling price.

- The submission applied palliative care costs in the PD health state after subsequent treatment, in addition to an end-of-life cost in the last month of life. The Committee considered that this may result in double-counting, as the end-of-life cost could have included palliative care costs.

4.4. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included using utility values from the TALAPRO-2 trial for all health states, correcting for costs, and consideration of treatment waning in extrapolations. These changes substantially increased the ICER to between SG$245,000 and SG$285,000 per QALY gained.

4.5. The Committee noted that based on one-way sensitivity analysis of the revised base case, PF utility was a key driver of the results. When the model parameters were varied within their uncertainty ranges, the ICERs remained unfavourably high.

4.6. Overall, based on findings from the CUAs, the Committee considered that talazoparib plus enzalutamide did not represent a cost-effective use of healthcare resources for patients with HRRm mCRPC in whom chemotherapy is not clinically indicated, at the price proposed by the company.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be less than SG$1 million over the first five years of listing talazoparib plus enzalutamide on the MOH List of Subsidised Drugs for patients with HRRm mCRPC in whom chemotherapy is not clinically indicated.

5.2. The Committee considered that the submission estimates and price-volume agreement (PVA) caps were high due to an overestimation of eligible patients, an optimistic uptake rate for talazoparib plus enzalutamide, and not incorporating relative dose intensity from the TALAPRO-2 trial. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG$1 million.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing talazoparib in combination with enzalutamide on the MOH List of Subsidised Drugs for treating patients with HRRm mCRPC in whom chemotherapy is not clinically indicated. The decision was based on the low clinical need, uncertain or unfavourable cost-effectiveness compared with treatment alternatives, and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Talazoparib 0.1 mg, 0.25 mg, 0.35 mg, and 0.5 mg capsules	Talazoparib in combination with enzalutamide for treating patients with homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated.	Not recommended for subsidy	Not recommended for MediShield Life claims

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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