Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

PART 1
For SCREEN confidential information redacted (▉)

Technology appraisal committee B [06 August 2025]

Chair: Charles Crawley

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Company: Pfizer

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on untreated hormone-relapsed* metastatic prostate cancer (mCRPC)

Causes

- Cause remains unknown. Environment, genetic factors (homologous recombination repair mutations), age, Black-African family background increase prostate cancer risk

Epidemiology

- 45,885 newly diagnosed cases in England and Wales (2019-2020)
- 13% of cases metastasise (spread to distant sites of body)
- 1.2% of all UK prostate cancer cases are hormone relapsed and metastatic
- 12,000 annual deaths attributable to prostate cancer

Diagnosis and classification

- Prostate cancer initially responds to androgen deprivation therapy (ADT) / hormone therapy (hormone sensitive) later becoming resistant to ADT (hormone relapsed)*

Symptoms and prognosis

- Symptom burden includes fatigue, pain, urinary frequency
- Stages of prostate cancer include localised, locally advanced and metastatic
- 5-year survival rate of mCRPC is 30%

*Hormone-relapsed (also known as hormone-resistant, hormone-refractory and castrate-resistant) prostate cancer.

Patient perspectives

Submissions from Prostate Cancer UK, TACKLE Prostate Cancer

Living with mCRPC

- For many it is a debilitating and life-changing condition
- People may experience bone pain, spinal cord compression, anaemia, fatigue
- Lack of current curative treatments for this disease stage has a high psychological and emotional burden

Unmet need

- Uncertainty remains with tolerability profiles and response rates of current treatment options. More treatment options with better clinical benefit needed because of non-curative nature of condition.
- Talazoparib with enzalutamide offers a non-steroidal, PARPi+ARPi treatment combination option that can be administered orally

Talazoparib with enzalutamide

- People who cannot tolerate chemotherapy or who do not want chemotherapy would benefit most from this treatment
- Side-effect profile maybe unsuitable for people with underlying medical issues

Note: NICE received one clinical expert submission, this has been summarised in the appendix

Abbreviations: ARPi, androgen receptor pathway inhibitor; PARPi: poly adenosine diphosphate ribose polymerase inhibitor,

Talazoparib (Talzenna, Pfizer) in combination with enzalutamide (Xtandi, Astellas Pharma)

Marketing authorisation	• Treatment in combination with enzalutamide of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated • MHRA marketing authorisation issued: 5th July 2024
Mechanism of action	• Talazoparib is a poly adenosine diphosphate ribose polymerase (PARP) inhibitor. It inhibits PARP1 and PARP2 preventing DNA repair. Enzalutamide is a new hormonal agent that inhibits the androgen receptor pathway (ARPi). When used together, talazoparib and enzalutamide may have a synergistic effect as androgen receptor blockade increases tumour cell sensitivity to PARP inhibition. • Suppression of homologous recombination repair (HRR) genes (for example BRCA1) and co-deletion of RB1 and BRCA2 enhance sensitivity to PARP inhibitors, especially in cases of resistance to androgen receptor blockade.
Administration	• Oral: talazoparib (0.1 or 0.25 mg), enzalutamide (40 mg)
Price	• Talazoparib – list price per pack: £1,655.00 per 30 capsules (PAS proposed) • Enzalutamide – list price per pack: £2,734.67 per 112 tablets (CAA available)

Abbreviations: ARPi, androgen receptor pathway inhibitor; BRCA, Breast Cancer Gene ; CAA: Commercial Access Agreement, HRR, homologous recombination repair ; PARP, poly adenosine diphosphate ribose polymerase; PAS, Patient access scheme; MHRA: Medicines and Healthcare products Regulatory Agency; RB1, retinoblastoma susceptibility gene 1

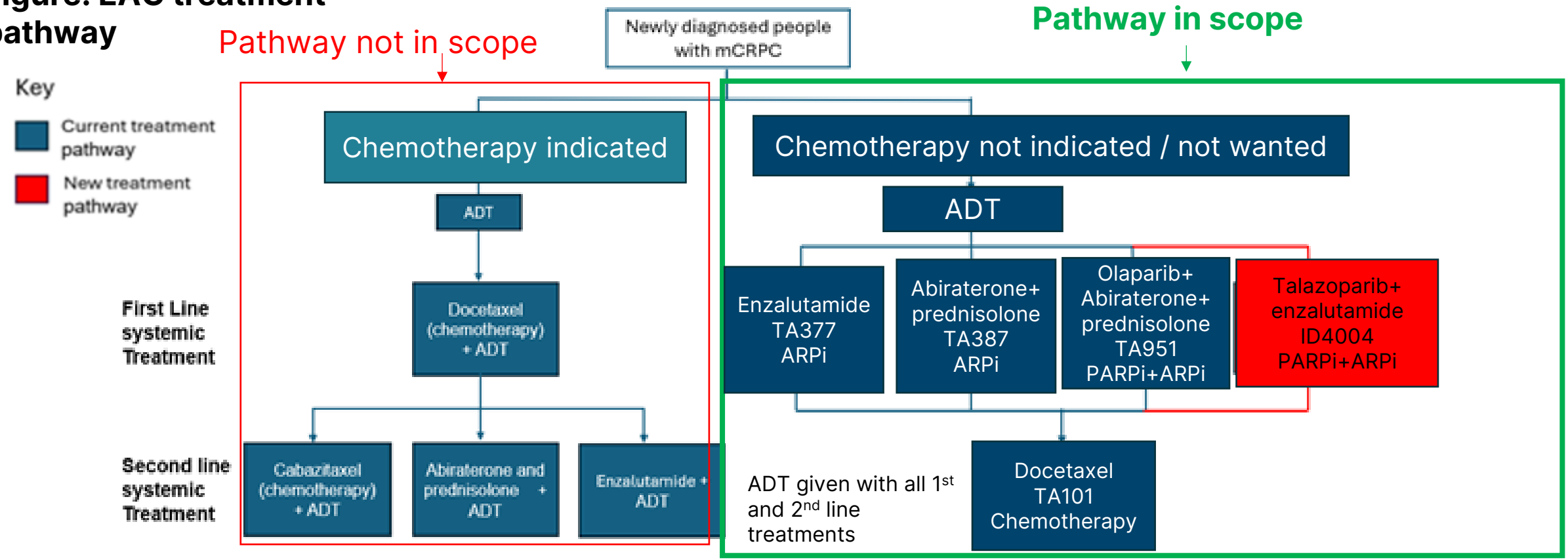
Key issues

Issue	ICER impact
Treatment pathway and comparators	Large
HRR deficient and non-deficient subgroups	Unknown
Reliability of indirect treatment comparison	Large
Time on treatment	Large
Post-progression assumption and utilities	Large

Abbreviations: HRR, homologous recombination repair genes; ICER, Incremental cost-effectiveness ratio

Key issues: Treatment pathway and comparators (1/3)

Figure: EAG treatment pathway



Differences between EAG and company 'chemotherapy not indicated' pathway:

- Pathway also includes people eligible for chemotherapy who may choose ARPis instead (→ chemotherapy 'not wanted' group)
- Prior to starting systemic therapy, watchful waiting is an option
- Second line also includes cabazitaxel as an option

Abbreviations: ADT: androgen deprivation therapy; ARPi, androgen receptor pathway inhibitor ; EAG: external assessment group, PARPi: poly adenosine diphosphate ribose polymerase inhibitor, TA: technology appraisal

Key issues: Treatment pathway and comparators (2/3)

Background:

- Company provided cost-utility analysis for talazoparib with enzalutamide (TALA+ENZ) versus olaparib with abiraterone (OLA+ABI).
- At clarification, upon EAG request, company provided a cost-utility analysis for TALA+ENZ versus ENZ

Company:

- Proposed positioning of TALA+ENZ:
  - → First-line systemic treatment for people with mCRPC for whom chemotherapy is not indicated and where OLA+ABI would otherwise be offered
- Unmet need:
  - → Abiraterone contraindicated population unable to access a PARPi + ARPi combination ~ clinical need remains for PARPi+ARPi combination treatment for population with variable prior history of ARPi
- Comparators:
  - → There is a distinct population eligible for OLA+ABI but not for ENZ and ABI monotherapies. Seeking optimised recommendation in this subpopulation.
- A fully incremental analysis not provided because ENZ is not considered a relevant comparator

Abbreviations: ARPi, androgen receptor pathway inhibitor; PARPi: poly adenosine diphosphate ribose polymerase inhibitor

Key issues: Treatment pathway and comparators (3/3)

EAG comments:

- **Comparators:** Since cost-comparison approach not appropriate, enzalutamide (ENZ) and abiraterone (ABI) are relevant comparators. Market share shows 50-56% get ENZ and 31%-38% get ABI. Company conflated ARPi effectiveness, tolerability and clinician preference with people eligible for ARPi monotherapies. Clinical expert could not identify subgroup that is only offered OLA+ABI and not ENZ / ABI monotherapies

- **Fully incremental analysis:** Company provided cost-utility analysis for TALA+ENZ versus OLA+ABI using TALAPRO-2 and PROpel adjusted trial data. At clarification, company provided model for TALA+ENZ versus ENZ using unadjusted TALAPRO-2 trial data. EAG could not do fully incremental analysis → cost-utility analysis for both comparators not in same population (adjusted versus unadjusted data).

Other considerations (National Clinical Lead for cancer drugs):

- ENZ and ABI are relevant comparators; they are commissioned in less fit population (ECOG 0-2) compared with OLA+ABI (ECOG 0 or 1).
- Fitter population (ECOG 0&1) can have all three options → MAs for all three options are in pre-chemotherapy (asymptomatic/mildly symptomatic)
- In this indication patient access per year is: 1350 for ENZ, 700 for ABI, 350 for OLA+ABI (→ OLA+ABI market share taken from mainly those who would have had abiraterone monotherapy and not enzalutamide)

Is there a definable subgroup receiving OLA+ABI but not ENZ or ABI?
Should ENZ and ABI monotherapies be included as comparators in the same cost-utility model as OLA+ABI?

Abbreviations: ARPi, androgen receptor pathway inhibitor; ECOG: Eastern Cooperative Oncology Group; MA, Marketing authoriation; OLA+ABI, olaparib with abiraterone

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Key clinical trial: TALAPRO-2

	TALAPRO-2 (n = 805)
Design	Two-part trial. Part 2 included in company submission and economic model: ongoing randomised, double-blind, placebo-controlled, phase 3 study.
Population	Adults with asymptomatic or mildly symptomatic mCRPC, receiving ongoing ADT, with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 Cohort 1: including everyone irrespective of homologous recombination repair (HRR) gene alterations Cohort 2: restricted to people with HRR gene alterations Cohort 1 included in company submission and economic model
Intervention	Talazoparib (0.5mg daily) in combination with enzalutamide (160mg daily) (n=402)
Comparator(s)	Placebo in combination with enzalutamide (160mg daily) (n=403)
Primary outcome	Radiographic progression or death (rPFS) by blinded independent central review (BICR)
Key secondary outcomes	Overall survival, rPFS (investigator assessed), objective response rate (investigator assessed and BICR), adverse events, health-related quality of life
Locations	287 sites in 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region
Used in model?	Yes (Cohort 1 only)
Subgroups	Pre-specified subgroup analyses included: age, geographical region, ECOG (0 vs 1), Gleason score, type of progression, baseline PSA, site of metastasis, HRR gene alteration status, previous taxane or novel hormonal therapy

Abbreviations: ADT, androgen deprivation therapy; BICR, blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group performance status, mCRPC, metastatic castration-resistant prostate cancer; HRR, homologous recombination repair, PSA: prostate specific antigen; rPFS, Radiographic progression or death

TALAPRO-2 trial results

	TALA+ENZ (n=402)	ENZ + Placebo (n=403)	HR (95% CI)
Median rPFS by BICR, months (95% CI)	33.1 (27.4, 39.0)	19.5 (16.6, 24.7)	0.667 (0.551, 0.807) P-value <0.0001
Median OS (95% CI), months	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)	0.796 (0.661, 0.958) P=0.0155

Note: Talazoparib and placebo given in combination with enzalutamide. Table adapted from addendum tables 1-2

Abbreviations: BICR: Blinded Independent Central Review; CI, confidence interval; CS, company submission; EAG, external assessment group; HR, hazard ratio; NR, not reported; OS, Overall survival; rPFS: radiographic progression-free survival

Figure: Kaplan-Meier plot of BICR-assessed rPFS

Cohort 1 Part 2 all-comers ITT population at final data cutoff 3rd Sept 2024 (N=805):
Compared to placebo with enzalutamide, talazoparib with enzalutamide (TALA+ENZ) shows:

- statistically significant and clinically meaningful improvement in BICR-assessed rPFS
- statistically significant and clinically meaningful improvement in overall survival (OS)

Key issues: HRR deficient and non-deficient subgroups (1/2)

Background:

- TALAPRO-2 trial included 2 cohorts. Cohort 1 (21% HRR deficient) and Cohort 2 (100% HRR deficient) are different populations.
- Final scope noted HRR 'deficient' and 'non-deficient' subgroups to be relevant.
- Company did not present cost-utility analysis by subgroup. Economic analysis used Cohort 1 only.
- At clarification, company provided clinical efficacy data for Cohort 2.

Table A: Comparison of Cohort 1 and Cohort 2 (September 2024 data cut)

	Talazoparib with enzalutamide	Placebo with enzalutamide	Hazard ratio (95% CI)
Cohort 1			
Sample size (n)	402	403	--
Median rPFS by BICR, months (95% CI)[a]	33.1 (27.4, 39.0)	19.5 (16.6, 24.7)	0.667 (0.551, 0.807) p<0.0001
Events (%)	202 (50.2)	231 (57.3)	--
Cohort 2			
Sample size (n)	200	199	--
Median rPFS by BICR, months (95% CI)[a]	30.7(24.3, 38.5)	12.3(11.0, 16.5)	0.468(0.359, 0.612) p<0.0001
Events (%)	99 (49.5)	127 (63.8)	

Table B: rPFS Comparison of Cohort 1 HRR subgroups (*August 2022 data cut)

	HRR deficient n = 169	HRR non-deficient n = 636	All-comers n = 805
Hazard ratio (95% CI)	0.46 (0.30, 0.70) p=0.0003	0.70 (0.54, 0·89) p=0.0039	0.63 (0.51, 0.78) p<0.0001

Abbreviations: HRR, homologous recombination repair; CI, Confidence interval; rPFS, Radiographic progression or death; BICR, Blinded Independent Central Review

*Agarwal 2025, EAG report 3.2.3.2

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Key issues: HRR deficient and non-deficient subgroups (2/2)

Company:

- Irrespective of their tumour's HRR status, talazoparib with enzalutamide (TALA+ENZ) could potentially be equally effective for people with mCRPC.
- TALA+ENZ gained marketing authorisation using Cohort 1 trial outcomes in 'adults with mCRPC for whom chemotherapy is deemed clinically inappropriate', regardless of their mutational status

EAG comments:

- PARP inhibitors (TALA/Olaparib)→ likely more effective in tumour cells that are HRR deficient.
- Clinical experts state: olaparib with abiraterone only offered for HRR deficient tumours, same expected for TALA+ENZ.
- TALAPRO-2 shows tumour's HRR status likely a treatment effect modifier → efficacy reduced in people with HRR non-deficient or unknown tumours (Table B slide 14). With synergistic effect of PARPI+ARPi would expect similar outcomes between HRR deficient vs non-deficient
- Cohort 2 shows substantially worse outcomes for ENZ versus Cohort 1 → Subgroup analysis would reduce uncertainty about comparative effectiveness of TALA+ENZ versus ENZ

Other considerations (Clinical expert):

- Clinical experts can decide whether to use it predominantly in HRR deficient cases.

Does Committee think the cost-utility analysis should model the subgroups included in the final scope?

Abbreviations: BRCA, Breast cancer susceptibility gene ; HRR, homologous recombination repair

Key issues: Reliability of indirect treatment comparison (1/2)

Company: Three ITC approaches taken for **TALA+ENZ versus OLA+ABI:** No studies directly compare the treatments - ITC conducted for outcomes of interest including: rPFS, OS

1.Proportional hazard NMA: Assumes hazards are proportional overtime. Cox proportional hazards model within a Bayesian framework used.

2.Fractional polynomial NMA: Allows for flexible, non-proportional hazard modelling. All OS analyses impacted by non-convergence and could not be used. rPFS fits associated with wide confidence intervals. Estimates considered not usable for modelling.

3.Unanchored MAIC: No common treatment arm, assumes all prognostic factors and effect modifiers included in the analysis and both trial baseline populations are comparable. TALAPRO-2 patient level data matched to PROpel and re-weighted.

Direct treatment comparison for **TALA+ENZ versus ENZ** using TALAPRO-2 trial data provided at clarification.

EAG comments: TALA+ENZ versus OLA+ABI: See critique on next slide.

- **TALA+ENZ versus ENZ:** low risk of uncertainty. Unweighted TALAPRO-2 data used → Comparison not included in same model as OLA+ABI - fully incremental analysis not done despite EAG request/NICE methods.
- **TALA+ENZ versus ABI**: Company did not include ABI as comparator. EAG assumes same clinical efficacy between ABI and ENZ (TA951 assumption) → ENZ arm from TALAPRO-2 used. Company's PH NMA showed reduced OS and rPFS for ABI versus ENZ

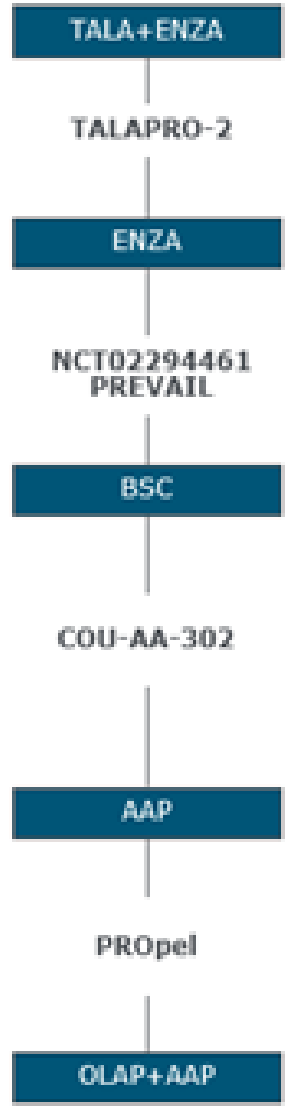

Figure: PH NMA network diagram

Key issue: Reliability of indirect treatment comparison (2/2)

Methods	Results (TALA+ENZ vs OLA+ABI)	EAG critique	Outcome
PH NMA	Fixed effects: rPFS: HR [redacted] 95% CrI [redacted] OS: HR [redacted]; 95% CrI [redacted] (Data cutoff: August 2022)	• PH assumption not met for rPFS or OS • Fixed effect analysis preferred • Analysis using August 2022 data cut preferred due to transparency in reporting	Violating PH assumption can lead to biased estimates and inaccurate conclusions – unanchored MAIC & FP NMA requested **Fully incremental analysis possible**
FP NMA	Not applicable	• Uncertainty in rPFS model fits validation. • Unable to validate some OS relative effect estimates	OS estimates not usable - MAIC/FP NMA blend needed. FP NMA not suitable for base case. **Fully incremental analysis possible**
Unanchored MAIC – (Company, EAG Basecase)	rPFS: HR: [redacted] [95% CI: [redacted]; [redacted]]) OS: HR: [redacted] [95% CI: [redacted]; [redacted]]) (Data cutoff: September 2024)	• Differences between trial baseline pain score (BPI-SF) could favour TALA • Expert concerned that time to mCRPC was key prognostic factor not adjusted	Results uncertain. No issues with proportionality/ indirectness of evidence. Most appropriate option - company and EAG base case. **Robust fully incremental analysis not possible**

Does Committee agree with the a) unadjusted MAIC used as base case for **TALA+ENZ vs OLA+ABI**, b) unweighted TALAPRO-2 data used for **TALA+ENZ vs ENZ** c) equal efficacy assumption between ENZ and ABI using unweighted TALAPRO-2 data for **TALA+ENZ vs ABI**

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Key Issue: Time on treatment

Background: Company submitted partitioned survival model with 3 health states: rPFS, progressive disease (PD), and death. PD health state split into time on subsequent treatment and time on palliative care.

Company

- TALA+ENZ: TTD data extrapolated using unweighted trial data (TALAPRO-2)
- OLA+ABI: Assumed TTD = rPFS based on landmark estimates from PROpel trial and CADTH submission as TTD trial data not available
- ENZ: TTD data extrapolated using unweighted trial data (TALAPRO-2 versus TALA+ENZ)
- Mean TTD: [redacted] months for TALA+ENZ and [redacted] months for OLA+ABI

EAG comments: TALA+ENZ: rPFS was longer in weighted data compared with unweighted data. Similar result expected with TTD. Using unweighted TTD favours TALA+ENZ (see appendix)

- OLA+ABI: TTD assumption did not align with prior NICE and CADTH appraisals:
  - CADTH assumed lower TTD than rPFS: rPFS (TTD) at 15 years = 12% (5%), 20 years = 7% (3%)
- EAG base case (based on clinical expert) assumed relationship between TTD and rPFS observed for:
  - TALA+ENZ applied to OLA+ABI and
  - ENZ applied to ABI

At FAC EAG note→ scenario where TTD=rPFS for all treatments is a reasonable alternative but may overestimate all treatment costs

	Mean rPFS (months)	Mean TTD (months)
TALA+ ENZ	Unweighted: [redacted] Weighted: [redacted]	Unweighted: [redacted] Weighted: [redacted]
OLA+ ABI	Unweighted: [redacted] Weighted: [redacted]	Unweighted: [redacted] Weighted: [redacted]

How does committee want TTD to be modelled?

Abbreviations: CADTH, Canada's Drug Agency; FAC, factual accuracy check; PD, progressive disease rPFS: radiographic progression-free survival; TTD, Time to treatment discontinuation

Key issue: Post-progression assumption and utilities

Background: NICE acquired permission to unredact utility values from TA951 - were shared with company and EAG after clarification prior to company factual accuracy check

Company: Post-progression utility values from TALAPRO-2 not used → small sample size and missing data. Model assumed cohort progress and enter palliative care immediately after stopping one line of subsequent treatment post-progression. Significant decline expected in palliative care state, assuming same utility as post-progression state is an overestimate. TA377 utilities used for post-progression and palliative care:

- post-progression: 0.658 ~ first line post-progression weighted mean utility from TA377 (Wolfe 2012, Diels 2014)
- palliative care: 0.5 ~ Swedish study reporting QoL of people one year prior to death from prostate cancer (Sandblom 2004)

EAG comments: Company utility values do not meet NICE reference case. Higher post-progression utility values reported in TA951/recent literature review: 0.65 – 0.775. Company revised palliative care cost at clarification. Company model assumes majority of time post progression was in palliative care (see appendix): Assumption of moving to palliative care after subsequent treatment does not apply for fixed treatment duration therapies and multiple lines of subsequent therapy can also be offered.

- Lower post-progression utility and higher palliative care cost favours TALA+ENZ → TALA+ENZ cohort spend more time progression free versus post-progression compared with OLA+ABI in company model
- TA951 post-progression utility value used in EAG base case for entire post progression state, including palliative care (0.775), reduced time spent in palliative care assessed in scenarios

How does Committee want post-progression utility and the transition to palliative care to be modelled?

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Equality considerations

Identified at scoping stage and in TA951: age, race and gender reassignment are protected under Equality Act 2010 and should be considered within equalities issues in this appraisal

- Risk of prostate cancer increases with age
- Prostate cancer disproportionately affects people from Black African, Caribbean, any other Black, Black British, or Caribbean background*
- Greater representation of people from ethnic minority backgrounds is needed to understand if study results are generalisable
- TA951 noted people of Ashkenazi Jewish ethnicity have a greater risk of having a BRCA mutation, and so have a higher risk of developing prostate cancer

*Source in notes (Down et al. 2024) BRCA, Breast cancer susceptibility gene; PARPi: poly adenosine diphosphate ribose polymerase inhibitor

Uncaptured benefits

Identified at scoping

Talazoparib with enzalutamide combination offers:

- a steroid free alternative: olaparib with abiraterone combination includes prednisolone (steroid) as a treatment component. This increases risk of steroid exposure which is difficult for a set of the population.
- an alternative PARPi+ARPi treatment option: Abiraterone is not first-choice option of newer hormonal treatment for some people. So, a combination containing different newer hormonal treatment (enzalutamide) and without steroid was said to promote equality and ensure all eligible patients have access to a PARPi combination

Is steroid exposure a key concern and what proportion of the population is affected?

Abbreviations: ARPi, androgen receptor pathway inhibitor; PARP, poly adenosine diphosphate ribose polymerase;

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Summary of company and EAG base case assumptions

EAG corrected company base case: 1. NICE's preferred eMIT prices for cabazitaxel and Radium-223 costs 2. corrected inflation for end-of-life costs

ICER impact: Small  Large 

Assumption	Company base case	EAG base case	Key issue?
Applies to comparison versus 'olaparib with abiraterone' and 'enzalutamide'			
Post progression utility	Post progression = 0.658 palliative care = 0.5 (TA377)	Post progression = 0.775 (TA951) - same value assumed for palliative care	Yes 
Drug wastage	Partially included	Fully applied, as per company scenario	No 
Terminal care cost	Included	Excluded, double counting with palliative care	No 
Applies only to comparison versus 'olaparib with abiraterone' (weighted model)			
Skeletal Related Events (SRE) – discussed in slide 29	Included - historical pooled data for olaparib with abiraterone	Excluded – scenario presented using TALAPRO-2 SRE data for all treatment arms	No 
Time to treatment discontinuation (TTD)	Unweighted TTD , OLA+ABI: TTD = rPFS	Adjusted TTD using comparative Radiographic progression or death(rPFS)	Yes 
Applies only to comparison versus 'enzalutamide' (unweighted model)			
Extrapolations - discussed in slides 25-28	Overall survival (OS), rPFS – log normal	OS – generalised gamma, rPFS - gamma	No 

Minor issue: Enzalutamide OS extrapolations (1/2)

Distribution	Goodness-of-fit		
	AIC	BIC	Sum rank
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]

Enzalutamide KM for OS overlaid with the extrapolated parametric survival curves

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan Meier; OS, Overall survival

Minor issue: Enzalutamide OS extrapolations (2/2)

Company preferred

EAG preferred

Distribution	Enzalutamide OS					
	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company:
OS - log-normal/exponential curves did not exhibit kinks, log-normal provided better visual fit.

EAG:
OS - Lognormal curve provides poor visual fit indicating use of curves not appropriate. Generalised gamma provides better visual fit

Which distribution provides the most plausible outcomes for OS?

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM, Kaplan Meier; OS, Overall survival

Minor issue: Enzalutamide rPFS extrapolations (1/2)

[redacted]

Distribution	Goodness-of-fit		
	AIC	BIC	Sum rank
Log-normal	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Enzalutamide KM for rPFS overlaid with the extrapolated parametric survival curves

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan Meier; rPFS, Radiographic progression or death;

Minor issue: Enzalutamide rPFS extrapolations (2/2)

Company preferred

EAG preferred

Distribution	Enzalutamide rPFS					
	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company:
rPFS - log-normal curve provided best statistical fit, had lowest sum AIC/BIC. Good visual fit, with no kinks observed in the plot.

EAG:
rPFS – EAG agreed with the curve selection, it preferred Gamma because it did not cause OS and rPFS to cross early on in the model

Which distribution provides the most plausible outcomes for rPFS?

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM, Kaplan Meier; OS, Overall survival; rPFS, Radiographic progression or death;

Minor issue: Skeletal related events

- Company assumed skeletal related events (SREs) rates higher for OLA+ABI versus TALA+ENZ
  - Based on TA831 (TA887 – Olaparib BRCA mutation positive mCRPC) and TA951 (OLA+ABI untreated mCRPC) trials
- EAG base case excludes SREs:
  - Based on EAG's clinical expert advice
  - TA831 (pooled data from ALSYMPCA, COU-AA-301 and AFFIRM) and TA951 (PROpel) trials over 10 years old and not relevant - patient population and bone health management has changed
  - Company's method for inclusion of SREs in model not robust. EAG scenario analysis assumes SREs occur at same rate as **TALAPRO-2** for all arms.

How should SREs be modelled?

Table A: SRE in company model

Skeletal-related event	Frequency	
	Talazoparib with enzalutamide	Olaparib with abiraterone
Spinal cord compression	[redacted]	15.5%
Radiation to bone	[redacted]	67.7%
Surgery to bone	[redacted]	4.1%
Pathologic bone fracture	[redacted]	12.9%

Table B: SRE safety population TALAPRO-2

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Any SRE (%)	[redacted]	[redacted]
Non-symptomatic fracture (%)	[redacted]	[redacted]
Radiotherapy to bone (%)	[redacted]	[redacted]
Spinal cord compression (%)	[redacted]	[redacted]
Surgery to bone (%)	[redacted]	[redacted]
Symptomatic fracture (%)	[redacted]	[redacted]

Abbreviations: BRCA, Breast cancer susceptibility gene; OLA+ABI, Olaparib with abiraterone; SRE, Skeletal related event; TALA+ENZ , Talazoparib with enzalutamide

Key issues and questions

Issue	ICER impact	Questions for committee
Treatment pathway and comparators	Large	Is there a definable subgroup receiving OLA+ABI but not ENZ or ABI? Should ENZ and ABI monotherapies be included as comparators in the same cost-utility model as OLA+ABI?
HRR deficient and non-deficient subgroups	Unknown	Does Committee think the cost-utility analysis should model the subgroups included in the final scope?
Reliability of indirect treatment comparison	Large	Does Committee agree with the a) unadjusted MAIC used as base case for **TALA+ENZ vs OLA+ABI**, b) unweighted TALAPRO-2 data used for **TALA+ENZ vs ENZ** c) equal efficacy assumption between ENZ and ABI using unweighted TALAPRO-2 data for **TALA+ENZ vs ABI**
Time on treatment	Large	How does Committee want TTD to be modelled?
Post-progression assumption and utilities	Large	How does Committee want post-progression utility and the transition to palliative care to be modelled?
Minor issue: Enzalutamide OS and rPFS extrapolations	Small	Which distribution provides the most plausible outcomes for OS and rPFS?
Minor issue: Skeletal related events	Small	How should SREs be modelled?

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Abbreviations: ABI, abiraterone; ENZ, enzalutamide ; MAIC, Matching adjusted indirect comparison; OLA+ABI, olaparib with abiraterone; OS, Overall Survival; rPFS, Radiographic progression or death; SREs, Skeletal related events ; TALA+ENZ, talazoparib with enzalutamide; TTD, Time to treatment discontinuation

Cost-effectiveness results when cPAS is included

Confidential discounts available for comparators – ICERs are presented in Part 2 slides - ICER ranges from base case and selected scenarios presented below

No.	Scenario (applied to company base case)	ICER (£/QALY) versus OLA+ABI (weighted)	ICER (£/QALY) versus ENZ (unweighted)	ICER (£/QALY) versus ABI (unweighted)
1	**Company base case**	Dominant	Less than £20,000	Not included
2	EAG corrected company base case	Dominant	Less than £20,000	Not applicable
3	EAG base case	Over £50,000	Over £20,000 but under £30,000	Over £50,000
4	Reduced time spent in palliative care	⇧ Increase	⇧ Increase	Not assessed
6	Apply rPFS Hazard Ratio to TTD	⇧ Increase	Not applicable	Not applicable
7	TTD equal to rPFS	⇩ Decrease	Not applicable	Not applicable
8	rPFS Fractional Polynomial NMA	⇧ Increase	Not applicable	Not applicable
9	OS and rPFS Hazard Ratio (HR) ABI vs ENZA from TA951 (1.19)	Not applicable	Not applicable	⇩ Decrease

Probabilistic results presented: For TALA+ABI versus ENZ comparison, there was a difference between the company's deterministic and probabilistic results.

Abbreviations: cPAS, Comparator discounts; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; OS, Overall survival ; rPFS, Radiographic progression or death ; TTD, Time to treatment discontinuation

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Supplementary appendix

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Decision problem

	Draft scope for consultation	Final scope for cost-comparison	Company	EAG
Population	People with hormone-relapsed metastatic prostate cancer who have not had prior systemic treatment		N/A	TALAPRO-2 population matched EAG's defined population of: adults with mCRPC who cannot have, or do not want, chemotherapy.
Intervention	Talazoparib in combination with enzalutamide			
Comparators	Enzalutamide, Abiraterone with prednisone or prednisolone, Docetaxel, Olaparib, **Olaparib with abiraterone** *(subject to NICE evaluation)	**Olaparib with abiraterone** (and prednisone or prednisolone)	Olaparib with abiraterone	• Olaparib with abiraterone was only relevant comparator for cost-comparison analysis • Olaparib with abiraterone, enzalutamide and abiraterone with prednisone or prednisolone are all in same position in treatment pathway as intervention arm and are all relevant comparators for cost-utility analysis
Outcomes	Overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life			
Subgroups	None included	If the evidence allows HRR status including: BRCA 1&2, ATM gene	No subgroup analyses were conducted	HRR status relevant subgroup. Company's economic analysis did not include cost-effectiveness split by HRR status

Abbreviations: BRCA, Breast cancer susceptibility gene ; HRR, homologous recombination repair

TTD and rPFS from TALAPRO-2

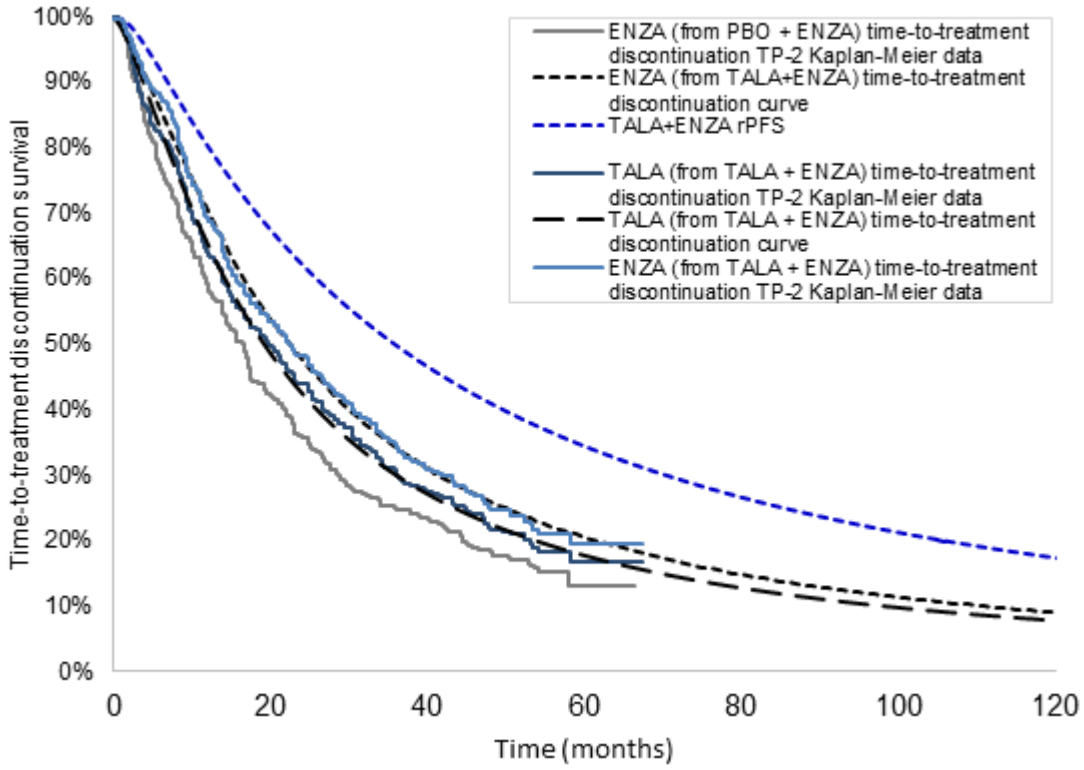

Figure A: Comparison of TTD and rPFS KM

Figure B: Comparison of TTD extrapolations and rPFS KM and extrapolation

Abbreviations: KM, Kaplan Meier; rPFS, Radiographic progression or death; TTD, Time to treatment discontinuation

Time spent per line of treatment in company model

	Talazoparib with enzalutamide (MAIC weighted)	Olaparib with abiraterone (MAIC weighted)	Talazoparib with enzalutamide (unweighted)	Enzalutamide (unweighted))
Time spent on 1st line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Time spent on 2nd line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Time spent in palliative care	[redacted]	[redacted]	[redacted]	[redacted]
% of time receiving 2nd line treatment in the progressed group	[redacted]	[redacted]	[redacted]	[redacted]
% of time receiving palliative care in the progressed group	[redacted]	[redacted]	[redacted]	[redacted]

The EAG calculated the time spent in each health state using the company base case economic model: This indicated that the majority of time post progression was assumed to be in palliative care

Clinical perspectives

Submissions from one clinical expert

Aim of treatment

Prolong overall survival, reduce progression, maintain or improve quality of life

Talazoparib with enzalutamide

- Not considered a step change
- Side effects include grade 3+ anaemia which may require closer monitoring, treatment interruption and transfusion. This is manageable within UK SACT clinics
- Talazoparib and enzalutamide are oral treatments
- Combination significantly delays time to cytotoxic chemotherapy

Abbreviations: SACT, Systemic Anti-Cancer Therapy