Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer

Technology appraisal committee B [4th October 2023]

Slides for public – contains no confidential information only

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Background on untreated metastatic hormone-relapsed prostate cancer

- Metastatic hormone-relapsed (or castration-resistant) prostate cancer (mCRPC) = cancer that has spread beyond the prostate and no longer responds to androgen deprivation therapy (ADT).
- Olaparib blocks enzymes that repair damaged DNA in cancer cells and as a result, cancer cells die.
- Abiraterone blocks and stops the body from making testosterone which can help slow down the growth of cancer.

Risk factors

- Risk of prostate cancer increases with age – most cases developed in people aged 50+.
- More common in people from a black-African family background, those with a family history of prostate cancer, and those with HRR (homologous recombination repair) mutations.

Epidemiology

- Estimated that 1,300 people will be diagnosed with mCRPC in 2023 with a 49% 5-year survival rate and a profound effect on quality of life.

Symptoms

- If the cancer has spread, symptoms can include tiredness, bone pain and unexplained weight loss.

Olaparib (Lynparza, AstraZeneca) in combination with abiraterone (and prednisone or prednisolone)

Technology details

Marketing authorisation	• Olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated • MHRA granted MA 15th March 2023.
Mechanism of action	• Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair, ultimately resulting in tumour cell death. • Abiraterone is a new hormonal agent (NHA) that inhibits androgen synthesis via cytochrome P450 17 alpha-hydroxylase in prostate cancer.
Administration	• Oral: olaparib (300 mg), abiraterone (1000mg), prednisone or prednisolone (5mg)
Price	• Olaparib and abiraterone both have confidential discounts • Prednisolone: £0.94 per 5mg tablets x 28

Abbreviation: MHRA, Medicines and Healthcare products Regulatory Agency; mCRPC, metastatic castration-resistant prostate cancer

Patient perspectives

Submissions from a patient expert and Prostate Cancer UK

- People may have more significant symptoms as the disease becomes more aggressive when hormone resistance occurs e.g., pain, fatigue, anaemia, weight loss and reduced appetite.
- People with mCRPC have limited treatments available → need for treatments that offer good clinical benefit and improvement in overall survival.
- Patients / families are disappointment that there are no curative treatments for mCRPC.
- Olaparib (TA887) available for people with BRCA1/2 mutation previously treated with NHA.
- Olaparib with abiraterone offers people not only another treatment choice, but more certainty around surviving for longer.

"Since starting on the combination of abiraterone, olaparib and prostap my PSA has stayed virtually undetectable"

NICE

Abbreviation: mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal treatment; BRCA, breast cancer gene; PSA, prostate-specific antigen

Other considerations

Equality considerations

- 1/6 people with prostates develop prostate cancer.
- Risk of prostate cancer increases with age.
- People with a prostate who do not identify as male can develop prostate cancer.
- Prostate cancer disproportionately affects people of a black ethnicity.
- People from Ashkenazi Jewish background have a 10x greater risk of having a BRCA gene mutation, which increases the risk of developing prostate cancer.

Innovation

- Olaparib plus abiraterone 1st combination therapy to be licensed for 1st line use in people with mCRPC for whom chemotherapy is not clinically indicated.

Uncaptured benefits

- Model unlikely to fully capture HRQoL benefits of delaying treatment with chemotherapy.

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Abbreviation: mCRPC, metastatic castration-resistant prostate cancer; HRQoL, health-related quality of life; BRCA, breast cancer gene

Key issues

Summary of issue	Resolved?	Uncertainty	ICER impact
Population - interpretation and implications of the MA	Partly	Structural	Unknown
BRCA subgroup efficacy	No	Structural	Large
Subsequent olaparib monotherapy	No	Structural	Unknown
Enzalutamide and abiraterone equivalence	No	Parameter	Large
Overall survival extrapolation	Partly	Parameter	Large

Resolved issues: testing costs, dosing calculations, utilities, modelling of adverse events, appropriateness of time to discontinuation extrapolations

Abbreviation: MA, marketing authorisation; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio

Decision problem

	Final scope	Company	EAG
Population	Adults with mCRPC for whom chemotherapy is not clinically indicated.	N/A	Trial not fully aligned with proposed population.
Intervention	Olaparib plus abiraterone (and prednisone or prednisolone)		
Comparators	• Enzalutamide • Abiraterone with prednisone or prednisolone	• Enzalutamide - main comparator • Abiraterone with prednisone or prednisolone - secondary comparator Rationale: enzalutamide used more than abiraterone (67% vs 33%)	Enzalutamide and abiraterone are equally relevant. Clinical advice: both used in practice.
Outcomes	Overall survival, progression-free survival, response rate, adverse effects, HRQoL		
Subgroups	If the evidence allows: • HRR status including: ↳ BRCA 1 & 2 ↳ ATM gene.	• HRR mutation status (pre-specified) • BRCA (given after clarification)	Key subgroup: people with / without BRCA mutations.

Does the committee accept that both abiraterone and enzalutamide are relevant comparators?

Abbreviations: HRQoL, Health-related quality of life; HRR, homologous recombination repair; BRCA, breast cancer gene; ATM, ataxia-telangiectasia mutated; mCRPC, metastatic castration-resistant prostate cancer

Treatment pathway

Taxane

NHA

Retreatment with olaparib, enzalutamide or abiraterone is not permitted; Docetaxel can be given twice
Olaparib monotherapy: after progression on new hormonal agent e.g., abiraterone or enzalutamide.
Radium-223: for adults with symptomatic bone metastases and no known visceral metastases
Cabazitaxel: requires previous docetaxel, ECOG 0/1. Does not cover those who had docetaxel then abiraterone or enzalutamide.

	Hormone sensitive	Hormone relapsed				
Non-metastatic	ADT Radical therapy- surgery or radiotherapy	Progression → ADT Darolutamide + ADT in high risk (TA660) Apalutamide + ADT in high risk (TA740)				
Metastatic	ADT (NG131) Docetaxel + ADT (NG131) Apalutamide + ADT (TA741) Enzalutamide + ADT (TA712) Darolutamide + docetaxel + ADT (TA903 - June 2023)	**Chemotherapy not indicated** Olaparib with abiraterone (ID3920)	**Chemotherapy 'not yet indicated'** Abiraterone (TA387) Enzalutamide (TA377) Watchful waiting	**Chemotherapy indicated** Docetaxel (TA101) – Karnofsky performance score 60% +	**Post-docetaxel** Abiraterone (TA259) Enzalutamide (TA316) Cabazitaxel (TA391) Docetaxel re-treatment Radium-223 (TA412) *Olaparib (BRCA only) – prior treatment with NHA (TA887)*	**Cannot tolerate docetaxel**

Abbreviations: ADT: androgen deprivation therapy; NHA, new hormonal agent; NG: NICE guideline; TA: technology appraisal

Key issue: Population (1/2)

Background

- Enzalutamide/abiraterone: adults with mCRPC in whom chemotherapy is not yet clinically indicated.
- Olaparib with abiraterone: adults with mCRPC in whom chemotherapy is not clinically indicated.
  - ↳ Company: not eligible for chemotherapy if 1) had docetaxel pre-mCRPC, and retreatment not permitted, 2) not fit enough to have docetaxel, 3) contraindicated to docetaxel.
  - ↳ 75% of PROpel eligible to receive chemotherapy = ineligible for olaparib with abiraterone?

Company

- Pathway changes since enzalutamide and abiraterone appraisals (2016) → docetaxel (2021) and enzalutamide (2022) available to treat metastatic hormone-sensitive prostate cancer.
  - Docetaxel not required before NHA - use clinical judgment, eligibility and/or patient choice
  - UK clinical experts: NHAs more efficacious, tolerable, and less toxic than docetaxel. Even if fit enough for chemotherapy, would still mostly treat with NHA.
- Olaparib with abiraterone MA reflects shift in pathway and PROpel trial → 25% of trial had docetaxel in pre-mCRPC setting, 75% were chemo-naïve = proportion of trial ineligible for olaparib.

Return to questions

Abbreviation: MA, marketing authorisation; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agents

Key issue: Population (2/2)

EAG comments

- MA hard to interpret - may impact pathway positioning and applicability to NHS population.
  - Interpreted literally = most of PROpel (75%) not eligible for olaparib with abiraterone within MA
    - ↳ Outcomes in PROpel population outcomes may be better than in MA population.
  - Implication: people chemotherapy-naïve, fit enough, and not contraindicated to docetaxel, should receive docetaxel before they receive olaparib plus abiraterone.
    - ↳ Aware not preferred option due to intensity, severity and side effects of chemotherapy.
- Company assume that when docetaxel not the preferred / most appropriate treatment (majority of cases) – chemotherapy considered 'not clinically indicated', despite being eligible to have it.
  - 'Not clinically indicated' → ineligible for chemotherapy or chemotherapy not preferred?
- "whom chemotherapy is not clinically indicated" implies chemotherapy clinically indicated for some.
  - Size of 'clinically indicated' group unknown in PROpel and NHS - hard to exclude docetaxel as relevant comparator and may limit results applicability to NHS.

Other considerations

- Clinical expert: almost all clinicians would use NHA before docetaxel for almost all patients.
- Prostate Cancer UK: MA doesn't match trial and may exclude people who benefit from treatment.

Return to questions

Where should olaparib with abiraterone be positioned in pathway? Is the trial population relevant and generalisable to this positioning? Is docetaxel a relevant comparator?

Clinical effectiveness

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Key clinical trial

	PROpel (n=796)
Design	Randomised, double-blind, placebo-controlled, phase 3 trial
Population	Adults with mCRPC who are untreated in the mCRPC setting.
Intervention	Olaparib plus abiraterone and prednisone or prednisolone (n=399)
Comparator(s)	Placebo plus abiraterone and prednisone or prednisolone (n=397)
Primary outcome	Radiographic progression or death (rPFS) by investigator assessment
Key secondary outcomes	Overall survival, adverse events, HRQoL, time to discontinuation, time to a symptomatic skeletal-related event
Locations	17 countries, 6.1% (n = 49) from the UK.
Used in model?	Yes
Subgroups	Pre-specified subgroup analyses included: HRRm status, baseline ECOG PS, age at randomisation, region, race, baseline PSA (prostate specific antigen)

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Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; HRQoL, health-related quality of life; HRRm, homologous recombination repair mutation; ECOG PS, Eastern Cooperative Oncology Group Performance Status

Clinical trial results

	rProgression free survival			Overall survival		
	Median months		HR (95% CI)	Median months		HR (95% CI)
	Olaparib	Placebo		Olaparib	Placebo	
ITT (N=796, 100%)	[redacted]	[redacted]	[redacted]	42.1	34.7	0.81 (0.67-1.00)
BRCAm (N=85, 11%)	[redacted]	[redacted]	[redacted]	NR	23.0	0.29 (0.14, 0.56)
Non-BRCA (N=693, 89%)	[redacted]	[redacted]	[redacted]	39.6	37.9	0.91 (0.73, 1.13)
HRRm (n = 226, 28%)	[redacted]	[redacted]	[redacted]	NR	28.5	0.66 (0.45–0.95)
non-HRRm (n = 552, 69%)	[redacted]	[redacted]	[redacted]	42.1	38.9	0.89 (0.70–1.14)

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Abbreviations: BRCA, breast cancer gene; HRR, homologous recombination repair mutation; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat

Key issue: BRCA subgroup efficacy

Background

- OS and PFS gains larger in BRCA subgroup than ITT and non-BRCA subgroup.
- Olaparib monotherapy (TA887) only licensed in people with BRCA1/2 mutations
- Recent advice to FDA: restrict olaparib + abiraterone license to people with BRCA mutation.

Company

- PROpel powered to show efficacy/safety in ITT population, regardless of biomarker status.
  - ↳ Subgroup analyses non-stratified and post-hoc - interpret results with caution.
- ITT population: 11% BRCAm, unlikely benefit is entirely driven by small subgroup.
- Olaparib + abiraterone = improved anti-tumour effect shows some efficacy in non-HRRm population.
- PROpel evidence should be considered on own merits - TA887 conclusions not applicable to this.

EAG comments

- Data strongly indicates OS and PFS benefits are larger for BRCA subgroup.
- Relative OS differences has significant impact on cost-effectiveness.

Other considerations

- Clinical expert: biological reason why olaparib's mechanism of action is different alone vs with NHA.
- Prostate cancer UK: olaparib + abiraterone likely to benefit non-BRCA HRRm similar to TA887.

Which populations are relevant for decision making – full MA (ITT), HRR or BRCA subgroup?

Return to questions

Abbreviation: FDA, Food and Drug Administration; BRCAm, breast cancer gene mutation; NHA, new hormonal agent; ITT, intention-to-treat; HRRm, homologous recombination repair mutation; OS, overall survival; PFS, progression free survival; MA, marketing authorisation

Key issue: Subsequent olaparib monotherapy

Background

- People with BRCAm who progress after NHA are eligible for olaparib monotherapy (TA887).
- [redacted]% of comparator arm had olaparib monotherapy, but ~10% of PROpel had BRCAm.

↳ EAG: underestimate comparator arm OS = overestimate olaparib + abiraterone cost effectiveness?

Company

- ~50% with mCRPC will have 1 line of therapy and not progress to have a subsequent treatment.
- Clinical experts: barriers to accessing olaparib monotherapy because of challenges in uptake, feasibility and/or failure rate of deriving BRCA testing.
- [redacted]

EAG comments

- Accept not all with BRCAm will have subsequent olaparib but use in PROpel likely less than NHS.
  - Issue more significant in BRCA subgroup → whole comparator arm eligible for olaparib.
- Lack of trial design generalisability causes model structure limitations - may be incapable of capturing QALY benefits in subgroup comparator arm, where most expected to have olaparib.

Other considerations

Clinical expert: 10% may be BRCA positive but only 2.5% would get olaparib in real world.

- Real world testing is a significant issue that takes time complete.

Return to questions

Is PROpel subsequent olaparib monotherapy use generalisable to the NHS population?

Key issue: Enzalutamide and abiraterone equivalence (1/2)

Background

- Company: enzalutamide and abiraterone are assumed clinically equivalent in the model = HR: 1.00
  - Used indirect methods to demonstrate relative efficacy between enzalutamide and abiraterone.
  - Exploratory OS NMA = HR: [redacted] (95% CrI: [redacted]). No PFS NMA, trials comparator arms - not considered clinically equivalent.
- EAG: ran broader search for non-randomised evidence and pooled 9 studies in meta-analysis = HR: 0.84, 95% CI: 0.8 - 0.9 → OS benefit in favour of enzalutamide.

Company

- OS NMA: no meaningful difference between abiraterone and enzalutamide – supported by 6 experts
  - ↳ EAG consider HR unreliable due to trial heterogeneity. Applies equally to EAG meta-analysis.
- EAG meta-analysis included:
  - ↳ Non-randomised studies - more prone to bias and confounding due to lower evidence standard.
  - ↳ People pre-treated with docetaxel (different risk profile) – not aligned with olaparib positioning.
- EAG suggest enzalutamide more effective, but EAG clinical advice said efficacy is similar.
- Only 1 prospectively designed comparative study for enzalutamide vs abiraterone.
  - ↳ No significant PFS (HR: 1.04, 95% CI: 0.9-1.3) or OS (HR: 1.00, 95% CI: 0.8-1.3) difference.

Return to questions

Abbreviations: PFS, progression-free survival; HR, hazard ratio; NMA, network meta-analysis; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; CI, confidence interval

Key issue: Enzalutamide and abiraterone equivalence (2/2)

EAG comments

- NMAs inappropriate for deriving effect estimates given heterogeneity → likely favour abiraterone.
- Company transitivity judgements inconsistent (if trial heterogeneity is low enough to do NMA).
  - Placebo arm differences judged invalid for a rPFS NMA but valid to run OS NMA.
- Recognise pairwise meta-analysis uncertainties, but not comparable with NMA limitations:
  - NMA assumptions are fundamentally different to those in meta-analysis e.g., transitivity.
  - Used random effect analysis to capture uncertainty from heterogeneity among studies.
  - Studies adjusted for prior docetaxel use - unaware of why it would be treatment effect modifier.
  - Non-randomised study limitations correct, but all included studies adjusted for confounding.
- Relative effectiveness uncertain, but balance of evidence indicates enzalutamide more efficacious.

Other considerations

- Clinical expert: relative efficacy of abiraterone and enzalutamide discussed for many years - conclusion is always that these drugs are considered equivalent with regard to efficacy.
  - Some patients/clinicians choose one over the other (e.g., diabetes, seizures.) but never heard anyone argue that OS benefit of enzalutamide vs abiraterone has a HR of 0.84.

What is the most accurate HR to model the relative effectiveness of enzalutamide and abiraterone: 1 (clinically equivalent) or 0.84 (enzalutamide clinically superior)?

Return to questions

Abbreviation: rPFS, radiographic progression free survival; NMA, network meta-analysis; OS, overall survival; HR, hazard ratio

Cost effectiveness

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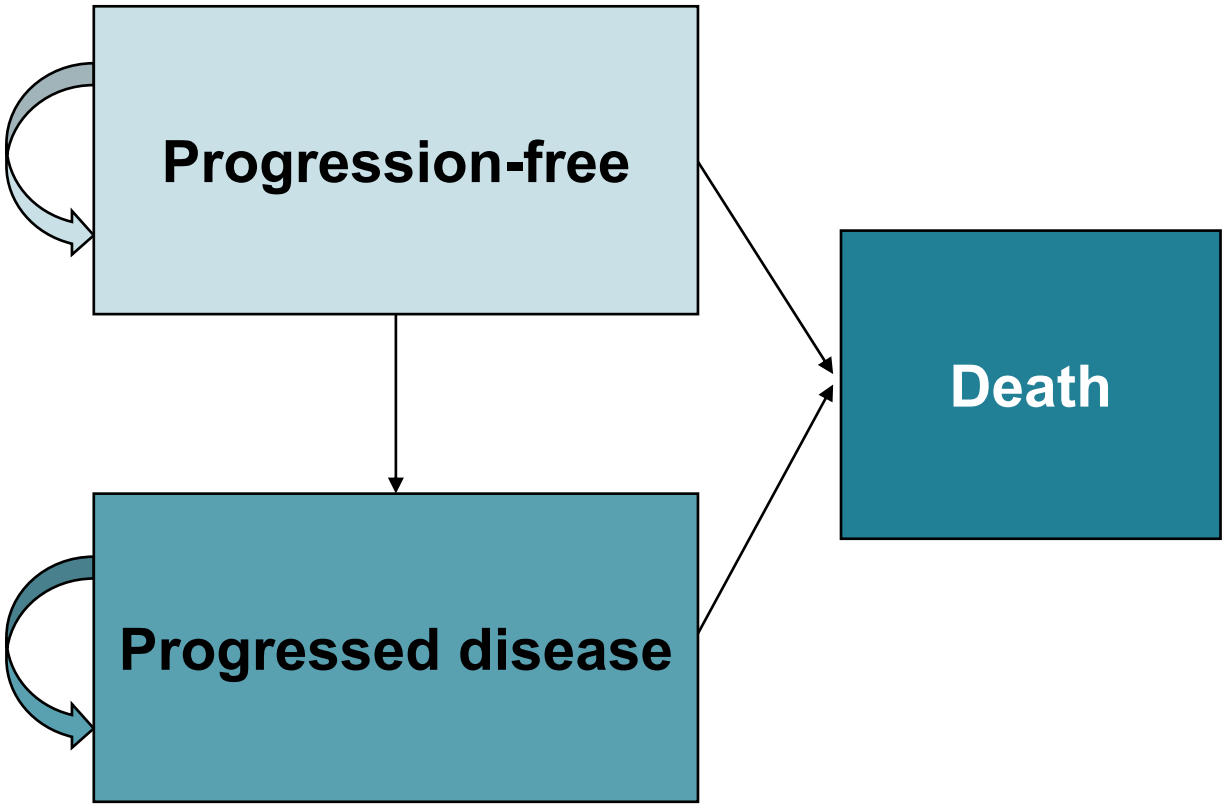
Company's model overview

Model structure – 3 state partitioned survival model



Technology affects **costs** by:

- Higher 1st line treatment costs.
- Lower subsequent treatment costs.

Technology affects **QALYs** by:

- Increased PFS.
- Increased OS.

Assumptions with greatest **ICER** effect:

- Population modelled: BRCA1/2 vs ITT.
- Assumption of clinical equivalence between enzalutamide and abiraterone.
- OS parametric curve.
- TTD parametric curve.

Abbreviation: OS, overall survival; PFS, progression free survival; ICER, incremental cost effectiveness ratio; ITT, intention to treat; TTD, time to discontinuation; BRCA, breast cancer gene; QALYs, quality-adjusted life years

Key issue: Overall survival extrapolation (1/2)

Background

- Company OS extrapolation curves: generalised gamma (base case), log-logistic (scenario)
- EAG: both curves are comparable statistically and visually - generalised gamma fits olaparib better but log-logistic curve fits abiraterone better.
- 10-year current treatment OS predictions differ: 2.6% (generalised gamma) vs 8.4% (log-logistic).

Company

- Both curves give reasonable estimates with slight underestimations across both treatment arms.
- Generalised gamma OS estimates marginally more aligned to latest landmark 4-year trial data.
- Median OS highly consistent with PROpel in both curves.
- Most clinical experts: generalised gamma most clinically plausible based on current treatments.

EAG comments

- Log-logistic and generalised gamma curves equally plausible OS extrapolation.
- Clinical advisor: 10-year survival estimates of between 8-10% are likely for current care options.

Other considerations

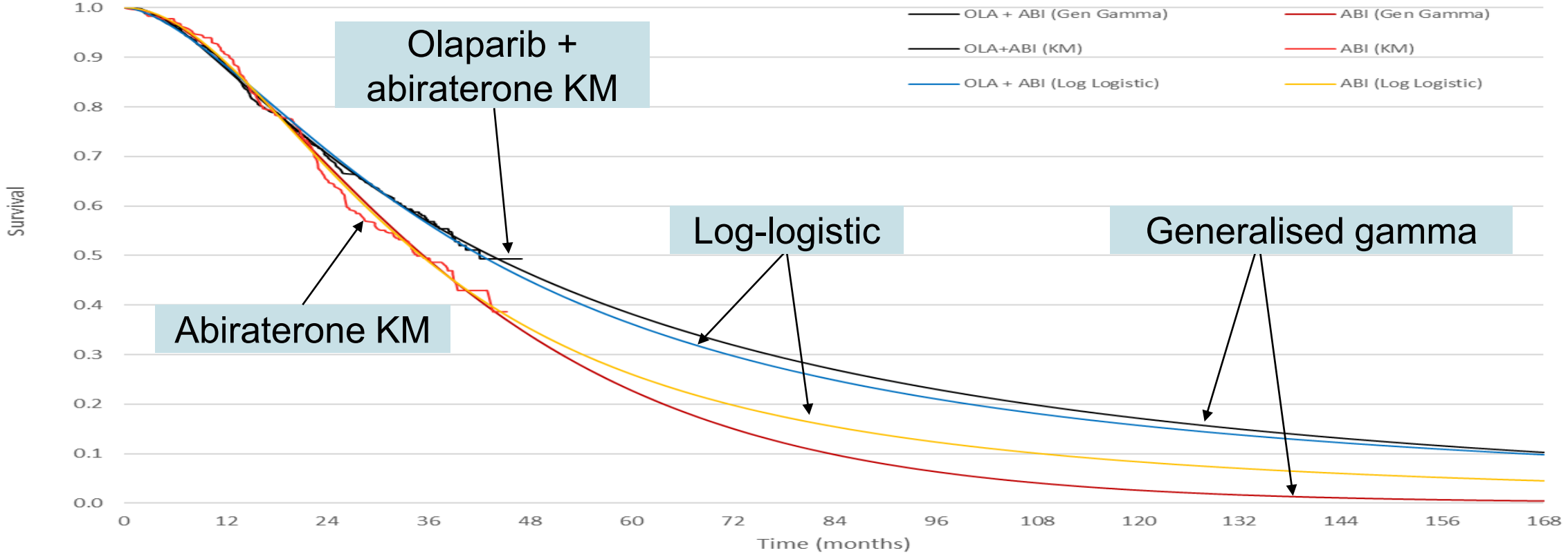
- Clinical expert: 8.4% survival at 10 years seems highly improbable. 2-3% much more realistic.

Which OS extrapolation curve is most appropriate – generalised gamma or log-logistic?

Return to questions

Abbreviation: OS, overall survival

Kev issue: Overall survival extrapolation (2/2)



	Olaparib + Abiraterone					Placebo + Abiraterone				
	Year 1	Year 2	Year 4	Year 10	Median	Year 1	Year 2	Year 4	Year 10	Median
PROpel	88.2%	70.2%	49.3%	-	42.1	90.6%	65.5%	38.7%	-	34.7
COU-AA-302	-	-	-	-	-	91.3%	69.7%	33.7%	-	34.7
Log-logistic	88.3%	71.2%	44.8%	15.7%	42.0	89.0%	67.7%	35.3%	8.4%	35.0
Gen Gamma	87.7%	70.5%	46.2%	17.1%	43.0	88.7%	68.3%	33.8%	2.6%	35.0

Abbreviation: KM, Kaplan-Meier

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Cost effectiveness results

Olaparib with abiraterone is not cost effective in any scenario

Key differences in assumptions	Company base case	EAG base case
HR: enzalutamide vs abiraterone	1.00	0.84
Population	ITT	ITT / BRCA
OS extrapolation	Generalised gamma	Generalised gamma / Log-logistic

Cost effectiveness scenario	Olaparib + abiraterone cost effective vs abiraterone / enzalutamide?
Company base case	No
EAG base case	No
Scenario analyses: applied to both company and EAG base case	
BRCA subgroup population	No
Non-BRCA subgroup population	No
OS extrapolation: Log-logistic	No
Enza vs abi preferred HR swapped: company (0.84); EAG ([redacted])	No

Note: this appraisal topic is not being considered for the severity modifier

Abbreviation: ITT, intention to treat; BRCA, breast cancer gene; OS, overall survival; HR, hazard ratio; enza, enzalutamide; abi, abiraterone

Summary slide

- Where should olaparib with abiraterone be positioned in the pathway?
  Is the trial population relevant and generalisable to this positioning?
  Is docetaxel a relevant comparator?
- Which populations are relevant for decision making – full MA (ITT), HRR or BRCA subgroup?
- Is PROpel subsequent olaparib monotherapy use generalisable to the NHS population?
- What is the most accurate HR to model the relative effectiveness of enzalutamide and abiraterone: 1 (clinically equivalent) or 0.84 (enzalutamide clinically superior)?
- Which OS extrapolation curve is most appropriate – generalised gamma or log-logistic?

Abbreviations: MA, marketing authorisation; ITT, intention-to-treat; HRR, homologous recombination repair; BRCA, breast cancer gene; HR, hazard ratio; OS, overall survival

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Thank you.