For public – contains no confidential information

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Technology appraisal committee B [09 March 2023]

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Company: Bayer

Key issues

Issue		Resolved?	ICER impact
Subgroups	• Cost-effectiveness results not given for subgroups in NICE scope	No	Unknown
ARASENS trial	• Reasons for censoring in ARASENS trial not reported	Yes	Unknown
	• Loss to follow-up in ARASENS trial not fully explained	Yes/Partially	Unknown
Network meta-analysis (NMA)	• Using unadjusted hazard ratios in NMA for trials that allowed crossover	No	Large
	• Out of date progression-free survival hazard ratio from ARCHES trial used in NMA	Partially	Large

Background on metastatic hormone-sensitive prostate cancer

Causes

- Prostate cancer is a condition in which tumours develop in the prostate – a gland in the male reproductive system
- Environmental and genetic factors associated with an increased risk of developing prostate cancer

Epidemiology

- Incidence increases with age and is higher in people of black African-Caribbean family origin and people with a family history of the condition
- 43,330 people were diagnosed with prostate cancer (13% metastatic) in England between 2019 and 2020
- Age standardised mortality rate for prostate cancer 45.5 for every 100,000 people in 2019

Diagnosis and classification

- Risk of progression (low, intermediate, high) based on PSA concentration, Gleason score (evaluate prostate cancer prognosis using a biopsy), clinical stage
- Hormone therapy (ADT) may be offered for intermediate or high-risk
- Hormone-sensitive prostate cancer population → people who have not had ADT or whose disease is continuing to respond to ADT

Abbreviations: ADT: androgen deprivation therapy; PSA: prostate-specific antigen

Patient perspectives (1)

Submissions from Prostate Cancer UK and Tackle

- "Incurable nature of advanced disease" can be difficult to psychologically manage – greater treatment choice is important
- Fear of cancer becoming hormone-resistant – patients report this is where they feel they are "running out of options"
- Slowing the progression of cancer and side effects and increasing survival are treatment aims
- Additional treatment option for recurrent or de novo prostate cancer responsive to hormone therapy
- Innovative approach of triple therapy is significant 'step change' in treatment strategies – multi-modal approach
- Only suitable for people who can have chemotherapy - chemotherapy associated side-effects
- When cancer progresses, treatment options will not allow further anti-androgen but may be suitable for other treatments e.g. further chemotherapy or radium-223

"17% of newly diagnosed men will have mHSPC. To be told that not only do you have cancer but also that it has already spread is a 'bombshell' of a moment. There are long term life changing consequences..."

"Newly diagnosed men comprise the largest group of patients eligible for the new treatment regime under appraisal"

"Many patients, particularly those in a younger age group and with no co-morbidities, would be willing to consider triple therapy…"

"Through talking with patients…this combination would still be a popular and needed treatment option for many patients"

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer

Patient perspectives (2)

Symptoms can vary and include:

- Metastasis related: spinal cord compression (bone metastasis); spontaneous fractures (bone metastasis);; neurological (brain metastasis)
- Morbidity associated with visceral metastases (liver and lung)
- Anaemia, thrombocytopenia, low white-blood cell count if the cancer affects bone marrow
- Weight loss, reduced appetite – concern for carers
- Urinary tract and renal problems

Current treatments for newly diagnosed metastatic prostate cancer, and metastatic prostate cancer responding to hormone therapy include: ADT alone; docetaxel + prednisolone/prednisone + ADT; enzalutamide + ADT

    - Or apalutamide + ADT for metastatic prostate cancer responding to hormone therapy but unable to have docetaxel

Disadvantages of darolutamide combination treatment: Chemotherapy related side-effects & administration in hospital

- Alopecia, neutropenia, fatigue, are consistent side effects with docetaxel
- Fatigue is a “life changing side-effect, hindering daily life and impacting family and carers”

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer

Equality considerations

Company report that: “prostate cancer is more common in Black African men than white men. The introduction of darolutamide plus docetaxel and ADT provides an alternative and more effective treatment option which will support all men with mHSPC”

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer

Treatment pathway

Taxane

ARPI

NHS approval is 1 ARPI in treatment pathway; people having darolutamide not eligible for 2nd ARPI when developing hormone-relapsed prostate cancer

	Hormone sensitive	Hormone relapsed		
Non-metastatic	ADT Radical therapy – surgery or radiotherapy	Progression → ADT ~~Enzalutamide + ADT in high risk~~ (TA580) Darolutamide + ADT in high risk (TA660) Apalutamide + ADT in high risk (TA740)		
Metastatic	Apalutamide + ADT (TA741) – only if docetaxel unsuitable ~~Abiraterone + ADT in high risk~~(TA721) ADT (NG131) Docetaxel + ADT (NG131) Enzalutamide + ADT (TA712) Darolutamide + docetaxel + ADT	**Chemotherapy 'not yet indicated'** Abiraterone (TA387) Enzalutamide (TA377) Watchful waiting	**Chemotherapy indicated** Docetaxel (TA101) – Karnofsky performance score 60% or more Olaparib (no prior taxane) - ongoing	**Post-docetaxel** Abiraterone (TA259) Enzalutamide (TA316) Cabazitaxel (TA391) Radium-223 (TA412) Docetaxel re-treatment Olaparib (prior taxane) – ongoing ^{177}Lu vipivotide tetraxetan – ongoing

- Is darolutamide + docetaxel + ADT positioning reflective of NHS practice?
- Who would have docetaxel + ADT rather than enzalutamide + ADT as 1st line treatment for mHSPC?
- What proportion would then have an ARTA? What proportion would progress with mHRPC?

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Abbreviations: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; ARTA: androgen receptor targeted agent; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer

Darolutamide (Nubeqa, Bayer)

Marketing authorisation	"The treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel" • MHRA license extension • Granted November 2022
Mechanism of action	Darolutamide binds to androgen receptors to block androgens from binding. This inhibits androgen receptor nuclear translocation and transcription. So, decreasing prostate cancer cell survival and growth

Administration	• Recommended dose: 600 mg (2 x 300 mg tablets), taken orally, twice daily
	• Continue until disease progression or unacceptable toxicity even if cycle of docetaxel is delayed, interrupted, or discontinued
	Reduce dose to 300 mg, twice daily for:
	  • Severe renal impairment (eGFR 15 to 29 ml/min/1.73 m^2), with no haemodialysis
	  • Moderate or severe hepatic impairment (Child-Pugh Class B and C)
	• People having darolutamide should have gonadotropin-releasing hormone analogue at the same time or should have had a bilateral orchidectomy

Price	• List price: £4,040 for 28 days treatment (112 x 300 mg tablets) • Patient access scheme is applicable

Abbreviations: eGFR: estimated glomerular filtration rate; MHRA: Medicines and Healthcare products Regulatory Agency

Decision problem

*including orchidectomy, LHRH agonist therapy, degarelix, monotherapy with bicalutamide

	Final scope	Company	EAG comments
Population	People with hormone-sensitive metastatic prostate cancer		
Intervention	Darolutamide + ADT + docetaxel		
Comparator	• ADT* • Docetaxel + ADT • Enzalutamide + ADT	• Exclude monotherapy with bicalutamide (anti-androgen)	• EAG clinical expert agree – considered inferior and not standard care
Outcomes	Overall survival; PFS; response rate; PSA response; time to PSA progression; adverse effects; HRQoL **Company add:** Time to – CRPC (biochemical and radiological progression); pain progression; SSE-free survival; 1st SSE; subsequent systemic antineoplastic therapy; worsening of disease-related physical symptoms; opioid use		• Company use CROD (time to CRPC or death) as proxy for PFS in model → appropriate • Clinical expert: CRPC definition is more sensitive than rPFS and better reflects clinical practice
Subgroups	• Newly diagnosed metastatic prostate cancer • High-risk metastatic prostate cancer	• Focus on intention-to-treat population • Present subgroup analyses for some prognostic factors	• Discussed as key issue

Abbreviations: ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; CROD: CRPC or death; HRQoL: heath-related quality of life; PSA: prostate-specific antigen; (r)PFS: (radiographic) progression-free survival; SSE: symptomatic skeletal event

Clinical effectiveness

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Key clinical trial - ARASENS

ARASENS trial characteristics	
Design	Phase 3, international, randomised, double-blind, placebo-controlled
Population	Metastatic hormone-sensitive prostate cancer
Intervention	Darolutamide + docetaxel + ADT
Comparator	Placebo + docetaxel + ADT
Duration	Median follow-up: Darolutamide OS: 43.7 months; placebo OS: 42.4 months
Primary outcome	Overall survival (time in days, from randomisation until death from any cause)
Key secondary outcomes	• Time to CRPC • Time to PSA progression • PSA response • Adverse events from treatment • HRQoL
Locations	23 countries (North America, Asia-Pacific, Europe, Australia, Brazil, Israel, Mexico); 29 out of 1,306 people from UK across 8 centres
Used in model?	Yes

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Abbreviations: ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; HRQoL: heath-related quality of life; OS: overall survival; PSA: prostate-specific antigen

ARASENS baseline characteristics

Baseline characteristic (full analysis set)		Darolutamide (n=651)	Placebo (n=654)
Age, years	Mean (SD)	[redacted]	[redacted]
Ethnicity, n (%)	White	345 (53)	333 (51)
	Black or African American	26 (4)	28 (4)
	Asian	230 (35)	245 (38)
	NR	43 (6)	46 (7)
Prostate cancer stage at initial diagnosis, n (%)	1	[redacted]	[redacted]
	2a or 2b	[redacted]	[redacted]
	3	[redacted]	[redacted]
	4	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
ECOG PS, n (%)	0	466 (72)	462 (71)
	1	185 (28)	190 (29)
	Missing	[redacted]	[redacted]

EAG: Well-balanced between arms but the following do not reflect clinical practice:

- **ECOG PS:** more ECOG 0 than expected in clinical practice → better outcomes/prognosis
  - But majority metastatic at diagnosis rather than with relapse (associated with worse outcomes/prognosis) – expect ECOG of at least 1
- **More de novo disease:** 86% in trial vs 55% expected in clinical practice – de novo disease have worse outcomes than relapsed
- **Ethnicity:** may be different to clinical practice – Black people not well represented in trial and overall have worse outcomes

Are the baseline characteristics generalisable to the NHS? How important are the differences? How is mHRPC defined in terms of response to treatment?

Abbreviations: ECOG PS: eastern cooperative oncology group performance status; NR: not reported; SD: standard deviation

ARASENS study design

*plus docetaxel plus ADT

Stratification at randomisation:
- Extent of disease
- ALP level

- n=1,306 (29 in UK)
- Darolutamide*: n=651
- Placebo*: n=654

Pre-specified subgroups:
- Extent of disease
- ALP level at baseline
- Age
- Race
- Geographical region
- PSA values
- ECOG PS
- Gleason Score
- Metastasis at initial diagnosis

Evaluate every 12 weeks until:
- Symptomatic disease progression
- Change in antineoplastic therapy
- Unacceptable toxicity
- Patient or physician decision
- Death
- Nonadherence

After discontinuation:
- Assessments approx. every 12 weeks for up to 1 year

Until end of study
- Main reason for discontinuing – clinical progression

EAG: Subsequent treatments of an ARTA post-progression in the intervention arm, is not reflective of NHS clinical practice

Abbreviations: ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ARTA: androgen receptor targeted agent; ECOG PS: eastern cooperative oncology group performance status; PSA: prostate-specific antigen

Key issue: Subgroups

*High-risk prognostic factors: Gleason score ≥8; ≥3 lesions on bone scan; measurable visceral metastases (exclude lymph node metastasis)

Background: Excluded subgroups in final scope: (i) high-risk (ii) newly diagnosed metastatic prostate cancer
- ARASENS included 'extent of disease' and 'metastasis at initial diagnosis' subgroups

Company: An inconsistent use of high-risk and newly diagnosed terms across mHSPC trials
- TA721 enzalutamide did not use because of inconsistent definitions & relevance to decision-making
- At TE: comparative efficacy estimates of darolutamide vs placebo

	Stratified HR (95% CI)	
Population	**OS**	**CROD**
ITT (n=1,305)	0.68 (0.57, 0.8)	0.41 (0.35, 0.47)
de-novo (n=[redacted])	[redacted]	[redacted]
High risk (n=[redacted])	[redacted]	[redacted]
Non- de novo/ high-risk	**EAG:** No results but would be more uncertain because small numbers	

- Consistent efficacy across subgroups
- Subgroups not included in NMA or modelled because limited data and inconsistencies across network

86% had metastatic disease at diagnosis (considered as de novo)

LATITUDE trial definition used (≥2 high-risk prognostic factors*)

EAG: Agree variation of 'high-risk' e.g. metastases site; disease volume
- Agree unlikely feasible to include subgroups in model or NMA with likely gaps in evidence network
- OS estimates of de novo disease similar to ITT ([redacted] [95% CI [redacted]] vs 0.69 [0.58-0.82]

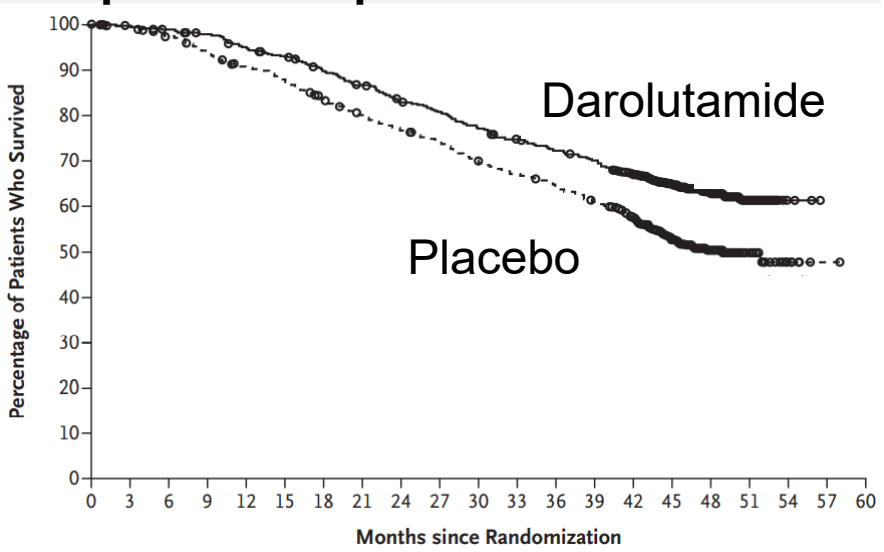
but = 86% of the population

Abbreviations: ITT: intention-to-treat; mHSPC: metastatic hormone-sensitive prostate cancer; NMA: network meta-analysis; OS: overall survival; TE: technical engagement

ARASENS overall survival results

Oct 2021 cut-off		Darolutamide (n=651)	Placebo (n=654)
Event, n (%)		229 (35)	304 (47)
Censored, n (%)		[redacted]	[redacted]
OS, months (95% CI)	Median	[redacted]	[redacted]
	Range inc. censored	[redacted]	[redacted]
Hazard ratio (95% CI)		0.68 (0.57, 0.80)	
P-value		<0.0001	

Kaplan-Meier plot of overall survival



Company: OS benefit despite more subsequent life-prolonging therapies in placebo vs darolutamide arm (76% vs 57% of people who discontinued and entered active or survival follow-up)

EAG: Company did not adjust OS for subsequent therapy with 2nd ARTA (NHS practice is 1 ARTA)

- EAG consider reasonable – an unlikely response to 2nd ARTA post-progression (see company post hoc analysis stratified by subsequent treatment)
- Post-hoc analysis showed some benefit for placebo arm but no adjustment for this – EAG consider reasonable because adjustment would be non-conservative and tend to favour darolutamide

Is there likely to be clinical benefit from having a subsequent ARTA after darolutamide?

Abbreviations: ARTA: androgen receptor targeted agents; OS: overall survival

Company's post-hoc post-progression survival analysis, stratified per subsequent treatment

Company: OS benefit not driven by additional ARTAs → no adjustment necessary

- Darolutamide: 'No difference' in PPS, with an ARTA or another subsequent treatment
- Docetaxel: 'clear PPS benefit' with an ARTA

Darolutamide + docetaxel + ADT

[redacted]

Docetaxel + ADT

[redacted]

EAG: Overlapping confidence intervals → suggest no survival difference between subsequent treatments

EAG: PPS should be interpreted with caution → question validity of 'clear PPS benefit' with docetaxel

- Docetaxel: ARTA vs. non-ARTA confidence intervals overlap for first 8 months, and last 20 months
- Uncertainty is unlikely due to lack of events at start and small numbers of patients at risk near the end
- However: no numbers of patients at risk, or summary statistics, given

Abbreviations: ARTA: androgen receptor targeted agent; OS; overall survival; PPS: post-progression survival

ARASENS time to CROD results (used in model)

	Darolutamide (n=651)	Placebo (n=654)
Event, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

[redacted]

Company: use exploratory composite outcome – 'time to CROD' from ARASENS as a proxy for PFS outcome in model

- Time to CROD = Time to CRPC (radiological or PSA progression) or death if no CRPC event
- Company consider time to CRPC a better measure of progression than rPFS alone (not measured in ARASENS and not reflective of clinical practice)

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Abbreviations: CI: confidence interval; CROD: castration-resistant prostate cancer or death; CRPC: castration-resistant prostate cancer; NE: not estimable; PSA: prostate-specific antigen; TE: technical engagement

Network meta-analysis

- Overview
- Results
- Key issues

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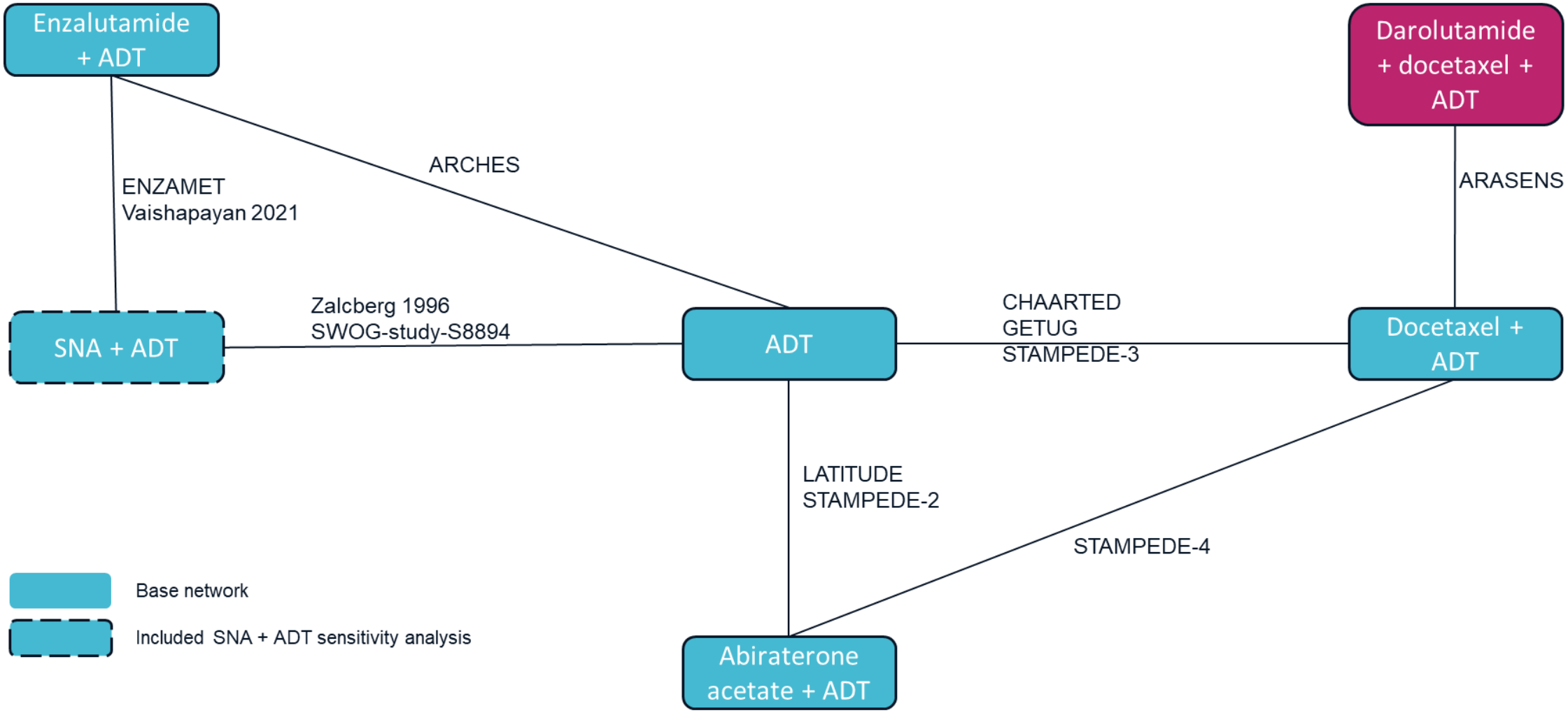
Company's network meta-analysis diagram



Abbreviations: ADT: androgen deprivation therapy; SNA: standard nonsteroidal anti-androgen

Network meta-analysis overview

= Allow crossover from placebo to intervention

Trial	Population	Treatment	N	PFS definition in base case NMA
ARASENS	mHSPC	Darolutamide + docetaxel + ADT vs. docetaxel + ADT	1,305	Time to CROD
ARCHES	mHSPC	Enzalutamide + ADT vs. ADT	1,150	rPFS
CHAARTED	mHSPC	Docetaxel + ADT vs. ADT	790	Time to clinical progression
GETUG-AFU 15	Non-castrate metastatic prostate cancer	Docetaxel + ADT vs. ADT	385	rPFS
LATITUDE	Metastatic castration-sensitive prostate cancer	Abiraterone + prednisone + ADT vs. ADT	1,199	rPFS
STAMPEDE-2	Metastatic hormone-naive prostate cancer	Abiraterone + prednisone + ADT vs. ADT	1,917	Failure-free survival
STAMPEDE-3		Docetaxel + ADT vs. ADT	1,086	
STAMPEDE-4		Abiraterone + ADT vs. ADT	566	

Company:

- 17.8% in ARCHES had prior docetaxel → company use HR from overall population because it is similar to HR from non-docetaxel treated group
- Duration of prior treatment poorly reported in studies identified

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Abbreviations: ADT: androgen deprivation therapy; ECOG PS: Eastern cooperative oncology group performance status; HR: hazard ratio; mHSPC: metastatic hormone-sensitive prostate cancer; NMA: network meta-analysis; OS: overall survival; PFS ; progression-free survival; PSA: prostate-specific antigen

Comparison of baseline characteristics in the network

Trial	Median age (range)	ECOG PS, %			Gleason score (%)			Median PSA level, ng/ml	Prostate cancer stage, %			
		0	≥1	Missing	>7	≤7	Missing		0-2	3	4	Missing
ARASENS	67 (41-89)	71	29	0.3	79	19	2	27	6	6	85	3
ARCHES	70 (43-93)	78	23	-	66	31	2.5	6				-
CHAARTED	63 (36-91)	69	31	-	63	-	38	50				-
GETUG-AFU 15	64 (57-70)	94	-	6	58	-	43	25				-
LATITUDE	68 (33-93)	55	45		98	-	3					-
STAMPEDE -2	67 (62-72)			-	75	-	25	53				-
STAMPEDE -3	65 (NR)	67	29	4	69	-	31	100	15	54	23	9
STAMPEDE -4	66 (NR)	80	20	-	78	-	23	55	13	63	19	6

Company: No studies excluded from NMA based on age; ECOG PS; Gleason score; PSA level; cancer stage

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Abbreviations: ECOG PS: Eastern cooperative oncology group performance score; NMA: network meta-analysis; ng/ml: nanograms per millilitre; NR: not reported; PSA: prostate-specific antigen

Treatment-effect modifiers for overall survival in ARASENS

EAG: All potential heterogeneity between trials not explored (important prognostic factors e.g. disease volume; synchronous/meta-synchronous) → uncertainty, but acknowledge lack of data to explore all potential modifiers

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Abbreviations: CI: confidence interval; ECOG: Eastern cooperative oncology group; HR: hazard ratio; PSA: prostate-specific antigen

Network meta-analysis model

Company's base case NMA:

- **OS:** fixed-effect NMA
- **PFS:** random-effect NMA → anticipated heterogeneity from different outcome definitions across studies

Relative efficacy of darolutamide for overall survival:

Model	Fixed effect base case, HR (95% CrI)	Random effect, uniform (0, 5), HR (95% CrI)
Darolutamide + docetaxel + ADT	-	-
Enzalutamide + ADT	[redacted]	[redacted]
Abiraterone + ADT	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]
ADT	[redacted]	[redacted]

NMA model fit statistics:

Model		Fixed effect	Random effect, uniform (0, 5)
Between-trial SD Mean (SD)	OS	[redacted]	[redacted]
	PFS	[redacted]	[redacted]
DIC	OS	[redacted]	[redacted]
	PFS	[redacted]	[redacted]

Company: Fixed effect NMA for overall survival based on model fit → lowest DIC

EAG: Agree models are appropriate

- Overall survival: both models give similar results, and no strong evidence of improved model fit for random-effect

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Abbreviations: ADT: androgen deprivation therapy; CrI: credible interval; DIC: deviance information criterion; HR: hazard ratio; mHSPC: metastatic hormone-sensitive prostate cancer; NMA: network meta-analysis; OS: overall survival; PFS ; progression-free survival; SD; standard deviation

Network meta-analysis results

Relative effect of darolutamide + docetaxel + ADT vs all other treatments:

	Base case NMA		Alternative NMA
	Overall survival	PFS	PFS
Model (95% CrI)	Fixed effect HR	Random effect HR	Random effect HR
Darolutamide + docetaxel + ADT	-	-	-
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]
Abiraterone + ADT	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]

PFS	From ARASENS	From other trials (closest matching)
Base case NMA	Time to CROD	Incorporates death: • rPFS; time to clinical progression; clinical PFS; FFS (radiological, clinical, PSA progression, or death from prostate cancer)
Alternative NMA	Time to CRPC	Not necessarily including death: • Time to biochemical PFS; time to subsequent therapy; FFS and PSA PFS

Abbreviations: ADT: androgen deprivation therapy; CrI: credible interval; CROD: time to castration-resistant prostate cancer or death; CRPC: castration-resistant prostate cancer; FFS: failure-free survival; HR: hazard ratio; NMA: network meta-analysis; PFS: progression-free survival; PSA: prostate-specific antigen

Key issue: Unadjusted hazard ratios in NMA – treatment switching

Background: Crossover possible in ARCHES and LATITUDE after primary data analysis and unblinding

- Company use unadjusted HRs (align with TA741) → as crossover adjustment methods have limitations
- **TA741:** Committee considered unadjusted **and** adjusted HRs because of uncertainties with:
  - Methods used to adjust for crossover, and appropriateness of adjustment
  - Adjusted may not reflect clinical practice (assume none in control arm subsequently have ARTA)
  - Unadjusted may mean having ARTA earlier than in practice (crossover after unblinding not progression)

OS HRs	ARASENS	ARCHES	LATITUDE
% switching	-	31%	12%
ITT	0.68 (0.57-0.8)	0.66 (0.53-0.81)	0.66 (0.56-0.78)
IPCW			0.63 (0.53-0.75)
RPSFTM		0.57 (0.45-0.7)	0.62 (0.52-0.72)

vs. darolutamide	OS, fixed effect NMA HR (95% CrI)	
	Company base case	EAG scenario (adjusted HR)
Enzalutamide + ADT	[redacted]	[redacted]
Abiraterone + ADT	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]
ADT	[redacted]	[redacted]

EAG: Less favourable treatment effect for adjusted HR

EAG: TA741 had crossover in pivotal trial, so using unadjusted HRs = conservative → underestimating efficacy

- Here, crossover is for comparators → unadjusted HRs may overestimate darolutamide relative efficacy
- Suggest a separate adjustment for crossover in ARCHES & LATITUDE to avoid overestimating efficacy

Abbreviations: ARTA: androgen receptor targeted agent; HR: hazard ratio; IPCW: inverse probability of censoring weighting; IPD: individual patient data; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PPS: post-progression survival; RPSFTM: rank-preserving structural failure time model

Key issue: Unadjusted hazard ratios in NMA – subsequent treatments

Background: Company argue adjusted HRs would underestimate darolutamide efficacy – prefer ITT

	ARASENS	ARCHES	LATITUDE
	Daro vs placebo, n	Enza vs placebo, n	Abir vs placebo, n
Subsequent ARTA	**Any:** 162 (25%) vs 370 (57%) **1st ARTA:** 113 (17%) vs 290 (44%)	33 (6%) vs 283 (49%)	75 (13%) vs 255 (42%)
Excluding switching		33 (6%) vs 103 (18%)	57 (10%) vs 183 (30%)

Company: ~80% have subsequent ARTA in practice

Company: Subsequent ARTA in placebo is disproportionally higher in ARASENS after adjustment → greater impact on survival for placebo from 1st ARTA → favours comparators

- Adjusted HRs do not consider other subsequent treatment impacts (including ARTAs) on survival
- Second ARTAs not expected to drive OS benefit (post-hoc PPS analysis & expert opinion)

Patient organisation: Subsequent treatments on progression (with abiraterone/enzalutamide) very common

EAG: Separate adjustment for impact of subsequent treatments informative but need IPD for comparator trials

- Placebo may have benefit from 1st ARTA, but partly informed by post-hoc PPS analysis (limitations, e.g. not statistically powered, based on smaller subset of people)
- Subsequent ARTA benefit based on post-hoc PPS; 2nd ARTA may have associated adverse effects
- Could adjust for subsequent treatments not in NHS practice (2nd ARTA) using ARASENS IPD – showing subsequent ARTAs favour placebo and reduce darolutamide efficacy, if not, stronger argument for adjusted

- Are unadjusted hazard ratios appropriate to use in the network meta-analysis?
- What percentage of people would have an ARTA at 2nd-line after docetaxel + ADT at 1st-line?

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Abbreviations: Abir: abiraterone; ARTA: androgen receptor targeted agent; Daro: darolutamide; Enza: enzalutamide; HR: hazard ratio; IPD: individual patient data; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PPS: post-progression survival

Out-of-date PFS hazard ratio from ARCHES used in network

Background: Latest PFS estimate (rPFS) in ARCHES not available at the time of company's SLR
- Longer-term FFS results also available from STAMPEDE-2

rPFS estimate	HR (95%CI)	Assessment
Original	0.39 (0.3-0.5)	Centralised independent review
Updated	0.63 (0.52-0.76)	Investigator-assessed
• **Crossover-adjusted**	0.55 (0.44-0.67)	

Company:
- Clinical experts: Not concerned long-term rPFS is driven by local investigator decision
- In clinical practice scans are not reviewed centrally/independently

Company: Updated base case NMA using latest estimates: rPFS from ARCHES and FFS from STAMPEDE-2
- Consistent with ARCHES OS data in network meta-analysis and median follow-up for longer-term OS
- rPFS from ARCHES more closely matches ARASENS follow-up in network meta-analysis
- NMA updated → apply latest HRs for both PFS and ToT because the HRs are interdependent in the model

EAG use latest rPFS and FFS in a scenario (not base case) → More favourable treatment effect for darolutamide vs enzalutamide
- Notably different HRs – uncertainty if rPFS in ARCHES uses same outcome definition as company's base case NMA

Is the long-term rPFS hazard ratios likely to be driven by the type of assessment used?

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Abbreviations: FFS: failure-free survival; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; (r)PFS: (radiographic) progression-free survival; SLR: systematic literature review; ToT: time on treatment

Cost effectiveness

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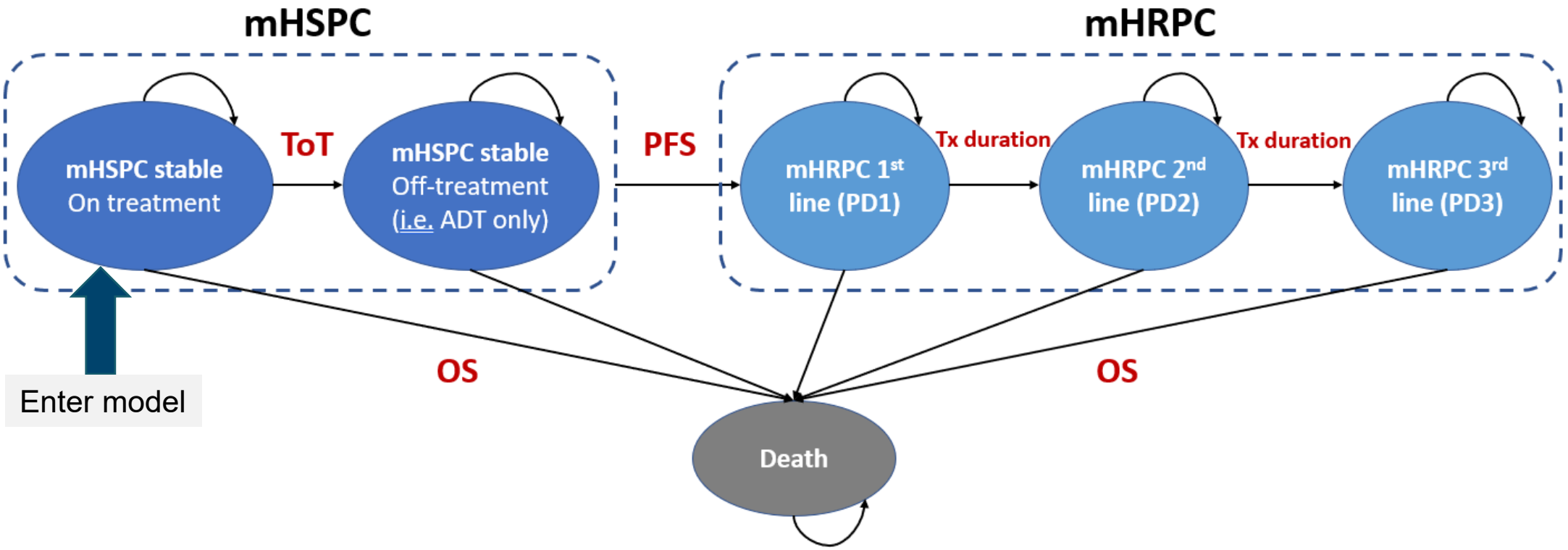
Company's model overview

3-health state, partitioned survival model



Overall survival	From ARASENS
Progression-free survival	ARASENS (time to CROD – includes death)

- mHSPC = time to CROD
- mHRPC = OS – time to CROD
- Dead = 1 – OS

Abbreviations: CROD: castration-resistant prostate cancer or death; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival: PFS: progression-free survival; ToT: time-on-treatment

Company's base case model: Key parameters

Population	Adults with mHSPC, eligible for chemotherapy (aligned with ARASENS ITT)
Baseline characteristics	ARASENS ITT: 66.8 years; 87% stage 4 metastatic prostate cancer
Intervention efficacy	Darolutamide + ADT + docetaxel (apply NMA HRs to extrapolated docetaxel data)
Comparator efficacy	• ADT + docetaxel (ARASENS); • ADT + enzalutamide, and ADT (apply NMA HRs to extrapolated docetaxel data)
Treatment duration	Darolutamide and enzalutamide – until disease progression or unacceptable toxicity; docetaxel – IV every 3 weeks for 6 cycles; ADT – background, continue indefinitely
Cycle length	28 days with half-cycle correction to costs and outcomes
Time horizon	34 years (lifetime)
Utilities	TA712 enzalutamide for mHSPC (EQ-5D-5L data from ARCHES and AFFIRM)
Resource use costs	Drug acquisition and administration; monitoring; subsequent treatment; adverse events; end-of-life
Adverse events	Include ARASENS grade ≥3; enzalutamide and ADT alone incidence from ARCHES; subsequent treatments in mHRPC from TA712
Adverse event disutilities	ARASENS (darolutamide + docetaxel + ADT and docetaxel + ADT); ARCHES (enzalutamide + ADT and ADT alone)

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Abbreviations: ADT: androgen deprivation therapy; HR: hazard ratio; ITT: intention-to-treat; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NMA: network meta-analysis;

Quality-adjusted life years in the model

Improved length of life:
- Increase overall and progression-free survival

Improved quality of life:
- Delay progression to mHRPC

→ **Increased quality-adjusted life years**

QALY benefits not captured in calculation by company:
- Fewer pDDI for darolutamide than enzalutamide
- Low blood-brain barrier penetration in pre-clinical and human studies

QALY weighting for severity:

Total QALYs people with mHSPC expected to have with current treatment		Expected total QALYs for the general population	QALY shortfall	
			Absolute	Proportional
ADT	[redacted]	10.5	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	10.5	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	10.5	[redacted]	[redacted]

Company: No multiplier for disease severity applied for any of the comparisons (absolute QALY shortfalls all <12 and proportional QALY shortfall all <85%)

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Abbreviations: ADT: androgen deprivation therapy; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; pDDI: potential drug-drug interactions; QALY: quality-adjusted life year

Health-related quality of life

Utility values from TA712, and include docetaxel disutility

Background: ARASENS did not collect EQ-5D data

Company: Use ERG-preferred utilities from TA712 enzalutamide for mHSPC (ARCHES and AFFIRM)

- Enzalutamide + ADT; docetaxel + ADT; ADT alone; → all relevant comparators

Health state		Utility value (original base case)
Metastatic hormone-sensitive prostate cancer		0.806
Metastatic hormone-relapsed prostate cancer	First-line	0.723
	Second-line	0.630
	Third-line+	0.530

In response to technical engagement: Company add 0.02 docetaxel disutility for 6 months;

- But also adjust disutility to account for proportion alive during 6 months

EAG: Company's utility values from TA712 are appropriate but prefer docetaxel disutility for 6 months – company's additional adjustment has negligible impact on ICER

- TA741 apalutamide for mHSPC: 0.02 docetaxel disutility for 1 year
  - TA741 clinical experts: docetaxel adverse effects likely to last 6-12 months
- EAG clinical experts: A generally lower HRQoL in mHSPC having docetaxel compared with enzalutamide + ADT, and ADT alone

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Abbreviations: ADT: androgen deprivation therapy; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; mHSPC: metastatic hormone-sensitive prostate cancer; NMA: network meta-analysis;

Comparison of company model with previous TAs

	ID3971	TA712	TA721	TA741
Comparator	ADT; docetaxel + ADT; enzalutamide + ADT	ADT; docetaxel + ADT		
Model	Partitioned survival model			
Average age (years)	66.8	70	67	
Time horizon	34 years (lifetime)	30 years (lifetime)	20 years	32 years (lifetime)
Cycle length	28 days	1 month	1 week for 1st year, then every 28 days	1 week
Half-cycle correction	Yes	No		Not stated
Treatment waning	No	Not in base case; explored by EAG		Not in base case; explored as scenario
Efficacy data	ARASENS	ARCHES; LATITUDE; ENZAMET	LATITUDE	TITAN
Utilities	ERG preferred utilities from TA712	ARCHES; AFFIRM	LATITUDE	SPARTAN; TITAN
Recommended?	-	Yes	No	Yes

- **TA712:** Enzalutamide for mHSPC (Jul 2021)
- **TA721:** Abiraterone for newly diagnosed high-risk mHSPC (Aug 2021)
- **TA741:** Apalutamide with ADT for mHSPC (Oct 2021)

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Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer; TA: technology appraisal

Treatment-effect waning – previous TAs in mHSPC

Company: Exclude treatment-effect waning – no previous mHSPC appraisals included it

Evaluation	Committee conclusion
TA712 enzalutamide for mHSPC: • Company predict OS benefit to last for time horizon (30 years) • STAMPEDE: initial survival benefit at 5 years with docetaxel + ADT (49%) vs ADT (37%) • But, no difference in OS after 8.5 years (23% vs 22%)	• Uncertain whether benefits of active treatment persist • In absence of long-term data for enzalutamide + ADT, EAG's scenarios where HR equalised between treatment options after 8.5 years were useful to assess uncertainty
TA741 apalutamide + ADT for mHSPC: • Antonarakis et al. (2016) study in advanced prostate cancer suggest resistance to newer androgen receptor inhibitors likely to develop with time	• An increase in ICER when varying treatment effect waning from 100% to 0% for 5 and 10 years

Are the treatment effects of darolutamide + docetaxel + ADT likely to wane over time? When should treatment start waning and for how long?

Abbreviations: ADT: androgen deprivation therapy; HR: hazard ratio; mHSPC: metastatic hormone-sensitive prostate cancer; OS; overall survival; TA: technology appraisal

Summary of company and EAG base case assumptions

Assumption		Company	EAG
Docetaxel disutility		6 months adjusted for proportion alive during 6 months	6 months
Subsequent treatment distribution for enzalutamide		TA712	
Costs	Diarrhoea adverse event	Included	
	End-of-life costs for people with cancer diagnosis	Included	
Survival distributions		• OS: log-logistic • PFS: log-normal • Time-on-treatment: generalised gamma	
Latest rPFS (ARCHES) and FFS (STAMPEDE-2) hazard ratios		Latest available data in NMA and applied to PFS and ToT because PFS and ToT HRs are interdependent in the model	Do not use latest estimates in base case

Assumptions with greatest effect on ICER :

- Survival distribution for OS, PFS, time-on-treatment
- Updated PFS HRs for ARCHES and STAMPEDE in NMA to PFS and time-on-treatment

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Abbreviations: FFS: failure-free survival; NMA: network meta-analysis; OS: overall survival; (r)PFS: (radiographic) progression-free survival; ToT: time-on-treatment

Cost-effectiveness results

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

The company and EAG ICERs are above the level considered an effective use of NHS resources, when confidential discounts are applied

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

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Thank you.

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Back-up slides

Censoring in ARASENS

Censoring does not bias time to CRPC or CROD

Background: No breakdown of people censored in trial and proportion censored for each reason

- Potential for informative censoring – bias time to CRPC therefore time to CROD used in model
- Specifically, if there is a difference between arms in censoring of people having subsequent systemic antineoplastic therapy without meeting criteria for CRPC and who were without post PSA progression event

Company post technical engagement submitted results:

		Darolutamide (n=651)	Placebo (n=654)
Censored, n (%)		[redacted]	[redacted]
Censoring reasons, n (%)	No CRPC at time of analysis	[redacted]	[redacted]
	No baseline or post-baseline assessment	[redacted]	[redacted]
	Prohibited new anticancer therapy before CRPC	[redacted]	[redacted]
	PSA progression after ≥2 consecutive missing assessments	[redacted]	[redacted]

Company:

- Most common reason: Darolutamide efficacy means less progression to CRPC ([redacted]) compared with placebo arm ([redacted]) → EAG consider reasonable

Company:

- Censoring for other reasons is small

EAG: satisfied censoring does not bias time to CRPC, therefore CROD in the model

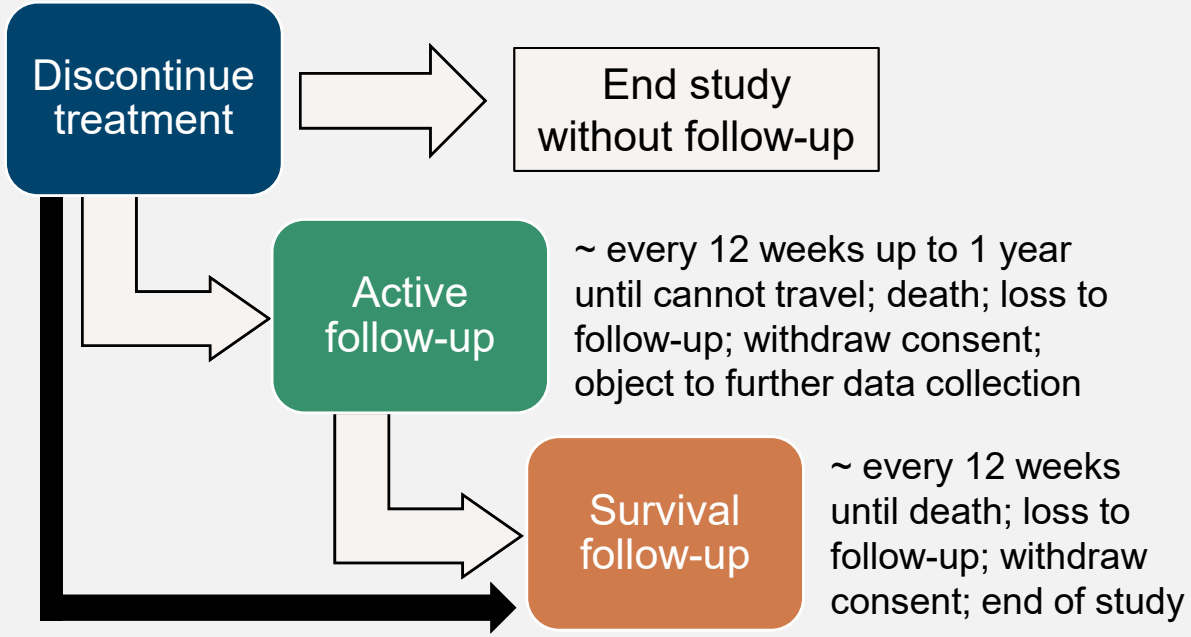
Abbreviations: CROD: castration-resistant prostate cancer or death; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen

Loss of follow-up in ARASENS

Higher discontinuation rates in treatment arm unlikely to bias model

Background: Unexplained imbalance between trial arms for people discontinuing treatment and not entering planned active follow-up – darolutamide: [redacted] ([redacted]) vs placebo [redacted] ([redacted]) → risk of attrition bias

Company give patient disposition in trial after discontinuing treatment after technical engagement



Can enter directly from treatment discontinuation because people can discontinue if they cannot travel or object to further data collection

Follow-up, n (%)	Darolutamide	Placebo
Active	[redacted]	[redacted]
Survival	[redacted]	[redacted]
End study	[redacted]	[redacted]

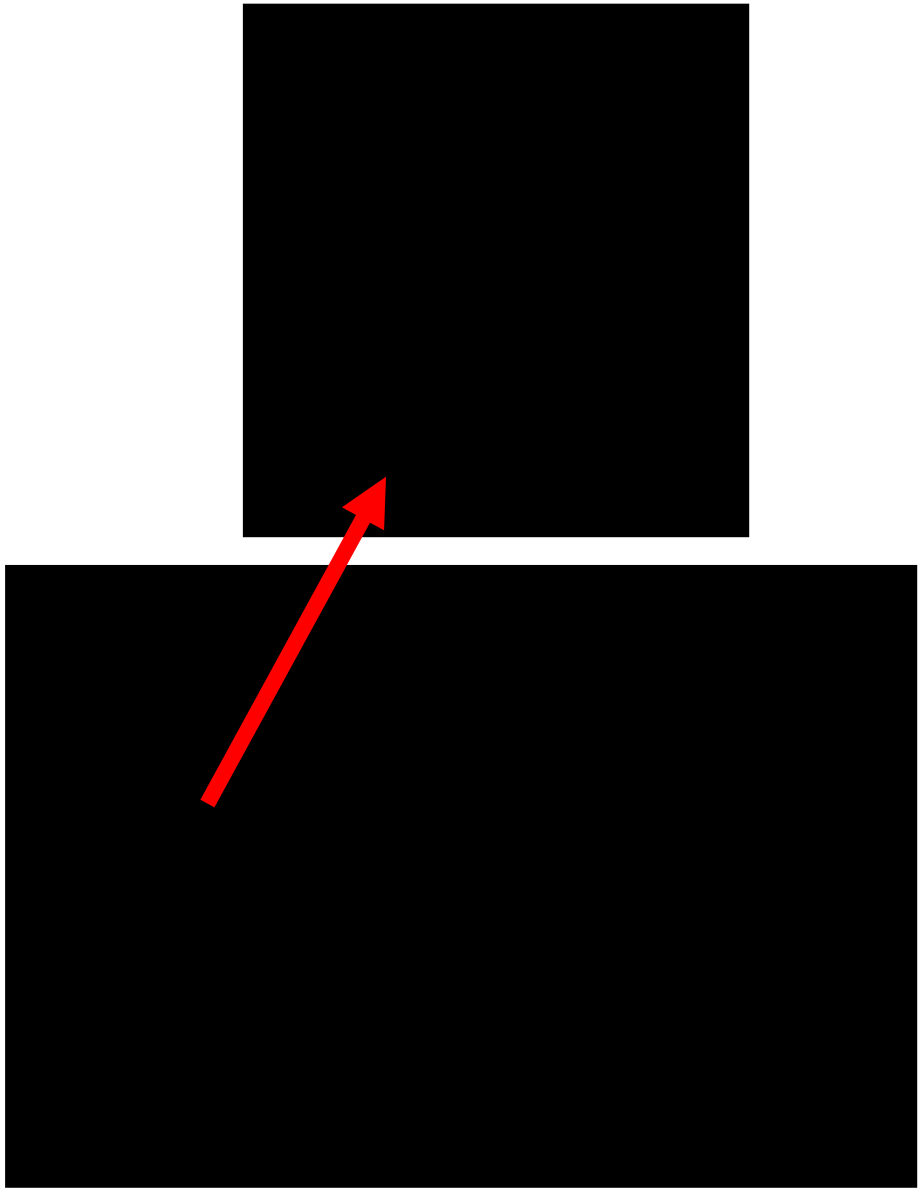
EAG: Satisfied with information that can enter survival follow-up from treatment discontinuation

- Note ~ [redacted] more enter active follow-up in placebo arm – unclear clinical effects but any difference unlikely to bias model
- % ending study for darolutamide arm is ~2x more than placebo – but represents small proportion

Modelling overall survival (1)

Overall survival AIC and BIC statistical fit statistics for docetaxel arm of ARASENS and OS extrapolations for docetaxel arm of ARASENS:

Model	AIC	BIC	Predicted % alive at (years)					
			1	2	3	5	7	9
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAARTED			94.9	83.6	71.7	46.5	23.9	23.9
STAMPEDE-3			91.7	76.9	65.4	48.8	35.2	21.4
ARASENS			90.3	76.8	63.8	N/A	N/A	N/A



Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival

Modelling overall survival (2)

Overall survival estimates over time for all modelled treatments:

OS	Hazard ratio in base case	Predicted % alive at (years)				
		2	5	10	20	30
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comparator OS curves calculated by applying network meta-analysis HRs to the docetaxel arm

Company: Log-normal in base case, log-logistic in scenario
After technical engagement update in line with EAG: Log-logistic in base case (both extrapolations are the most conservative but log-logistic is less optimistic)

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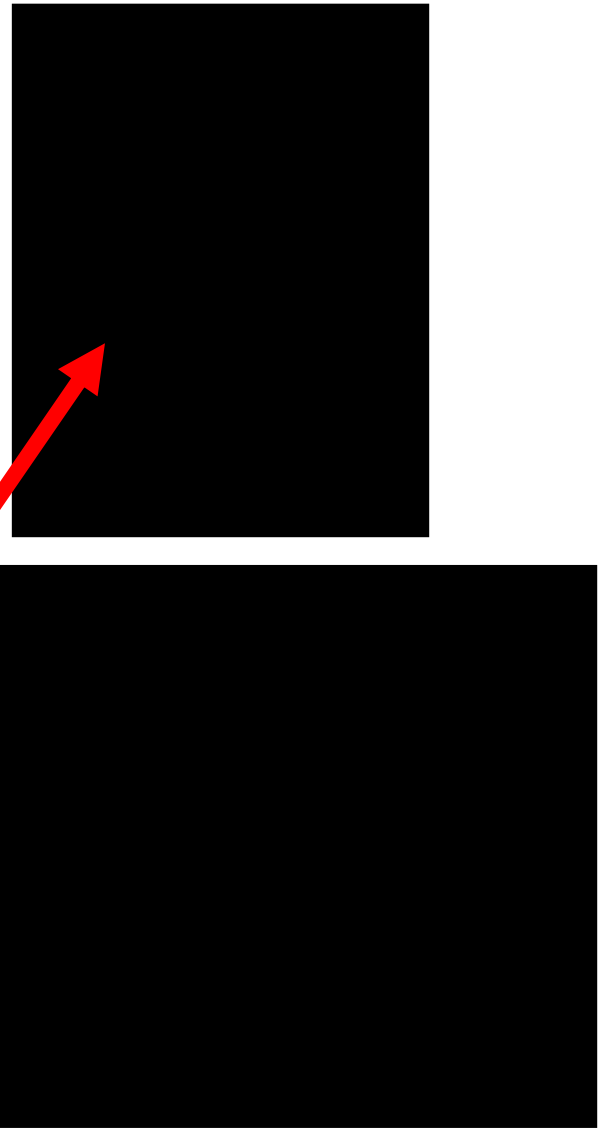
Abbreviations: ADT: androgen deprivation therapy; HR: hazard ratio; OS: overall survival

Modelling time to CROD (PFS in model) (1)

AIC and BIC statistical fit statistics for docetaxel time to CROD and time to CROD extrapolations:

Model	AIC	BIC	Predicted % alive at (years)					
			1	2	3	5	7	9
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAARTED cPFS			77.5	60	46.2	36.6	30.5	N/A
CHARTED time to CRPC			67.1	44.7	32.9	29.9	22.4	N/A
STAMPEDE-3 rPFS			81.5	61.5	49.6	36.6	29	21.3
ARASENS			63.1	37.8	25	N/A	N/A	N/A



Company: Expect ARASENS results to be lower as death included

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; (c)PFS: (clinical) progression-free survival; CROD: castration-resistant prostate cancer or death; CRPC: castration-resistant prostate cancer; Gen.: generalised

Modelling time to CROD (2)

Time to CROD estimates over time for all modelled treatments:

OS	Hazard ratio	Predicted % alive at (years)				
		2	5	10	20	30
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Comparator PFS curves calculated by applying network meta-analysis HRs to the docetaxel arm

Company: Generalised gamma in base case, log-logistic in scenario
After technical engagement update in line with EAG: Log-normal

NICE Abbreviations: ADT: androgen deprivation therapy; PFS: progression-free survival; CROD: castration-resistant prostate cancer or death; hazard ratio

Modelling time-on-treatment (1)

AIC and BIC statistical fit statistics for darolutamide ToT and darolutamide ToT extrapolations:

Model	AIC	BIC	Predicted % alive at (years)					
			1	2	3	5	7	9
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARASENS			82.5	63.1	53.1	N/A	N/A	N/A
Modelled time to CROD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Company: ARASENS ToT mostly informed by adherence to placebo (6 cycles docetaxel, then placebo)

- No publicly available long-term ToT data available – clinical experts: not a large gap expected between ToT and progression

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CROD: castration-resistant prostate cancer or death; ToT; time on treatment

Modelling time-on-treatment (2)

Time on treatment modelled using darolutamide + docetaxel + ADT arm from ARASENS as an anchor and NMA HRs applied to get comparator time on treatment

Time to treatment estimates over time for all modelled treatments:

OS	Hazard ratio	Predicted % alive at (years)				
		2	5	10	20	30
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company: Log-logistic in base case, Gompertz in scenario
After technical engagement update in line with EAG: Generalised gamma

EAG: Agree time on treatment should be similar to time to CROD
Clinical expert: Proportion of people remaining on treatment with darolutamide after 10 years is optimistic – expect unlikely more than 10% → EAG prefer using generalised gamma

Abbreviations: ADT: androgen deprivation therapy; CROD: castration-resistant prostate cancer or death;