Part 1 slide handouts for public [redacted]

NICE National Institute for Health and Care Excellence

Chair's presentation

Abiraterone for untreated high-risk hormone-sensitive metastatic prostate cancer [ID945]

2nd appraisal committee meeting, 10 July 2018

Committee B

Lead team: Bill Turner, Nigel Westwood, Nicholas Latimer

Chair: Amanda Adler

ERG: Aberdeen Health Technology Appraisal Group

NICE technical team: Jessica Cronshaw, Mary Hughes, Ross Dent, Jasdeep Hayre

Company: Janssen

ACD: preliminary recommendation

Abiraterone plus androgen deprivation therapy is not recommended, within its marketing authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adults

no analyses reflected the committee's preferred assumptions

Treatment pathway

Comparators are androgen deprivation therapy (ADT) and docetaxel + ADT

HORMONE SENSITIVE Metastatic	'hormone relapsed' Metastatic *(also known as 'castrate resistant')*			
New diagnosis	Before chemotherapy indicated	Chemo-therapy indicated	After docetaxel	Cannot tolerate docetaxel
ADT Docetaxel + ADT Abiraterone + ADT?	• Abiraterone TA387 • Enzalutamide TA377 • Watchful waiting	Docetaxel TA 101	• Abiraterone TA259 • Enzalutamide TA316 • Cabazitaxel TA391 • Radium 223 TA412 (symptomatic bone mets. only)	• Radium 223 TA412 (symptomatic bone mets. only)

Current appraisal high risk

Committee heard that docetaxel can be offered again to people who had it for hormone sensitive disease after the disease has progressed and is hormone relapsed; company's model did not reflect this

TA, technology appraisal

Abiraterone (Zytiga, Janssen)

Marketing authorisation	• Indicated with prednisone or prednisolone for treating newly diagnosed **high risk + metastatic** hormone sensitive prostate cancer (mHSPC) in adults in combination with androgen deprivation therapy (ADT) • 'High risk' is defined as 1. Gleason score ≥8 (aggressive/likely to spread) 2. 3 or more lesions on bone scan 3. Visceral metastasis (excluding lymph nodes) • Note: Abiraterone also indicated for metastatic castrate resistant prostate cancer (mCRPC) before or after chemotherapy • NHS England does not commission abiraterone twice or enzalutamide after abiraterone
Cost	• Maximum list price cost per patient per year £35,653 • A 'commercial arrangement' is proposed but not yet approved. Same as existing commercial access arrangement.

LATITUDE

International randomised double-blind placebo-controlled

Population

- Adults
- Newly diagnosed
- High risk mHSPC
  - as per marketing authorisation
- ECOG performance status 0,1,or 2

n=597
Abiraterone 1000 mg once daily + prednisolone 5 mg once daily + ADT*

1:1 randomisation

Treat until disease progression or unacceptable toxicity
60 months follow up
(study unblinded after 1st interim analysis, 30 months follow up, crossover permitted)

n=602
ADT* + placebo

Endpoints

Co-1°

- Overall survival
- Radiographic progression free survival (investigator assessed)

2°

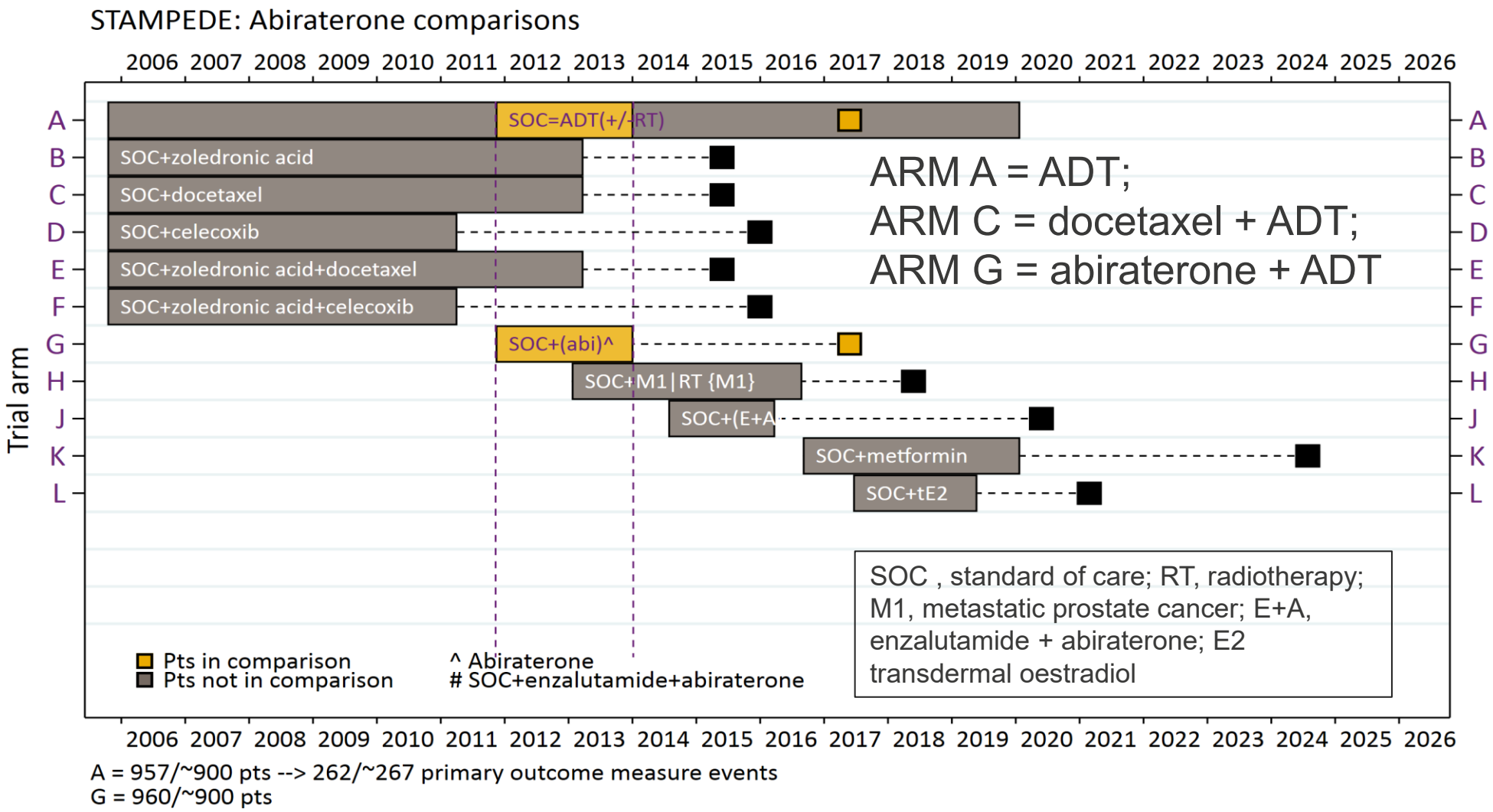
- Time to:
  - Starting chemotherapy
  - Next skeletal-related event
  - Pain progression
  - Subsequent therapy
  - PSA progression
- Quality of life (including EQ-5D-5L)
- Safety

** Luteinizing hormone-releasing hormone agonist or bilateral orchidectomy*

STAMPEDE:

Multi-arm, multi-stage platform trial localised or metastatic – subgroup for metastatic HSPC, but not 'high-risk' metastatic

Yellow bars show populations in pre-planned comparison of abiraterone + ADT vs. ADT



Trial evidence by comparator

	Direct comparison	Indirect comparison
Abiraterone + ADT vs. ADT	• LATITUDE • STAMPEDE	
Abiraterone + ADT vs. docetaxel + ADT	• STAMPEDE	• GETUG-AFU 15 CHAARTED – Open label RCTs (newly diagnosed high-volume metastatic hormone sensitive subgroups) – comparing docetaxel + ADT vs. ADT

Results for abiraterone + ADT vs comparator

- *For docetaxel comparison, committee preferred direct comparison;*
- *Heard from clinicians effect unlikely to vary by risk level (high/low)*

	Direct comparison		Indirect comparison	
ADT alone	**PFS**	**OS**		
	LATITUDE **0.47** (0.39 to 0.55)	LATITUDE **0.62** (0.51 to 0.76)		
	metastatic STAMPEDE **0.43** (0.36 to 0.52)	metastatic STAMPEDE **0.61** (0.49 to 0.75)		
Docetaxel + ADT	**PFS**	**OS**	**PFS**	**OS**
	metastatic STAMPEDE **0.69** (0.50 to 0.95)	metastatic STAMPEDE **1.13** (0.77 to 1.66)	LATITUDE + CHAARTED + GETUG-AFU 15 **0.76** (0.53 to 1.10)	LATITUDE + CHAARTED + GETUG-AFU 15 **0.92** (0.69 to 1.23)

company used in model

committee preferred

Cost effectiveness model – 2 approaches

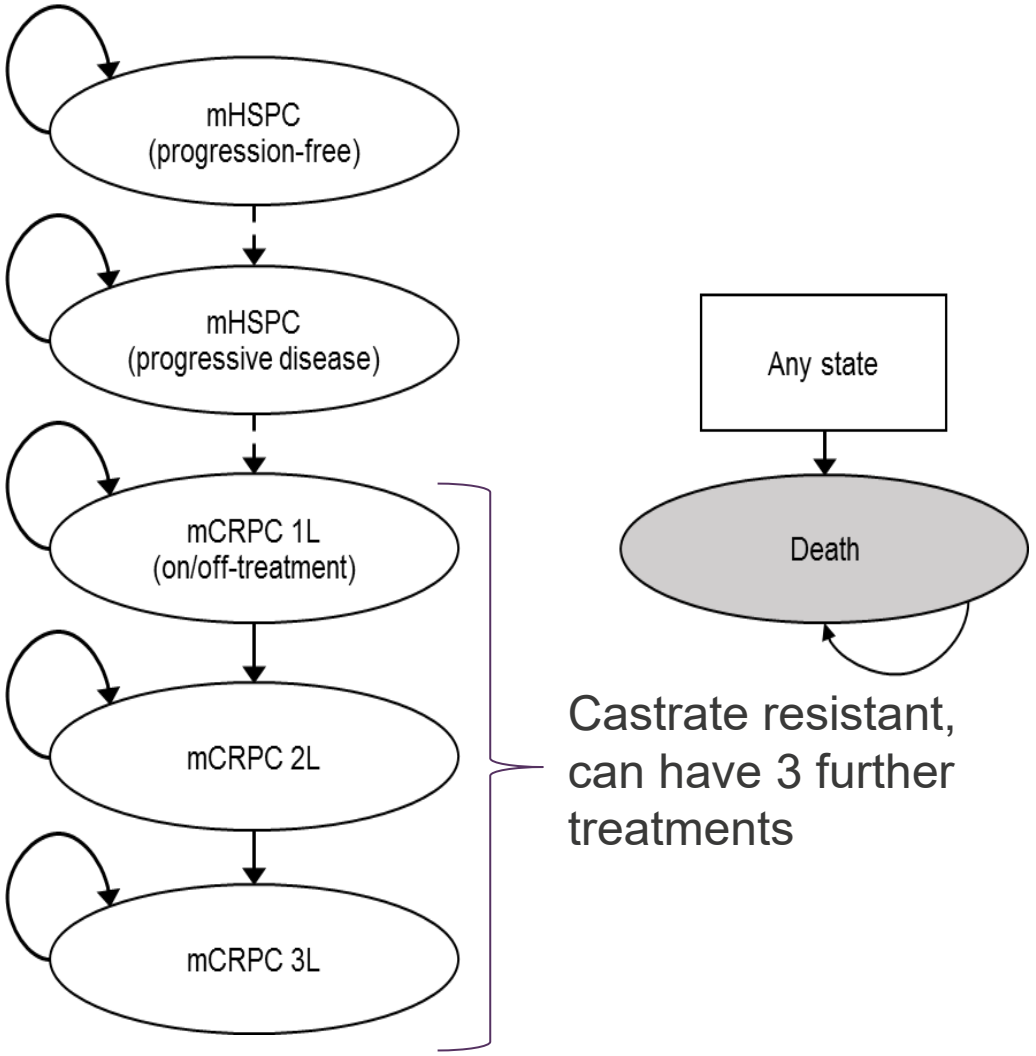
Used LATITUDE data for 1st 5 months then multistate modelling (MSM)

Base case '<u>MSM/TA387</u>'

- LATITUDE to inform transitions in hormone sensitive states
- TA387 model (COU-AA-302 trial) to inform transitions in hormone relapsed states
- Calibrated modelled overall survival to LATITUDE overall survival

Alternative approach '<u>MSM</u>'

- LATITUDE to inform transitions in all health states
- Time on 1st treatment for hormone relapsed prostate cancer from COU-AA-302
- No additional calibration



Committee did not choose between approaches as results from both lacked validity

ACD consultation responses

- Consultee comments from:
  - Janssen
  - Prostate cancer UK

- Company new evidence:
  - Network meta-analyses using STAMPEDE data only and results of independent network meta-analyses of abiraterone vs. docetaxel
  - Survey of clinical experts on docetaxel use
  - Adjusted economic model
    - Different proportions of follow-on treatment
    - Scenario analyses varying effectiveness of abiraterone vs. docetaxel overall survival hazard ratio
- Company does not provide:
  - Quality of life data from the same source (STAMPEDE) for each treatment

Committee's considerations/company response

Topic	Issue	Company's response	Match committee's preference?
Treatments in castrate resistant phase	There are more treatment options if 1st treatment is docetaxel rather than abiraterone	Updated base case to include docetaxel retreatment and to reflect different proportions of follow-on treatments	No – although docetaxel is included in sequences, the same number of treatments available across arms
Best data to compare abiraterone and docetaxel	Company did not include STAMPEDE high-risk subgroup, committee prefer direct comparison which shows no survival benefit	Did not provide relevant data, uses HRs from indirect comparison which shows survival benefit	No
Estimated survival	Implausible: survival in hormone relapsed phase similar in all arms despite different number of therapies available in each arm	Scenario analysis varying overall survival hazard ratio	No – when overall survival HR =1.0, survival is still longer with abiraterone
Best data for quality of life	Did not include STAMPEDE quality of life data	Did not provide relevant data	No

Consultation comments: identifying patients unsuitable for docetaxel

Committee discussion
No clear-cut criteria to define people who can have abiraterone, but not docetaxel

Company: 40% of people with newly diagnosed mHSPC have chemotherapy, suggesting that 60% have ADT alone (Rulach et al., 2017) (n.b. high risk?)

Prostate Cancer UK – Criteria exist defining who cannot have docetaxel:

- NHS England clinical commissioning policy statement:
  - Contra-indications: hypersensitivity to taxanes, WHO performance status 3-4, peripheral neuropathy, bone marrow suppression, life-limiting illnesses
- TA412 Radium-223 dichloride for hormone-relapsed prostate cancer

TA412 Radium-223 recommended for treating hormone-relapsed prostate cancer with symptomatic bone metastases and no known visceral metastases, if:

- already had docetaxel or
- docetaxel is contraindicated or is not suitable

"Clinical experts confirmed that there are people who cannot take docetaxel but who can take radium-223", namely renal impairment, taking immunosuppressants, poor performance status

◉ *Is it reasonable to consider separately people who cannot have docetaxel?*

Consultation comments: clinical evidence

	Committee conclusion	Company ACD response
Follow-on treatments	Follow-on treatments in LATITUDE did not reflect those used in the UK, whereas those in STAMPEDE did (ACD 3.5)	• In LATITUDE abiraterone + ADT arm a small number had therapies not available in the UK ○ 10% had enzalutamide ○ 3% had abiraterone again • In STAMPEDE a similar proportion (10%) had enzalutamide and abiraterone (3%) after abiraterone
Abiraterone vs. docetaxel		
STAMPEDE	Favoured direct comparison; ideally, data from patients with **high-risk** metastatic disease from STAMPEDE (ACD 3.6)	• Did not provide STAMPEDE data • Metastatic subgroup (n=342) not powered to detect OS differences; high-risk subgroup even smaller – indirect comparison does not find a statistically significant difference • New network using published data from 3 sources including STAMPEDE (next slide)

New evidence: relative effectiveness of abiraterone and docetaxel

Company conducted another network meta-analysis using only STAMPEDE arms

	PFS hazard ratio (95% CI/CrI)	OS hazard ratio (95% CI/CrI)
Direct comparison: STAMPEDE metastatic subgroup	0.69 (0.50, 0.95)	1.13 (0.77, 1.66)
Indirect: LATITUDE + CHAARTED + GETUG-AFU 15	0.76 (0.53, 1.10)	0.92 (0.69, 1.23)
Indirect: LATITUDE + CHAARTED + GETUG-AFU 15 + mSTAMPEDE	[redacted]	[redacted]
Indirect: 3 STAMPEDE arms only	[redacted]	0.91 (0.72, 1.15)

- Company also provide 'independent' published networks using same trials:
  - Vale et al. (2018) abiraterone highest probability of being most effective treatment but difference in survival benefit is 1% to 9% at 3 years
  - Wallis et al. (2017) no statistically significant difference between abiraterone and docetaxel for overall survival

◉ *Has the committee seen new evidence to change its preference for effect estimates from directly randomised comparisons?*

◉ *Is there a survival benefit for abiraterone over docetaxel?*

Consultation comments: subsequent therapies

Committee discussion

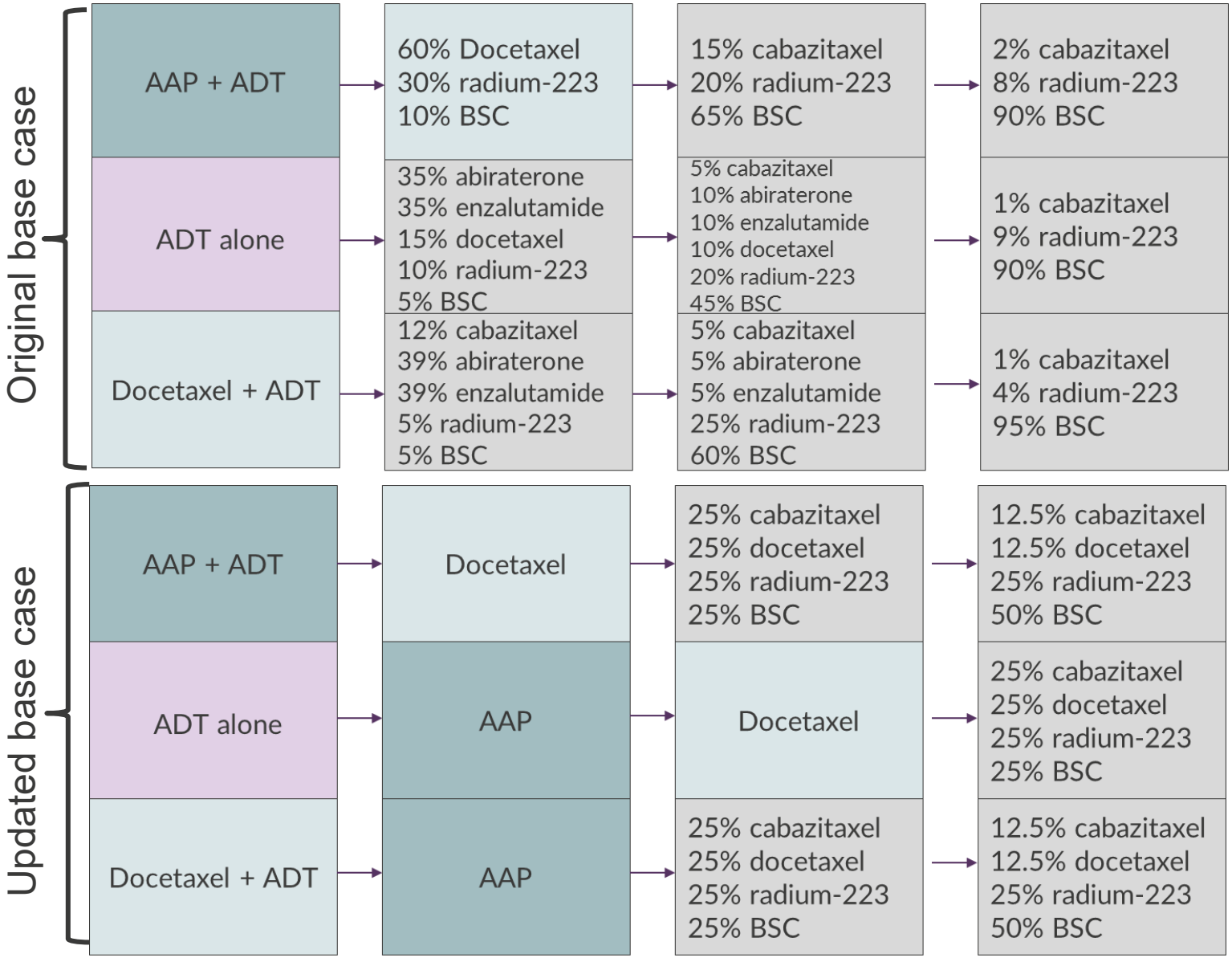
- Having abiraterone plus ADT results in fewer treatment options when hormone-relapsed than having ADT alone or docetaxel plus ADT when hormone-sensitive
- People who have (dose-limited) docetaxel 1st-line can have docetaxel again because the benefit of docetaxel is not exhausted

Company

- "No robust clinical evidence to suggest that docetaxel re-challenge has significant clinical benefit or it would be widely used in the NHS following docetaxel + ADT"
  - **14% (i.e. 44/315) had docetaxel re-challenge in STAMPEDE** [Arm C]
- GETUG-AFU showed docetaxel re-challenge was of limited benefit
  - authors suggest that taxane re-challenge with cabazitaxel could be preferred
- Company surveyed 27 UK clinicians that manage prostate cancer:
  - docetaxel re-challenge **up to 25% which company uses in updated model**
  - 2 respondents identified cabazitaxel as relevant treatment for re-challenge

◉ *Has the committee heard evidence to change its conclusion that re-challenge with docetaxel is offered in the NHS?*

Company original/revised model: follow-on treatments



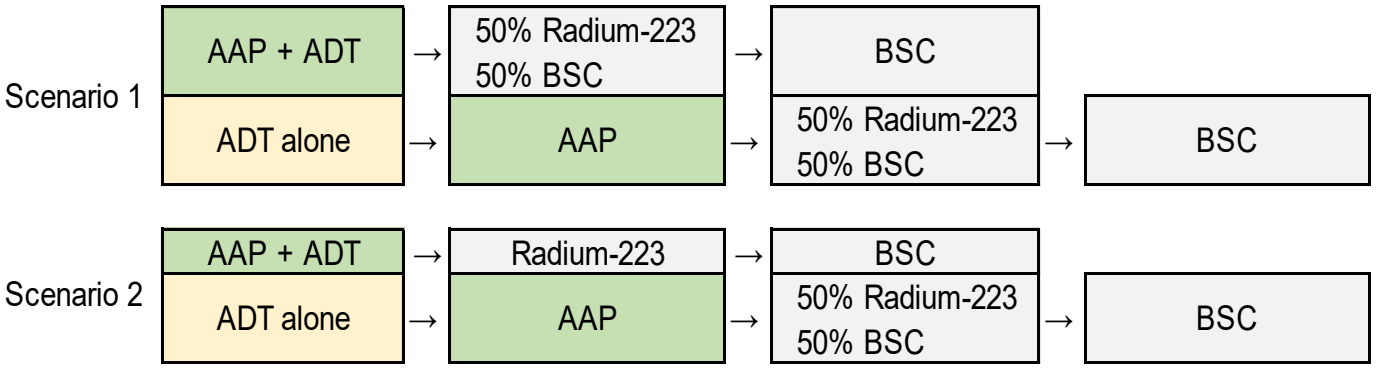
Rationale for changes:

- Abiraterone most likely treatment after ADT/docetaxel
- Docetaxel most likely treatment after abiraterone
- **25% of patients have docetaxel again (clinical survey)**
- No abiraterone after enzalutamide and vice versa
- Enzalutamide assumed equivalent to abiraterone so not modelled separately
- **ERG:** although company added docetaxel in to some treatment sequences, the number of available treatments is the same in each arm

Do follow-on treatments reflect NHS practice? Do the revised treatment sequences address the committee's concerns about a different number of follow-on treatments being available depending on the initial treatment?

ERG comments: follow-on treatments

- If most people have ADT because docetaxel is unsuitable, implausible that people having ADT as 1st treatment go on to have docetaxel in hormone relapsed phase
  - company scenario analyses remove docetaxel from follow-on treatment sequences for abiraterone + ADT vs. ADT alone comparison



- Company assumes all follow-on treatment have equal efficacy, so changing proportions changes only the costs
- **ERG uses original follow-on treatment proportions from ERG report in exploratory base case for docetaxel comparison**

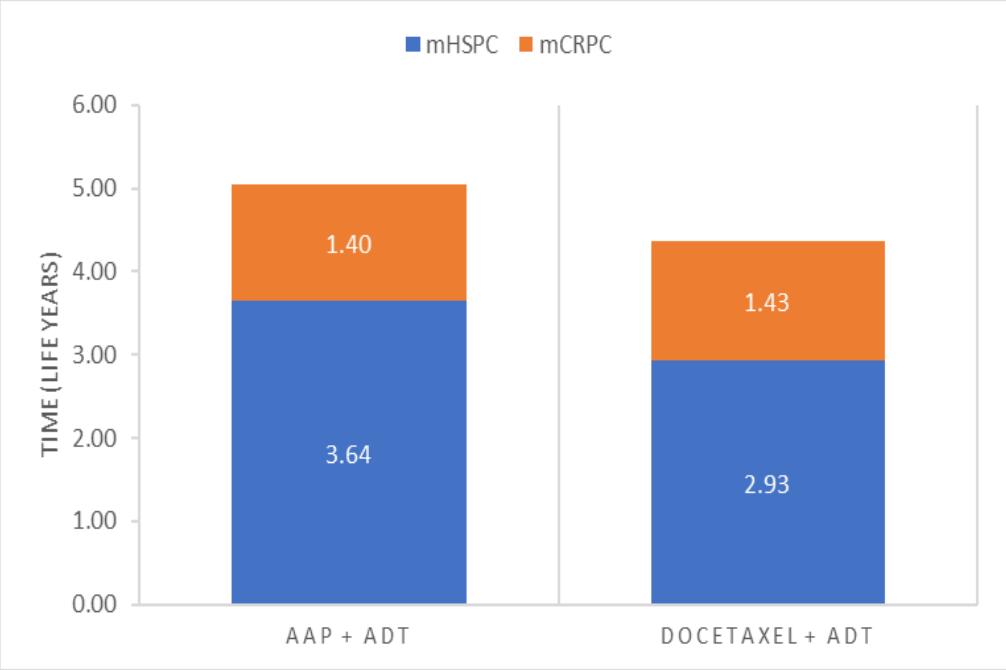
◉ Do the company's scenario analyses for the ADT alone comparison reflect clinical practice? Does the model account for both costs and benefits? What is the best data source for follow-on treatments?

Consultation comments: modelled overall survival

Committee conclusion: if the model reflected NHS treatment, the benefits of abiraterone plus ADT in delaying progression might be balanced by the benefits of more follow-on treatment options after ADT alone or docetaxel plus ADT

Company:

- Do not agree that overall survival is the same for abiraterone and docetaxel
- Model has face validity for duration of time spent pre- and post-progression across treatment arms
  - Base case, modelled post-progression survival longer for docetaxel (1.43 years) than abiraterone (1.40 years) but not sufficient to offset gains from longer PFS with abiraterone



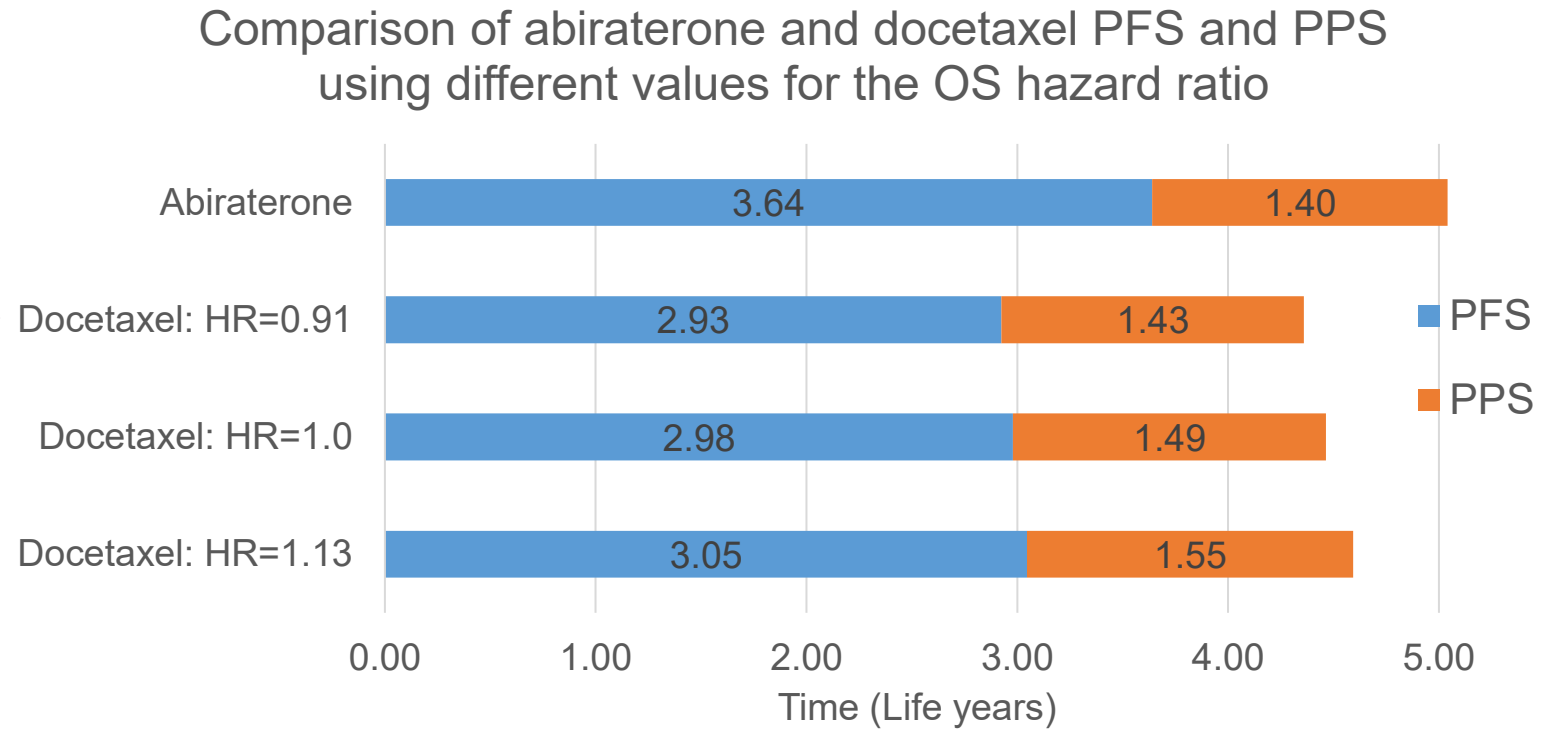
ERG disagree, results of post-progression survival modelling lack validity:

- If all patients start in post progression state, patients who had abiraterone for hormone sensitive disease live 1.61 years, longer than patients who had ADT (1.59 years) or docetaxel (1.58 years)
- This is despite a higher proportion in the abiraterone arm having best supportive care as the next treatment

New company analyses: varying OS hazard ratio

Company base case NMA including LATITUDE

HR from STAMPEDE direct comparison



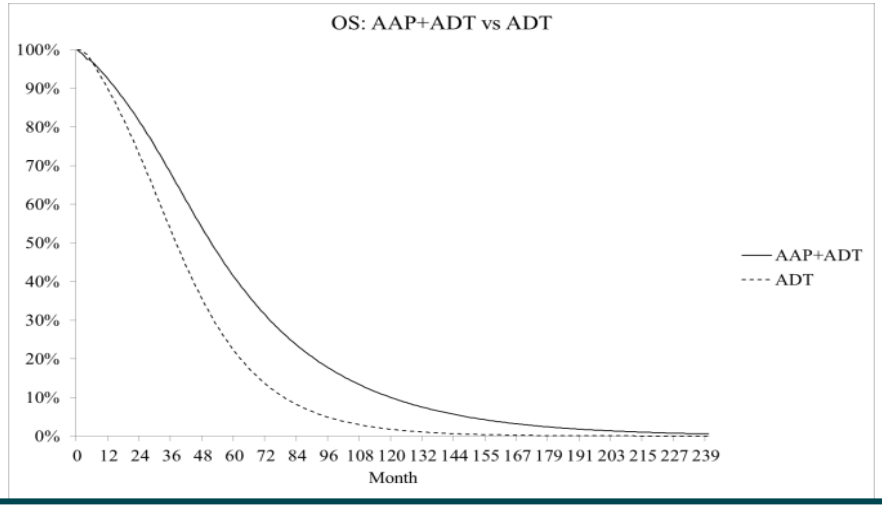
ERG:

- Mortality rate after progression with abiraterone should be higher than after docetaxel because people who have had docetaxel can have more effective treatments
- Setting the OS hazard ratio to 1 does not equalise survival from start of treatment:
  - the probability of dying before or after progression is the same for both arms
  - but, probability of dying much lower pre- than post-progression (0.14% vs. 0.93%)
  - docetaxel patients stay in post progression longer than abiraterone patients but this does not outweigh benefit of abiraterone patients staying longer in pre progression
- Overall survival equal when HR is 1.89 (MSM/TA387 model) and 1.24 (MSM model)

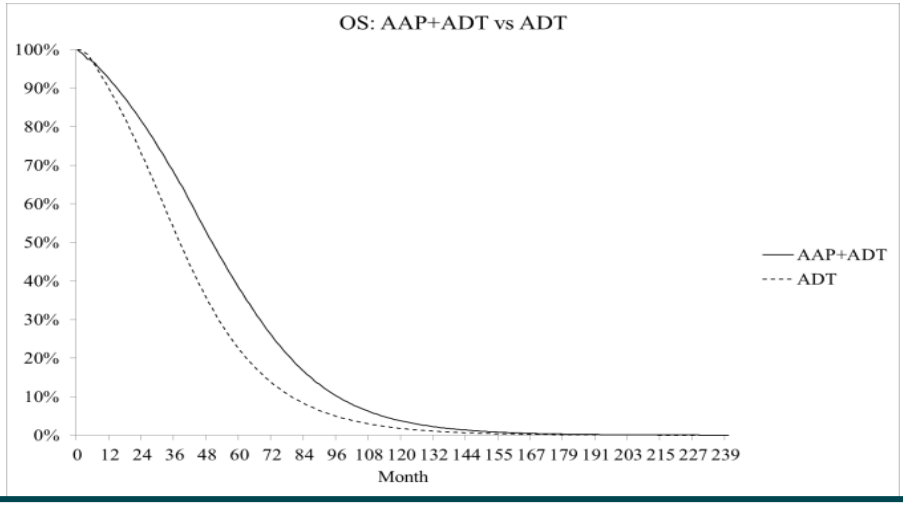
ERG comments: duration of benefit

- Company has not explored limiting the duration of benefit
- ERG explores the impact of limiting the duration of benefits when comparing abiraterone with ADT
  - implemented by applying the ADT transition probabilities from 40, 60 and 80 months (40 months is the longest follow-up in the LATITUDE trial)

Unlimited duration of benefits: OS curve



Duration of benefits = 40 months: OS curve



- Given concerns about modelling of abiraterone vs. docetaxel, ERG has not explored duration of benefit for this comparison

◉ Is it plausible that the benefits of abiraterone + ADT compared with ADT alone persist indefinitely? Is it more plausible to assume the benefits last for 40, 60 or 80 months?

Modelling approach

Committee: did not choose preferred modelling approach as neither produced plausible results

Company: MSM/TA387 model is appropriate because:

- LATITUDE overall survival data are immature
- some follow-on treatments in LATITUDE not available in NHS

ERG:

- MSM/TA387 model uses non-standard methods to compensate for poor fit of modelled overall survival from TA387 to LATITUDE Kaplan-Meier data
- Calibrating TA387 curves to LATITUDE curves negates argument that LATITUDE post-progression and overall survival curves are not relevant to NHS practice

- **Most important difference between models is the amount of time spent on 1st line, 2nd line and 3rd line treatment in the hormone relapsed phase**
  - in MSM/TA387 model patients spend majority of time post progression in 1st line treatment for hormone relapsed disease
  - in the MSM model time is more evenly balanced between 1st line and 2nd line, and a longer time on 3rd line treatments **(ERG view: this is more plausible)**

◉ *Which modelling approach does committee prefer?*

Consultation comments: health related quality of life data for docetaxel

Committee discussion

- Would prefer EQ-5D data from STAMPEDE ideally for subgroup with metastatic and high-risk disease for abiraterone plus ADT, docetaxel plus ADT and ADT alone
- Company applied a utility decrement for docetaxel in economic model and also for adverse effects, so there might be double counting for adverse events

Company

- Did not obtain STAMPEDE data
- No longer applies off-treatment disutility in the docetaxel + ADT arm

ERG:

- To capture adverse events after initial docetaxel treatment, company originally used utility data from abiraterone + ADT arm – now use values from ADT arm.
  - More reasonable to use abiraterone values as docetaxel more similar in efficacy to abiraterone than ADT
- Data suggests a quality of life **increment** associated with completing a course of docetaxel and before disease progression
  - scenario applies increment of [redacted] (50% of the increment of abiraterone vs. ADT)

◉ *How should quality of life for patients on docetaxel be modelled?*

Summary: company revised base case

Change	Rationale
Corrected implementing of CAA (commercial access arrangement), tunnel state error and resource use costs for enzalutamide and -233	We have accepted the ERG's corrections
Equalised the frequency of bone scans	ERG: no evidence for more bone scans with docetaxel
Used LATITUDE utility coefficients for adverse events	ERG: LATITUDE values more plausible
Changed follow-on treatment proportions	To include docetaxel re-challenge and reflect plausible NHS sequences
Applied a fixed treatment cost for docetaxel, radium-223 and cabazitaxel as a one off cost	Better captures the costs associated with therapies that have a fixed number of doses than discontinuation curves
Used a different network (all trials) to model abiraterone vs docetaxel OS HR of 0.91	NMA covers the whole evidence base, *(does not reflect committee preference)*
Applied docetaxel compliance to administration and resource use costs	Reflects committee preference
Utility decrement after docetaxel removed (ADT AE utility decrements applied instead)	Reflects committee preference (*but source of utility remains the same)*

Summary: ERG changes to company revised base case

Change	Rationale
Adjusted follow-on treatment proportions for abiraterone + ADT vs docetaxel + ADT	In line with ERG original base case
[redacted]	Improbable that only [redacted] of patients will still be taking abiraterone at 40 months [redacted]
Applied abiraterone + ADT quality of life decrements for serious adverse events and skeletal related events to docetaxel arm after initial treatment course	Company used decrements associated with ADT alone, but efficacy of docetaxel + ADT is more similar to abiraterone +ADT than ADT
MSM model: LATITUDE market share data for follow-on treatments applied to docetaxel arm	Implementation error: company applied only applied market share data to abiraterone arm

Key scenario analyses:

- Limit duration of benefit for abiraterone at 40, 60 and 80 months
- Quality of life increment after docetaxel
- Overall survival HR and PFS HR from STAMPEDE for abiraterone + ADT
- HR to equalise overall survival
- Company follow-on treatment proportions

Cost-effectiveness results

Results are confidential and will be presented in a private part of the appraisal committee meeting (part 2) because they include confidential discounts for subsequent treatments

Cancer Drugs Fund

- When the uncertainty in clinical and cost effectiveness data is too great to recommend for routine use, the committee can recommend in CDF if:
  - ICERs have plausible potential to be cost-effective
  - Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
  - Data collected (including research underway) will be able to inform subsequent update (normally within 24 months)
- Company has not proposed that abiraterone is considered for the CDF

◉ *Could additional data collection address the uncertainties associated with the abiraterone and docetaxel overall survival comparison?*