

Chair's presentation

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

3rd appraisal committee meeting, 15 January 2020

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 not recommended, within its marketing authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adults

Because none of the analyses reflected the committee's preferred assumptions

Abiraterone (Zytiga, Janssen)

Mechanism	Inhibits androgen synthesis via cytochrome P450 17 alpha-hydroxylase in testes, adrenals, and in prostate cancer
Marketing authorisation November 2017	<p>With androgen deprivation therapy (ADT) and either prednisone or prednisolone in adults with prostate cancer that is:</p> <ul style="list-style-type: none"> • newly diagnosed • high risk • metastatic • hormone sensitive <p>In clinical trials, 'high risk' is defined as at least 2 of:</p> <ol style="list-style-type: none"> 1. Gleason score ≥ 8 (aggressive/likely to spread) 2. 3 or more lesions on bone scan 3. Visceral metastasis (excluding lymph nodes) <p>Note: Abiraterone also indicated for metastatic castrate resistant prostate cancer (mCRPC) before or after chemotherapy. Abiraterone or enzalutamide in NHS given only once.</p>

History of appraisal

Committee meeting 1 May 2018

- Company proposed same commercial access agreement (CAA) from abiraterone later in disease
- Appraisal consultation document (ACD) released, not recommended as:
 - model generated implausible survival benefit for abiraterone + ADT vs. docetaxel + ADT because follow-on treatments not modelled appropriately
 - Company did not fully use data from key trial STAMPEDE

Consultation

Committee meeting 2 July 2018

- Same CAA proposed:
 - NHS England - cannot apply
- Some, but not all, committee's concerns addressed using same model as original submission
- Draft recommendation: not recommended
- ACD prepared but not released to allow commercial discussions between company and NHS England
- ACD shared with company + Evidence Review Group (ERG)

Appraisal suspended for price negotiations

Today's meeting

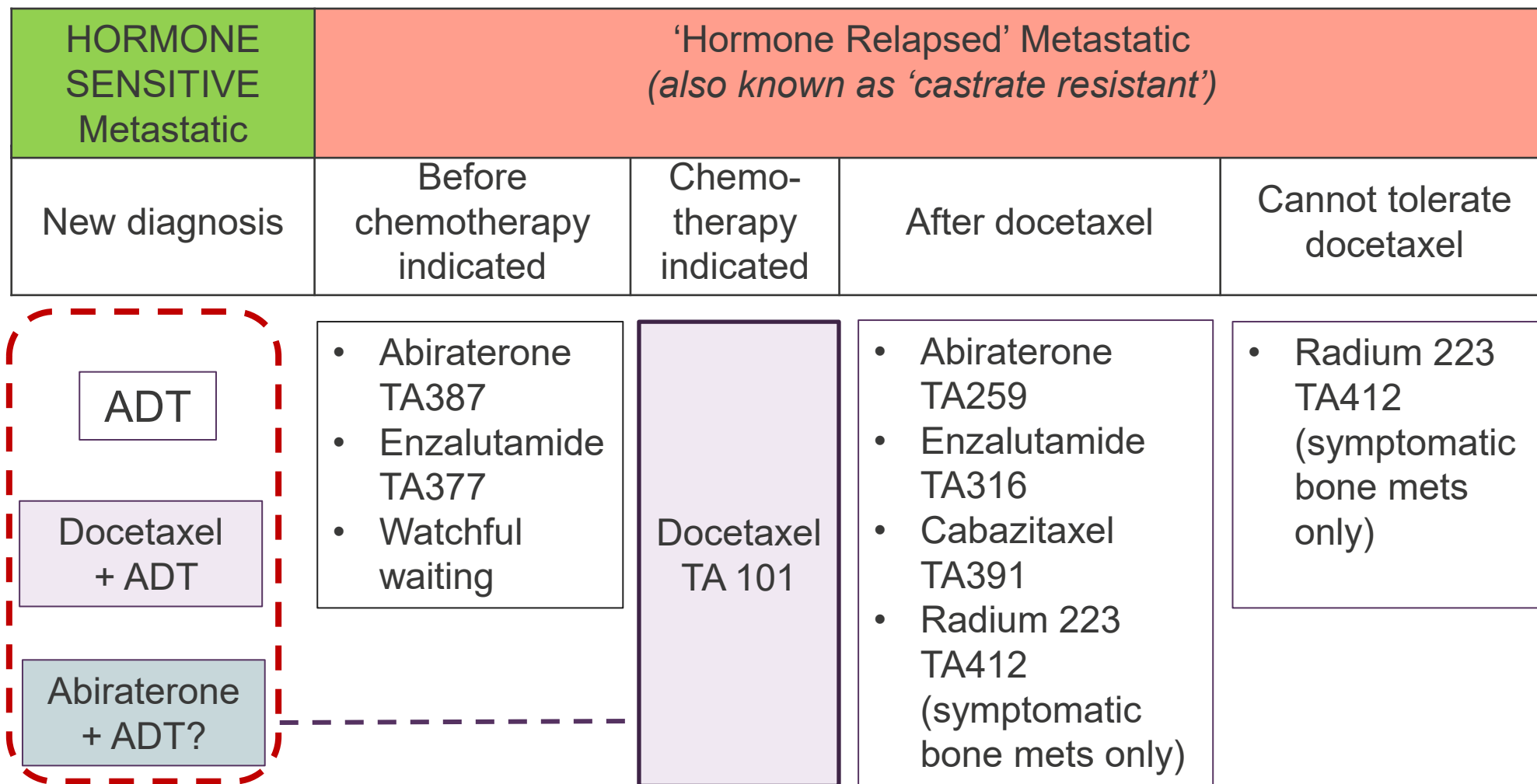
- **List price abiraterone (hormone-sensitive prostate cancer)**
- New modelling approach: partitioned survival model
- Company propose committee considers people 'ineligible for chemotherapy' separately - contrary to committee's previous conclusions
- Company and NHS England will continue negotiations based on committee's preferred assumptions

Key issues

<p>Extending length of life</p>	<p>Does abiraterone + ADT extend overall survival compared with docetaxel + ADT?</p> <p>How to extrapolate progression free survival and overall survival beyond end of trials?</p> <p>Has a large effect on modelled overall survival and the incremental cost effectiveness ratios (ICERs)</p>
<p>Subpopulations</p>	<p>Committee identified 2 subpopulations: people not fit enough for docetaxel and people who chose not to take docetaxel.</p> <p>Is there sufficient new evidence for the committee to change its conclusions that ‘it could not consider separately the clinical and cost effectiveness of abiraterone in people who cannot have docetaxel, or only consider ADT alone as a comparator?’</p>
<p>Follow-on treatments</p>	<p>Is the company’s approach to determining time on treatments for hormone relapsed prostate cancer appropriate?</p>
<p>Quality of life</p>	<p>Is the company’s utility decrement for docetaxel + ADT (from a survey) plausible and consistent with EQ-5D data from STAMPEDE?</p>

Treatment pathway metastatic disease

Comparators: 1. ADT, 2. docetaxel + ADT; abiraterone (enzalutamide) given **once**



Current appraisal high risk only

- NHS England commissions 6 cycles of docetaxel*
- Docetaxel can be offered again after for hormone relapsed disease; company’s original model did not reflect this*
- As above, abiraterone or enzalutamide only once*

Docetaxel does not have a marketing authorisation for hormone-sensitive disease

- Off-label docetaxel is commissioned by NHS England
 - Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer' NHS England Reference: [B15/PS/a]
- Since last committee meeting, NICE updated prostate cancer guideline NG131 (May 2019)
 - recommends docetaxel as an option for people who have newly diagnosed metastatic prostate cancer who do not have significant comorbidities as follows:
 - start treatment within 12 weeks of starting androgen deprivation therapy **and**
 - use six 3-weekly cycles at a dose of 75 mg/m² (with or without daily prednisolone)

Recap: committee conclusions about populations and comparators (1st meeting)

Cannot have docetaxel

- Some people choose not to have docetaxel and some not fit enough for it:
 - Poor performance status WHO 2 ‘with caution’
 - contra-indications include significant peripheral neuropathy, poor bone marrow function, significant co-morbidity (e.g. cardio-vascular or respiratory disease)
NHS England Reference: [B15/PS/a]
- For these people ADT alone = relevant comparator
- However, LATITUDE and STAMPEDE, key clinical trials for this appraisal included only people with Eastern Cooperative Oncology Group status 0, 1 or 2, good bone marrow function, and without any condition that would interfere with participation
- ACD “The committee was aware that it had not been presented with evidence of abiraterone’s effectiveness in people who cannot take docetaxel, because these people were excluded from LATITUDE and STAMPEDE.”

Don’t choose docetaxel

- ACD* Committee concluded ‘it would be inappropriate to only consider abiraterone for those who choose to have ADT and not those who chose to have docetaxel’

* Text from ACD prepared after second committee meeting

Clinical trial evidence direct and indirect comparisons

Abiraterone + ADT compared with:

Comparison	Trial name	Design
ADT alone		
Direct	LATITUDE	<ul style="list-style-type: none"> Blinded RCT: newly diagnosed high risk metastatic hormone sensitive prostate cancer; co-primary endpoint PFS and OS Trial unblinded after 1st interim analysis @30 months, crossover permitted
	STAMPEDE	<ul style="list-style-type: none"> Adaptive UK RCT in a wider population than marketing authorisation: newly diagnosed locally-advanced or metastatic hormone sensitive prostate cancer Data for metastatic subgroup; not stratified by low/high risk
Docetaxel + ADT		
Direct	STAMPEDE	Abiraterone + ADT arm vs. docetaxel + ADT arm
Indirect: <i>Network meta-analyses</i>	GETUG-AFU 15	Open label RCTs with subgroups of newly diagnosed high-volume metastatic hormone sensitive comparing docetaxel + ADT vs. ADT
	CHAARTED	ADT vs. ADT
	LATITUDE	Included
	STAMPEDE	Sensitivity analysis only (metastatic subgroup)

Recap: results for abiraterone + ADT vs comparators

- 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	<div style="border: 2px solid red; padding: 5px; display: inline-block; margin-bottom: 10px;">company used in model</div> <div style="border: 2px solid green; padding: 5px; display: inline-block; margin-top: 10px;">committee preferred</div>	
	LATITUDE	LATITUDE		
	0.47 (0.39 to 0.55)	0.62 (0.51 to 0.76)		
	metastatic STAMPEDE	metastatic STAMPEDE		
	0.43 (0.36 to 0.52)	0.61 (0.49 to 0.75)		
Docetaxel + ADT	PFS	OS	PFS	OS
	metastatic STAMPEDE	metastatic STAMPEDE	LATITUDE + CHAARTED + GETUG-AFU 15	LATITUDE + CHAARTED + GETUG-AFU 15
	0.69 (0.50 to 0.95)	1.13 (0.77 to 1.66)	0.76 (0.53 to 1.10)	0.92 (0.69 to 1.23)

Recap: original modelled survival of abiraterone + ADT vs. docetaxel + ADT implausible

- Committee concluded ‘no evidence that abiraterone plus ADT improves overall survival compared with docetaxel plus ADT’
- But company’s modelling predicted greater survival even if hazard ratio for overall survival for abiraterone + ADT vs. docetaxel + ADT is
 - 1.00, suggesting no difference
 - 1.13 from STAMPEDE, suggesting people having docetaxel + ADT live longer

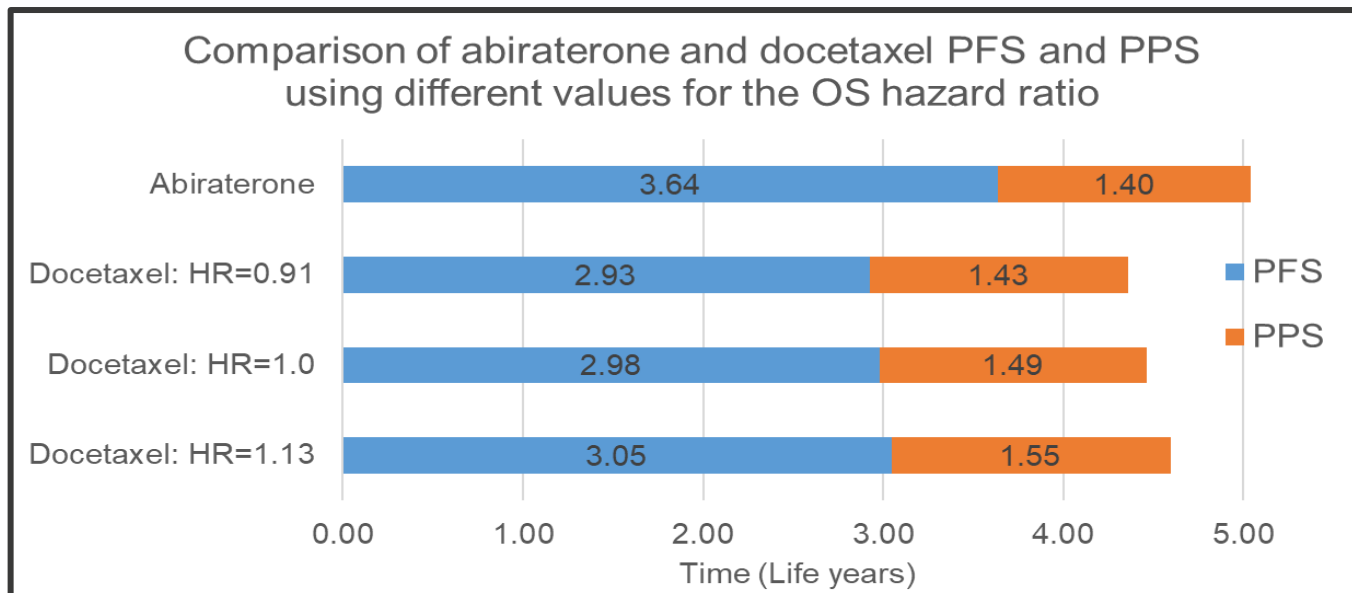


Figure from 2nd committee meeting slides (from model data). PFS: progression free survival; PPS post-progression survival

Committee: company’s approach to modelling does not provide plausible estimates of post-progression survival or overall survival; therefore does not generate valid estimates of cost effectiveness

Recap: original model did not account for fewer treatment options after abiraterone

- People who take abiraterone + ADT have fewer treatment options after progression:
 - **ADT** → 1. abiraterone or enzalutamide → 2. docetaxel → 3. cabazitaxel or radium-223
 - **Docetaxel + ADT** → 1. abiraterone or enzalutamide → 2. docetaxel again → 3. cabazitaxel or radium-223
 - **Abiraterone + ADT** → 1. docetaxel → 2. cabazitaxel or radium-223
- More treatment options = greater survival once cancer becomes hormone relapsed?
- Committee recognised ‘in the UK... the choice of next treatment depends on knowing the first treatment, unlike in the blinded LATITUDE trial
- Original model included same number of subsequent treatments in each arm, so company did not include benefits of having more treatment options
- Original model used trial for abiraterone in castrate resistant disease to inform Markov model

Committee: ‘it was not possible to determine a plausible ICER for abiraterone plus ADT compared with ADT or with docetaxel plus ADT’

And ‘estimates of survival from STAMPEDE after a patient needed a next treatment were likely more relevant to clinical practice in England than those from LATITUDE’

Recap: data from STAMPEDE not fully used

- Committee considered STAMPEDE most relevant as it is open-label UK based trial
 - follow-on treatment more likely to reflect UK clinical practice than LATITUDE
- Population in STAMPEDE broader than license for abiraterone
 - STAMPEDE data from metastatic subgroup, but not ‘high-risk’
- Quality of life: both LATITUDE and STAMPEDE collected EQ-5D (company stated EQ-5D results for docetaxel not available to company from STAMPEDE)

	Quality of life on treatment	Adverse events
ADT alone	EQ-5D data LATITUDE	Published values
Abiraterone plus ADT	<ul style="list-style-type: none"> • EQ-5D data LATITUDE • Utility increase for being on abiraterone compared with ADT alone 	
Docetaxel plus ADT	Company survey; utility decrement when treated with docetaxel.	

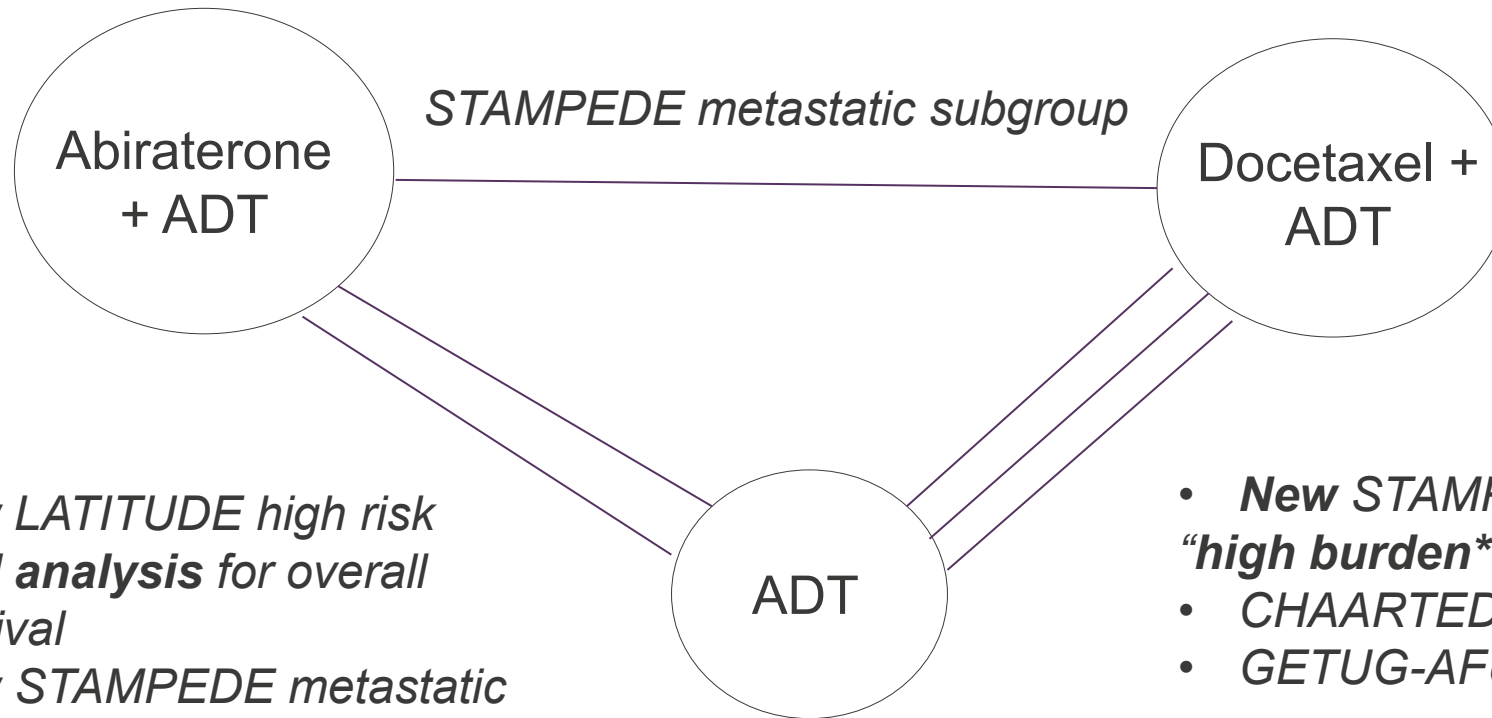
Committee: ‘preferable to use EQ-5D data from the subgroup of people from STAMPEDE with metastatic and high-risk hormone-sensitive prostate cancer’ because same trial had data on all treatments

Consultation comments

- None: NICE did not release appraisal consultation document for consultation
- Appraisal was 'suspended'
- Company submitted new data and new model
- Critiqued by ERG

New data and model for today's discussion

Bold text shows new data



- ***New LATITUDE high risk final analysis for overall survival***
- ***New STAMPEDE metastatic high risk subgroup***

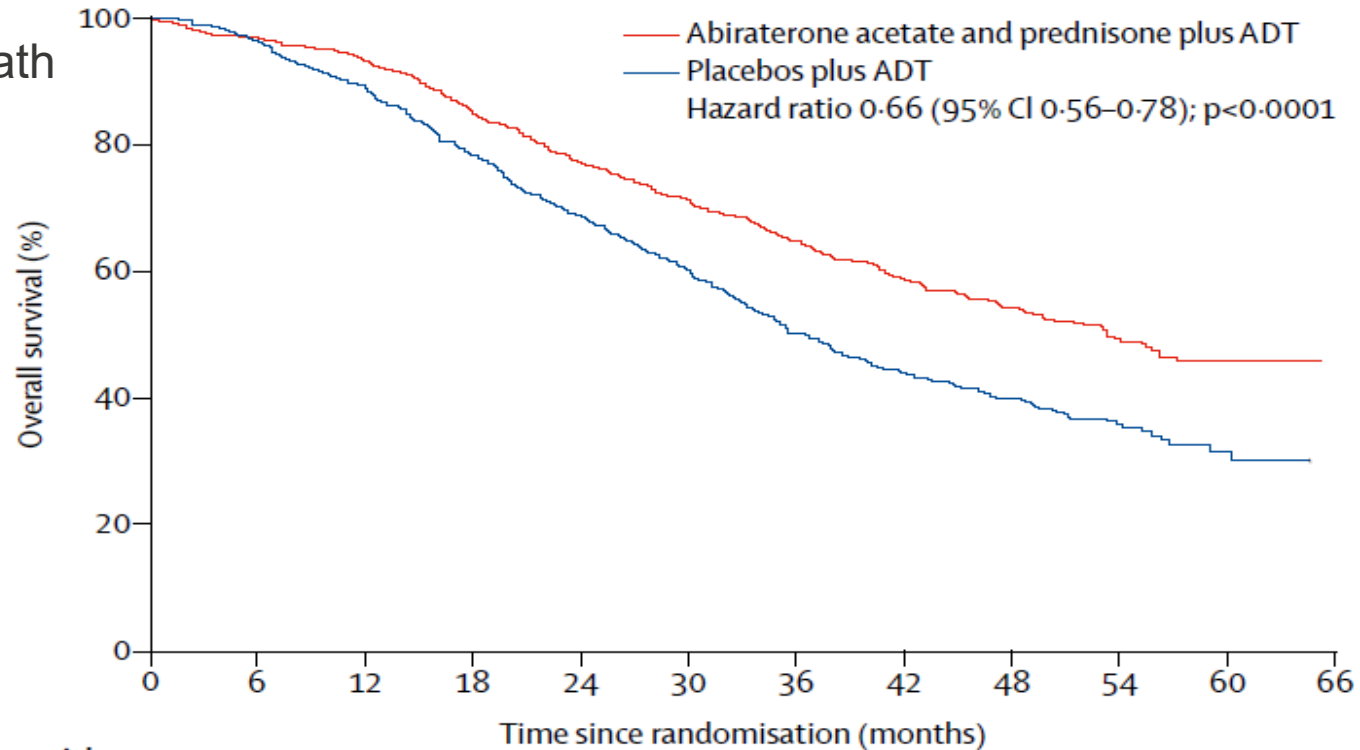
- ***New STAMPEDE metastatic “high burden* subgroup” in scenario***
- ***CHAARTED “high volume*”***
- ***GETUG-AFU 15 “high volume*”***

NICE * Company: similar to high risk

Overall survival LATITUDE final analysis

August 2018: 275 (46%) abiraterone group and 343 (57%) ADT alone group had died

Median months to death
Abiraterone: 53.3
ADT alone: 36.5



	0	6	12	18	24	30	36	42	48	54	60	66
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

n.b. more censored values in abiraterone group

New results for abiraterone + ADT vs comparators

		Direct comparison		Indirect comparison network meta-analysis (NMA)	
ADT alone	LATITUDE final analysis	0.47 (0.39 to 0.55)	0.66 (0.56 to 0.78)	company used in model	
	STAMPEDE: high risk	0.46 (0.36 to 0.59)	0.54 (0.41 to 0.70)		
	Meta-analysis LATITUDE + STAMPEDE	*** *****	*** *****		
Docetaxel + ADT		PFS	OS	PFS	OS
		Metastatic but not high-risk STAMPEDE		LATITUDE + CHAARTED + GETUG-AFU 15 + STAMPEDE (high burden subgroups for docetaxel + ADT vs. ADT)	
		0.69 (0.50 to 0.95)	1.13 (0.77 to 1.66)	*** *****	*** *****

Company continues to use indirect comparison for abiraterone vs. docetaxel

- Company does not provide methods for updated Bayesian network meta-analysis
- Company reiterates that indirect data more robust than direct
 - notes more censoring in docetaxel + ADT in STAMPEDE suggesting healthier patients remained, favouring docetaxel
 - n.b. in LATITUDE more censoring in abiraterone arm
- Company states in original submission ‘there was heterogeneity between the measures used to determine disease progression across all four trials in the network’
- ERG prefers using indirect network in model rather than STAMPEDE data only

© *For comparison to docetaxel, should model use direct or indirect (network) evidence?*

Scenario around updated network meta-analyses to compare abiraterone to docetaxel

- After company resubmitted, STAMPEDE published post hoc subgroup analyses docetaxel + ADT vs ADT by burden of metastases: company considers similar to 'high risk' (Clarke et al 2019)
- Company provided new analyses including data from Clarke et al 2019
 - some data may be double-counted because it is a subgroup of Sydes et al 2018, (whole metastatic subgroup from STAMPEDE), so provided results +/- Sydes et al 2018

	Hazard ratio (95% CI)	
	Progression Free Survival	Overall Survival
Updated network meta-analysis - company base case	*** (*****)	*** (*****)
Updated network meta-analysis including Clarke et al 2019 and Sydes et al 2018	*** (*****)	*** (*****)
Updated network meta-analysis including just Clarke et al 2019 and not Sydes et al	*** (*****)	*** (*****)

© If an indirect network is preferable to a direct comparison, which network to use?
Does abiraterone + ADT improve overall survival compared with docetaxel + ADT

Chemotherapy-ineligible subgroup

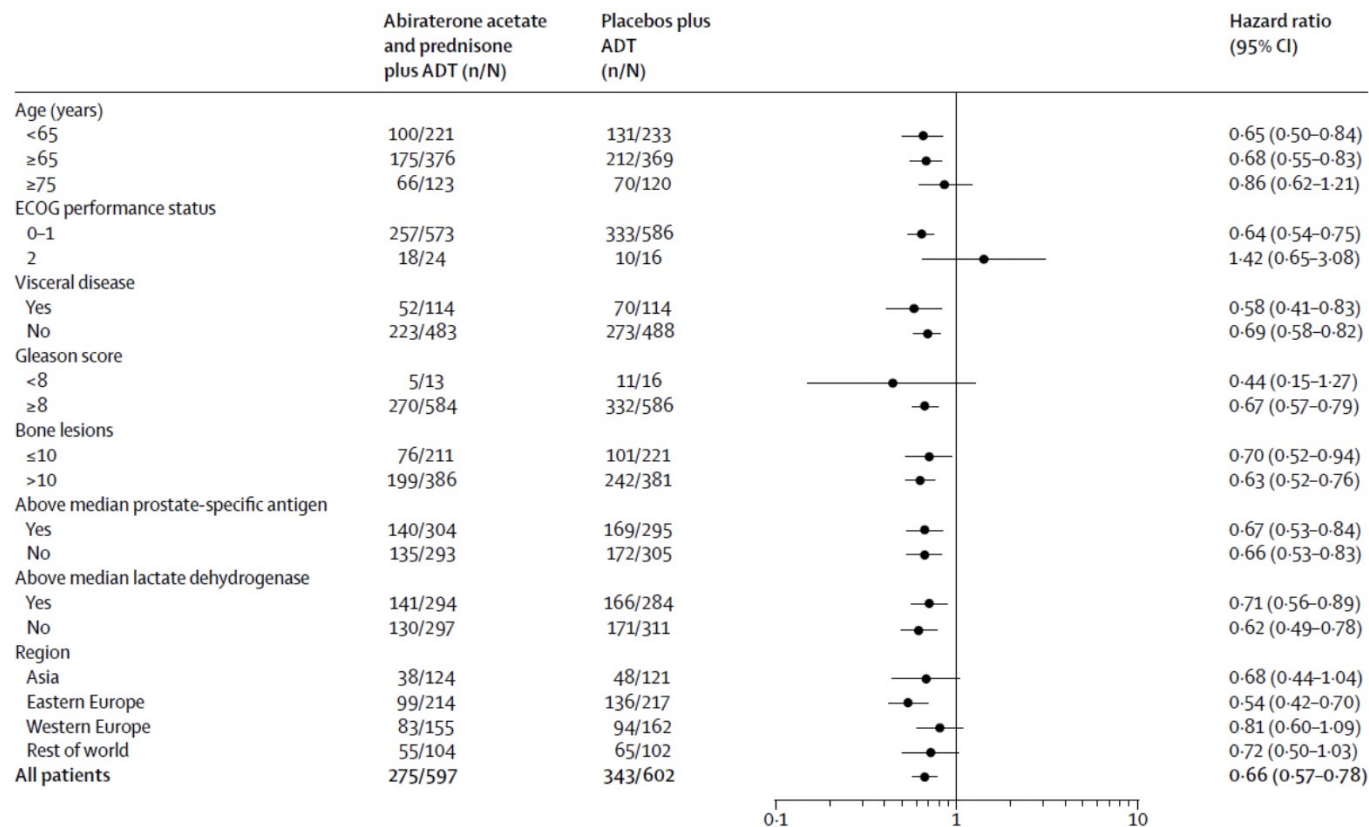
- Company make case that results for abiraterone + ADT vs. ADT comparison relevant for population who cannot have docetaxel
- Previous meetings noted that some people choose not to have docetaxel → population who cannot have docetaxel but can have abiraterone difficult to define
- ERG's clinical expert:
 - patients considered ineligible for docetaxel would be generally sicker with ECOG ≥ 3
 - the [extrapolated PFS and OS] based on the LATITUDE trial, in which all patients were ECOG 2 or lower, may therefore overestimate PFS and OS in both arms
 - lack of data to determine if the relative treatment effects (i.e. the hazard ratios for PFS and OS) are generalisable to a sicker cohort
- For chemotherapy ineligible population, would not expect substantial proportions of people to have docetaxel (or cabazitaxel) after abiraterone + ADT or ADT alone
 - would expect greater use of best supportive care and radium-223

NICE

Subgroup analyses don't support case for considering chemo-ineligible* subgroup

Company: All subgroup analyses consistent with the overall study results, except the subgroup of patients with an ECOG performance status score of 2 (HR=1.42)

Figure 3: Subgroup analyses of OS [LATITUDE, ITT population]



*** People who cannot take docetaxel**

● Committee previously concluded 'could not consider separately the clinical and cost effectiveness of abiraterone in people who cannot have docetaxel.'
 Has the committee seen evidence to change its conclusion?
 What is the implication for pairwise vs. incremental analyses?

NHS England comments on defining chemotherapy-ineligible subgroup

NHS England stated it would be possible to include criteria for clinicians to check on Bluteq authorisation forms, whether they are prescribing abiraterone because:

<p>7. I confirm that I have assessed this patient's eligibility for receiving upfront docetaxel plus ADT and have concluded that the patient cannot or should not or has chosen not to be treated with docetaxel.</p> <p>Please mark below which of these 3 clinical scenarios apply to this patient:</p> <p><input type="radio"/> the patient commenced docetaxel and has had to discontinue docetaxel within 2 cycles of its start on account of life-threatening toxicity (<u>ie</u> the patient CANNOT receive docetaxel)</p> <p><input type="radio"/> the patient has significant comorbidities which preclude treatment with docetaxel (<u>ie</u> the patient SHOULD NOT be treated with docetaxel) and this has been fully discussed with the patient. It is recommended that validated systems of scoring clinical frailty are used as part of the oncology assessment as to explaining the benefits and risks of the treatment options of chemotherapy and abiraterone</p> <p><input type="radio"/> the patient has been fully consented regarding the advantages and disadvantages of both upfront docetaxel chemotherapy and abiraterone and also that the use of upfront abiraterone would result in there being no further possible treatment with any androgen receptor targeted agents when the patient's disease progresses and also that the patient may not be fit enough to receive docetaxel when the patient's disease progresses. After such informed consent, the patient has chosen to receive upfront abiraterone (<u>ie</u> the patient has CHOSEN NOT to be treated with docetaxel).</p>	<p><input type="radio"/> <input type="radio"/></p> <p>Yes No</p>
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● Should the chemotherapy-ineligible subgroup include people who cannot and who choose not to have docetaxel?

New model: partitioned survival not Markov

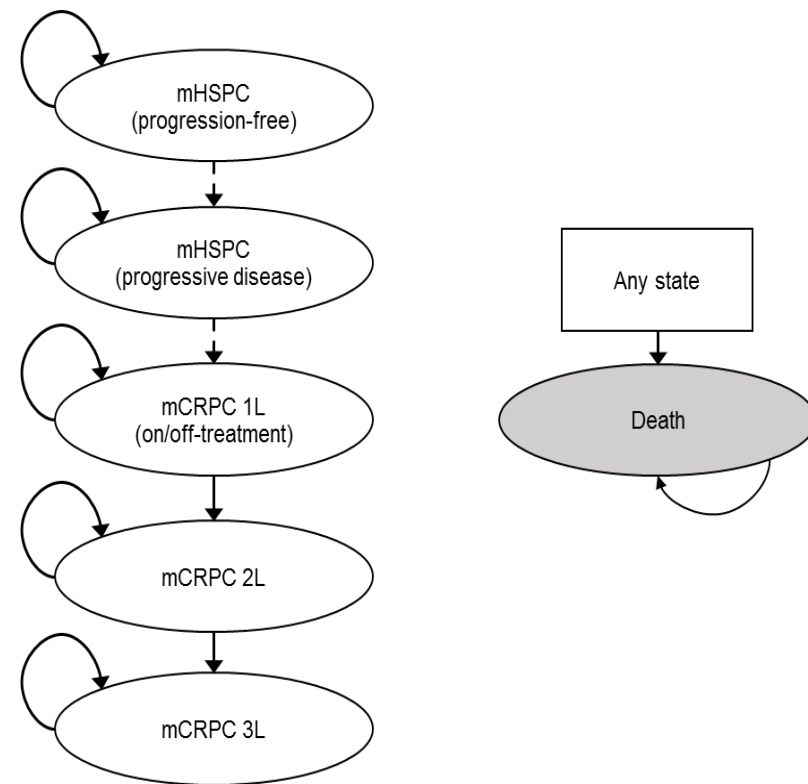
Allows modelling PFS and OS from different sources or analyses

Original model – Markov model

- probability of transitioning between health states from LATITUDE data or for hormone resistant health states from TA387 (abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated)

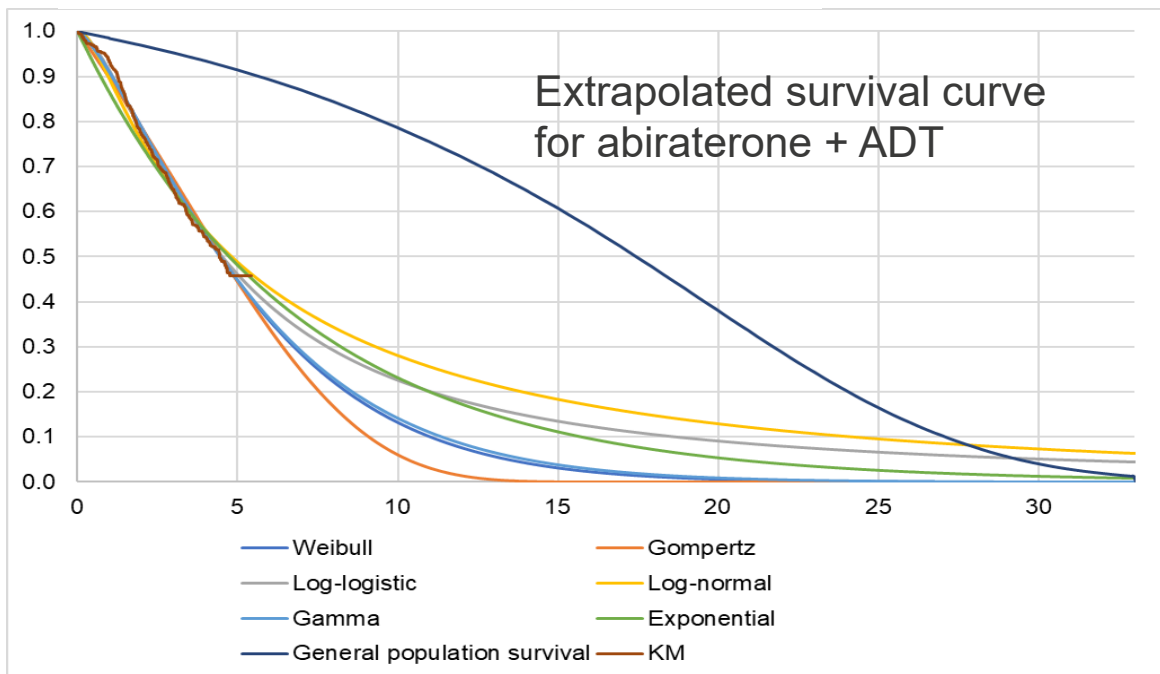
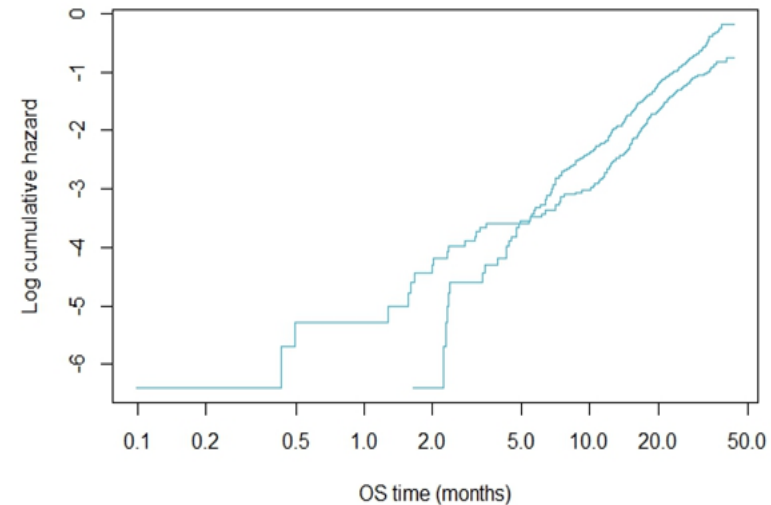
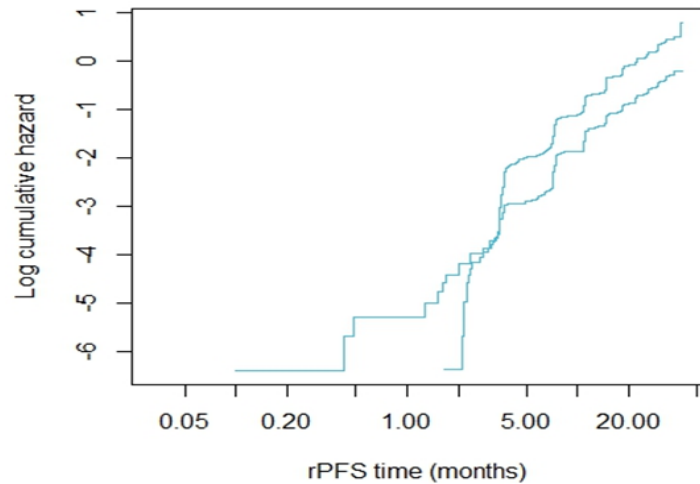
New model – Partitioned survival model

- Same health states as previous model and people can have 3 further lines of treatment
- Progression free survival extrapolated from LATITUDE trial data end of trial
- Overall survival extrapolated from LATITUDE trial data Aug 2018
- Post progression survival = difference between extrapolated PFS and extrapolated OS
- Can set hazard ratio to 1.00 for abiraterone vs. docetaxel



Extrapolating progression free & overall survival

Company extrapolates with Weibull and log-logistic distributions, fitting curves to each arm separately because hazards not proportional for either PFS and OS



Company provided analyses with:

- Weibull (pessimistic for OS)
- log-logistic (optimistic for OS)

ERG:

- Gompertz 'not completely implausible for OS'

Extrapolating progression free & overall survival

ERG: Weibull plausible, log-logistic optimistic, Gompertz 'not completely implausible'

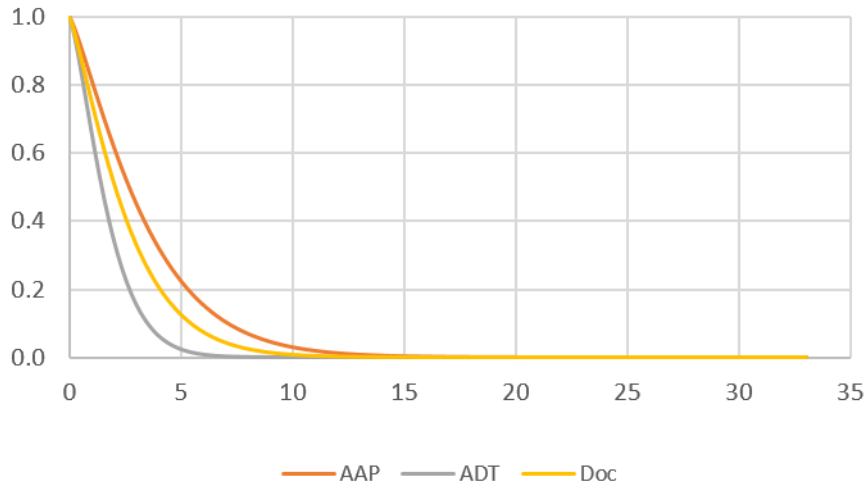
- Modelling arms separately results in cycle specific proportional reduction in hazard of progression and mortality vs. ADT alone increases over entire time horizon of model
 - the survival curves do not converge as would be expected
- To address this the ERG runs scenarios where hazards are equal from 8 or 10 years

	ADT alone			Abiraterone + ADT			Docetaxel + ADT		
	5 years	10 years	20 years	5 years	10 years	20 years	5 years	10 years	20 years
Progression free									
Weibull	2%	0%	0%	22%	3%	0%	Company applies hazard ratios from network meta-analysis		
Log-logistic	8%	3%	1%	29%	13%	5%			
Gompertz	2%	0%	0%	21%	1%	3%			
Alive									
Weibull	28%	3%	0%	44%	13%	1%	Company applies hazard ratios from network meta-analysis		
Log-logistic	30%	11%	4%	46%	22%	9%			
Gompertz	28%	1%	0%	44%	6%	0%			

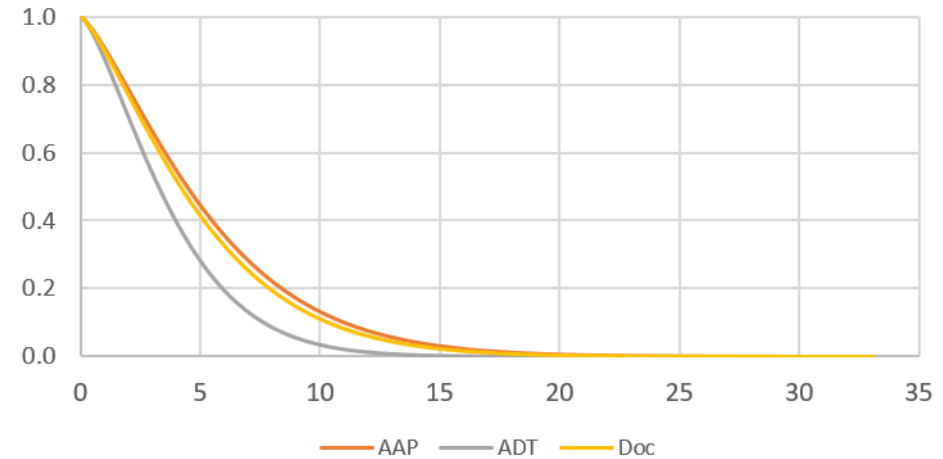
Long-term modelled relative treatment effect

Company base case (Weibull)

a) Progression free survival

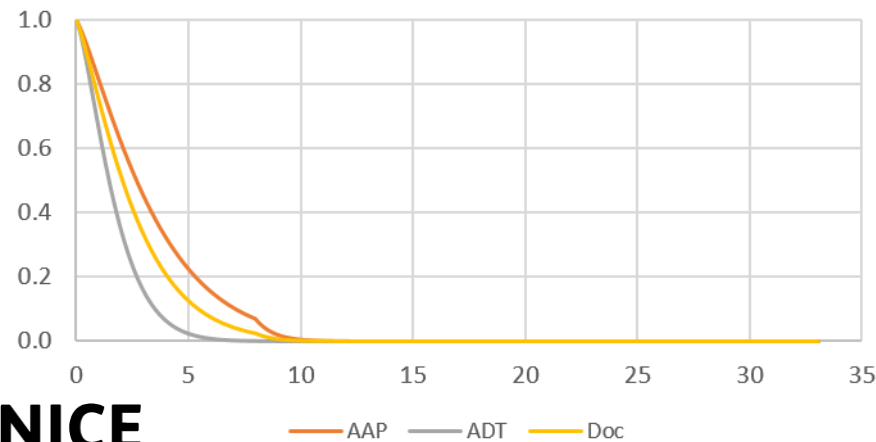


b) Overall Survival



**ERG scenario: treatment effect wanes after 8 years (hazards equalized)
- fewer people progression free/alive at 8 to 15 years**

a) Progression free survival

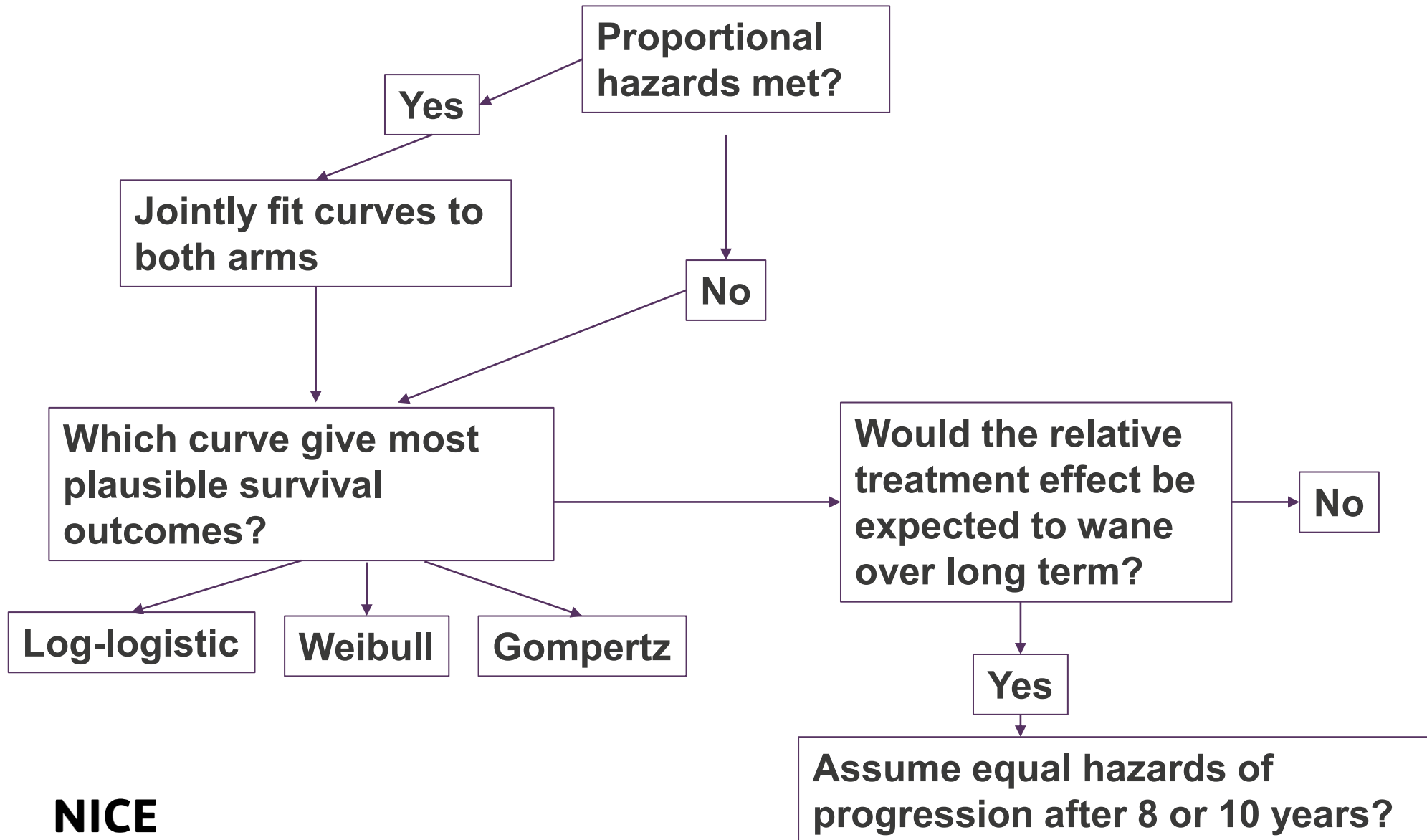


b) Overall Survival



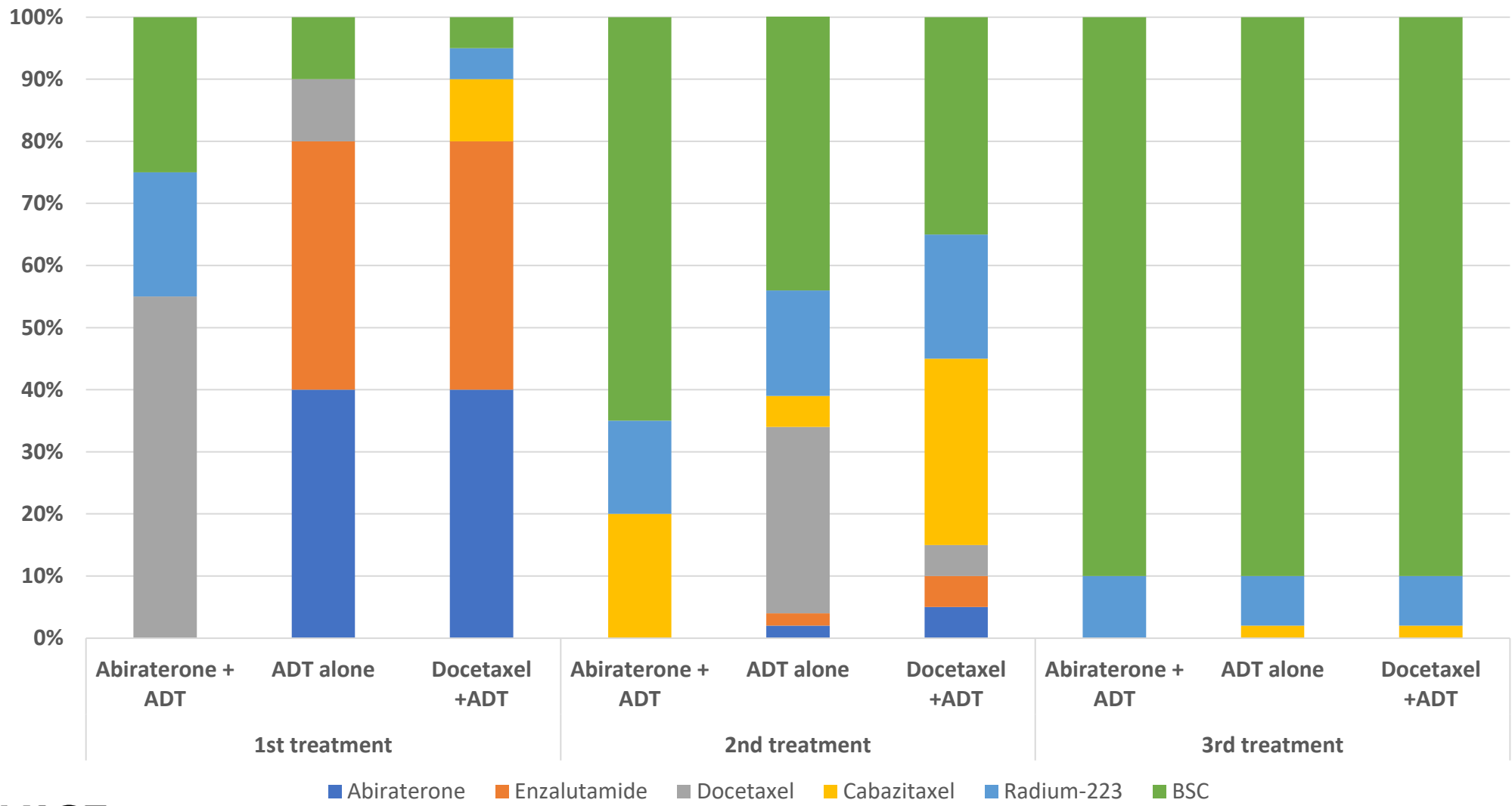
Decisions: extrapolating beyond end of trials

key drivers of cost effectiveness



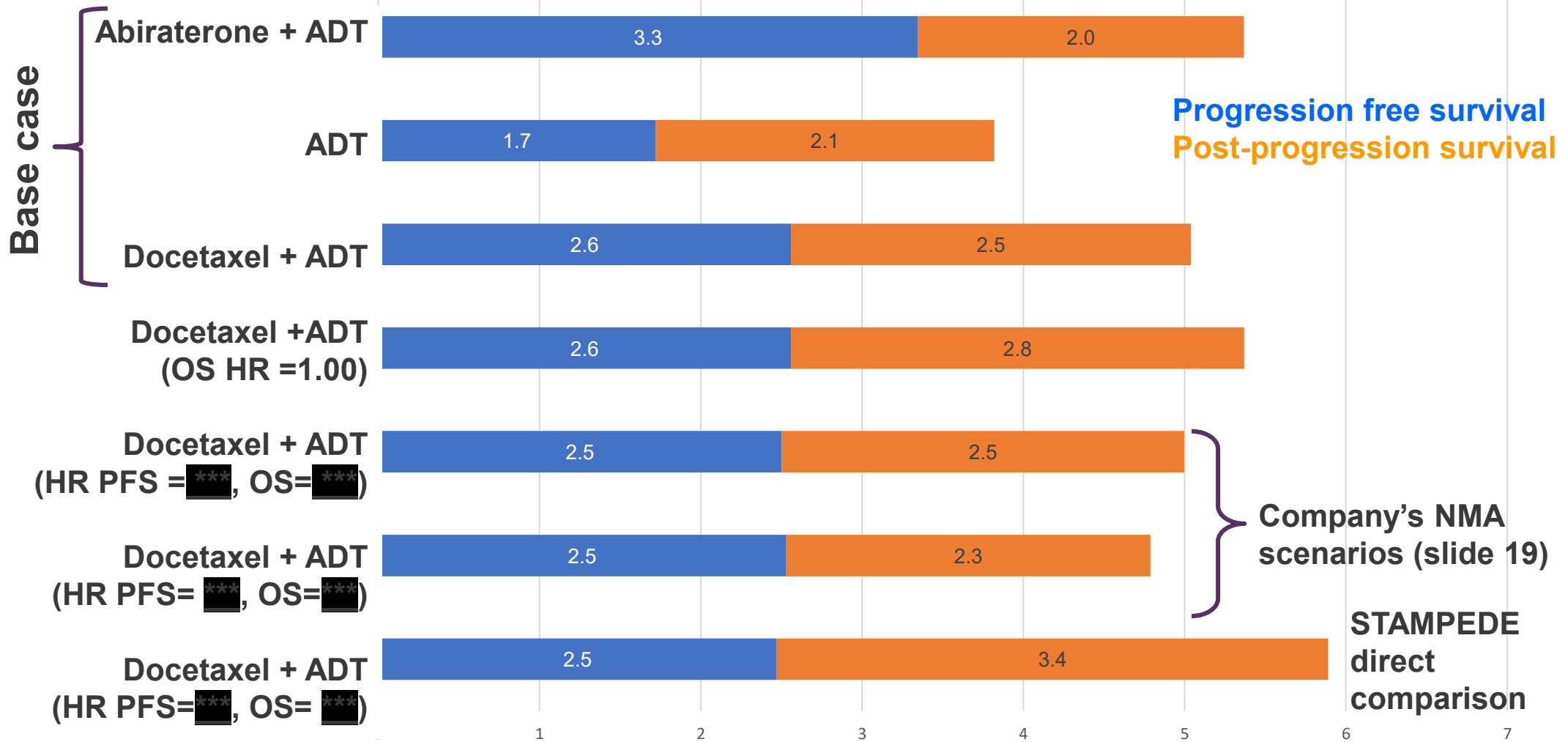
Modelled treatment in hormone relapsed setting

- Company now uses current market shares. ERG clinical adviser agrees
- Modelled drug costs based on these market shares; modelled survival not dependent on which drug person received



Modelled post-progression survival

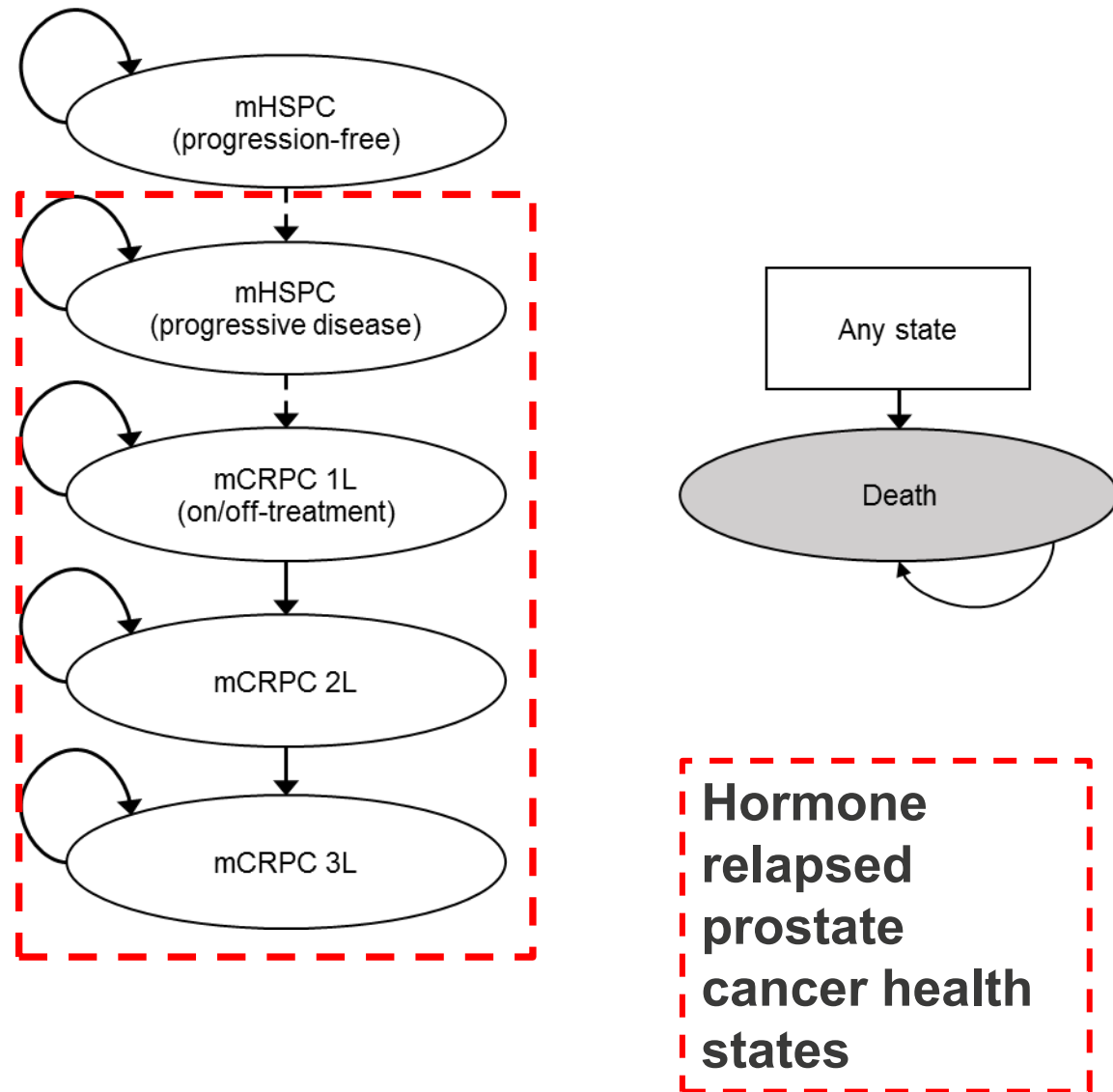
Modelled post-progression survival (once hormone-relapsed) greater with docetaxel + ADT than abiraterone + ADT



© In absence of modelling of more active treatment health states after docetaxel + ADT than abiraterone + ADT, is the model capturing the likely survival benefit of having more treatment options?

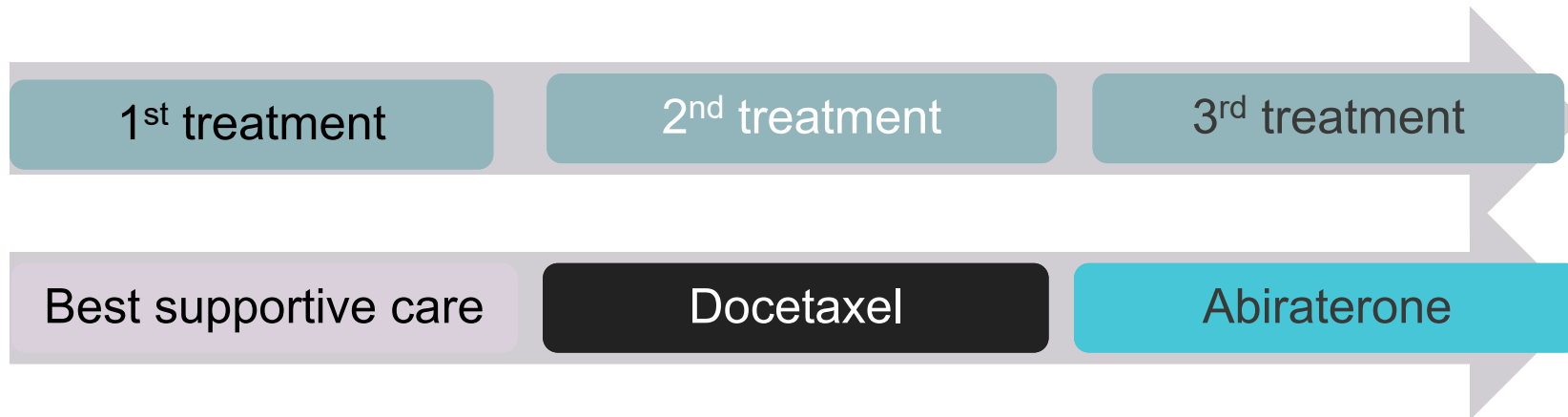
Time spent in hormone relapsed cancer health states

- Total time in hormone relapsed prostate cancer health states = OS- PFS
- Time spent in each line of hormone relapsed prostate cancer estimated from control arm of TA387
“Abiraterone for metastatic hormone-relapsed prostate cancer before chemotherapy indicated”
Best supportive care → docetaxel → abiraterone
- Weighted to account for differences in post progression survival in current appraisal and survival in TA387 (population: hormone-relapsed chemotherapy not yet indicated, not high risk)



Time on treatment in hormone relapsed states

- Time in hormone relapsed prostate cancer health states = OS - PFS
- Time spent in each state estimated from control arm of TA387 “Abiraterone for metastatic hormone-relapsed prostate cancer **before** chemotherapy indicated”



- Company weighted time on treatment to account for differences in post progression survival in current appraisal and survival in TA387
 - $(1L \text{ mCRPC duration} = 1L \text{ mCRPC duration (TA387)} \times (\text{mean post progression survival (current model)}/1L + 1L \text{ off treatment} + 2L \text{ mCRPC durations(TA387))$

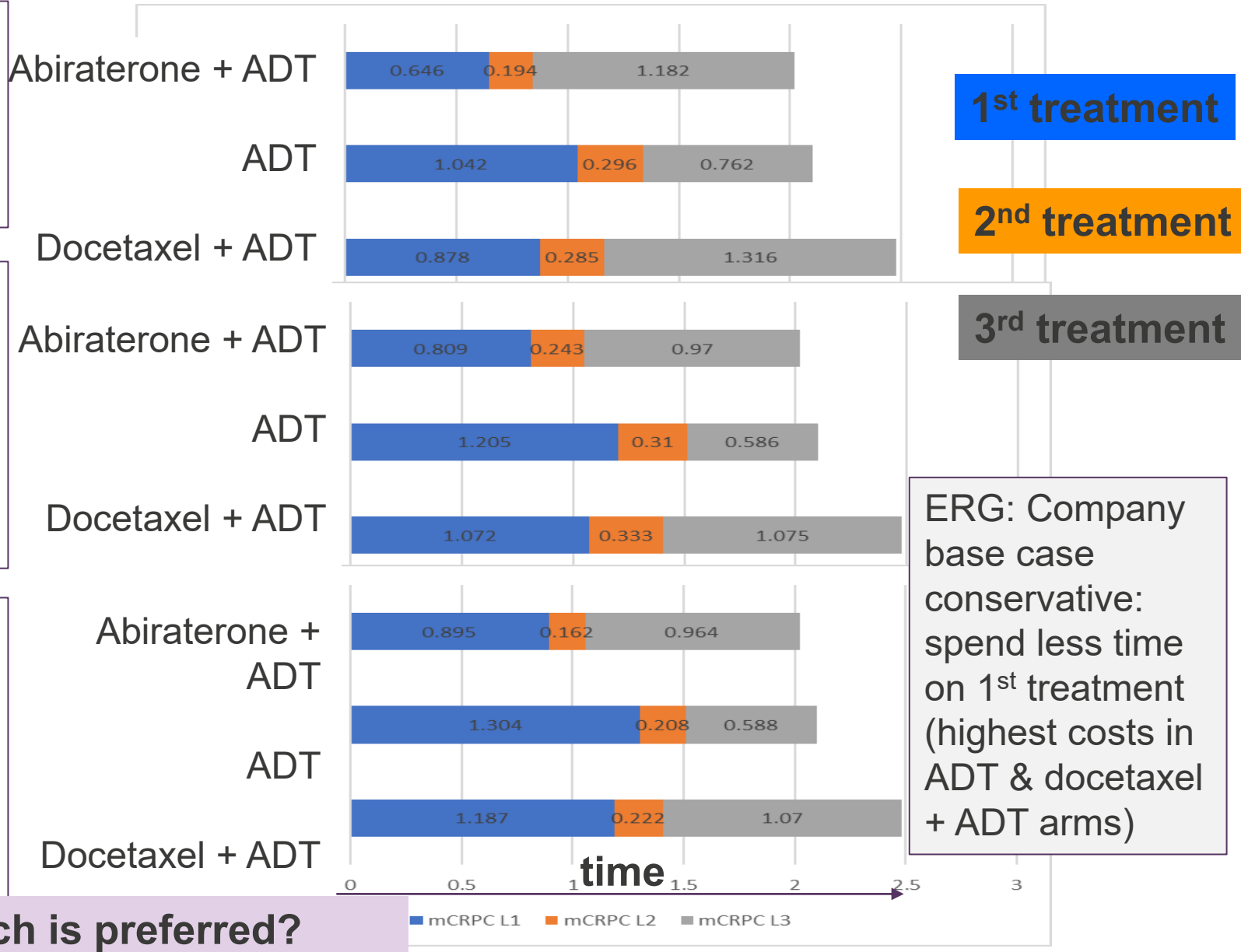
Scenarios: time in hormone relapsed health states

Scenarios change time spent on 1st treatment relative to subsequent treatments

Company base case
 Time in each health state = time on BSC → docetaxel → abiraterone (TA387) + adjusted for post-progression survival

Company scenario 1
 Time in each health state = time on BSC → docetaxel → abiraterone (TA387) + adjusted for post-progression survival + death before progression in LATITUDE

Company scenario 2
 Time in each health state = time on abiraterone → docetaxel → BSC (TA387) + adjusted for post-progression survival + adjusted for death before progression in LATITUDE



ERG: Company base case conservative: spend less time on 1st treatment (highest costs in ADT & docetaxel + ADT arms)

Which approach is preferred?

Quality of life on docetaxel

- Committee preferred quality of life data from STAMPEDE if available; company says no new published EQ-5D data
- Unresolved issue at previous meetings was quality of life on docetaxel
- Addition of docetaxel to 1st-line long term hormonal therapy in prostate cancer (STAMPEDE) Woods et al 2019, economic analysis of docetaxel + ADT vs. standard care for NICE prostate cancer guideline:
 - 0.02 disutility for being on docetaxel in 1st year
- Company: base-case analysis applies **** decrement over 18 weeks
→ roughly equivalent to a decrement of 0.02 applied over 1 year

Is the company's utility decrement for docetaxel + ADT (from a survey) plausible and consistent with EQ-5D data from STAMPEDE?

Cost-effectiveness results with:

- List price for abiraterone taken for hormone sensitive prostate cancer
- Patient access scheme prices for abiraterone taken later in treatment pathway for hormone-relapsed prostate cancer
- Patient access scheme prices for enzalutamide, cabazitaxel + radium-223 taken later in treatment pathway for hormone-relapsed prostate cancer

will be shown to committee in private PART 2 of the meeting.

NICE