Slides for public (AIC redacted)

Lead team presentation

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer [945]

1st Appraisal Committee meeting

Committee B

Lead team: Bill Turner, Nigel Westwood, Nicholas Latimer

Chair: Amanda Adler

ERG: Aberdeen HTA Group

NICE technical team: Mary Hughes, Jasdeep Hayre

Company: Janssen

10 May 2018

Key Issues: clinical

- Are there people who can take:
  - ADT, but not abiraterone + ADT? Who are they?
  - abiraterone + ADT but not docetaxel + ADT ? Who are they?
- For abiraterone + ADT vs. ADT, are estimates for overall survival from LATITUDE robust? If not, is this accounted for in part by:
  - Differences in follow-on treatments in LATITUDE vs. NHS?
  - Differences in when treatment stops in LATITUDE vs. NHS?
- For abiraterone +ADT vs. docetaxel + ADT, which estimate of clinical effectiveness is most robust?
  - Direct, randomised, evidence from STAMPEDE for broader population?
  - Indirect non-randomised, unadjusted evidence from network meta analysis?
- How is quality of life on and after:
  - Abiraterone + ADT? /Docetaxel + ADT?
- Is there any further data from STAMPEDE that would support the company submission?

Prostate cancer disease background

- >8000 people newly diagnosed with metastatic prostate cancer in UK (2014)
- Newly diagnosed people **with** metastatic prostate cancer have poorer prognosis than people who present with localised disease but **later** develop metastases
- Complications can include lower urinary tract symptoms and bone pain/spinal cord compression
- Prostate cancer is an androgen dependent disease. Inhibiting testosterone with ‘androgen deprivation therapy’ (ADT) is key to treatment while people remain ‘hormone sensitive’
- While most people initially respond to androgen deprivation therapy, most progress within 1 to 2 years to being hormone relapsed (“castrate resistant”)

Patient experience

Experience of current treatments

- Treatment improves life expectancy, but reduces quality of life
- Problems with treatment include fatigue, “chemo fog” (an inability to concentrate) and loss of libido
- Stressful for people with prostate cancer (+ carers) to know treatments will eventually fail. May worry about what the next treatment may be, its side effects and whether they can cope with it.

Patient experience/ thoughts on having option of abiraterone + androgen deprivation therapy (ADT)

- No curative treatments, so all life-extending treatment options welcomed
- Particular unmet need for people who cannot have or tolerate docetaxel + ADT
- A person receiving abiraterone reported: “After almost 4 years of treatment I have very few problems. I am very active….. [and] busy around the house and garden. I don’t have, or need, a carer”

Abiraterone (Zytiga, Janssen)

Mechanism	Selective androgen synthesis inhibitor of cytochrome P450 17 alpha-hydroxylase. Blocks androgen production in testes, adrenals, and in prostatic tumour
Marketing authorisation **November 2017**	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) In clinical trials, '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

Decision problem

◉ *ERG agrees with company's comparators, does committee?*

	Final NICE scope	Decision problem - company	Rationale if different from scope
Population	Newly diagnosed high risk metastatic **hormone-naïve** prostate cancer (mHNPC)	Newly diagnosed, high-risk, **hormone-sensitive** (mHSPC)	mHNPC = mHSPC because if people are newly diagnosed, they are hormone naïve (and hormone sensitive)
Intervention	Abiraterone + prednisone + ADT		
Comparators	1. ADT alone (including orchidectomy, luteinising hormone-releasing hormone [LHRH] agonist therapy or monotherapy with bicalutamide) 2. Docetaxel + ADT	1. ADT alone (including LHRH agonist therapy) 2. Docetaxel + ADT	Orchidectomy & bicalutamide monotherapy not included → Company's experts suggest rarely used in UK

ERG, evidence review group; mHSPC, metastatic hormone sensitive prostate cancer; ADT, androgen deprivation therapy

Treatment pathway

◉ *How is the choice between treatments made?*

HORMONE SENSITIVE Metastatic	'CASTRATE RESISTANT' Metastatic *(also known as 'hormone-relapsed')*		
New diagnosis	No/mild symptoms before chemotx indicated	Chemo-therapy indicated	After chemotherapy

Current appraisal

ADT

- Abiraterone TA387
- Enzalutamide TA377
- Watchful waiting

Abiraterone + ADT

- Watchful waiting

Docetaxel + ADT

Docetaxel TA 101

- Abiraterone TA259
- Enzalutamide TA316
- Cabazitaxel TA391
- Radium 223* TA412

- Enzalutamide TA316
- Cabazitaxel TA391
- Radium 223* TA412

- Abiraterone TA259
- Enzalutamide TA316
- Cabazitaxel TA391
- Radium 223* TA412

ADT, androgen deprivation therapy; TA, technology appraisal; Chemotx, chemotherapy

‘Hormone Sensitive’ 1st treatments

	Androgen deprivation therapy	Abiraterone + prednisolone + ADT	Docetaxel (off-license) (+ADT) NHS England
Route	Injection	Oral	Intravenous
Dosing	4- weekly	Daily until progression	6 cycles (cycle = 3 weeks)
Prednisolone	None	5 mg daily	For 1st 3 weeks
Eligibility	Caution: osteoporosis; spinal cord compression; ureteric obstruction; diabetes	Caution: Hepatotoxic. Liver function tests throughout treatment. Monitor fluid retention for congestive heart failure	Karnofsky performance status of 60% or more (~20% considered unsuitable for docetaxel) Contraindications: severe allergic reaction, myelo-suppression, severe liver disease
◉ *Are there clearly-characterised people who cannot have some treatments?*			
Other factors affecting choice	Mono- vs. combination therapy: survival benefit		• Support of carer • Travel for treatment • Toxicity • Alcohol content of docetaxel formulation

Clinical trial evidence: overview

What is the most robust evidence for decision making?

	Trial	Design
Abiraterone + ADT vs. ADT		
Direct	LATITUDE	Blinded RCT, newly diagnosed **high risk** metastatic hormone sensitive prostate cancer (mHSPC)
	STAMPEDE	Blinded adaptive RCT, UK MRC, all treatments in this appraisal in a wider population (**newly diagnosed localised or metastatic HSPC**) than indicated for abiraterone + ADT. Data for metastatic subgroup, but not stratified by low/high risk
Abiraterone + ADT vs docetaxel + ADT		
Direct	STAMPEDE	Abiraterone + ADT arm vs. docetaxel + ADT arm
Indirect: Network meta-analyses	GETUG-AFU 15	Open label RCTs (newly diagnosed **high volume** metastatic hormone sensitive subgroups) comparing docetaxel + ADT vs. ADT
	CHAARTED	
	LATITUDE	Included
	STAMPEDE	Sensitivity analysis only (metastatic subgroup)

LATITUDE: overview

abiraterone + ADT vs. ADT

Trial population

- Adults
- Newly diagnosed (<3 months)
- high risk mHSPC
  - (1) Gleason score of ≥8
  - (2) ≥3 lesions on bone scan;
  - (3) measurable visceral (excluding lymph node disease) metastasis
- with ECOG performance status 0,1,or 2

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

Double-blinded
1:1 randomisation

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

ADT alone*
n=602

Endpoints

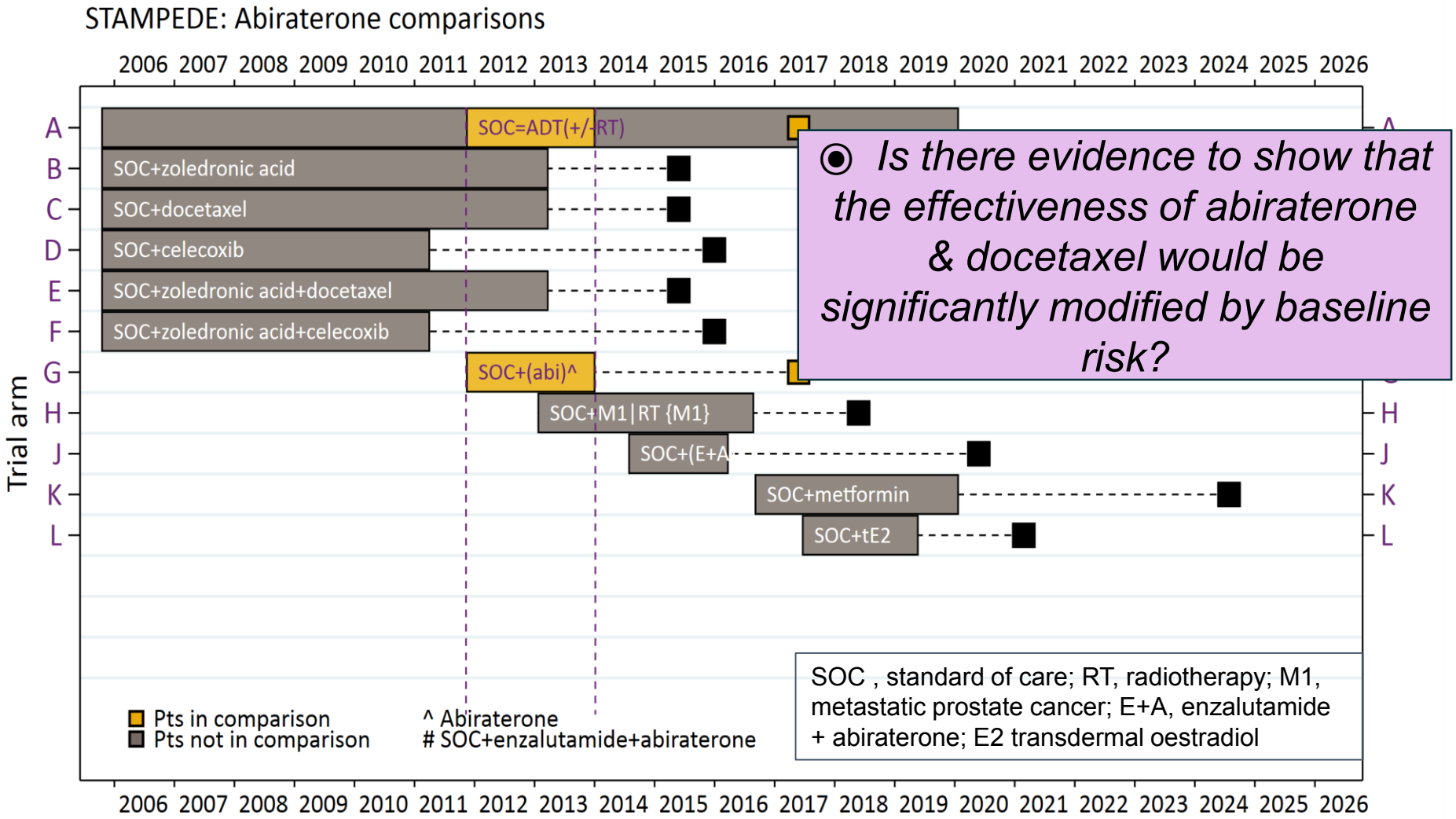
1°
- Overall survival
- Radiographic progression free survival (investigator assessed)

2°
- Time to:
  - Starting chemotherapy
  - Next SRE
  - Pain progression
  - Subsequent therapy
  - PSA progression
- QoI (including EQ-5D-5L)
- Safety

*LHRH or bilateral orchidectomy

STAMPEDE: trial arms

ARM A = ADT; ARM C = docetaxel + ADT; ARM G = abiraterone + ADT



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

LATITUDE primary outcomes

Trial ended early after 1st interim analysis 30.4 months follow up

	ADT n=602	AAP + ADT n=597
Radiographic progression free survival (rPFS)		
Median rPFS (months)	14.8	33.0
Hazard ratio	**0.47** (95% CI 0.39 to 0.55) p<0.001	
Overall survival		
Deaths n (%)	237 (39%)	169 (28%)
Median survival months (95% CI)	34.7 (33.0, not reached)	Not reached
Hazard ratio	**0.62** (95% CI 0.51 to 0.76) p<0.001	
Adjusting overall survival for follow-on treatments (Inverse Probability Censoring Weighting)		
% follow-on treatment	40.9	20.9
Adjusted hazard ratio	**0.48** (95% CI 0.36 to 0.63) p<0.0001	

2nd interim analysis results [not used in model] (41 months follow up, unblinded and crossover allowed) **********

STAMPEDE: PFS and overall survival

Metastatic subgroup (40 months follow up)

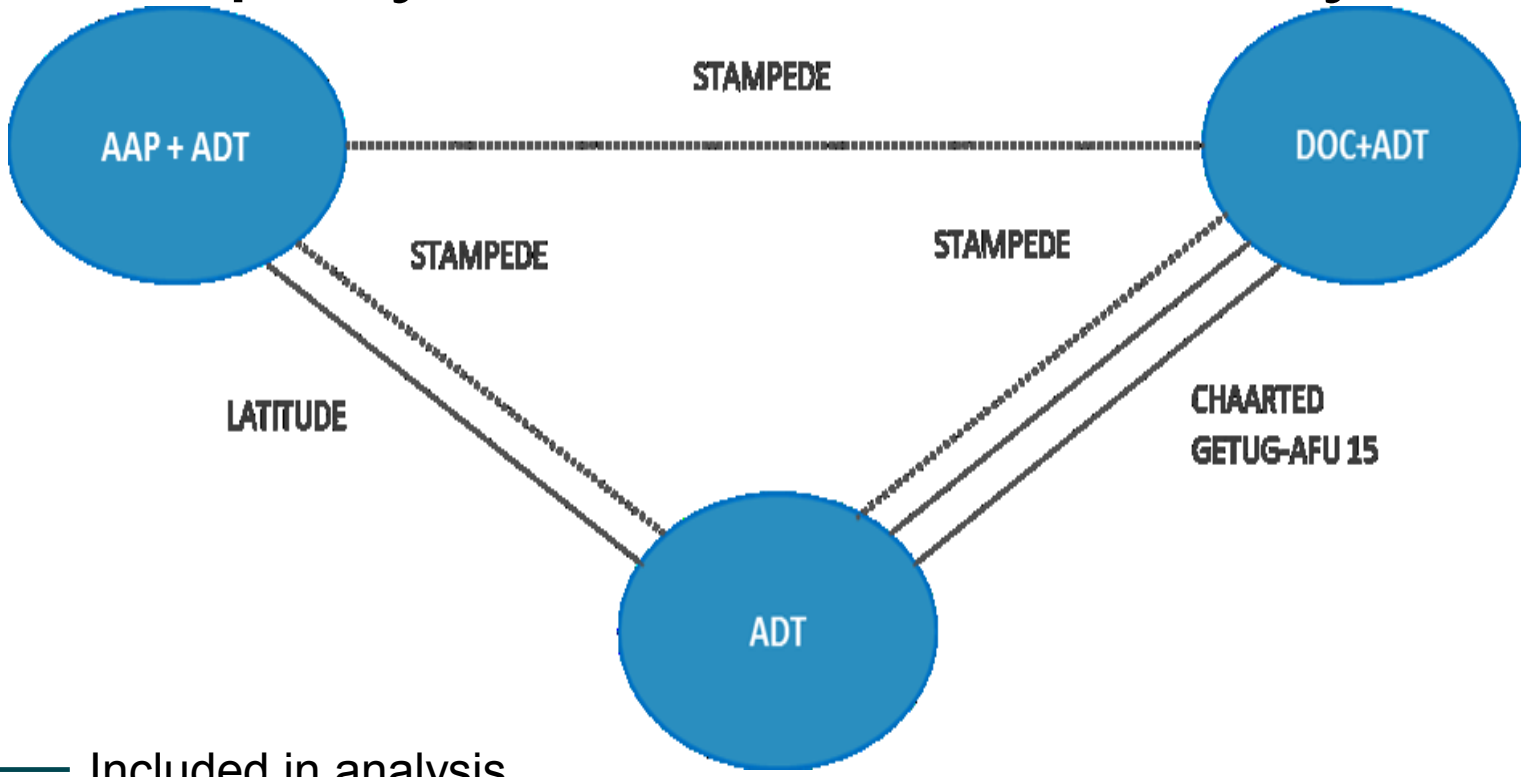
◉ *Is the clinical effect of abiraterone + ADT vs ADT similar in LATITUDE + STAMPEDE? (Hazard ratio rPFS LATITUDE = 0.47; OS = 0.62)*

	ADT n=502	AAP + ADT n=500
Radiographic progression free survival (PFS)		
Hazard ratio	**0.43,** 95% CI 0.36 to 0.52	
Failure free survival (FFS)		
Hazard ratio	**0.31,** 95% CI 0.26 to 0.37	
Overall survival		
Deaths n (%)	218 (43.4)	150 (30.0)
Hazard ratio	**0.61,** 95% CI 0.49 to 0.75	

Definitions of progression outcomes in STAMPEDE:

- failure free survival: radiologic, clinical, PSA progression or death from prostate cancer.
- PFS defined as radiologic or clinical progression or death from prostate cancer

Indirect comparison: trials included in company's network meta-analysis



Included in analysis

Included in sensitivity analysis

AAP, abiraterone + prednisolone; ADT, androgen deprivation therapy; Doc, docetaxel

***ERG** concerned about comparability of STAMPEDE data to other trials in network*

Differences between trials included in network meta-analysis

Treatment/ dosing*	Variable definitions of ADT and scheduling of docetaxel
Population	• GETUG-AFU 15 + CHAARTED 'High Volume' subgroup, defined as ≥1 of: - 3 or more bone lesions - visceral bone metastases N.B High Risk includes these criteria + Gleason score ≥8 • STAMPEDE: no subgroup data for high risk or high volume
Follow-on therapies	Different proportion have follow-on treatments • LATITUDE: AAP + ADT: 32%; ADT 54% • GETUG-AFU 15: not reported • CHAARTED: Doc + ADT 60%; ADT 73% • STAMPEDE: AAP + ADT 79%; ADT 89%
Trial outcomes	Different measures of disease progression • LATITUDE: rPFS based on RECIST 1.1 and PCWG2 • GETUG-AFU 15 based on rPFS RECIST 1.0 and PCWG2 • (STAMPEDE, CHAARTED no rPFS outcomes)

ADT, Androgen deprivation therapy; AAP abiraterone + prednisolone; Doc, docetaxel; RECIST, Response Evaluation Criteria in Solid Tumours; PCWG2, Prostate Cancer Working Group 2; rPFS, radiographic Progression Free Survival

Comparison direct vs indirect results

- *What is the best source of estimate for abiraterone + ADT vs. docetaxel + ADT? Abiraterone + ADT vs. ADT ?*

	PFS hazard ratio (95% CI)	OS hazard ratio (95% CI)
Direct randomised evidence: STAMPEDE metastatic subgroup (mSTAMPEDE)		
AAP + ADT vs docetaxel + ADT	0.69 (0.50 to 0.95)	1.13 (0.77 to 1.66)
AAP + ADT vs ADT	0.43 (0.36 to 0.52)	0.61 (0.49 to 0.75)
Direct randomised evidence: LATITUDE intention to treat		
AAP + ADT vs ADT	0.47 (0.39 to 0.55)	0.62 (0.51 to 0.76)
Direct randomised evidence: CHAARTED newly diagnosed + high volume subgroup		
Docetaxel + ADT vs ADT	Not reported by company	0.63 (0.49 to 0.81)
Direct randomised evidence: GETUG-AFU 15 newly diagnosed + high volume subgroup		
Docetaxel + ADT vs ADT	0.61 (0.44 to 0.83)	0.78 (0.54 to 1.12)
Indirect comparison: LATITUDE + CHAARTED + GETUG-AFU 15		
AAP + ADT vs docetaxel + ADT	0.76 (95% CrI 0.53 to 1.10)	0.92 (95% CrI 0.69 to 1.23)
Indirect comparison: LATITUDE + CHAARTED + GETUG-AFU 15 + mSTAMPEDE		
AAP + ADT vs docetaxel + ADT	**********	**********

Common adverse events

listed in summary of product characteristics

◉ *Which drug is better tolerated?*

Abiraterone	Docetaxel
• Urinary tract infection • **Low potassium levels** • **High blood pressure** • **Peripheral swelling** • Increased liver enzymes Other important adverse effects: • Heart problems • Liver problems • Fractures • Allergic alveolitis	• **Low neutrophils (+/- accompanying fever**) • **Low red blood cells** • **Low blood platelets** • **Peripheral neuropathy** • Taste disturbances • **Difficulty breathing** • Inflamed mouth lining • **Diarrhoea** • **Nausea +vomiting** • Hair loss • Skin and nail reactions • Muscle pain • Loss of appetite • Infections • **Fluid retention** • **Weakness** • Allergic reactions

Network meta analysis of LATITUDE + GETUG-AFU 15: Less anaemia, constipation, peripheral oedema with abiraterone than docetaxel, but more hot flushes

Bold text: *costs and impact on quality of life of adverse events included in the economic modelling*

LATITUDE: Quality of life summary

Quality of life better with abiraterone + ADT than ADT

◉ *Is there evidence that quality of life is better on abiraterone before disease progression? After disease progression? Are there data from STAMPEDE that would support the evidence?*

Quality of life measure	Results	In model?
EQ-5D-5L	AAP + ADT better than ADT until disease progression	Yes
Functional Assessment of Cancer Therapy-Prostate (FACT-P)	Time to FACT-P score worsening: • AAP + ADT 12.9 vs. ADT 8.3 months • **HR 0.85 (95% CI 0.74, 0.99)**	No
Brief Pain Inventory short form	Time to pain progression • AAP + ADT not reached vs. ADT 16.6 months • **HR 0.70 [95% CI: 0.583-0.829]**	No

Key Issues: cost effectiveness

- **Survival model outputs**: Does survival after progression depend on:
  - 1st treatment received?
  - Follow-on treatments in castrate resistant (hormone relapsed) disease?
  - Is it plausible that post progression survival same across modelled treatment arms?
- **Survival -MSM/TA387 vs. MSM approach**: Which data best model survival in mCRPC after progressing in mHSPC?
  - LATITUDE for hormone sensitive disease extrapolated? Or,
  - trial COU-AA-302 for castrate resistant disease before chemotherapy TA387 - do the trial populations / treatment pathways match?
- **Utility**: Are the values by treatment and adverse events plausible? Can STAMPEDE provide quality of life data?
- **Costs**: Do the follow-on treatments reflect NHS reality?
- **Costs**: What is the expected frequency of bone scans for mHSPC cancer, does this differ by treatment?
- **Costs**: What is the expected compliance to treatment on abiraterone? Should this be included?
- **Model outputs**: Are they valid?

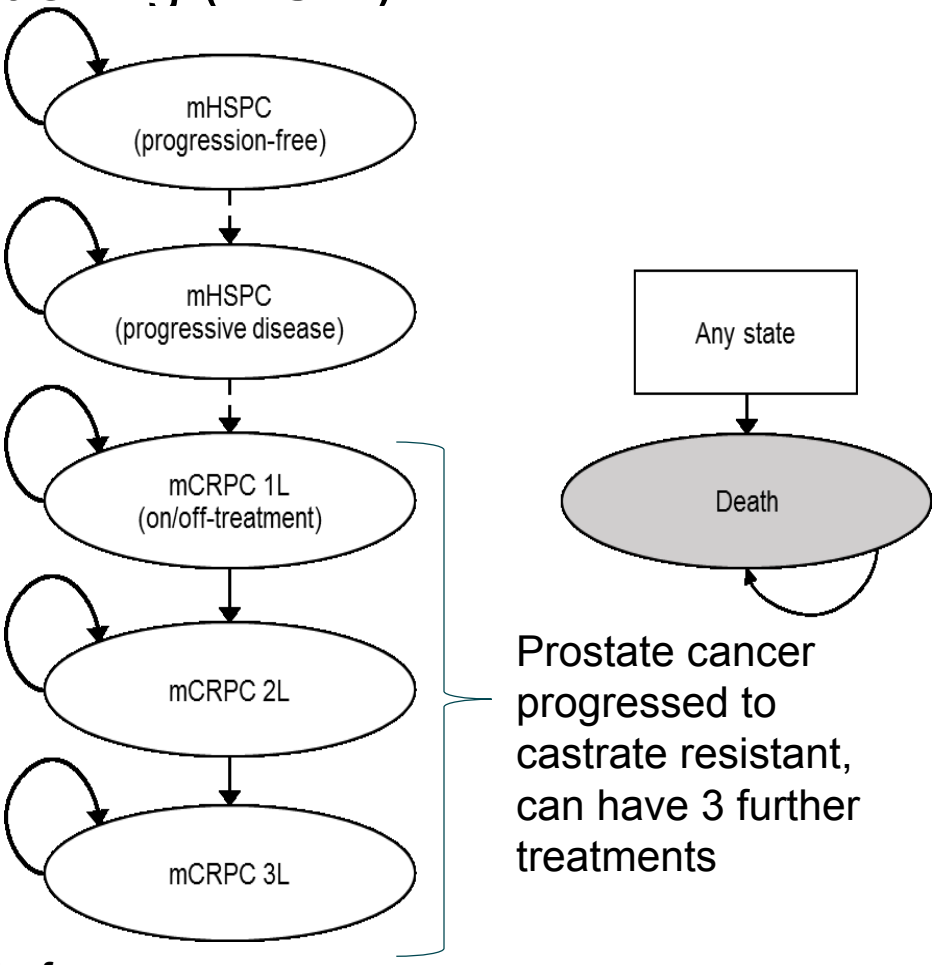
Cost effectiveness model

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

2 approaches for multistate model

1) **Base case** (**MSM/TA387**) used
   - Data from LATITUDE to inform transitions in hormone sensitive states (mHSPC)
   - Data from TA387 model (COU-AA-30 trial) to inform transitions in castrate resistant states (mCRPC)
   - + calibration to adjust modelled overall survival to align with LATITUDE overall survival

2) **Alternative approach** (**MSM**)
   - Data from LATITUDE used to inform transitions all health state
   - Time on 1st treatment for castrate resistant prostate cancer from COU-AA-302 (trial for TA387)
   - No additional calibration



Data from
- LATITUDE: AAP + ADT vs. ADT
- network meta analysis AAP + ADT vs docetaxel + ADT

Modelling of castrate resistant states
Company base case MSM/TA387 approach

- Survival curves from TA387 model depend on 1st treatment for castrate resistant prostate cancer

1st treatment castrate resistant	Survival estimates	Costs
Active • Docetaxel • Abiraterone • Enzalutamide • Cabizitaxel • Radium-223	All active treatments assumed to have same effectiveness. Used survival curves for sequence starting with abiraterone from TA387 model	% of people receiving each type of active treatment for castrate resistant prostate cancer, and best supportive care from market share estimates
Non active • Best supportive care	Used survival curves for sequence starting with best supportive care from TA387 model	

- Market share estimates also used to estimate % receiving each 2nd and 3rd treatment for castrate resistant prostate cancer. But active/non active 2nd and 3rd treatments don't affect modelled survival , only costs
- After applying TA387 survival estimates, company then calibrated modelled survival to match overall survival estimates from LATITUDE

Company's rationale for using data from TA387 for castrate resistant states

- In LATITUDE More people received subsequent treatment in ADT arm than abiraterone + ADT arm
- Subsequent treatments received in LATITUDE do not reflect NHS treatment pathway

LATITUDE	AAP + ADT (n=597)	ADT alone (n=602)
People with life-extending subsequent therapy n (%):	125 (20.9)	246 (40.9)
Docetaxel	106 (17.8)	187 (31.1)
Enzalutamide	30 (5.0)	76 (12.6)
Cabazitaxel	11 (1.8)	30 (5.0)
Radium-233	11 (1.8)	27 (4.5)
AAP	10 (1.7)	53 (8.8)

- **Do subsequent treatments in LATITUDE bias survival estimates?**
  - After adjusting for subsequent treatments: hazard ratio for overall survival declines to **0.48** (95% CI 0.36 to 0.63)
  - Adjusting for non-UK treatments → minimal difference (results not shown by company / "not robust")
- **Sufficient LATITUDE data to model survival in castrate resistant states?** Of people who had subsequent therapy ********** in the AAP + ADT arm and ********** in ADT arm had a second progression free survival event

◉ *Extrapolate unadjusted survival estimates from LATITUDE using MSM modelling? Or supplement with data from TA387 (MSM/TA387)?*

Applicability: TA387 data for this appraisal

COU-AA-302 was trial of abiraterone vs. best supportive care for mCRPC before chemotherapy indicated. Trial population:

- Asymptomatic or mildly symptomatic:
- ECOG 0 or 1
- Worse pain last 24 hrs score 0-3
- No visceral metastases

◉ would COU-AA-302 population have a similar prognosis to people with high risk metastatic hormone sensitive prostate cancer having subsequent treatments once cancer is castrate resistant?

Modelled survival in TA387 based on **sequence** of treatments

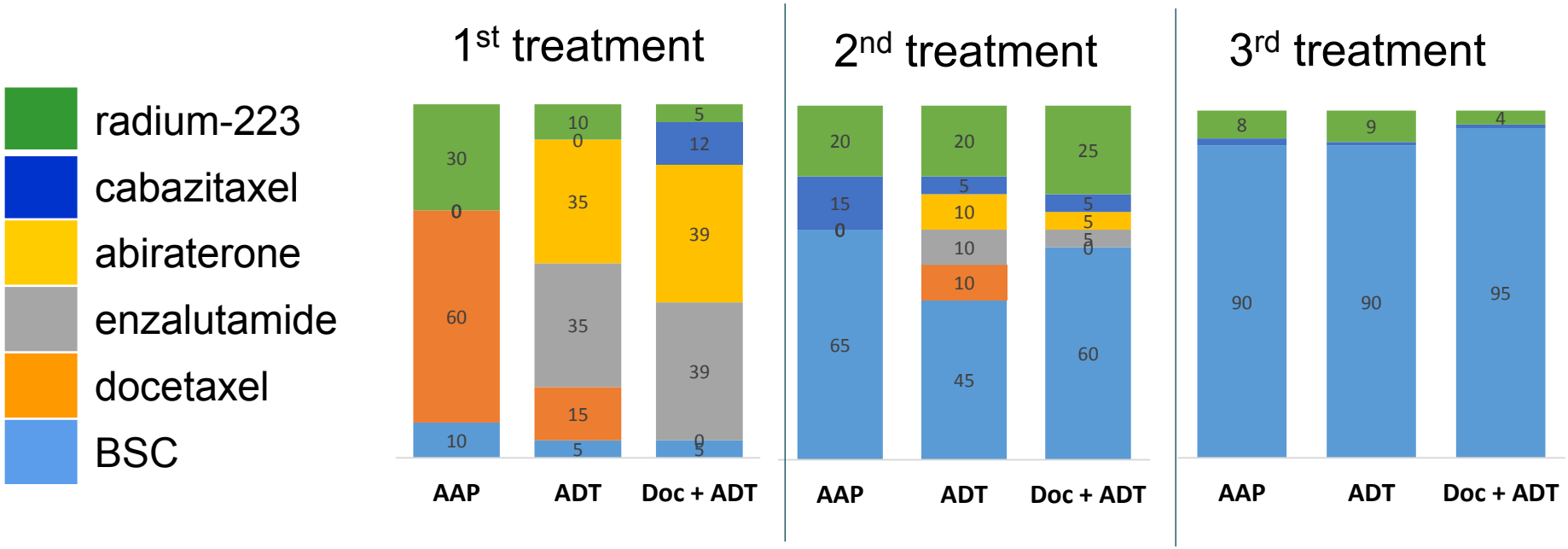
'1st treatment'

◉ Are the modelled sequences from TA387 applicable for modelling castrate resistant health state transitions for people having either an active treatment or best supportive care as first treatment for castrate resistant prostate cancer?

Modelled subsequent treatments for castrate resistant prostate cancer

Company's estimates of current market share of treatments for castrate resistant prostate cancer in MSM/TA387

◉ Do these treatment (below) for mCRPC reflect what people in NHS would receive after relapse on treatments for mHSPC?

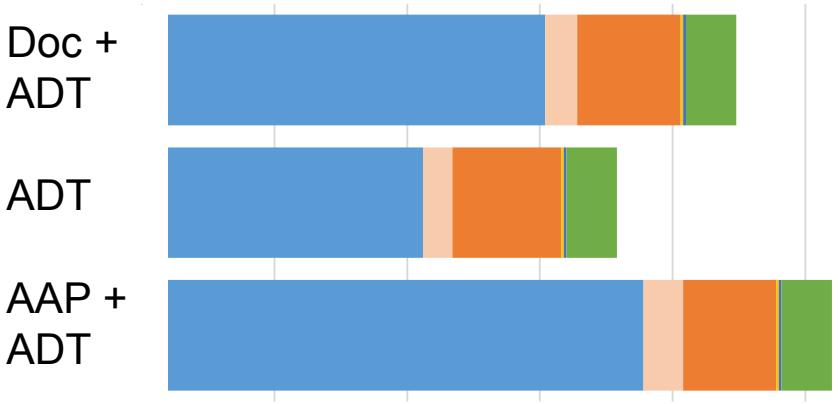


Plausibility of modelled survival outcomes

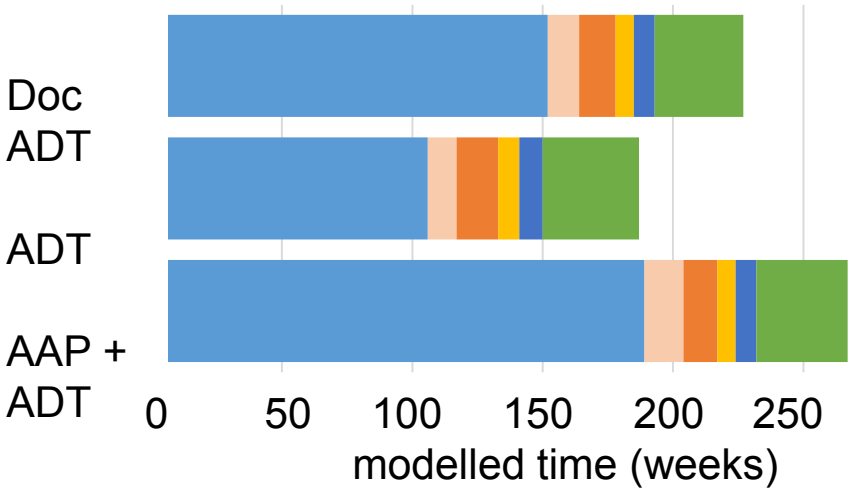
- Both model approaches→ post progression survival similar in all arms
- Time spent (weeks) in each castrate resistant health state differs between approaches

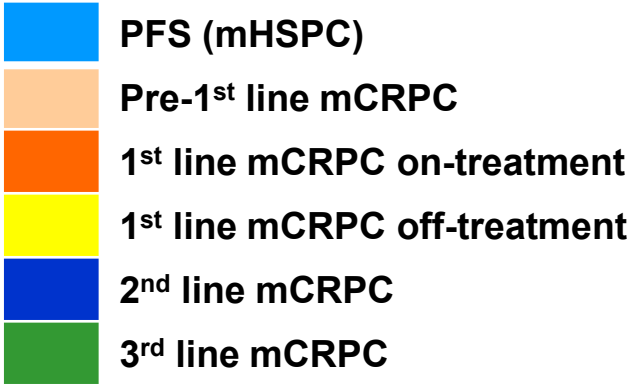
◉ Would post progression survival (after hormone sensitive prostate cancer) be the same after AAP + ADT (where a lower % of people have further active treatments-[not best supportive care]) than after ADT alone (where a higher % have active treatments)?

MSM/TA387



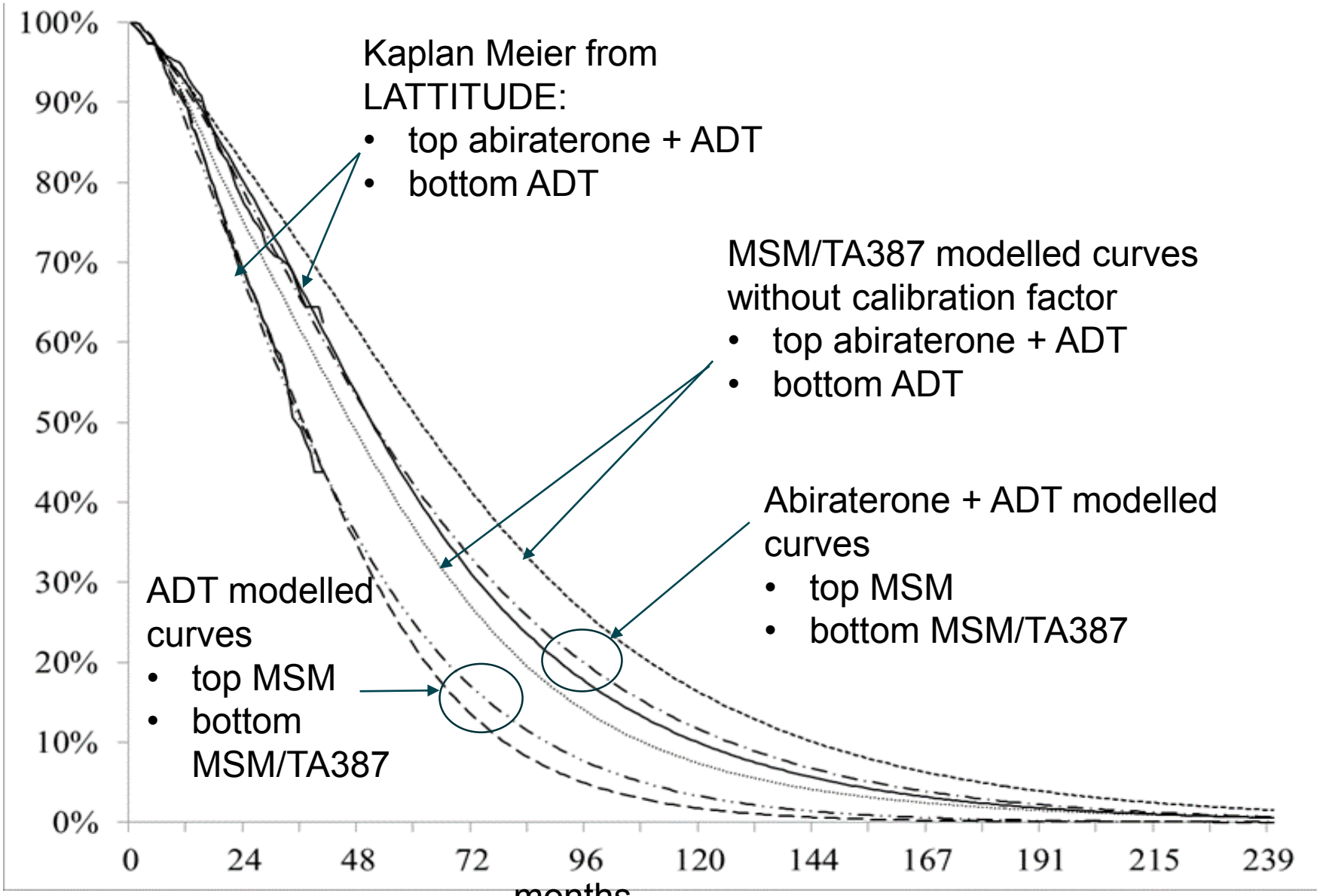
MSM





Plausibility of modelled survival outcomes

Kaplain Meier vs. modelled



Sources of utility data

Health state	Quality of life data	Utility values used in model
HORMONE SENSITIVE		
Pre- and post-progression	EQ-5D-5L from LATITUDE: baseline until 60 months, death or loss to follow-up	• Mapped to EQ-5D-3L utility using 'crosswalk' algorithm (Van Hout) • + regression analysis of trial data to identify factors influencing quality of life
on/off abiraterone		
on/off docetaxel	Company's Time Trade-Off study. Non-randomly selected 200 members of public who valued a description of a person's experience in 3 health states	Time trade off for typical high risk person: 1. On ADT 2. On docetaxel + ADT 3. After 6 docetaxel cycles on ADT alone
Adverse event	Literature - not LATITUDE analyses	Literature
CASTRATE RESISTANT		
Health states	From TA387, included an increment of 0.021 for people receiving abiraterone as a follow-on treatment	

◉ *Best source? Include pre-progression EQ-5D from STAMPEDE n=700?*

Modelled utility value by health state

◉ *Are differences between treatments and for adverse events plausible?*

State	AAP + ADT	ADT	Docetaxel + ADT
mHSPC pre-progressed	********** **********	*******	********** **********
mHSPC pre-progressed (with AE/SRE)	********** **********	*******	******* *******

Disutility for adverse events/skeletal related events (AE/SRE)	
Company base case: value from literature	*******
Company scenario: value from LATITUDE regression	*******

ERG: Assumption that quality of life worse after docetaxel (+ ADT) compared with ADT alone not consistent observations reported in literature (CHAARTED and GETUG AFU 15 trials)
ERG: Preferred using data from LATITUDE regression for adverse event disutility
COMPANY: identified error in its modelling utility decrements for AE/SRE not applied to docetaxel + ADT arm in mHSPC health states (correction suggested after ERG report received at NICE)

Other modelling assumptions

	Company assumption	ERG assumption
Treatment compliance abiraterone (+ADT) for mHSPC	For abiraterone a compliance rate of **% was applied to abiraterone costs. Estimated from LATITUDE by ratio of: Area under progression free survival KM curve to Area under time to treatment discontinuation curve	Company's approach does not fully take into account impact of censoring, numbers at risk + timing of assessments on shape of curves in estimates ERG estimated compliance of **% for AAP + ADT and **% for ADT using "*Percent of doses (tablets) taken out of the protocol-specified dose*" for safety population (LATITUDE Clinical Study Report)
Number of bone scans	Company model assumes a bone scan at ** weeks and every ** weeks thereafter at a cost of £292 for people in the modelled docetaxel + ADT arm only	ERG could not find evidence to support a difference in bone scan number between treatments Assumed **equal number** of bone scans in each modelled treatment arm

◉ *What does committee prefer? Company's, ERG's or neither?*

ERG exploratory base case

Assumption	Company assumption	ERG exploratory base case
Disutility values for adverse events and skeletal related events	Literature ******	LATITUDE regression ******
Utility decrement after docetaxel in hormone sensitive health state	Applied decrement	No decrement
Compliance estimates for abiraterone in hormone sensitive health state	Estimated from LATITUDE data (progression free survival + time to treatment discontinuation curves)	Compliance estimates from safety population in LATITUDE from clinical study report
Proportion of people receiving best supportive care in castrate resistant health states	Higher proportion in abiraterone + ADT arm	Same proportion in each modelled treatment arm
ERG also corrected some minor modelling errors and provided results for MSMTA387 & MSM modelling approach		

Company identified errors in own modelling

Submitted corrections in response to its fact check of ERG report

Error	ERG comment	Impact on ICER (calculated by ERG)
1) Did not include utility decrements for adverse events + skeletal related events for docetaxel + ADT in hormone sensitive health state.	Appropriate to include correction which applies these decrements in base case **(results presented in confidential appendix)**	Company + ERG base case: **decreases ICER vs. docetaxel + ADT**. Larger decrease in ERG base case (which uses larger utility decrements from regression).
2) Did not limit to 10 cycles for docetaxel and 4 cycles for radium-223 for castrate resistant prostate cancer	Agree was an error Implementation of limits in model complex→ time constraints limit ERG validation	Results with correction 2 + 3 **not** presented today because corrections not fully validated by ERG
3) commercial access agreement for abiraterone taken in castrate resistant prostate cancer incorrectly implemented	Unclear what the correction has addressed and how.	

Company's & ERG's base case results

Results are confidential and will be presented in private part of appraisal committee meeting (part 2) because of confidential discounts to subsequent treatments