NICE National Institute for Health and Care Excellence

Chair's presentation

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

4th committee meeting 10 December 2020

Post appeal

Committee B

Chair: Amanda Adler

Lead team: Bill Turner, Nigel Westwood, Nicholas Latimer

ERG: Aberdeen Health Technology Appraisal Group

NICE technical team: Jessica Cronshaw, Mary Hughes, Ross Dent, Lorna Dunning, Jasdeep Hayre, Nicole Elliott

Appeal team: Amanda Adler, Sanjeev Patel, Nicholas Latimer, Ross Dent, Helen Knight

Company: Janssen

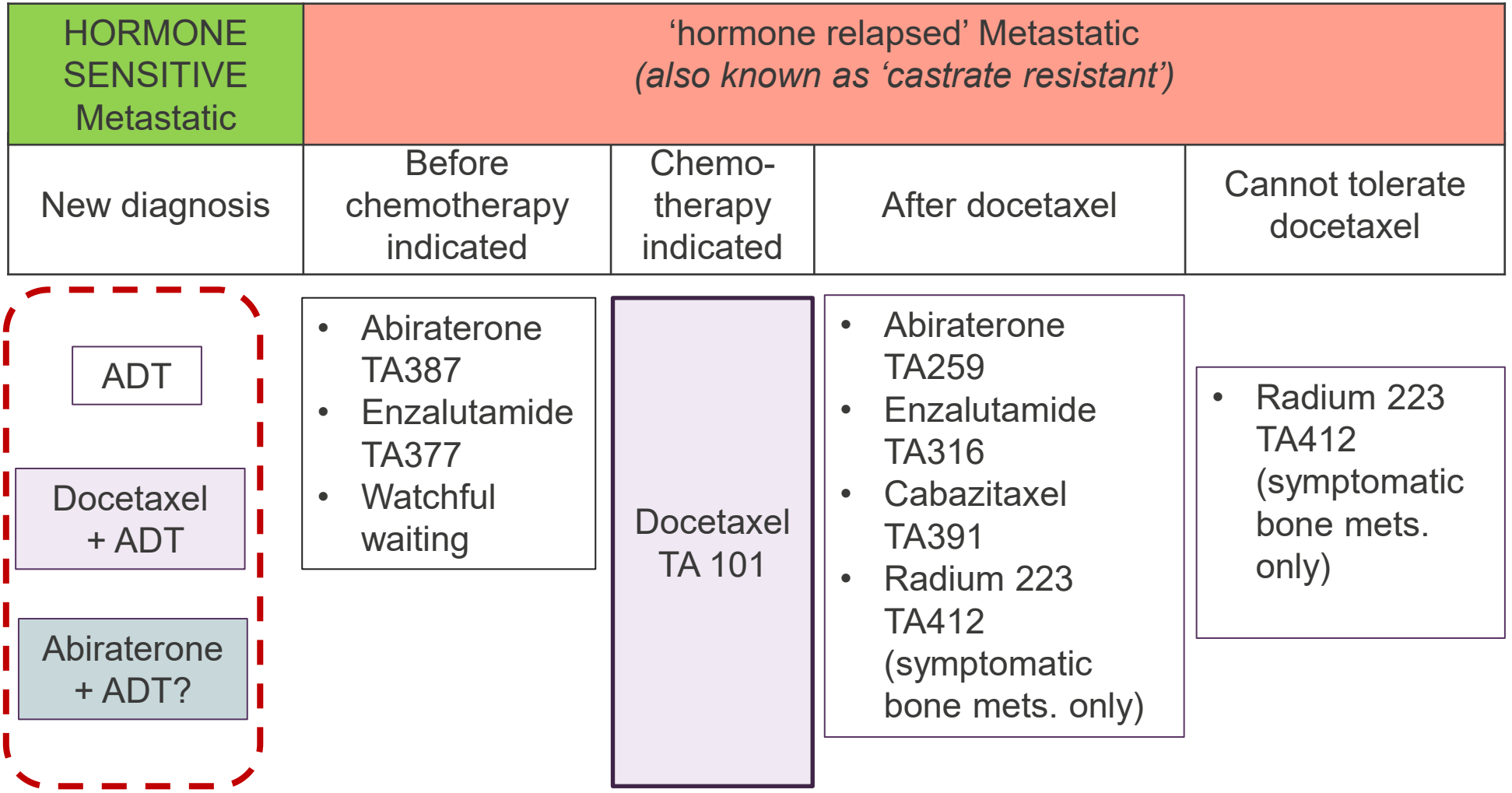
Post appeal meeting

- ‘If 1 or more of the appeal points are upheld and it is necessary for the final draft guidance to be returned to the advisory committee, the Guidance Executive will aim to consider the appeal decision within 15 working days of receipt. The Guidance Executive will decide how to act on the decision of the Appeal Panel.’
- Guidance Executive recognised that:
  - company’s appeal related to committee making incorrect decision on basis of evidence in front of it.
  - British Uro-oncology Group (BUG) and patient groups argued that NICE prevented them from submitting relevant information for the committee to consider. Guidance Exec agreed that NICE should ask if there was anything these groups wanted to submit that they felt they had previously been prevented from doing.
- Today: “The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address these points...”

Outline

1. Abiraterone in treatment pathway
2. History of appraisal
3. Recap clinical and cost effectiveness from previous 3 meetings
4. Summary of appeal points – upheld and dismissed
5. Appeal points by topic
6. Consideration of new evidence
7. In light of above, consider if guidance should change related to whether abiraterone reflects a clinically and cost-effective use of NHS resources across its indication-specific marketing authorisation?
    - Prices of abiraterone confidential
    - Prices of follow-on treatments also confidential discounts

Treatment pathway



TA, technology appraisal

History of appraisal

Committee meetings and NHS England

Consultation

Appraisal suspended for price negotiations

Meeting 1
May 2018

- Company proposed same commercial access agreement (CAA) for later in disease
- Model generated implausible results
- Company did not fully use data from STAMPEDE
- Appraisal consultation document (ACD) released: not recommended

Meeting 2
July 2018

- Same CAA proposed: but NHS England did not approve
- Same model as original submission
- ACD prepared + shared with company + Evidence Review Group (ERG) to allow commercial discussions between company and NHS England

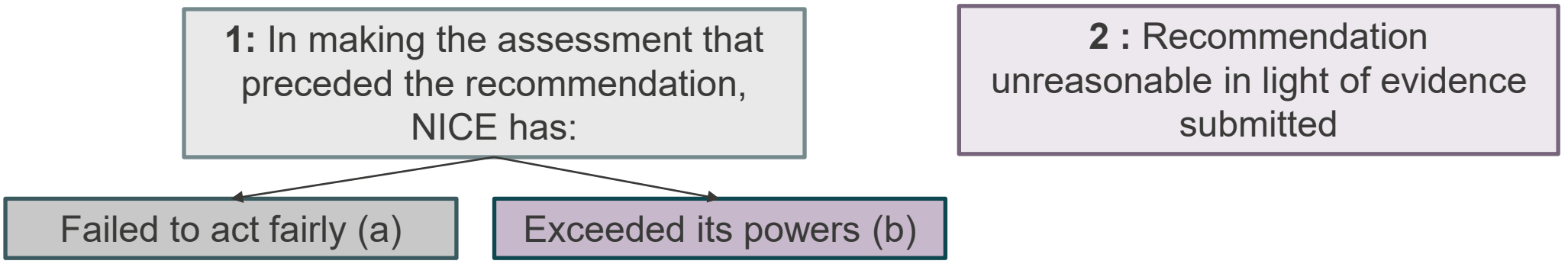
Meeting 3
January 2020

- List price
- New modelling approach
- No ACD/FAD released. NICE provided NHS England with committee's preferred modelling assumptions to allow ongoing pricing negotiations between NHS England and company

June 2020

- Janssen and NHS England could not agree a price.
- Final Appraisal Determination (FAD) released based on list price abiraterone: not recommended

History –2 grounds of appeal



- 22 appeals points passed scrutiny and passed to appeal – others rejected
  - Prostate Cancer UK + Tackle Prostate Cancer (jointly)
  - British Uro-oncology Group (BUG)
  - Janssen
- 'An appeal is not an opportunity to reopen arguments and issues that the advisory committee has decided on. It is not possible to appeal against the final draft guidance because a consultee does not agree with it.'*
- 'New evidence or information that was not presented to the Committee, or re-analysis of existing evidence or information, must not be presented in the appeal letter or at the hearing, and will not be considered by the Appeal Panel.'*
- 16 appeals points successfully defended by Committee
- 6 appeal points upheld
- 2 requests to clarify wording in Final Appraisal Determination

*NICE Guide to the technology appraisal and highly specialised technologies appeal process

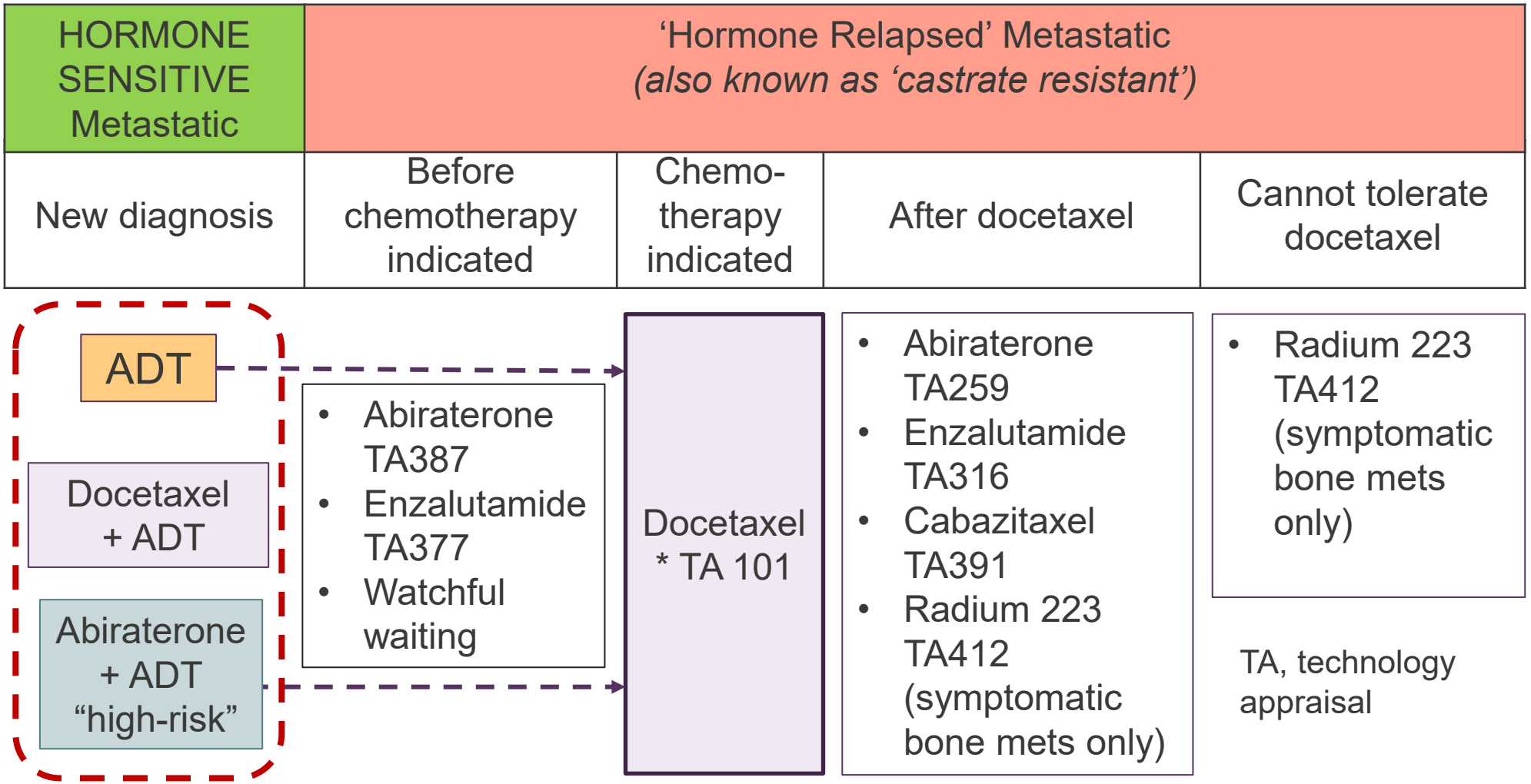
Recap: clinical and cost effectiveness

Abiraterone (Zytiga, Janssen)

Mechanism	Inhibits androgen synthesis via cytochrome P450 17 alpha-hydroxylase in testes, adrenals, and in prostate cancer
Marketing authorisation **November 2017**	With androgen deprivation therapy (ADT) and either prednisone or prednisolone in adults with prostate cancer that is: • **newly diagnosed** • **high risk** • **metastatic** • **hormone sensitive** In clinical trials, 'high risk' is defined as at least 2 of: 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 before **or** after chemotherapy. Abiraterone or enzalutamide in NHS given only once.

Treatment pathway metastatic disease

Comparators: 1. ADT alone 2. docetaxel + ADT;
Abiraterone (or enzalutamide) only given ***once in the treatment pathway***



NHS England commissions 6 cycles of docetaxel
Docetaxel can be offered again after ADT alone or abiraterone + ADT for hormone relapsed disease

Decision problem

Company proposes a subgroup 'chemo-ineligible'

	Final NICE scope	Decision problem - company	Rationale if differs from scope
Population	Newly diagnosed High risk metastatic Hormone-naïve	Newly diagnosed High risk metastatic Hormone-sensitive (mHSPC)	Same
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 rarely used
Subgroup		'Chemo-ineligible (docetaxel-ineligible) subgroup'	20% unsuitable for chemotherapy

NICE

Docetaxel

No marketing authorisation for hormone-sensitive metastatic disease

- NHS England commission off-label docetaxel use
  - 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]
- NICE 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:
    - treat within 12 weeks of starting androgen deprivation therapy **and**
    - six 3-weekly cycles at 75 mg/m^2 with or without daily prednisolone

Clinical trial evidence

Direct and indirect comparisons provided by company

Compared to ADT alone

Direct evidence	LATITUDE	• Blinded RCT: newly diagnosed high risk metastatic hormone sensitive prostate cancer; co-1º endpoint PFS and OS • Trial unblinded after 30 months, crossover permitted
	STAMPEDE	• Adaptive open-label UK RCT: newly diagnosed locally-advanced or metastatic hormone sensitive prostate cancer • Data for metastatic subgroup; includes both low/high risk

Compared to docetaxel + ADT

Direct evidence	STAMPEDE	• N=502 ADT alone, N=500 abiraterone, N=115 docetaxel • Comparison between abiraterone and docetaxel post-hoc • No analyses for abiraterone vs docetaxel in high-risk
Indirect evidence: network meta-analyses	CHAARTED GETUG-AFU15	• Open label docetaxel + ADT vs. ADT • Subgroups aligned with population in marketing authorisation
	LATITUDE	• Included: abiraterone + ADT vs. ADT
	STAMPEDE	• High burden metastatic subgroups for docetaxel +ADT vs ADT

Recap: results for abiraterone + ADT vs comparators

Direct comparison preferred for all comparators
For docetaxel comparison, preference to use hazard ratio of 1 for OS

		Direct comparison		Indirect comparison network meta-analysis (NMA)	
ADT alone	LATITUDE final analysis	PFS: 0.47 (0.39 to 0.55)	OS: 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	*** **********	*** **********	Committee preferred	
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)	*** (**********)	*** **********

Defining subgroup who cannot take docetaxel

Various approaches - who cannot take docetaxel, but can take abiraterone

Committee meeting 1	Committee meeting 2	Committee meeting 3
Patient expert noted unmet need for treatment option for people who cannot take chemotherapy NHS commissioning policy notes people have to be fit enough for docetaxel to take it Company: • no definition of people who cannot have docetaxel but can have abiraterone Clinical experts: • no clear cut definition	NHS England Commissioning policy for docetaxel • Poor overall performance status WHO performance 3 to 4, peripheral neuropathy, poor bone marrow function, life-limiting illness • Use with caution in people with a WHO performance status of 2 • Few absolute contraindications TA412 • Renal impairment, immunosuppressants, poor performance status	NHS England lead for CDF • Cannot/should not/chooses not to have docetaxel • Committee FAD 3.2. "agreed that there are no clear-cut clinical criteria to define who can have abiraterone in combination, but not docetaxel in combination ..there is no supporting evidence on the safety or effectiveness of abiraterone in combination for people who cannot have docetaxel in combination"

People with poor performance status not in trials

- LATITUDE and STAMPEDE…. included only people with adequate haematological function, an Eastern Cooperative Oncology Group (ECOG) status or WHO performance status of 0, 1 or 2

Health related quality of life and utility values

Committee preferred EQ-5D data from STAMPEDE for docetaxel

Treatment	Quality of life - treatment	Quality of life - adverse events
ADT alone	EQ-5D data from LATITUDE	Published utility values for adverse effects and skeletal-related events
Abiraterone	EQ-5D data from LATITUDE. Company modelled a further utility **increase** for being on abiraterone compared with ADT alone.	Published utility values for adverse effects and skeletal-related events
Docetaxel	Survey commissioned by the company. Company modelled a further utility **decrement** for being on docetaxel	Published utility values for adverse effects and skeletal-related events

- Committee noted that STAMPEDE collected EQ-5D data for a UK population randomised to abiraterone .. to docetaxel ..and to ADT alone. Committee preferred these data but company did not provide them.
- ERG provided scenario based on reported quality of life on docetaxel used for cost-effectiveness modelling of docetaxel for NICE clinical guideline: prostate cancer based on EQ-5D data from STAMPEDE
- 'In the absence of these data, the committee concluded the ERG's estimate was likely to be broadly appropriate' Final Appraisal Determination 3.11

Committee's preferred modelling assumptions around extrapolating clinical trial data

Final Appraisal Determination 3.13

For whole population

	Company base case	Committee preference
Type of analysis	Pairwise deterministic (vs. docetaxel + ADT and vs. ADT separately)	Probabilistic incremental
Extrapolation PFS	Weibull	Weibull
Extrapolation OS	Weibull (pessimistic) log-logistic (optimistic)	Weibull Generalised gamma
Treatment effect OS abiraterone + ADT vs. docetaxel + ADT	HR from network meta-analysis hazard ratio ***	Assume hazard ratio 1 as no survival benefit demonstrated from NMA or STAMPEDE data

Scenarios also considered helpful:

Overall survival docetaxel + ADT vs. abiraterone + ADT
- Hazard ratio = 1.13 (STAMPEDE)

Treatment waning
- Assume equal hazards of progression and overall survival at 8 or 10 years

Cost effectiveness results

Confidential because subsequent treatments have confidential PAS

- FAD: 'Cost-effectiveness estimates ..were considerably higher than the range normally considered a cost-effective use of NHS resources'
- Compared with ADT, incremental cost effectiveness ratio (ICER) at list price >> £50,000 per QALY gained, compared docetaxel + ADT ICER double this

1st treatment for hormone sensitive prostate cancer

Abiraterone hormone sensitive prostate cancer

- Proposed commercial access agreement which NHS England did not accept
- List price used

Subsequent treatments hormone relapsed prostate cancer

Abiraterone hormone relapsed, before or after docetaxel

- Commercial access agreement prices

Enzalutamide

- Patient access scheme prices

Cabazitaxel

- Patient access scheme prices

Radium-223

- Patient access scheme prices

Appeal

Summary 22 points in 8 topics,16 dismissed; 6 upheld

Topic	Points	Number	Appellants/NICE number	Topic
1	1 2	2	Janssen 1a1a BUG 1a2	Quality of Life
2	3 4 5 6	4	BUG 2.4 BUG 2.5 BUG 2.1 BUG 2.6	Overall survival including accounting for subsequent treatments
3	7 8 9 10 11 12	6	**Janssen 1a2c - process** **Janssen 2.1 - perversity** **PCUK/TPC 2.1 - perversity** BUG 2.2 Janssen 1a3 Janssen 2.2	**Cannot take docetaxel**
4	13 14 15	3	Janssen 1a6 Janssen 1a7 BUG 2.3	Subsequent Treatments
5	16 17	2	**Janssen 1a4 - process** BUG 1a1	**Transparency**
6	18 19	2	Janssen 1a1b BUG 1a4	Non health objectives and COVID
7	20 21	2	**PCUK/TPC 1a1 - process** **BUG 1a3 - process**	**Inequalities and discrimination**
8	22	1	Janssen 1b8	Safety

Upheld: failed to act fairly

Appellant	Appeal point
Janssen 1a 2c	Committee's conclusion that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" does not provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223 (technology appraisal 412)
PCUK1a	NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.
BUG 1a 3	That the failure of the Committee to consider the STAMPEDE group's recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision.
Janssen 1a 4	The conclusions of the Appraisal Committee in relation to the cost-effectiveness of abiraterone in this appraisal are opaque.

Upheld: unreasonable in light of evidence

Appellant	Appeal point
PCUK/TPC 2.1	Recommendation is unreasonable in light of the evidence submitted to NICE concerning the effectiveness of abiraterone in patients who cannot receive docetaxel.
Janssen 2.1	The Appraisal Committee's conclusion that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" is unreasonable in the context of the available evidence.

Dismissed: failed to act fairly

Appellant	Appeal point – failed to act fairly by:
BUG 1a1 + 1a2	Not requesting and/or not considering the STAMPEDE group's recent cost-effectiveness analysis and recently presented quality of life data referred to in the appeal letter
BUG 1a 4	Not taking into account COVID-19
Janssen 1a 1a	Failing to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured: (a) capture of benefits in the QALY for abiraterone
Janssen 1a 1b	Appraisal Committee has failed to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured: (b) Aspects of the technology that relate to non-health objectives of the NHS.
Janssen 1a 3	Not providing reasons to explain its view that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel
Janssen 1a 6	Stating "the clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT in this trial" based on unpublished data that have not been disclosed or confirmed.
Janssen 1a 7	focussing on number of subsequent treatment options rather than outcomes relies on an irrelevant consideration.

Dismissed: unreasonable in light of evidence

Appellant	Appeal point – unreasonable to state
BUG 2.2	"It is not appropriate to consider separately the clinical and cost-effectiveness of abiraterone in combination in people who currently have ADT alone"
BUG 2.3	"The clinical experts explained that people who have previously had docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again (for up to an additional 10 cycles)"
BUG 2.4	"Comparison of abiraterone and docetaxel suggest that there may be no difference in overall survival"
BUG 2.5	"Magnitude of OS benefit for abiraterone may be over-estimated"
BUG 2.6	"Neither STAMPEDE nor LATITUDE likely capture all the benefit on overall survival of follow-on treatments used in NHS clinical practice"
Janssen 2.2	That abiraterone's benefits may be different in those patients who are unable to receive docetaxel

Discussion order and submitted evidence

Order:

1. Transparency
2. Defining ‘chemo – ineligible subgroup’
   - Is there a group who is contraindicated or otherwise unsuitable for docetaxel?
   - Who will define this group?
   - What is the definition?
   - What is the best source of data to model this subgroup?
3. Inequalities
4. Rewording

Submitted evidence:

Prostate Cancer UK and BUG responded with data:

- New: Proportions of people having docetaxel by age
- New: Longer overall survival data for abiraterone + ADT vs ADT from STAMPEDE for whole population
- New: Quality of life data from STAMPEDE for whole population
- Seen previously: Clinical effectiveness by age/ patient characteristics

Transparency

Transparency

Janssen 1a.4	Cost-effectiveness of abiraterone in this appraisal opaque
Appellant	NICE states 'merely that the ICERs were "considerably higher" or "higher" [than the usual range considered cost-effective]' 'Without that information, parties did not know what they had to do to secure a positive outcome.'
NICE	NICE accepted could have been clearer in publishing an ICER range
Panel	• 'Tension between confidentiality and transparency is not a new issue' • 'Panel understands that publication of an exact ICER would enable anyone with access to the economic model to deduce the actual price' • NICE 'must now consider whether it is possible to give any more precise indication of the ICERs calculated, while not compromising the confidentiality of competitor pricing. For example, a range might be given, within which the actual ICER falls.' • NICE 'must ensure that participants in the appraisal are given a chance to make observations on the ICERs and anything driving the ICERs, and that the Committee can consider those observations and whether the guidance should be revised as a result.' • 'One way to achieve this could be a further round of consultation'

◉ *What is the Institute (NICE) doing on this issue?*

Defining ‘chemo-ineligible’ subgroup

'Docetaxel is contraindicated or unsuitable' better than company's terminology of 'chemotherapy-ineligible'

Letter from Prostate Cancer UK, Tackle Prostate Cancer, BUG

Dear Sir/Madam,

Ahead of the appraisal committee meeting of abiraterone for newly diagnosed hormone sensitive metastatic prostate cancer on 10 December, Prostate Cancer UK, Tackle Prostate Cancer and the British Uro-Oncology Group (BUG) would like to offer a slightly different strategy for considering abiraterone that could simplify the appraisal and respond to the findings of the appeal panel. As in the appraisal of radium-223 in 2016, looking at a population "for whom docetaxel is contraindicated or unsuitable",[1] rather than those "chemotherapy-ineligible", may help reach a positive decision.

Defining 'chemo-ineligible subgroup' (1)

Appellant Janssen 1a 2c	"There are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" does not: (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223.
NICE	• 'Noted clinical expert opinion that fitness for docetaxel is not necessarily clear cut or easy to operationalise' • With appraisal of Radium-223, Committee were specifically given evidence of the efficacy of the therapy in patients who could not take docetaxel • Committee had considered cost-effectiveness in patients who could not have docetaxel by looking at the cost-effectiveness of abiraterone against ADT alone. The conclusion was that abiraterone is not cost-effective for this group.
Panel	• 2 appraisals concerned the same disease, and both attempted to define a group of patients who could not receive docetaxel • Reasons for departing from the approach taken in a previous closely-related appraisal had not been made sufficiently transparent

TA412: radium-223 for treating hormone-relapsed prostate cancer with bone metastases

ALYSMPCA trial included people not suitable for docetaxel

Radium-223 dichloride is recommended as an option for treating hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases in adults, only if:

- they have already had docetaxel or
- **docetaxel is contraindicated or is not suitable for them**

Patient Population:
The target population is patients with progressive symptomatic HRPC, with at least two skeletal metastases on bone scan and no known visceral metastases.
Specifically the target population is

- Patients who have received docetaxel
- Patients who are not fit enough to receive docetaxel
- Patients not willing to receive docetaxel,
- Patients for whom docetaxel is not available for other reasons

Defining ‘chemo-ineligible’ subgroup (2)

Appellant PCUK/TPC 2.1	‘When the Committee were struggling to define the populations who cannot take docetaxel, they should have consulted clinical experts for guidance and sought additional sources of information’
NICE	‘Clinical expert opinion that fitness for docetaxel is not necessarily clear cut or easy to operationalise’ ‘need to operationalise any definition in a way that could be applied consistently in clinical practice and they had heard from clinical experts that this was difficult’ ‘Committee did not ignore the chemotherapy-unfit group, but just were not provided with any evidence or analyses for that group’
Panel	‘Committee’s conclusion that “there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination” was not clear. Given that clinical criteria to define eligibility for docetaxel do exist, the Panel judged that a reasonable Committee should give clear reasons why these criteria were not suitable in the current appraisal.’

Defining 'chemo-ineligible group'(3)

Appellant Janssen 2.1	• **Oncologists make 'decisions on a day-to-day basis about which patients can receive docetaxel. The NHSE commissioning policy for docetaxel also provides clear criteria to operationalise this. The Blueteq criteria from NHSE proposed at the third Committee meeting also provide a workable set of criteria.'**
NICE	• 'Doctors have a sense of who would not do well with chemotherapy, but this can nevertheless be difficult to define.' • 'Committee were aware of the need to operationalise any definition in a way that could be applied consistently in clinical practice and they had heard from clinical experts that this was difficult. This clinical opinion came over very strongly at the time of the Committee meeting' • 'Challenge was not simply to define men who couldn't take docetaxel, but those could take abiraterone but not docetaxel.'
Panel	NICE 'should explicitly consider whether it is possible to define a group of patients who are ineligible/unsuitable for docetaxel, before going on to consider whether there is evidence available for the effectiveness and cost-effectiveness of abiraterone in that group. If it concludes that approaches taken in other settings are not suitable in this appraisal, it should give clear reasons for this.'

Recap: PCUK comments on ACD

There are numerous sources which set out the clinical criteria to define people who are unable to receive docetaxel which should be considered.

Paragraph 3.3 of the Clinical Commissioning Policy Statement for docetaxel in combination with ADT[i] includes:

- severe prior hypersensitivity reaction to taxanes
- poor overall performance status (WHO performance status 3-4, caution for those with performance status 2)
- pre-existing significant peripheral neuropathy
- poor bone marrow function due to extensive disease or other prior haematological problems
- significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient

Paragraph 4.31 of the FAD for TA412 for radium 223[ii] sets out criteria for defining the people for whom docetaxel is not suitable:

- contraindications to docetaxel such as hypersensitivity to the active substance, a neutrophil count of less than 1.5x109/litre, or severe liver impairment
- a platelet count of less than 100x109/litre
- ongoing treatment with an immunosuppressant for any condition
- an ECOG performance status of 3 or greater
- comorbidities and an ECOG performance status of 2 or greater
- comorbidities, including:
    - poor cognition or social support, which results in inability to understand treatment and provide consent

◉ *How do clinicians/NHS England define who can take abiraterone but not docetaxel? Can this definition be operationalised?*

NICE

Ref: Consultation comments to ACD

‘Equality and discrimination’

Equality considerations

Do the assessments leading to the recommendations or the recommendations:

- exclude from full consideration any people protected by the equality legislation who fall within the patient population for which abiraterone is licensed?
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- have any adverse impact on people with a particular disability or disabilities.

Inequalities (2) – taken together by Appeal panel

PCUK/TPC 1a.1 BUG 1.a3	‘NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.’ ‘That the failure of the Committee to consider the STAMPEDE group’s recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision.’
Appellant	People ‘ineligible for or who would not take chemotherapy…clearly existed. Those men tended to be older...’ Failure to provide abiraterone discriminates on age ‘A failure by the Committee to identify a population who would not receive docetaxel. PCUK had tried to respond with evidence.’
NICE	‘Avoid making recommendations based on age, race or gender’ ‘Subgroups are avoided if a drug is effective in a whole patient population.’ ‘In this case, it is comorbidities and frailty, rather than age per se, that affects access to docetaxel.’ ‘If committees were to increase ICER thresholds for older people they would have to reduce thresholds for other groups (e.g. children)’
Panel	Panel ‘finds that the current reasoning around the failure to define this subgroup does not address the fact that the subgroup will tend to comprise older men.’ ‘The Panel wishes to be clear that although equality legislation requires this subgroup to be more fully considered it does not necessarily follow that in this case, after appropriate consideration, special provision will need to be made for them.’

Submissions post appeal: new, not previously submitted

Ref	Trial	Pop'n	Comparison	Outcome	Cut-off, follow up (median)	Comments	Relevance
James et al 2020	STAMPEDE	High risk	Abiraterone vs. ADT	Survival	Apr 2020 6.1 years	To inform extrapolation	Model
Rush et al un-published	STAMPEDE	High and low risk	Abiraterone vs ADT Docetaxel vs. ADT	Quality of life ********	Dec 2019 2 years	Better, but did not reach the pre-defined value for clinical significance Not EQ-5D	Appeal

Ref	Description of data	Comments	Relevance
Clarke et al un-published	Cost effectiveness analysis abiraterone + ADT vs. ADT based on STAMPEDE data	**********	Not appeal; not reference case
PCUK Un-published	% of people having docetaxel by age using data from Raw data: Get Data Out from www.cancerdata.nhs.uk/getdataout/prostate	Docetaxel use declines with age	Appeal

Also submitted published papers which had been included during appraisal (Clarke et al 2019, James et al 2017, Hoyle et al 2019, Fizazi et al 2019)

PCUK: fewer older people take chemotherapy

Data chemotherapy uptake most recent data available

Age	Metastatic incidence	Chemotherapy incidence	% chemotherapy
****	****	****	****
****	****	****	****
****	****	****	****
****	****	****	****

◉ *Is age associated with chemo-unsuitable or chemo-use?*

Clinical effectiveness of abiraterone by age

STAMPEDE: effect modification by age

- Overall survival hazard ratio increases in older people suggesting less clinically effective
- Prof. James: Other causes of death 'dilute' effect of prostate cancer → progression free survival (PFS) a better measure of effectiveness".

STAMPEDE cohort ADT alone vs abiraterone combination James et al 2017

Outcome	subgroup		ADT alone no. event/N	Abiraterone combination event/N	Hazard ratio (95% CI)	P value for interaction
Overall survival	Age	<70 years	180/596	110/603	0.51 (0.40 to 0.45)	0.003
		≥ 70 years	82/361	74/357	0.94 (0.69 to 1.29)	
Failure free survival*	Age	<70 years	361/596	174/596	0.26 (0.22 to 0.32)	0.04
		≥ 70 years	174/361	83/357	0.36 (0.28 to 0.47)	

◉ *Is age an effect modifier for effectiveness of abiraterone?*

* Subgroup analysis not presented for progression free survival: Failure free survival is time to 1st of PSA failure, progression of metastases or death from prostate cancer. Progression free survival does not include PSA failure

LATITUDE subgroup analyses

No data presented people who could/could not have abiraterone but not docetaxel

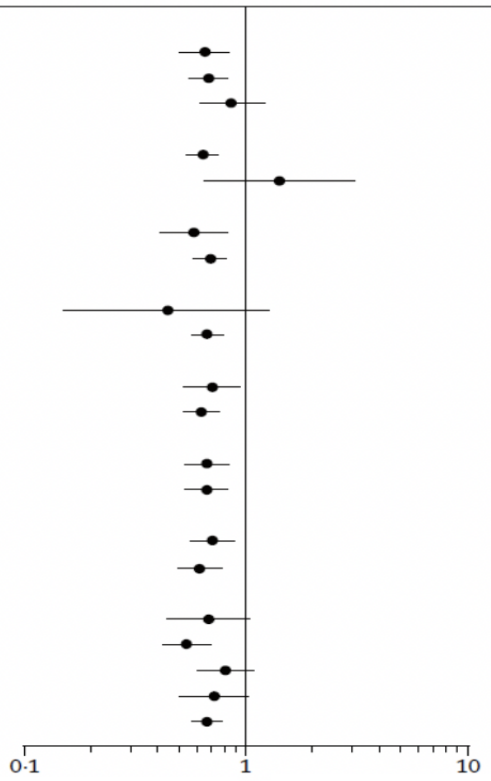
STAMPEDE: all eligible for docetaxel, LATITUDE: 97% performance status 0 or 1

LATITUDE subgroup results estimates less benefit for abiraterone on overall survival for:

- Patients ≥ 75 yrs - HR 0.86
- ECOG performance status score of 2 HR 1.42

Fizazi et al 2019

	Abiraterone + ADT	Placebo + ADT	Hazard ratio (95% CI)
Age (years)			
<65	100/221	131/233	0·65 (0·50–0·84)
≥65	175/376	212/369	0·68 (0·55–0·83)
≥75	66/123	70/120	0·86 (0·62–1·21)
ECOG performance status			
0–1	257/573	333/586	0·64 (0·54–0·75)
2	18/24	10/16	1·42 (0·65–3·08)
Visceral disease			
Yes	52/114	70/114	0·58 (0·41–0·83)
No	223/483	273/488	0·69 (0·58–0·82)
Gleason score			
<8	5/13	11/16	0·44 (0·15–1·27)
≥8	270/584	332/586	0·67 (0·57–0·79)
Bone lesions			
≤10	76/211	101/221	0·70 (0·52–0·94)
>10	199/386	242/381	0·63 (0·52–0·76)
Above median prostate-specific antigen			
Yes	140/304	169/295	0·67 (0·53–0·84)
No	135/293	172/305	0·66 (0·53–0·83)
Above median lactate dehydrogenase			
Yes	141/294	166/284	0·71 (0·56–0·89)
No	130/297	171/311	0·62 (0·49–0·78)
Region			
Asia	38/124	48/121	0·68 (0·44–1·04)
Eastern Europe	99/214	136/217	0·54 (0·42–0·70)
Western Europe	83/155	94/162	0·81 (0·60–1·09)
Rest of world	55/104	65/102	0·72 (0·50–1·03)
All patients	**275/597**	**343/602**	**0·66 (0·57–0·78)**



◉ *What is the best source of data to reflect people who unsuitable/contraindicated for docetaxel?*

Post appeal submission: James et al 2020

Using year of recruitment in STAMPEDE as proxy for chemo-fitness

- Initially STAMPEDE eligibility required patients to be suitable for all treatment options
- In 2013 docetaxel arm closed but ADT and abiraterone + ADT continued recruiting:
  - **********
  - **********
- **********

Publication	Follow up period	Hazard ratio
Hoyle et al 2019	Data to Feb 2017 Median 3.3 years	0.54 (95% CI; 0.41 to 0.7)
**********	********** **********	**********

ERG:

- People for whom docetaxel unsuitable likely to be older
- Comparing the pre and post 2013 hazard ratio from STAMPEDE is not a subgroup analysis of people can or cannot have docetaxel
- The STAMPEDE publications do not identify a specific sub-population of patients who would be considered ineligible for docetaxel.

◉ *Is year of recruitment a proxy for being 'chemo-ineligible'?*

Post appeal submission: STAMPEDE quality of life analysis

Does not include EQ-5D data collected by STAMPEDE

- Unpublished: quality of life in abiraterone + ADT and docetaxel + ADT arm of STAMPEDE
- **********
- **********

ERG - paper does not:

- **********
- **********
- **********
  - **********
- **********
  - **********
  - **********.

◉ *Is this paper consistent with current modelling?*

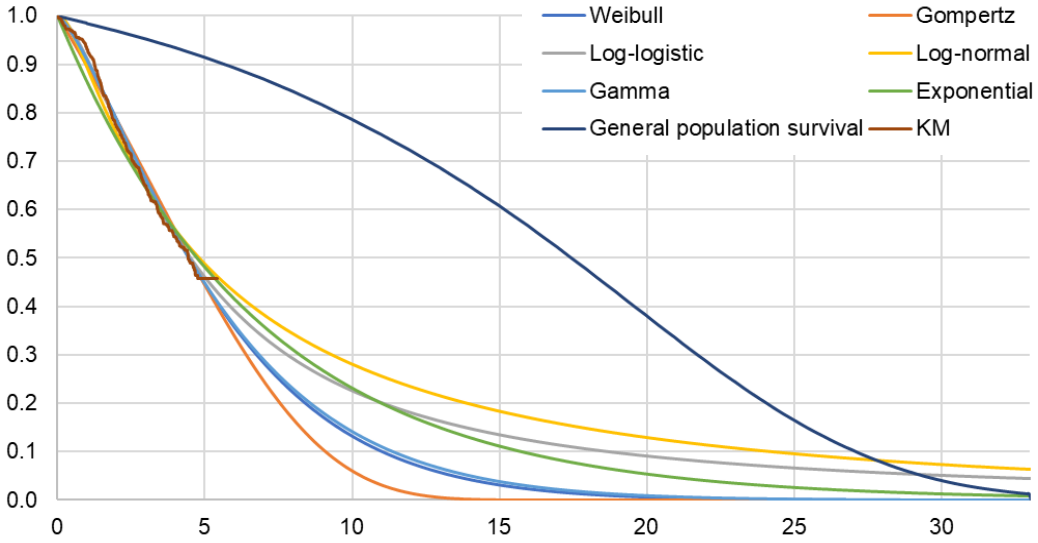
Post appeal submission: James et al 2020

Longer follow up from STAMPEDE for abiraterone + ADT vs. ADT

STAMPEDE additional follow up data 2020

[redacted]

Modelled extrapolations of LATITUDE data



Modelled 8yr survival: **Weibull < 20%**

Log-logistic ~ 25%

ERG:

- Committee preferred Weibull extrapolations based on data available at 3rd meeting
- Company's log logistic extrapolation of LATITUDE data may be plausible
- Low numbers at risk in extended follow up

◉ *With more mature STAMPEDE data, what curve is most appropriate to extrapolate LATITUDE?*

Text clarifications

Dismissed appeal points: clarify FAD text (1)

FAD – final appraisal determination

FAD text	Appellant Janssen 1b 8	Appeal panel
Section 3.2 "Committee was not presented with evidence of abiraterone's effectiveness in people who cannot take docetaxel. Without this evidence, it could not say whether abiraterone would be safe or effective in this group".	'Assertion by the Appraisal Committee that it is required to say whether abiraterone is "safe" in patients who cannot take docetaxel assumes the role of the regulatory authority'	Appeal panel: dismissed point 'Was satisfied Committee had properly considered adverse events only in the context of their impact on clinical and cost-effectiveness and had not assumed role of regulator' 'Consider whether the relevant wording of the FAD could be improved, to make clear that the point being made is around uncertainty of the impact of adverse events on clinical and cost-effectiveness.'

Dismissed appeal points: clarify FAD text (2)

FAD text	Appeal point BUG 2.1	Appeal team	Appeal panel
"…the treatments offered in the trials after the disease progresses do not reflect those offered in the NHS, where more people on standard care have effective treatments after their disease progresses than in the trials." "Neither STAMPEDE nor LATITUDE likely to capture all the benefit on overall survival of follow-on treatments used in NHS clinical practice"	Conclusion that STAMPEDE did not reflect NHS practice - unreasonable	• Statement based on only 55% of patients initially treated with ADT alone had follow-on treatment with abiraterone or enzalutamide • Lower than 80% market share estimated in company's model • Committee considered because abiraterone (+enzalutamide) for hormone refractory disease not available at start of STAMPEDE (2005) because abiraterone guidance published 2016	Appeal panel: **dismissed** Agreed with conclusion; asked to make clear there is a plausible reason for the apparent discrepancy - that abiraterone not available during earlier part of STAMPEDE

PART 2