NICE National Institute for Health and Care Excellence

Part 1	No confidential information
Public handouts	

Chair's presentation

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

5th committee meeting, 9th June 2021
Committee B
Chair: Amanda Adler
Lead team: Bill Turner, Nigel Westwood, Nicholas Latimer
ERG: Aberdeen Health Technology Appraisal Group
NICE technical team: Emma Douch, Nicole Elliott
Company: Janssen

Recommendation in Appraisal Consultation Document (ACD)

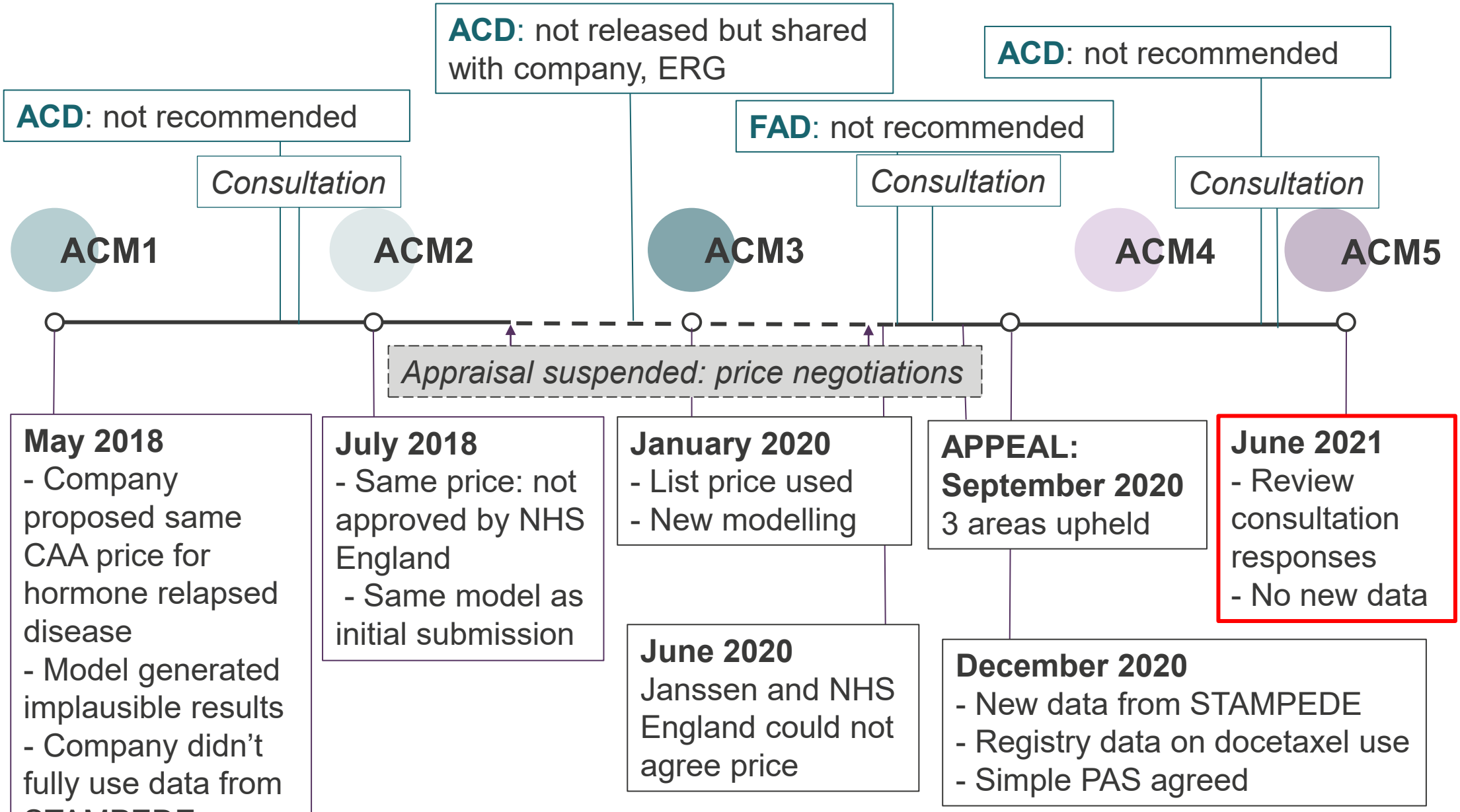
1. Abiraterone with prednisone or prednisolone plus androgen deprivation therapy (ADT) is **not recommended**, within its marketing authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adults.

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' defined as ≥2 of: 1. Gleason score ≥8 (aggressive/likely to spread) 2. ≥3 lesions on bone scan 3. Visceral metastasis (excluding lymph nodes) Note: Abiraterone also indicated for metastatic **castrate (hormone) resistant** prostate cancer before **or** after chemotherapy.
List price	Cost per patient per year: £35,653 Confidential discount available to NHS

History of appraisal

4 previous meetings



ACD, appraisal consultation document; ACM, appraisal committee meeting; CAA, commercial access agreement; ERG, evidence review group; FAD, final appraisal document

Decision problem

Company proposes a 'chemo-ineligible' subgroup

	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	Same
Intervention	Abiraterone + prednisone + ADT		
Comparators	1. ADT alone (orchidectomy, luteinising hormone-releasing hormone 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	None	'Chemo-ineligible' (docetaxel-ineligible)	20% unsuitable for chemotherapy

Issues for 5th meeting

Estimates of cost effectiveness unchanged from last committee meeting

- Does an alternative source of evidence exist for chemo-ineligible subgroup?

Recap: clinical and cost effectiveness

Treatment pathway for prostate cancer

In NHS, use abiraterone OR enzalutamide, not both, only once

Can have docetaxel twice: fewer options post abiraterone than comparators

<table>
<tr><th></th><th>Hormone sensitive</th><th colspan="3">Hormone relapsed</th></tr>
<tr><td>Non-metastatic</td><td>ADT
Radical therapy (surgery or radiotherapy)</td><td colspan="3">ADT
Enzalutamide + ADT not recommended in high risk of metastases (TA580)
Darolutamide + ADT in high risk (TA660)
Apalutamide + ADT in high risk (ongoing appraisal)</td></tr>
<tr><td>Metastatic</td><td>ADT
Docetaxel + ADT
Abiraterone + ADT in high risk?
Enzalutamide + ADT (draft FAD published, final guidance 14 July)
Apalutamide + ADT (ongoing appraisal)</td><td>Chemotherapy not yet indicated
Abiraterone
Enzalutamide
Watchful waiting</td><td>Chemotherapy indicated
Docetaxel
Olaparib BRCA 1/2 (ongoing appraisal)</td><td>Post-docetaxel
Abiraterone
Enzalutamide
Cabazitaxel
Radium 223*
*bone metastasis only</td></tr>
</table>

BRCA, BReast Cancer; TA, technology appraisal; NG, NICE guideline; ADT, androgen deprivation therapy

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 without significant comorbidities as follows:
    - treat within 12 weeks of starting androgen deprivation therapy **and**
    - 6 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		PFS	OS		
	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)	Committee preferred source	
	Meta-analysis LATITUDE + STAMPEDE	[redacted]	[redacted]		
Docetaxel + ADT	OS	PFS	OS	PFS	OS
	No difference in effect	Metastatic but not high-risk STAMPEDE		LATITUDE + CHAARTED + GETUG-AFU 15 + STAMPEDE (high burden subgroups for docetaxel + ADT vs. ADT)	
	1.0	**0.69** (0.50 to 0.95)	**1.13** (0.77 to 1.66)	[redacted]	[redacted]

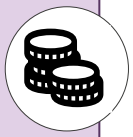
Cost effectiveness results

Confidential because subsequent treatments have confidential PAS

1st treatment for hormone sensitive prostate cancer

Abiraterone hormone sensitive prostate cancer

- Proposed commercial access agreement not accepted by NHS England
- Simple PAS used



ICERS compared with		
	Docetaxel in combination	**>£100,000** per quality adjusted life year (QALY) gained
	ADT alone	**>£30,000** per quality adjusted life year (QALY) gained

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

Appraisal consultation document summary

Topic	Committee conclusion
Comparators	ADT alone and docetaxel + ADT
Subgroup	If after considering whole population, abiraterone not cost effective, reasonable to consider group who cannot or should not take docetaxel.
Defining subgroup	Docetaxel not used in people with: • Contraindications: listed in summary of product characteristics and NHS England's clinical commissioning policy statement • Poor performance status: WHO or Eastern Cooperative Oncology Group [ECOG] performance status 3 or 4, some people with performance status 2 (in whom docetaxel used with caution) • Significant comorbidity (e.g. cardiovascular, respiratory or liver disease): another life-limiting illness • Peripheral sensory neuropathy or poor bone marrow function • Poor cognition or social support
Evidence for subgroup	People with poor performance status not in LATITUDE and STAMPEDE • Needed adequate haematological function and ECOG or WHO performance status 0, 1 or 2

Topic	Committee conclusion
Treatment pathway	1st treatment determines follow-on treatments when condition hormone relapsed
Evidence	For comparison to ADT, both LATITUTE and STAMPEDE appropriate
	For comparison to docetaxel, direct comparison preferred
Results	Abiraterone more effective (OS and PFS) than ADT alone
	Uncertainty about the magnitude of long-term survival gain
	Abiraterone more effective than docetaxel for PFS but not overall survival
Survival in UK	STAMPEDE better than LATITUTE for survival estimates related to follow-on treatments
'Chemo-ineligible'	Committee not presented with data on effectiveness of abiraterone compared with ADT specific to people for whom docetaxel is contraindicated or unsuitable
	Abiraterone in combination appears less effective in people at risk for not being able to have docetaxel, but the data are limited and uncertain
	Baseline risks to estimate absolute effectiveness of abiraterone in people who cannot have docetaxel not presented
	Overall survival estimates from LATITUDE include follow-on docetaxel; would not apply to people who can't have docetaxel
	Age, performance status, year of STAMPEDE recruitment not suitable as proxies

Topic	Committee conclusion
Model structure	• Partitioned survival model preferred • No modelling reflective of treatment pathway, costs and benefits for 'chemo-ineligible' subgroup
Extrapolating OS	Log-logistic preferred
Extrapolating PFS	Weibull preferred
Costs	• Company's model includes the costs of follow-on treatments in the NHS, but not the full benefits of these treatments
Utilities source	• Prefer STAMPEDE EQ-5D data from high-risk metastatic population *Company did not provide data* • ERG's assumption acceptable: • Abiraterone + ADT, ADT alone: LATITUDE EQ-5D • Docetaxel: Utility ↓ of 0.02 from STAMPEDE whole population
Committee base-case preferences	• Incremental probabilistic analyses • Hazard functions for OS and PS - as above • No survival benefit of abiraterone over docetaxel

Consultation comments

ACD consultation responses

Company

- Janssen

Web comments

Informal comments by
1 clinical expert from
STAMPEDE who represents:

- British Uro-oncology Group (BUG)
- Institute of Cancer Research (ICR)

Patient & Professional

- Prostate Cancer UK
- Peter Clark, Cancer Drugs Fund clinical lead, NHS England

Further evidence requested in 'chemo-ineligible' subgroup by committee

No new evidence submitted by the company or consultees

Unmet need in 'chemo-ineligible' subgroup

Poor outcomes on ADT alone; no other (current) treatment options if cannot have docetaxel

ACD: *"The committee recognised that there was an unmet need .."*

PCUK: Clear unmet need

People who cannot have docetaxel:

- Should not be *"denied an average additional 15 months of life"* without abiraterone
- Frequently excluded from trials: old age, potential poorer performance status
- Can have abiraterone if hormone relapsed: benefit in hormone sensitive setting also

Some meeting the chemotherapy unsuitable criteria can benefit from abiraterone

Company: '*Area of great unmet need ..'*

ICR: Denying abiraterone in this setting is a *'tragedy for many thousands of men..'*

About [redacted] cannot or should not take docetaxel*

- May 20- Apr 21: [redacted] started abiraterone for hormone-sensitive prostate cancer under interim COVID-19 regulations
- NHS guidance for COVID-19 recommended starting abiraterone only in people "intolerant of enzalutamide"
- [redacted] starting enzalutamide or abiraterone had comorbidities precluding docetaxel use

*Source: Cancer Drugs Fund lead, NHS England

When to use abiraterone

Larger survival benefit for abiraterone upfront vs. when hormone relapsed

ACD: *"..having abiraterone in combination at this position in the pathway limits the options for follow-on treatments for people who develop hormone-relapsed disease…."*

Company: ***"….****most value is gained when novel therapies are used as early as possible"*

- N.B. Committee has previously recognised its remit is to appraise abiraterone in proposed indication, rather than its positioning in the treatment pathway

PCUK:

- Without abiraterone at 1st line, cannot access until hormone relapsed *"when treatment benefits and quality of life are greatly reduced."*

No specific data for 'chemo-ineligible' subgroup

No data sources specific to subgroup; Full trial populations should act as proxy

ACD: *"No data were presented specifically for the group of people who cannot take docetaxel."*

PCUK: *"This evidence is not available"*

Committee setting precedent by requesting subgroup specific data:

- Likely no data in 'chemo-ineligible' for other new technologies

Abiraterone more effective than ADT alone but data too limited to determine ICER

Use whole population STAMPEDE & LATITUDE data as proxy because:

1. Trial participants frequently fitter than general population
2. Treatment effect maintained in STAMPEDE cohort including 'chemo-ineligible'
3. No biological reason for efficacy difference in people who cannot have chemotherapy

Company: not justified to request data for 'chemo-ineligible' subgroup

"*Unsuitability for docetaxel*" not a:

- LATITUDE or STAMPEDE exclusion criteria
- Treatment effect modifier: different mechanism of action to docetaxel

ICR: "unfitness" for docetaxel not absolute: largely subjective within STAMPEDE population

Suitable proxy for 'chemo-ineligible' subgroup

Concerns about using subgroup data to represent this population

Proxy	Hazard ratio (95% confidence interval)	ACD conclusion	Stakeholder comments
Age years STAMPEDE		*Increasing age not only risk factor for docetaxel intolerance*	**Company**: non-metastatic patients included: fewer deaths as generally younger, earlier stage • No mention of age or frailty in ACD
<70	0.51 (0.40, 0.65)		
≥70	0.94 (0.69, 1.29)		
Age years LATITUDE			**Company:** interaction not significant (p = 0.42) **PCUK:** small sub-groups, high uncertainty. • Confounded: increasing age = more co-morbidities, poorer health status.
<65	0.65 (0.50, 0.84)		
≥65	0.68 (0.55, 0.83)		
≥75	0.86 (0.62, 1.21)		
ECOG in LATITUDE		*ECOG = 2 group small (n=40), interpret with caution*	**Company**: ECOG 2 subgroup too small to reliably detect treatment effect **PCUK:** Abiraterone RCTs in hormone-relapsed showed efficacy difference by ECOG, results for overall population accepted
0 & 1	0.64 (0.50, 0.75)		
2	1.42 (0.65, 3.08)		
STAMPEDE recruitment		*2013-14 data included people who had docetaxel: not only 'chemo- ineligible'*	**PCUK:** post Apr 2013 cohort included some 'chemo-ineligible' with increased frailty scores **ICR**: post Apr 2013: higher median age, upper age, ECOG status BUT more favourable results than when 'chemo-ineligible' excluded
Nov 11 - Jan 13	0.69 (0.53, 0.90)		
Apr 13 - Jan 14	0.59 (0.44, 0.78)		

‘Chemo-ineligible’ data sources considered

Multiple sources for further data considered by stakeholders; no appropriate sources available

Potential data source	Reason unavailable
Do a clinical trial specific to 'chemo-ineligible'	**ICR:** Demonstrated effective in these people when hormone relapsed • Unlikely to be funded
	Company: Unethical: abiraterone proven superior to ADT only
Extract data as per ACD ‘framework’ from STAMPEDE high risk metastatic population	**Company:** Not all characteristics in ACD framework collected in STAMPEDE
	PCUK: Not possible: many characteristics similar to trial exclusion criteria
Welsh and Scottish Cancer Registries	**PCUK:** No baseline characteristics recorded
Open Safely database	**PCUK:** Limited by Control of Patient Information notice Required evidence outside of scope
Systemic anti-cancer therapy database during COVID	**PCUK:** Few people started abiraterone during COVID • Doesn’t resolve clinical and cost effectiveness uncertainty in ‘chemo-ineligible’ subgroup
Clinician survey on expected benefit in subgroup	**PCUK:** Low clinician response rate

◉ *What is the best source of data for people who cannot/should not take docetaxel?*

Appeal: 22 points -16 dismissed, 6 upheld (bold)

Topic	Appellants/NICE number
Quality of Life (2)	Janssen 1a1a BUG 1a2
Overall survival including accounting for subsequent treatments (4)	BUG 2.4 BUG 2.5 BUG 2.1 BUG 2.6
Cannot take docetaxel (6)	**Janssen 1a2c - process** **Janssen 2.1 - perversity** **PCUK/TPC 2.1 - perversity** BUG 2.2 Janssen 1a3 Janssen 2.2
Subsequent Treatments (3)	Janssen 1a6 Janssen 1a7 BUG 2.3
Transparency (2)	**Janssen 1a4 - process** BUG 1a1
Non health objectives and COVID (2)	Janssen 1a1b BUG 1a4
Inequalities and discrimination (2)	**PCUK/TPC 1a1 - process** **BUG 1a3 - process**
Safety (1)	Janssen 1b8

6 upheld appeal points addressed in ACD

***ACD 3.24**: "The points upheld in appeal are addressed"*

Appeal point	ACD	Addressed by:
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 earlier appraisal of Radium-223 (technology appraisal 412)	3.3	Framework developed to identify people who cannot take docetaxel
Recommendation unreasonable in light of evidence submitted to NICE concerning effectiveness of abiraterone in patients who cannot receive docetaxel.		
Committee's conclusion "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" unreasonable in context of available evidence.		
Committee's conclusions on cost effectiveness opaque because it did not provide ICER range	3.21	Figure stated above which ICER lies
NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision	3.23	Call for further information in 'chemo-ineligible' subgroup: none presented
Failure of the Committee to consider STAMPEDE group's recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision		

Appeal point: PCUK

"the committee's conclusions on cost effectiveness are opaque because it did not provide an ICER range".

ACD included statement:

- Over £100,000 per quality-adjusted life year (QALY) gained when compared with docetaxel in combination
- Over £30,000 per QALY gained compared with ADT alone
- Not possible to publish a narrow range because the ICERs using list prices have been previously published and the company stated that this would allow back calculation of its discount for abiraterone

Cost-effectiveness results

All estimates of incremental cost effectiveness ratios are reported in PART 2 slides because they include confidential PAS discounts for comparators;

They are unchanged from 4th committee meeting