Committee slides [ACIC]

NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Chair presentation

Chair: Amanda Adler
Technology Appraisal Committee B
Lead team: Anna Pracz, Rhiannon Owen, Nigel Westwood
ERG: Southampton Health Technology Assessments Centre
Technical team: Harsimran Sarpal, Aminata Thiam, Carl Prescott, Henry Edwards
Company: Janssen-Cilag
7th July 2021– 3rd meeting

Recommendation in Appraisal Consultation Document (ACD)

Apalutamide plus androgen deprivation therapy (ADT) **not recommended** for treating prostate cancer in adults with:

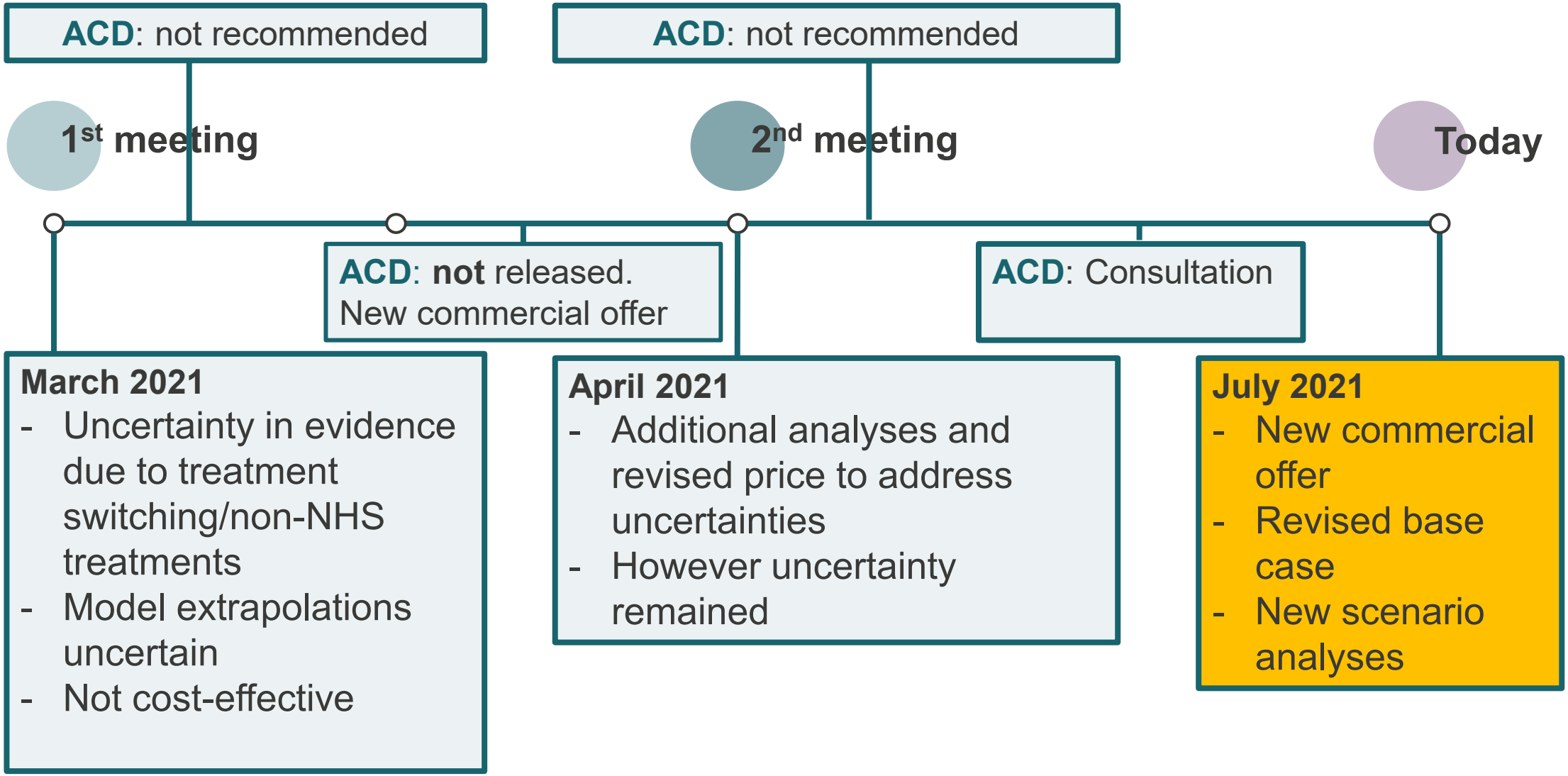
- non-metastatic disease hormone-relapsed at high risk of metastasising
- metastatic hormone-sensitive disease

Apalutamide (Erleada, Janssen)

Marketing authorisations	In adult men – in combination with androgen deprivation therapy (ADT) for: 1. Non-metastatic castration-resistant* prostate cancer **at high risk** of developing metastatic disease *(Jan 2019)* 2. Metastatic hormone-sensitive prostate cancer *(Jan 2020)* ***NOTE: committee considered indications separately***
Mechanism	Androgen receptor antagonist
Administration & dose	Oral; 240 mg single daily (4 x 60mg tablets)
Treatment discontinuation	Administered until disease progression or unacceptable toxicity
Price	List price: £2,735 per pack of 112 tablets Patient access scheme (PAS) discount in place (confidential)
*Also known as hormone-relapsed	

History of appraisal

2 previous committee meetings



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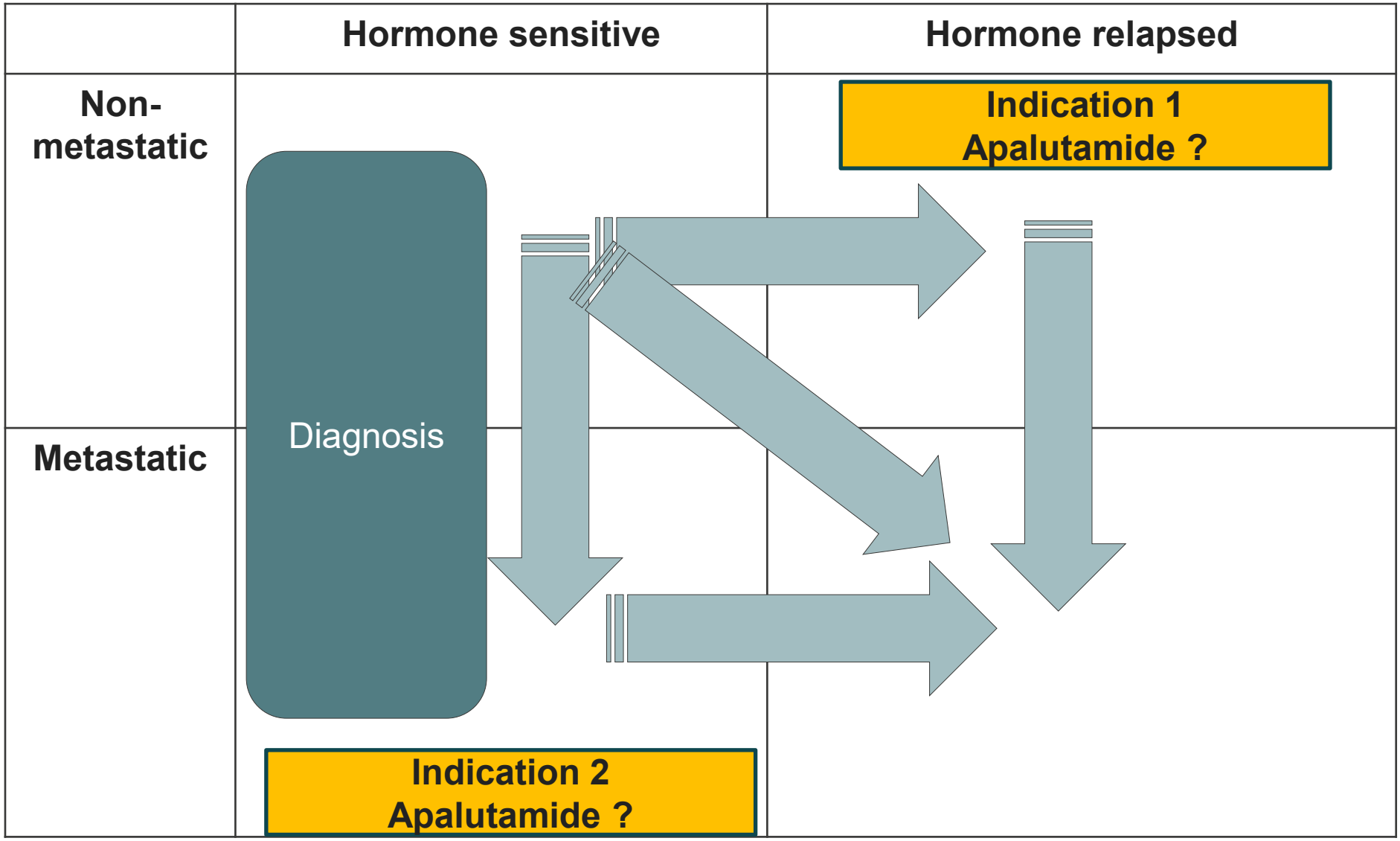
ACD, appraisal consultation document

Prostate cancer – diagnosis and progression

By metastatic or not, and responsiveness to hormone therapy

Hormone relapsed defined by response to treatment

Apalutamide has 2 indications – committee will address separately



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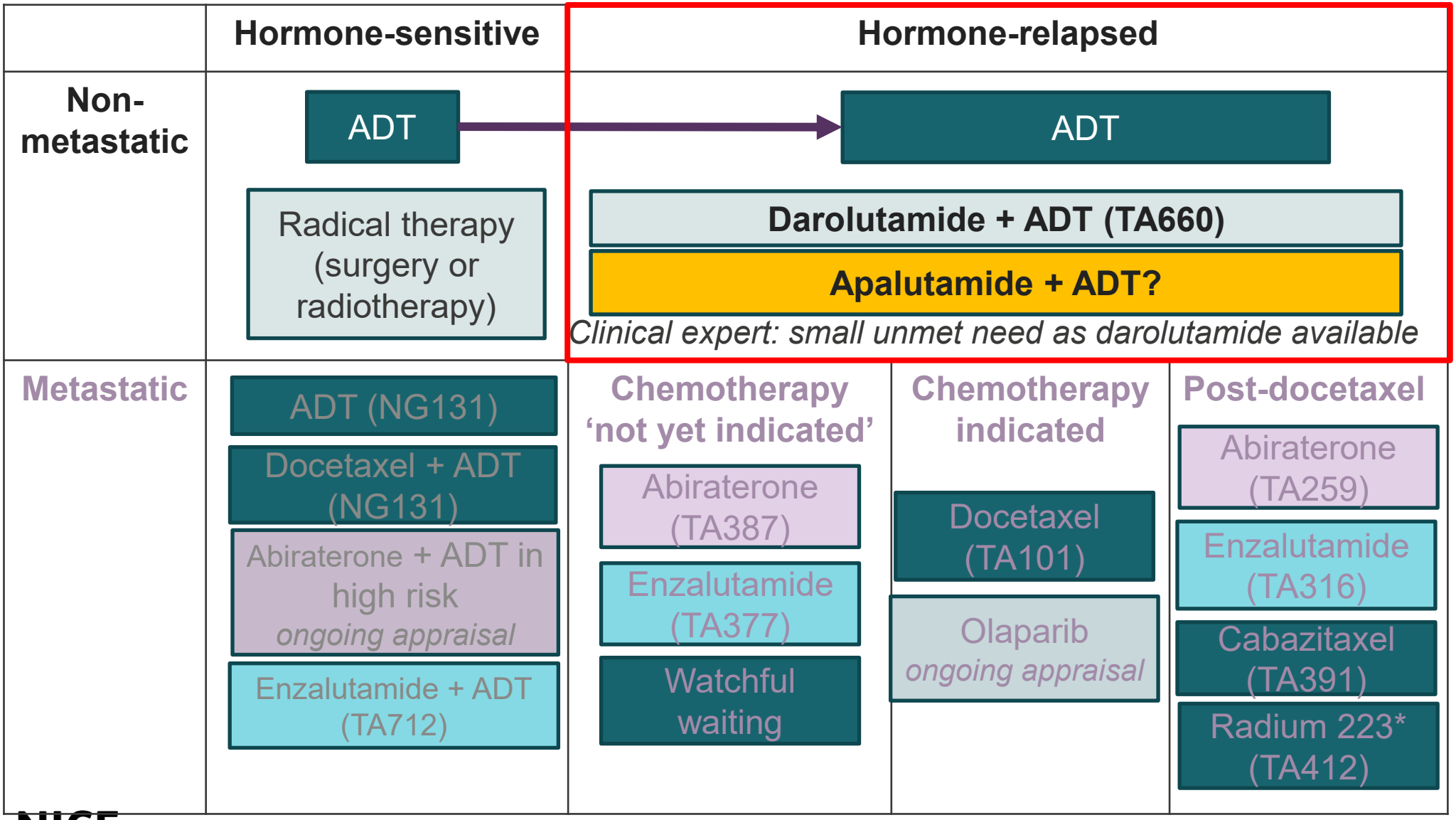
Non-metastatic Hormone-relapsed (‘upper right’)

Treatment non-metastatic, hormone-relapsed

ACD: ADT alone is comparator

Darolutamide not in clinical practice at start of this appraisal



NICE

TA, technology appraisal, NG NICE guideline, ADT, androgen deprivation therapy

*bone metastasis only

Appraisal Consultation Document (ACD): Apalutamide plus ADT not recommended

Why committee made these recommendations

- Clinical trials suggested benefit, but amount of benefit uncertain because:
  - Treatment switching from comparator to intervention arm after progression
  - People in clinical trials could have non-NHS treatments and thus any associated benefits/adverse events
  - Choice of statistical method to adjust for this uncertain
- Model extrapolations uncertain:
  - Metastases-free survival: should explore more flexible models
  - PFS2: based on immature data
- Because of uncertainty, ICER “in the middle of the range” £20-30k

Recap: clinical and cost effectiveness

SPARTAN trial

ACD: SPARTAN is appropriate for decision making

- Phase III, placebo-controlled, multinational (26 countries including UK)
- Cross-over allowed after study unblinding, at final analysis for metastases-free survival May 2017
- Patients received subsequent therapies for metastatic disease
- Company adjusted cost effectiveness results on overall survival and progression free survival on 1st subsequent treatment (PFS2) in model

Population N=1207
- **Non-metastatic**
- High risk of metastasising =
- PSA doubling time ≤ 10 months
- Hormone-relapsed
- 3 PSA rises at least 1 week apart, with last PSA > 2 ng/mL
- ECOG performance status

R 2:1

Apalutamide 240mg daily + ADT n=806

Placebo + ADT n=401

1º endpoint
- Metastases-free survival (MFS)= time to metastases or death ▲

2º endpoint incl.
- Overall survival (OS) ▲
- Time to metastasis

Other endpoints incl. progression free survival on 1st subsequent treatment (PFS2▲); quality of life (EQ-5D-3L, FACT-P)

Analyses:
1. May 2017 – ***final analysis for MFS***
2. May 2019
3. Feb 2020 – ***final for OS and PFS2***

▲ *Endpoints inform economic model*

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ECOG: Eastern Cooperative Oncology Group; PSA: prostate specific antigen

SPARTAN: results for apalutamide + ADT vs comparator

Apalutamide + ADT is clinically effective compared with placebo + ADT

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1º metastases-free survival	Apalutamide + ADT N=806	Placebo + ADT N=401
Median MFS months (95% CI)	40.5 (29.7 to 40.5)	15.7 (14.6 to18.4)
Events, n (%)	209 (25.9)	210 (52.4)
Hazard ratio	0.30 (0.24 to 0.36), p<0.0001	

2º overall survival	Apalutamide + ADT	Placebo + ADT
Median OS months (95% CI)	73.9 (61.2 to NE)	59.9 (52.8 to NE)
Events, n (%)	274 (34.0)	154 (38.4)
Hazard ratio	0.78 (0.64 to 0.96), p=0.0161	

2º progression-free survival on 1st subsequent treatment	Apalutamide + ADT	Placebo + ADT
Median PFS2 months (95% CI)	55.6 (53.0 to 61.7)	41.2 (37.8 to 46.6)
Events, n (%)	319 (39.6)	190 (47.4)
Hazard ratio	[redacted]	

NICE

ACD, appraisal consultation document; ADT, androgen deprivation therapy; CI, confidence interval; MFS, metastases-free survival; OS, overall survival; PFS2, progression-free survival on 1st subsequent treatment

SPARTAN: adjusting overall survival + 'PFS2' for crossovers and non-NHS practice

Trial impacted by (and adjusted for) crossover and non-NHS practice

- 'Modified' RPSFTM used
- **Crossover**: SPARTAN: 19% (76/401) on placebo + ADT → apalutamide + ADT
- **Could receive >1 new hormonal agents** following disease progression, e.g. abiraterone or enzalutamide.
  - Not NHS England commissioning policy
  - **Exposure to subsequent treatments:**
    - Apalutamide + ADT: 371 (46.0%); [includes [redacted] abiraterone, [redacted] enzalutamide]
    - Placebo + ADT: 279 (69.6%) [includes [redacted] abiraterone, [redacted] enzalutamide]

Whole population	Unadjusted	Adjusted
OS: HR (95% CI)	0.78 (0.64 to 0.96); p = 0.0161	0.77 (0.64 to 0.94); p-value NR
PFS2: HR (95% CI)	[redacted]	[redacted] p-value NR

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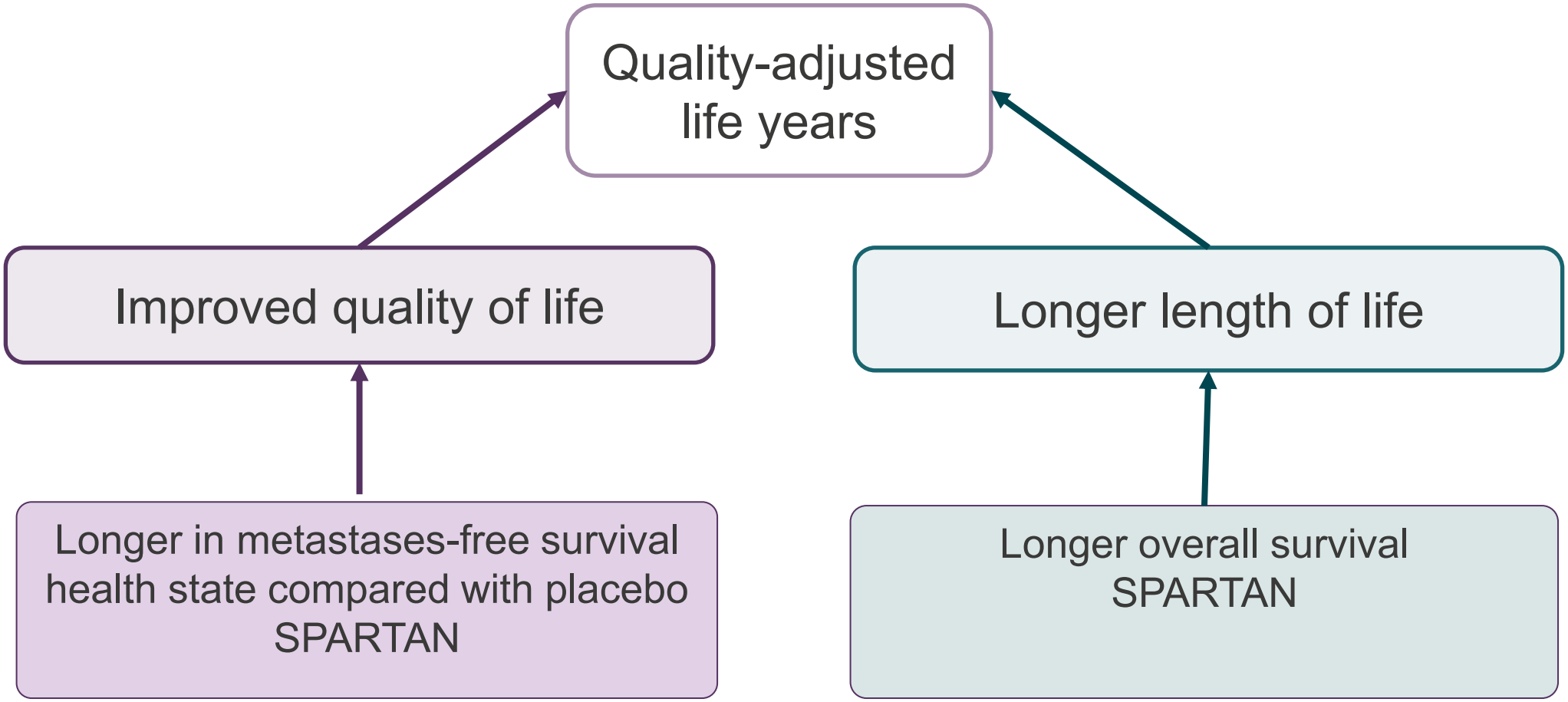
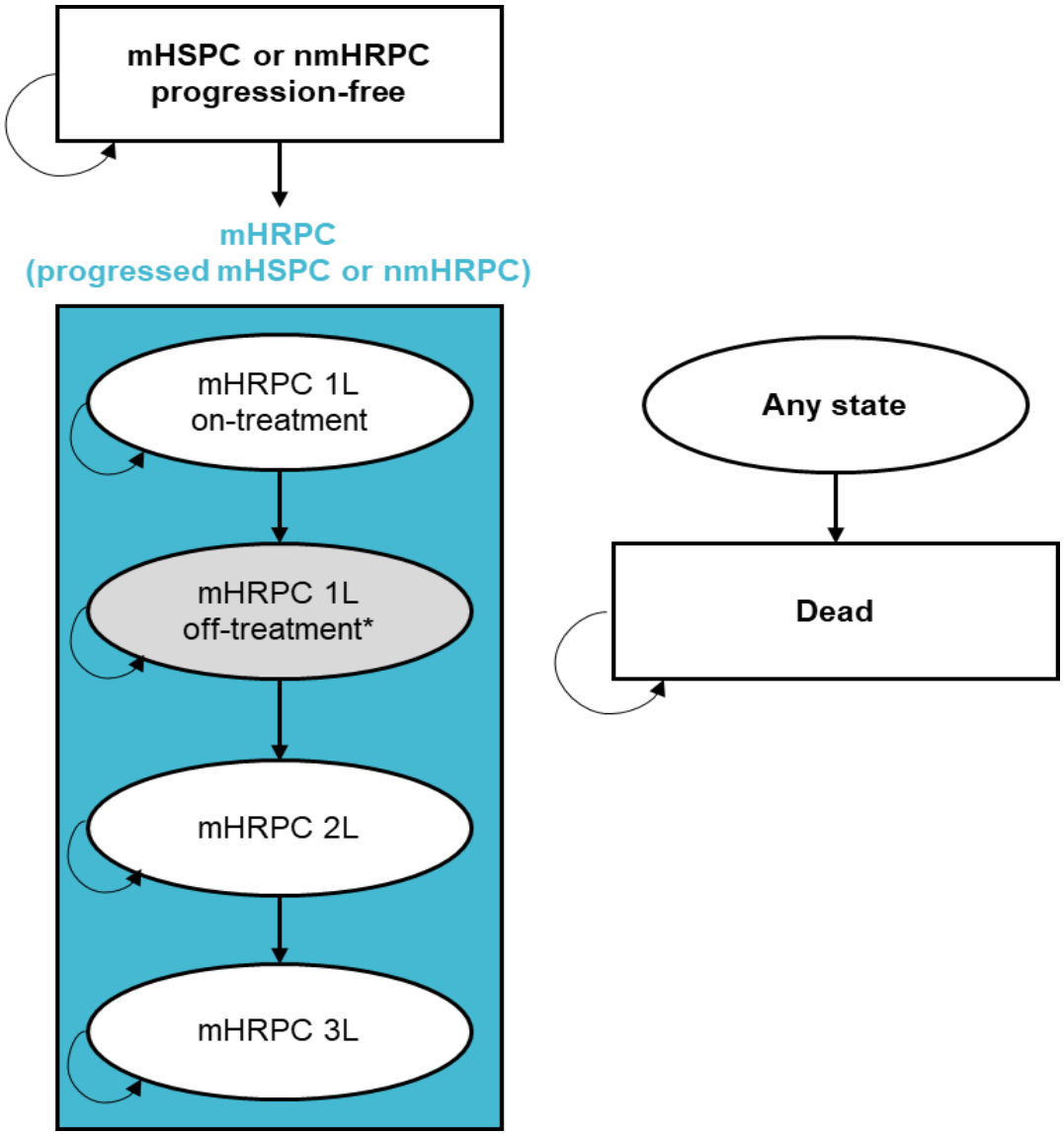
ADT: androgen deprivation therapy; HR: hazard ratio; IPCW: Inverse probability of censoring weighting OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; RPSFTM: rank preserving structural failure time model

How quality-adjusted life years accrue in company's model

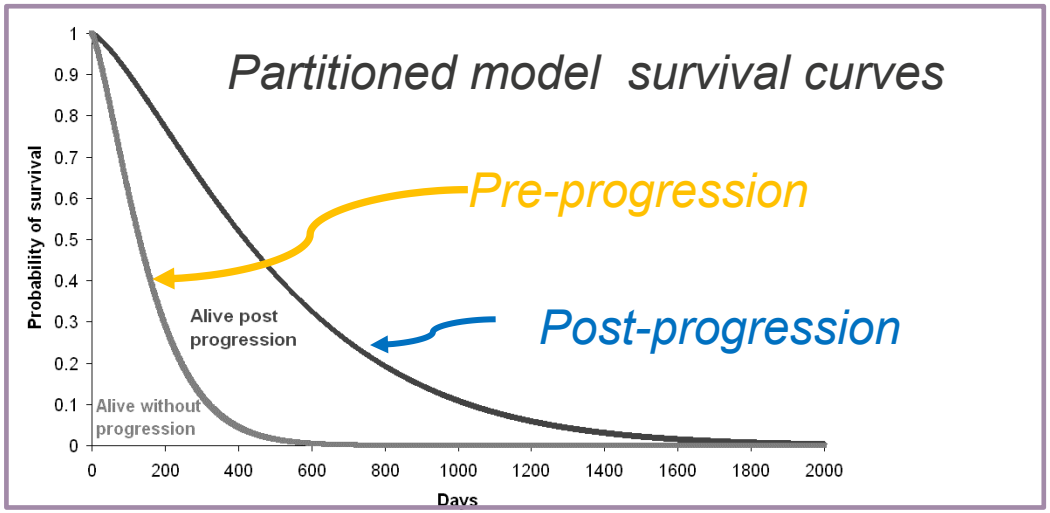


Company model to estimate cost effectiveness

ACD: Model structure appropriate for decision making



- Partitioned survival model then multiple health states for subsequent therapies
- Patient can receive up to 3 lines of subsequent therapy
- Efficacy from extrapolated MFS and OS from SPARTAN
- 1-week cycle
- Lifetime horizon (32 years)
- 3.5% discounting



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1L: first-line; 2L: second-line; 3L: third-line; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.

ACD conclusions + uncertainties (1/3)

Non-metastatic hormone-relapsed disease

Topic	Committee conclusion	To discuss	ACD
Treatment Pathway	• Only 1 'newer androgen receptor inhibitor' would be used in NHS prostate cancer treatment pathway	No	3.1
Unmet need	• Less unmet need for non-metastatic hormone-relapsed than for non-metastatic hormone-sensitive	No	3.2
Clinical management	• Treatment aims to delay metastasis • People would welcome additional option	No	3.3, 3.4
Clinical effectiveness	• Apalutamide plus ADT extended or improved: metastases-free survival, overall survival, PFS2 and health-related quality of life, vs placebo plus ADT	No	3.6, 3.7
Adjusting for crossover/2nd novel	• Address uncertainties of 'modified' RPSFTM, or • Explore other methods in more detail	Yes	3.8

ACD conclusions + uncertainties (2/3)

Non-metastatic hormone-relapsed disease

Topic	Committee conclusion	To discuss	ACD
Adjustment for 2nd novel: using COU-AA-302 (abiraterone) trial	• Using COU trial to adjust apalutamide for impact of >1 novel drug would over-adjust, because COU population had only 1 novel drug • Approach is uncertain so adjustment may not be needed. Explore: With/without adjusting for survival benefit of 2nd newer androgen receptor inhibitor; with adjusting for costs of treatment not offered in NHS	Yes	3.9, 3.10
Adjusted and unadjusted hazard ratios for overall survival and PFS2	• Adjusting for crossover from placebo to apalutamide assumes placebo patients would not get 1st novel treatment in NHS, yet they would – should explore	Yes	3.11, 3.12
Generalisability	• SPARTAN generalisable	No	3.13
Safety profile	• Adverse effects with apalutamide are tolerable	No	3.20

ACD conclusions + uncertainties (3)

Non-metastatic hormone-relapsed disease

Topic	Committee conclusion	To discuss	ACD
Model structure	• Model structure appropriate	No	3.21
Extrapolation MFS/OS/PFS2	• MFS: Explore more flexible model • OS and PFS2: extrapolation uncertain	Yes	3.22-3.24
Treatment waning	• Likely small impact on cost-effectiveness	No	3.28
Treatment costs	• Cost of apalutamide might have been underestimated	Yes	3.29
Utility values	• Unadjusted (for 'relative decline ratio') utility values most appropriate for decision making • *N.b. company base case now includes committee-preferred approach*	No	3.30
Cost-effectiveness estimates	• Not cost effective - ICER should be in the "middle of the range" of £20-£30k • ERG's analyses better reflected committee's preferences	Yes	3.35-3.37
Innovation	• Apalutamide not innovative	Yes	3.42

Summary of responses to appraisal consultation document

Non-metastatic hormone-relapsed prostate cancer

ACD consultation responses

Company

- Janssen
  - New commercial offer
  - Revised base case
  - No new evidence

Web comments

- No web comments

Patient & Professional

- **Prostate Cancer UK**
- **British Uro-oncology Group (BUG)**

Company provides new scenarios to address committee concerns:

- Unadjusted for 2nd novel therapy and cross-over
- Adjusted only for treatment switching and not cross-over
- Time on treatment equal to progression free survival

Patient and clinical organisation comments

Non-metastatic hormone-relapsed prostate cancer

New choice of treatment

- Darolutamide (NICE TA660) approval important for non-metastatic hormone relapsed prostate cancer, but clinicians and patients experts would welcome choice of apalutamide
- Economic modelling uncertainties "would apply similarly" to assessment for darolutamide. "If anything, the follow-up of the SPARTAN trial is significantly longer than the ARAMIS (darolutamide) trial and therefore likely to reduce the uncertainties in the economic modelling".

Innovation

- "Concerned by the committee's consideration of innovation"
- **Darolutamide excluded as comparator** yet used as reason to deny innovation – inconsistent
- "The committee should treat the submission of the treatment as a "**freeze in time**" and base all decisions on provision at that time."

◉ *Should committee 'freeze in time'? Comparators don't change but other inputs do*

Company: NICE error post-progression survival

ACD conclusions:

- Committee wants company to:
  - justify difference in post-progression survival between treatments
  - scenarios including = post-progression survival between treatments
  - *N.b ADT alone already longer post progression survival than apalutamide*

Company: factual inaccuracy NICE slides (confirmed by ERG):

- Values were incorrect
- Feedback from UK clinical experts: plausible that apalutamide + ADT would result in a significant post-progression survival benefit
- Company also presented scenario where post-progression survival = between treatment arms

Life-year before and after progress in NICE slides and company model MFS- Weibull

◉ *Are company's values plausible? Coherent with other indication?*

ACD, appraisal consultation document; ADT, androgen deprivation therapy: MFS- metastatic progression-free survival

Company: Adjusting for cross-over and 2nd newer agent

Company: modified RPSFTM reliable, other options not feasible

ACD: Committee wants company to:

- Explore other methods in more detail
- Consider uncertainties of modified RPSFTM such as:
  - Costs of treatment not offered in the NHS
  - Unadjusted PFS2 in COU-AA-302 trial

Company: maintains modified RPSFTM reliable, and other methods not viable and not feasible to re-explore within existing timelines. Instead noted:

- **Costs of treatments not offered in the NHS** – company not clear why committee state costs of treatment are an "uncertainty of the modified RPSFTM approach"; subsequent treatments and their sequencing reflect NHS practice
- **Appropriate to adjust for crossover?** – crossover driven by unbinding not progression. In SPARTAN 19% of patients crossed over, so OK to adjust. Scenarios explored.
- **Using unadjusted PFS2 in COU-AA-302 trial** – no risk of bias from crossover as the COU-AA-302 used to adjust SPARTAN not impacted by crossover
- **Impact of over adjusting for subsequent novel agent use** – company agrees with committee using COU-AA-302 data may over adjust outcomes

NICE ◉ *Does the committee consider modified RPSFTM to be appropriate?*

ACD, appraisal consultation document; PFS2, Secondary progression free survival on; RPSFTM: rank preserving structural failure time model

ERG: Adjusting 2nd newer receptor inhibitor

ERG: considerably bigger impact on PFS2 than overall survival

ERG:

- Reiterated adjusting SPARTAN PFS for cross-over in COU-AA-302 have more pronounced effect on HRs than OS; would likely increase cost-effectiveness estimates
- Noted that the independent data monitoring committee (IDMC) recommended unblinding the study and allowing cross-over from the placebo arm to active therapy
- 17% (93 out of 542) initially enrolled in the placebo arm went on to receive abiraterone. No reason to believe that PFS was not affected by treatment cross-over

◉Should company adjust SPARTAN for cross-over, or not? And for 2nd novel agent, or not?
◉ Should company adjust COU-AA-302 trial PFS2 for cross-over?
◉ Is it reasonable to use the COU-AA-302 trial for adjustment?

ACD, appraisal consultation document; HR, hazard ratio; OS, overall survival; PFS, progression free survival; PFS2, progression-free survival on 1st subsequent treatment; RPSFTM, rank preserving structural failure time model

Company: Extrapolating beyond trial re flexible modelling

ERG: parametric survival curves do not provide a close enough fit

Company has assumed ERG scenario

ACD conclusions:

- Committee wants to see more flexible model fitted because of uncertainty

Company: maintains extrapolations are appropriate

- Committee request possibly driven by NICE's error on post-progression survival
- Existing standard parametric approaches imperfect but appropriate:
  - Informed by clinical experts; (we) chose pessimistic ('conservative') curves
  - No indication of hazards in either treatment arm changing distinctly at any point
  - Visual inspection of the Kaplan-Meier data also shows there is no indication of the hazard function distinctly changing over time, with patients experiencing PFS, PFS2 and OS events at a relatively constant rate
    - *N.B. Committee's statement motivated by looking at curves*

ERG:

- Reiterated that committee requested flexible models because parametric survival curves did not provide a close enough fit for the long-term estimates of MFS
- Would also have liked to see alternative scenarios using flexible modelling that fits more closely to ERG's clinical experts' opinion

◉ *Committee response to not being presented with request?*

Company ACD comments: Modelled cost of apalutamide

Company: costs are captured fully, unlike committee opinion

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ACD conclusions:

- Cost in model are minimum of either time-to-treatment discontinuation (TTD) until progression, or metastases free survival curves
- Company may have underestimated cost of apalutamide

Company's ACD response:

- Maintains costs are **captured fully**
  - TTD and PFS curves converge over time; convergence causes some extrapolations to cross
  - Treat to progression only, so modelled based on minimum of TTD and PFS extrapolations
  - Cost may be over-estimated, as people could discontinue due to disease progression and other reasons

ERG ACD response:

- Cost of apalutamide not underestimated
- Appropriate to cap costs assuming there are no more patients on treatment than remain progression-free

SPARTAN apalutamide KM curves: MFS and TTD

◉ *Why would costs be 'overestimated'?*

ACD: appraisal consultation document; ADT, androgen deprivation therapy, ERG, evidence review group; PFS, progression free survival; SmPC, summary of product characteristics; TTD, time-to-treatment discontinuation; TOT, time on treatment

Company revised base case assumptions for 3rd committee meeting

Company updated base case includes:
• Adjusting for treatment switching and 1 novel therapy restriction
• Using unadjusted utility values for second-line and third-line hormone-relapsed metastatic prostate cancer

Scenario analysis
• Unadjusted for treatment switching, non-NHS treatments
• Adjusted only for treatment switching and not cross-over
• Modelled cost of apalutamide ('crossing curves'): Time on stopping treatment equal to progression free survival

Innovation and equality

Innovation:

- ACD: Apalutamide not innovative for non-metastatic hormone relapsed prostate cancer

Equality

- ACD: Recommendations apply to all people with prostate cancer

Responses:

Innovation

- Patient group: darolutamide excluded as comparator yet used as reason to deny innovation

Equality

- No further issues raised

◉ *Is apalutamide innovative for non-metastatic hormone-relapsed prostate cancer?*

Committee preferences vs company base case

Red not addressed by company

- Company's revised base includes committee's preferred assumptions which are also ERG preferred assumptions

Issues	Committee preference	Company and ERG base case
Adjusting for crossover/2nd novel: method used	Would like company to explore alternative methods	• No change: ('modified' RPSFTM retained in base case)
Adjusting for crossover/2nd novel: Explore with/without	Would like company to explore with/without adjustment	No change. Explored • Unadjusted for 2nd novel therapy and cross-over • Adjusted only for novel therapy and not cross-over
Extrapolating curves	• MFS: Weibull used by company; explore flexible • PFS2: Weibull • OS: generalised gamma	• MFS: No change • PFS2: Weibull • OS: generalised gamma
Utilities	TA377 (enzalutamide)	✓
Treatment waning	Small impact on results	• No change: No treatment waning
Apalutamide costs were *minimum* of TTD or MFS – capped & so possibly underestimated	No action suggested but some uncertainty noted	• No change to base case (argued costs not underestimated • Scenario presented: Time on treatment equal to PFS
Costs of non-NHS drugs	Exclude	• No change: was never included

HR, hazard ratio; MFS, metastases-free survival; OS, overall survival; PFS2, progression-free survival on 1st subsequent treatment; RPSFTM, rank preserving structural failure time model; TA, technology appraisal

Cost-effectiveness results

All ICERs are reported in PART 2 slides because of confidential agreements information

Metastatic, hormone-sensitive (“lower left”)

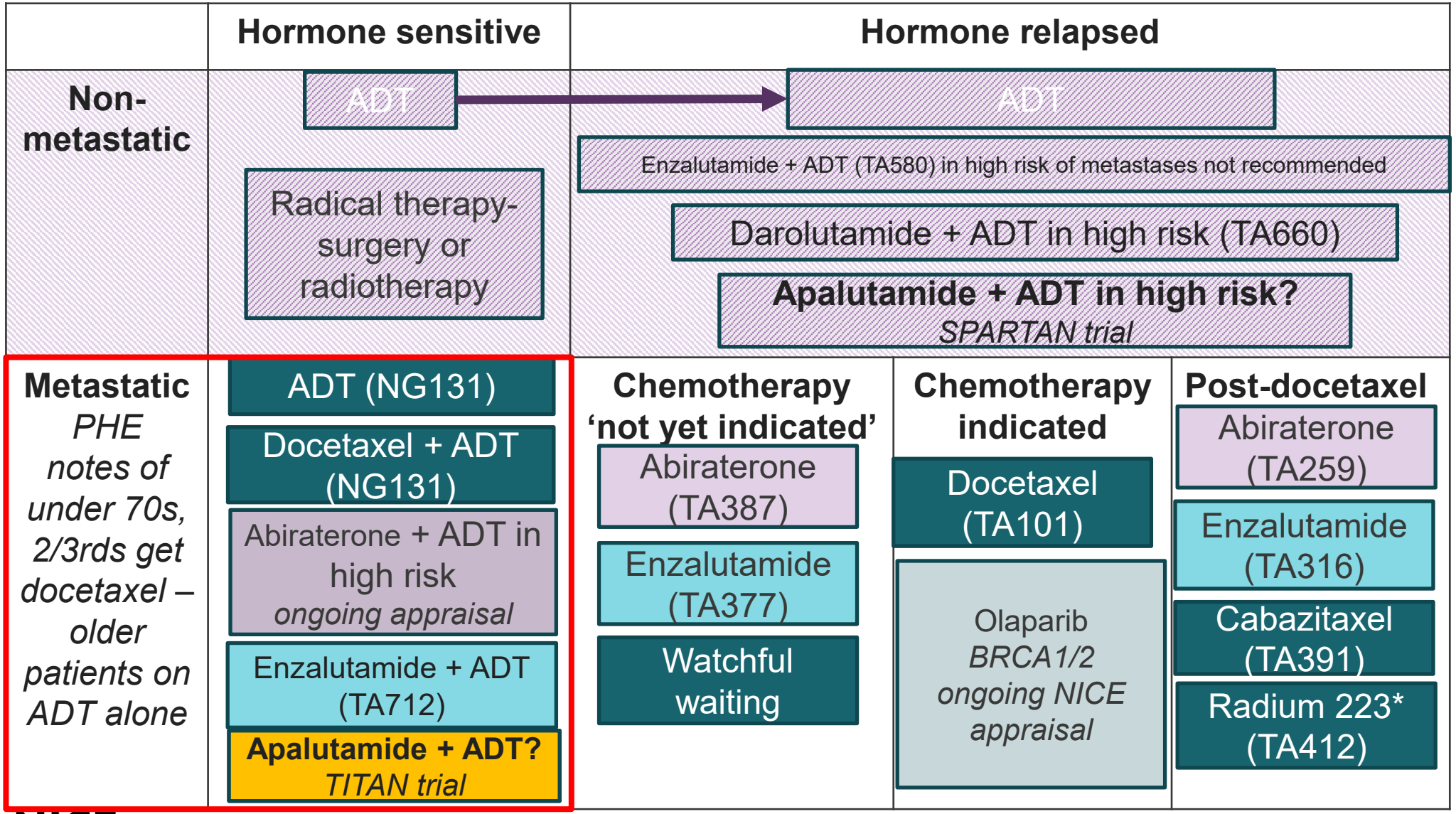
Appraisal Consultation Document (ACD): Apalutamide plus ADT not recommended

Why committee made these recommendations

- Amount of benefit uncertain because:
  - Treatment switching
  - People in clinical trials could have non-NHS treatments
  - Choice of adjustment used to account for the above
- Model extrapolations uncertain:
  - Radiographic progression-free survival and overall survival: more flexible models should be explored
  - PFS2: based on immature data
- Because of uncertainty, ICER should be “middle of range” £20-30k

Treatment pathway for prostate cancer

Comparators: ADT alone - only one if cannot take docetaxel - and docetaxel plus ADT
Docetaxel can be offered twice; abiraterone OR enzalutamide only once



NICE

PHE, Public Health England, TA, technology appraisal, NG NICE guideline, ADT, androgen deprivation therapy

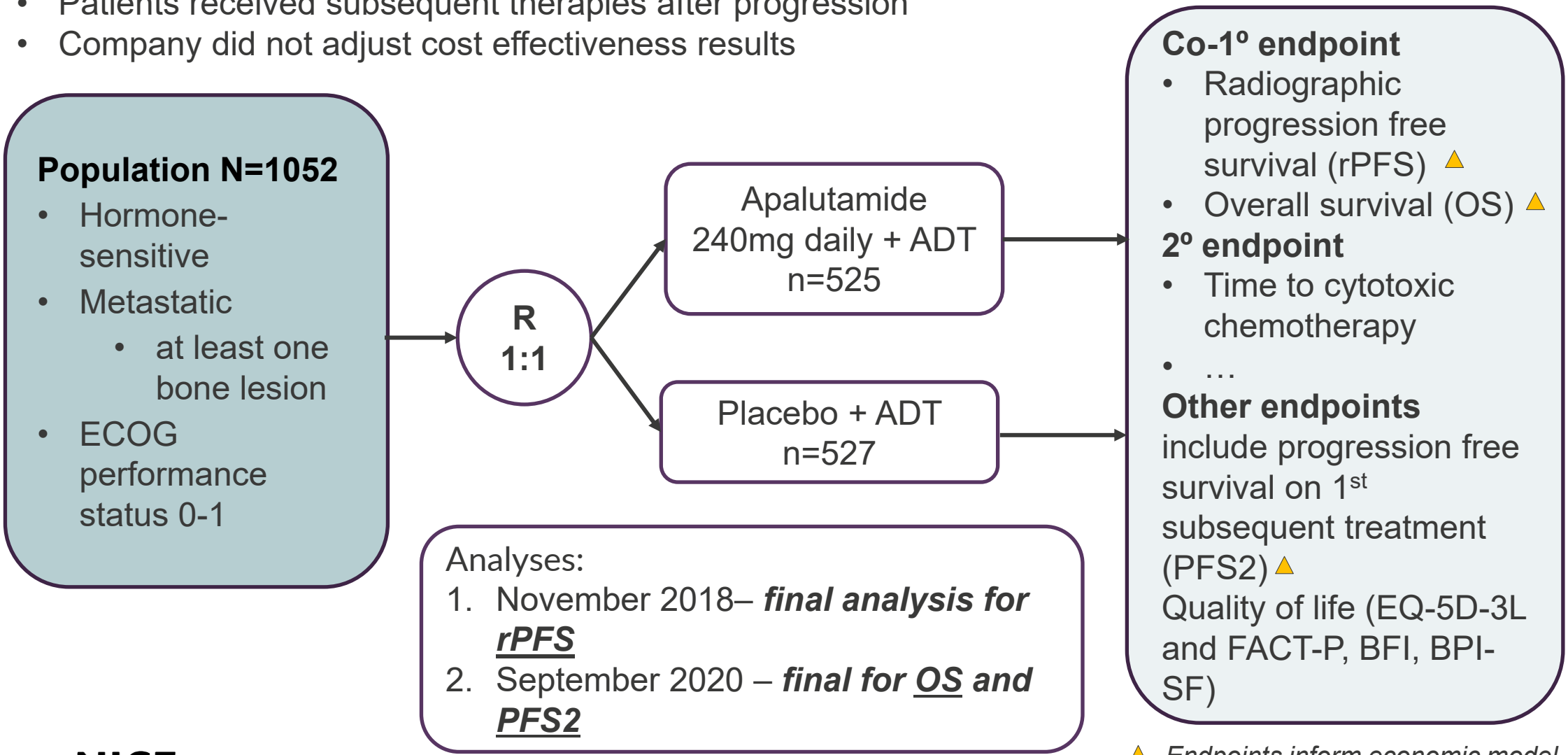
*bone metastasis only

Recap: clinical and cost effectiveness

TITAN trial

ACD: TITAN appropriate for decision making

- Phase III, placebo-controlled, multinational
- Cross-over allowed after study unblinding, at final analysis for radiographic progression free survival
- Patients received subsequent therapies after progression
- Company did not adjust cost effectiveness results



▲ *Endpoints inform economic model*

NICE

EQ-5D-3L: EuroQoL five-dimensions – three levels; FACT-P: Functional Assessment of Cancer Therapy Prostate Module, BFI: Brief Fatigue Inventory, BPI-SF: Brief Pain Inventory -short form

TITAN trial outcomes

ACD: Apalutamide + ADT is effective compared with placebo + ADT

1º co-primary radiographic progression free survival (rPFS)	Apalutamide + ADT N=525	Placebo + ADT N=527
Median rPFS months (95% CI)	NE (NE to NE)	22.1 (18.5 to 32.9)
Events, n (%)	134 (25.5)	231 (43.8)
Hazard ratio	0.5 (0.4 to 0.6), p<0.0001	

1º co-primary overall survival	Apalutamide + ADT	Placebo + ADT
Median OS months (95% CI)	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio	[redacted]	

2º progression-free on 1st subsequent treatment	Apalutamide + ADT	Placebo. + ADT
Median PFS2 months (95% CI)	NE (NE to NE)	NE (45.8 to NE)
Events, n (%)	153 (29.1)	200 (37.9)
Hazard ratio	0.7 (0.5 to 0.9), p<0.0001	

ACD, appraisal consultation document; ADT, androgen deprivation therapy; CI, confidence interval; MFS, metastases-free survival; NE: Not estimable; OS, overall survival; PFS2, progression-free survival on 1st subsequent treatment

Source: CS Figure 23 p 111

Company used 'modified' RPSFTM to adjust overall survival and PFS2 for treatment switching

Crossovers: **TITAN:** [redacted] in placebo + ADT → apalutamide + ADT

ITT population	Unadjusted	Adjusted (final analysis)
OS: HR (95% CI)	[redacted]	[redacted]
PFS2: HR (95% CI)	[redacted]	[redacted]

Could receive >1 new hormonal agents following disease progression, e.g. abiraterone or enzalutamide.

- Against NHS England commissioning policy
- Exposure to subsequent treatments:
  - Apalutamide + ADT: [redacted]; [including : [redacted] abiraterone, [redacted] enzalutamide]
  - Placebo + ADT: [redacted] [including: [redacted] abiraterone, [redacted] enzalutamide]

Committee in ACD: Address uncertainties of modified RPSFTM, costs of treatments not offered in the NHS and unadjusted PFS2

ADT: androgen deprivation therapy; HR: hazard ratio; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; RPSFTM: Rank Preserving Structural Failure Time Model

Compared with docetaxel + ADT, overall survival

Network meta-analysis show that apalutamide + ADT offers an advantage

Comparison OVERALL SURVIVAL		Fixed effect company base case
ADT alone	HR (95% CrI)	[redacted]
	Probability that HR <1	[redacted]
Docetaxel + ADT	HR (95% CrI)	[redacted]
	Probability that HR <1	[redacted]

ACD: Apalutamide plus ADT offers an advantage over docetaxel plus ADT for efficacy and safety

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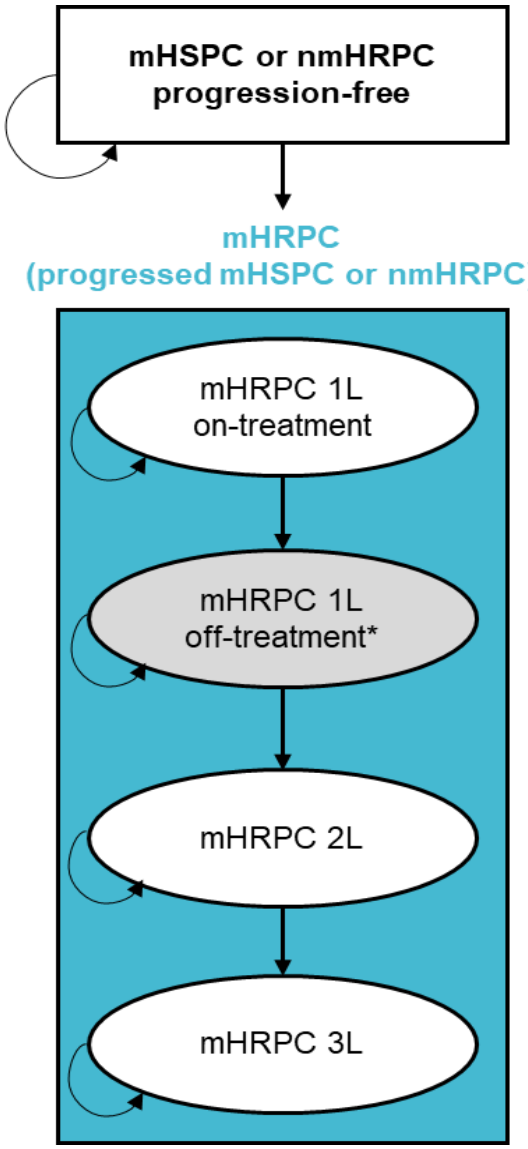
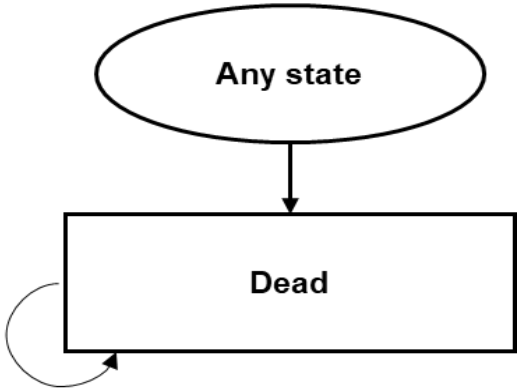
ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival

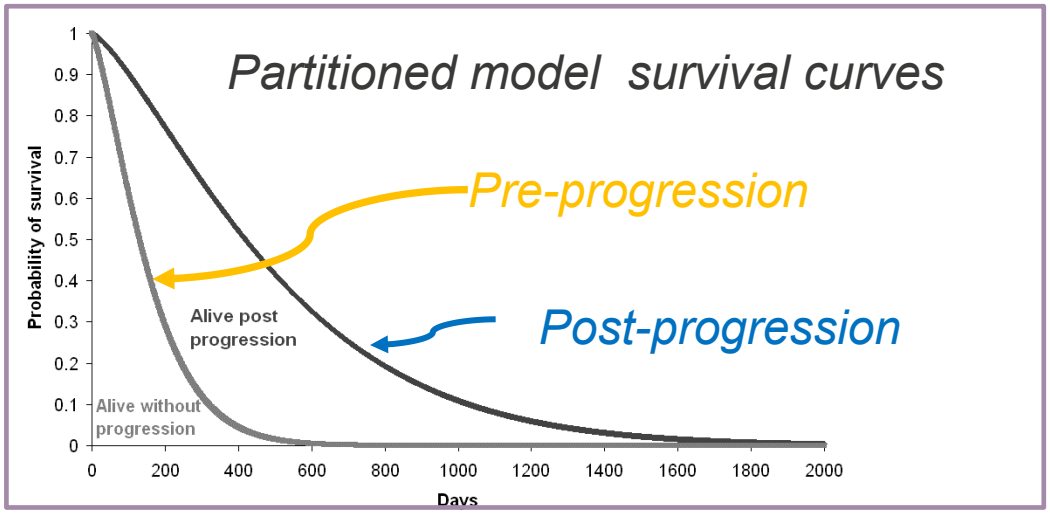
Company model to estimate cost effectiveness

ACD: Model structure appropriate for decision making





- Partitioned survival model then multiple health states for subsequent therapies
- Patient can receive up to 3 lines of subsequent therapy
- Efficacy from extrapolated MFS and OS from SPARTAN
- 1-week cycle
- Lifetime horizon (32 years)
- 3.5% discounting



NICE

1L: first-line; 2L: second-line; 3L: third-line; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.

ACD conclusions + uncertainties (1/3)

Metastatic hormone-sensitive prostate cancer

Topic	Committee conclusion	To discuss	ACD
Treatment Pathway	• In NHS, only 1 newer androgen receptor inhibitor	No	3.1
Unmet need	• Greater unmet need for metastatic prostate cancer than for non-metastatic cancer (n.b. at time of writing)	No	3.2
Clinical management	• People would welcome more treatments options	No	3.3,3.4
Scope of the appraisal	• Consider full licence. If not cost-effective then will consider docetaxel ineligible; although no clinical evidence presented	Yes	3.5
Clinical effectiveness	• Apalutamide + ADT extended radiographic progression-free survival, overall survival, and PFS2 compared with ADT alone	No	3.14, 3.15

ACD conclusions + uncertainties (2/3)

Metastatic hormone-sensitive prostate cancer

Topic	Committee conclusion	To discuss	ACD
Adjusting for crossover and 2nd novel treatment	• Committee to consider both adjusted & unadjusted, including for costs of treatments not available in NHS • Company to explore other methods in more detail or address uncertainties of modified RPSFTM approach	Yes	3.16, 3.17
Indirect treatment comparison vs docetaxel	• Apalutamide may offers survival advantage over docetaxel	Yes	3.18
Generalisability	• TITAN generalisable	No	3.19
Model structure	• Model structure appropriate	No	3.21

ACD conclusions + uncertainties (3)

Metastatic hormone-sensitive prostate cancer

Topic	Committee conclusion	To discuss	ACD
Extrapolation of rPFS/OS/PFS2	• Would like to see more flexible model for extrapolations	Yes	3.25-3.27
Treatment waning	• Small impact on cost-effectiveness	No	3.28
Treatment costs	• Cost of apalutamide might be low	Yes	3.29
Utility values	• Unadjusted utility values most appropriate	Yes	3.30
Cost-effectiveness estimates	• Acceptable ICER <£25k. Apalutamide not cost effective for across marketing authorisation population or for people who cannot have docetaxel	Yes	3.35-3.37
Innovation	• Depends on ongoing appraisals for enzalutamide and abiraterone	Yes	3.43

Summary of responses to appraisal consultation document

ACD consultation responses

Company

- Janssen
  - New commercial offer
  - Revised base case
  - No new evidence

Web comments

- No web comments

Patient & Professional

- Prostate Cancer UK
- British Uro-oncology Group (BUG)

Company provides new scenarios to address committee concerns:

- Unadjusted for 2nd novel therapy and cross-over
- Adjusted only for 2nd novel therapy and not cross-over
- Assume equal post-progression survival
- Removing chemotherapy as a subsequent treatment
- Reducing the utility values by a decrement of 0.1
- Unadjusted subgroup analyses in locally advanced/primary progressive patients, low volume patients and chemotherapy-unsuitable patients

Patient and clinical organisation comments

Unmet need

- Majority of population do not want to have chemotherapy or are unsuitable for chemotherapy
- Provides alternative for people who do not tolerate enzalutamide – data from SACT and NHS England's interim guidance during COVID-19, where abiraterone is only offered if people are enzalutamide intolerant, suggests this is around 10%

Effectiveness

- For people who cannot take docetaxel, "committee should accept the effectiveness of apalutamide from whole-population' ..'rather than an older-age subgroup"
- '…presuming these patients are older and more unwell, is not justified – the population is broader than this in clinical practice'
  - *N.b. committee aware, had noted would not make age-defining guidance*

Innovation

- "..committee's consideration of innovation" has "**no logical basis**"
- **Treatment is either innovative or not**, and decision should be based on point at which topic was submitted – this cannot be determined retroactively based on other results

SACT: systematic anti-cancer therapy

Company ACD comments: Docetaxel ineligible population (1)

Company: multiple factors contribute docetaxel suitability

ACD conclusions:

- People cannot/should not or choose not to take docetaxel.
- Agree to use company's terminology of 'chemotherapy ineligible'.

Company:

- Multiple factors contribute for docetaxel suitability. Main groups who do not receive docetaxel including:

Subgroups	Justification
Metastasis stage at diagnosis of M0 (non-metastatic)	People do not meet the NHS England docetaxel commissioning policy requirement to "have newly diagnosed, metastatic prostate cancer
Low volume disease	Docetaxel not as effective in low volume disease, therefore not routinely offered to people in this subgroup
Baseline ECOG score of 1	3 "proxy sub-groups" selected to represent people with poor fitness and/ or co-morbidity that would make them '**unsuitable for treatment with chemotherapy**'
Over age 75	
ECOG score of 1 aged > 75 years	Clinical prognostic factors which do not meet NHS England docetaxel commissioning policy inclusion criteria

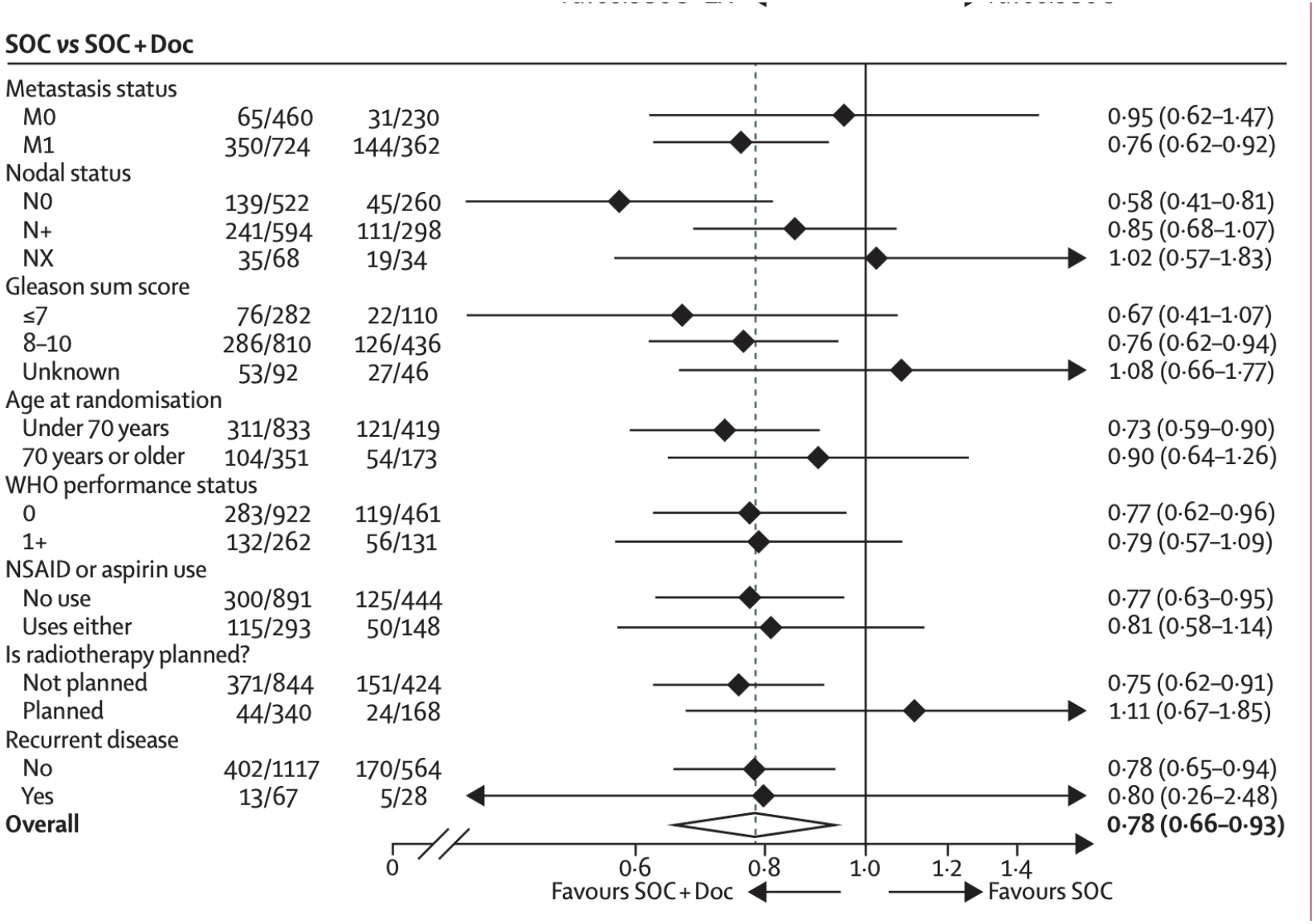
Definition of ECOG

widely used method to assess the functional status of a patient
NHS commissioning document on docetaxel considers WHO performance status 3 to 4 ''contraindication' and 'caution' for performance status 2

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf

ECOG 1 included in STAMPEDE docetaxel



◉ *Is ECOG 1 in line with evidence of people who are 'chemotherapy ineligible'?*

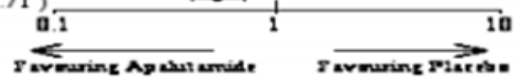
Company ACD comments: Docetaxel ineligible population (2)

Company: apalutamide effect generalisable to docetaxel ineligible subgroups because no subgroup differences within trial

N.b. trial did not include people who in general cannot take docetaxel

Overall Survival Subgroup Analysis

Subgroup	HR (95% CI)	Placebo Event/N	Placebo Med	Apalutamide Event/N	Apalutamide Med
All subjects	0.65 (0.53, 0.79)	235/527	52.2	170/525	NE
Baseline ECOG performance status					
0	0.68 (0.52, 0.89)	134/348	52.2	94/328	NE
1	0.56 (0.42, 0.76)	101/178	32.3	76/197	NE
Geographic region					
EU/NA	0.75 (0.52, 1.07)	66/173	52.2	53/173	NE
Other	0.62 (0.49, 0.78)	169/354	44.0	117/352	NE
Bone metastasis only at baseline					
Yes	0.50 (0.37, 0.67)	115/269	NE	70/289	NE
No	0.85 (0.65, 1.11)	120/258	48.7	100/236	NE
Visceral disease at baseline					
Yes	0.76 (0.47, 1.23)	43/72	30.1	27/56	40.8
No	0.65 (0.52, 0.80)	192/455	52.2	143/469	NE
Gleason score at Diagnosis					
<=7	0.67 (0.46, 0.98)	63/169	NE	48/174	NE
>7	0.64 (0.51, 0.81)	172/358	43.7	122/351	NE
Prior docetaxel use					
Yes	1.12 (0.59, 2.12)	17/55	NE	21/58	NE
No	0.61 (0.50, 0.76)	218/472	48.7	149/467	NE
Age (years)					
<65	0.57 (0.40, 0.80)	90/182	41.7	49/149	NE
65-74	0.74 (0.55, 0.99)	95/232	NE	81/243	NE
>=75	0.65 (0.43, 0.99)	50/113	52.2	40/133	NE
Baseline PSA above median					
Yes	0.67 (0.52, 0.86)	126/240	38.9	115/286	NE
No	0.54 (0.39, 0.75)	109/287	NE	55/239	NE
Baseline LDH above ULN					
Yes	0.91 (0.57, 1.47)	34/60	28.4	34/60	38.2
No	0.61 (0.49, 0.77)	188/442	52.2	128/443	NE
Baseline ALP above ULN					
Yes	0.55 (0.42, 0.74)	119/180	28.7	79/177	NE
No	0.72 (0.55, 0.95)	115/345	52.2	90/346	NE
mHSPC					
High volume	0.70 (0.56, 0.88)	175/335	38.7	134/325	NE
Low volume	0.52 (0.35, 0.79)	60/192	NE	36/200	NE
Metastasis stage at initial diagnosis					
M0	0.39 (0.22, 0.69)	29/59	41.2	20/85	NE
M1	0.68 (0.55, 0.85)	199/441	48.7	140/411	NE
Number of bone lesions					
<=10	0.69 (0.52, 0.93)	108/331	NE	76/318	NE
>10	0.54 (0.41, 0.71)	127/196	26.9	94/207	NE



NICE

Company ACD comments: Docetaxel ineligible population (3)

ERG: company's subgroup analyses uncertain

Company provided scenario analyses with:

- Reduced utility values applied in each health state for patients unsuitable for chemotherapy
- Assumes that no patients will receive docetaxel or cabazitaxel as subsequent treatment options (given that patients who are unsuitable for docetaxel at baseline may never receive chemotherapy at any point in the treatment pathway)

ERG :

- Reiterate caveats about uncertainties in trial subgroup analyses, including low numbers of patients in some subgroups and lack of sufficient statistical power
- Company proposes 5 subgroups based on TITAN who do not receive docetaxel, but only age and performance status in previous discussions
- Re scenario analyses: ERG has not checked survival extrapolations and model fit statistics for each subgroups for TTD, rPFS, PFS, PFS2 and OS
- Highlights that company used same OS estimates for chemotherapy ineligible and whole TITAN populations; expected company to use sub-group specific OS estimates

ACD: appraisal consultation document, ERG, evidence review group; OS: overall survival; PFS: progression free survival; PFS2-progression free survival on subsequent treatment; TTD, time-to-treatment discontinuation; TOT, time on treatment

People who cannot/should not take chemotherapy (1)

Draft guidance for abiraterone [ID945] includes a paragraph on: “Identifying who cannot or should not have docetaxel involves assessing a person’s risks and may include people who cannot take abiraterone”

- “Defining the group.. is complicated”
- NHS England’s commissioning policy indicates that someone may not be fit enough for docetaxel if:
  - Poor overall performance status (World Health Organization [WHO] performance 3 to 4)
  - Pre-existing peripheral neuropathy
  - Poor bone marrow function or a life-limiting illness
  - “used with caution” in people with WHO performance status of 2 and “there are few absolute contraindications for docetaxel therapy”
- CDF lead: “many factors besides a person’s performance status may affect whether they could have docetaxel” including patient choice after hearing the risks and benefits of each available treatment.
- “Clinical experts explained that, while creating an exhaustive list of criteria for this group is unfeasible, developing a framework would be possible”
- CDF lead “explained that a clinician assesses a person’s suitability for having docetaxel based on contraindications, fitness, comorbidities and preference”

People who cannot/should not take chemotherapy (2)

ID945 continued

- "People for whom docetaxel is unsuitable or contraindicated would include":
  - Contraindications to docetaxel
  - Poor performance status which includes ECOG 3-4 and sometimes 2
  - Significant comorbidity
  - Peripheral sensory neuropathy or poor bone marrow function
  - Poor cognition or social support"
- "Prescribing clinicians should assess individual risks and potential benefits of having docetaxel" including "advantages and disadvantages of all treatment options"
  - clinical experts: "some people who would not be fit enough for treatment with docetaxel would also not be fit enough for abiraterone, & would be offered ADT alone"
- Committee "concluded that identifying people in whom docetaxel was contraindicated or unsuitable would be based on a clinical framework considering individual patient risk, and may include people who cannot or should not take abiraterone".

◉ Has committee seen anything in this appraisal that would affect the definition of people who cannot/should not have chemotherapy, used in ID945 (abiraterone)?

Company: NICE error post-progression survival

Post progression survival now longer for apalutamide vs ADT alone

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Life-year before and after progress in NICE slides and company model (rPFS-Weibull)

ERG ACD response:

- Confirms the pre- and post survival presented by the company
- Considers the approach taken by the company to address committee's requested scenario of equal post-progression survival for both treatment arms is reasonable and appropriate

◉ *Are company's values plausible? Coherent with other indication?*

Company: Adjusting for cross-over and 2nd newer receptor inhibitor

Company: modified RPSFTM reliable, other options not feasible

ACD: Committee wants company to:

- Explore other methods in more detail
- Consider uncertainties of modified RPSFTM such as:
  - Costs of treatment not offered in the NHS
  - Unadjusted PFS2 in COU-AA-302 trial

Company: maintains modified RPSFTM reliable, and other methods not viable and not feasible to re-explore within existing timelines. Instead noted:

- **Costs of treatments not offered in the NHS** – company not clear why committee unsure costs of treatment to be an "uncertainty of the modified RPSFTM approach"; treatments reflect NHS practice
- **Appropriateness of adjusting for crossover** – crossover driven by unbinding and not progression. In TITAN 40% of patients crossed over, so adjusting appropriate
- **Using unadjusted PFS2 in the COU-AA-302 trial** – company agrees with committee using COU-AA-302 data may 'over adjust' outcomes

ACD: appraisal consultation document; ERG, evidence review group; OS, overall survival: PFS2: progression-free survival on 1st subsequent treatment; RPSFTM, rank preserving structural failure time model

ERG: Adjusting 2nd newer receptor inhibitor

ERG: considerable bigger impact on PFS2 than overall survival

ERG:

- Reiterated adjusting TITAN PFS for cross-over in COU-AA-302 have more pronounced effect on HRs than OS; would likely increase cost-effectiveness estimates
- Noted that the independent data monitoring committee (IDMC) recommended unblinding the study and allowing cross-over from the placebo arm to active therapy
- 17% (93 out of 542) initially enrolled in the placebo arm went on to receive abiraterone. No reason to believe that PFS was not affected by treatment cross-over

◉Should company adjust TITAN for cross-over, or not? And for 2nd novel agent, or not?
◉ Should company adjust COU-AA-302 trial PFS2 for cross-over?
◉ Is it reasonable to use the COU-AA-302 trial for adjustment?

ACD: appraisal consultation document; ERG, evidence review group; OS, overall survival: PFS2: progression-free survival on 1st subsequent treatment

Company: Extrapolating beyond trial - flexible modelling

ERG: parametric survival curves do not provide a close enough fit

Company has assumed ERG scenario

ACD conclusions:

- Committee would have liked to see a more flexible model fitted because of uncertainty

Company: maintains extrapolations appropriate

- Committee request possibly driven by error in NICE slides on post-progression survival
- Existing standard parametric approaches imperfect but appropriate:
  - Informed by clinical experts; (we) chose pessimistic ('conservative') curves
  - No indication of hazards in either treatment arm changing distinctly at any point
  - Visual inspection of the Kaplan-Meier data shows no indication of hazard function distinctly changing over time, with patients experiencing PFS, PFS2 and OS events at a relatively constant rate

ERG:

- Reiterated that committee requested flexible models because parametric survival curves did not provide a close enough fit for the long-term estimates of MFS
- Would also have liked to see alternative scenarios using flexible modelling that fits more closely to ERG's clinical experts' opinion

◉ *Committee response to not being presented with request?*

Company ACD comments: Modelled cost of apalutamide

Company: costs are captured fully unlike committee opinion

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ACD conclusions:

- Cost in model are minimum of either time-to-treatment discontinuation (TTD) until progression, or metastases free survival curves
- Company may have underestimated cost of apalutamide

Company's ACD response:

- Maintains costs are **captured fully**
  - TTD and PFS curves converge over time; convergence causes some extrapolations to cross
  - Treat to progression only, so modelled based on minimum of TTD and PFS extrapolations
  - Cost may be over-estimated, as people could discontinue due to disease progression and other reasons

ERG:

- Cost of apalutamide not underestimated
- Appropriate to cap costs assuming that there are no more patients on treatment than who remain progression-free

TITAN apalutamide Kaplan–Meier curves: rPFS and TTD

◉ *Why would costs be 'overestimated'?*

ACD: appraisal consultation document; ADT, androgen deprivation therapy, ERG, evidence review group; PFS, progression free survival; TTD, treatment discontinuation; TOT, time on treatment

Company revised base case assumptions for 3rd committee meeting

Company updated base case include:
• Unadjusted utility values for 2nd + 3rd line treatments
• Using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%)
• Using the ERG-preferred Gompertz extrapolation to model PFS2
• Adjusting for treatment switching and the restriction to 1 novel therapy

Scenario analysis
• Unadjusted
• Adjusted only for treatment switching and not for 2nd novel agent
• Assume equal post-progression survival
• Set time on treatment equal to PFS
• Removing chemotherapy as a subsequent treatment for comparison to ADT
• Reducing the utility values by a decrement of 0.1
• Unadjusted subgroup analyses in locally advanced/primary progressive patients, low volume patients and chemotherapy-unsuitable patients – not requested by committee

NICE

ACM: appraisal committee meeting; PFS, progression free survival; PFS2: progression-free survival on 1st subsequent treatment

Innovation and equality

Innovation:

- ACD: Apalutamide *may* be innovative for hormone-sensitive metastatic prostate cancer (depending on enzalutamide recommendation)

Equality

- ACD: Committee took into account older people in its recommendations who could not or should not have docetaxel

Responses:

Innovation

- Patient group: innovation cannot be determined 'retroactively' based on other results

Equality

- No further issues raised

◉ *Does recommendation of NICE re enzalutamide change whether apalutamide is innovative? Retroactive or current?*

Committee preferences vs company base case (1)

Issues	Committee preference	Company and ERG base case
Adjusting for crossover/2nd novel: method used	Would like company to explore	No change: ('modified' RPSFTM retained in base case)
Adjusting for crossover/2nd novel: Explore with/without	Would like company to explore with/without adjustment	Base case: adjusted. Explored • Unadjusted for 2nd novel therapy and cross-over • Adjusted only for novel therapy and not cross-over
Extrapolating rPFS/OS/PFS curves	Explore flexible methods	• No change
Utilities for 2nd and 3rd line treatments after progression	Unadjusted TA377 (enzalutamide)	✓
Incidence rates for docetaxel adverse events	Pooled neutropenia (15.4%) & febrile neutropenia (10.6%)	✓
Treatment waning	Small impact on results	• No change: No treatment waning
Apalutamide costs were *minimum* of TTD or MFS – capped & so possibly underestimated	No action suggested but added uncertainty	• No change to base case (argued costs not underestimated • Scenario presented: Time on treatment equal to PFS
Costs of non-NHS drugs	Exclude	• No change – not included

NICE

ADT, Androgen deprivation therapy: RPFSTM, PFS, progression free survival; Rank preserving failure structure time model, TA, Technology appraisal;

Committee preferences vs company base case (2)

- Company explored chemotherapy-ineligible population using proxies:
  - Remove chemotherapy as a subsequent treatment
  - Reduce utility values by 0.1
  - Age >75 (unsuitable due to fitness/comorbidity)
  - Metastasis stage at diagnosis M0 (these patients do not meet criteria for NHS England commissioning policy for docetaxel which requires patients to “have newly diagnosed, metastatic, prostate cancer)
  - Low volume (LV) disease (docetaxel not as effective in this subgroup; according to CHAARTED and GETUG-AFU trials, add-on docetaxel showed no survival benefit in LV disease vs ADT alone. So LV not routinely offered docetaxel in clinical practice)
  - ECOG: Eastern Cooperative Oncology Group (ECOG) 1 (unsuitable due to fitness/comorbidity)
  - ECOG 1 & age >75 (unsuitable due to fitness/comorbidity)

Cost-effectiveness results

All ICERs are reported in PART 2 slides because of confidential agreements information