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NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Lead team presentation

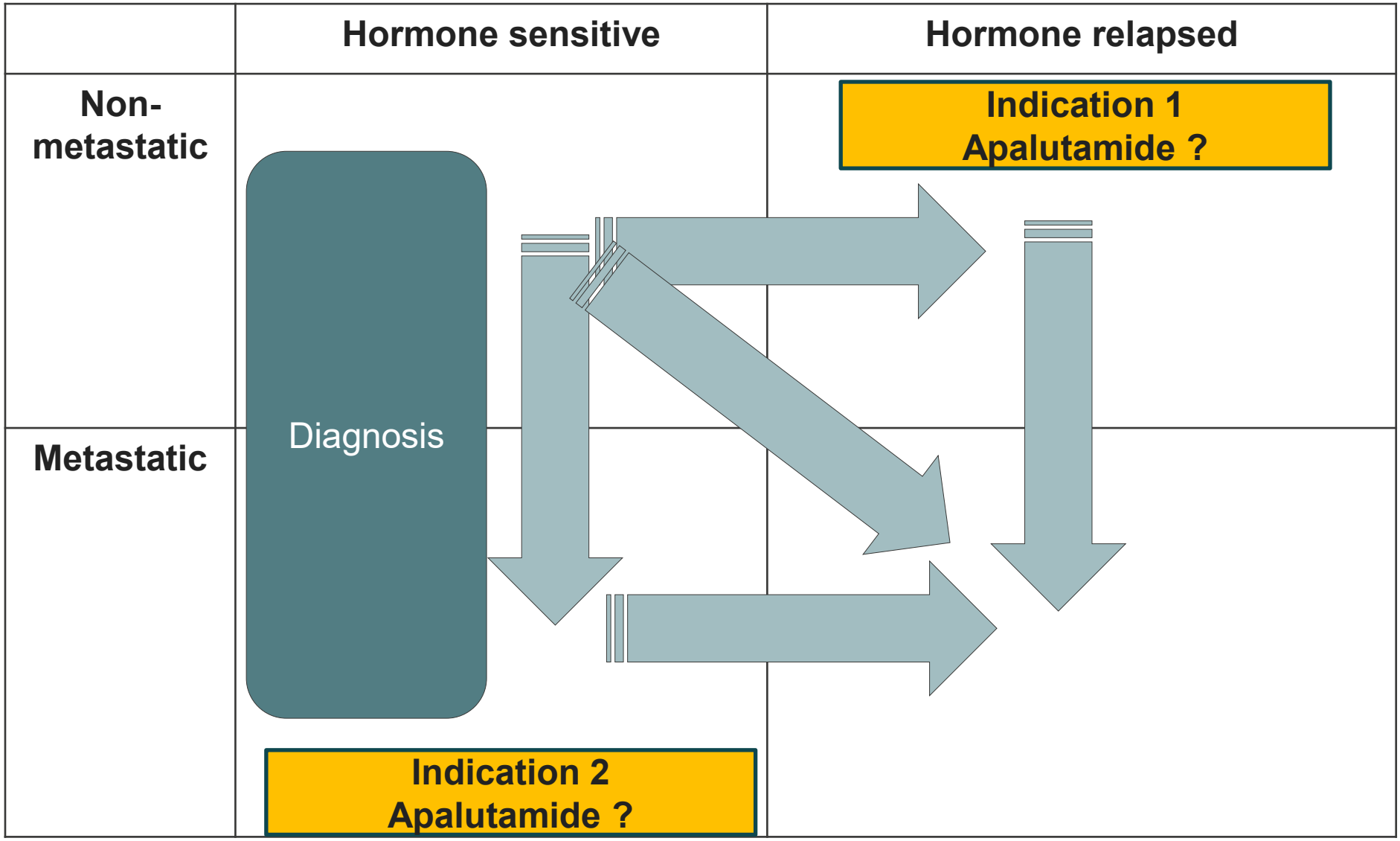
Chair: Amanda Adler
Technology Appraisal Committee B
Lead team: Anna Pracz (clinical) Rhiannon Owen (cost), Nigel Westwood (lay)
ERG: Southampton Health Technology Assessments Centre (SHTAC)
Technical team: Aminata Thiam, Carl Prescott, Henry Edwards
Company: Janssen-Cilag
4 March 2021 virtual committee meeting

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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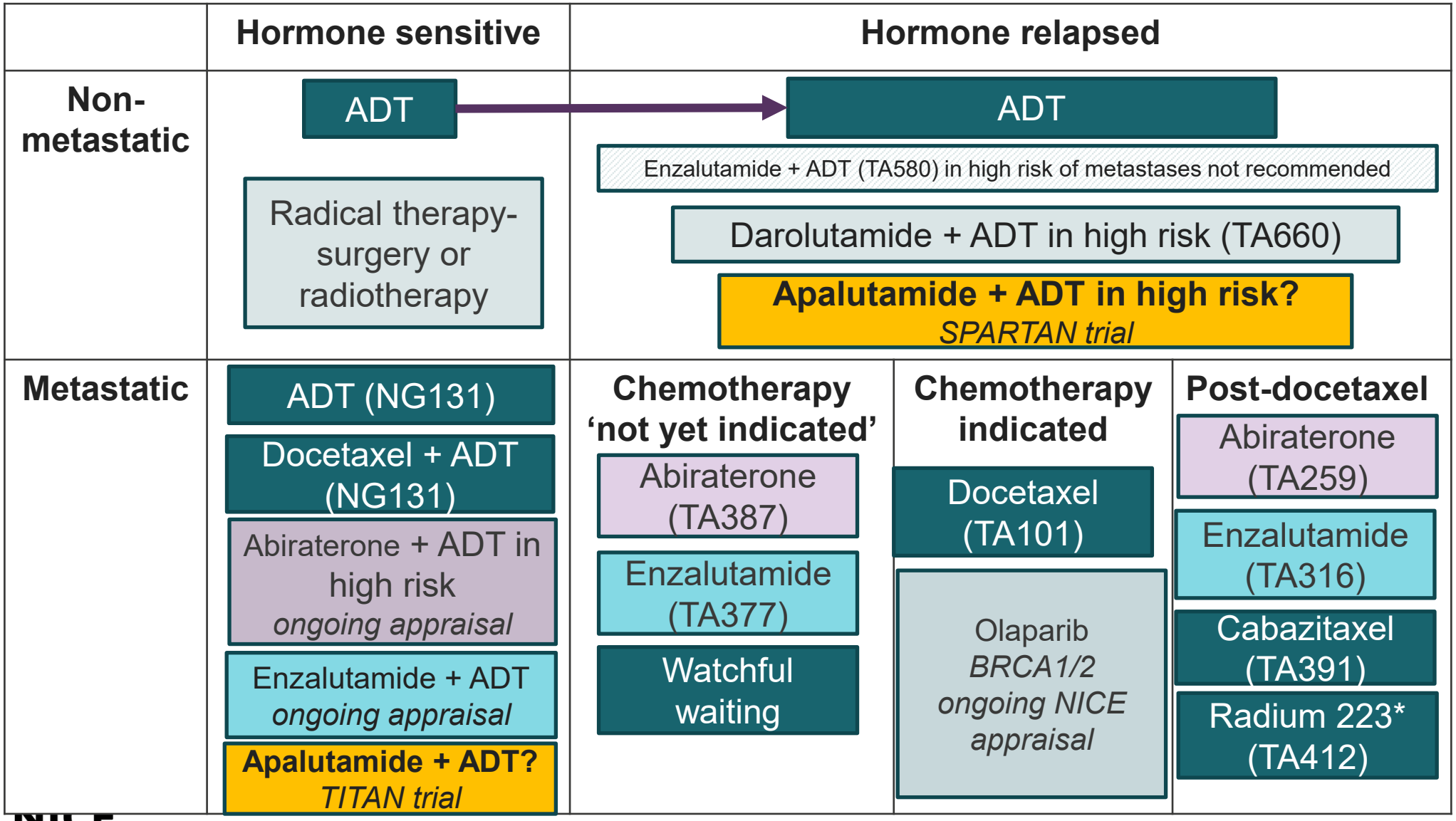
Apalutamide (Erleada, Janssen)

Marketing authorisations	In adult men for the treatment of: 1. non-metastatic castration-resistant prostate cancer* at high risk of developing metastatic disease *(Jan 2019)* 2. metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy (ADT**) *(Jan 2020)* ***NOTE: committee to consider indications separately***
Mechanism of action	Androgen receptor antagonist. Decreases cancer cell proliferation, causing cancer cell death and tumour regression
Administration & dose	Oral; recommended dose: 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 non-metastatic prostate cancer ** both indications used in combination with ADT

Treatment pathway for prostate cancer

Androgen deprivation therapy (ADT) continues despite hormone relapsed
Docetaxel can be offered twice; abiraterone OR enzalutamide only once



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

*bone metastasis only

Non-metastatic Hormone-relapsed

Key issues: clinical and cost effectiveness
Non-metastatic, hormone-relapsed

Clinical issues

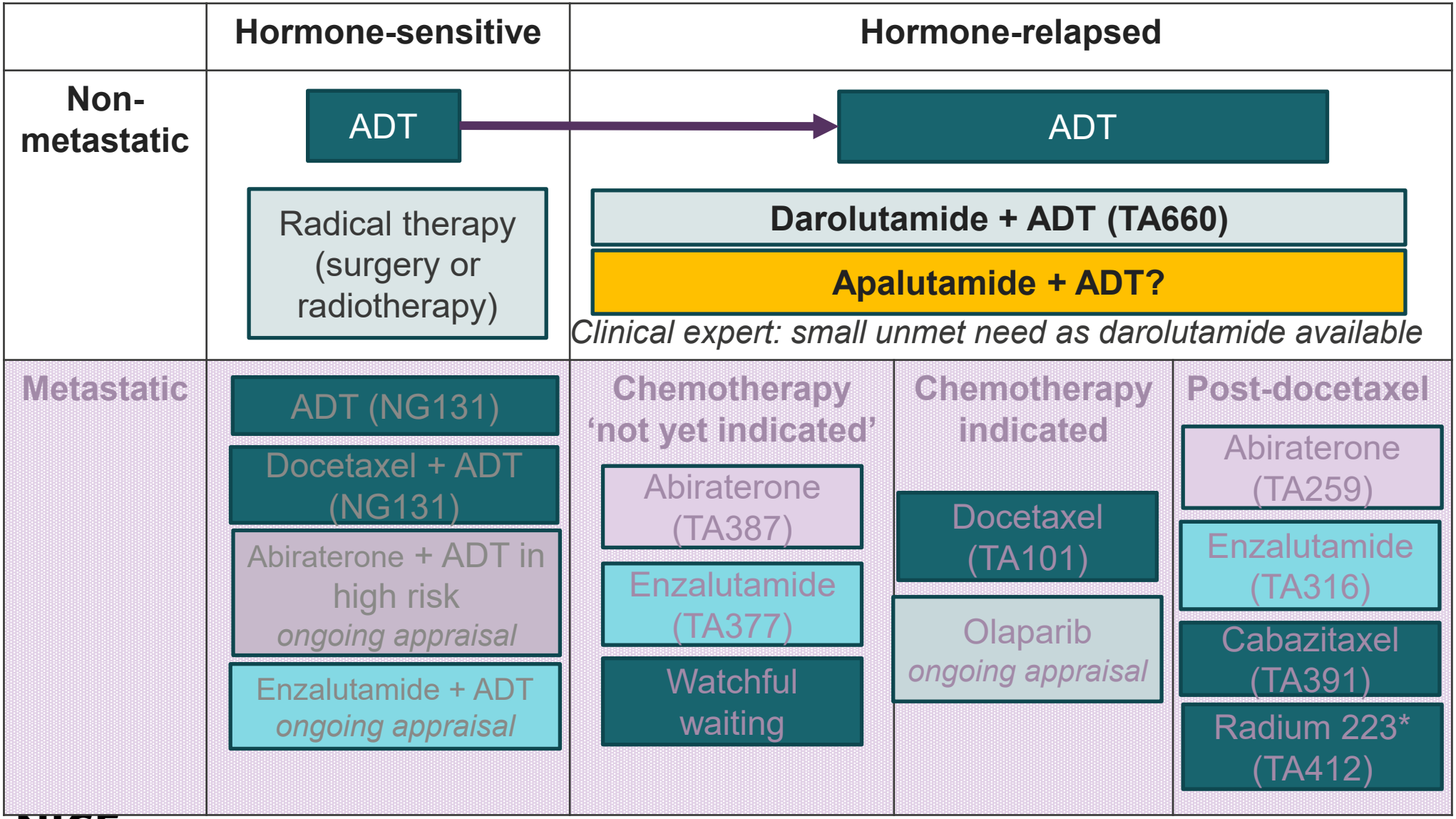
- Is it reasonable to adjust at the same time for both ‘crossing over’ and taking abiraterone or enzalutamide more than once?
- Is it appropriate to adjust using “modified” Rank Preserving Structure Failure Time Models ?
- Adjusting for crossover in abiraterone trial (COU-AA-302): adjusted only for overall survival (OS), should adjust also for the ‘second’ progression free survival (PFS)?

Cost effectiveness issues

- Extrapolation of survival curves: which distributions are most appropriate?
- Should utility values be adjusted to reflect population differences between apalutamide and abiraterone trial? What source of utility value is more appropriate?

Treatment non-metastatic, hormone-relapsed

- *Darolutamide not in clinical practice at start of this appraisal, so not a comparator*



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

*bone metastasis only

Apalutamide (Erleada, Janssen)
Non-metastatic, hormone-relapsed

Limited to 'high risk' of metastasising

Marketing authorisation	In adult men for the treatment of: • non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease
Mechanism	Androgen receptor antagonist
Administration & dose	• Oral • Recommended dose: 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 offered and in place (confidential)

Background

Non-metastatic, hormone-relapsed

- If cancer responds to androgen deprivation therapy (ADT) it remains 'hormone-sensitive; if it stops it is 'hormone-relapsed'
- Standard care is to continue ADT despite cancer being hormone-relapsed,
- Darolutamide + ADT (TA660, November 2020) now an option for treatment
- Disease monitored by measuring prostate specific antigen (PSA) in blood
- 'Disease progression' when metastases occur
- Metastases detected using imaging: MRI or CT scan
- Apalutamide licence limited to '**at high risk of metastases**'
  - PSA ≥ 2 ng/millilitre + PSA doubling time of ≤10 months
  - 60% of non-metastatic hormone-relapsed is high risk (TA580 enzalutamide)
- Aim of treatment is to delay metastases
- Metastatic disease associated with pain and reduced quality of life and survival
- Disease progresses to metastatic hormone-relapsed prostate cancer in ~15-16 median months for patients receiving ADT (company submission)

Patient perspective (1): Living with condition

Many symptoms often have debilitating impact and cause psychological distress:

- Fatigue
- Pain, usually caused by cancer that has spread to bones, impacts mobility
- Urinary problems: emptying bladder, incontinence, blood in urine, kidney problems
- Bowel problems: constipation, diarrhoea, faecal urgency or incontinence, pain, bowel obstruction, flatulence
- Sexual problems: reduced libido, erection difficulties. Impacts relationships
- Broken and fractured bones caused by bone thinning, impairing mobility
- Lymphoedema, manifests as swollen/disfigured extremities or truncal regions
- Anaemia, caused by damage to bone marrow
- Metastatic spinal cord compression as cancer cells grow in or near spine. May occur in 1 to 12% of patients, requires urgent care, and if not treated can lead to paralyses
- Hypercalcaemia, caused by calcium leaking from bones into blood, leading to nausea, vomiting and constipation
- Eating problems that can result in malnutrition

Patient perspective (2)

Living with the condition

- Stress of "*knowing something is happening but not knowing where*" can be immense. Adequate therapy with treatments which produce an acceptable side effect profile would be of immense value
- *"To be honest, to know my disease is worsening but not being able to have any treatment is unbearable. In a strange way I would feel better if you had told me I had definitely got spread - at least I would be getting some treatment now. At least I would have an end-point to relate to."*

Apalutamide treatment

- **Quality of life:** Maintain good quality of life while on treatment. Given orally, does not require specialised admin or hospital treatment; monitoring organised locally, follow-up appointments done remotely
- **Subsequent treatments:** Taken long-term i.e. until progression. If used early in pathway, will restrict choice of subsequent treatments e.g. abiraterone or enzalutamide. But, most would opt for earlier and more effective treatment overall rather than 'save' such drugs for later

Decision problem

Non-metastatic, hormone-relapsed

NICE must appraise drugs within their license

Darolutamide (TA660) not a comparator - considered unlikely to be in practice in time for appraisal

	Final scope issued by NICE	Company submission	Rationale for difference
Population	Adults with non-metastatic, hormone-relapsed prostate cancer	Adults with **high-risk** non-metastatic, hormone-relapsed prostate cancer	Licence is for those at high risk of developing metastatic disease, per SPARTAN trial
Intervention	Apalutamide + ADT		
Comparators	ADT alone		
Outcomes	• Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	Scoped outcomes plus: • Metastases-free survival • Time to symptomatic progression • Time to PSA progression • 2nd progression-free survival • Time to initiation of cytotoxic chemotherapy • Time to metastasis	Company provides extra data as 'supportive'

ADT, androgen deprivation therapy; PSA: prostate specific antigen

ERG report issues
Non-metastatic, hormone-relapsed

Issue	Company response to TE
Treatment switching: 'Modified RPSFTM' used to adjust trial results for crossover & no. of subsequent treatments (to better reflect NHS), but not peer-reviewed & potentially not valid	Accounted for abiraterone trial crossovers Provided IPCW results
Survival curve extrapolation: large impact on cost effectiveness estimates	Justified curve choice
Utility values for 2nd & 3rd line: More rationale needed re source & adjustment. Used TA387 (abiraterone) utilities for later stage (hormone-relapsed, metastatic prostate cancer) before chemotherapy, adjusted using relative decline ratio assuming similar decline	Justified and maintained utility choice

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IPCW: Inverse probability of censoring weighting; RPSFTM: Rank Preserving Structure Failure Time Models; TE: technical engagement

Clinical effectiveness

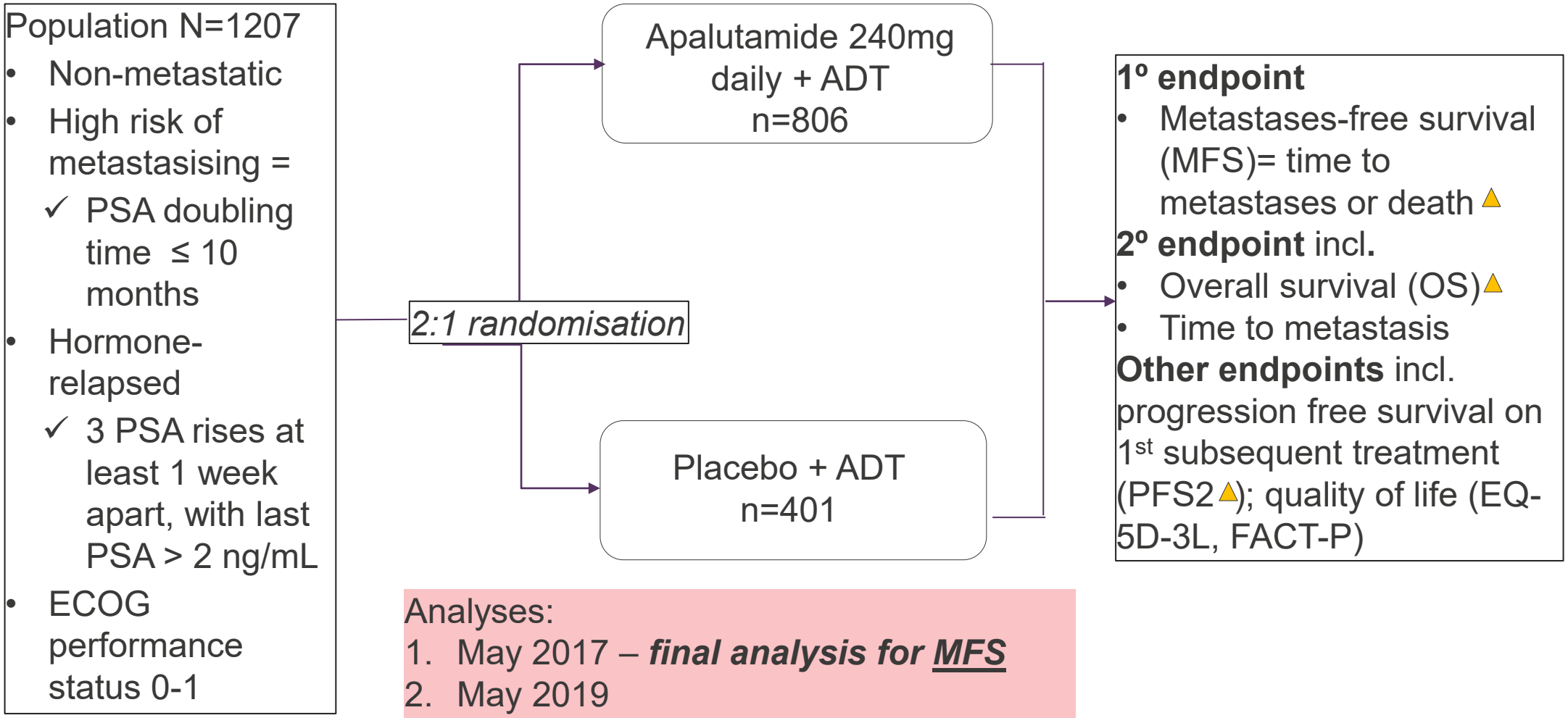
Non-metastatic, hormone-relapsed

Key clinical issues
Non-metastatic, hormone-relapsed

- Is it reasonable to adjust at the same time for both ‘crossing over’ and taking abiraterone or enzalutamide more than once?
- Is it appropriate to adjust using “modified” Rank Preserving Structure Failure Time Models ?
- Adjusting for crossover in abiraterone trial (COU-AA-302): adjusted only for overall survival (OS), should adjust also for the ‘second’ progression free survival (PFS)?

SPARTAN trial

- Phase III, placebo-controlled, multinational (26 countries, 15 UK sites, [redacted])
- Cross-over allowed after study unblinding, at final analysis for metastases-free survival May 2017
- Patients received subsequent therapies
- Company adjusted cost effectiveness results on overall survival and progression free survival on 1st subsequent treatment (PFS2) in model

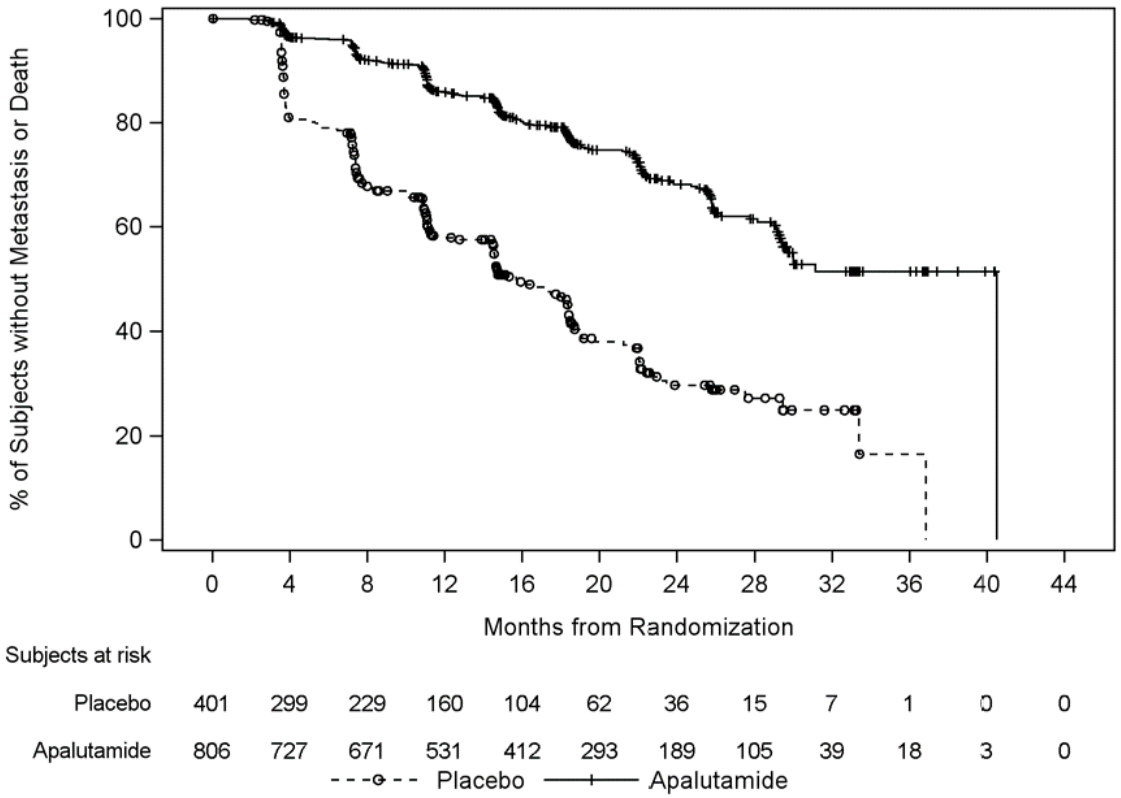


▲ *Endpoints inform economic model*

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

SPARTAN 1º outcome metastases-free survival

Intention to treat analyses, 1st and final analysis for 1º endpoint May 2017



	Apalutamide + ADT N=806	Placebo + ADT N=401
Number (%) of patients with event	209 (25.9)	210 (52.4)
Number (%) of patients censored	597 (74.1)	191 (47.6)
Median MFS months (95% CI)	40.5 (29.7–40.5)	15.7 (14.6–18.4)
Hazard ratio	0.30 (0.24–0.36) p<0.0001	

- Median MFS extended by nearly 25 months for apalutamide +ADT vs. placebo +ADT

◉ *Does randomization to apalutamide increase time to metastases compared with placebo? Are these data mature?*

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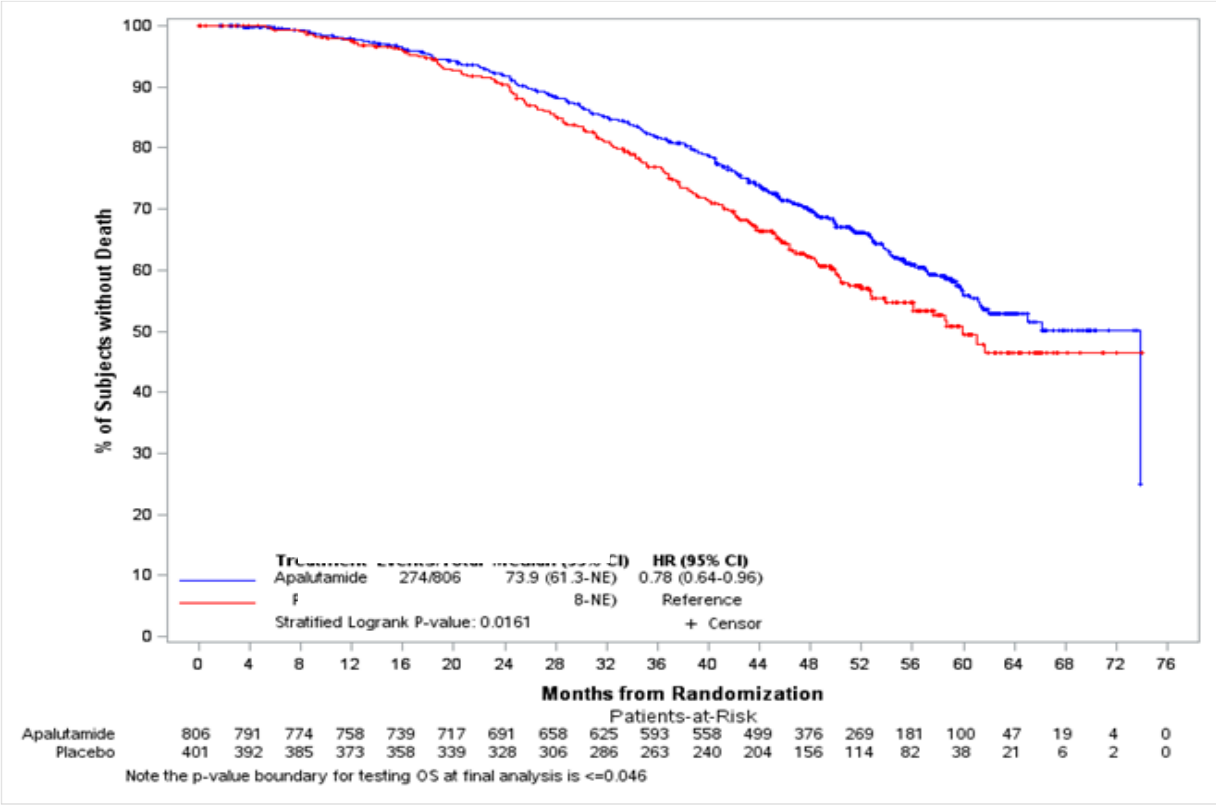
Source: CS Figure 10 p 72

ADT, androgen deprivation therapy; CI, confidence interval; MFS, metastases-free survival

SPARTAN 2º outcome overall survival (OS)

Intention to treat analyses, 3rd and final analysis for 2º endpoint Feb 2020



	Apalutamide + ADT N=806	Placebo + ADT N=401
Number (%) of patients with event	274 (34.0%)	154 (38.4%)
Number (%) of patients censored	[redacted]	[redacted]
Median OS months (95% CI)	73.9 (61.21–NE)	59.9 (52.80–NE)
Hazard ratio	0.78 (0.64–0.96), p=0.0161	

- ❑ Median OS extended by 14 months for apalutamide + ADT vs placebo + ADT

◉ *Does randomization to apalutamide increase overall survival compared with placebo? What p value was included in statistical analysis plan? Are these data mature? Is confounding of estimate affected by cross-over?*

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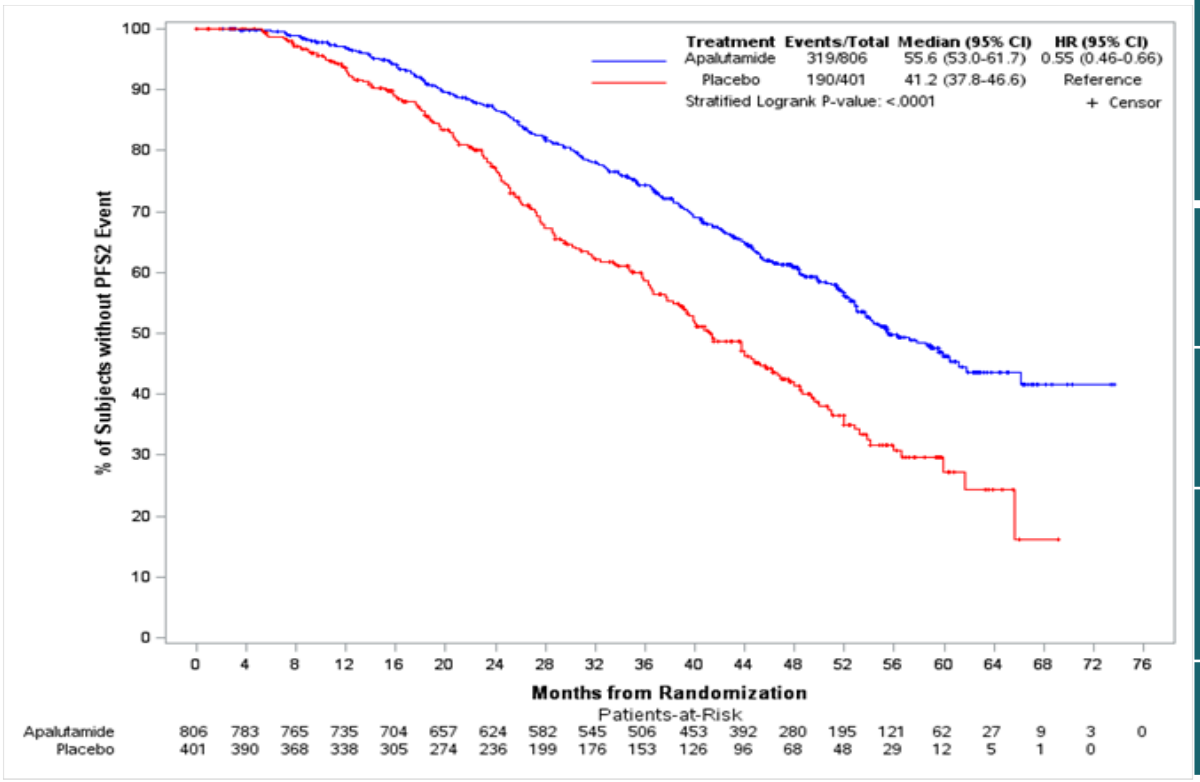
Source: CS Figure 11 p 75

NE: not estimable, CI: confidence interval; OS: overall survival

SPARTAN 2º progression-free survival on 1st subsequent treatment (PFS2)

Intention to treat analyses, 3rd and final analysis for 2º endpoint Feb 2020
Company uses in model



	Apalutamide + ADT N=806	Placebo + ADT N=401
Number (%) of patients with event	319 (39.6%)	190 (47.4%)
Number (%) of patients censored	XXX XXX	XXX XXX
Median PFS2 months (95% CI)	55.6 (53.0-61.7)	41.2 (37.8-46.6)
Hazard ratio	0.56 (0.47-0.68) p<0.0001	

❑ Median PFS2 extended by 14 months for apalutamide + ADT vs placebo + ADT

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Source: CS Figure 12 p 77

CI: confidence interval; PFS2: progression-free survival on 1st subsequent treatment

SPARTAN safety profile

Final analysis; clinical cut-off date 1st February 2020

AE, n (%)	Apalutamide + ADT (n = 803)		Placebo + ADT (n = 398)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All causality AEs	781 (97.3%)	449 (55.9%)	371 (93.2)	373 (93.7%)
Drug-related AEs [a]	XXX	XXX	XXX	XXX
AEs leading to treatment discontinuation	120 (14.9%)	-	29 (7.3%)	-
Drug-related AEs leading to treatment discontinuation	XXXX	-	XXXX	-
All-causality SAEs [b]	290 (36.1%)	XXXX	99 (24.9%)	XXXX
Drug-related SAEs[a]	XXXX	-	XXXX	-
Fatal SAEs	24 (3.0%)	-	2 (0.5%)	-
Fatal drug-related SAEs[a]	1 (0.1%)	-	XXXX	-

Source: reproduction of CS Table 24, footnotes edited. AE: adverse event; SAE: serious adverse event
[a] Adverse events reported as related. [b] Excludes Grade 5. Notes: Percentages are based on the Safety population. For each category patients are counted only once even if they experienced multiple events in that category.

Adverse events of special interest included skin rash (XXXX in apalutamide arm vs XXXX in placebo+ADT arm; biggest difference), fall, fracture, hypothyroidism and seizure.

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SPARTAN results adjusting OS + PFS2 for crossovers and non-NHS practice

Background

Simultaneous for:

- **Crossover**: unblinding at interim cut-off, potentially underestimating relative benefit of apalutamide + ADT for PFS2 and OS

  SPARTAN: 19% (76/401) in placebo + ADT → apalutamide + ADT

- **Receive >1 new hormonal agents**: following disease progression, some patients received >1 new treatments such as apalutamide, abiraterone or enzalutamide. Need to align with NHS England commissioning policy which restricts use of new agents to 1 per patient.

Exposure to subsequent treatments:

- Apalutamide + ADT: 371 (46.0%); [new treatment includes XXabiraterone, XXenzalutamide]
- Placebo + ADT: 279 (69.6%) [includes XXabiraterone, XXenzalutamide]

- Unadjusted and adjusted hazard ratios for OS and PFS2

Intention to treat 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 not reported
PFS2: HR (95% CI)	0.57; 95% CI 0.47 to 0.68; p < 0.0001	XXXXXX p-value not reported

ADT: androgen deprivation therapy; HR: hazard ratio; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment

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◉ Is it reasonable to adjust for both crossovers and more than 1 new treatments?

Company's choice of method to adjust

- Company used 'modified' Rank Preserving Structure Failure Time Models' method
- Explored methods recommended by NICE* but did not choose because:
  - Rank Preserving Structure Failure Time Models (RPSFTM) / Iterative Parameter Estimation (IPE)
    - without use of external data ''in practice data available in the trial are not sufficient to allow to estimate these multiple parameters reliably''
  - Inverse probability of censoring weighting (IPCW)
    - provided results in response to ERG request but did not use it because 'counter-intuitive', 'clinically implausible'
  - Two-stage method
    - not appropriate: insufficient data and requires 'secondary baseline' at time of switching
    - data for MFS, OS and PFS2 come from different times
  - Company included methods producing less favourable estimates only *"to ensure a conservative approach to cost-effectiveness is taken and that Committee time is optimised by focus on clinically plausible scenarios".*

MFS: metastases-free survival; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; *TSD: technical support document 16

Company chose 'modified RPSFTM' to adjust OS and PFS2 for treatment switching

Company

- Uses unpublished method described by Diels et al. – no peer review
- Uses external data from COU-AA-302 trial - abiraterone in metastatic hormone relapsed disease - to estimate, and adjust for, survival benefit of taking abiraterone or enzalutamide after progression
- Provided results from 2 data cuts of COU-AA-302 trial (abiraterone):
  - Interim analysis (IA3): impact should be minimal - only 0.55% had crossed over
  - Final analysis (FA): crossover may affect estimates (17% switched to active treatment)
- Assumed common treatment effect, but not explored; likely to bias against apalutamide, as more apalutamide patients received 2nd subsequent therapy
- **Company base case: 'modified' RPSFTM adjusted hazard ratios for OS and PFS2 without recensoring, IA3**

Stakeholders

- Comparator company:
  Should consider all available methods as no method fully aligns with SPARTAN
  To adjust for abiraterone/enzalutamide may not suffice – patients in practice would receive other agents e.g. docetaxel, radium-223, or cabazitaxel following apalutamide + ADT vs ADT alone. Should adjust for these treatments.
- Clinical expert: In NHS, use 'novel hormonal therapies' only once in pathway

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ADT: androgen deprivation therapy; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; RPSFTM; Rank Preserving Structure Failure Time Models

ERG note limitations to company's approach

Could not verify 'modified' RPFSTM as company did not provide individual patient data

- Using COU-AA-302 (abiraterone trial) appropriate
- Choice of interim or final data has limited impact on adjusted OS HRs in company base case

OS	Adjusted with interim data 3	Adjusted with final analysis
ITT population HR (95% CI)	[redacted]	[redacted]
RPSFTM without recensoring	[redacted]	[redacted]
RPSFTM with recensoring	[redacted]	[redacted]

- Treatment in COU-AA-302 had considerably bigger impact on estimates for PFS2 than on OS Suggests PFS2 crossover adjustment in COU-AA-302 would have more pronounced effect on adjusted HRs in SPARTAN, increasing ICERs
- Reasonable to assume that abiraterone or enzalutamide after abiraterone or enzalutamide will not prolong survival more than ADT alone; clinical expert advice & literature supports this
  - Patients who become resistant have 15-30% response rate to 2nd line (Antonarakis *et al.*)
- Assumption of 'common treatment effect' incorrect because of cross-resistance effect of abiraterone & enzalutamide - likely to underestimate apalutamide effect
- Other methods: company did not provide cost-effectiveness results for each method as requested. ERG could not verify results.
- Company model includes HRs *without* recensoring. NICE DSU 14 recommends conducting both analyses with and without re-censoring of adjusted survival estimates

◉ *Is the committee satisfied with the company's approach?*
◉ *Should company adjust for 'PFS2' in COU-AA-302 ?*

ADT: androgen deprivation therapy; HR: hazard ratio; IA3/FA: intermediate/final analysis; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; RPSFTM; Rank Preserving Structure Failure Time Models; TE: technical engagement

Key clinical issues
Non-metastatic, hormone-relapsed

- Is it reasonable to adjust at the same time for both ‘crossing over’ and taking abiraterone or enzalutamide more than once?
- Is it appropriate to adjust using “modified” Rank Preserving Structure Failure Time Models ?
- Adjusting for crossover in abiraterone trial (COU-AA-302): adjusted only for overall survival (OS), should adjust also for the ‘second’ progression free survival (PFS)?

Cost effectiveness

Non-metastatic, hormone-relapsed

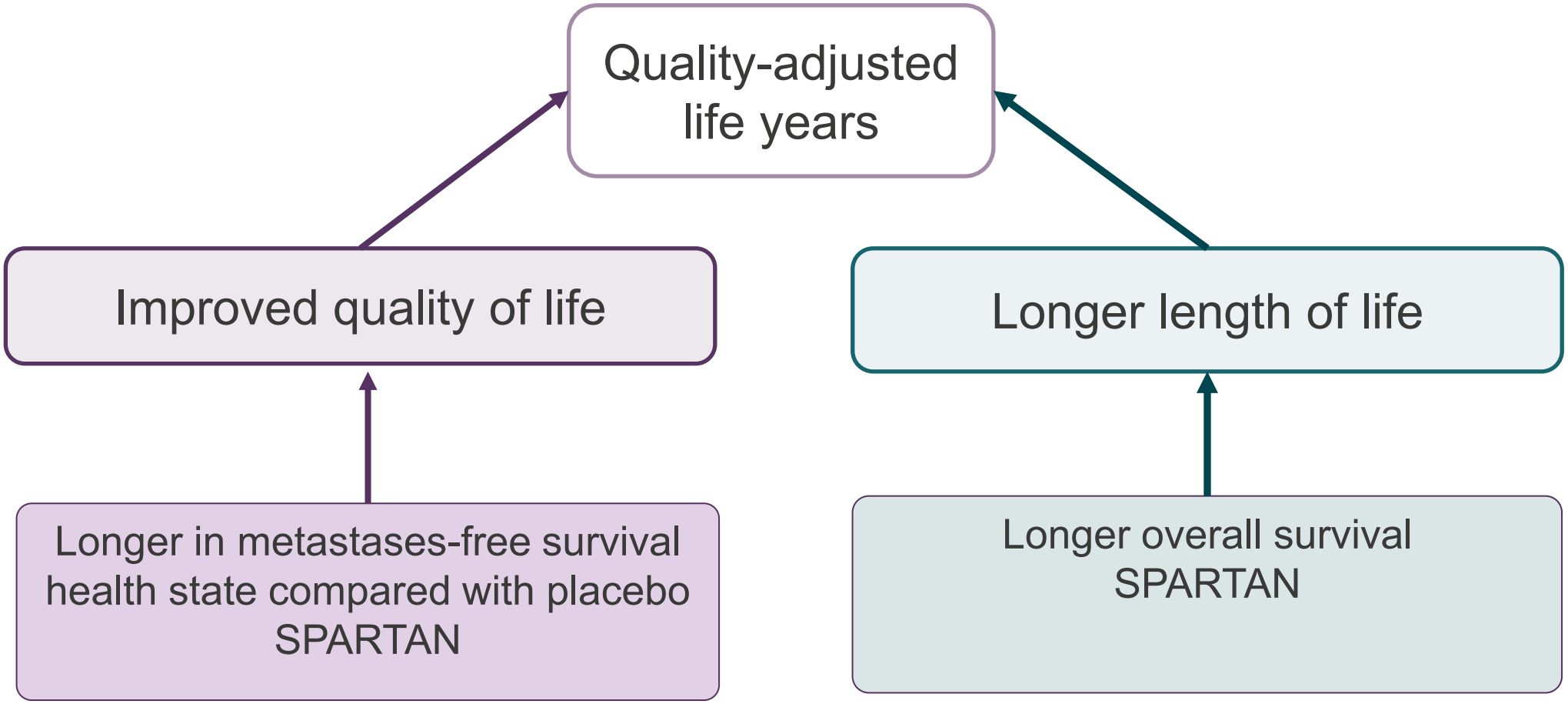
Key cost effectiveness issues
Non-metastatic, hormone-relapsed

- Extrapolation of survival curves: which distributions are most appropriate?

- Should utility values be adjusted to reflect population differences between apalutamide and abiraterone trial? What source of utility value is more appropriate?

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

Non-metastatic, hormone-relapsed



Comparison of life-year before and after progression in company base case

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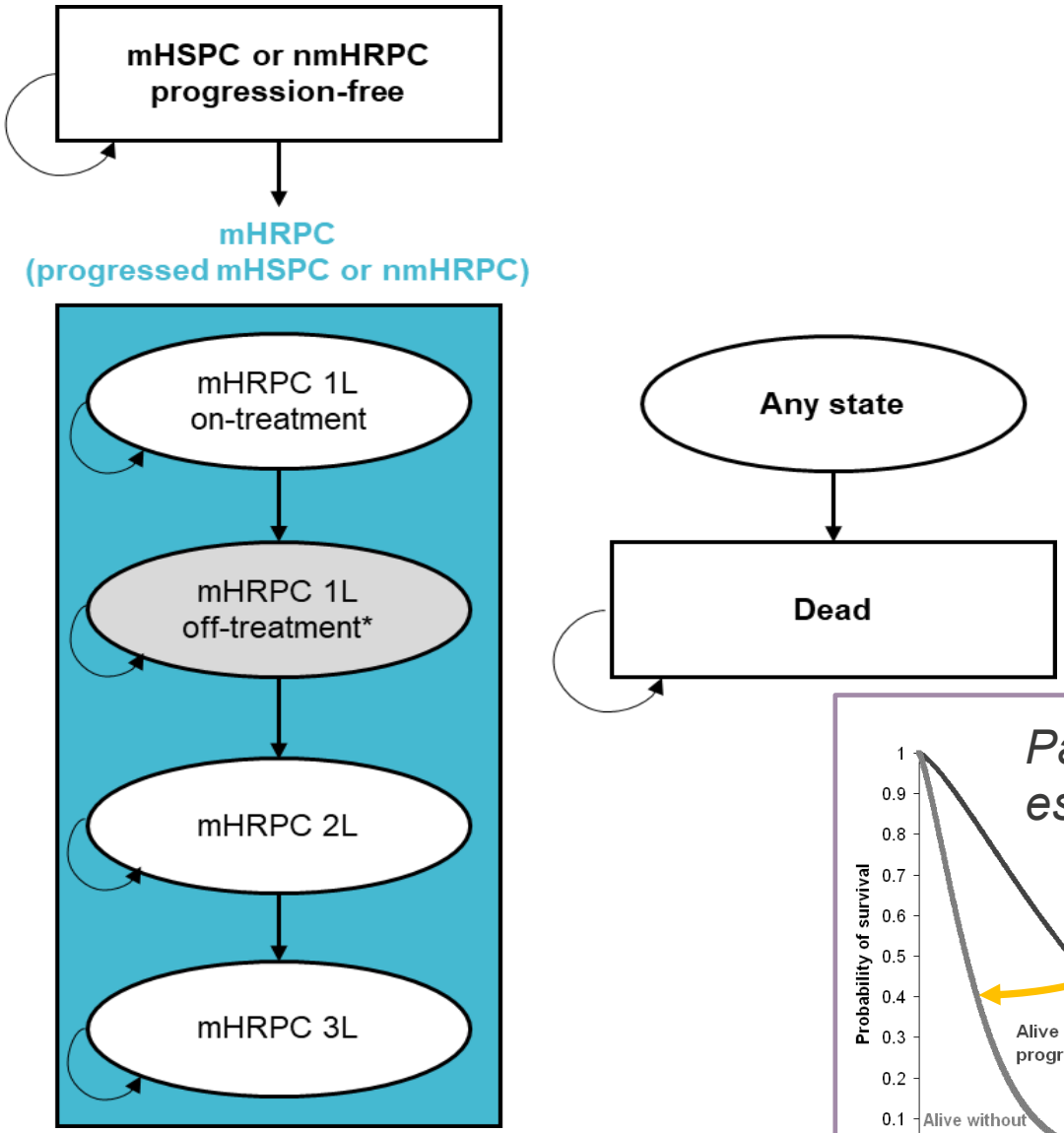
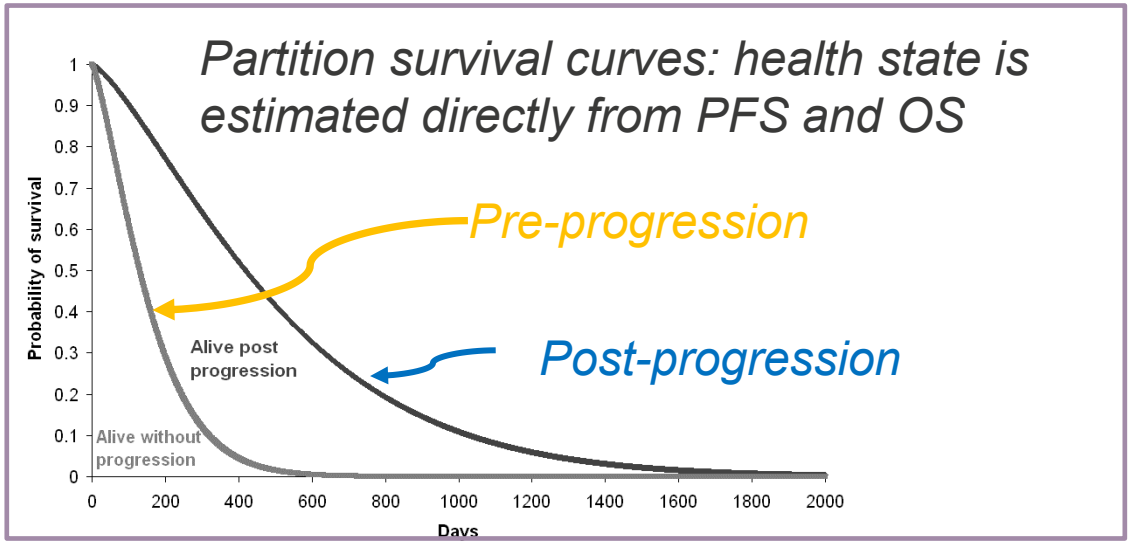
Based on company's model; produced by NICE

Company model to estimate cost effectiveness



- Partitioned survival model but use of multiple health states to model subsequent therapy
- Efficacy informed by extrapolated MFS and OS (SPARTAN)
- 1-week cycle
- Lifetime horizon (32 years)
- Patient can receive up to 3 lines of subsequent therapy
- 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.

Extrapolating metastases-free survival beyond trial

Company and ERG choose Weibull for both treatments; ERG notes key driver

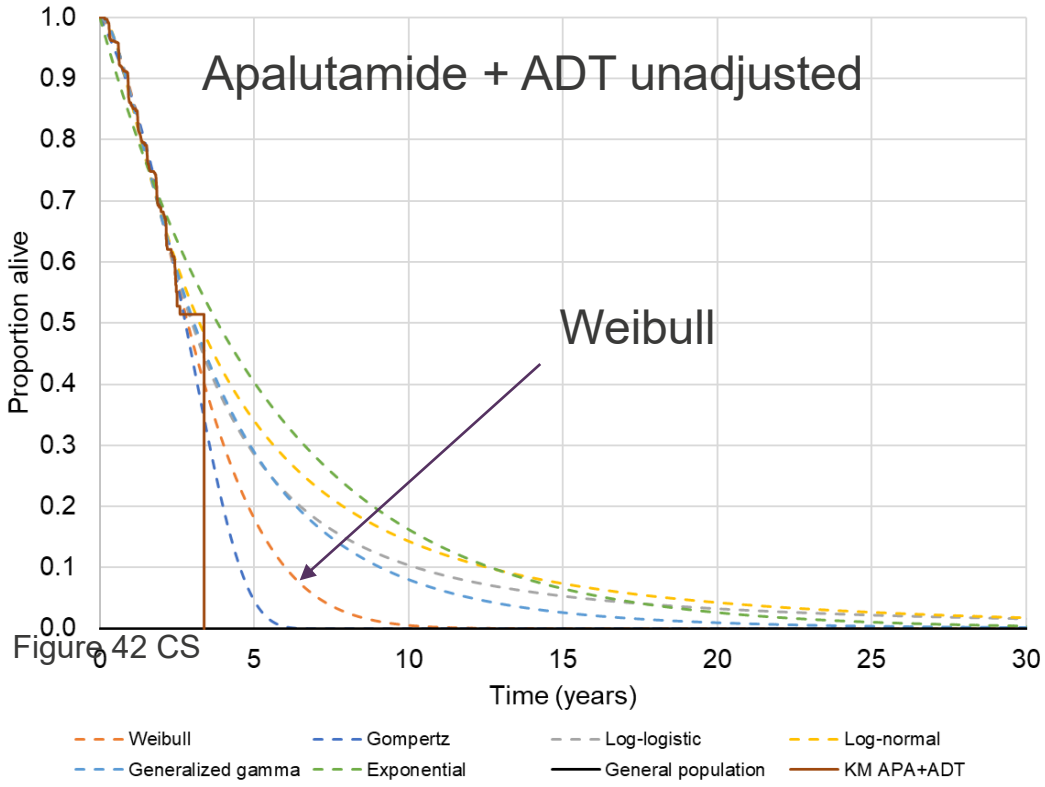
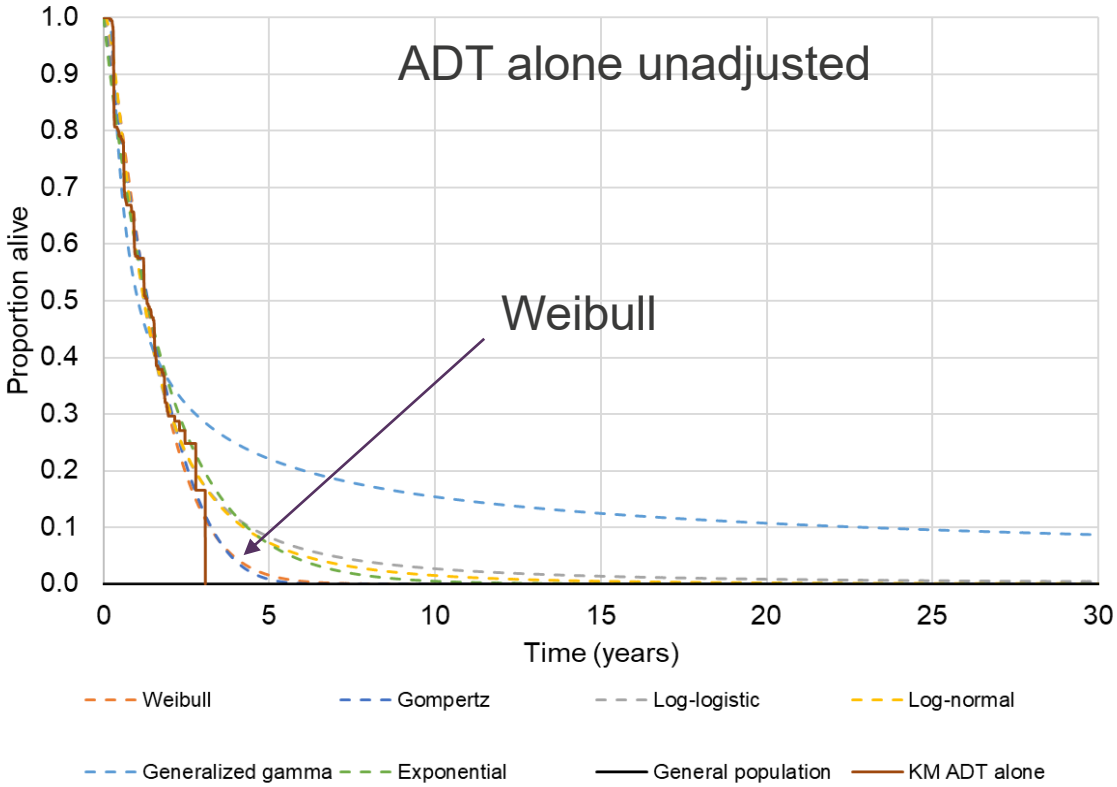


Figure 42 CS



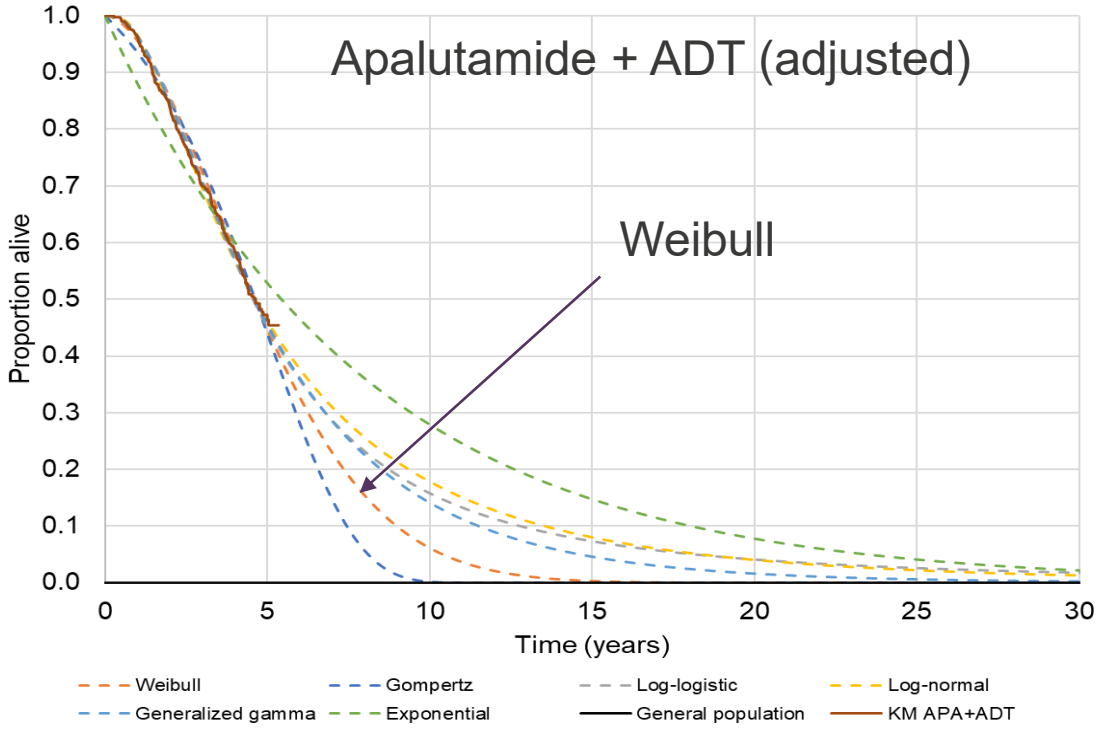
Company: heard from clinicians **Weibull** most plausible for both arms. Fit curves 'independently'. Believes Weibull may underestimate MFS at 10 years for apalutamide

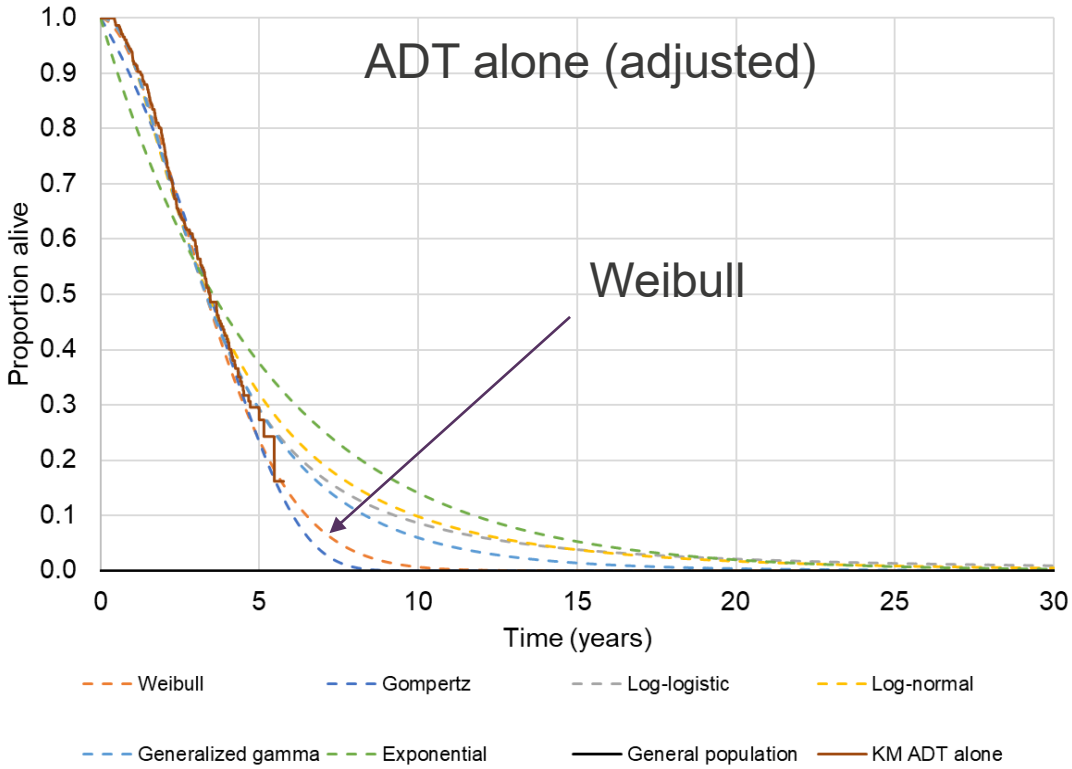
◉*Is Weibull appropriate to extrapolate MFS?*
Is independent fitting appropriate?
Should company consider more flexible models?

ERG: models underestimate MFS at 5 and 10 years in ADT arm, except generalised gamma which has a clinically implausible long tail, but may overestimate MFS with apalutamide.
Chose **Weibull** although has a large impact on model results.
More flexible models e.g. piecewise modelling more appropriate.

Extrapolating progression-free survival on 1st subsequent treatment (PFS2)

Company and ERG chose Weibull fit





- Company: **Weibull** (both arms); fitted jointly; data adjusted for novel therapy restriction and crossover without re-censoring
- ERG: Average AIC/BIC vs. other models. Agree **Weibull** but data immature so likely uncertainty

◉*Is Weibull an appropriate survival fit to extrapolate PFS2 or should company consider other approaches? Is jointly fitting curves appropriate?*

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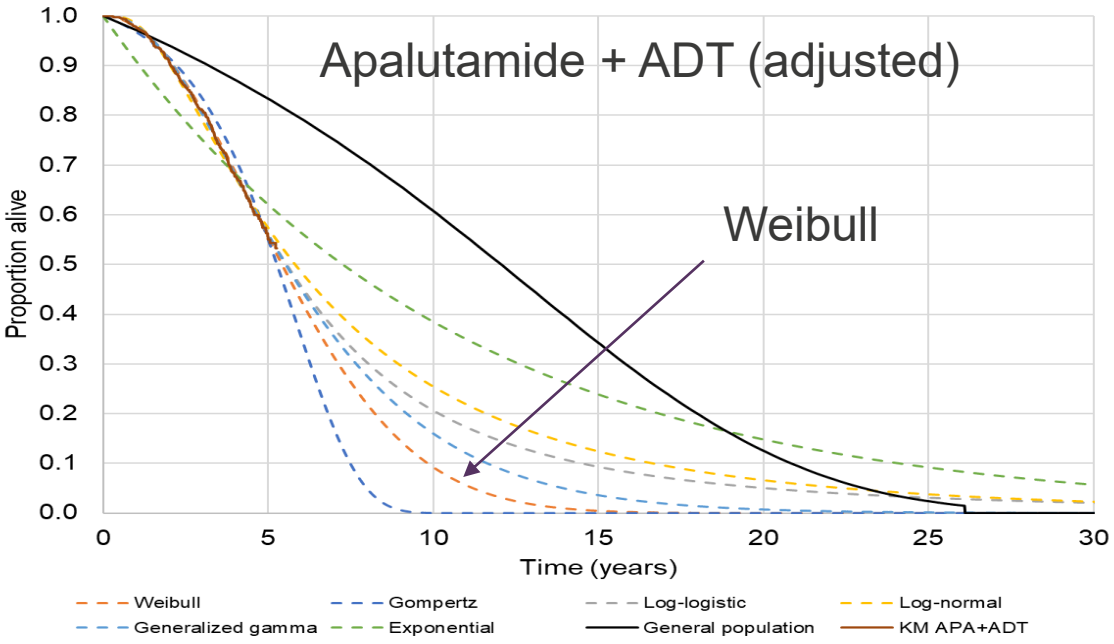
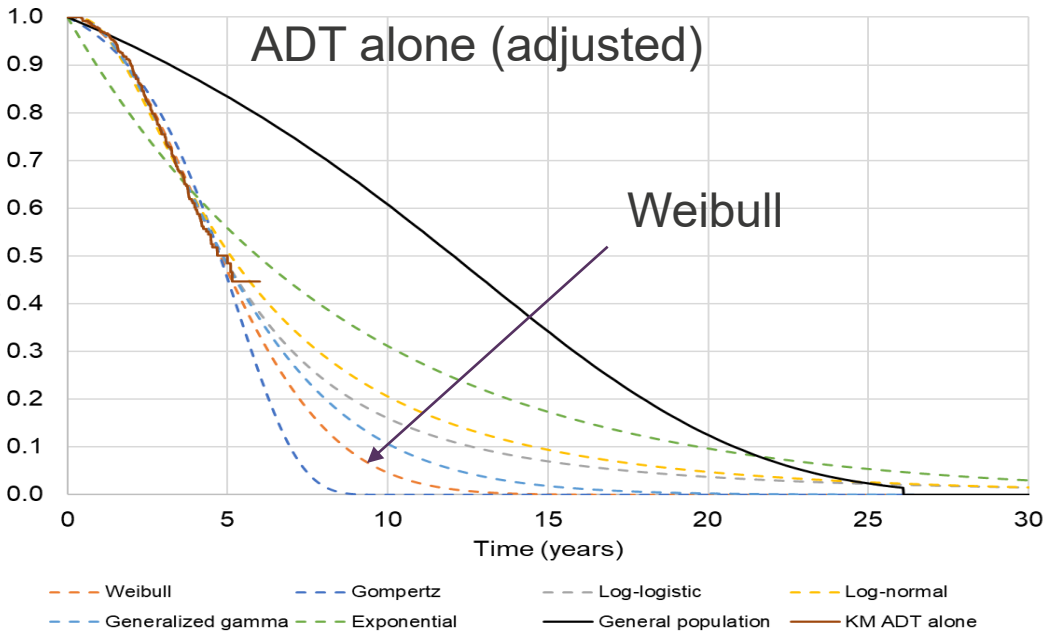
Figure 47 CS

Extrapolating overall survival beyond trial

Company could not use ADT historical data*





- Company: did not use historical ADT arm because of limited data available and because SPARTAN had longer follow-up than other studies. Used **Weibull** (both arms) fitted jointly; data adjusted for novel therapy once + crossover without re-censoring
- ERG: could not verify claim about historical data. Data immature. Weibull for both arms underestimates survival at 10 and 15 years; **generalised gamma** both arms fitted jointly. After technical engagement which preceeded this meeting, company changed to generalised gamma. Emerging evidence that abiraterone and enzalutamide 'resistance' can develop – may also occur with apalutamide.

◉*Is generalised gamma an appropriate survival fit to extrapolate? Is jointly fitting appropriate? Should company consider other approaches?*

*Company conducted exploratory analysis using external data from 3 trials identified in a systematic review

Time on treatment

- 6 distributions fitted individually to time-on-treatment (TTD) data for apalutamide + ADT
  - However, several extrapolations for TTD crossed with metastases-free survival (MFS) curves because of convergence of MFS and TTD curves at end of SPARTAN trial. Clinical feedback considered not feasible & contradicts summary of product characteristics.
- Therefore company modelled TTD using a proxy: [redacted]
  - [redacted]
  - [redacted]

Stakeholders

•Comparator company: not clear which data-cut informs time on treatment – if later cut than MFS then would likely have more people stopping treatment, could underestimate treatment costs

Extrapolating beyond trial, waning

Company

- Could not identify longer term data
- Selected curves in line with NICE technical documents

Stakeholders

- Comparator company
  - If recommended, patients would lose access to novel therapies enzalutamide and abiraterone, therefore new pathway would have lower survival
  - Model should include treatment waning
  - Model should include 'reversal of OS benefit' for apalutamide vs ADT after someone progressed to metastatic disease
  - Company should adjust MFS to remove confounding of therapies not permitted for in the UK
- Clinical expert agree with Weibull

ERG

- Choice of extrapolation drives cost effectiveness
- More flexible modelling approaches (e.g. piecewise) more appropriate
- Literature suggests that resistance to novel therapies, such as enzalutamide and abiraterone, is likely to develop with time. Could apply to apalutamide but need more evidence. Insufficient evidence to conclude on duration of benefit.

ADT: androgen deprivation therapy; MFS: metastases-free survival; mHRPC: metastatic hormone relapsed prostate cancer; OS: overall survival

Utilities for metastatic hormone-resistant disease*

Company adjusted values, ERG did not

Background

- Utilities for 1st line treatment for pre- and post-progression from SPARTAN (EQ-5D 3L)
- 2nd /3rd line: company derived applying 'relative decline ratio', utility from TA387 (abiraterone)
- ERG note that company assumes a similar relative decline between abiraterone and apalutamide; unlikely as trial has different starting populations. Appears to underestimate utility values for 2nd and 3rd line

Company

- Not appropriate to use unadjusted TA387 (abiraterone, mHRPC) utilities given population differences
- Maintain that derived utilities are appropriate based on NICE DSU technical document 12
- Same approach accepted in NICE ID945 (abiraterone, high risk metastatic hormone-naive)

ERG comments

- ERG prefers to use utilities from TA377 (enzalutamide for metastatic hormone-resistant disease [mHRPC]) with no adjustment
  - Company 2nd and 3rd line adjusted utilities significantly lower than TA377 and TA580 (enzalutamide for non-metastatic hormone-relapsed disease).
  - Utilities from TA387 (abiraterone for mHRPC) for 2nd line mHRPC uncertain; not clearly defined as 1L/ 2L/3L mHRPC
- Estimate for 3rd line metastatic hormone relapsed disease in TA387 taken from another study by Sandblom *et al*, so not possible to adjust in same way as for 2nd line
- Conduct scenario analysis with TA387

NOTE: Patients with non-metastatic hormone relapsed disease will progress to **metastatic hormone-relapsed prostate cancer (mHRPC).* This slide only discusses utility values for the population that progresses to metastatic hormone-resistant disease.

Utilities for metastatic hormone relapsed disease

Comparator company

- Utility values should link to subsequent therapies e.g. after apalutamide patients mainly receive docetaxel, negatively affecting utility
- Applying same utilities can bias cost-effectiveness favoring apalutamide
- Utilities in metastatic hormone resistance disease should be equal whether one progressed from nmHRPC (or mHSPC)
- Company should explore utilities from previous appraisals rather than SPARTAN (& TITAN) separately, which yields inconsistent values

Patient group

- Symptoms (e.g. fatigue, pain, increasing urinary symptoms) and thus quality of life depends on individual patient, disease stage, and progression of disease
- Earlier treatments increase time to progression and onset of reduction in quality of life
- Increased patient quality of life has considerable positive effect on carers

Clinical expert

- Appears minimal different between company and ERG quality of life estimates

	Company	ERG: TA387 (abiraterone)	ERG: TA377 (enzalutamide)
Pre-progression	XXXXXX	XXXXXX	0.8233
1st line mHRPC	XXXXXX	XXXXXX	0.771
2nd line mHRPC	XXXXXX	0.625	0.658
3rd line mHRPC	XXXXXX	0.500	0.612

- *Should utility values be adjusted to reflect population differences or not?*
- *What source of utility value is more appropriate?*

NICE

mHSPC: metastatic hormone sensitive prostate cancer; nmHRPC: non-metastatic hormone relapsed prostate cancer; TITAN: trial for mHSPC indication

Cost-effectiveness estimates

All incremental cost effectiveness ratios are reported in PART 2 slides because they include confidential discounts

In part 2 committee will see company analyses and ERG exploratory analyses

- ERG conducted a range of scenario analyses including:
  - Apply different approaches to adjusting estimates of survival for crossover and use >1 novel therapy
  - Apply adjusted utility values for 2nd and 3rd lines metastatic hormone relapsed health states, the company's original assumption
  - Use alternative sources to estimate utility values 2nd and 3rd lines metastatic hormone relapsed health states (TA387)
  - Apply incidence of neutropenia and febrile neutropenia offered by company in response to technical engagement (36.3% and 18.2% respectively)

Innovation

- New anti-androgen receptor inhibitor, significant clinical benefit
- Benefits not captured in QALY:
  - High risk non-metastatic, hormone-relapsed disease: ADT and darolutamide available
  - Apalutamide will offer chance for patients to receive active treatment rather than standard of care which cannot delay time to progression
  - Potential to simplify disease management and reduce strain on NHS capacity and resources as does not require concomitant corticosteroids and associated monitoring
  - Heavy psychological burden of receiving ADT alone for patient and carer; significant benefits to mental health and caregiver burden

◉ *Is apalutamide a step-change in treatment and offer benefits not captured in modelling?*

Equality

- No issues raised during scoping
- Recommendations should apply to “adults” with prostate cancer rather than “men”, to avoid excluding people who are transgender

◉ *Are there equalities issues?*

End of life
Non-metastatic, hormone-relapsed

- Both criteria must be met:
  1. Treatment is indicated for patients with short life expectancy, normally <24 months
  2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- Company – did not comment in submission
- ERG – end of life not met because did not pass first criterion
  - 1st criterion: Not met, "the life expectancy of patients treated with ADT would normally be greater than 24 months" and SPARTAN median OS approx. 60 months
  - 2nd criterion: Met, median improvement in life expectancy 14 months

Key cost effectiveness issues
Non-metastatic, hormone-relapsed

- Extrapolation of survival curves: which distributions are most appropriate?

- Should utility values be adjusted to reflect population differences between apalutamide and abiraterone trial? What source of utility value is more appropriate?

Metastatic, hormone-sensitive

Apalutamide (Erleada, Janssen)

Metastatic, hormone-sensitive

Not limited to 'high risk'

Marketing authorisation	In adult men for the treatment of: • metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy
Mechanism	Androgen receptor antagonist
Administration & dose	• Oral • Recommended dose: 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 Confidential patient access scheme ('PAS') discount in place

Background

Metastatic, hormone-sensitive

- Treatment options: ADT or docetaxel for patients considered fit enough
  - Docetaxel not licensed, but NHS England commissions for up to 6 cycles
  - Can get it later in treatment pathway as well
- 27% **newly** diagnosed receive docetaxel; decreased during pandemic *
- ERG: no robust evidence to confirm benefit of ADT on overall survival, but it is gold standard treatment for metastatic prostate cancer
- Apalutamide + ADT is new treatment option, particularly for those not eligible for or are unwilling to receive docetaxel
- Aim of treatment is to delay disease progression
  - disease progresses to metastatic hormone-relapsed prostate cancer in ~21 months for patients on ADT alone

**During COVID-19 pandemic, to reduce hospital attendance and toxicity-related admissions, enzalutamide + ADT - administered orally at home - offered instead of docetaxel - IV infusion at hospital - for patients with newly diagnosed metastatic disease.*
Patients intolerant of enzalutamide can switch to abiraterone.
NG161 NHS England interim treatment options during the COVID 19 pandemic (nice.org.uk)

Does not affect appraisal today

ADT, androgen derivation therapy

Patient perspective

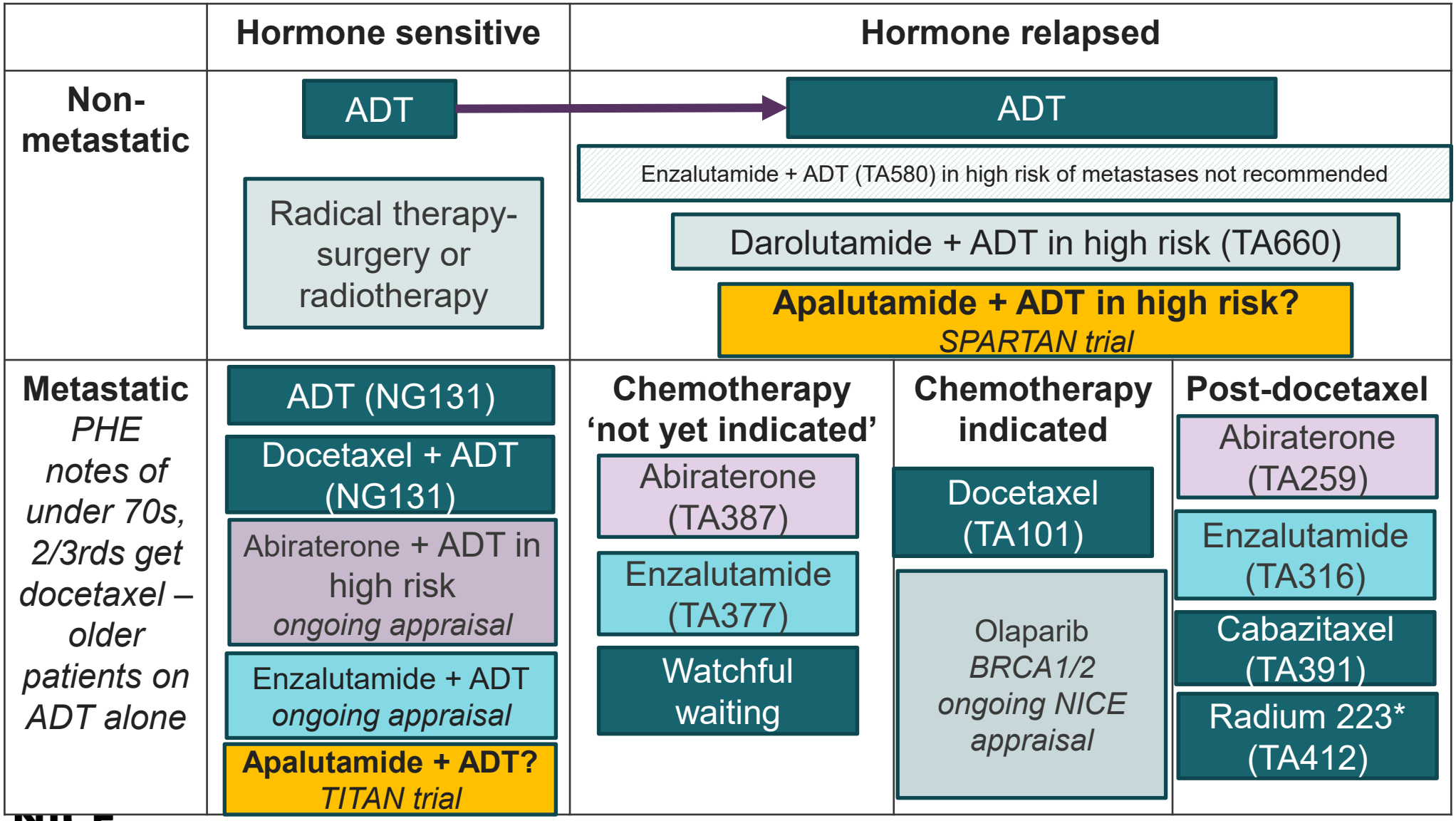
Living with condition and benefits of apalutamide

- Diagnosis of metastatic hormone sensitive prostate cancer a ‘bombshell’
- Causes deep emotional and psychological distress for patients, families and carers
- Particularly true for those diagnosed when asymptomatic
- Significant number of relatively young people with young families
- Diagnosis takes “over the life of the patient not only immediately but often for the whole of the life…remaining”
- Patients need swift and definitive treatment options
- Reduce risk of death**:** shown in TITAN trial compared with placebo + ADT
- **Quality of life:** Maintain good quality of life while on treatment. Given orally, does not require specialised admin or hospital treatment; monitoring organised locally, follow-up appointments done remotely
- **Adverse events:** Apalutamide associated with more frequent grade 3/4 events vs ADT+ placebo (42% vs. 41%), most common was rash (27% vs. 9%)
- **Subsequent treatments:** Taken long-term i.e. until progression. If used early in pathway, will restrict choice of later treatments with abiraterone or enzalutamide. But, most would opt for earlier and more effective treatment overall rather than ‘save’ such drugs for later. At later stage docetaxel may still be option, but often not tolerated. Radium223 may be appropriate.

Source: patient organisation submission

Treatment pathway for prostate cancer

Androgen deprivation therapy (ADT) continues despite hormone relapsed
Docetaxel can be offered twice; abiraterone OR enzalutamide only once



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

*bone metastasis only

Decision problem

Metastatic, hormone-sensitive

	Final scope issued by NICE	Company submission	Rationale for difference
Population	Adults with metastatic, hormone-**sensitive** prostate cancer		Company makes case for subgroup of patients ineligible or unsuitable for docetaxel
Intervention	Apalutamide + ADT		
Comparators	• ADT • Docetaxel + ADT • Abiraterone + prednisone or prednisolone and ADT *(limited to high-risk of progression, ongoing NICE appraisal)* • Enzalutamide + ADT *(ongoing NICE appraisal)*	• ADT • Docetaxel + ADT	Abiraterone and enzalutamide not routinely commissioned
Outcomes	• Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	As per scope plus: • Radiographic progression free survival • 2nd progression free survival	

ADT, androgen deprivation therapy

ERG report issues
Metastatic, hormone-sensitive

Issue	Company response to TE
Treatment switching: 'Modified RPSFTM' used to adjust trial for crossover & no. of subsequent treatments (to better reflect NHS), but not peer-reviewed & potentially not valid	Accounted for abiraterone crossovers; updated original 'modified' RPFSTM with final analysis of TITAN (cut-off September 2020) Provided IPCW results
Docetaxel ineligible subgroup: No evidence available for subgroup, unclear if main population efficacy generalisable	Defined chemo-ineligible subgroup
Survival curve extrapolation: large impact on cost effectiveness estimates	Justified curve choice. Found mHSPC longer term data but concluded not appropriate to use
Utility values for 2nd & 3rd line: More rationale needed re source & adjustment. Used TA387 (abiraterone) utilities for mHRPC before chemotherapy, adjusted using relative decline ratio assuming similar decline	Justified and maintained utility choice
Duration of docetaxel AE treatment costs: Docetaxel given for 6 cycles but adverse event costs applied over time horizon	Agree original company approach overestimates cost, but ERG approach may underestimate.

NICE

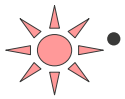
New issue, specific to hormone-sensitive, metastatic indication

IPCW: Inverse probability of censoring weighting; mHRPC: metastatic hormone resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; RPSFTM: Rank Preserving Structural Failure Time Model

Key issues for clinical and cost effectiveness

Many in common with non-metastatic hormone-relapsed indication

Clinical issues

- Is it reasonable to adjust for both crossovers and more than 1 new hormonal agents?
- Is it appropriate to use “modified” Rank Preserving Structural Failure Time Model?
- In abiraterone trial (COU-AA-302) company adjusted for cross-over only for overall survival, should it have considered progression-free survival too?
-  Is there evidence for apalutamide in subgroups of chemo-eligible or chemo non-eligible?

Cost effectiveness issues

- Extrapolation of survival curves: which distributions are most appropriate?
-  How long do adverse events for docetaxel last? Is 6 months realistic?
-  What incidence for febrile neutropenia and neutropenia caused by docetaxel should model contain?
- What source of utility values is more appropriate?

 New issue, specific to metastatic, hormone-sensitive indication

Clinical effectiveness

Metastatic, hormone sensitive

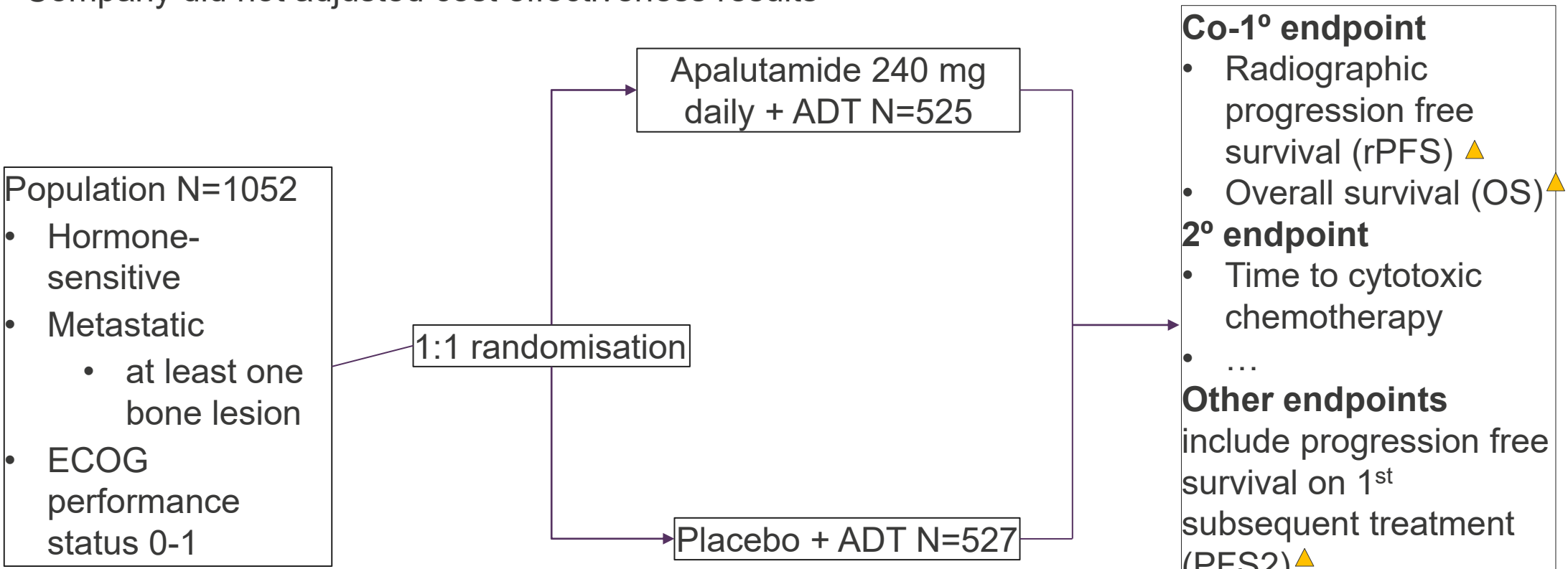
Key clinical issues

Many in common with non-metastatic hormone relapsed indication

- Is it reasonable to adjust for both crossovers and more than 1 new hormonal agents?
- Is it appropriate to use “modified” Rank Preserving Structural Failure Time Model?
- In abiraterone trial (COU-AA-302) company adjusted for cross-over only for overall survival, should it have considered progression-free survival too?
- Is there evidence for apalutamide in subgroups of chemo-eligible or chemo non-eligible?

TITAN trial

- Phase III, placebo-controlled, multinational (23 countries, n=36 UK patients).
- Cross-over allowed after study unblinding, at final analysis for radiographic progression free survival
- Patients received subsequent therapies after progression
- Company did not adjusted cost effectiveness results



Analyses:
1. November 2018– ***final analysis for rPFS***
2. September 2020 – ***final for OS and PFS2***

▲ *Endpoints inform economic model*

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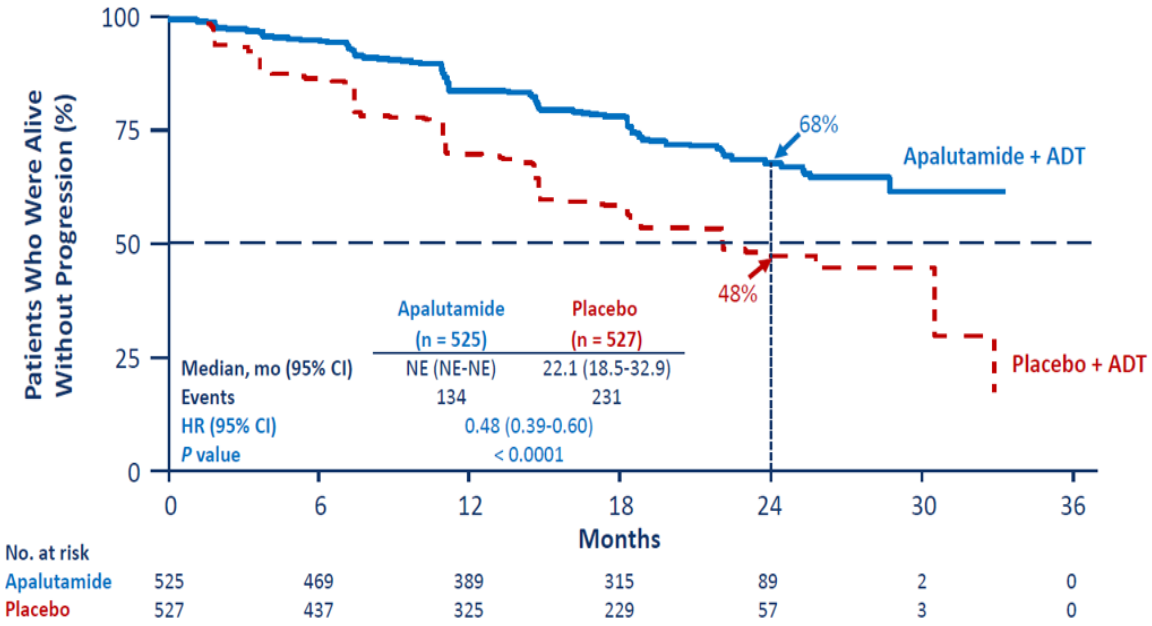
EQ-5D-3L: EuroQoL five-dimensions – three levels; FACT-P: Functional Assessment of Cancer Therapy Prostate Module, BFI: Brief Fatigue Inventory, BPI-SF: Brief Pain Inventory -short form

TITAN 1º co-primary radiographic progression free survival (rPFS)

Intention to treat analyses, first analysis for 1º endpoint - November 2018



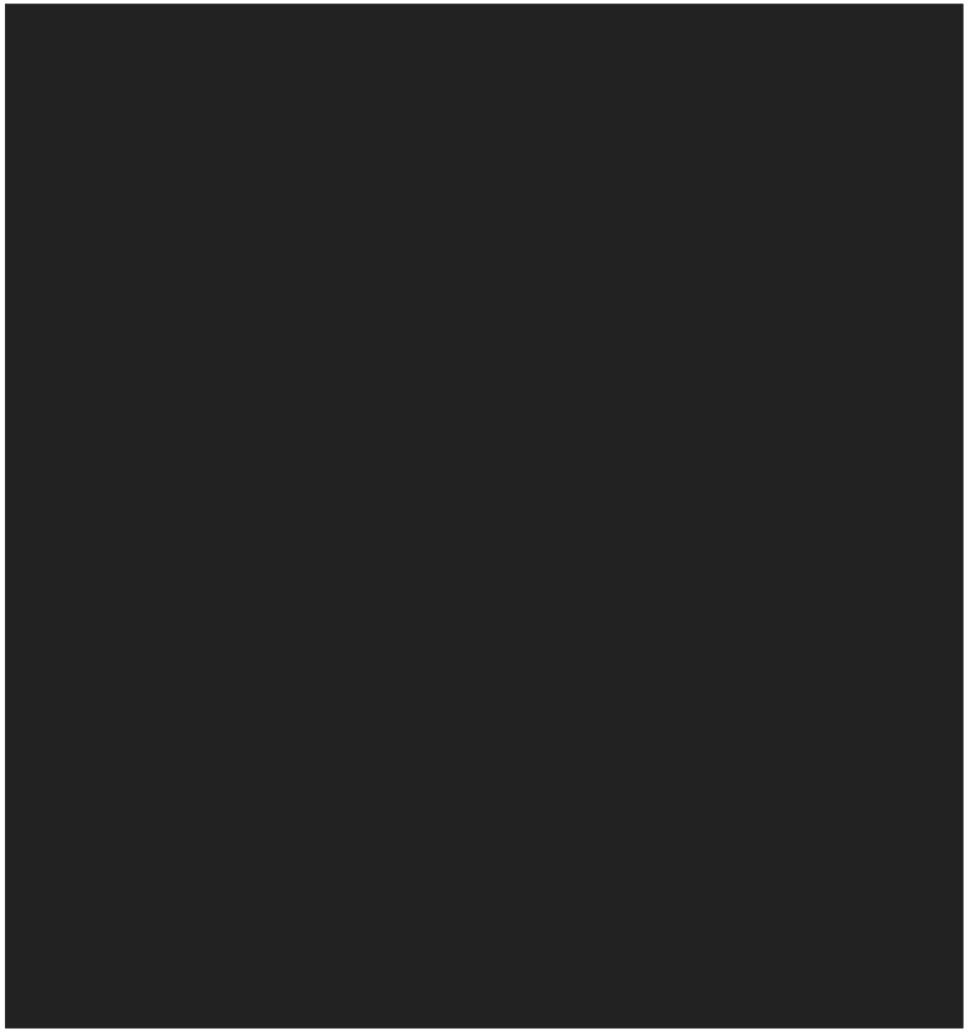
	Apalutamide + ADT N=525	Placebo + ADT N=527
Number (%) of patients with event	134 (25.5)	231 (43.8)
Number (%) of patients censored	391 (74.5)	296 (56.2)
Median rPFS months (95% CI)	NE (NE, NE)	22.1 (18.5, 32.9)
Hazard ratio	0.5 (0.4 to 0.6), p<0.0001	

NE: Not estimable

Source: CS Figure 23 p 111

TITAN 1º co-primary overall survival (OS)

Intention to treat analyses, final analysis for 1º endpoint - September 2020



	Apalutamide + ADT N=525	Placebo + ADT N=527
Number (%) of patients with event	XXXXX	XXXXX X
Number (%) of patients censored	XXXXX	XXXXX X
Median OS months (95% CI)	XXXXX	XXXXX X
Hazard ratio	XXXXX	

NE: Not estimable

Source: Company TE response Figure 7 p 61

TITAN 2º progression-free on 1st subsequent treatment (PFS2)

Intention to treat analyses, final analysis for 2º endpoint; data immature September 2020

	Apalutamide + ADT N=525	Placebo. + ADT N=527
Number (%) of patients with event	XXXXX	XXXXX
Number (%) of patients censored	XXXXX	XXXXX
Median PFS2 months (95% CI)	XXXXX	XXXXX
Hazard ratio	XXXXX	

NE: Not estimable

NICE

Source: Company TE response Figure 9 p 61

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

Company base case: unadjusted OS and PFS2, final analysis

Company

- Crossovers: **TITAN:** 40% (288/527) in placebo + ADT → apalutamide + ADT
- Received >1 new hormonal agents:

Exposure to subsequent treatments:
- Apalutamide + ADT: [redacted] [including new agents: [redacted] abiraterone, [redacted] enzalutamide]
- Placebo + ADT: [redacted] [including new agents: [redacted] abiraterone, [redacted] enzalutamide]

- Used TITAN final analysis (September 2020)
- Company used different censoring rules for PFS2 of TITAN interim analysis and final analyses to ensure "*PFS2 events were more than OS events and hence preserve modelling approach used in original submission…Using original censoring rules would result in implausible PFS2 KM curves that lie above respective OS curves for each treatment arm*"
  - Original: patients censored at last known date alive, or date prior to 2nd subsequent therapy/ Alternative: patients not censored at start of 2nd subsequent therapy
- Unadjusted and adjusted hazard ratios for OS and PFS2

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

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

ERG's comments on adjusting for treatment switching

Company (contd.)

- Common treatment assumption not explored; likely to bias against apalutamide, as more apalutamide patients in TITAN received 2nd novel therapy
- Considered IPCW but concluded not viable
- **Company base case: unadjusted hazard ratios for OS and PFS2**

ERG

- More appropriate to use adjusted hazard ratios for OS/PFS2, final analysis of COU-AA-302 (used in ERG base case)
- Reiterates that methodological guidance from NICE Decision Support Unit recommends **re-censoring** of adjusted survival estimates
- Alternative censoring rules generated lower of the 2 HRs & narrower confidence intervals. Gives slightly more favourable estimate of clinical effectiveness of apalutamide
- Company's interpretation of IPCW is reasonable

◉ How should trial be adjusted to reflect NHS practice? Has company justified its approach? Censoring or re-censoring?

ADT: androgen deprivation therapy; HR: hazard ratio; IPCW: Inverse probability of censoring weighting; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment

Apalutamide + ADT compared with docetaxel + ADT, overall survival

Network meta-analysis show that apalutamide + ADT offers an advantage over ADT alone and is favourable versus docetaxel + ADT

	Comparison		Fixed effect (company base case)
Docetaxel ineligible/ unsuitable subgroup	Apalutamide + ADT vs ADT alone	HR (95% CrI)	[redacted]
		Probability that HR <1	[redacted]
Docetaxel-eligible subgroup	Apalutamide + ADT vs docetaxel + ADT	HR (95% CrI)	[redacted]
		Probability that HR <1	[redacted]

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

Company makes case for subgroup of patients ineligible or unsuitable for docetaxel

Background

- Company: docetaxel-ineligible is mHSPC key subgroup. But no evidence to inform subgroup
- Company conducted network meta-analysis (NMA) to assess effectiveness & safety of apalutamide vs. docetaxel for 6 outcomes (OS, rPFS, PFS2, Time to PSA progression, overall adverse events (AEs) and serious AEs; only OS and PFS2 directly informs economic model)

Company

- Subgroup defined in abiraterone appraisal
  - people who have contraindications to docetaxel as listed in summary of product characteristics for docetaxel and NHS England's clinical commissioning policy statement for docetaxel + ADT*
  - For example, poor performance status, significant comorbidity, peripheral sensory neuropathy etc..
  - 27% mHSPC received docetaxel, but likely underestimated due to usage restriction during COVID-19. At least 75% of mHSPC patients currently chemo ineligible/unsuitable

ERG comments

- Possible to infer likely generalisability of TITAN to mHSPC population from consistent effects observed across the OS subgroup analyses
  - But inherent limitations of clinical trial subgroup analyses preclude definitive conclusions about generalisability
- Eligibility criteria in abiraterone appraisal would also apply
- NMA method appropriate

*www.england.nhs.uk/2016/01/treatment-prostate-cancer/

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ADT: androgen deprivation therapy; mHSPC: Metastatic sensitive relapsed prostate cancer; OS: overall survival; PFS2: progression-free survival on 1st subsequent treatment; rPFS: radiographic PFS; PSA: Prostate-specific antigen

Stakeholders' comments on subgroup of patients ineligible or unsuitable for docetaxel

Stakeholders

- Comparator company:
  - Not clear whether TITAN population fully reflective of chemo ineligible population; may have different clinical characteristics & prognosis affecting clinical and cost-effectiveness
- Patient organisations:
  - Docetaxel eligibility discussed in previous NICE appraisals
  - Generally accepted; there are patients 'unsuitable' for docetaxel, but no standard criteria
  - Often older patients due to side effects
  - Frailty scores may be part of decision process, but ultimately should be individual clinician and patient choice
- Clinical expert:
  - Docetaxel ineligibility discussed in previous appraisal
  - Several factors can be listed, but not feasible to get this as a subgroup from TITAN

◉ *What evidence is required to address apalutamide in people who cannot or should not take docetaxel?*

TITAN safety profile

Company: manageable safety profile

	Apalutamide plus ADT (n = 524)	Placebo plus ADT (n = 527)
TEAEs, total, n (%)	507 (96.8)	509 (96.6)
TEAEs, drug-related, n (%)	315 (60.1)	219 (41.6)
TEAEs, Grade 3-4, n (%)	221 (42.2)	215 (40.8)
TEAEs, Grade 3-4, drug-related, n (%)	66 (12.6)	31 (5.9)
SAEs, total, n (%)	104 (19.8)	107 (20.3)
SAEs, drug-related, n (%)	10 (1.9)	4 (0.8)
SAEs, Grade 3-4, n (%)	84 (16.0)	86 (16.3)
TEAE-related discontinuation, n (%)	42 (8.0)	28 (5.3)
TEAE-related discontinuation, drug-related, n (%)	17 (3.2)	4 (0.8)
TEAE-related deaths, n (%)	10 (1.9)	16 (3.0)
TEAE-related deaths, drug-related, n (%)	0 (0.0)	0 (0.0)
Deaths within 30 days of last dose, n (%)	18 (3.4)	23 (4.4)
Death due to prostate cancer, n (%)	8 (1.5)	7 (1.3)
Death due to AE, n (%)	10 (1.9)	16 (3.0)

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ADT: androgen deprivation therapy; AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Key clinical issues

Many in common with non-metastatic hormone relapsed indication

- Is it reasonable to adjust for both crossovers and more than 1 new hormonal agents?
- Is it appropriate to use “modified” Rank Preserving Structural Failure Time Model?
- In abiraterone trial (COU-AA-302) company adjusted for cross-over only for overall survival, should it have considered progression-free survival too?
- Is there evidence for apalutamide in subgroups of chemo-eligible or chemo non-eligible?

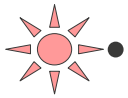
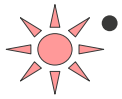
New issue, specific to metastatic, hormone-sensitive indication

Cost effectiveness

Metastatic, hormone sensitive

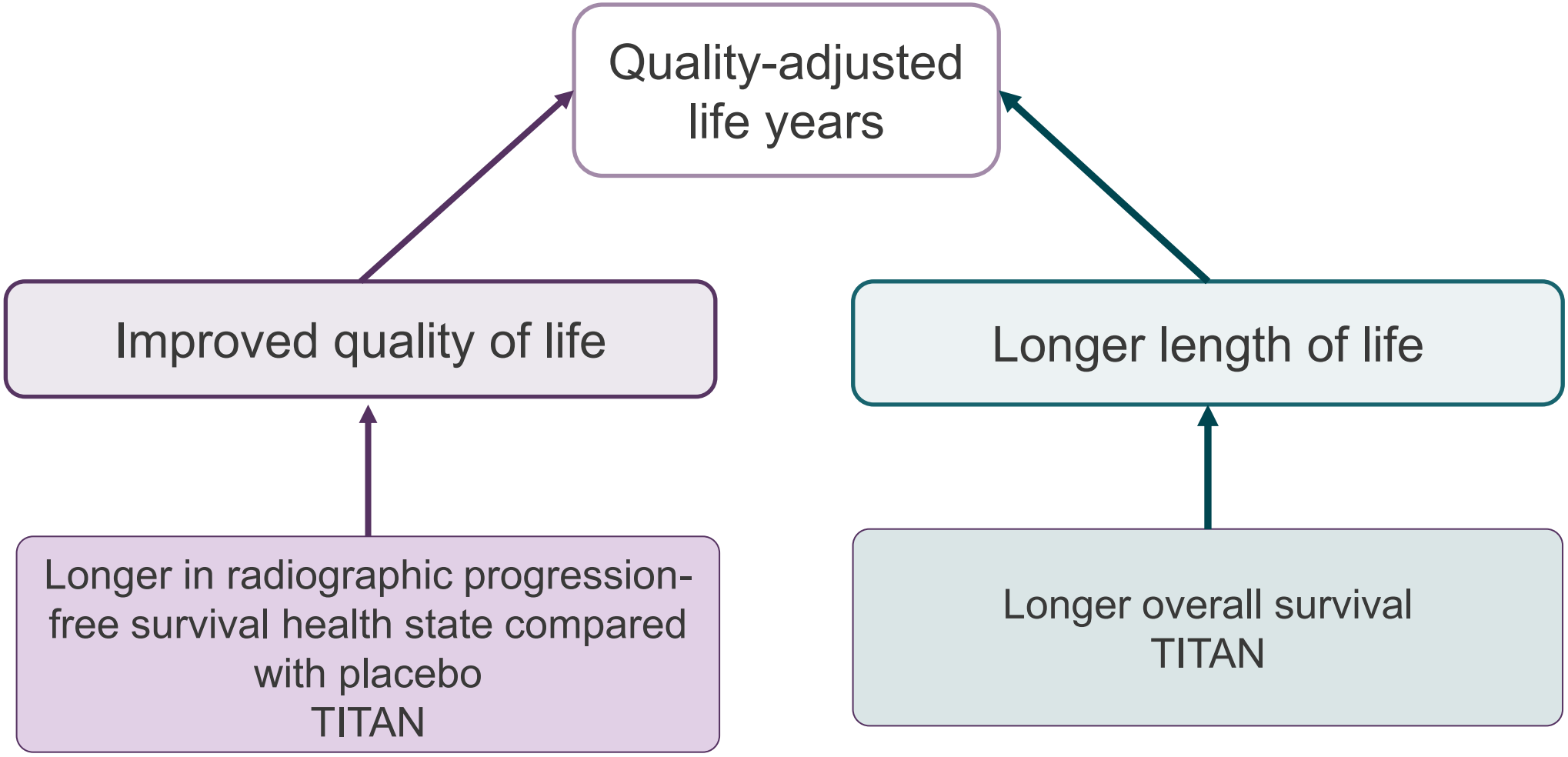
Key cost effectiveness issues

Some common with non-metastatic hormone relapsed indication

- Extrapolation of survival curves: which distributions are most appropriate?
-  How long do adverse events for docetaxel last? Is 6 months realistic?
-  What incidence for febrile neutropenia and neutropenia caused by docetaxel should model contain?
- What source of utility values is more appropriate?

 New issue, specific to metastatic, hormone-sensitive indication

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

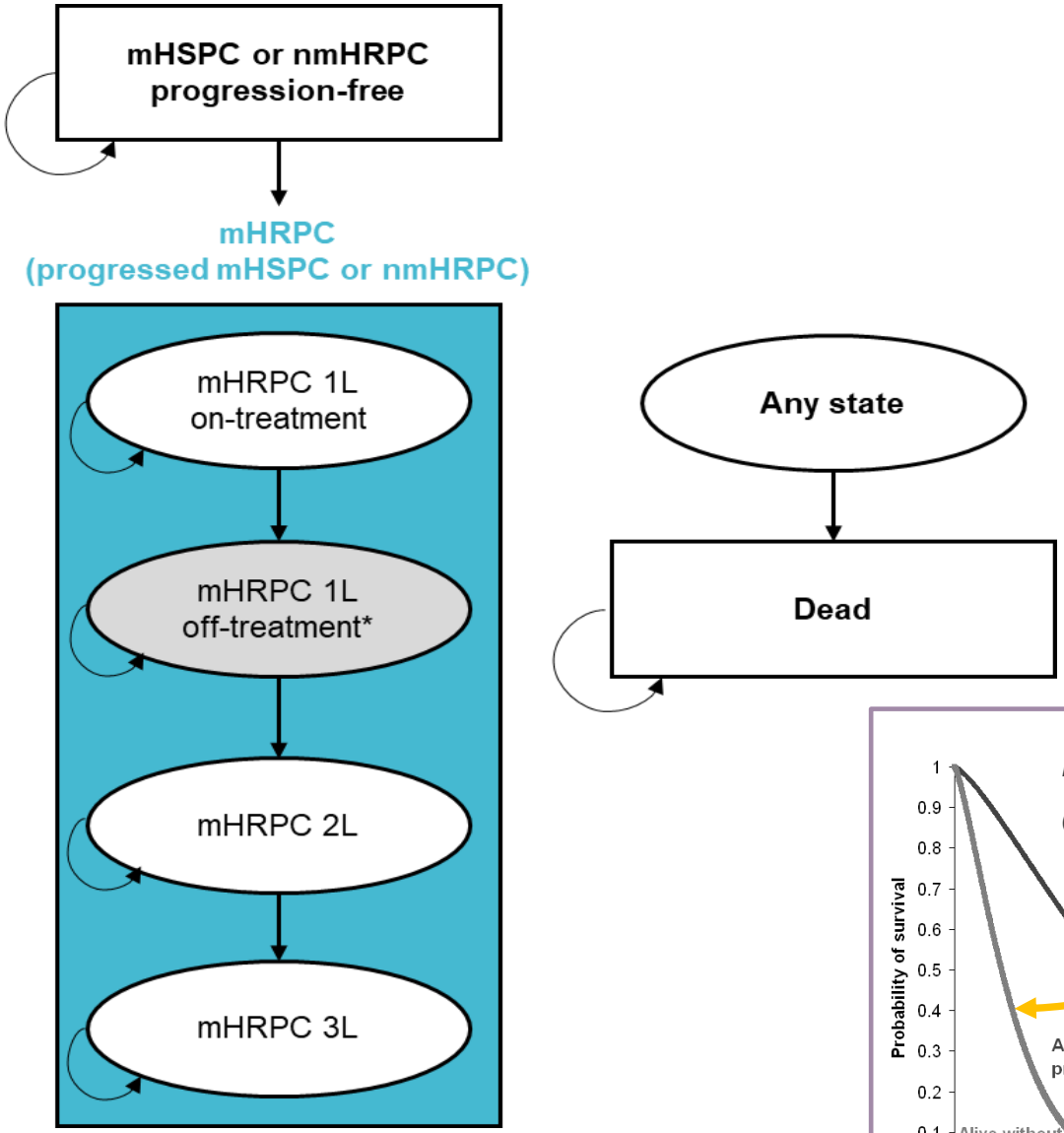


Comparison of life-year before and after progression in company base case

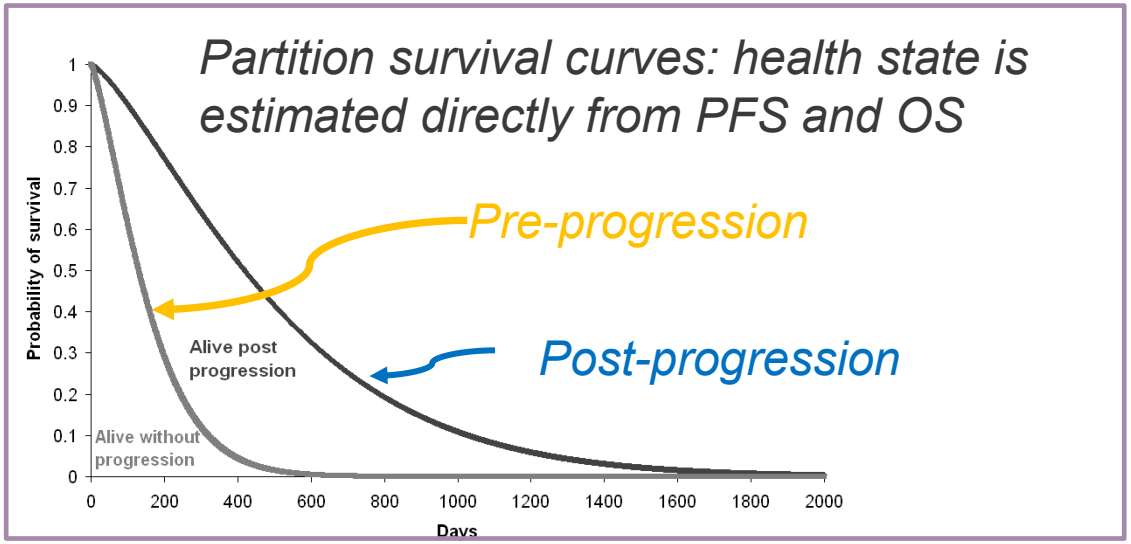
NICE

Based on company's model; produced by NICE

Company model



- Partitioned survival model but use of multiple health states to model subsequent therapy
- Efficacy informed by extrapolated rPFS and OS (TITAN)
- 1-week cycle
- Lifetime horizon (32 years)
- Patient can receive up to 3 lines of subsequent therapy
- 3.5% discounting



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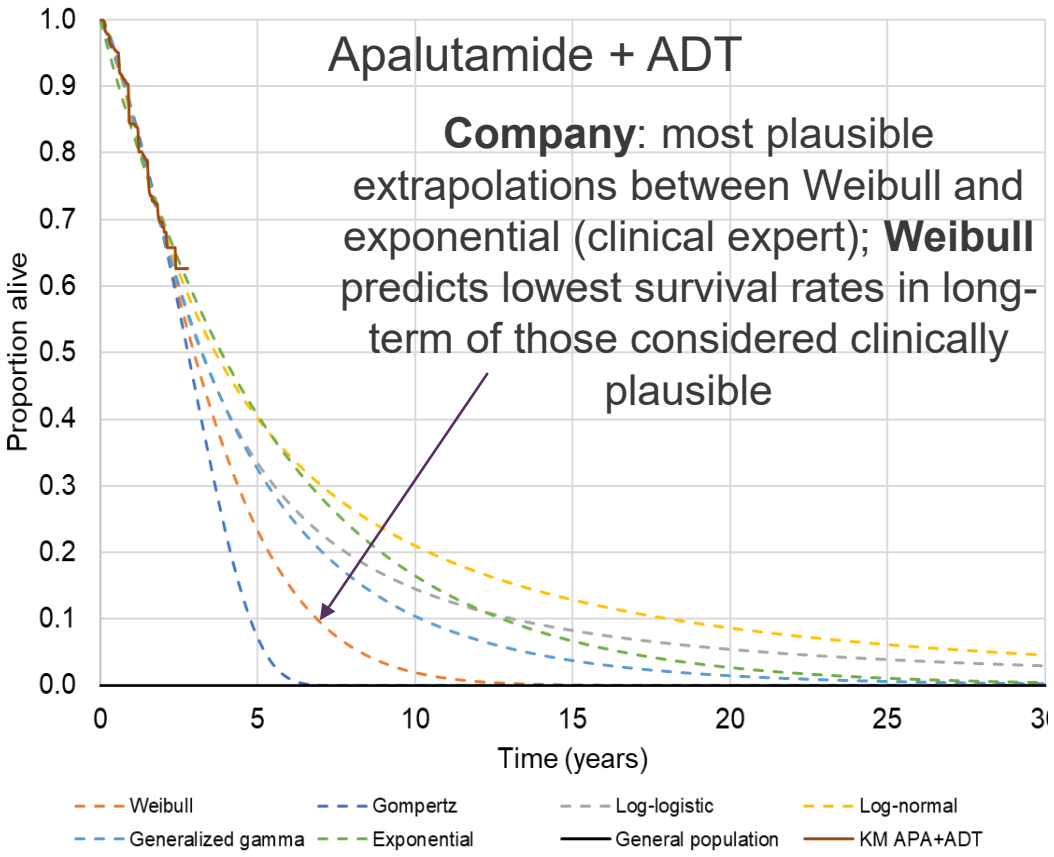
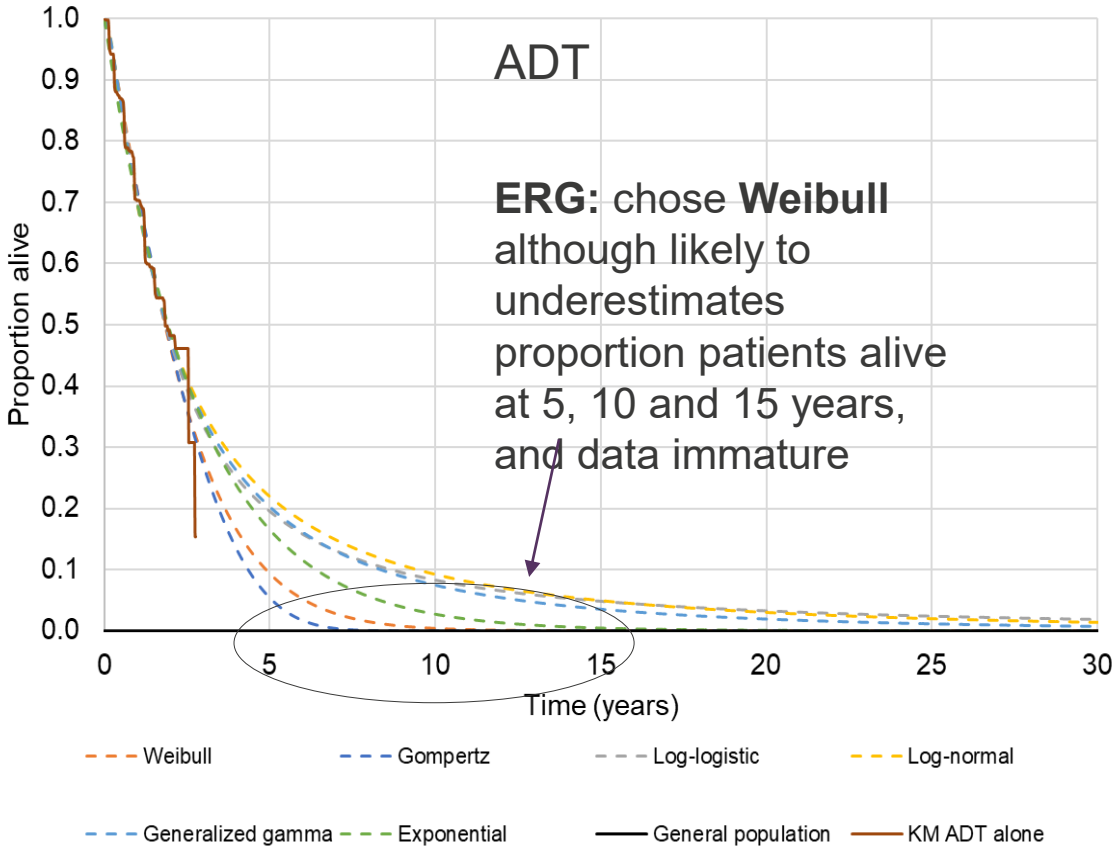
1L: first-line; 2L: second-line; 3L: third-line; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer, OS: overall survival, rPFS: radiographic progression-free survival

Extrapolating radiographic progression-free survival

Company chose Weibull independently fit to both treatments



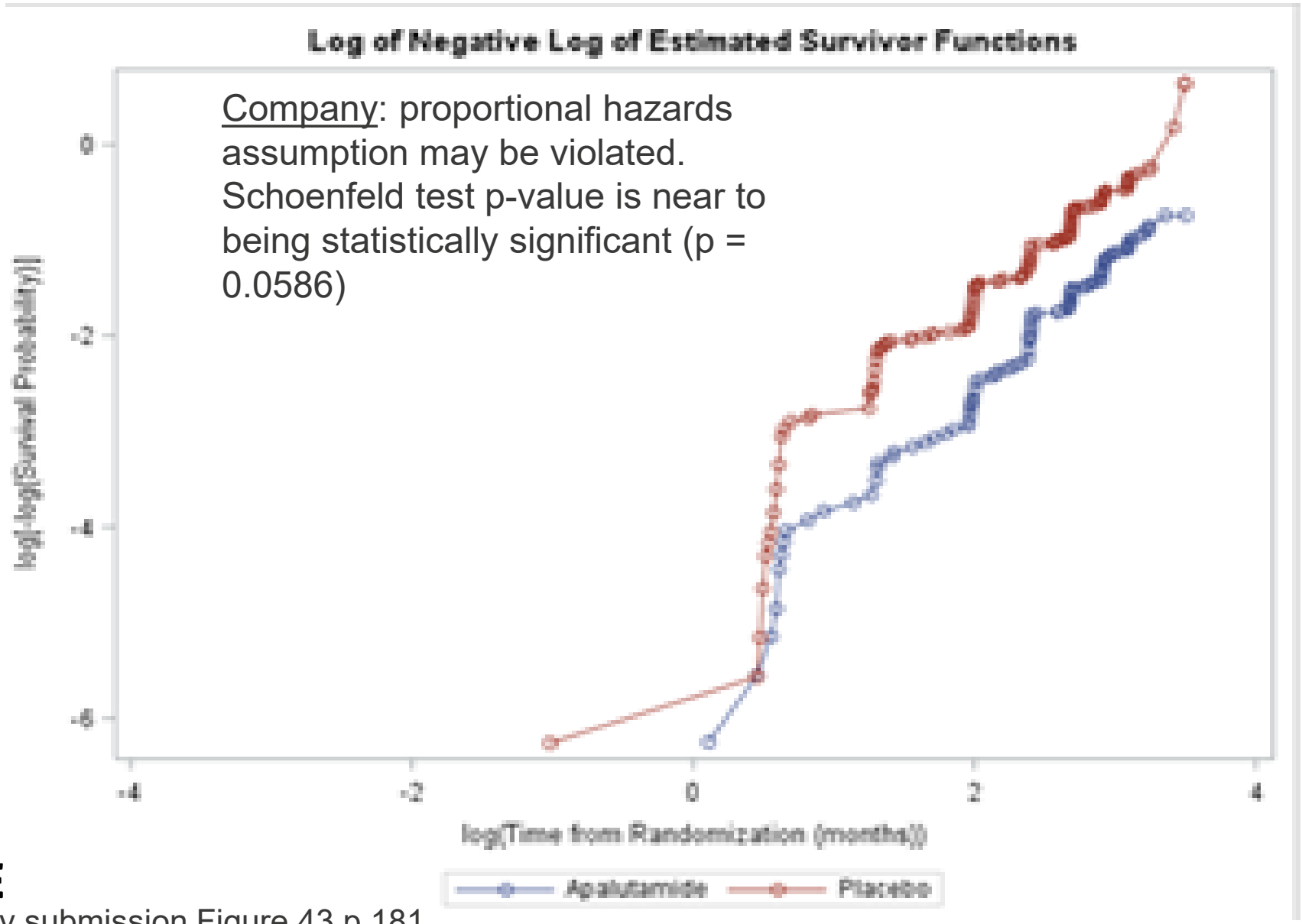


ERG: choice of survival extrapolation has large impact on model results

◉*Which distribution is most appropriate for rPFS?*

Radiographic progression-free survival

Hazard plots: curves becomes parallel after week 16



Company submission Figure 43 p.181

Overall survival (OS) extrapolation for apalutamide + ADT

Company chooses jointly-fitted Weibull; ERG favours flexible models

COU-AA-302 trial of abiraterone in metastatic hormone relapsed disease before docetaxel indicated

Apalutamide + ADT **(unadjusted)**

Apalutamide + ADT **(adjusted** with RPSFTM COU-AA-302 final analysis)

ERG: Agree Weibull more conservative than generalised gamma but more flexible models are appropriate. Clinical advice suggests that Weibull fits in ADT arm underestimates patient survival at 10 and 15 years which favours apalutamide. Base case: adjusted

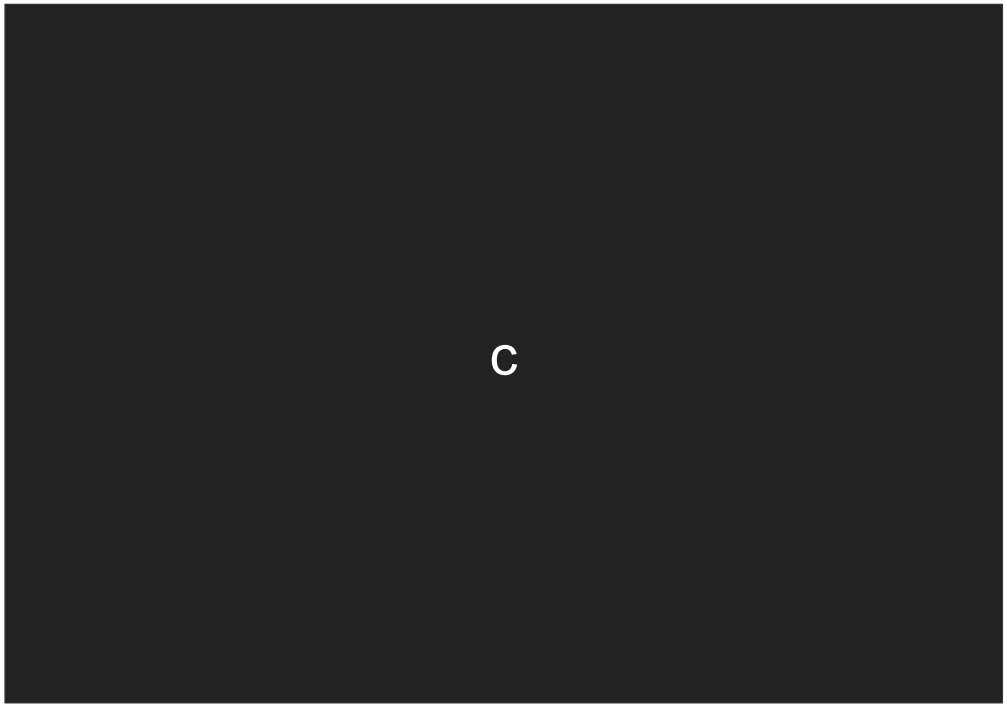
NICE ◉*What is the best way to model overall survival given immature data?*

Fig 28&30 Company response to TE

Extrapolating progression-free on 1st subsequent treatment (PFS2) for apalutamide + ADT

Company chose Weibull, ERG chose Gompertz

Apalutamide + ADT **(unadjusted)**



Apalutamide + ADT **(adjusted)**

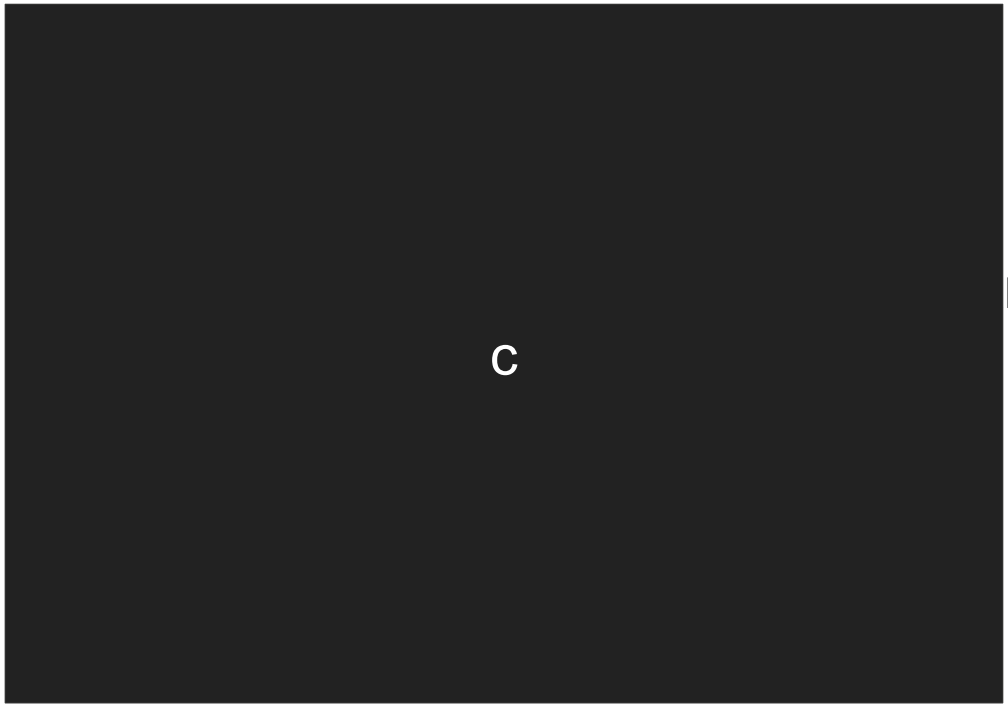


Fig 29 Company response to TE

◉*Which distribution is most appropriate for PFS2?*

Time on treatment

- 6 distributions fitted individually to time-on-treatment (TTD) data for apalutamide + ADT
  - However, several extrapolations for TTD crossed with radiographic progression-free survival (rPFS) curves because of convergence of rPFS and TTD curves at end of TITAN trial. Clinical feedback considered not feasible & contradicts summary of product characteristics.
- Therefore company modelled TTD using a proxy: [redacted]
  - [redacted]
  - [redacted]

Stakeholders

•Comparator company: not clear which data-cut informs time on treatment – if later cut than rPFS then would likely have more people stopping treatment, could underestimate treatment costs

Extrapolating TITAN survival curves

Company

- **Extrapolating overall survival**
  - Used historical survival data for ADT in "informed fits" approach (Pennington 2018)
  - That is, validating extrapolations with external data
- **Extrapolating rPFS**:
  - All curves good visual fit to observed data;
  - Feedback from 5 clinical experts other curves may be plausible, Weibull most appropriate
  - Can’t use available PFS extrapolations data because of differing definitions of progression and way data were collected
  - Weibull independently fitted does not assume proportional hazards. Instead, Weibull assumes hazard function can either increase or decrease monotonically
  - Weibull curve preferred in some previous submissions in prostate cancer

Stakeholder

- Comparator company
  - If recommended, patients would lose access to novel therapies enzalutamide and abiraterone, therefore new pathway would have lower survival
  - Treatment waning and potential reversal of OS benefit for apalutamide vs ADT should be implemented on progression to mHRPC in model.
  - rPFS should be adjusted to remove confounding of any therapies not permitted in UK
- Clinical expert agree with Weibull

Duration adverse event + costs – docetaxel

Company and ERG disagree on appropriate duration

Company:

- Applies cost of adverse events from docetaxel over lifetime, Gravis *et al.* 2013
- Uses rates of febrile neutropenia and neutropenia from Gravis et al may be low compared with 'real world' NHS data (Patrikidou et al 2017)
- Disagrees with ERG's approach of modelling adverse events for 6 months
- Notes that patients may stop docetaxel, but continue ADT which has adverse effects

ERG comments

- Cost overestimated
- Docetaxel given for 6 cycles and majority of AEs costs are during 18-week period
- Costs of adverse events should only be costed up to trial follow-up duration (26 weeks)

Comparator company

- Should include cost of pharmacist dispensing time for oral therapies
- Model should include different frequency of monitoring by treatment

Patient organisations

- Quality of life data shows decrease over 2 years for docetaxel vs abiraterone
- Variety of symptoms during weeks sometimes months after docetaxel

Clinical expert

- Some docetaxel side-effects e.g. neuropathy last. Better to use 1 year duration
- Adverse effects can be debilitating even up to 1 year after people stopped taking it

◉ *How long do adverse events for docetaxel last? Is a duration of 6 months realistic?*

Incidence adverse events with docetaxel

Company and ERG differ on rates of neutropenia

ERG

- Company used 36.3% for neutropenia and 18.2% for febrile neutropenia
- Company source: small sample, absence of patient numbers, lower incidence numbers
- ERG used 10.6% and 15.4% for febrile neutropenia and neutropenia, respectively, based on pooled data and estimated combined rates **(ERG base case)**

Adverse event rate, Grade 3-4	GETUG-AFU 15 trial Gravis *et al.* 2013	Real world data Patrikidou *et al* 2017	STAMPEDE trial James *et al.* 2017	CHAARTED trial Sweeney *et al.* 2016
N patients	189	Not reported	550	390
Febrile neutropenia	7%	18%	15%	6%
Neutropenia	32%	36%	12%	12%

Table 2 ERG critique

◉ *What incidence for febrile neutropenia and neutropenia should be used?*

Utilities for metastatic hormone-resistant disease*

	Company	ERG: TA387 (abiraterone)	ERG: TA377 (enzalutamide)
Pre-progression	XXXX	XXXX	0.805
1st line mHRPC	XXXX	XXXX	0.698
2nd line mHRPC	XXXX	0.625	0.658
3rd line mHRPC	XXXX	0.500	0.612

◉ *What source of utility value is most appropriate?*

- *Company adjusted* abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated in adults
- *ERG TA387 (abiraterone)*
- *ERG TA377 (enzalutamide)*

NOTE: Patients with non-metastatic hormone relapsed disease will progress to **metastatic hormone-relapsed prostate cancer (mHRPC).* This slide only discusses utility values for the population that progresses to metastatic hormone-resistant disease.

Metastatic hormone sensitive: model assumptions

Issues	Company base case	ERG base case	Agree?
Treatment switching and extrapolation			
Type of crossover and adjusting for non-NHS use of abiraterone/enzalutamide	Unadjusted, final analysis data from COU-AA-302	'Modified' RPFSTM using final analyses from COU-AA-302	X
Extrapolating progression-free survival of 1st treatment after progression	Weibull	Gompertz	X
Utilities			
Utilities for 2nd and 3rd line treatments after progression	Adjusted utilities based on TA387 (abiraterone)	Unadjusted utilities based on TA377 (enzalutamide)	X
Docetaxel adverse events			
Duration of adverse event costs for docetaxel	Applied for 6 months and costs for ADT alone thereafter		✓
Incidence of grade ≥3 neutropenia and febrile neutropenia for docetaxel	36.3% neutropenia and 18.2% febrile neutropenia	15.4% neutropenia) and 10.6% febrile neutropenia	X

Cost-effectiveness estimates

All incremental cost effectiveness ratios are reported in PART 2 slides because they include confidential discounts

In part 2 committee will see company analyses and ERG exploratory analyses

- ERG conducted a range of scenario analyses :
  - Different approaches to adjust survival estimates for crossover and use >1 novel therapy
  - Use independently fitted curves with the Weibull distribution to extrapolate PFS2
  - Apply adjusted utility values for 2nd and 3rd line mHRPC health states (company's original assumption)
  - Use alternative sources to estimate utility values for 2nd and 3rd line mHRPC health states (TA387 abiraterone)
  - Apply incidence of neutropenia and febrile neutropenia used by company in response to TE (36.3% and 18.2% respectively).

Innovation and equalities issues in metastatic hormone sensitive disease

◉ *Is apalutamide a step-change in treatment and offer benefits not captured in modelling for metastatic hormone sensitive disease?*

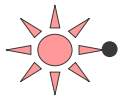
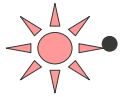
◉ *Are there equalities issues in metastatic hormone sensitive disease for people who cannot or should not take docetaxel?*

End of life
Metastatic, hormone-sensitive

- Both criteria must be met:
  1. Treatment is indicated for patients with short life expectancy, normally <24 months
  2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- Company – did not comment in submission
- ERG – end of life not met because did not pass first criterion
  - 1st criterion: Not met
    - TITAN median OS not yet reached
    - Mean OS assumed for ADT in company base case was 4.6 years
  - 2nd criterion: Met
    - Mean gain in life expectancy was:
      - Vs docetaxel: 6 months
      - Vs ADT alone: 17 months

Key cost effectiveness issues

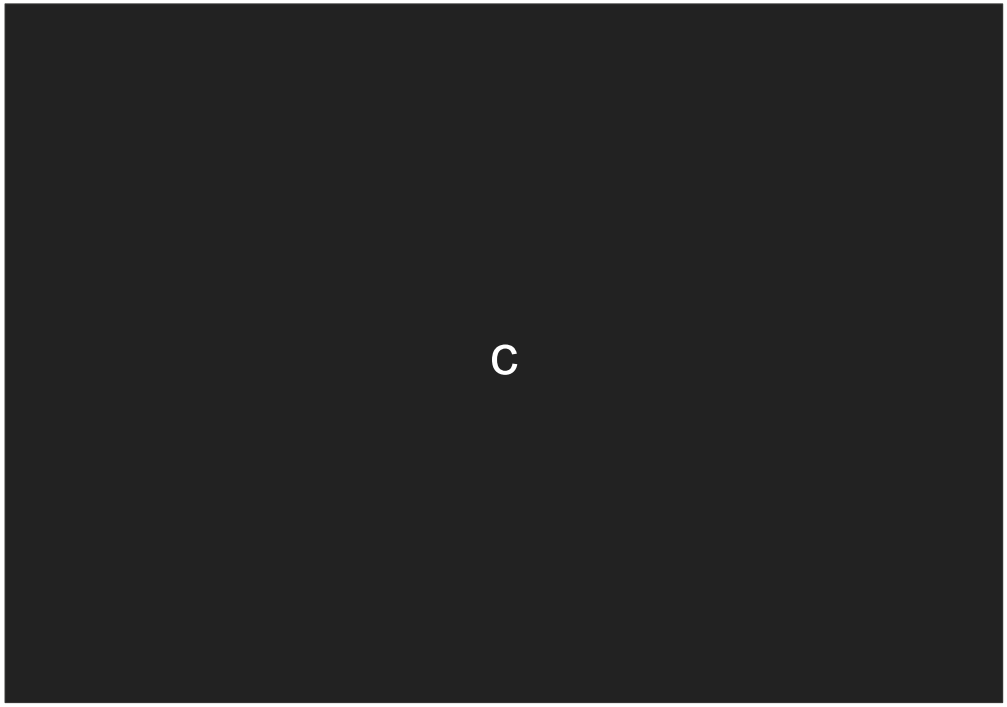
Some common with non-metastatic hormone relapsed indication

- Extrapolation of survival curves: which distributions are most appropriate?
-  How long do adverse events for docetaxel last? Is 6 months realistic?
-  What incidence for febrile neutropenia and neutropenia caused by docetaxel should model contain?
- What source of utility values is more appropriate?

Back up slides

Overall survival (OS) extrapolation for ADT alone

ADT **(unadjusted)**



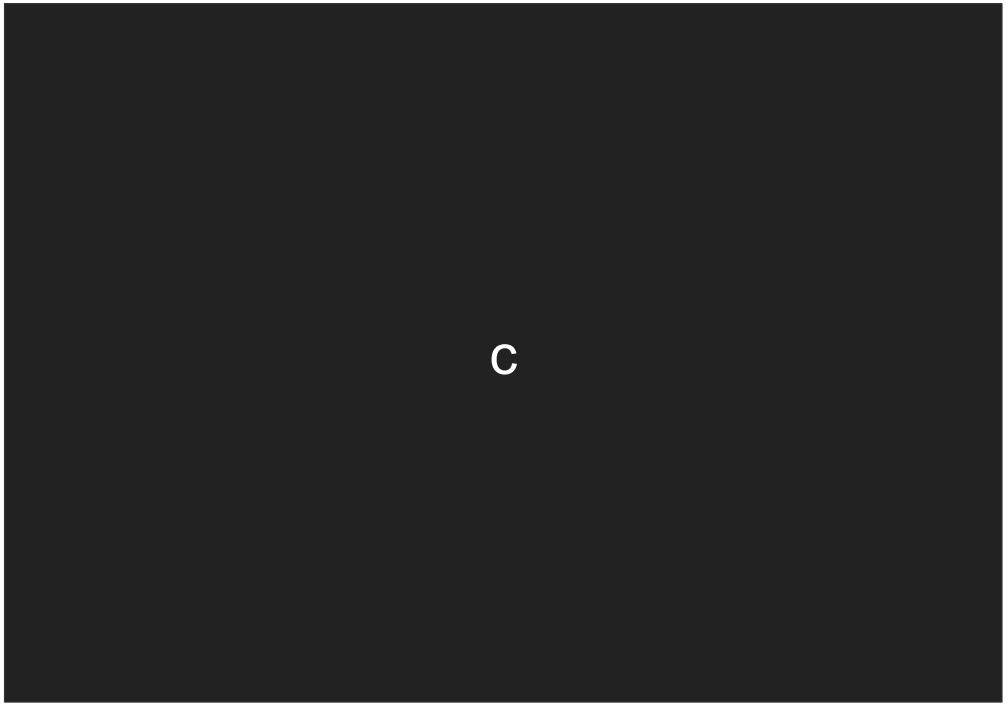
ADT **(adjusted** with RPSFMM COU-AA-302 final analysis)

Fig 28&30 Company response to TE

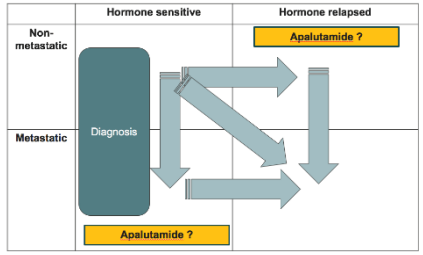
Extrapolating progression-free on 1st subsequent treatment (PFS2) for ADT alone

ADT **(unadjusted)**

ADT **(adjusted; using RPFSTM COU-AA-302 FA)**



Therapies after disease progresses to metastatic hormone-relapsed disease



Company	ERG	Stakeholders
Assumed patients with mHRPC receive same therapies after progressing from either nmHRPC or mHSPC Proportion of patients receiving subsequent treatments for nmHRPC and mHSPC is estimated from company's mHSPC advisory board	Reasonable estimates but inappropriate that patients with mHSPC treated with ADT also received docetaxel as a subsequent treatment for people ineligible/unsuitable for docetaxel, as by definition, they are not able to receive docetaxel. Unlikely to have a large impact on ICER due to low cost of docetaxel Need to seek experts opinion on plausible estimate	<u>Comparator company</u> Cost of subsequent treatments appears applied for entire duration of each mHRPC state, rather than being treatment-specific (from their respective clinical trials). May overestimate true cost of subsequent therapy especially for costly therapies like enzalutamide and abiraterone. Mismatch between time spent in each subsequent mHRPC state and actual treatment received. For example, company applies best supportive care as 1st treatment following apalutamide, but in clinical practice these patients will likely receive docetaxel <u>Patient organisation</u>: insufficient evidence to determine a benefit from having abiraterone or enzalutamide after progressing on apalutamide <u>Clinical expert</u>: some patients decline docetaxel in in hormone sensitive phase, but they could accept it when disease progresses to hormone relapsed