NICE National Institute for Health and Care Excellence

Slide handouts for public [redacted]

Enzalutamide for non-metastatic hormone-relapsed prostate cancer [ID1359]

- 2nd appraisal committee meeting

Committee B, 19th February 2019 (previous meeting December 2018)

Chair: Amanda Adler

ERG: Aberdeen Health Technology Assessment Group

NICE technical team: Adam Brooke, Ahmed Elsada, Nicole Elliott

Company: Astellas

Recommendation in Appraisal Consultation Document (ACD)

‘Enzalutamide is not recommended, within its marketing authorisation for treating high-risk hormone-relapsed non-metastatic prostate cancer in adults.’

[redacted]

Enzalutamide (XTANDI®, Astellas)

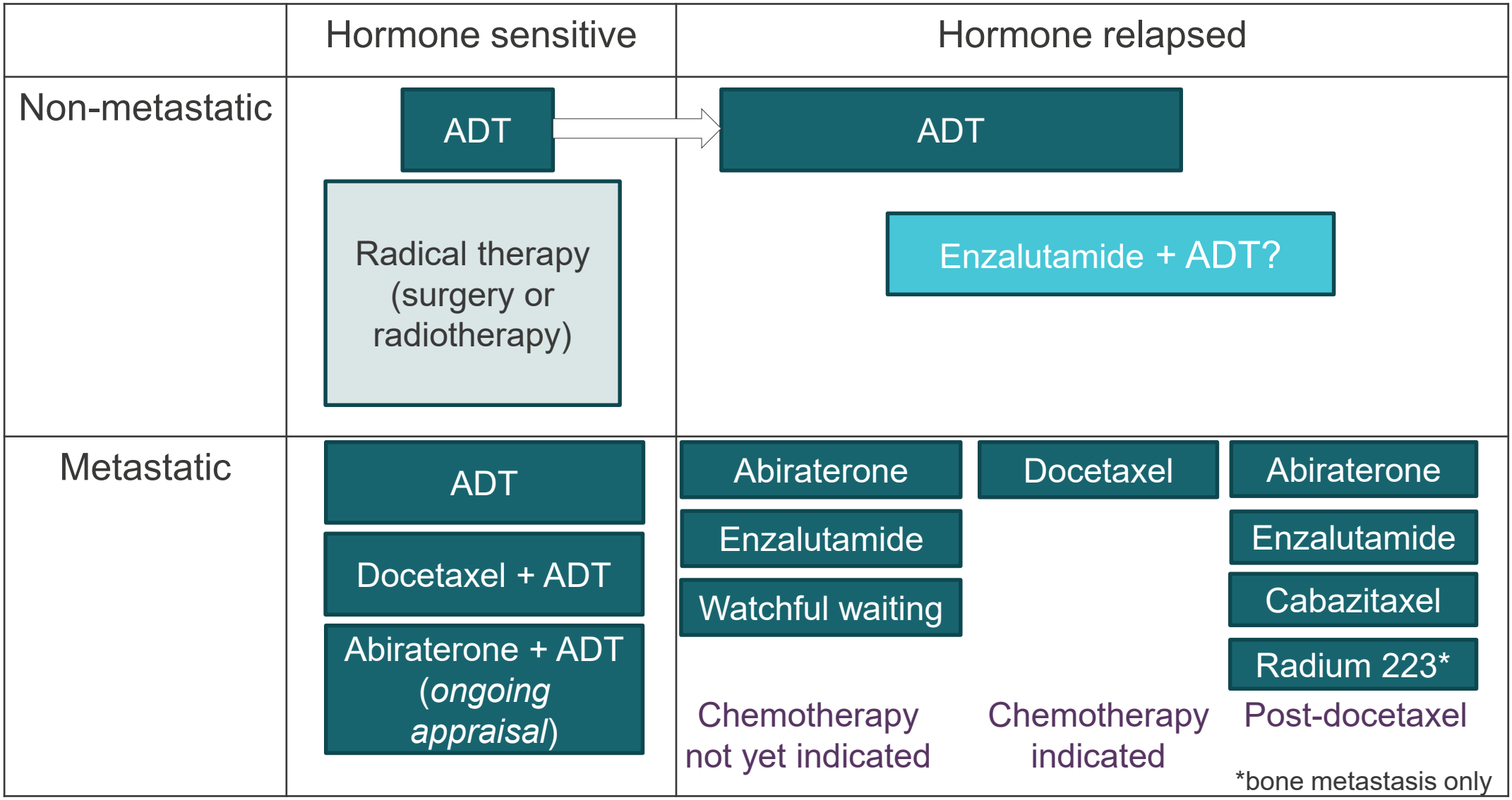
Mechanism of action	• Androgen receptor signalling inhibitor
Marketing authorisation	• "Treatment of adult men with non-metastatic castration-resistant* cancer" (September 2018)
Administration and dose	• 40mg taken orally 4 times daily (160mg)
List price	• £2,734.67 per pack of 112 capsules (annual cost of treatment approximately £35,670) • A confidential discount to the list price has been agreed
Other indications	• "Treatment of adult men with metastatic castration resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated" • "Treatment of adult men with metastatic castration resistant prostate cancer whose disease has progressed on or after docetaxel therapy"

*Note: hormone-relapsed is updated terminology

[redacted]

Treatment Pathway

NHS: Use abiraterone OR enzalutamide, not both, only once



Decision Problem

Population	**High risk non-metastatic hormone-relapsed prostate cancer**
Intervention	Enzalutamide + androgen deprivation therapy (ADT)
Comparator	Androgen deprivation therapy
Outcomes	- **Metastasis-free survival*^** - Time to prostate-specific antigen progression - **Overall survival*** - **Time to stopping treatment*** - **Adverse effects of treatment*** - **Health-related quality of life***

***Used in the economic model**

^ progression-free survival with metastasis as only measure of progression

'High risk' of metastasis defined by the company as:

- an absolute prostate specific antigen (PSA) level of 2 ng/mL or more
- a PSA doubling time of 10 months or less.

Committee: company's definition does not match what is considered high risk in clinical practice, but this is not expected to affect the generalisability of trial results

[redacted]

Professional group comments

Current treatment options

- Clinicians continue to offer ADT even after hormone-relapse because stopping would increase testosterone and decrease time to metastasis

Clinical need

- Unmet need for treatment that improves metastasis free survival, but very few patients now in this group because:
  - Fewer patients develop hormone-relapsed disease before metastasis because clinicians are starting fewer people on ADT
  - Fewer patients without metastatic disease and more patients with metastatic disease because improved imaging diagnoses metastatic disease earlier

Treatment benefit

- Enzalutamide delays onset of metastasis but does not increase overall survival
- Does not show that enzalutamide delays decrease in quality of life
- No clear benefit from moving enzalutamide from metastatic to non-metastatic setting

[redacted]

Summary of clinical evidence

PROSPER
Randomised placebo-controlled trial

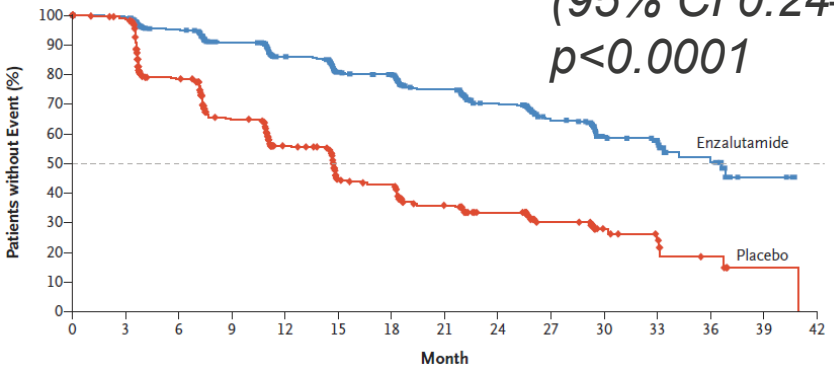
Population
- High risk non-metastatic hormone-relapsed setting
- ECOG Performance Scores 0-1

Treatment arms
- Enzalutamide + ADT (n=933)
- Placebo + ADT (n=468)

Outcomes:
- Metastasis-free survival (primary)
- Overall survival
- Quality of Life
- Safety data

[redacted]

Hazard Ratio 0.29
(95% CI 0.24–0.35)
p<0.0001

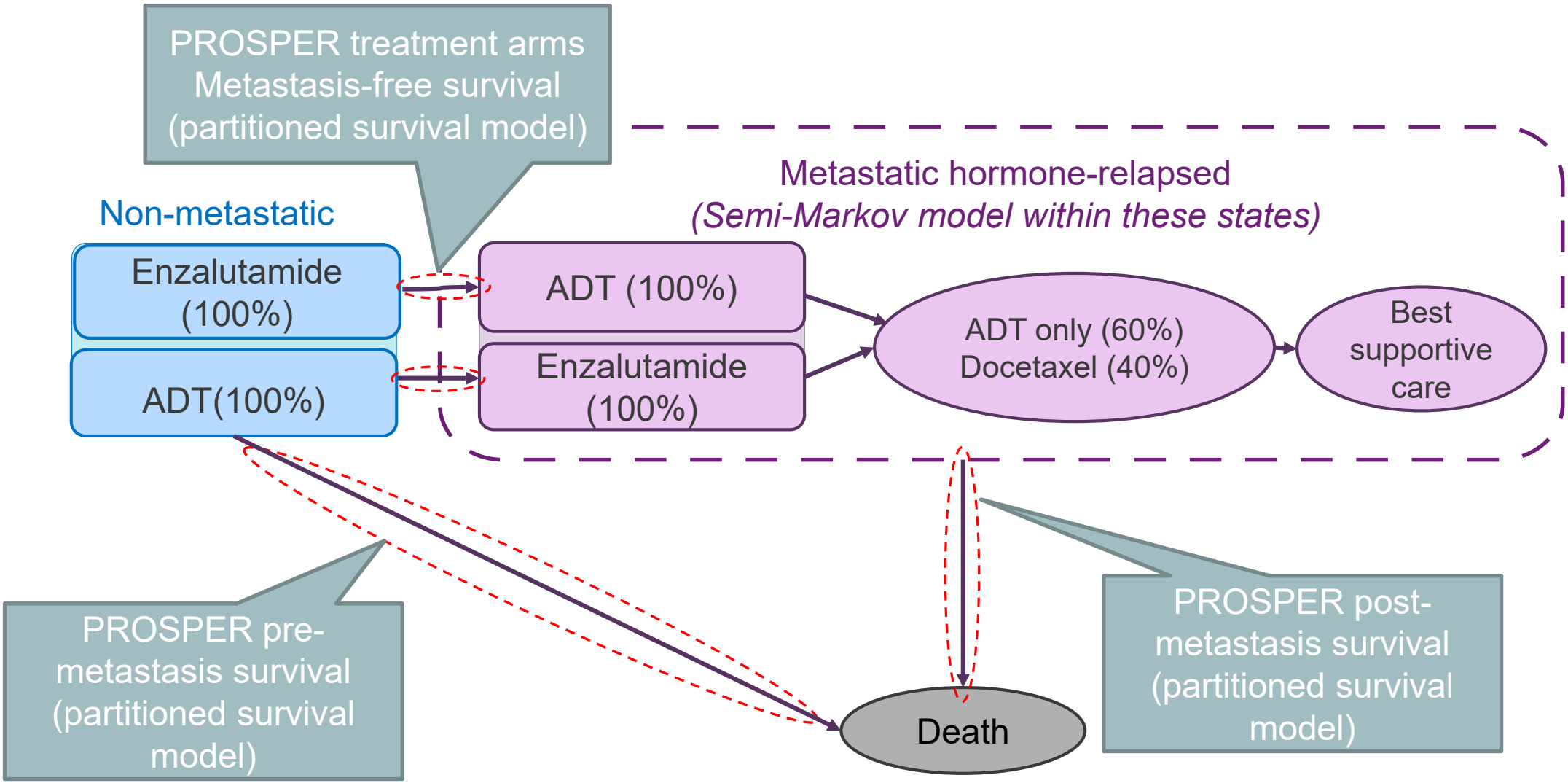


Metastasis-free survival: enzalutamide delays metastasis by 22 months versus placebo

[redacted]

Overall survival: data immature, and no evidence that enzalutamide delays death versus placebo

Company model: Semi-Markov partitioned survival model



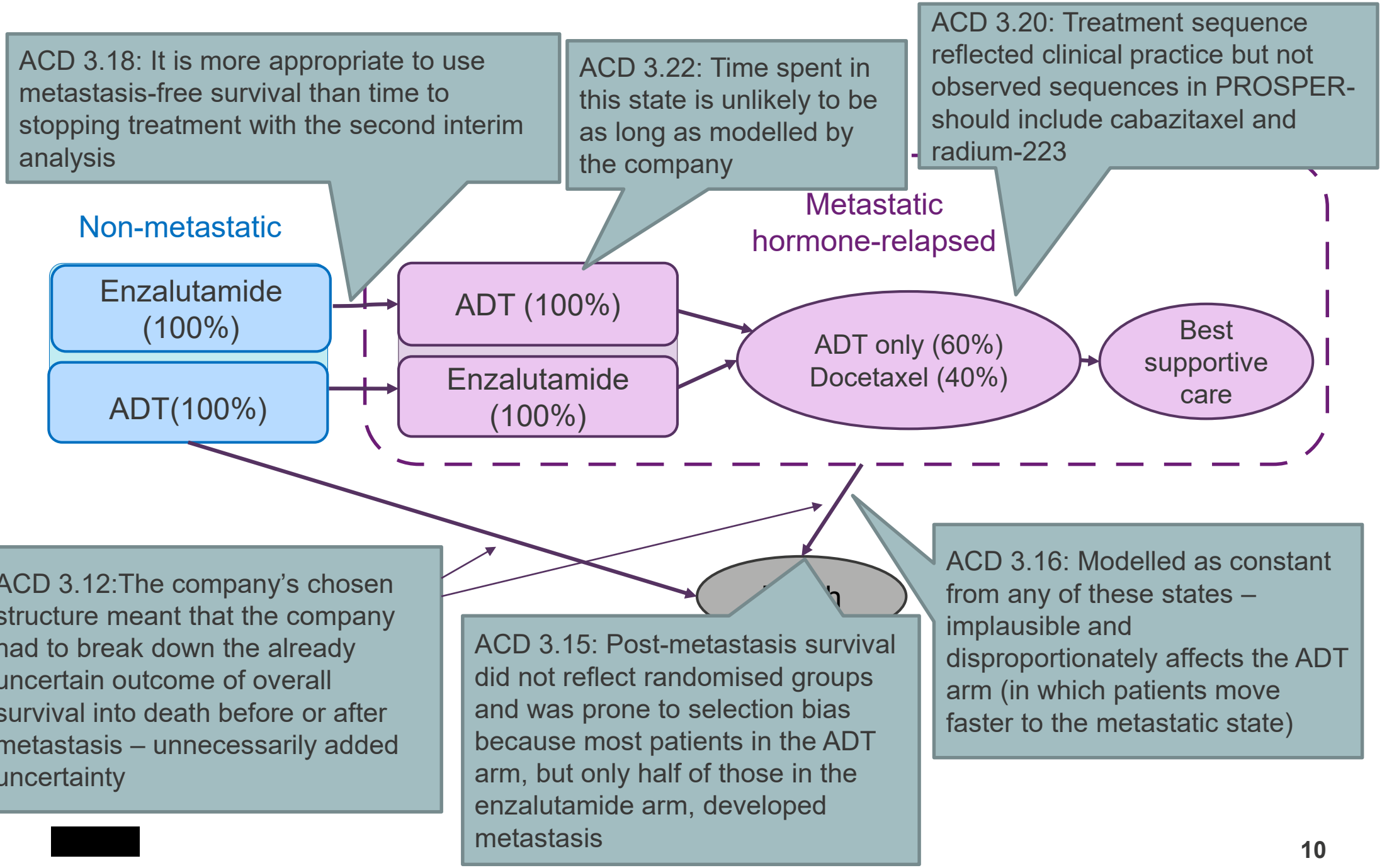
Monthly cycle length, 20-year time horizon (starting age 73.5), 3.5% annual discount rate, includes adverse events

[redacted]

Committee conclusions - clinical

Topic	Committee conclusions	ACD
Treatment Pathway	New position in treatment pathway. Using enzalutamide at an earlier position in treatment pathway would mean it would not be an option later	3.1
Relevant comparators	Androgen Deprivation Therapy (ADT) is standard of care	3.3
Population	High risk. Company criteria do not match what is considered high risk in clinical practice – PSA doubling less than 6 months	3.4
Trial population	Generalisable to the UK population	3.6
Primary outcome	Enzalutamide increases metastasis-free survival	3.7
Overall survival	No evidence that enzalutamide confers benefit. Kaplan-Meier data show divergence [redacted] Enzalutamide may be less effective if used earlier in treatment pathway than if used later	3.8, 3.9
Subsequent treatments	Confound overall survival – company should have adjusted for effect of subsequent treatments	3.10
Quality of life	Not enough evidence to show enzalutamide has a benefit compared to placebo at 22 months	3.11

Committee conclusions - cost



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ACD Consultation

Contributing consultation comments

- Company (Astellas):
  - **Do not present new analysis**
  - **No new patient access scheme**
  - Respond to ACD comments
- Professional Groups:
  - National Cancer Research Institute Prostate Clinical Studies Group

[redacted]

Overall survival data maturity – company response to ACD

ACD committee conclusion:

- *'overall survival data presented by the company were immature, and provided too few deaths to detect a statistically significant difference between treatment arms.'*

Astellas:

- PROSPER was powered for its primary endpoint – metastasis-free survival
- Elderly population may die from natural causes or unrelated comorbidities before their cancer – it is challenging to demonstrate a statistically significant benefit
- Strong scientific rationale for why delaying metastasis can only have a positive impact on patients' quality of life and the risk of cancer-related death
- A meta-analysis with apalutamide shows 'statistically significant overall survival benefit' - 'This supports the view that there have not yet been enough OS events in the individual studies'

❖ ***Has committee seen new evidence to change its view that data are immature and that enzalutamide prolongs life when offered in non-metastatic disease?***

[redacted]

Enzalutamide relative efficacy – company response to ACD

ACD committee conclusion:

- *'enzalutamide may be less effective with respect to overall survival when used earlier in the treatment pathway, both absolutely and relatively.'*

- Astellas: cites New England Journal of Medicine editorial-
  - "Despite the high rates of subsequent therapy, both trials showed improvements in all secondary end points"
    - N.B. overall survival was a secondary endpoint, but data did not show an increase in survival
  - "The benefit–risk evaluation suggests that treatment with either drug (enzalutamide or apalutamide) is better than waiting until the appearance of metastases"
- Professional Group:
  - 'the absolute benefit of enzalutamide appears to be more, not less, if the drug is given later'
  - No evidence that suggests benefit of enzalutamide is greater if used earlier in the pathway. There is such evidence for Abiraterone and Docetaxel, so we may have said that for other similar drugs, earlier appears to be better.'

Subsequent treatments – company response

ACD committee conclusion:

- *'company should have adjusted for the effect of the subsequent treatments not available in the NHS and for which there is evidence of a survival benefit.'*

- Astellas: Insufficient evidence that sequential use of enzalutamide and abiraterone have additional survival benefit. "Limited to <7% of patients in enzalutamide arm at time of first interim analysis"
  - N.B. At second analysis – [redacted] of patients have sequential enzalutamide or abiraterone
  - For percentages of those that discontinue treatment, see graph below.
- Therefore, we believe that it is unlikely that subsequent treatments had a meaningful impact on overall survival – should not be adjusted for

All subsequent treatments of patients who stop treatment

Health-related quality of life – company response

ACD committee conclusion:

- *'there was not enough evidence from PROSPER to show that enzalutamide improved quality of life compared with placebo after 22 months' follow-up.'*

- Astellas: Patients are generally asymptomatic until metastasis, prolonging the period before metastases develop delays deterioration rather than improving quality of life.
- 'Although enzalutamide was used as an add-on to ADT, it did not have a negative impact on overall quality of life'
- 'It significantly delayed **time to deterioration** of several subscales of the patient-reported outcome questionnaires' (shown below)
- N.B. time to deterioration of quality of life not used in modelling – model assumes utility increase

Instrument	Median time, months [95%CI]		Hazard Ratio [95% CI]
	Enzalutamide	Placebo	Enzalutamide vs placebo
EQ-VAS	[redacted]	[redacted]	0.75 [0.63, 0.90]

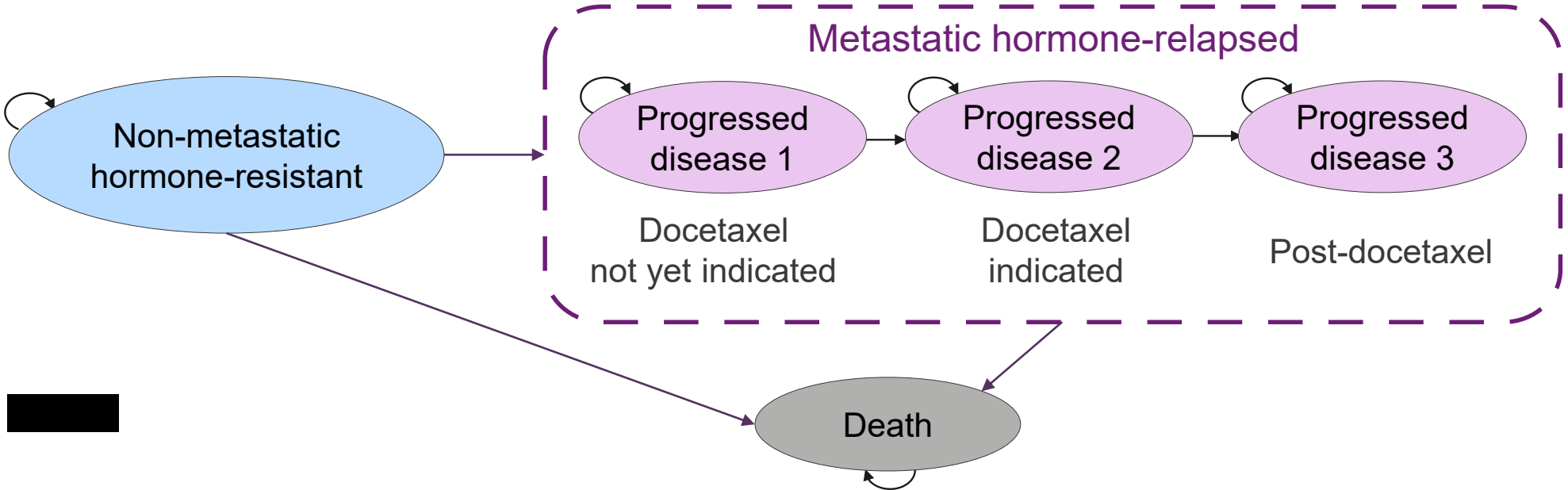
[redacted]

Model structure – company response

ACD committee conclusion:

- *'model structure chosen by the company introduced additional uncertainty.'*
- *'company should have at least validated the output against a 3-state partitioned model.'*

- 3-state partition model is not useful for early-stage disease, Markov provides flexibility
- TA377: 'survival in each state is likely to differ' – same rationale for this point in the pathway. Markov approach allows modelling different survival rates for each state
- Results of single overall survival curve scenario #7 are expected to produce similar results to a partitioned survival model (analysis not provided)
- ERG comment on scenario #7: Likely to be true but remains problematic because it uses immature OS data with a sizeable extrapolated benefit in favour of enzalutamide



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Data available from PROSPER – company response

ACD committee conclusion:

- *'More appropriate to use metastasis-free survival than time to stopping treatment.'*
- *'More appropriate to use data from the second interim analysis.'*

- Astellas: Individually, both statements are logical. However, they are not structurally independent so there are methodological problems to mixing data from two different data cuts.
- Maintain that first interim analysis should be the base case

	Overall survival	Metastasis-free survival
Company base case	**Interim analysis 1** (pre-/post-metastasis survival)	**Final analysis 1** (data not available from time of second interim analysis)
Committee preference	**Interim analysis 2** (pre-/post-stopping treatment survival)	**Final analysis 1**
Company alternative preference	**Interim analysis 2** (pre-/post-stopping treatment survival)	Time to stopping treatment (proxy) from **interim analysis 2**

[redacted]

ERG comment – Data available from PROSPER

ACD committee conclusion:

- *'More appropriate to use metastasis-free survival than time to stopping treatment.'*
- *'More appropriate to use data from the second interim analysis.'*

- Company are correct to note ERG were cautious about combining metastasis-free survival data from 1st interim analysis with survival data from second interim analysis.
- However, the ERG has a preference towards this analysis because:
  - It uses more robust measure of progression to metastasis
  - It generates a more modest survival benefit compared to the base case (appropriate given the lack of significant difference between the two treatment arms)
- Time to stopping treatment is only a proxy for metastasis which may be susceptible to bias, patients that are more likely to discontinue placebo then the curves will overestimate the rate of progression to metastasis in the placebo + ADT group.

[redacted]

Model output – predicted survival does not match overall survival

ACD committee conclusion:

- *'Disconnection between observed and modelled overall survival data.'*

- All parametric curves fitted to PROSPER patient-level data and extrapolated used NICE DSU guidance.
- Placebo + ADT post-metastasis survival arm has been externally validated from overall survival data from PREVAIL trial
- ERG comment : Not appropriate to use PREVAIL to guide extrapolation of placebo arm because PREVAIL represented an enzalutamide naïve cohort

Observed survival

Predicted survival by model