NICE National Institute for Health and Care Excellence

Part 1 slides for projector
[REDACTED]

# Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

# Lead team presentation

Lead team: Ed Wilson, Nigel Westwood, Stuart Williams

Chair: Amanda Adler

Evidence research group (ERG): Aberdeen HTA Group

Technical team: Verena Wolfram, Ross Dent, Nicole Elliott

Company: Astellas

13 May 2020 – virtual meeting

# Key issues

- Enzalutamide does not have a marketing authorisation for this indication – population could change
- Company present 2 trials – one of which uses a comparator not used in the UK
- Immature data for overall survival based on interim analyses
- Is it appropriate to pool trial data comparing enzalutamide to androgen deprivation therapy?
  - Unclear methods of pooling data for overall survival
- Extrapolating beyond trial uncertain as most people were still alive at last analyses
- More life-extending treatment options available after comparators than enzalutamide

# COVID-19 update

## Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England

- For treatments that are 'less immunosuppressive' **or** 'can be administered at home..' **or** 'less resource intensive' **and** 'is feasible' **and** 'there is likely to be adequate capacity …to deliver the treatment'
- Option to give enzalutamide with androgen deprivation therapy for people with newly diagnosed metastatic disease instead of docetaxel to reduce toxicity and potential for hospital admission
- For patients intolerant of enzalutamide, option to switch to abiraterone
- Changes for an 'initial 3-month period only' from 23 April 2020
- 'Treatment regimens will revert to standard commissioned position…unless this guidance is updated'
- 'These interim treatment changes do not constitute NICE guidance'
- All patients who start on an 'interim treatment during the COVID-19 pandemic should be allowed to continue the treatment'
- NICE technology appraisals will supersede any changes

*https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381*

# Clinical effectiveness

# Disease background – prostate cancer

- **41,201** new cases in the UK in 2017
  - most are 'hormone sensitive' (i.e. respond to androgen deprivation therapy (ADT)) not 'hormone relapsed'
    - of these about **17%** present with metastases
- Most stop responding to ADT after 1 to 2 years → hormone-relapsed
- Over time diseases progress from localised to metastatic
- Poorer prognosis for those presenting with metastases than those presenting with localised disease and developing metastases later
- Complications can include lower urinary tract symptoms, bone pain/spinal cord compression, death

# Treatment pathway for prostate cancer

- *4th appraisal for enzalutamide*
- *NHS: use abiraterone OR enzalutamide, not both, only once*
- *Can have docetaxel twice → fewer options post Enza than comparators*

<table>
<tr><th></th><th>Hormone sensitive</th><th colspan="3">Hormone relapsed</th></tr>
<tr><td>Non-metastatic</td><td>ADT<br><br>Radical therapy (surgery or radiotherapy)</td><td colspan="3">ADT<br><br>Enzalutamide + ADT (not recommended)<br>License limits to ‘high risk’, defined by company as<br>• absolute prostate specific antigen (PSA) ≥2 ng/mL<br>• rate disease progression, PSA doubling ≤10 months</td></tr>
<tr><td>Metastatic</td><td>ADT<br>Docetaxel + ADT<br>Abiraterone + ADT in high risk (ongoing appraisal)<br>Enzalutamide + ADT?</td><td>Chemotherapy not yet indicated<br>Abiraterone<br>Enzalutamide<br>Watchful waiting</td><td>Chemotherapy indicated<br>Docetaxel</td><td>Post-docetaxel<br>Abiraterone<br>Enzalutamide<br>Cabazitaxel<br>Radium 223*<br>*bone metastasis only</td></tr>
</table>

# Patient and carer perspective

| | |
|---|---|
| **Unmet need** | Limited treatment options for people with hormone sensitive metastatic prostate cancer (ADT, docetaxel + ADT)<br><br>People who are unable to have docetaxel have limited options |
| **Quality of life** | Diagnosis of metastatic disease causes stress and anxiety to people with the disease and their carers |
| **Advantages of enzalutamide** | Oral treatment<br><br>Could have similar or better effectiveness as docetaxel + ADT |
| **Side effects** | Headache, back pain and hot flushes<br><br>Enzalutamide is contra-indicated in people with raised blood pressure or heart disease and people with a history of seizures |

# Enzalutamide (Astellas)

| | |
|---|---|
| **Marketing authorisation** | • Expected 2020<br>• Expected indication: metastatic hormone-sensitive prostate cancer |
| **Existing marketing authorisations** | Indicated for:<br>• metastatic castration-resistant prostate cancer that progressed on or after docetaxel therapy<br>• metastatic castration-resistant prostate cancer that is asymptomatic or mildly symptomatic after failure of androgen deprivation therapy when chemotherapy is not yet clinically indicated<br>• high-risk non-metastatic castration-resistant prostate cancer |
| **Mechanism of action** | • Binds androgen receptor resulting in blocking androgen binding, inhibiting nuclear translocation and inhibiting gene transcription |
| **Administration and dose** | • Administered orally<br>• 40mg tablets<br>• Single daily dose of 160 mg (as four × 40 mg tablets) |
| **Cost** | • £2,734.67 for 112 unit pack<br>• Enzalutamide has a simple discount patient access scheme |

# Decision problem

*Direct comparative evidence for ADT only*

*Abiraterone + ADT not a comparator; appraisal not concluded*

| | NICE final scope | Company submission |
|---|---|---|
| **Population** | People with metastatic hormone-sensitive prostate cancer | |
| **Intervention** | Enzalutamide + androgen deprivation therapy (ADT) | |
| **Comparators** | 1. ADT<br>2. Docetaxel + ADT<br>3. Abiraterone + ADT<br>(ongoing appraisal for *newly diagnosed high-risk* disease) | 1. ADT<br>2. Docetaxel + ADT<br>3. Not in submission: abiraterone appraisal not concluded, not standard NHS care |
| **Outcomes** | • Time to prostate-specific antigen progression<br>• Progression-free survival<br>• Overall survival<br>• Adverse effects of treatment<br>• Health-related quality of life | Same as final scope plus:<br>• Time to treatment discontinuation<br>• Time to new antineoplastic therapy |
| **Subgroups** | • Newly diagnosed metastatic<br>• High-risk disease metastatic | None |

# Clinical evidence versus ADT

*Trials differ by comparators, concomitant docetaxel, definition of PFS*

| | ARCHES | ENZAMET |
|---|---|---|
| **Design** | Double blind; open-label extension | Open label |
| **Population** | • Metastatic prostate cancer<br>• ECOG performance status 0 or 1 | • Metastatic prostate cancer<br>• ECOG performance status 0 to 2<br>• 40% of people had docetaxel + enzalutamide – excluded from submission |
| **Intervention** | Enzalutamide + ADT | Enzalutamide + ADT |
| **Comparator** | Placebo + ADT | Conventional non-steroidal anti-androgens (flutamide, nilutamide, bicalutamide) + ADT |
| **Subgroups** | • Prior use of docetaxel<br>• Disease volume at baseline | • Prior use of docetaxel<br>• Disease volume at baseline |
| **1° endpoint** | **Progression-free survival - radiographic** | Overall survival |
| **2° endpoints** | • Overall survival<br>• Time to PSA progression<br>• Time to start of new therapy<br>• Time to castration resistance<br>• Time to 1st sympt skeletal met<br>• Quality of life including EQ-5D-5L | • **Progression free survival - clinical (imaging, symptoms, signs)**<br>• PSA progression<br>• Quality of life including EQ-5D-5L |

**Stakeholders:** ARCHES better reflects NHS; ENZAMET comparator not used in NHS

⊙ *Why is ENZAMET comparator not used in UK? Implications for results?*

# Baseline characteristics

*Volume of disease and Gleason scores are different*

| | ARCHES | | ENZAMET (excluding those taking docetaxel) | |
|---|---|---|---|---|
| | ENZA+ADT (n=574) | PLA+ADT (n=576) | ENZA+ADT (n=309) | NSAA+ADT (n=313) |
| Age, median years | 70 | 70 | XX | XX |
| **ECOG performance status at study entry** | | | | |
| 0 | 78% | 77% | XX | XX |
| 1 | 22% | 23% | XX | XX |
| 2 | NA | NA | XX | XX |
| **Total Gleason score at initial diagnosis** | | | | |
| <8 | 30% | 33% | XX | XX |
| ≥8 | 67% | 65% | XX | XX |
| Unknown | Not reported | Not reported | XX | XX |
| **Volume of disease** | | | | |
| Low | 38% | 35% | XX | XX |
| High | 62% | 65% | XX | XX |

Trials include only few people from the UK (ARCHES XX; ENZAMET XX)

⊙ *Are the differences between studies likely to affect modelling, and if so, how?*

# Progression-free survival

*Company uses ARCHES in model; did not pool data because different definitions in trials (radiographic in ARCHES, clinical in ENZAMET)*

| Study results (final analysis minimum of 262 events had occurred) | | | | |
|---|---|---|---|---|
| | ARCHES (rPFS, independent central review) | | ENZAMET (cPFS) (excluding those taking docetaxel) | |
| | ENZA + ADT (n=574) | PLA + ADT (n=576) | ENZA + ADT (n=309 of 593) | NSAA + ADT (n=313 of 562) |
| **Events** | n=91 (16%) | n=201 (35%) | Not reported | Not reported |
| **Hazard ratio (95% CI)** | 0.39 (0.30 to 0.50) | | 0.34 (0.26 to 0.44) | |
| **Median PFS (95% CI)** | Not reached | 19 months (17 to 22) | Not reported | Not reported |

used in model

⊙ *Should the company have pooled the data?*

# Overall survival results, interim analyses vs. ADT

*Data immature (<8% dead in ARCHES)*
*Final analysis at 342 events in ARCHES and 470 events in ENZAMET*
*Company pools ARCHES and ENZAMET for model*
*NSAA = Conventional non-steroidal anti-androgens: flutamide, nilutamide, bicalutamide*

| Trial results (interim results) | | | | |
|---|---|---|---|---|
| | ARCHES | | ENZAMET (excluding those taking docetaxel) | |
| | ENZA + ADT (n=574) | PLA + ADT (n=576) | ENZA + ADT (n=309 of 593) | NSAA + ADT (n=313 of 562) |
| **Events n (%)** | 39 (7%) | 45 (8%) | 50 (16%) | 88 (28%) |
| **Hazard ratio (95% CI)** | 0.81 (0.53 to 1.25) | | 0.53 (0.37 to 0.74) | |
| **Median OS** | Not reached | Not reached | Not reached | Not reached |
| **Median follow up** | 14 months | | 37 months | |

⊙ *What is committee's view on immaturity of data?*

# Indirect comparison to compare with docetaxel

*Company performed a network meta-analysis of trials*

- No trials directly compare enzalutamide with docetaxel
  - ARCHES and ENZAMET compared enzalutamide with ADT
  - 3 trials compared docetaxel plus ADT with ADT (STAMPEDE, CHAARTED, GETUG)
- 7 trials compared NSAA + ADT with ADT (HR: [redacted])
- Heterogeneity in trials
  - ENZAMET had lower proportion of people with high volume disease ([redacted]) than ARCHES (62%) and STAMPEDE (60 to 64% overall)


Adapted from company submission

latest STAMPEDE-1 results included

**PFS**

| | Hazard ratio: PFS (95% CI) |
|---|---|
| Fixed effects: Enzalutamide vs docetaxel | [redacted] |

**Overall survival**

| | Hazard ratio: OS (95% CI) |
|---|---|
| Fixed effects: Enzalutamide vs docetaxel | [redacted] |
| Random effects: Enzalutamide vs docetaxel | [redacted] |

**N**

⊙ *What do the results show for comparing the 7 trials comparing ADT and NSAA + ADT?*

# Pooled overall survival vs. ADT

*Company pools ARCHES and ENZAMET for model despite different comparators*

**Trial results (interim results)**

| | ARCHES | | ENZAMET (excluding those taking docetaxel) | |
|---|---|---|---|---|
| | ENZA + ADT (n=574) | PLA + ADT (n=576) | ENZA + ADT (n=309 of 593) | NSAA + ADT (n=313 of 562) |
| Events n (%) | 39 (7%) | 45 (8%) | 50 (16%) | 88 (28%) |
| Hazard ratio (95% CI) | 0.81 (0.53 to 1.25) | | 0.53 (0.37 to 0.74) | |
| Median OS | Not reached | Not reached | Not reached | Not reached |
| Median follow up | 14 months | | 37 months | |

**Pooled analysis**

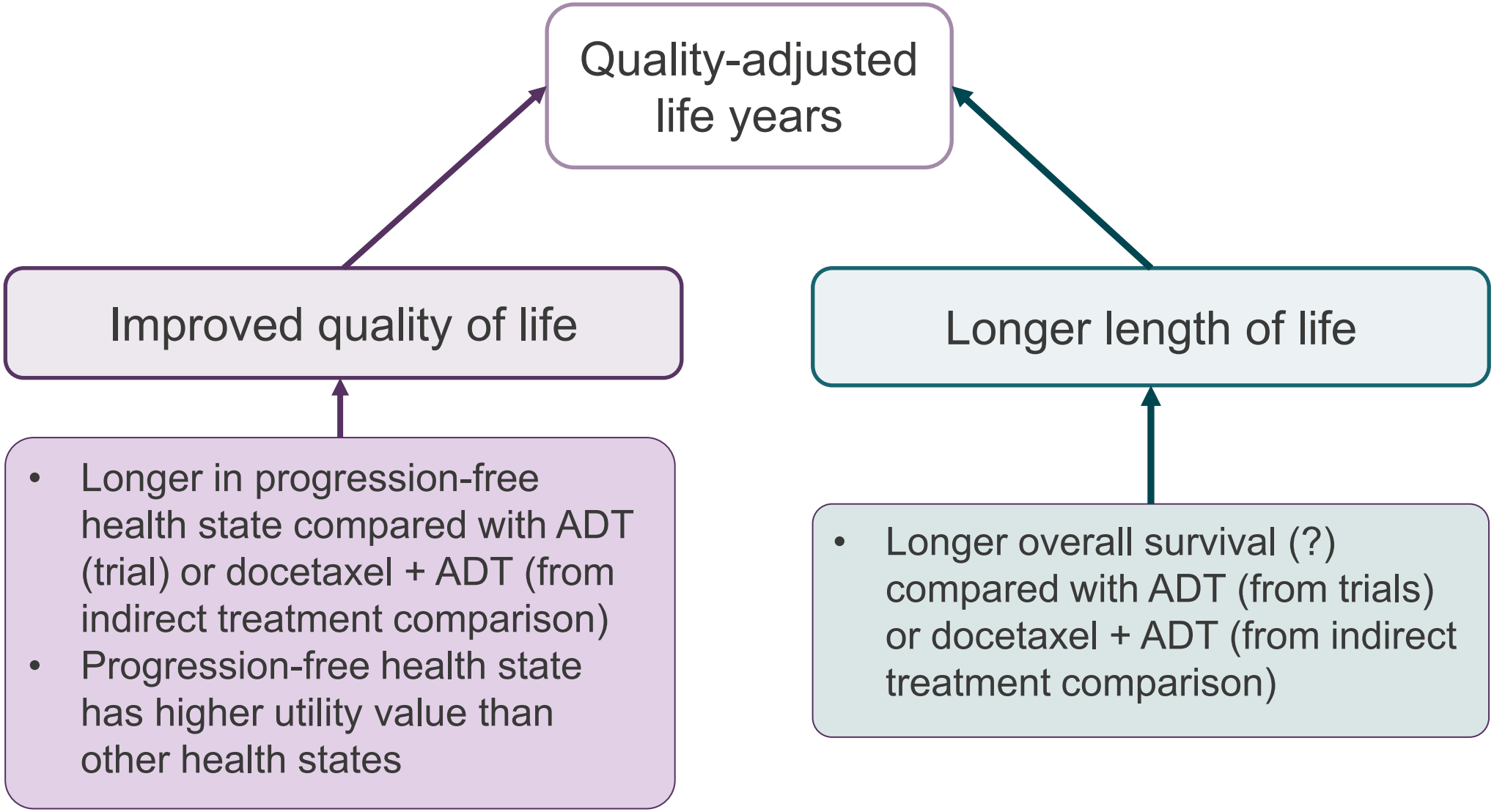
| | ENZA+ADT (n=883) | ADT±NSAA (n=889) |
|---|---|---|
| Events | 89 | 133 |
| Hazard ratio (95% CI) | [redacted] | |

Company uses these values in model

- *Are the control treatments equally effective?*
- *Is it appropriate to combine trial results given comparator in ENZAMET?*
- *What method did the company use to pool the data?*

# Cost effectiveness

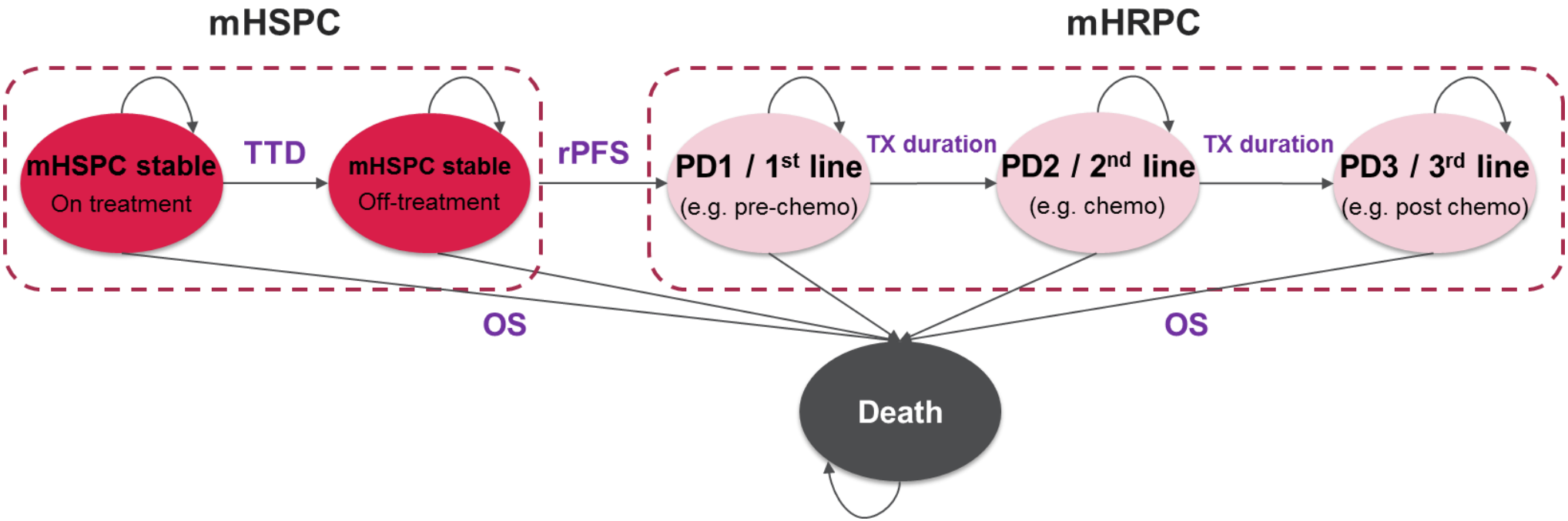
# Overview of how quality-adjusted life years accrue in company's model



# Company used partitioned survival model

*Divided by hormone sensitive and hormone relapsed*

- Contains 6 health states, each line of subsequent therapy = different utility values




- In progression-free health state people can stop treatment before their disease progressed (so called 'off-treatment' sub-state)

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mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease

# Extrapolating overall survival beyond trial

*ERG considers company's choice of Weibull too optimistic for enzalutamide*

- Company jointly fitted parametric models to pooled trial data for ADT and enzalutamide
- Company: previous studies suggest 7-year OS on ADT is 27-34% → log-logistic fits best, but estimates for enzalutamide too high so used **Weibull** in both arms
- Took ADT curve, applied hazard ratio from network meta-analysis for docetaxel curve

**Predicted overall survival for ADT alone**

| | Gompertz | Weibull | Log-logistic | Log-normal |
|---|---|---|---|---|
| Year 5 | XX | XX | XX | XX |
| Year 7 | XX | XX | XX | XX |
| Year 8.5 | XX | XX | XX | XX |
| Year 10 | XX | XX | XX | XX |
| Year 20 | XX | XX | XX | XX |
| AIC | XX | XX | XX | XX |
| BIC | XX | XX | XX | XX |

**Predicted overall survival for enzalutamide + ADT**

| | Gompertz | Weibull | Log-logistic | Log-normal |
|---|---|---|---|---|
| Year 5 | XX | XX | XX | XX |
| Year 7 | XX | XX | XX | XX |
| Year 8.5 | XX | XX | XX | XX |
| Year 10 | XX | XX | XX | XX |
| Year 20 | XX | XX | XX | XX |
| AIC | XX | XX | XX | XX |
| BIC | XX | XX | XX | XX |

**Clinical expert response:** ADT OS at 10 years = 8%, enza OS at 10 years =15%, 20 years =0%

- ERG's clinical expert: OS for enzalutamide 15% at 10 years, and 0% at 20 years
- Suggests best curves may be **Weibull for ADT**, **Gompertz for enzalutamide**
- ERG base case uses the Weibull for ADT and applies hazard ratio from network meta-analysis for enzalutamide vs ADT. Estimates XX OS at year 5 and XX at year 10 for enzalutamide

# Overall survival extrapolations company and ERG

*ERG queries if some people on enzalutamide live up to 20 years+ per Weibull*

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⊙ *Which extrapolation likely best reflects reality?*

# Extrapolating progression-free survival beyond trial

*ERG concerned that company underestimates survival for people on standard care*

- Company fitted same parametric models to ARCHES only data for ADT and enzalutamide
- Company: previous studies suggest 5 year PFS on ADT is 19% → generalised gamma most closely reflects, but estimates for enzalutamide too high: chose **log-normal** in both arms
- Took ADT curve, applied hazard ratio from network meta-analysis for docetaxel curve

**Predicted PFS for ADT alone**

| | Log-logistic | Log-normal | Exponential | Gamma |
|---|---|---|---|---|
| Year 5 | XX | XX | XX | XX |
| Year 8.5 | XX | XX | XX | XX |
| Year 10 | XX | XX | XX | XX |
| Year 20 | XX | XX | XX | XX |
| AIC | XX | XX | XX | XX |
| BIC | XX | XX | XX | XX |

**Predicted PFS for enzalutamide plus ADT**

| | Log-logistic | Log-normal | Exponential | Gamma |
|---|---|---|---|---|
| Year 5 | XX | XX | XX | XX |
| Year 8.5 | XX | XX | XX | XX |
| Year 10 | XX | XX | XX | XX |
| Year 20 | XX | XX | XX | XX |
| AIC | XX | XX | XX | XX |
| BIC | XX | XX | XX | XX |

**Clinical expert response:** ADT alone 5-year PFS = 20%, 10-year PFS =10%

**ERG** notes STAMPEDE PFS for ADT = 13% at year 5 and 6% at year 8.5

- ERG's clinical expert: PFS for enzalutamide ~20% to 30% at 5 years, and 0 to 10% at 10 years
- Suggest best curves may be **exponential for ADT**, **log-logistic for enzalutamide**
- ERG base case uses exponential for ADT and applies hazard ratio from network meta-analysis for enzalutamide vs ADT. Estimates XX PFS at year 5 and XX at year 10 for enzalutamide

# PFS extrapolations company and ERG

*ERG considers company's choice may overestimate PFS for enzalutamide at later years and underestimate PFS for standard care*

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⊙ *Which extrapolation likely best reflects reality?*

# Treatments during hormone-relapsed disease

*Difference between trials and NHS practice for life-extending therapies*
*Company 'adjusts' by removing costs, but not effectiveness*

- **Recap:** In NHS there are
  - After ADT or docetaxel, 4 treatment options: docetaxel, enzalutamide/abiraterone, cabazitaxel or radium-223
  - After enzalutamide, 3 treatment options : docetaxel, cabazitaxel or radium-223
- In enzalutamide arm of ARCHES 54% had abiraterone or enzalutamide after progression → can only have once in NHS
- Company modelled subsequent treatments based on expert opinion, not ARCHES

**First subsequent antineoplastic therapies in ARCHES trial and used in model**

| | Enzalutamide + ADT (n=574) | | | Placebo + ADT (n=576) | | |
|---|---|---|---|---|---|---|
| | Observed (n) | % of those with subsequent treatment * | % in company base case (1L) | Observed (n) | % of those with subsequent treatment * | % in company base case (1L) |
| **Overall** | 46 | - | - | 135 | - | - |
| **Docetaxel** | 11 | 34% | 60% | 52 | 43% | 10% |
| **Abiraterone** | 13 | 41% | - | 28 | 23% | 35% |
| **Enzalutamide** | 4 | 13% | - | 28 | 23% | 35% |
| **ADT** | 4 | 13% | 40% | 12 | 10% | 20% |
| **Other** | 14 | - | | 15 | - | |

*Excluding 'other'. May sum to more than 100% because of rounding

# Treatments during hormone-relapsed disease

- If subsequent treatments in NHS do not reflect trial, overall survival estimate from trial may not apply to NHS:
  - in trial, people may get benefit from having enzalutamide or abiraterone as a treatment after enzalutamide which they wouldn't get in the NHS, but company did not include these costs in model
  - people who get docetaxel might 'catch up' and live longer as they have more treatment options available in NHS
    - credible interval around overall survival hazard ratio for enzalutamide versus docetaxel from network meta-analysis includes 1.0 suggesting equal survival

**Stakeholder responses to technical engagement**

- Subsequent treatment options in ENZAMET not aligned to NHS practice
- Effect of subsequent treatment options on long-term outcomes uncertain
- Impact of subsequent treatment is minimal compared with initial treatment effect

**ERG provide scenarios with equal long-term survival for enzalutamide and docetaxel**

- ⊙ *How should the company adjust for treatments not available in the NHS and which have been shown to extend life?*
- ⊙ *Does ERG scenario address the uncertainty in the docetaxel comparison?*

# Long-term effectiveness of enzalutamide versus ADT alone and docetaxel plus ADT

*There are no long-term data for validation*

- No head-to-head data for enzalutamide versus docetaxel
- STAMPEDE randomised trial compared docetaxel to ADT ALONE
- STAMPEDE overall survival for docetaxel and ADT similar at 8.5 years

| Overall survival from STAMPEDE | | |
|---|---|---|
| | ADT alone | Docetaxel plus ADT |
| 5 years | 37% | 49% |
| 8.5 years | 22% | 23% |

- ERG provided scenario analysis where long-term effectiveness is similar across all treatment options from 8 years onwards

**Stakeholder responses to technical engagement**

- Conflicting responses whether treatment effects similar after 8 years
  - ✗ Hormone treatments maintain effect; in LATITUDE durability of treatment effect was observed after median follow-up of 4.3 years for abiraterone
  - ✗ Company's STAMPEDE extrapolation suggest different effects beyond 8.5 yrs
  - ✓ STAMPEDE shows treatment effects similar after 8 years

⊙ *Are effects of ADT, docetaxel and enzalutamide likely to be similar after 8.5 yrs?*

# Duration of treatment and drug costs

*Company uses treatment discontinuation (TTD), ERG prefers PFS*

| | ARCHES | | ENZAMET (excluding those taking docetaxel) | |
|---|---|---|---|---|
| | ENZA + ADT (n=574) | PLA + ADT (n=576) | ENZA + ADT (n=309 of 593) | NSAA + ADT (n=313 of 562) |
| Events (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Hazard ratio | [redacted] | | [redacted] | |
| Median TTD | Not reached | [redacted] | Not reached | [redacted] |

Company uses in model

**ERG** concerned that company might underestimate costs of enzalutamide

- Uses PFS in preferred base case
- In alternative base case, log-logistic adjusted so TTD not higher than PFS

**Stakeholder responses to technical engagement**

- Conflicting responses as to whether treatment stops before progression
  - ✓ Stops because of side effects or changes in general health
  - ✗ Stops when disease progresses

⊙ *What is the best measure of duration of treatment? How to extrapolate?*

# Cost effectiveness company's and ERG's models

*Overall survival extrapolation and post-progression treatments drive cost effectiveness*

| | Company updated base case | ERG base case |
|---|---|---|
| **Overall survival extrapolation** | | |
| ADT | Weibull fitted to pooled trial data | |
| Enzalutamide + ADT | Weibull fitted to pooled trial data | Hazard ratio from network meta-analysis (enza vs ADT XXXXXXXXX) |
| Docetaxel + ADT | Hazard ratio from network meta-analysis (docetaxel vs ADT XXXXXXXXX) | |
| **PFS extrapolation** | | |
| ADT | Log-normal fitted to ARCHES | Exponential fitted to ARCHES |
| Enzalutamide + ADT | Log-normal fitted to ARCHES | Hazard ratio from network meta-analysis (enza vs ADT XXXXXXXXX |
| Docetaxel + ADT | Hazard ratio from network meta-analysis (docetaxel vs ADT XXXXXXXXX | |
| **Time to treatment discontinuation extrapolation** | | |
| Enzalutamide + ADT | Exponential | Log-logistic in alternative base case |

# Innovation

Company:

- Unmet need for treatments for people who cannot take docetaxel or are unwilling to accept chemotherapy
- Orally administered rather than IV infusion at hospital for docetaxel
- Docetaxel requires regular monitoring - full blood cell count and liver function tests
- Serious adverse events associated with docetaxel such as (febrile) neutropenia or thrombocytopenia or of burdensome adverse events such as sensory and motor peripheral neuropathy can persist a long time after treatment stops

# Equality

- No issues identified

# Cost-effectiveness results

**Cost-effectiveness results including discounts for post-progression treatments are presented in private in part 2 because of the confidentiality of these discounts**