NICE National Institute for Health and Care Excellence

Darolutamide with androgen deprivation therapy for treating non-metastatic hormone-relapsed prostate cancer [ID1443]

Lead team presentation

Chair: Amanda Adler
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Company: Bayer

9th September 2020 virtual meeting

Preview: key issues

- Is ARAMIS trial generalizable to UK clinical practice?
- Would some people stop treatment with darolutamide before their cancer metastasized? Do the trial data used in the model underestimate time on darolutamide and costs?
- Are the 20-year modelled survival estimates for darolutamide realistic?
- Would you expect post-metastatic survival to be longer after darolutamide + ADT than after ADT?
  - Different number of active treatment options?
  - Treatment effect carry over?
  - Does the ERG scenario equalizing hazards at 5 years give plausible model outcomes → lower post-metastatic and overall survival with darolutamide + ADT than company model?
- Is darolutamide innovative?

Darolutamide (*Nubeqa*, Bayer)

Non-steroidal androgen receptor inhibitor (ARI)

Structurally distinct to other ARIs: enzalutamide and apalutamide

Marketing authorisation (March 2020)	Treatment of adults with non-metastatic castration-resistant prostate cancer at high risk of developing metastatic disease
Administration	600 mg (2 x 300 mg) orally, 2x daily with food Taken with androgen deprivation therapy (ADT) or surgical castration Reduce dose to 1 x 300 mg tablet 2x daily for: • Severe kidney impairment, not on dialysis • Moderate liver impairment (Child-Pugh Class B)

Treatment pathway

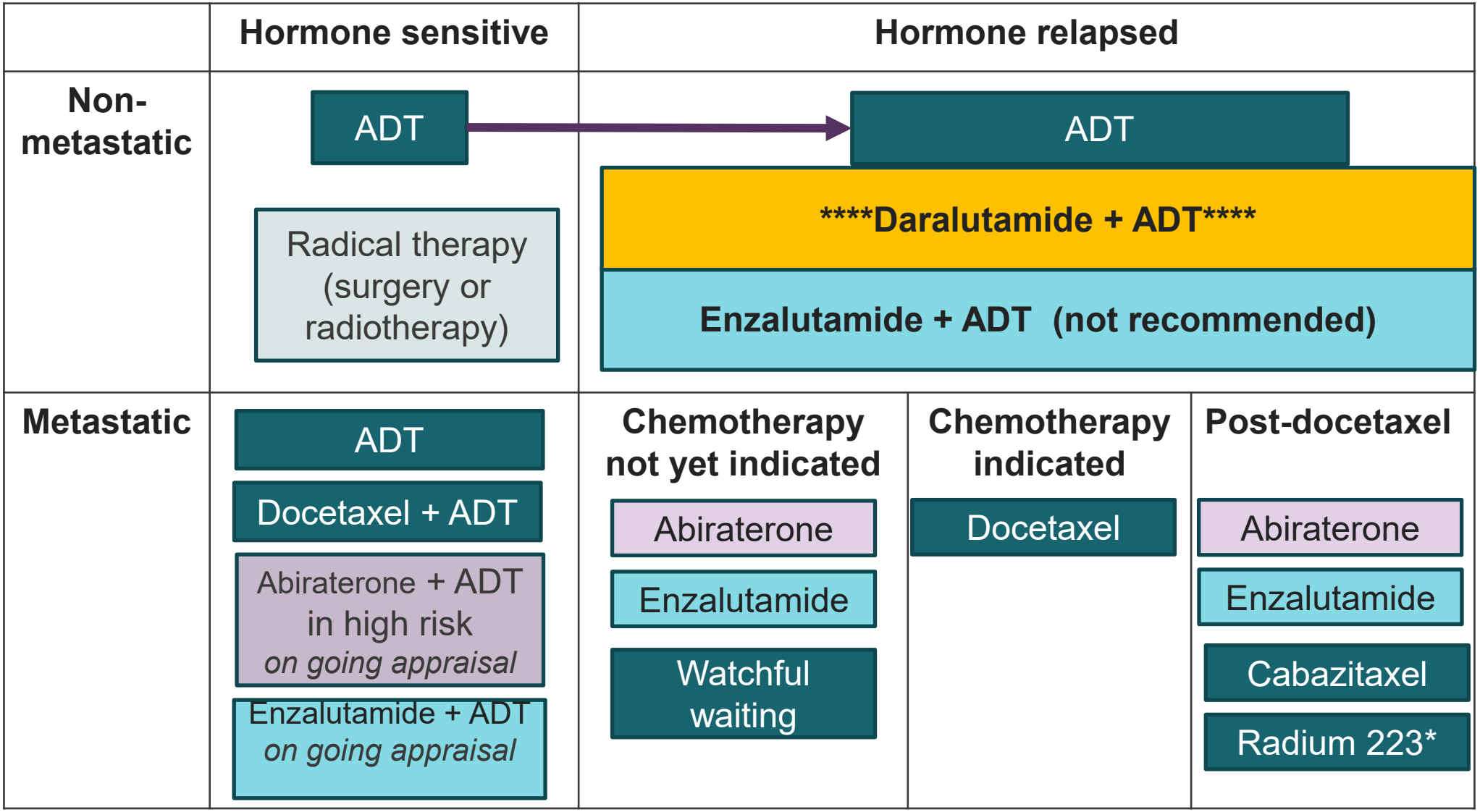
- Abiraterone/ enzalutamide only used once in pathway.
- Company: after darolutamide 0% will have enzalutamide, fewer people have abiraterone than after ADT. Technical engagement: likely significant cross resistance of enzalutamide/abiraterone after darolutamide → no clinical benefit of this sequence

HORMONE SENSITIVE non-metastatic	High risk hormone relapsed non-metastatic	Hormone Relapsed (castrate resistant) metastatic			
Newly diagnosed	Newly diagnosed or progressed from hormone sensitive	Before chemotherapy indicated	Chemo-therapy indicated	After docetaxel	Cannot tolerate docetaxel
• ADT • Docetaxel + ADT (NG131) *Abiraterone + ADT* *Awaiting appeal for high risk metastatic hormone sensitive prostate cancer* **NICE**	• Continue ADT • Darolutamide + ADT? *Enzalutamide not recommended TA580* *Apalutamide ID1534 restarted*	• Abiraterone (TA387) • Enzalutamide (TA377) • Watchful waiting	Docetaxel (TA101)	• Abiraterone (TA259) • Enzalutamide (TA316) • Cabazitaxel (TA391) • Radium 223 (TA412) bone mets only	Radium 223 (TA412) bone mets only

TA, technology appraisal, NG NICE guideline

Treatment pathway for prostate cancer

- *By hormone sensitivity and metastases*



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*bone metastasis only

Technical report issues

Resolved at technical engagement
For discussion: low/moderate ICER
For discussion: larger ICER impact

Issue	Company submission	Technical engagement response
Treatment pathway	After darolutamide no enzalutamide, limited abiraterone	No follow-on enzalutamide. abiraterone unclear
Trial overall survival estimates. Trial immature, follow on treatments different to NHS practice	Majority alive in each arm at end of trial. More people had abiraterone/enzalutamide after darolutamide and fewer people had abiraterone/enzalutamde after ADT than expected in NHS	No scenarios. No expected clinical benefit of abiraterone/enzalutamide after darolutamide.
Different data cuts in model	2018 data for metastatic free survival, 2019 data for time on treatment	Unresolved. ERG adjusts for data cuts assumes fewer people stop darolutamide before metastasis ↑ ICER
Time on treatments for metastatic disease	Means used for estimating utility values, medians used for estimating costs	Company updated base case with consistent use of means
Monitoring	New retrospective cohort not estimates in previous technology appraisal	Company's estimates more plausible than ERGs
Plausibility of modelled outcomes	Darolutamide arm ~2% alive at 20 years Longer metastasis free survival after darolutamide, fewer active treatment options than after ADT	Unresolved. ERG's model equalises hazards at 5 years→ reduced overall survival and post- metastasis survival darolutamide arm. Company says over-adjusts

Non-metastatic hormone relapsed prostate cancer: background

- If cancer responds to androgen deprivation therapy (ADT) it is ‘hormone sensitive’
- If it stops responding to ADT it is ‘hormone relapsed’
- ~15% **new** cases of prostate cancer hormone relapsed;
- ~16% of these non-metastatic
- May have lower urinary tract symptoms such as poor stream and frequency
- Treatment option for non-metastatic hormone relapsed prostate cancer (nmHRPC) continue ADT (despite being hormone relapsed).
- Disease monitored by measuring prostate specific antigen (PSA)
- Disease progresses (disease progression) when metastases occur
- Metastases detected using imaging: MRI scan or CT scan
- License limited to ‘at high risk of metastases’ - PSA ≥ 2ng/millilitre + doubling time of ≤10 months.
- Metastatic disease associated with increased pain, reduced quality of life and reduced survival
- ~33% of people will develop metastases within 2 years of diagnosis
- Aim of treatment is to delay metastases

Patient perspectives

Impact on quality of life

- Know cancer is not responding to ADT, but can't access next treatment until cancer metastasises
- Can be a source of considerable distress and may be of long duration until spread is positively identified
- "*The significant psychological distress is in addition to any physical symptoms that may also be experienced by the patient at that time*".
- "*To be honest, to know my disease is worsening but not being able to know where this is happening and in addition 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*."

Unmet need

- "*Currently the only option to patients with a rapidly rising PSA, other than just seeing their PSA continue to rise and waiting for metastases to be found, is to request more sensitive scans such as Choline PET or Ga^{68} PSMA scanning which may detect metastases earlier. These are not readily available to all patients*."

Side effects

- Note appears to be fewer side effects of darolutamide compared with enzalutamide and abiraterone

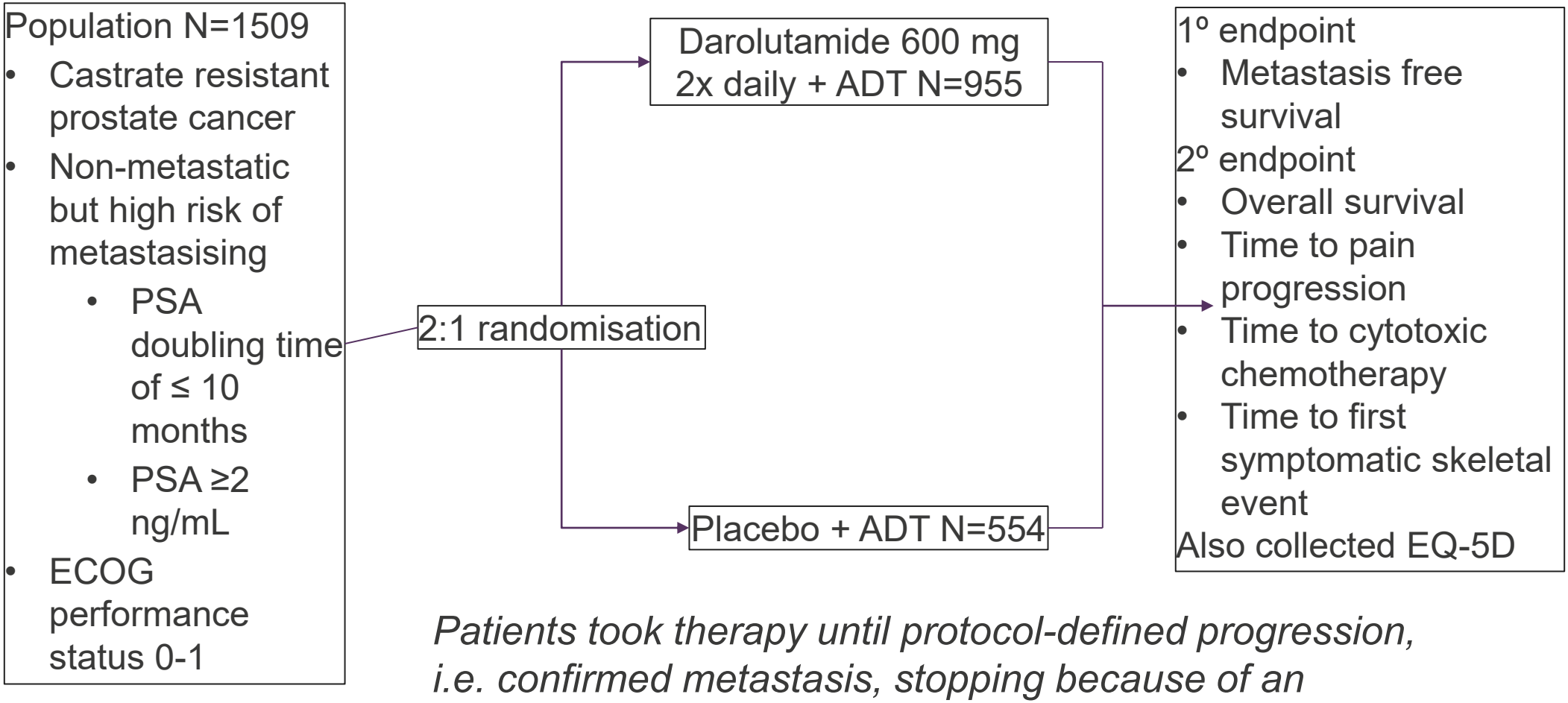
Decision problem

Narrower high-risk population reflects marketing authorisation
*High-risk = prostate-specific antigen (PSA) of ≥2 ng/millilitre **+** PSA level doubling time ≤ 10 months (N.B. same as indication for enzalutamide TA580)*

	Final scope issued by NICE	Decision problem in company submission
Population	Adults with non-metastatic hormone-relapsed prostate cancer	Adults with non-metastatic castration-resistant prostate cancer **at high risk of developing metastatic disease**
Intervention	Darolutamide + androgen deprivation therapy, ADT	Darolutamide + ADT
Comparator(s)	ADT	ADT
Outcomes	• Metastasis-free survival • Time to PSA progression • Overall survival • Adverse effects of treatment • Health-related quality of life	as per scope

Clinical trial: ARAMIS

Double-blind, placebo controlled international (36 countries). No extension. Cross-over allowed – after study unblinding, at final analysis for metastasis free survival. Company did not adjust results in model



Patients took therapy until protocol-defined progression, i.e. confirmed metastasis, stopping because of an adverse event, or withdrawn consent.

ARAMIS screened for metastases

Same screening techniques as trial used in clinical practice
Company developed 'alternative censoring rules'

At baseline, all patients recruited without metastatic disease had:

- whole-body radionuclide bone scan and computed tomography (CT) or magnetic resonance imaging (MRI) of pelvis, abdomen, and chest
- Patients with metastases excluded
- Baseline scans re-analysed by blinded central imaging review identifying patients with metastases at baseline that had not been identified by the investigators at randomization.
- Company uses 'alternative censoring rules' – censors rather than excludes

Comments at technical engagement:

- Prostate Cancer UK noted that CT and bone scans may not detect all metastases
- Suggest PSMA PET-CT and whole-body MRI may be more sensitive
- Cite a retrospective study of 200 patients, 55% diagnosed with high-risk non-metastatic disease by conventional imaging diagnosed with metastatic disease after PSMA-PET scan (Fendler et al 2019)

◉ *Are the patients in ARAMIS like those who might be offered darolutamide in NHS practice? Implications of censoring?*

Fendler, W. P et al. (2019) Clinical Cancer Research, clincanres, 1059

Aramis- statistical analysis plan

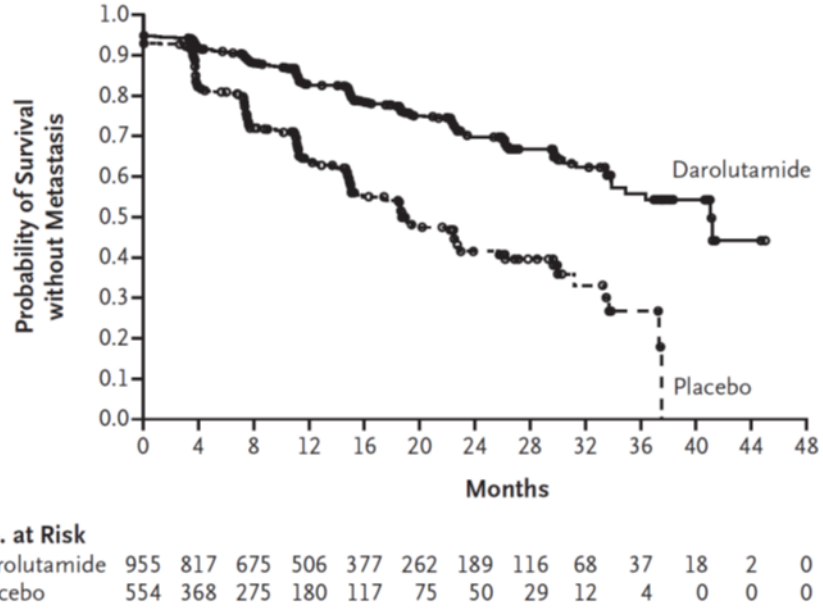
Intention to treat analyses

Analysis of outcomes	Pre-planned number of events	Date met endpoint	Statistical significance	Comment
1º: metastasis free survival (i.e. time to metastases or death)	At time when 437 events occur; for effect size of 0.75 at 90% power	**Sept 2018**	0.05	Chest, abdomen, and pelvic CT/MRI and nuclear medicine bone scan will be performed at screening (baseline) and every 16 weeks until confirmed metastasis
2º: Overall survival	240	Interim: as above Sept 2018 Final **Nov 2019**	Alpha split 0.02 shared with symptomatic skeletal events; 0.002 at interim and 0.018 at final	All other 2º endpoints e.g. time to next cancer treatment - interim and final analyses

Other	
'Alternate censoring rules'	In manufacturer submission and model: baseline metastases 'censored' at day 0 – in statistical plan?

ARAMIS 1º outcome metastasis-free survival

- Time from randomisation to confirmed evidence of metastasis (independent blinded central imaging review) or death from any cause
- 3rd September 2018 (events driven cut off : pre-planned)
- Darolutamide + ADT increased metastasis free survival vs. ADT



	Darolutamide + ADT N=955	Placebo N=554
Number (%) of patients with event	221 (23.1%)	216 (39.0%)
Number (%) of patients censored	734 (76.9%)	338 (61.0%)

	Darolutamide + ADT	Placebo + ADT
Median (months)	40.4	18.4
Hazard ratio	0.41 95% CI 0.34 to 0.50	

ARAMIS 2◦ outcome: overall survival

Darolutamide improved survival but data immature, most people alive at final analysis

	Final analysis (15 November 2019 data-cut)	
	Darolutamide + ADT N=955	Placebo+ADT N=554
Number (%) of patients with event	****	****
Number (%) of patients censored	****	****
Overall survival (months)		
Median time to event [95% CI]	****	****
Range (observed deaths)	****	****
Range (censored values)	****	****
Hazard ratio: Darolutamide/ Placebo [95% CI] [a]	****	
2-sided p-value log rank test (p<** for statistical significance)**	****	

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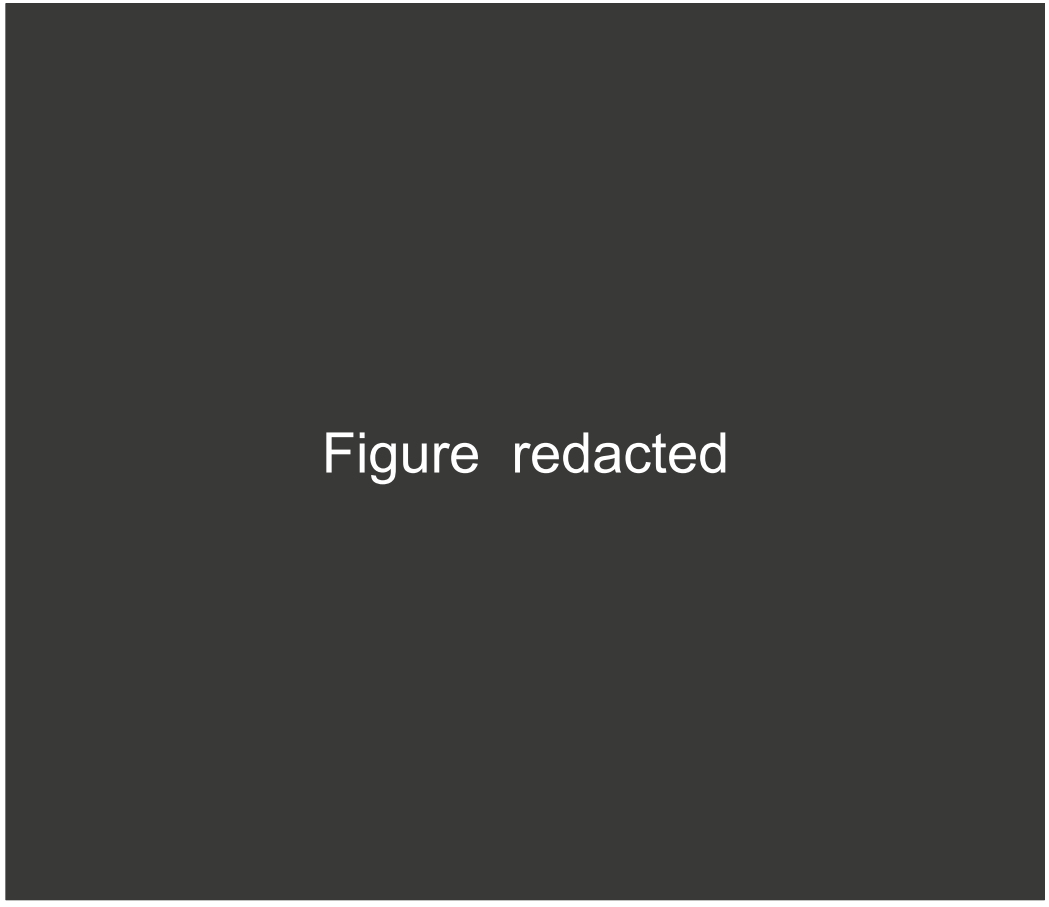
* could not report due to censored values

N.B. data rounded

Company adjusted overall survival in ADT arm for crossover to darolutamide

- At final analysis for metastasis free survival ARAMIS unblinded
- Crossover to darolutamide permitted
- 170 of 554 randomised crossed over
- Company used 2 methods to adjust ADT arm for overall survival
  - Iterative parameter estimates
  - Rank preserving structural failure time (RPSFTM)
- Company suggested
  - adjustment had small effect
  - adjustment increases uncertainty
  - Chose to use unadjusted data in modelling
  - A 'conservative' approach



◉ *Is it appropriate to adjust, and did the company justify the assumptions underlying these methods? Does committee agree that no adjustment is conservative?*

Follow-on treatments metastatic disease in ARAMIS

Company and ERG differ in whether trial over or underestimates survival benefit; company in its base case does not adjust for potential different follow on treatments to clinical practice

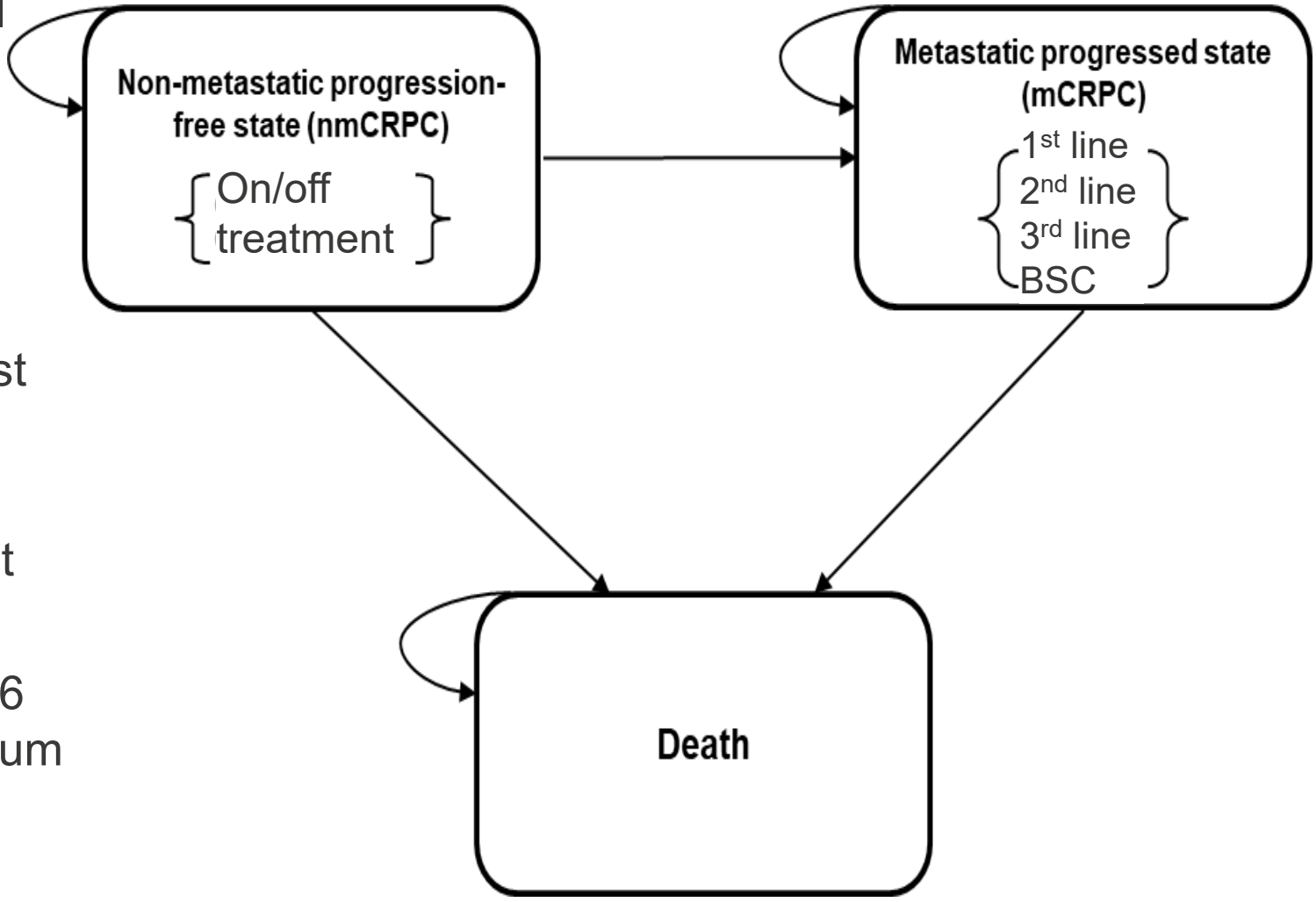
	Final analysis (15 Nov 2019 data-cut)	
	Darolutamide+ADT	Placebo+ADT
Randomised n	955	554
Discontinued treatment n/N (%)	[redacted]/955 [redacted]%	[redacted]/554 [redacted]%
Therapy for metastatic disease	170	167
Docetaxel	[redacted]/170 [redacted]%	[redacted]/167 [redacted]%
Enzalutamide	[redacted]/170 [redacted]%	[redacted]/167 [redacted]%
Abiraterone, abiraterone acetate	[redacted]/170 [redacted]%	[redacted]/167 [redacted]%

- ERG suggests placebo + ADT arm **longer in real life than trial suggests**: lower % had life-extending abiraterone or enzalutamide than in NHS but difficult to adjust for.
- Company: darolutamide survival **longer in real life than trial suggests**: abiraterone/enzalutamide ineffective after darolutamide, fewer people had radium-223 in trial than in NHS

◉ *Is it appropriate to adjust? Without adjustment which way does it bias the results?*

Company model

- Partitioned survival model
- Used extrapolated metastasis free survival curves, and overall survival curves from ARAMIS
- Progressed state to capture heterogeneous treatment pathways post progression
- 28 day cycles (darolutamide treatment cycle)
- mean age at start = 73.6 years, assumed maximum age 100 years
- 3.5% discounting

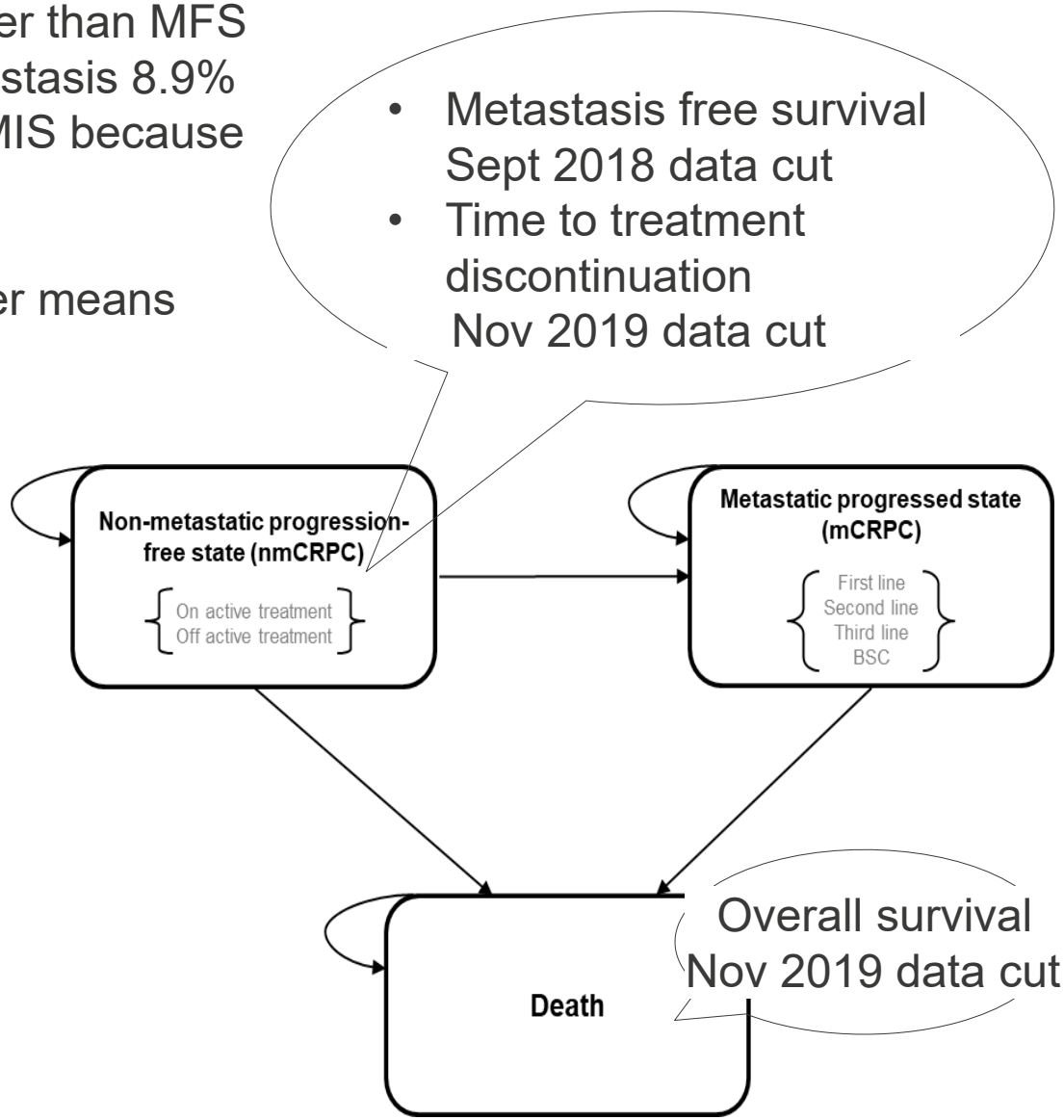


Company: uses data from different times for metastasis free survival + time on treatment

Time to treatment discontinuation (TTD) determines drug costs

- ERG: Time to darolutamide discontinuation shorter than MFS
- Company: people stop darolutamide before metastasis 8.9% stopped darolutamide before metastasis in ARAMIS because of adverse events
- MFS final data Sept 2018
- TTD shorter in Nov 2019 than Sept 2018 – shorter means lower costs
- → costs of darolutamide underestimated?

Figure redacted



◉ *Which data cut is appropriate?*

Company: used 2019 TTD because no data on MFS data after 2018

- Company: There is no difference between **time to antineoplastic therapy** for 2018 and 2019
- Suggests MFS curve would be similar at later date → valid to use 2018 MFS data in model
- ERG: not a good proxy for MFS low % progressed patients started next therapy

Time on treatment. Blue 2018 darolutamide Red 2019 darolutamide

Figure redacted

Time to antineoplastic therapy. Blue 2018 darolutamide, Red 2019 darolutamide

Figure redacted

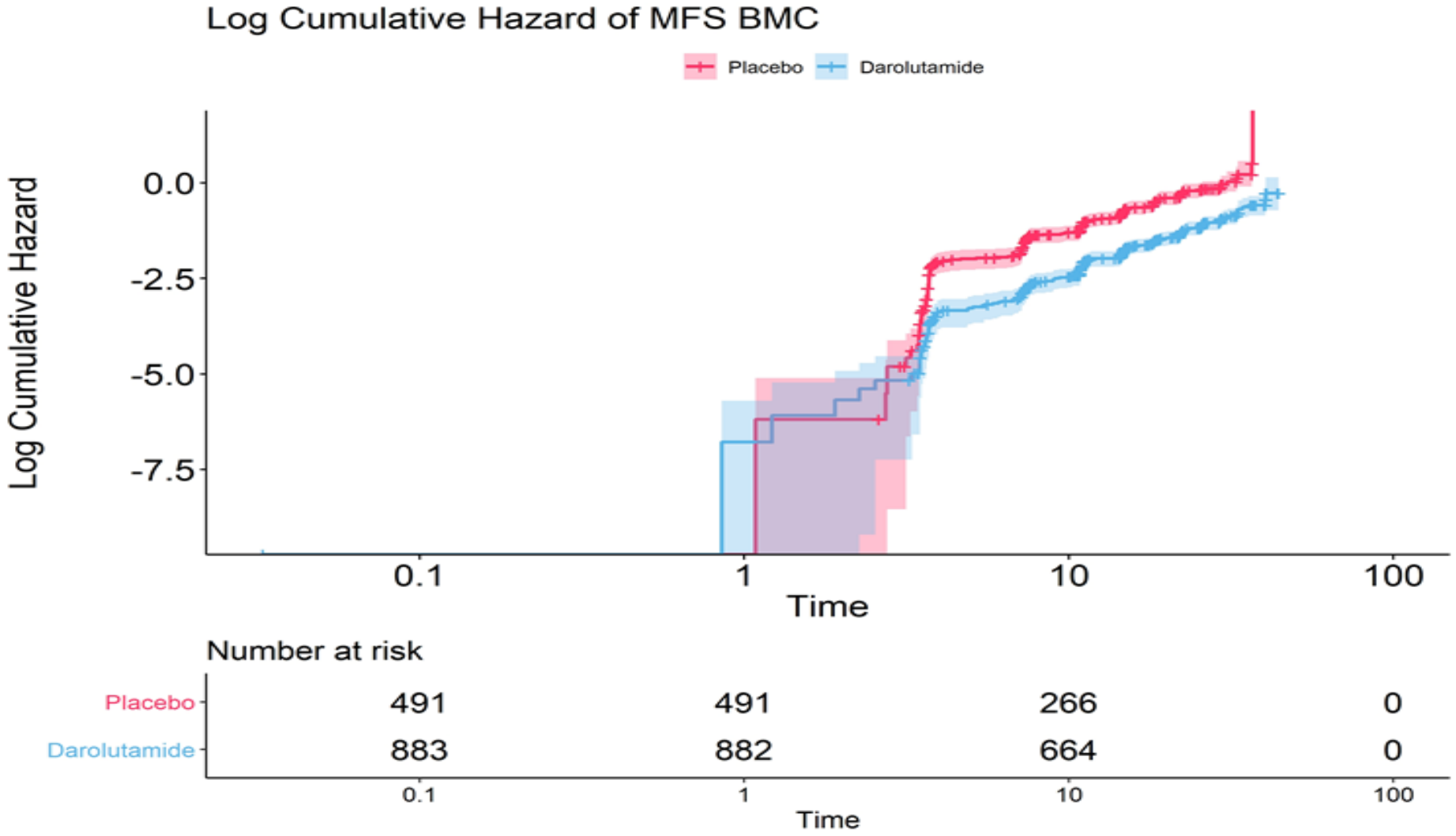
◉ *Does this justify using 2019 data for TTD?*

Extrapolating beyond end of trial metastasis free survival for darolutamide and ADT alone

Company extrapolating metastasis free survival

2018 metastasis survival estimates which censored people with metastases at baseline
(all modelling used survival estimates which censored people with metastases at baseline)

Company: proportional hazards assumption did not hold →
used separate parametric models to extrapolate beyond trial period in each arm



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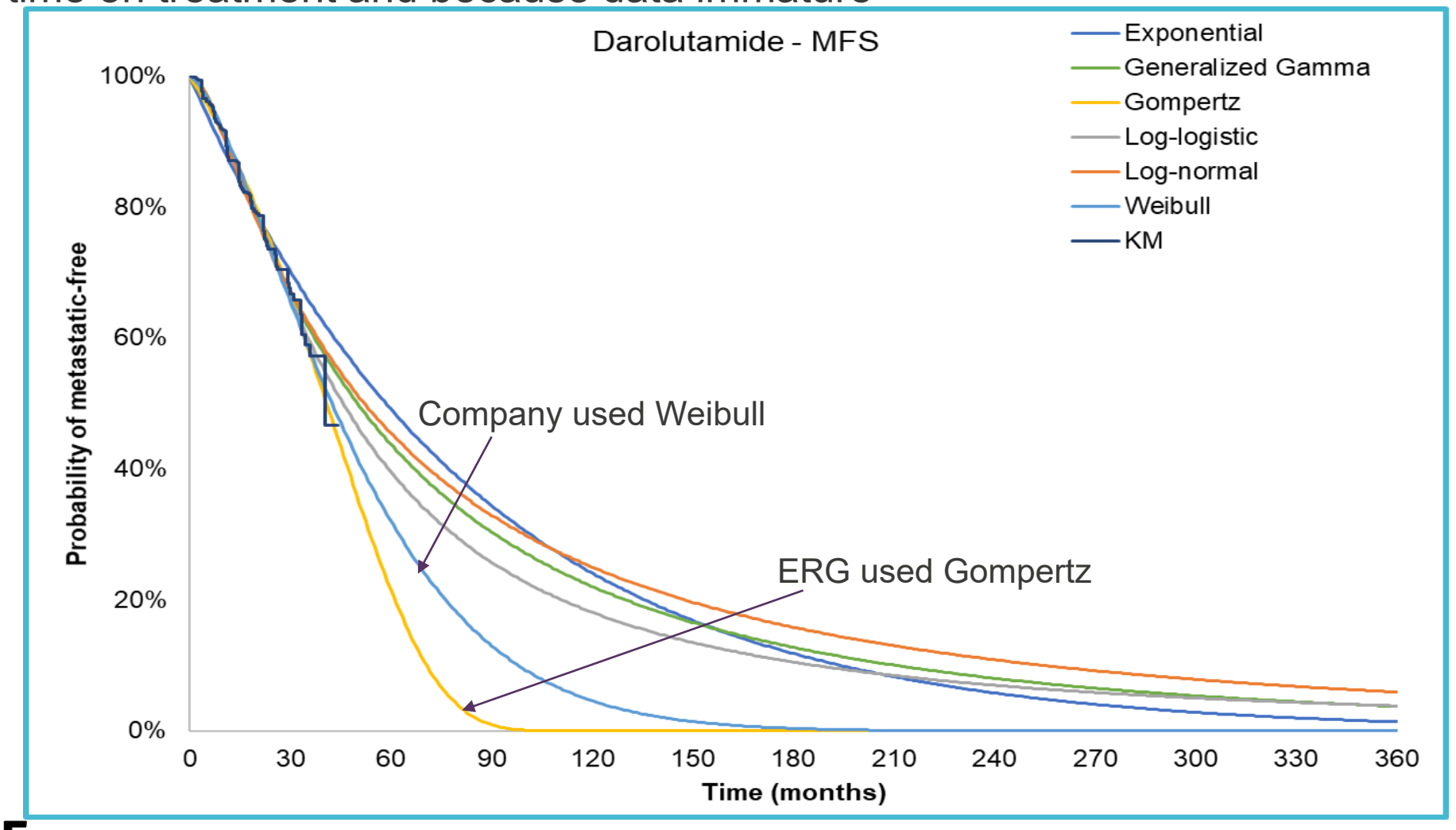
Company extrapolation metastasis free survival: darolutamide

ERG agreed Weibull ( ) best fitting distribution for Sept 2018 data
but uses more pessimistic Gompertz ( ) to compensate for mismatch between
MFS + time on treatment and because data immature



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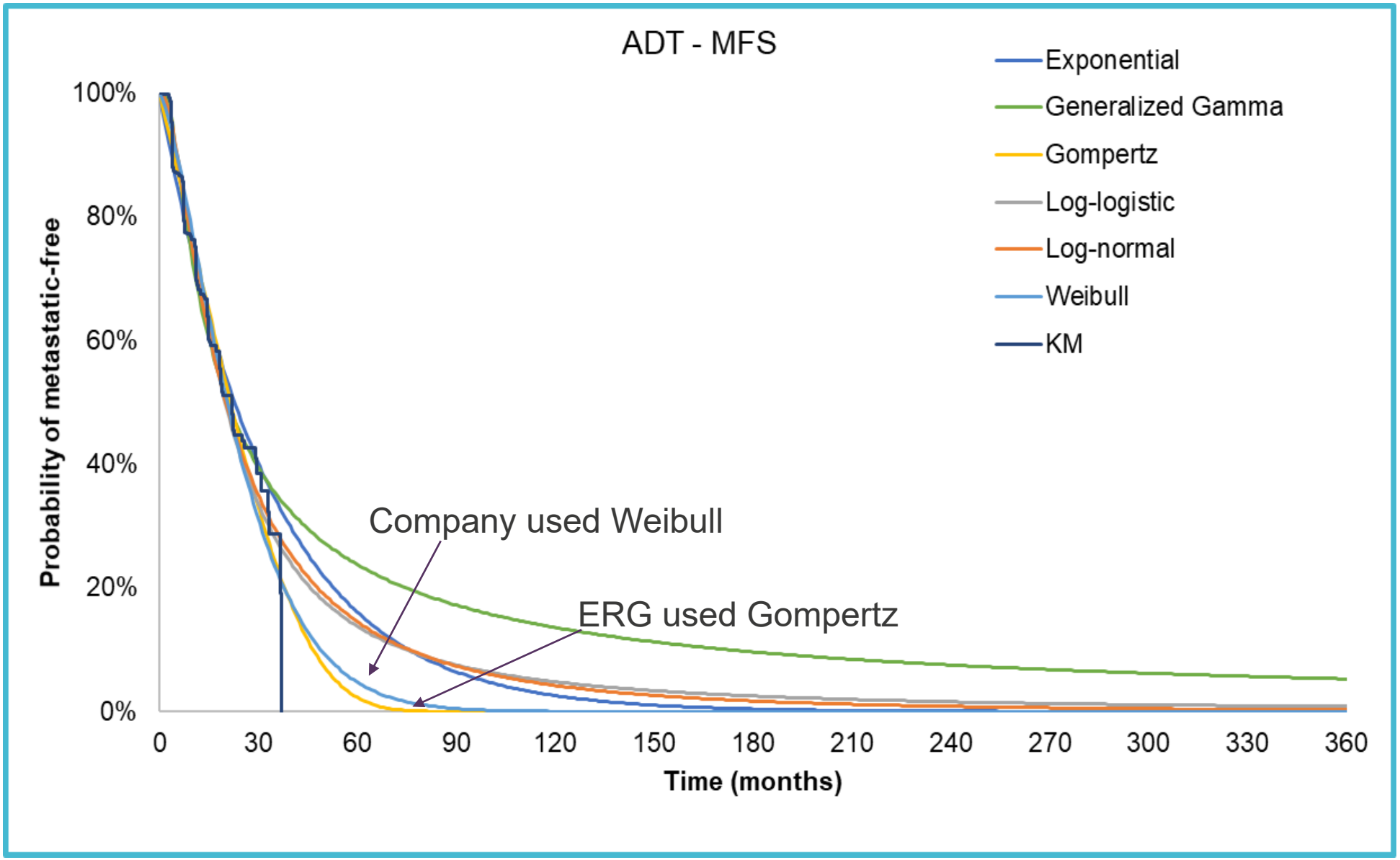
◉ *Which curve?*

Company extrapolation metastasis free survival: ADT



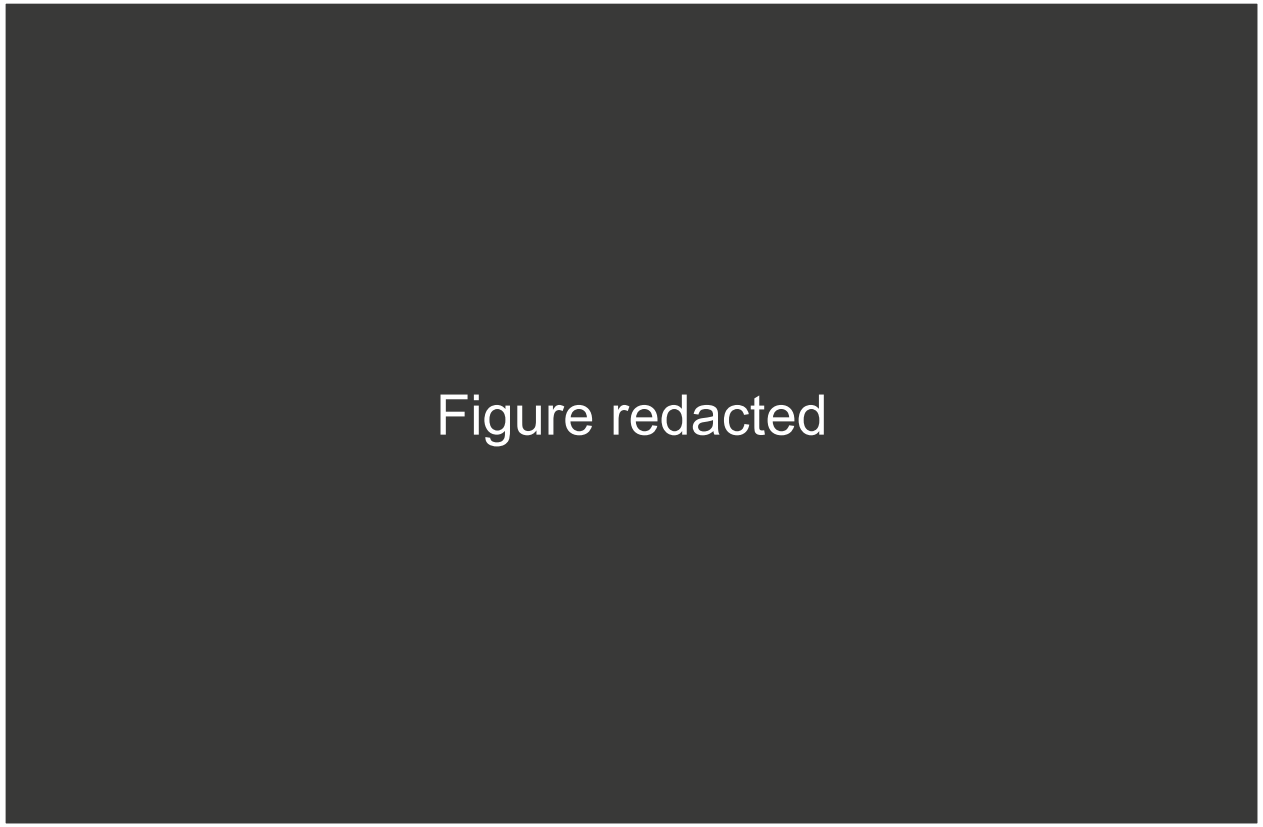
◉ *Which curve?*

Extrapolating beyond end of trial overall survival for darolutamide and ADT alone

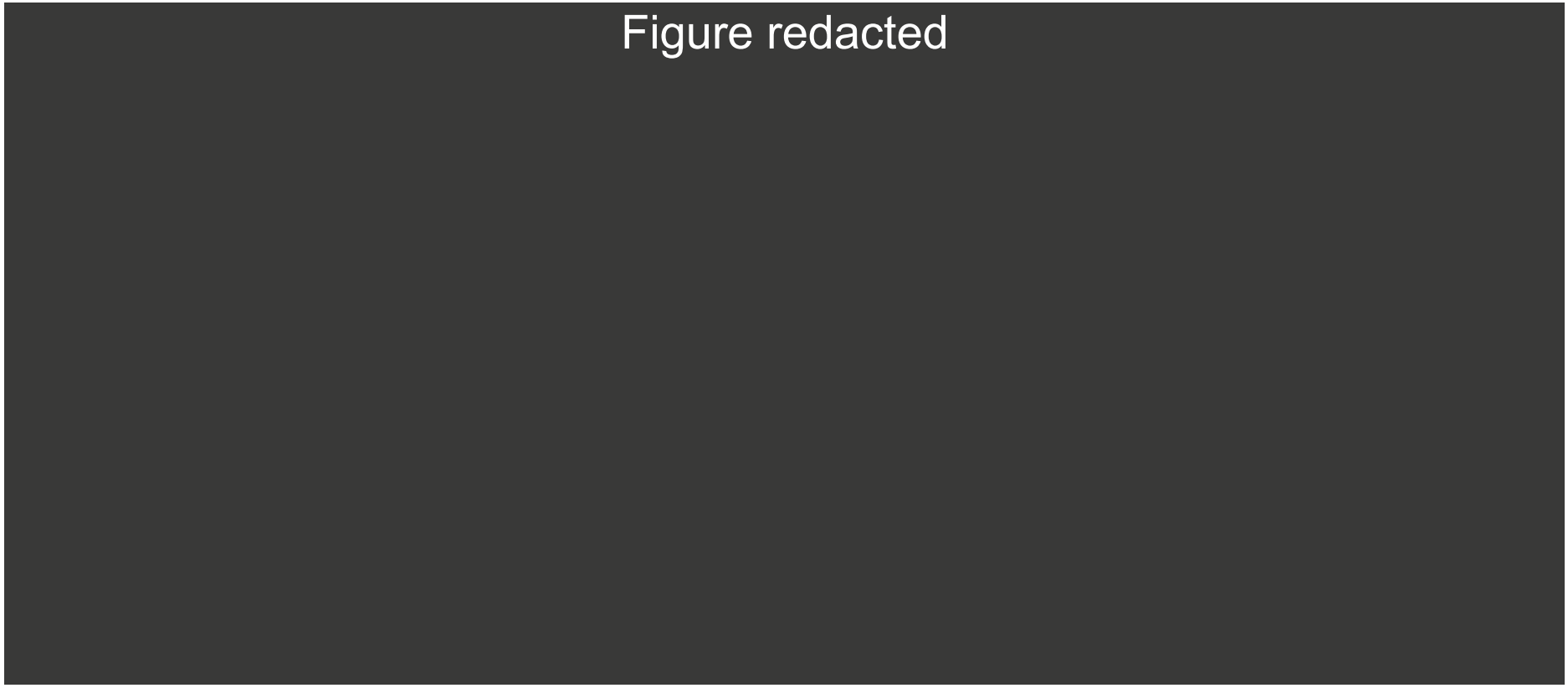
Company extrapolation of overall survival

Data immature - at final analysis in ARAMIS only [redacted] of people in darolutamide + ADT arm and [redacted] of people in ADT arm had died

Company: proportional hazards assumption not met.
Used separate parametric models to extrapolate beyond trial period in each arm



Company extrapolation of overall survival and ERG comment



	Parametric model for overall survival	5 years	10 years	15 years	20 years
Darolutamide + ADT	Generalised gamma	63%	7%	0%	0%
	Weibull	66%	28%	9%	2%
ADT	Weibull	50%	9%	1%	0%

Modelling follow-up treatments

Company modelled treatments after metastases

Company anticipates 3 follow on treatments

Treatment for non-metastatic disease	Darolutamide + ADT	ADT	Darolutamide + ADT	ADT	Darolutamide + ADT	ADT
	1st		2nd		3rd	
No treatment/BSC	17.5%	3.5%	35.0%	15.0%	80.0%	50.0%
ADT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Abiraterone	2.5%	42.5%	5.0%	5.0%	2.5%	2.5%
Enzalutamide	0.0%	42.5%	0.0%	5.0%	0.0%	2.5%
Docetaxel	60.0%	10.0%	15.0%	50.0%	0.0%	5.0%
Radium-223	20.0%	1.5%	20.0%	20.0%	7.50%	20.0%
Cabazitaxel	0.0%	0.0%	25.0%	5.0%	10.0%	20.0%

- *What reflects life?*
- *Fewer active treatment options after darolutamide + ADT than after ADT?*
- *Would some people have abiraterone after ADT? Why not 0% like enzalutamide?*

Company estimates of time on follow on treatments in metastatic disease

- Metastatic progressed state has 3 ‘substates’ then cohort has best supportive care

Times in each treatments

- Duration based on appraisals of enzalutamide and abiraterone for people with metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377 and TA387)
- Mean times estimated from median times + assuming a exponential distribution (updated after technical engagement)

Treatment costs

- Applied as 1-off costs, weighted by distribution of treatments and their costs and treatment duration

Utility values

- Takes into account people who have abiraterone/enzalutamide as 1st treatment have better utility than people who have docetaxel

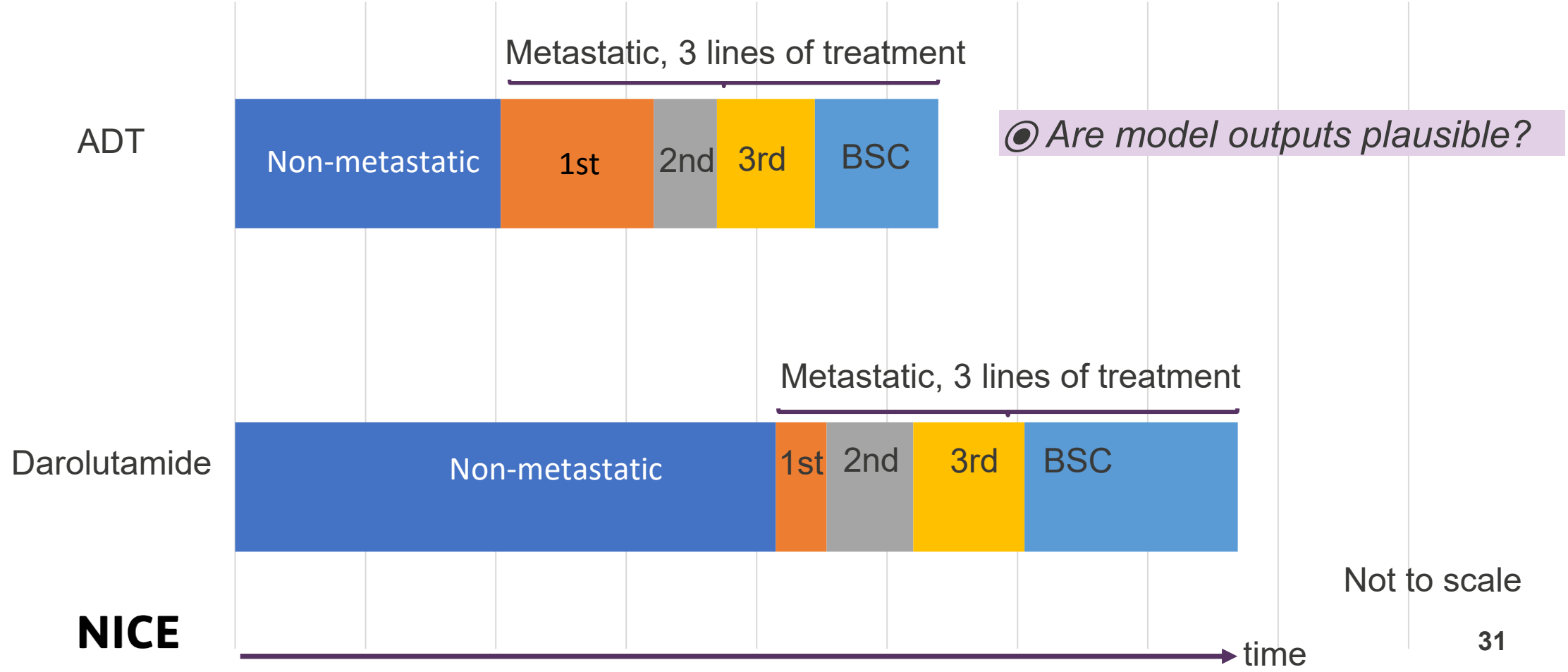
ERG comments on company modelling of treatments for metastatic prostate cancer

ERG comment on company model	ERG alternative approach
1) Overestimates duration of abiraterone/enzalutamide taken as 2nd/3rd treatment because assumes same duration as though it were 1st treatment 2) Illogical results: Sum of modelled treatment durations for metastatic cancer in ADT arm exceed overall modelled life years in metastatic health state	Alternative treatment durations for abiraterone/enzalutamide based on reported progression free and treatment durations for these taken as 2nd or 3rd treatment
Duration of best supportive care as 1st/2nd/3rd treatment is based on reported durations of active treatments for metastatic cancer	Duration of best supportive care based on the observed duration of best supportive care (ADT alone) before chemotherapy indicated for metastatic prostate cancer (PREVAIL trial)

Company model: estimates greater post-metastatic survival with darolutamide + ADT than with ADT

Implausible to ERG as more active treatment options after ADT than darolutamide + ADT

- Company model estimates ~2 months extra survival with metastatic disease in darolutamide + ADT modelled arm than ADT modelled arm
- N.B. modelling does not link assumptions on treatments for metastatic disease with overall or post metastasis survival



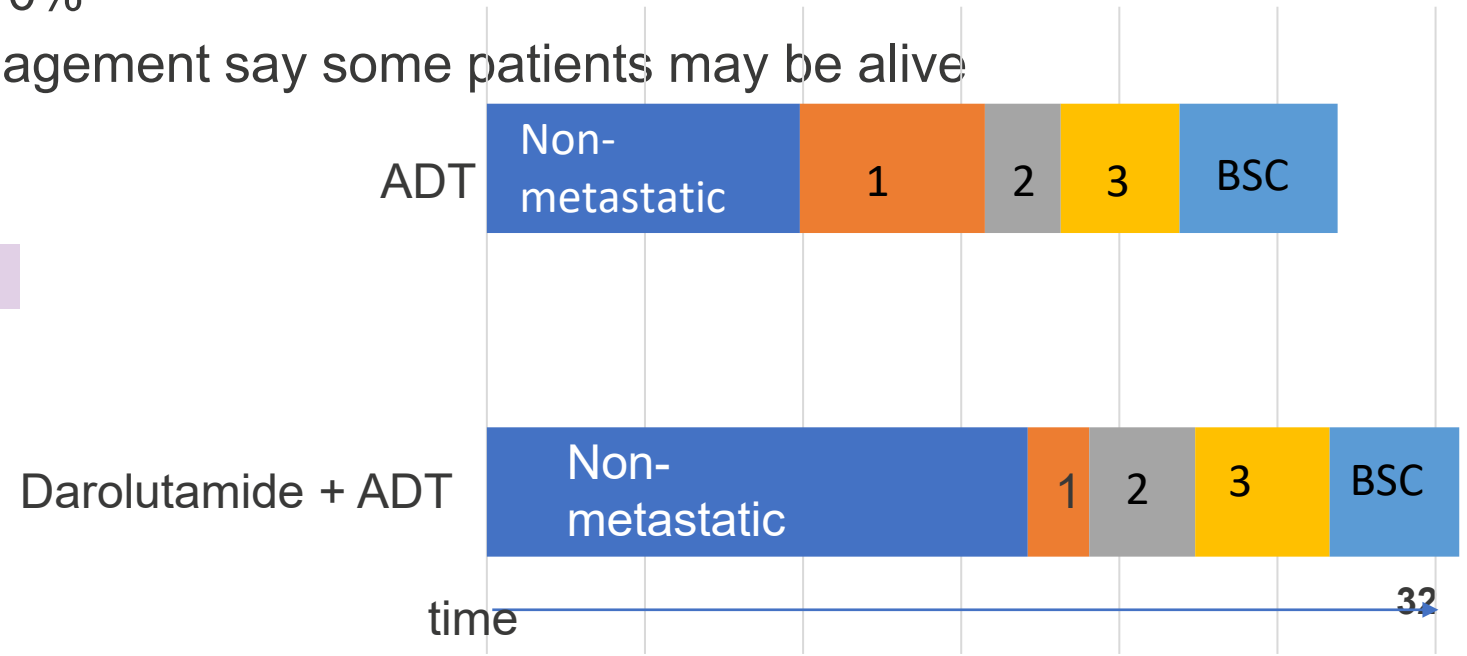
How ERG addresses concerns with overall survival

ERG uses 2 assumptions on overall survival in its exploratory base case

1. Average of generalised gamma and Weibull to extrapolate overall survival in darolutamide + ADT arm
2. Equalises hazards of mortality after 5 years

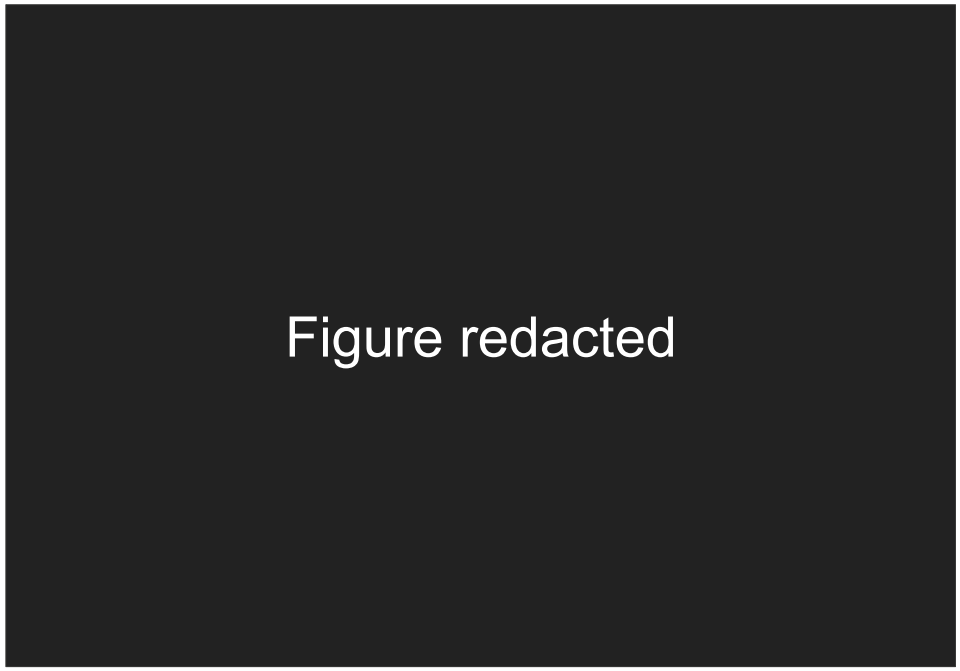
- Time in metastatic health state now longer in ADT arm vs. darolutamide arm (~8 months)
- Less time on best supportive care after 3 lines of treatment for metastatic cancer in darolutamide arm
- Reduced darolutamide overall survival
  - 20 year survival now 0%
  - Clinicians during engagement say some patients may be alive

◉ *Outputs plausible?*



Technical engagement response to ERG concerns on overall survival modelling

- Company: post metastatic progression in ARAMIS showed no difference between arms but may be confounded by the 170 patients crossing over and receiving darolutamide before progression



- Company survey of clinicians:
  - Would not expect survival of patients with metastatic disease following progression on darolutamide + ADT to be any worse than 3-4 months less than those on progressing on ADT alone.
  - Company note in ERG preferred base case difference ~8 months; if use 7 year cut off→ 3 month difference

◉ model outputs plausible?

Company's utility values

Company models:

- Same quality of life darolutamide + ADT or ADT alone for non-metastatic disease
- Better quality of life once cancer metastasised in ADT arm than darolutamide + ADT arm because fewer people have docetaxel

	Darolutamide +ADT	ADT
Non metastatic hormone-relapsed prostate cancer		
source	EQ-5D from ARAMIS	
value	0.813	0.813
Metastatic hormone-relapsed prostate cancer		
Value after technical engagement	0.731	0.777
Company applied disutility values for adverse events and symptomatic skeletal events. Durations were from TA580 and TA377. Decrements for adverse/skeletal were from range of studies and populations.		

mCRPC: metastatic castrate resistant prostate cancer

Costs: drugs

- Drug costs:
  - Darolutamide includes patient access scheme
  - ADT: a blended basket of common ADT treatments
    - including leuprorelin (40%), goserelin (30%), triptorelin (20%) and buserelin (10%) – In line with the clinical experts' opinion in validation meeting
  - Patient access scheme applied for Radium-223 as also made by Bayer
  - List price for all other drugs
    - ERG provides confidential appendix with patient access schemes for abiraterone, enzalutamide and cabazitaxel

Costs: monitoring

ERG and company differ

- Company: retrospective cohort study from large NHS trust (2011- 2019) 44 people with nmHRPC
- ERG: frequencies estimated by ERG for TA580 enzalutamide for nmHRPC

Technical engagement responses

- Clinical expert and patient group (TACKLE) said people have fewer scans, also clinical expert fewer nurse visits than ERG estimate but this varies
- Clinical expert: company estimate of consultant appointment (£109) better than ERG's (£194)

	Non-metastatic hormone-relapsed		Metastatic hormone-relapsed	
	Company base case: (IQVIA study)	ERG base case: TA580	Company base case: (IQVIA study)	ERG base case: TA580
Outpatient visit - Consultant	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks
Outpatient visit - nurse	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks
Community nurse visit	[redacted]	Every 6 weeks	[redacted]	Every 6 weeks
CT scan	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks

◉ *Which estimate? Plausible?*

ERG exploratory base case

Original base case assumptions

- Pessimistic extrapolation Gompertz for September 2018 MFS to align more closely with time on treatment
- Equalise mortality to ADT arm from 5 years
- Revised monitoring costs from TA580
- Oncology specific outpatient visit unit cost and revised ADT admin unit cost
- Revised terminal care costs

Additional assumptions after technical engagement

- + company revised approach to metastatic state after technical engagement (use same approach for modelling utility and costs in metastatic state)
- + follow on treatment duration extrapolated mean
- + follow on time on best supportive care after ADT based on PREVAIL (trial of enzalutamide before chemotherapy indicated for mHRPC)
- + state and treatment durations for enzalutamide/abiraterone as 2nd/ 3rd treatment for mHRPC based on observed data for this position in treatment pathway (rather than when taken as 1st treatment)

Additional ERG scenarios around its base case

	Metastasis free survival extrapolation model	Darolutamide OS	post metastasis survival darolutamide vs. after ADT (months)
	ERG base case (Gompertz)	darolutamide equalised to ADT arm at 5 years	- 8.3
1	Gompertz	equalised to ADT arm 7 years	-3.1
2	Gompertz	average of Nov 2019 generalised gamma and Weibull	0.11
3	Weibull extrapolation of Nov 2019 darolutamide TTD	equalised to ADT arm from 5 years	-8.3
4	Weibull extrapolation	equalised to ADT arm from 11 years	-3.7
5	Weibull extrapolation	equalised to ADT arm from 12 years	-2.4
6	Weibull extrapolation	equalised to ADT arm from 13 years	-1.4
7	Weibull extrapolation	equalised to ADT arm from 14 years	-0.6
8	Weibull extrapolation	average of Nov 2019 generalised gamma and Weibull OS extrapolations	-8.0
9	Weibull extrapolation of darolutamide 2019 TTD	Equalised to ADT from 11 years	-3.7
10	Weibull extrapolation	OS taken as the average of Nov 2019 generalised gamma and Weibull OS extrapolations for darolutamide, and Weibull extrapolation of darolutamide 2019 TTD	-8.0

Equality issues

Scoping
Often variation in accessing NICE approved treatments according to geographical area.

Response to technical engagement: patient organisation
Some patients, particularly older men, are unable to tolerate chemotherapy. Therefore, they could potentially receive sub-optimal therapy. This could be interpreted as an equality issue where the age of the patient discriminated against them if another, equally effective, treatment was available but not being offered or approved. Darolutamide could be an alternative to docetaxel in nmhrPCa were it available to older men.

Comment from NICE technical team
- **Not equality issues**
- **Docetaxel is not a comparator for darolutamide.**
- **NICE unlikely to make recommendations for groups based on age**

Innovation

- Step change in treatment:
  - No NICE recommended treatment options for nmHRPC except ADT- unmet need
  - Delays time to metastasis from 18 to 40 months- extends time can live without symptoms
  - First treatment to improve overall survival vs. ADT in this population
  - Does not cross blood brain barrier less risk of seizures, falls, fatigue, mental impairment than enzalutamide (+apalutamide) (enzalutamide potential later line treatment if don't have darolutamide)
- Potential factors not captured in the QALY calculation
  - Anxiety of knowing are at high risk of metastasis would still be present if darolutamide available, but less so because know it delays metastases
  - Patients want *"to live as long as I can in the best way that I can"*

◉ *Is darolutamide innovative?*