PART 1 for PROJECTOR – contains no confidential information

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Technology appraisal committee A [10 September 2024]

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Company: Menarini Stemline UK

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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ER+ / HER2- advanced breast cancer with an ESR1 mutation

ESR1 is an acquired mutation after endocrine therapy, particularly aromatase inhibitors

Epidemiology

- At diagnosis, ~13% ABC/mBC. ~35% early/LA BC progress to mBC within 10 years of diagnosis
- 70% to 80% BC is ER+/HER2- subtype
- ~50% of BC treated with AIs have ESR1-mut on disease progression. No UK statistics on ER+/HER2-ESR1-mut ABC/mBC. Company estimates 2,559 may be eligible to have elacestrant

Diagnosis and classification

- Genomic testing for ESR1-mut is not currently established practice in UK
- Company suggests using CE-marked in-vitro diagnostic test to detect ESR1-mut in blood sample e.g. liquid biopsy and polymerase chain reaction testing

Prognosis

- ESR1-mut leads to oestrogen-independent ER activation and loss of sensitivity to AIs, but not other ETs such as selective oestrogen receptor degraders (e.g. elacestrant, fulvestrant)
- BC with ESR1-mut has faster disease progression and worse survival than without ESR1 mutation

- What is the approximate size of the eligible population?

NICE

Abbreviations: ABC / LA BC / mBC / BC, advanced / locally advanced ‘ metastatic breast cancer; AI, aromatase inhibitor; CE, Conformite Europeenne; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2

Patient perspectives

Secondary breast cancer affects all aspects of life for person and their family

Submissions from Breast Cancer Now, Make 2nds Count and METUPUK

- Incurable secondary BC is distressing for person, family and carers
  - Uncertainty, living in fear, feelings of hopelessness and sadness; financial impact; carers and children may have to take time off from work or school to care and manage childcare or study
- Priority to extend life and quality of life and delay need for chemotherapy
- Limited treatment options for ER+/HER2- BC that has progressed on ET
  - No targeted treatments for ESR1-mut BC
- Elacestrant is an oral tablet so would be convenient to take
  - Has less harsh side effects than chemotherapy → less disruption and improved quality of life
- People would like clarity about ESR1-mut testing: type and sensitivity of the test and possible option for re-testing if negative

"We live from scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing"

"A new treatment would be wonderful, giving me the chance to live a fuller, more normal life, as well as the hope of more time with my family and friends"

"Desire to find treatments that will halt progression and extend life for as long as possible… To retain quality of life and spend time with their loved ones."

Abbreviations: BC, breast cancer; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2

Clinical perspectives

Step change in management of ESR1-mut breast cancer

Submission from clinical expert

- Limited options available before moving onto chemotherapy
- Elacestrant may delay need for chemotherapy and maintain quality of life
    - Step change in management – non-chemotherapy option after CDK4/6i therapy
    - Help with capacity in chemotherapy units
- ESR-1 mut testing needed at point of progression after CDK4/6i therapy
    - Repeat tumour biopsy or ctDNA testing

"Primary aims are to prolong life and maintain quality of life. An important and relevant secondary aim is to defer or avoid the need for cytotoxic chemotherapy"

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumour deoxyribonucleic acid; ESR1-mut, oestrogen receptor 1 mutation

Elacestrant (KORSERDU)*

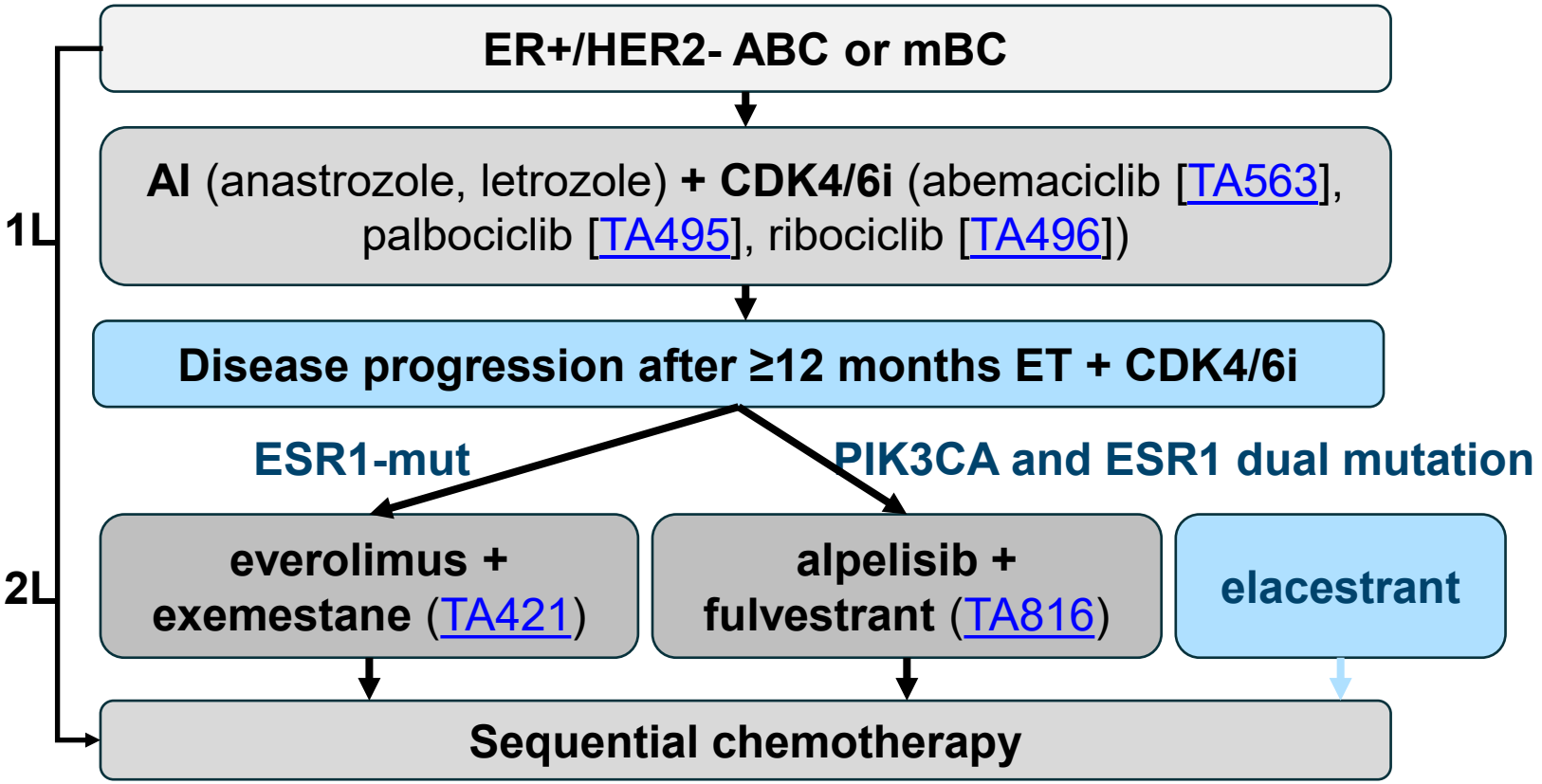
Marketing authorisation (MHRA 6/12/23)	• Postmenopausal women and men with ER+ HER2- locally advanced or metastatic BC with an activating ESR1 mutation who have disease progression after ≥1 line of ET including a CDK4/6i
Mechanism of action	• Nonsteroidal, selective oestrogen receptor degrader • Stops oestrogen-dependent cancer cells from growing by binding to and degrading ER, blocking oestrogen's ability to bind to BC cells
Administration	Oral tablet 345mg once daily
Proposed list price (excluding VAT)	• Cost per 28-pack of tablets: 86mg for [redacted] and 345mg for [redacted] • Patient access scheme applies

*See appendix - slide 30

 Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; ESR1, oestrogen receptor 1; ET, endocrine therapy; HER2, human epidermal factor receptor 2

Treatment pathway and company positioning of elacestrant

Elacestrant is positioned in a narrower population than its marketing authorisation



EAG clinical expert comments

- Progression after 1L in ABC/mBC would switch to 2L options:
  - different AI ± everolimus **or**
  - tamoxifen **or**
  - alpelisib + fulvestrant^
- Elacestrant taken orally – preferable alternative to fulvestrant

^PIK3CA and no previous fulvestrant

Company clinical experts

- Endocrine monotherapy rarely used in proposed population

- Does the treatment pathway reflect standard care in NHS?
- Is the company positioning of elacestrant for people with disease progression following ≥12 months ET + CDK4/6i appropriate?
- Should tamoxifen be included as a comparator?

Abbreviations: 1L/2L, first / second line; ABC / mBC, advanced / metastatic breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issues

Key issues	ICER impact
1. Comparators: should tamoxifen be included as a comparator? (slide 7)	Unknown
2. Elacestrant clinical evidence in ESR1-mut and PIK3CA + ESR1-mut subgroups • Are the post-hoc analyses sufficient to suggest elacestrant is clinically effective in ESR1-mut and PIK3CA + ESR1-mut subgroups? (slide 13) • Are the unanchored MAICs suitable for decision making? (slide 15)	Unknown
3. OS extrapolation for elacestrant for ESR1-mut subgroup (slide 18) • Which OS distribution is preferred? Company's log-logistic or EAG's gamma? • Are the other distributions for PFS and OS in both subgroups used in the company and EAG's base case appropriate?	Large
4. Modelling treatment duration for comparators (slide 19) • How should TTD be modelled for Flatiron comparators? Assume TTD = PFS or adjust TTD curves using an assumed hazard ratio relative to comparator PFS?	• ESR1-mut: small • PIK3CA + ESR1-mut: moderate
5. ESR1-mutation testing (slide 20) • How would ESR1-mut testing be done in the NHS? • Should the cost of the ESR1-mut test be included in the economic model? • Should the cost be adjusted for prevalence of ESR1-mut?	Small
6. Other: severity modifier (slide 21); equality, uncaptured benefits (slide 24)	Unknown

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; MAIC; matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment

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EMERALD*

EAG: standard care (physician's choice of endocrine monotherapy) not representative of NHS practice

478 postmenopausal women or men (≥18 years), ER+, HER2-, LA/mBC
Disease progression within 28 days after 1 to 2 lines of ET for A/mBC, including CDK4/6i with fulvestrant or AI
1 line of chemotherapy for A/mBC

▼

228 ESR1-mut (cell-free circulating DNA; blood samples analysed using Guardant360 CDx
ESR1 mutations: any missense mutation in codons 310 – 547)

159 ESR1-mut	**62 PIK3CA + ESR1-mut**
78 elacestrant vs 81 standard care	27 elacestrant vs 35 standard care

Primary endpoint: imaging review committee-assessed PFS

EAG comments

Standard care (fulvestrant, anastrozole, letrozole or exemestane monotherapy)

- Monotherapy after progression on CDK4/6i not representative of NHS practice
- Fulvestrant not used as a single agent (NICE TA239)
- Switching from non-steroidal AI to drug that works in same way is rarely done
- ~92% had no prior tamoxifen, unclear why tamoxifen was not an option

Sample size: final PFS analysis conducted after 140 vs pre-specified 160 events for ESR1-mut → reduced power so results are uncertain

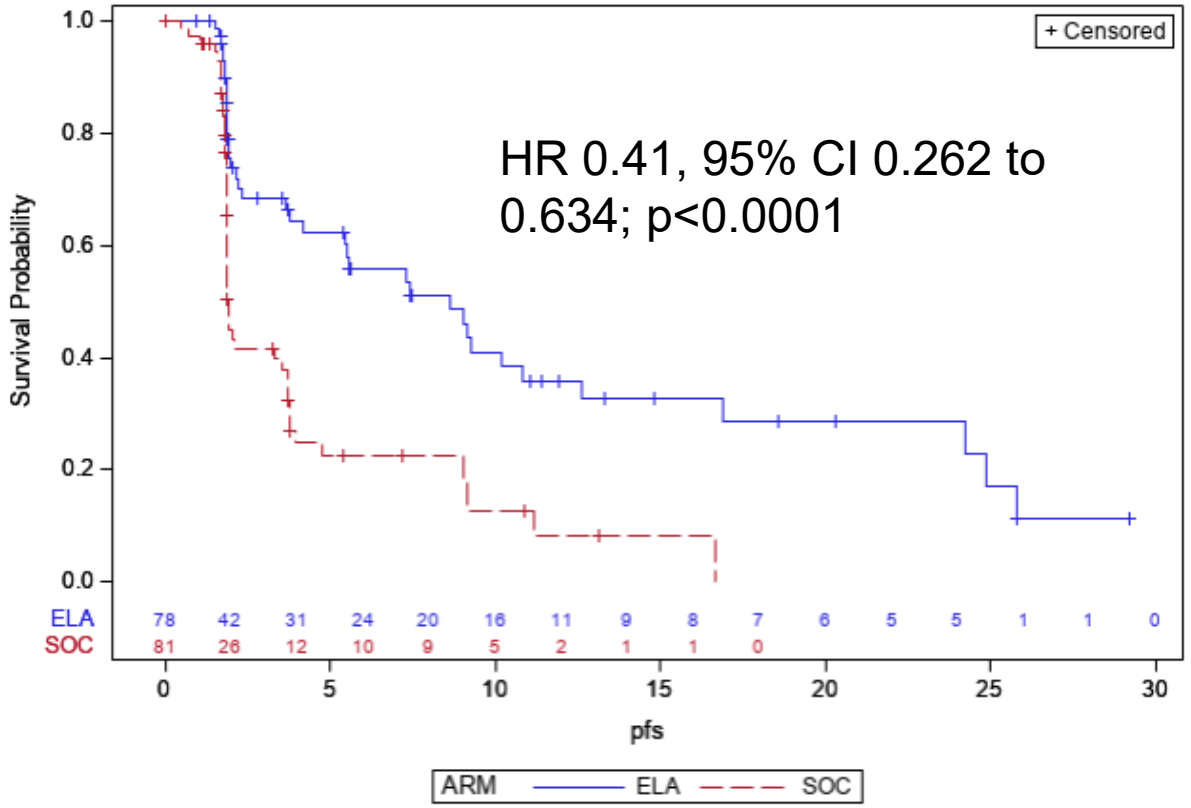
Abbreviations: AI, aromatase inhibitor; A / LA / mBC, advanced / locally advanced / metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; ESR1, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

*See appendix – Slides 31-34

ESR1-mut: PFS and OS (data cut 2 Sept 2022)

Subgroup had ≥12 months of ET + CDK4/6i. SC data not used in model

Kaplan–Meier plot of IRC-assessed PFS



Kaplan–Meier plot for OS

Median PFS months (95% CI)	Elacestrant	Standard care
	8.61 (4.14 to 10.84)	1.91 (1.87 to 3.68)

NICE

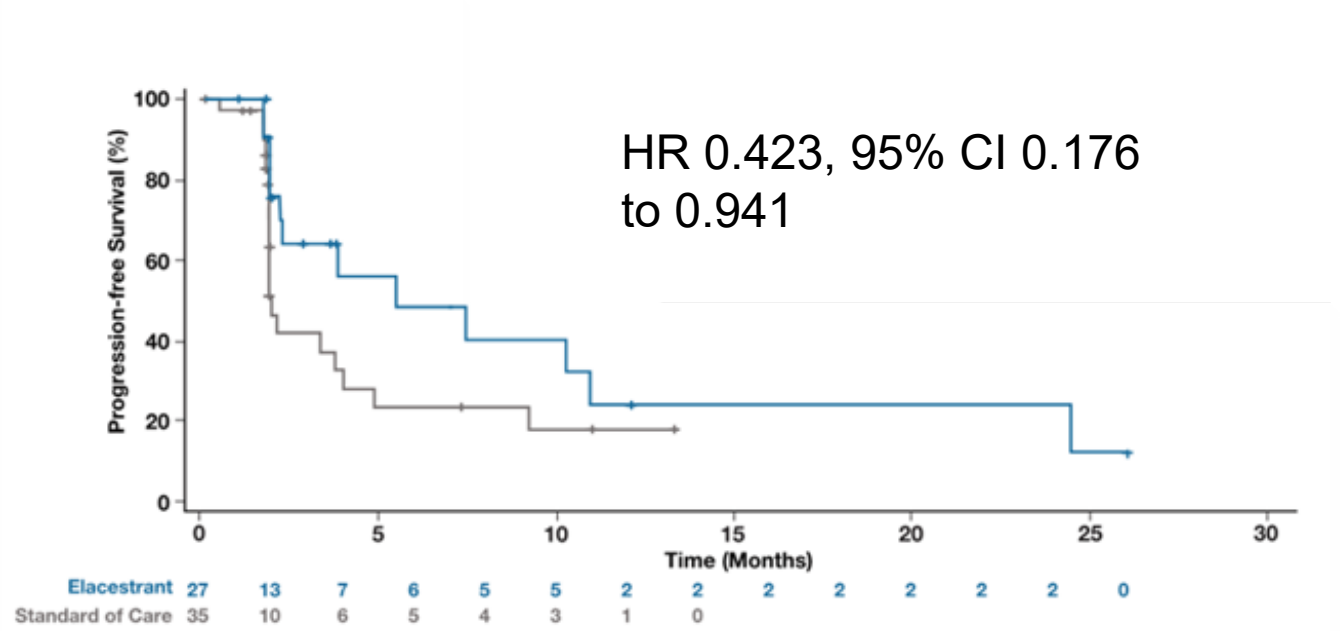
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, Confidence interval; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HR, hazard ratio; IRC, imaging review committee; OS, overall survival; PFS, progression free survival; SC, standard care

PIK3CA + ESR1-mut: PFS and OS (data cut 2 Sept 2022)

Subgroup had ≥12 months of ET + CDK4/6i. SC data not used in model

EAG: caution in interpretation of results because of small sample size and imbalances between arms in baseline characteristics

Kaplan–Meir plot of IRC-assessed PFS



HR 0.423, 95% CI 0.176 to 0.941

Median PFS months (95% CI)	Elacestrant	Standard care
	5.45 (2.14 to 10.84)	1.94 (1.84 to 3.94)

Kaplan–Meier plot for OS

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HR, hazard ratio; IRC, imaging review committee; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SC, standard care

Key issue: Elacestrant clinical evidence

EAG: EMERALD not statistically powered to detect changes in post hoc subgroups but comparative effectiveness estimates with standard care not used in model

Company

- Used post hoc analyses of EMERALD data to provide clinical effectiveness evidence for elacestrant in the 2 proposed subgroups, ESR1-mut and PIK3CA + ESR1-mut, both with ≥12 months of ET + CDK4/6i

EAG comments

- Caution in interpreting results, especially for PIK3CA + ESR1-mut subgroup:
  - EMERALD not statistically powered for subgroups so statistical significance cannot be inferred → not confirmatory
  - Small sample sizes (e.g. PIK3CA + ESR1-mut: 13% of randomised population)
  - Selection bias with unclear impact: arms imbalanced on baseline characteristics (e.g. PIK3CA + ESR1-mut: more people on elacestrant had certain adverse prognostic factors suggesting slightly more ABC than people on standard care

- Are the post-hoc subgroup analyses sufficient to suggest elacestrant is clinically effective in the ESR1-mut and PIK3CA + ESR1-mut subgroups?

Abbreviations: ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Unanchored matching-adjusted indirect comparisons*

EAG: MAICs results are highly uncertain because key prognostic factors are not included due to limited data and small sample sizes

Company

- To compare impact of elacestrant on PFS and OS with everolimus + exemestane (ESR1-mut) and with alpelisib + fulvestrant (PIK3CA + ESR1-mut), company conducted unanchored MAICs using IPD from EMERALD reweighted by key patient characteristics to match mean/median characteristics from Flatiron
  - Flatiron: real world database of US-based clinical data (n=32 ever + exe, n=33 alpelisib + fulvestrant)

EAG comments

- NICE DSU TSD 18: unanchored MAICs lack common comparator, strong assumption that all effect modifiers and prognostic factors are accounted for so absolute outcomes can be predicted from covariates
- Key limitation: data available for only 3 of 14 prognostic factors identified by company for matching
  - Included: age, prior chemotherapy, number of treatment lines for mBC
  - Implicitly included: menopausal status, duration of prior CDK4/6i, ER expression
  - Excluded: ECOG PS, number of metastatic sites, bone metastases, visceral metastases, time since diagnosis, ductal vs lobular BC, de novo vs recurrent, de novo vs progressed
- Other key prognostic factors not included e.g. tumour grade, circulating tumour cell count, Ki67 level, family background (Cuyún Carter et al. 2021)
- Other limitations: small effective sample sizes after weighting and imbalances in weighted prognostic factors between arms; unclear if Flatiron population progressed on CDK4/6i + fulvestrant or AI
- Alternative RWE Patient360 Breast may have provided more data on prognostic factors

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DSU TSD, Decision Support Unit technical support document; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESR1-mut, oestrogen receptor 1 mutation; ever, everolimus; exe, exemestane; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; mBC, metastatic breast cancer; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

*See appendix – Slides 35-37

Unanchored MAIC results: PFS and OS

EAG: inferences of statistical significance should not be made because of limitations of unanchored MAIC. Results used in economic model

ESR1-mut: elacestrant vs everolimus + exemestane

	Median (95% CI)		Elacestrant vs EVE + EXE HR (95% CI)
	Elacestrant weighted	Everolimus + exemestane	
PFS	[redacted]	[redacted]	0.59 (0.36, 0.96)
OS	[redacted]	[redacted]	0.64 (0.35, 1.16)

*See appendix for survival curves – slide 38

PIK3CA + ESR1-mut: elacestrant vs alpelisib + fulvestrant

	Median (95% CI)		Elacestrant vs ALP + FUL HR (95% CI)
	Elacestrant weighted	Alpelisib + fulvestrant	
PFS	[redacted]	[redacted]	1.05 (0.5, 2.2)
OS	[redacted]	[redacted]	0.8 (0.33, 1.92)

*See appendix for survival curves – slide 39

- Are the unanchored MAICs suitable for decision making?
- Is elacestrant clinically effective?

Abbreviations: ALP + FUL, alpelisib + fulvestrant; CI, confidence interval; ESR1-mut, oestrogen receptor 1 mutation; EVE + EXE, everolimus + exemestane; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NR, not reported; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

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Key issue: Survival extrapolations

Company and EAG agree on survival distributions except for elacestrant OS for ESR1-mut

Company

- Used patient-level data from EMERALD for elacestrant and pseudo patient-level data from KM curves for Flatiron comparators to extrapolate long-term PFS and OS for ESR1-mut and PIK3CA + ESR1-mut subgroups
- Applied MAIC weights to elacestrant patient-level data to align prognostic characteristics in Flatiron comparators
- Chose distributions based on fit to KM estimates using visual inspection, AIC and BIC statistics and clinical plausibility of long-term extrapolations
- Fitted OS and PFS curves for elacestrant and comparators independently

EAG comments

- High uncertainty in extrapolations because of limited sample sizes for subgroups from EMERALD and Flatiron and use of data from unanchored MAIC
- Preferred gamma distribution for elacestrant OS ESR1-mut subgroup because of good statistical and visual fit in both arms and similar survival projections after year 5

Base case	ESR1-mut				PIK3CA + ESR1-mut			
	Elacestrant		Everolimus + exemestane		Elacestrant		Alpelisib + fulvestrant	
	PFS	**OS**	PFS	OS	PFS	OS	PFS	OS
Company	Lognormal	**Loglogistic**	Lognormal	Gamma	Lognormal	Weibull	Lognormal	Gamma
EAG		**Gamma**						

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issue: OS extrapolations for ESR1-mut*

Large impact

Base case	ESR1-mut, elacestrant OS extrapolation
Company	Log-logistic
EAG	Gamma

Distribution	Model fit			ESR1-mut: OS estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier n=[redacted]	-	-	-	86.6%	51.6%	14.7%	-	-
Gompertz	332.93	337.64	2	83.9%	56.6%	24.3%	0.1%	0%
Log-logistic	**334.04**	**338.75**	**4**	**83.5%**	**54.6%**	**34.5%**	**15.7%**	**4.3%**
Weibull	332.50	337.21	1	83.8%	54.7%	29.6%	5.2%	0%
Gamma	**333.35**	**338.06**	**3**	**82.8%**	**54.4%**	**32.4%**	**9.8%**	**0.3%**

- What is the clinical plausibility of the year 5 and year 10 extrapolations for log-logistic and gamma curves?
  - Which OS distribution is preferred for elacestrant?
- Are the other distributions for PFS and OS in both subgroups used in the company and EAG's base case appropriate?

*See appendix for PFS and OS extrapolations for ESR1-mut – Slides 41-43
*See appendix for PFS and OS extrapolations for PIK3CA + ESR1-mut – Slides 44-45

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issue: Modelling treatment duration

Moderate impact

Uncertainty about time on treatment for comparators

Company

- Elacestrant time to treatment discontinuation (TTD): used KM curves from EMERALD
- Comparators' TTD data not available from Flatiron: assumed TTD = PFS

EAG comments

- Potential bias in using different TTD assumptions for elacestrant and comparators → overestimate comparators' treatment costs relative to elacestrant if some people stop comparator treatments before progression, as observed for elacestrant
- Elacestrant EMERALD data used in the model shows a difference between TTD and PFS, with some people stopping treatment before progression
  - Difference between company's TTD estimates for elacestrant and alpelisib + fulvestrant in PIK3CA + ESR1-mut subgroup is especially marked
- EAG disagrees with company's assumption for comparators, but uses it in its base case
- Provides scenarios adjusting comparators' TTD curves using an assumed HR (0.8 for ESR1-mut and 0.5 for PIK3CA + ESR1-mut) relative to comparators' PFS

- How should TTD be modelled for Flatiron comparators? Use company's assumption that TTD = PFS or EAG's scenarios adjusting TTD curves with an assumed hazard ratio relative to comparator PFS?

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; HR, hazard ratio; KM, Kaplan–Meier; PFS, progression-free survival; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation

Key issue: ESR1 mutation testing

Small impact

Background

- BC genetic testing before treatment is routine using tissue sample and digital PCR assay
- Digital PCR could be used to test for ESR1-mut and eligibility for elacestrant, but needs repeat biopsy
- EMERALD ESR1-mut testing: blood sample and ctDNA test
- North Thames NHS Genomic Laboratory Hub provides ctDNA test for ESR1-mut (Marsden360 assay)

Company

- Base case: assumed £300 per digital PCR test on liquid biopsy (based on NIHR interactive costing tool) and 50% prevalence of ESR1 mutation = £600 per case identified for treatment

EAG comments

- NHS Genomic Medicine Service (GMS) provided cost estimates of ctDNA tests for ESR1-mut: current £1700 and £850 that assumes future testing approach using large next generation sequencing (NGS) panel
- Disagree with prevalence for PIK3CA + ESR1-mut: used 20% based on EAG clinical expert opinion
- EAG scenarios: NHS GMS cost estimates for ctDNA (£850 or £1,700) ± adjustment for prevalence

- How would ESR1-mut testing be done in the NHS? Would everyone who progresses on CDK4/6i + AI be tested? Would there be repeat testing?
- Should the cost of the ESR1-mut test be included in the model?
  - If yes, should testing be done by tissue biopsy or liquid biopsy on ctDNA?
  - If liquid biopsy, should test be done using droplet PCR detecting only ESR1 variants or an NGS panel?
- Should cost be adjusted for prevalence of ESR1-mut?
  - If yes, are the following plausible: 50% for ESR1-mut and 20% for PIK3CA + ESR1-mut?

Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor deoxyribonucleic acid; ESR1-mut, oestrogen receptor 1 mutation; PCR, polymerase chain reaction; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

QALY weightings for severity*

Background

- **Mean age in years. Company:** ESR1-mut [redacted]; PIK3CA + ESR1-mut [redacted]. **EAG:** ESR1-mut [redacted]; PIK3CA [redacted]
- **Discount rate:** 3.5% (cost and QALYs)
- **Proportion of females:** [redacted]

QALY weight	Absolute shortfall	Proportional shortfall
1	<12	<85%
X 1.2	12 to 18	85% to 95%
X 1.7	≥18	≥95%

		QALYs of people without condition (based on trial population characteristics)	QALYs of people with the condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
ESR1-mut	**Company base case**	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	EAG base case	[redacted]	[redacted]	[redacted]	[redacted]	1.2
PIK3CA + ESR1-mut	**Company and EAG base case**	[redacted]	[redacted]	[redacted]	[redacted]	1.0

- Is applying a QALY weighting for severity for the ESR1-mut subgroup appropriate?

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY, quality adjusted life year

*See appendix – slide 47

Summary of company and EAG base case differing assumptions

ESR1-mut subgroup

Assumption	Company base case	EAG base case
Population age	[redacted] years Source: EMERALD	[redacted] years Source: Flatiron
OS extrapolation: elacestrant	Log-logistic	Gamma
Everolimus acquisition cost	BNF 2024 (packs of 30 tablets) 2.5mg: £1,020 5mg: £1,912.50 10mg: £2,272.05	eMIT 2023 (packs of 30 tablets) 2.5mg: £403.03 5mg: £471.99 10mg: £536.65

PIK3CA + ESR1-mut subgroup

Assumption	Company base case	EAG base case
Population age	[redacted] years Source: EMERALD	[redacted] years Source: Flatiron
Prevalence of positive cases after ESR1-mut testing	50%	20%

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

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Other considerations

Innovation: company comments

- Elacestrant: oral, first UK licensed treatment option for targeted ESR-1 mutation in BC
- 'Step-change' in management addressing unmet need for people with limited options

Equality: stakeholders did not identify any equality issues

Managed access: company has not submitted a managed access proposal

Are there any equality issues to be considered?
Are there any uncaptured benefits?

Abbreviations: BC, breast cancer; ESR1-mut, oestrogen receptor 1 mutation

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Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

- Company and EAG base case ICERs: >£30,000
- All scenarios >£30,000
  - Only scenario <£30,000 is log-normal elacestrant OS extrapolation for PIK3CA + ESR1-mut subgroup
- All key issues have been explored in scenario analyses and have moderate impact on ICER
- PFS and OS extrapolations have largest impact on ICER

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issues

Key issues	ICER impact
1. Comparators: should tamoxifen be included as a comparator? (slide 7)	Unknown
2. Elacestrant clinical evidence in ESR1-mut and PIK3CA + ESR1-mut subgroups • Are the post-hoc analyses sufficient to suggest elacestrant is clinically effective in ESR1-mut and PIK3CA + ESR1-mut subgroups? (slide 13) • Are the unanchored MAICs suitable for decision making? (slide 15)	Unknown
3. OS extrapolation for elacestrant for ESR1-mut subgroup (slide 18) • Which OS distribution is preferred? Company's log-logistic or EAG's gamma? • Are the other distributions for PFS and OS in both subgroups used in the company and EAG's base case appropriate?	Large
4. Modelling treatment duration for comparators (slide 19) • How should TTD be modelled for Flatiron comparators? Assume TTD = PFS or adjust TTD curves using an assumed hazard ratio relative to comparator PFS?	• ESR1-mut: small • PIK3CA + ESR1-mut: moderate
5. ESR1-mutation testing (slide 20) • How would ESR1-mut testing be done in the NHS? • Should the cost of the ESR1-mut test be included in the economic model? • Should the cost be adjusted for prevalence of ESR1-mut?	Small
6. Other: severity modifier (slide 21); equality, uncaptured benefits (slide 24)	Unknown

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; MAIC; matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation

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Thank you

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment

Supplementary appendix

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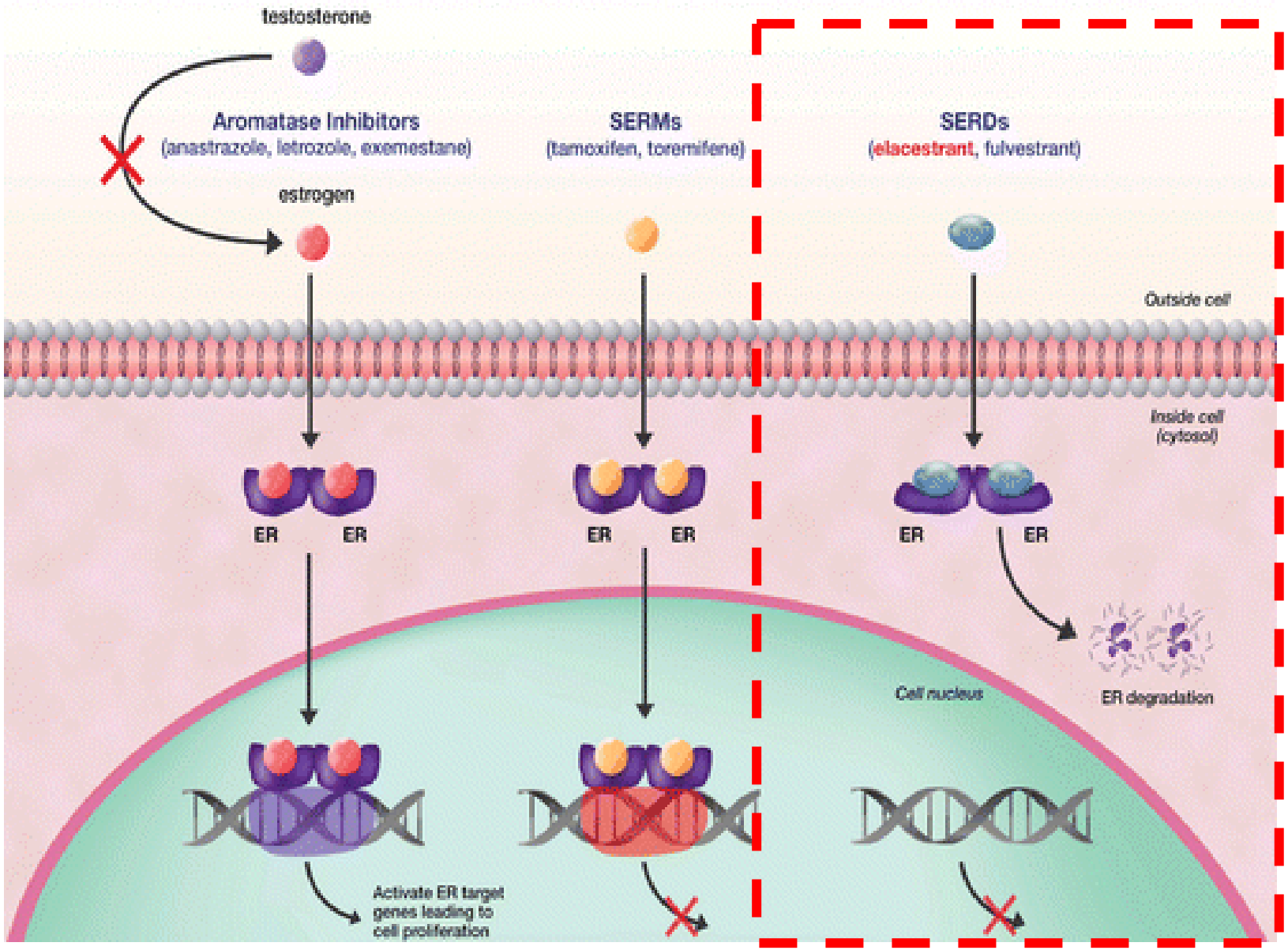
Elacestrant mechanism of action



Abbreviations: SERD, selective oestrogen receptor degrader; SERM, selective oestrogen receptor modulator

*Link to Elacestrant

EMERALD (10/05/2019 to 08/2024 estimated)

Location	17 countries (54% from Europe): Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Greece, Hungary, Ireland, Israel, Italy, Portugal, South Korea, Spain, USA, **UK (n=12; 9 ESR1-mut)**
Sample	N=478 (239 elacestrant vs 239 SC). N=228 ESR1-mut (115 elacestrant vs 113 SC) N=159 ESR1-mut (78 elacestrant vs 81 SC) N=62 PIK3CA + ESR1-mut (27 elacestrant vs 35 SC)
Design	Phase 3, open-label, active-controlled, multicentre trial. 1:1 randomisation stratified for ESR1-mut status, prior fulvestrant, presence of asymptomatic visceral metastasis
ESR1-mut test	Evaluated in cell-free circulating DNA at a central laboratory; blood samples were analysed using the Guardant360 CDx (GuardantHealth, RedwoodCity, CA). ESR1 mutations defined as any missense mutation in codons 310 - 547
Population	• Postmenopausal women or men (≥18 years), histologically/cytologically proven ER+/HER2- BC • LA or mBC not amenable to curative therapy • Disease progression during or within 28 days after treatment with 1 to 2 prior lines of ET for ABC or mBC, including CDK4/6i with fulvestrant or an AI • Progression during or within 12 months of adjuvant ET = 1 line of ET for aBC or mBC • ECOG performance status 0 or 1 and measurable disease per RECIST version 1.1 or evaluable bone-only disease with ≥1 lytic or mixed lytic-blastic bone lesion **Excluded:** Child-Pugh Score > Class A
Comparison	Elacestrant vs standard care (physician's choice: fulvestrant, anastrozole, letrozole or exemestane)
Outcomes	**Primary:** IRC-assessed progression free survival. **Key secondary:** OS, response rate (ORR, CBR and DOR), AEs (Grade 3+ in 2%+), HRQoL (EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE) For post-hoc subgroups, data cut for PFS and OS 2 September 2022 and 8 July 2022 for patient-reported outcome data *Link to EMERALD

Imbalance in baseline characteristics of post hoc subgroups

For the PIK3CA + ESR1-mut subgroup, EAG considers people in elacestrant arm to be [redacted] than in standard care arm. The impact of these imbalances is unclear

ESR1-mut

- Fulvestrant as prior therapy for ABC or mBC ([redacted])
- Mammalian target of rapamycin (mTOR) inhibitor as prior therapy for ABC or mBC ([redacted])

PIK3CA + ESR1-mut

- Median age ([redacted])
- Visceral metastasis ([redacted])
- mTOR inhibitor as prior therapy for ABC or mBC ([redacted])
- 1 prior line of ET for ABC or mBC ([redacted])
- 2 prior lines of ET ([redacted])

*Link to EMERALD

Abbreviations: A / LA / mBC, advanced / locally advanced / metastatic breast cancer; AE, adverse event; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimension-5 Level; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; IRC, Imaging review committee; HER2, human epidermal factor receptor 2; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumours; SC, standard care

EQ-5D-5L results

Company used EQ-5D-5L data for overall ESR1-mut subgroup mapped to EQ-5D-3L using Hernández-Alava et al. algorithm to estimate health state utilities in its base case

	EQ-5D-5L scores at end of treatment			
	ESR1-mut		PIK3CA + ESR1-mut	
	Elacestrant	Standard care	Elacestrant	Standard care
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Health state utilities used in company's base case

- Progression-free [redacted] (95% CI: [redacted])
- Progressed disease [redacted] (95% CI: [redacted])

*Link to EMERALD

Abbreviations: EQ-5D-3/5L, EuroQol-5 Dimension-3/5 Level; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SD, standard deviation

Adverse events

*Link to EMERALD

Event, n (%)	ESR1-mut		PIK3CA + ESR1-mut	
	Elacestrant (n=[redacted])	Standard care (n=[redacted])	Elacestrant (n=[redacted])	Standard care (n=[redacted])
Any treatment emergent AE	[redacted]	[redacted]	[redacted]	[redacted]
AE grade ≥3 in ≥ 2% of patients (in economic model)	[redacted]	[redacted]	[redacted]	[redacted]
AE leading dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
AE reported in ≥10% of patients in either trial arm				
Nausea	30 (39)	11 (15)	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	16 (21)	6 (8)	[redacted]	[redacted]
Diarrhoea	16 (21)	9 (12)	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Headache	13 (17)	9 (12)	[redacted]	[redacted]
Decreased appetite	12 (15)	5 (7)	[redacted]	[redacted]
Dyspepsia	10 (13)	3 (4)	[redacted]	[redacted]
Hot flush	9 (12)	7 (9)	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood cholesterol increased	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Unanchored MAIC – prognostic factors identified by company

Characteristics	In MAIC?	Comments
Age	Yes	Flatiron restricted to ≥50 years
Prior chemotherapy	Yes	
Number of treatment lines in metastatic setting	Yes – for ET	Number of prior ET included as only number of prior lines of ET available
Menopausal status	Partial	Implicit: older women in Flatiron
ECOG PS	No	Presence of ~25% unknown ECOG in Flatiron
Number of metastatic sites	No	Excluded due to lack of data
Bone metastases / bone metastases only	No	Excluded due to lack of data
Visceral metastases	No	Excluded due to lack of data
Length of time on prior CDK4/6i	Partial	Implicit from population restriction (prior CDK4/6i ≥12 months)
Time since original diagnosis	No	Discrepancy in data: only time since stage III diagnosis in Flatiron
ER expression	Partial	Implicit from population restriction (focus on ESR1-mut)
Histology (ductal vs lobular)	No	Excluded due to lack of data
De novo vs recurrent (i.e. diagnosed in adjuvant setting)	No	Excluded due to lack of data
De novo vs progressed	No	Excluded due to lack of data

*Link to MAIC

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; MAIC, matching-adjusted indirect comparison

Key issue: Unanchored MAICs

MAICs results are highly uncertain: Key prognostic factors are not included because of limited data and small sample sizes

EAG comments

- Comparators' trials: none tested for ESR1-mut → used Flatiron RWD
- Limitations of unanchored MAIC:
  - No matching on key prognostic factors such as bone metastases, number of metastatic sites and de novo vs recurrent/progressed disease.
  - Small effective sample sizes after weighting and imbalances in weighted prognostic factors between elacestrant and comparators, particularly in PIK3CA + ESR1-mut subgroup
  - Company did not state how data on duration of previous ET was identified in Flatiron. EAG assumed exposure time for previous CDK4/6i = exposure time for previous ET
  - Company provided limited details on methods of searching for relevant sources of RWE
  - Unclear if Flatiron population progressed on CDK4/6i + fulvestrant or AI, the target population for elacestrant
  - Imbalance in baseline characteristics of weighted elacestrant population and comparators because of missing data on ECOG status for 25% Flatiron
- Alternative RWE Patient360 Breast (ConcertAI) in scenario analysis may provide more comprehensive data on prognostic factors (not provided by Company)

*Link to MAIC

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; MAIC, matching-adjusted indirect comparison; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWD, real world data; RWE, real world evidence

MAIC baseline characteristics: EMERALD and Flatiron

Characteristic		ESR1-mut			PIK3CA + ESR1-mut		
		Elacestrant		Everolimus + exemestane	Elacestrant		Alpelisib + fulvestrant
		Unweighted	Weighted		Unweighted	Weighted	
N / ESS		78	[redacted]	32	27	[redacted]	33
Age	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)	ECOG 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ECOG 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ECOG 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior ET	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior chemotherapy in ABC or mBC	Yes (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Link to MAIC

Abbreviations: A / mBC, advanced / metastatic breast cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESR1-mut, oestrogen receptor 1 mutation; ESS, effective sample size; ET, endocrine therapy; MAIC, matching-adjusted indirect comparison; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SD, standard deviation

ESR1-mut: MAIC PFS and OS (elacestrant vs everolimus + exemestane)

EAG: inferences of statistical significance should not be made because of limitations of unanchored MAIC. Used in economic model

Unweighted and MAIC-weighted PFS

Unweighted and MAIC-weighted OS

*Link to MAIC results

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival

PIK3CA + ESR1-mut: MAIC PFS and OS (elacestrant vs alpelisib + fulvestrant)

EAG consider inferences of statistical significance should not be made because of limitations of unanchored MAIC. Used in economic model

Unweighted and MAIC-weighted PFS

[redacted]

Unweighted and MAIC-weighted OS

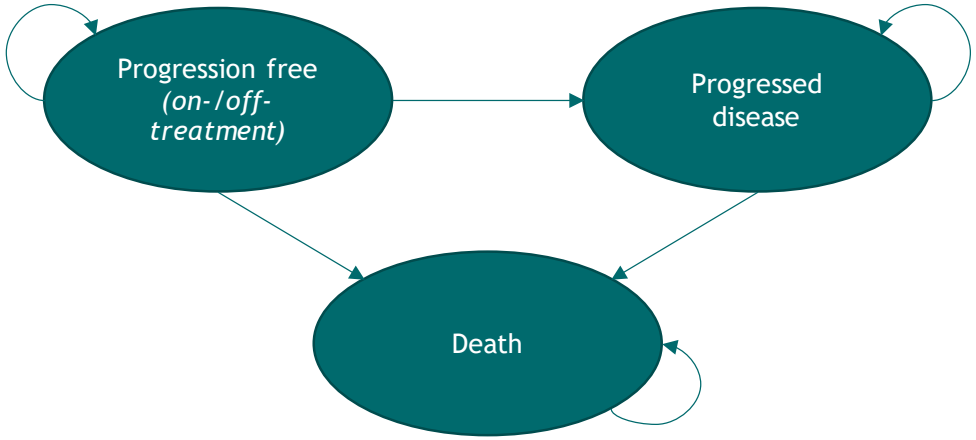
[redacted]

*Link to MAIC results

Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Company's model overview

Model structure



- Partitioned survival model with 3 states: progression-free (pre-progression; on or off treatment), progressed disease (post-progression) and death
- Includes constraints to ensure that:
  - % on treatment < PFS
  - % progression free < OS
  - Risk of death is no lower than for age- and sex-matched general population
- Lifetime horizon (37 years); 1-week cycle, no half-cycle correction; NHS/PSS perspective, 3.5% discounting
- ESR1-mut: [redacted]
- PIK3CA + ESR1-mut: [redacted]

- Technology affects **costs** by:
  - Increasing treatment cost for ESR1-mut
  - Decreasing treatment cost for PIK3CA + ESR1-mut
  - Costs to introduce ESR1-mut testing
- Technology affects **QALYs** by:
  - Increasing OS
  - Maintaining QoL for longer (extended PFS)
- Assumptions with greatest ICER effect:
  - Choice of OS extrapolations for elacestrant and resulting difference in survival relative to comparators
  - Differences in treatment duration for elacestrant (based on EMERALD) and comparators (assumed equal to PFS)
  - Use of MAIC hazard ratios to model comparator survival curves compared with independently fitted curves (using MAIC-adjusted data for elacestrant)

Abbreviations: BSA, body surface area; ESR1-mut, oestrogen receptor 1 mutation; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY, quality-adjusted life year; QoL, quality of lifes

ESR1-mut: PFS extrapolations

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Everolimus + exemestane								
Kaplan-Meier	-	-	-	14.6%	-	-	-	-
Exponential	150.53	151.99	7	12.5%	1.5%	0.2%	0%	0%
Gen. gamma	146.20	150.60	5	7.2%	0.4%	0%	0%	0%
Gompertz	148.74	151.67	6	5.9%	0.0%	0%	0%	0%
Log-logistic	144.20	147.14	1	8.4%	1.8%	0.7%	0.2%	0%
Log-normal	**144.84**	**147.77**	**3**	**9.0%**	**1.2%**	**0.3%**	**0%**	**0%**
Weibull	145.69	148.62	4	5.5%	0.0%	0%	0%	0%
Gamma	144.62	147.55	2	5.9%	0.1%	0%	0%	0%
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	34.3%	29.3%	-	-	-
Exponential	250.31	252.67	4	37%	13.4%	5%	0.7%	0%
Gen. gamma	212.37	219.44	1	31.1%	20.7%	16.5%	12.3%	8.3%
Gompertz	250.63	255.34	5	36.2%	18.4%	11.9%	7.4%	5.4%
Log-logistic	245.92	250.64	3	30.8%	14.2%	8.6%	4.4%	1.7%
Log-normal	**242.02**	**246.73**	**2**	**32.2%**	**14.2%**	**7.8%**	**3.1%**	**0.7%**
Weibull	252.31	257.02	7	37.1%	13.6%	5.1%	0.7%	0%
Gamma	252.13	256.84	6	36.4%	12.3%	4.2%	0.5%	0%

EAG and company base case

*Link to Survival extrapolations

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; PFS, progression free survival

ESR1-mut: OS extrapolations

Distribution	Model fit			OSI estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Everolimus + exemestane								
Kaplan-Meier	-	-	-	62.3%	37.5%	28.1%	14.1%	-
Exponential	173.17	174.63	1	63.7%	40.3%	25.7%	10.4%	1.1%
Gen. gamma	176.57	180.97	7	63.4%	40.3%	27.0%	13.3%	3.1%
Gompertz	175.10	178.03	5	62.7%	40.2%	26.7%	12.7%	2.9%
Log-logistic	174.32	177.25	2	62.3%	38.6%	26.6%	15.3%	6.5%
Log-normal	175.23	178.16	6	61.2%	40.2%	29.0%	17.4%	7.1%
Weibull	175.10	178.03	4	64.6%	40.1%	24.7%	9.2%	0.7%
Gamma	**175.01**	**177.94**	**3**	**64.8%**	**39.8%**	**24.4%**	**9%**	**0.7%**
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	86.6%	51.6%	14.7%	-	-
Exponential	342.10	344.45	7	74.3%	54.8%	40.7%	22.5%	5%
Gen. gamma	334.16	341.23	5	83.8%	55.3%	26.8%	1.3%	0%
Gompertz	332.93	337.64	2	83.9%	56.6%	24.3%	0.1%	0%
Log-logistic	**334.04**	**338.75**	**4**	**83.5%**	**54.6%**	**34.5%**	**15.7%**	**4.3%**
Log-normal	337.04	341.75	6	80.5%	54.3%	37.4%	19.3%	5.4%
Weibull	332.50	337.21	1	83.8%	54.7%	29.6%	5.2%	0%
Gamma	**333.35**	**338.06**	**3**	**82.8%**	**54.4%**	**32.4%**	**9.8%**	**0.3%**

EAG and company base case | Company base case | EAG base case

*Link to OS extrapolations ESR1-mut

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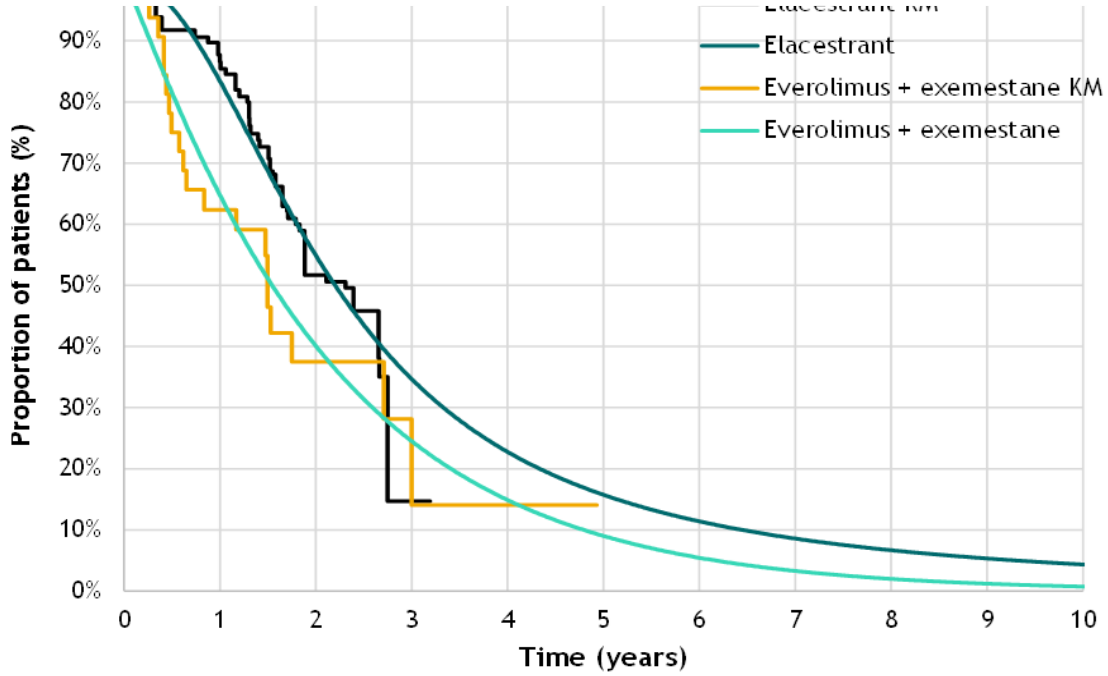
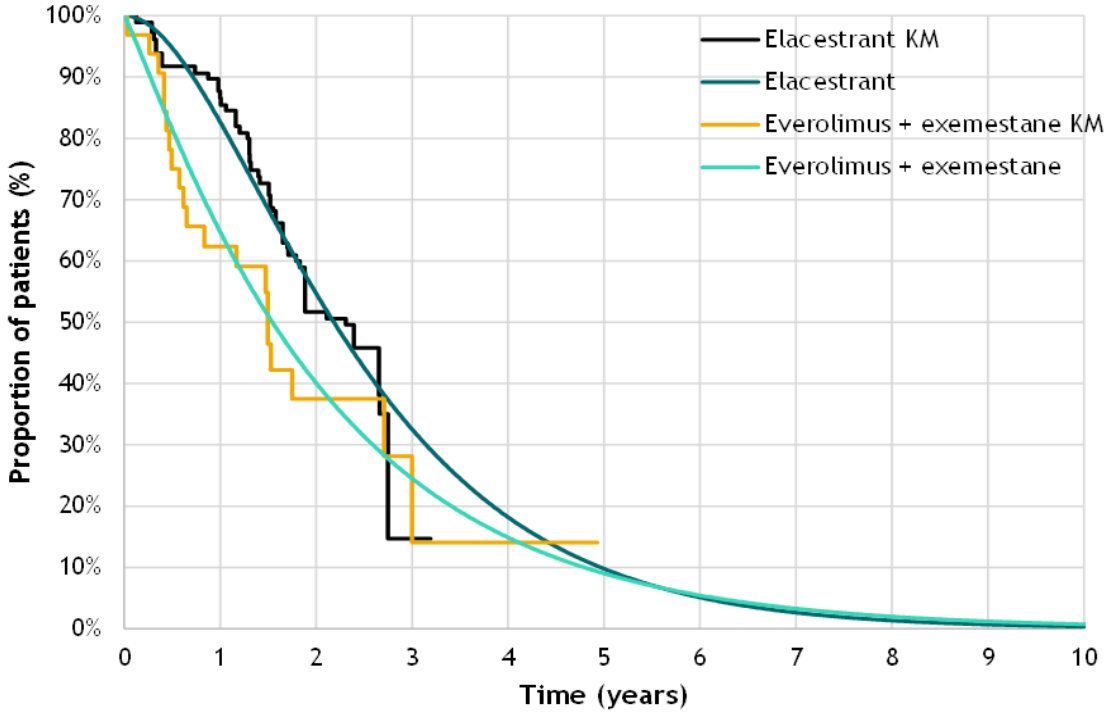
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; OS, overall survival

ESR1-mut: OS extrapolations – company and EAG base case

Company base case
Elacestrant = log-logistic
Everolimus + exemestane = gamma



EAG base case
Elacestrant = gamma
Everolimus + exemestane = gamma



*Link to OS extrapolations ESR1-mut

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Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; KM, Kaplan-Meier; OS, overall survival

PIK3CA + ESR1-mut: PFS extrapolations

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Alpelisib + fulvestrant								
Kaplan-Meier	-	-	-	30.2%	5%			-
Exponential	163.80	165.29	7	27.8%	7.6%	2.1%	0.2%	0%
Gen. gamma	156.23	160.72	2	21.2%	5%	1.9%	0.5%	0.1%
Gompertz	161.48	164.47	6	28.5%	1.4%	0%	0%	0%
Log-logistic	156.73	159.72	4	20.3%	4.6%	1.8%	0.5%	0.1%
Log-normal	**154.52**	**157.51**	**1**	**21%**	**3.5%**	**0.8%**	**0.1%**	**0%**
Weibull	157.98	160.97	5	24.9%	1.5%	0%	0%	0%
Gamma	156.42	159.41	3	22.7%	1.8%	0.1%	0%	0%
Elacestrant (weighted to alpelisib + fulvestrant)								
Kaplan-Meier	-	-	-	21.1%	-	-	-	-
Exponential	84.72	86.01	4	30.7%	9.2%	2.8%	0.3%	0%
Gen. gamma	73.32	77.20	1	21.5%	12.4%	9%	6.1%	3.5%
Gompertz	86.66	89.25	7	30.6%	10.5%	4.2%	0.9%	0.1%
Log-logistic	84.16	86.75	3	23%	8.5%	4.6%	2%	0.7%
Log-normal	**82.84**	**85.43**	**2**	**24.3%**	**8%**	**3.5%**	**1%**	**0.1%**
Weibull	86.46	89.05	6	29.8%	7.2%	1.6%	0.1%	0%
Gamma	86.06	88.65	5	28.4%	6.2%	1.3%	0.1%	0%

EAG and company base case

*Link to Survival extrapolations

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

PIK3CA + ESR1-mut: OS extrapolations

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Alpelisib + fulvestrant								
Kaplan-Meier	-	-	-	84.7%	55.1%	34.4%	-	-
Exponential	126.69	128.18	6	76.4%	58.1%	44.4%	26%	6.7%
Gompertz	123.71	126.71	5	85.3%	61.4%	31.8%	0.6%	0%
Log-logistic	122.44	125.43	4	86.1%	56%	34%	14.1%	3.3%
Log-normal	122.33	125.32	2	84.8%	55.3%	35.3%	15.4%	2.9%
Weibull	122.33	125.32	3	86.5%	58.3%	31.8%	5.2%	0%
Gamma	**122.14**	**125.13**	**1**	**86.1%**	**56.8%**	**32.7%**	**8.6%**	**0.2%**
Elacestrant (weighted to alpelisib + fulvestrant)								
Kaplan-Meier	-	-	-	88.8%	73.6%		-	-
Exponential	90.62	91.92	7	83.2%	68.9%	57.3%	39.7%	15.7%
Gompertz	88.00	90.59	1	92.5%	73.4%	37.7%	0%	0%
Log-logistic	89.17	91.76	4	91.9%	70.9%	50.3%	24.9%	6.8%
Log-normal	89.65	92.24	5	90.4%	69.7%	52.5%	30.6%	9.9%
Weibull	**88.61**	**91.20**	**2**	**92.1%**	**71%**	**46.1%**	**11.4%**	**0%**
Gamma	88.96	91.56	3	91.4%	70.4%	49.1%	20%	1.3%

EAG and company base case

*Link to Survival extrapolations

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; OS, overall survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Elacestrant TTD extrapolation for subgroups

Distribution	Model fit			ESR1-mut: Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Kaplan-Meier	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	455.13	457.48	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	431.34	438.41	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	453.91	458.62	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	442.37	447.08	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	438.63	443.34	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Model fit			PIK3CA + ESR1-mut: Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Kaplan-Meier	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	121.56	122.78	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	108.23	111.89	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	120.73	123.17	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	111.60	114.04	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	113.09	115.53	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

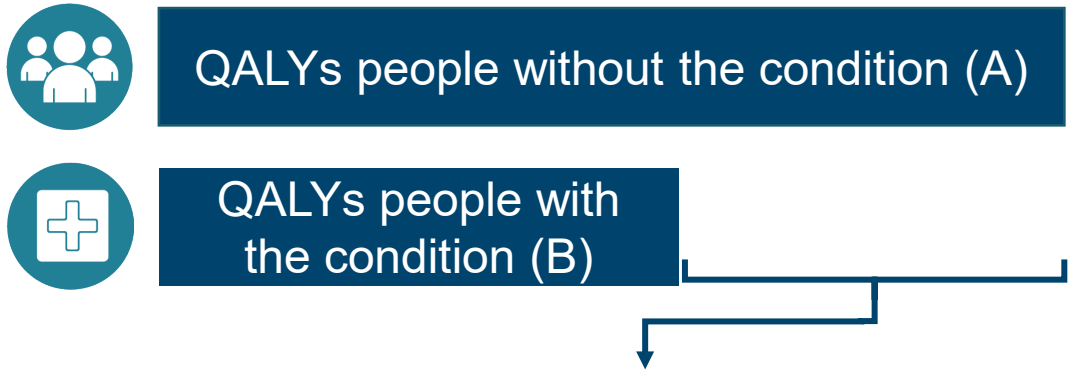
EAG and company base case

*Link to Survival extrapolations

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ESR1-mut, oestrogen receptor 1 mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

*Link to QALY weighting for severity

Abbreviations: QALY, quality-adjusted life year