PART 1 for PROJECTOR – contains no CON 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 [Second meeting: 12 November 2024]

Chair: Radha Todd

External assessment group: Southampton Health Technology Assessments Centre

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Company: Menarini Stemline UK

Draft guidance consultation

Preliminary recommendation

Elacestrant is **not recommended**, within its marketing authorisation, for treating oestrogen receptor (ER)-positive HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 1 line of endocrine therapy including a cyclin-dependent kinase (CDK) 4 and 6 inhibitor in:

- women, trans men and non-binary people after menopause
- men

DG consultation responses

- Company: new analyses; revised PAS
- Patient organisations: Breast Cancer Now, METUPUK
- Clinical expert

Abbreviations: DG, draft guidance; EAG, Evidence Assessment Group; ESR1, oestrogen receptor 1; PAS, patient access scheme

Background

RECAP

ER+ HER2- ESR1-mut advanced or metastatic breast cancer

- ~50% BC treated with ET acquire ESR1-mut on disease progression (worse survival than BC & no ESR1-mut)
- Genomic testing for ESR1-mut is not established practice in UK

Treatment pathway, company positioning and marketing authorisation of elacestrant (Korserdu)

Marketing authorisation: postmenopausal women and men with ER+ HER2- LA / mBC with an activating ESR1 mutation who have disease progression after ≥1 line of ET including a CDK4/6i

Company target population (narrower than MA)
ER+ HER2- ESR1-mut a/mBC with disease progression after **≥12 months** ET + CDK4/6i

- **ESR1-mut**
  everolimus + exemestane (TA421)
- **PIK3CA + ESR1 dual mutation**
  alpelisib + fulvestrant (TA816)

Company positioning of elacestrant

Committee considerations from ACM1

- Data for target population from **post hoc** subgroups of EMERALD
- Company presented data for ESR1-mut **mixed** subgroup (single ESR1-mut & PIK3CA / ESR1 dual-mutated) vs EE only is inappropriate because PIK3CA + ESR1 dual mutated subset would have AF
  - Preferred to see analyses for ESR1-mut only subgroup vs EE

Abbreviations: ABC / LA / mBC / BC, advanced / locally advanced / metastatic breast cancer; ACM, appraisal committee meeting; AF, alpelisib + fulvestrant; CDK4/6i, cyclin-dependent kinase 4 / 6 inhibitor; EE, everolimus + exemestane; ER, oestrogen receptor; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2; MA, marketing authorisation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisals

Elacestrant: clinical evidence

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EMERALD: phase 3 open-label active-controlled multicentre randomised trial

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; up to 1 line of chemotherapy for a/mBC

159 disease progression after **≥12 months** ET + CDK4/6i and **ESR1-mut ± PIK3CA**

62 ESR1-mut **+** PIK3CA dual mutated subset

	EMERALD vs active control (fulvestrant, anastrozole, letrozole or exemestane monotherapy) DC Sept 2022		**ITC (comparator data from Flatiron) – results used in economic model**	
	Hazard ratio (95% confidence interval), p value			
	ESR1-mut mixed Elacestrant (n=78) vs control (n=81)	**Dual mutated Elacestrant (n=27) vs control (n=35)**	**ESR1-mut mixed Elacestrant (n=[redacted]) vs EE (n=[redacted])**	**Dual mutated Elacestrant (n=[redacted]) vs AF (n=[redacted])**
PFS	0.41 (0.26 – 0.634), p<0.01	0.42 (0.18 – 0.94), p NR	0.59 (0.36 – 0.96)	1.05 (0.5 – 2.2)
OS	[redacted]	[redacted]	0.64 (0.35 – 1.16)	0.8 (0.33 – 1.92)

Committee considerations from ACM1

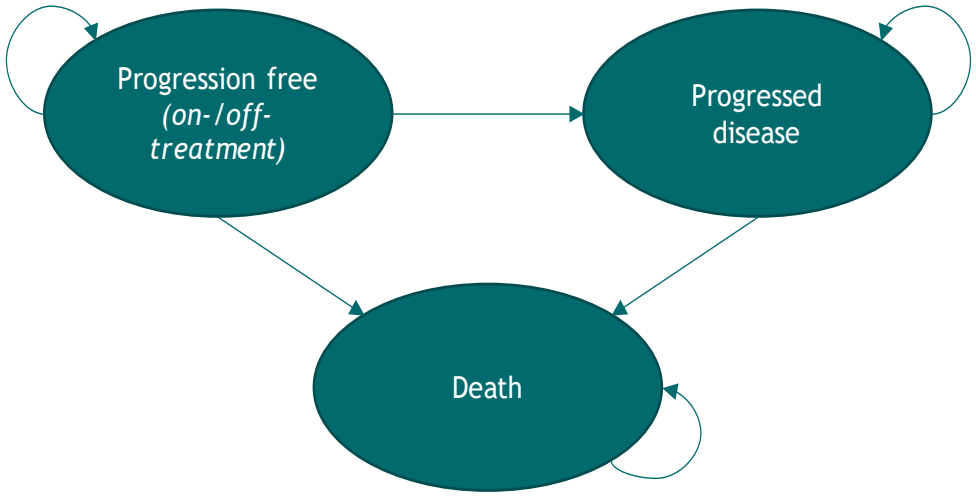
- **EMERALD:** PFS (primary endpoint); active control not likely representative of NHS practice; post hoc subgroups with imbalances in baseline characteristics especially for dual mutated subgroup; uncertain OS (company stated there are no more planned data cuts)
- **ITC:** further uncertainty in results because of methodological limitations of unanchored MAIC; ESR1-mut mixed subgroup compared to only EE; uncertainty in clinical effectiveness → exploratory cost minimisation analysis

Abbreviations: a / LA / mBC, advanced / locally advanced / metastatic breast cancer; ACM, appraisal committee meeting; AF, alpelisib + fulvestrant; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DC, data cut; EE, everolimus + exemestane; ER, oestrogen receptor; ESR1, oestrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal factor receptor 2; ITC, indirect treatment comparison; n, number; NR, not reported; OS, overall survival; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ^effective sample size

Company's model

RECAP

Model structure



- 3-state partitioned survival model: PF (pre-progression; on/off treatment), PD (post-progression), death
- Constraints:
  - % on treatment < PFS
  - % PF < OS
  - Risk of death is not lower than general population
- Lifetime horizon (37 years); 1-week cycle, no half-cycle correction; NHS/PSS perspective, 3.5% discounting
- **ESR1-mut mixed:** [redacted]
- **PIK3CA + ESR1 dual mutated:** [redacted]

Committee considerations from ACM1

- **OS extrapolation:** based on data from unanchored MAICs so high uncertainty
  - **ESR1-mut mixed vs EE only:** committee preferred EAG's gamma with OS capped at ~5 years (OS for EE not higher than elacestrant)
- **Modelling treatment duration for comparators:** inappropriate to assume TTD = PFS → some people may stop EE/AF because of toxicity. Preferred analyses to be based on evidence of TTD
- **ESR1-mut testing:** include cost of ESR1 mutation testing of [redacted] per case for both groups (ESR1-mut only and dual mutated)

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Abbreviations: ACM, appraisal committee meeting; AF, alpelisib + fulvestrant; BSA, body surface area; EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PSS, Personal Social Services; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

Key issue: Composition of subgroups and comparators (1)

Company maintains ESR1-mut mixed vs EE only is appropriate

Background

- Company presented data for 2 subgroups
  - ESR1-mut **mixed** (single ESR1-mut & PIK3CA / ESR1 dual-mutated) vs EE only
  - Dual mutated vs AF only
- BlueTEQ: of 5,500 people starting a CDK4/6i for a/mBC, 500 had EE and 300 had AF for progressed disease
- Committee preferred to see analyses for ESR1-mut only vs EE only
- Committee uncertain if tamoxifen and chemotherapy (oral capecitabine) should be included as comparators

Company response to DG consultation

- No change to subgroup analyses. Maintains ESR1-mut mixed vs EE only is appropriate
  - Similar % with dual mutation in EMERALD (35%) and Flatiron (34%)
    Flatiron representative of EE use in clinical practice
  - Clinical advice to company: EE considered for everyone (no restriction on specific biomarker), EE used in dual mutation if AF is contraindicated (e.g. diabetes) or people prefer oral regimen
- ESR1-mut only analysis does not resolve uncertainties and is inappropriate because it does not reflect UK clinical practice and reduces sample size while not being able to identify which people with a dual mutation would have EE vs AF in clinical practice
- Tamoxifen used in few people but not where elacestrant would be considered
- Chemotherapy reserved for imminent risk of organ failure, exhausted other ET or primary endocrine resistant

Abbreviations: a/mBC, advanced / metastatic breast cancer; AF, alpelisib + fulvestrant; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DG, draft guidance; EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issue: Composition of subgroups and comparators (2)

Clinical experts agree AF is preferred to EE in dual mutated BC

Clinical experts (n=2)

- Both experts agree that in dual mutated, AF preferred to EE. AF and EE have similar toxicity
  - AF not used: contraindications (diabetes ~10-20%), prior use of fulvestrant or if PIK3CA mutation results are not available at time of relapse on CDK4/6i
- One clinical expert noted a lack of enthusiasm for alpelisib because of toxicity and lack of impressive response rates in the real world (same applies to EE) → some people prefer cytotoxic chemotherapy (capecitabine)

Patient and professional groups

- Some people with PIK3CA mutations do not have AF because it is unsuitable or concerns about toxicity

EAG comments

- Company seems to have misinterpreted DG
- Company's model does not allow ESR1-mut mixed to be compared to EE and AF at the same time, only EE

- What is used to treat dual mutated BC in the NHS? Alpelisib + fulvestrant or everolimus + exemestane?
- Is it appropriate to compare ESR1-mut mixed with EE only?
- Should separate analyses be conducted for ESR1-mut only vs EE only?
- Are tamoxifen and chemotherapy relevant comparators?

Abbreviations: AF, alpelisib + fulvestrant; AI, aromatase inhibitor; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DG, draft guidance; EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; ET, endocrine therapy; n, number; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issue: OS extrapolation for ESR1-mut mixed subgroup

Company updated base case with committee's preferred modelling approach from ACM1

Background

- OS extrapolation for elacestrant for ESR1-mut mixed: company preferred log-logistic vs EAG preferred gamma
- Committee preferred EAG's gamma with OS capped at ~5 years (OS for EE not higher than elacestrant)
  - Preferred to have seen analyses with ESR1-mut only subgroup

Company response to DG consultation

- Updated base case: Gamma OS, underlying hazard of death capped by underlying hazard of EE gamma OS
- Scenario analyses: 1) Average S(t): average of log-logistic and gamma OS at each time point. 2) Average h(t): average of underlying hazard functions of log-logistic and gamma OS at each time point
- Clinical feedback: all 3 scenarios reasonable, average h(t) preferred based on 10-year landmark analysis

Model		Landmark survival estimates at Year:				
		1	2	3	5	10
Elacestrant	Log-logistic	83.5%	54.6%	34.5%	15.7%	4.3%
	Average S(t)	83.1%	54.5%	33.4%	12.7%	2.3%
	Average h(t)	83.1%	54.5%	33.4%	12.4%	1.2%
	Gamma + capped h(t)	**82.8%**	**54.4%**	**33.3%**	**12.3%**	**1.0%**
	Gamma	82.8%	54.4%	32.4%	9.8%	0.3%
Everolimus + exemestane Gamma		64.8%	39.8%	24.4%	9.0%	0.7%

EAG comments: company updated base case and scenarios correctly implemented

- Which modelling approach of OS extrapolation for elacestrant for ESR1-mut mixed subgroup is preferred? Company updated gamma + capped h(t) vs average S(t) vs average h(t)?

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; OS, overall survival

Key issue: Modelling treatment duration for comparators

Uncertainty about time on treatment for comparators

Background

- Company assumed for comparators TTD = PFS
- Committee considered inappropriate to assume TTD = PFS → some people may stop EE/AF because of toxicity. Preferred analyses to be based on evidence of TTD for comparators

Company response to DG consultation

- Updated base case using EAG's exploratory scenarios from ACM1: adjusting comparators' TTD curves using an assumed HR (0.8 for ESR1-mut mixed and 0.5 for dual mutated) relative to comparators' PFS
  - No data sources to support TTD to PFS HRs, but estimates are similar to that used in TA816 (AF)

EAG comments

- Company's approach is reasonable given lack of better information but TA816 supporting evidence is weak
- Provide scenario analysis to investigate sensitivity to changes in the HRs for TTD vs PFS

- How should TTD be modelled for Flatiron comparators? Use company's updated base case using assumed HRs to adjust TTD curves relative to comparator PFS?
  - **ESR1-mut mixed:** HR 0.8 (base case) vs scenarios 0.7 and 0.9?
  - **Dual mutated:** HR 0.5 (base case) vs scenarios 0.4 and 0.6?

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Abbreviations: ACM, appraisal committee meeting; AF, alpelisib + fulvestrant; DG, draft guidance; EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; HR, hazard ratio; PFS, progression-free survival; TTD, time to treatment discontinuation

Key issue: ESR1 mutation testing

Background

- Company 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
- Committee concluded cost of ESR1-mutation testing of [redacted] for each case identified (as advised by NHS GMS) should be included for both subgroups

Company response to DG consultation

- Updated base case: excluded cost of ESR1-mut testing
  - Cost of introducing NGS panel for all mutations should be excluded from model for elacestrant
    - 3 future treatments that would need mutation testing: capivasertib + fulvestrant (ID6370; PIK3CA/AKT1/PTEN-altered), camizestrant (ESR1-mut), inavolisib (PIK3CA)
  - Cost of [redacted] is higher than cost of introducing ESR1-mut testing alone at £300 for droplet PCR test

EAG comments: included cost of ESR1-mut testing as advised by NHS GMS in its base cases

Other considerations

- **NICE final scope:** economic modelling should include costs related to diagnostic testing for ESR1 and where relevant, PIK3CA mutations in people with ER+ HER2- LA / mBC who would not otherwise have been tested. Sensitivity analysis without cost of diagnostic test (NICE HTE manual, section 4.8)
- **TA816 / TA652:** cost of PIK3CA mutation testing included in base case

- Should the cost of the ESR1-mut test be included in the model?
- If yes, what cost should be used? PCR droplet test at £300 per test or NGS panel at [redacted] per test?
- Would everyone who progresses on CDK4/6i + ET be tested? Would there be repeat testing?

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DG, draft guidance; ESR1-mut, oestrogen receptor 1 mutation; GMS, Genomic Medicine Service; LA/m BC, locally advanced / metastatic breast cancer; PCR, polymerase chain reaction; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisal

QALY weightings for severity

Company response to DG consultation

- Company updated base case using the EAG's base case values from the MAIC-adjusted baseline age:
  - **Mean age in years. Company and EAG:** ESR1-mut mixed [redacted]; Dual mutated [redacted]
- **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 mixed	**Company updated and EAG base case**	[redacted]	[redacted]	[redacted]	[redacted]	1.2
Dual mutated	**Company updated and EAG base case**	[redacted]	[redacted]	[redacted]	[redacted]	1.0

EAG comments: company does not address committee's preferred analysis of ESR1-mut only subgroup

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

Abbreviations: DG, draft guidance; ESR1-mut, oestrogen receptor 1 mutation; MAIC; matching-adjusted indirect comparison; QALY, quality adjusted life year

Other considerations

Company response to DG consultation

- Target population narrower than marketing authorisation: ER+ HER2- ESR1-mut a/mBC with disease progression after **≥12 months** ET + CDK4/6i
  - Accepts 12-month threshold will be implemented by NHSE if recommended
  - Maintains clinically relevant and appropriate given 3 monthly scans for progression
- Cost minimisation analysis is not appropriate
  - Clinical community consider elacestrant to not be equally effective to EE

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

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

Abbreviations: a/mBC, advanced / metastatic breast cancer; 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

Summary of company updated and EAG base case assumptions

Difference in company updated and EAG base case: ESR1-mut testing included by EAG and excluded by company

Company maintains ESR1-mut mixed subgroup vs EE only is appropriate

ESR1-mut mixed subgroup

Assumption	Company updated and EAG base case
Population age	[redacted] years (Source: Flatiron)
OS extrapolation: elacestrant	Gamma + capped h(t)
TTD for everolimus + exemestane	TTD vs PFS HR, set to 0.8
Everolimus acquisition cost	eMIT 2023

Dual mutated: PIK3CA + ESR1-mut subgroup

Assumption	Company updated and EAG base case
Population age	[redacted] years (Source: Flatiron)
TTD for alpelisib + fulvestrant	TTD vs PFS HR, set to 0.5

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Abbreviations: EE, everolimus + exemestane; ESR1-mut, oestrogen receptor 1 mutation; HR, hazard ratio; OS, overall survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment duration

Cost-effectiveness results

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

ESR1-mut mixed subgroup

- Company updated base case with 1.2 QALY weight < £30,000 per QALY gained
- EAG base case with 1.2 QALY weight > £30,000 per QALY gained

Dual mutated subgroup

- Company updated base case < £30,000 per QALY gained
- EAG base case < £30,000 per QALY gained

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Abbreviations: ESR1-mut, oestrogen receptor 1 mutation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year

Key issues	ICER impact
1. Composition of subgroups and comparators (slide 6-7) • What is used to treat dual mutated BC in the NHS? Alpelisib + fulvestrant or everolimus + exemestane? • Is it appropriate to compare ESR1-mut mixed with EE only? • Should separate analyses be conducted for ESR1-mut only vs EE only? • Are tamoxifen and chemotherapy relevant comparators?	Unknown
2. OS extrapolation for elacestrant for ESR1-mut mixed group (slide 8) • Which modelling approach of OS extrapolation for elacestrant for ESR1-mut mixed subgroup is preferred? Company updated gamma + capped h(t) vs average S(t) vs Average h(t)?	Moderate

3. Modelling treatment duration for comparators (slide 9)
• How should TTD be modelled for Flatiron comparators? Use company's updated base case using assumed HRs to adjust TTD curves relative to comparator PFS?
  • **ESR1-mut mixed:** HR 0.8 (base case) vs scenarios 0.7 and 0.9?
  • **Dual mutated:** HR 0.5 (base case) vs scenarios 0.4 and 0.6?
	Small

4. ESR1-mutation testing (slide 10) • Should the cost of the ESR1-mut test be included in the model? • If yes, what cost should be used? PCR droplet test at £300 per test or NGS panel at [redacted] per test? • Would everyone who progresses on CDK4/6i + ET be tested? Would there be repeat testing?	Moderate
5. Other: severity modifier (slide 11); equality, uncaptured benefits (slide 12)	Unknown

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Abbreviations: EE, everolimus + exemestane; 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

End of Part 1

NICE National Institute for Health and Care Excellence

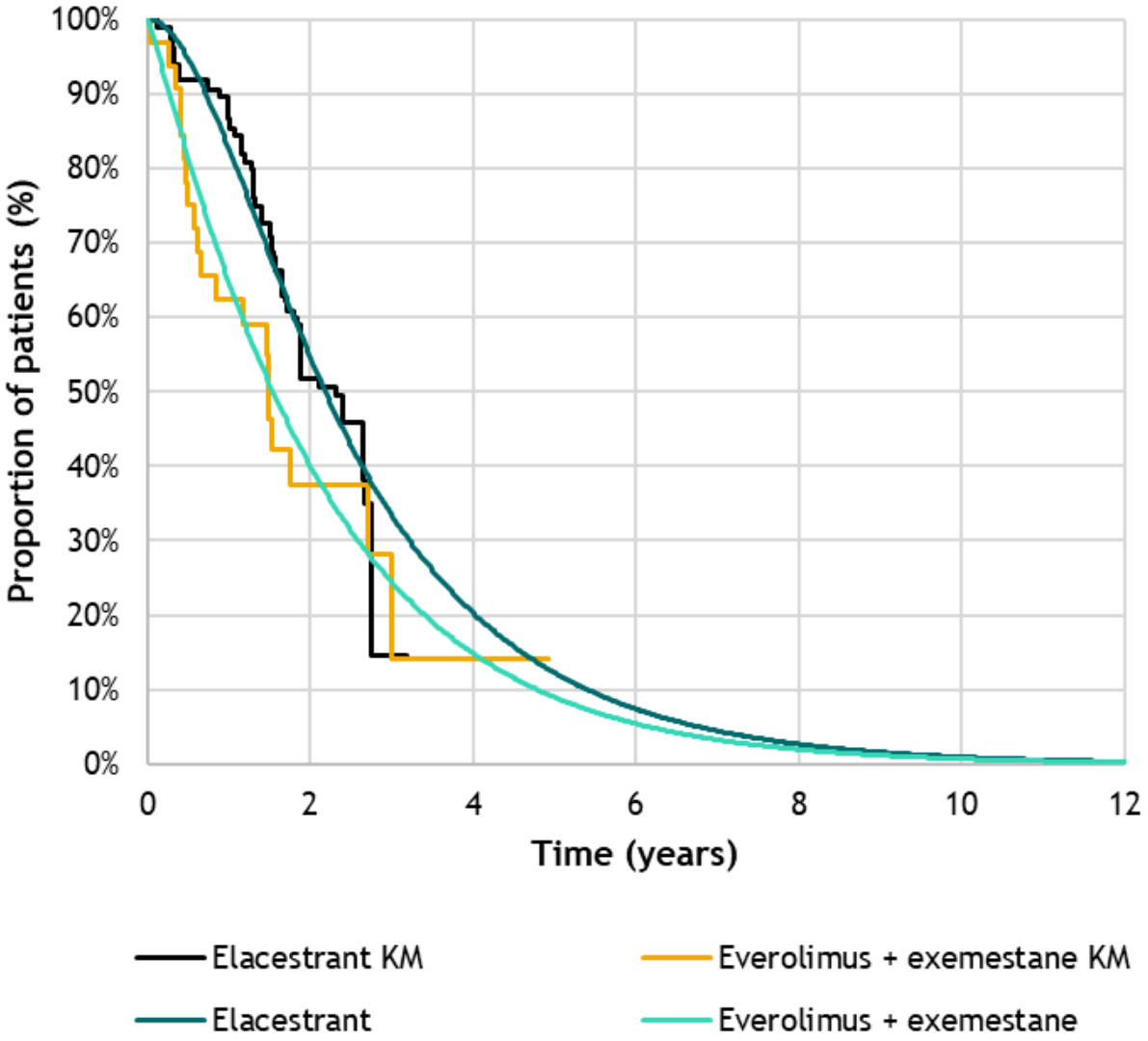
Back-up slides

NICE National Institute for Health and Care Excellence

Key issue: OS extrapolation for ESR1-mut mixed subgroup

Company updated base case with committee's preferred modelling approach from ACM1

Gamma + capped h(t) company updated base case

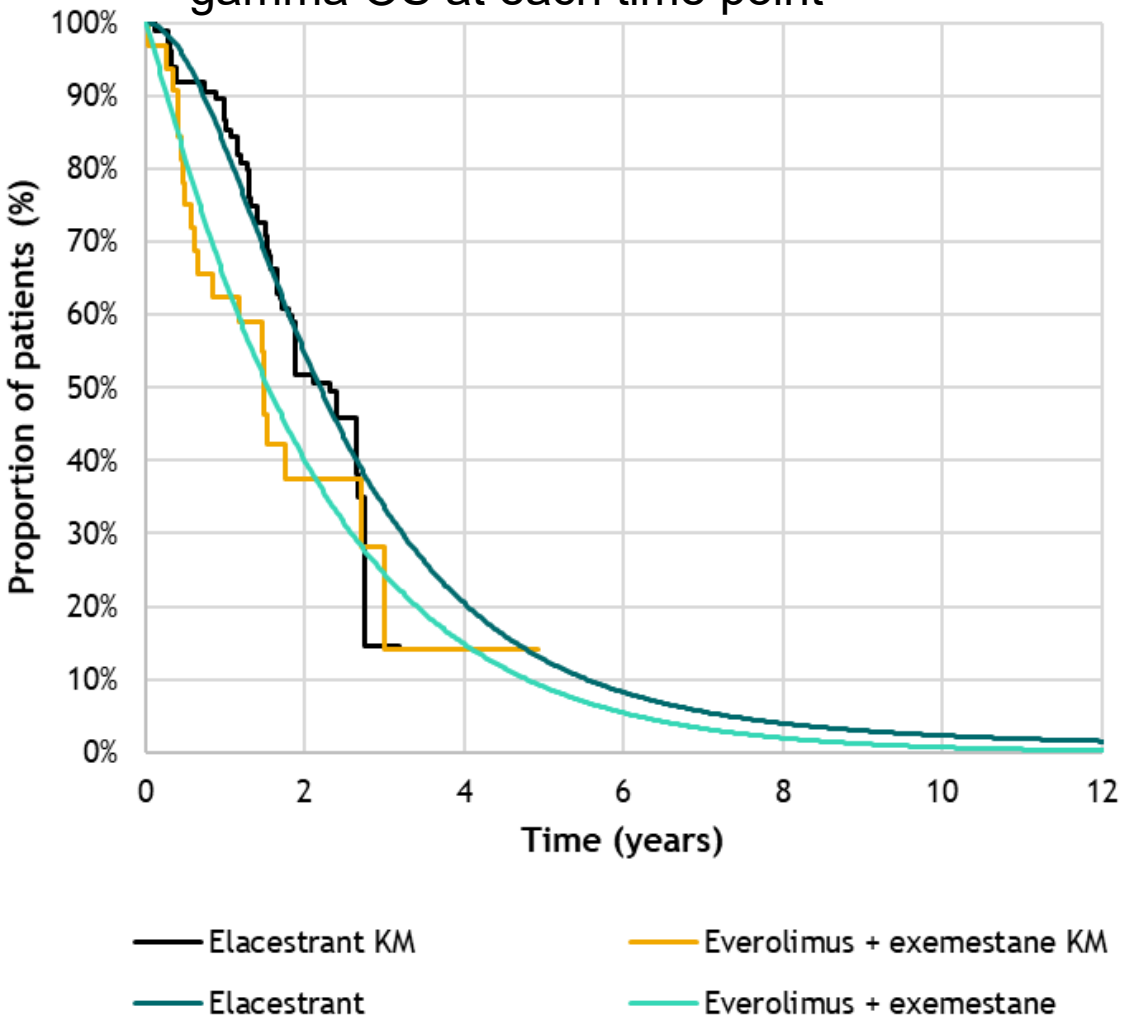


*OS extrapolation for ESR1-mut mixed

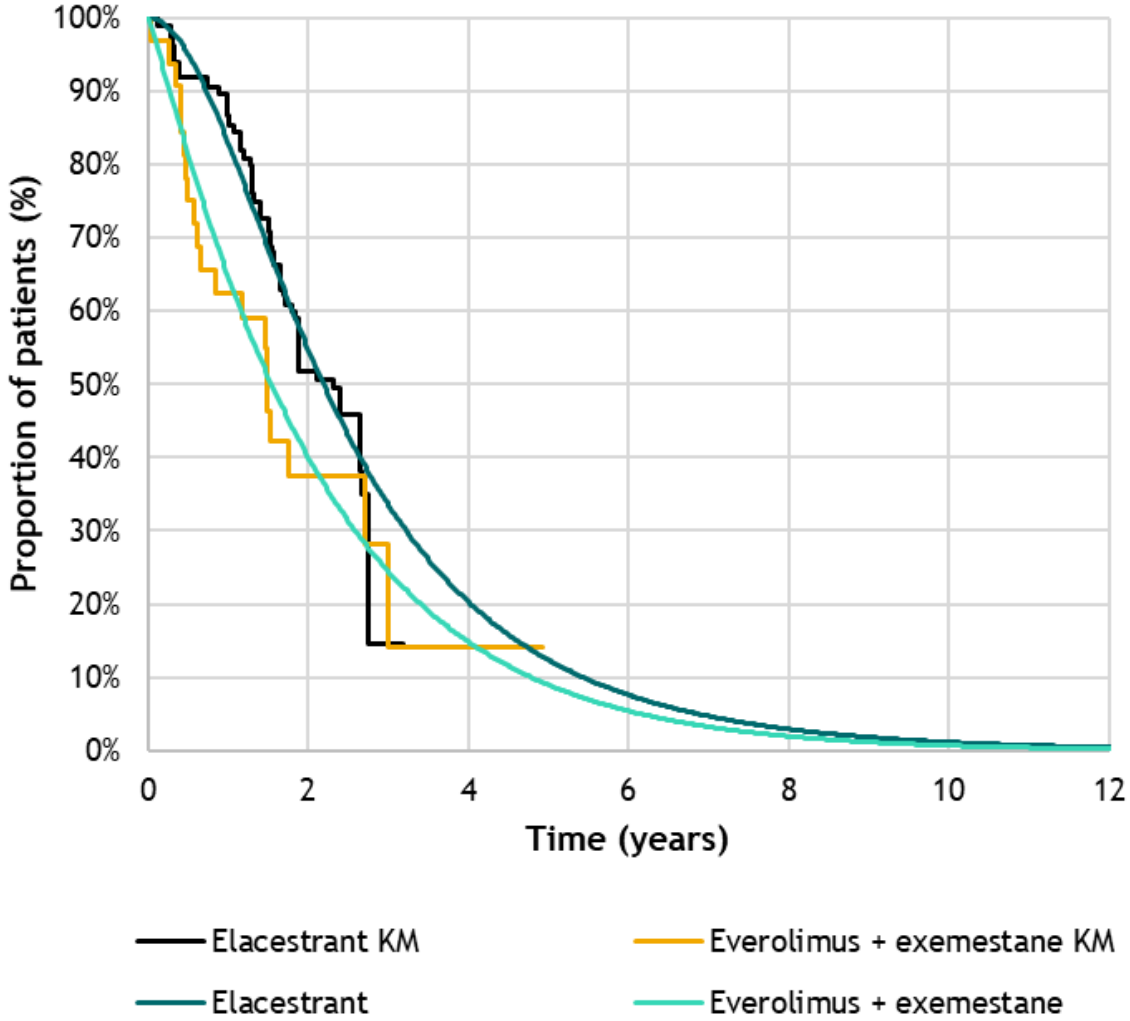
Abbreviations: ACM, appraisal committee meeting; ESR1-mut, oestrogen receptor 1 mutation; KM, Kaplan–Meier; OS, overall survival

Key issue: OS extrapolation for ESR1-mut mixed subgroup scenarios

Average S(t): average of log-logistic and gamma OS at each time point



Average h(t): average of underlying hazard functions of log-logistic and gamma OS at each time point



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

*OS extrapolation for ESR1-mut mixed