NICE National Institute for Health and Care Excellence

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Abemaciclib for adjuvant treatment of hormone receptor positive, HER2-negative, node-positive early breast cancer [ID3857]

Lead team presentation (Part 1)

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Company: Eli Lilly

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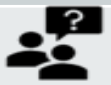
Key Clinical issues

Issue	Impact
1. Eligible population at high risk of recurrence: ***a)*** *are people who are eligible to receive abemaciclib known to have any residual disease at baseline?* ***b)****Is the aim of treatment with abemaciclib to prevent recurrence of disease?* ***c)****When is a recurrence of disease likely to occur*?	
2. **Generalisability of monarchE results to clinical practice**: *are patients at high risk of recurrence identified in monarchE cohort 1 easily identifiable and those that would be selected as high risk of recurrence in NHS clinical practice?*	
2. **Lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness**: *is a difference in treatment effect for outcomes expected for premenopausal and postmenopausal women ?*	
3. **Lack of generalisability of monarchE to clinical practice in terms of endocrine therapy type:** *are premenopausal women likely to receive tamoxifen instead of an aromatase inhibitor in clinical practice? Is this likely to have an impact on treatment effect and cost-effectiveness estimates?*	

Key

Model driver	
Unknown impact	

Abemaciclib (Verzenios, Eli Lilly)

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor. Blocks cell cycle progression leading to suppression of tumour growth

Anticipated marketing authorisation	• Abemaciclib in combination with endocrine therapy is expected to be indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence • In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist
Administration	• **Abemaciclib**: 1 x 150 mg oral tablet twice daily, continuous • **Endocrine therapy (ET)**: according to smPC for 5-10 years Abemaciclib should be taken until recurrence, for a maximum of 2 years, or until unacceptable toxicity occurs

⊙ *Why should abemaciclib be taken for a maximum of 2 years?*
⊙ *What is the clinical reasoning behind 2 years?*
⊙ *Does 2 years make clinical sense from a NHS clinical perspective?*

Early hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) breast cancer

- **Breast cancer** is the most common cancer in the UK.
  - Approximately 46,700 women in England and Wales diagnosed each year
- **Early** - cancer restricted to the breast, or breast and nearby lymph nodes, has not spread to other parts of the body
- **Hormone receptor-positive** (HR+) breast cancer cells co-express oestrogen or/and progesterone. HER2 is a receptor for a growth factor. Breast cancer cells with lower levels of HER2 receptors are HER2-negative (HER2−)
- **HR+/HER2** − most common subtype ~70% of all breast cancers
- 30% of patients with early breast cancer (EBC) relapse following primary treatment leading to incurable advanced or metastatic disease
- **No effective targeted therapies** available for patients with HER2− early breast cancer
  - Standard of care: cytotoxic chemotherapy, radiotherapy, and/or ET

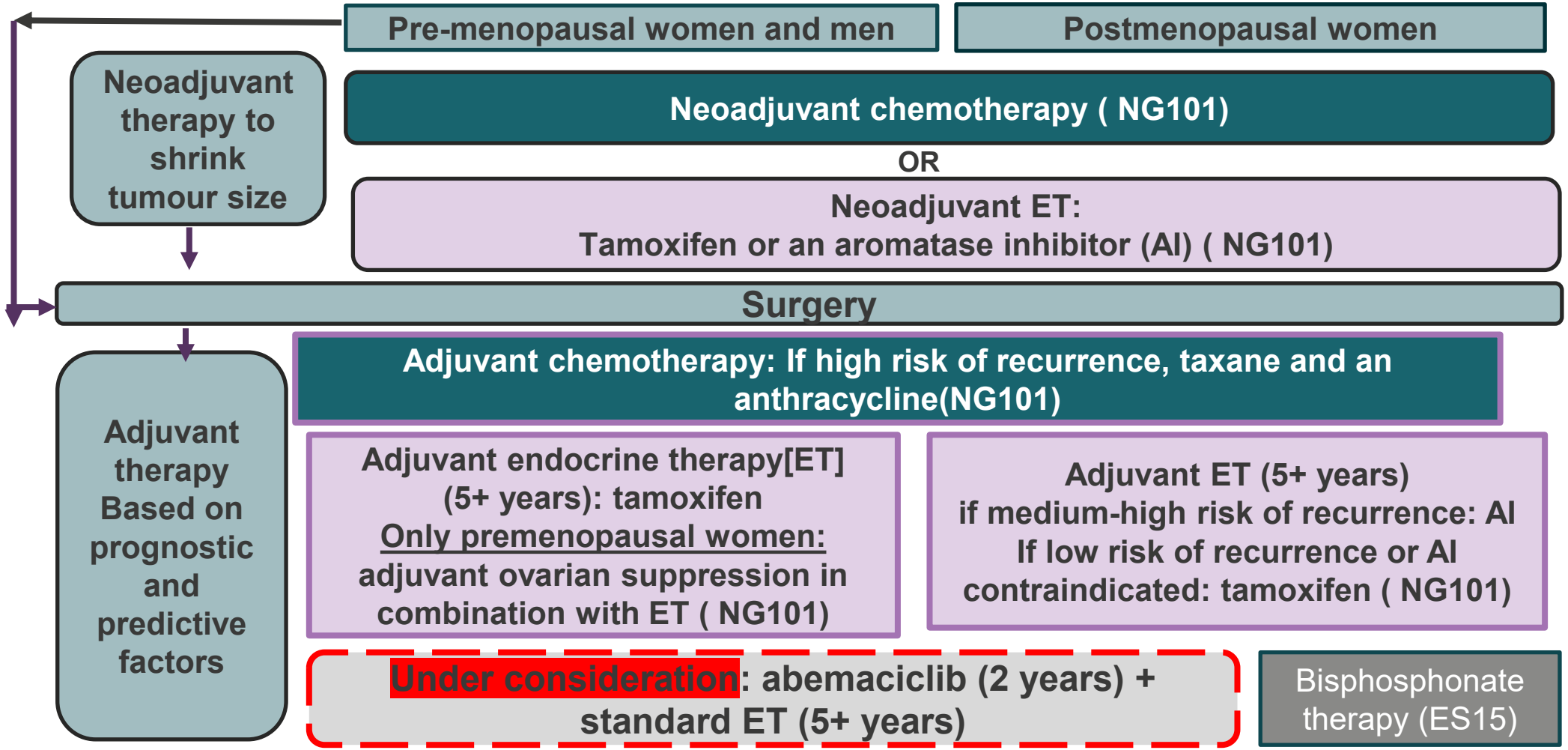
Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with hormone receptor-positive, HER2-negative, node-positive EBC after definitive surgery of the primary breast tumour, who are at high risk of recurrence	Same
Intervention	Abemaciclib in combination with standard ET	Abemaciclib in combination with standard ET
Comparators	Standard ET	Standard ET
Outcomes	• **Primary outcome**: invasive disease-free survival (IDFS) • overall survival (OS) • recurrence-free survival • response rate • adverse events • health-related quality of life (HRQoL)	As per scope with the addition of: • distant relapse free survival (DRFS)

Eligible population likely to receive abemaciclib in clinical practice:

- *Are people who are eligible to receive abemaciclib known to have any residual disease at baseline?*
- *Is the aim of treatment with abemaciclib to prevent recurrence of disease?*
- *When is a recurrence of disease likely to occur?*

Treatment Pathway: HR+ HER2- early breast cancer at high risk of recurrence



- *What adjuvant treatments are used in clinical practice for the population under consideration?*
  - *adjuvant chemotherapy appears to be an alternative to adjuvant ET*
- *Is adjuvant ET alone the appropriate comparator for people at high risk of recurrence?*
- *Are patients likely to receive other treatments alongside adjuvant ET in clinical practice?*

Patient and carer perspectives (Breast Cancer Now)

- Initial diagnosis is shocking, and the fear of breast cancer returning or spreading to other parts of the body (typically the bone, lungs, liver and brain) where it becomes incurable causes considerable stress and fear for both patients and their loved ones
- Hormone therapy can have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy
- Several potential side effects, which can have a negative impact on patient's quality of life. Treatment is generally well tolerated and managed, with medication and treatment breaks where necessary. For many the potential benefits of the treatment will outweigh the risk of side effects

"My diagnosis came 2 months after losing my husband to lung cancer and with 2 teenage sons, it was devastating news. I am so pleased that already abemaciclib looks favourable, but the anxiety is only lessened slightly. I am currently waiting for counselling due to high recurrence anxiety"

"Whilst on the treatment, I fortunately didn't suffer any major side effects. These were a slight worsening of problems caused by aromatase inhibitor (AI) drugs. I had an episode of stomach upset which they gave me a 2 week break for. Other than that, I struggled with fatigue, but we think that may have been more induced by the AI. After trying all 3 AIs I have settled on anastrazole and realised that fatigue and joint aches are part of life now. I would take abemaciclib in a heartbeat again if offered it. I do know that not everyone is as lucky as I was in term of side effects

Clinical expert perspective

- **Main aim of treatment -** prevent recurrent/advanced cancer developing after surgery
- Risk of recurrence is higher with some clinical and/or pathological risk factors
  - e.g. a large number of positive lymph nodes, large tumour size, or a high cellular proliferation as measured by tumour grade or biomarkers.
  - **significant unmet need** in this population and new treatment options to help prevent early breast cancer from returning is of great value
- **Small number of patients will fulfil criteria for adjuvant abemaciclib** due to strict criteria for patient selection in monarchE
  - Eligible population: 4 or more positive nodes, or 1-3 positive nodes with either grade 3 disease, a tumour of at least 5 cm, or high Ki-67 status. (Higher levels of Ki-67 protein are indicative of a fast-growing, aggressive tumour)
  - Ki-67 unlikely to be used widely as limited number of oncology centres have access (lack of consensus for assessing Ki-67)
- **Abemaciclib more demanding than ET**
  - monthly appointments with oncology, blood tests & chemo-unit appointments
- Delays due to toxicities and subsequent burden on appointments with GP and oncologists:
  - Risk of sepsis is less than 2% with CDK4/6 and 0% with ET. Small risk of transaminitis and clots. Haematological disorders less common with abemacicilib than other CDK4/6.

Primary clinical evidence: monarchE

Design	Phase III, active-controlled, randomised, open-label, double-blind trial
Location	International: 611 centres, 38 countries, including the UK
Population	HR+, HER2−, node-positive EBC at high risk of recurrence (**n=5,637**) ITT population consists of 2 cohorts(**199 UK patients**): **Cohort 1:** Tumour involvement in ≥4 ipsilateral ALNs, or pathological tumour involvement in 1–3 ALNs as well as either: Grade 3 disease (at least 8 points on Bloom Richardson grading system) Primary tumour size ≥5 cm (**n=5,120**) - **Subject of this appraisal** **Cohort 2:** patients at high risk of recurrence based on pathological tumour involvements in 1–3 ALNs and a high (≥20%) Ki-67 index (**n=517**)
Intervention	Abemaciclib for up to 2 years + ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5-10 years
Comparator	ET (tamoxifen, toremifene, letrozole anastrozole or exemestane; with or without ovarian suppression) for 5 to 10 years
Outcomes	**Primary:** invasive disease-free survival (IDFS) defined by STEEP system **Secondary:** Distant relapse–free survival, overall survival (OS), patient-reported outcomes and safety outcomes

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Abbreviations: ALN; axial lymph nodes, EBC; early breast cancer, ITT; intention to treat

Baseline characteristics (cohort 1)

Characteristic	Abemaciclib + ET (N=******)	ET alone (N=******)
Female, n (%)	*******	*******
Male, n (%)	*******	*******
Age, years		
Mean (SD)	*******	*******
Menopausal status, n		
Premenopausal	*******	*******
Postmenopausal	*******	*******
Oestrogen receptor status		
Positive	*******	*******
Negative	*******	*******
HER2 status at initial diagnosis		
Negative	*******	*******
Prior adjuvant therapy		
Chemotherapy	*******	*******
ET	*******	*******

⊙ *The majority seem to have had abemaciclib after other adjuvant therapy, would this be the case in clinical practice?*

Issue 1: Generalisability of monarchE results to clinical practice

Background

- No clear definition of high risk of recurrence in NG101; cohort 1 from monarchE may be more relevant to NHS

Company

- Positive CHMP opinion received for EBC indication based on Cohort 1 from monarchE
- Comparison of monarchE Cohort 1 baseline characteristics with a UK real world evidence (RWE) study supports assumption that patients in this cohort are generalisable to UK clinical practice
- Base case analysis updated after technical engagement to use monarchE cohort 1 data (instead of ITT)

⊙ *Is this group of patients identifiable and relevant to NHS practice?*

monarchE results: Invasive disease-free survival

Primary outcome, cohort 1

Data cut : 01 April 2021

monarchE results: Overall survival

secondary outcome, cohort 1

Data cut : 01 April 2021

monarchE results: Adverse events

Safety population

Data cut : 01 April 2021

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 TEAE	2,745 (98.4)	2,486 (88.8)
Patients with ≥1 CTCAE ≥ Grade 3 TEAE	[redacted]	[redacted]
Patients with ≥1 CTCAE ≥ Grade 3 TEAE related to study treatment	[redacted]	[redacted]
Patients who discontinued all study treatment due to an AE	181 (6.5)	30 (1.1)
Patients who died due to an AE on study treatment	[redacted]	[redacted]

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; N = number of patients in the safety population; n = number of patients in the specific category; SAE = serious adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Issue 2: Comparators depend on menopausal status leading to bias in effectiveness

Background

- ET type depends on menopausal status; bias may be introduced due to differences in comparators for pre and postmenopausal patients
  - outcomes for invasive disease-free survival and disease relapse free survival are better for premenopausal women.

Company

- Subgroup analyses - no statistically significant differences for ***menopausal status at diagnosis*** for invasive disease-free survival (IDFS) and distant relapse free survival (DRFS)(Cohort 1 of monarchE)
  - Highly uncertain due to lower patient numbers
- ***Menopausal status at diagnosis*** may not reflect 'functional' menopausal status at the time of treatment (ovarian function suppression may be considered for premenopausal women with HR+ EBC)
- Clinical expert opinion: premenopausal women treated with ovarian suppression (i.e 'functionally postmenopausal') - treated the same as postmenopausal women with similar treatment benefits observed.
  - At least [redacted] of overall premenopausal subgroup in monarchE should be considered functionally postmenopausal at the time of treatment.
  - No difference in outcomes → only difference would be costs.
  - Relatively low costs of ET therapy → limited impact cost effectiveness
- Previous NICE appraisals for HR+, HER2- breast cancer not considered by menopausal status.

Subgroup analysis: Invasive disease-free survival rate

by menopausal status, cohort 1

Pre-menopausal

Months	Treatment Effect/Difference 2-sided p-Value
12	[redacted]
24	[redacted]
36	[redacted]

Post-menopausal

Months	Treatment Effect/Difference 2-sided p-Value
12	[redacted]
24	[redacted]
36	[redacted]

ERG

- Disagrees with the company conclusion that *there is no difference because no statistically significant difference*
- Does not matter that there is CI overlap between subgroups;
  - appropriate form of cost-effectiveness analysis is one where a set of estimates for only 1 subgroup is used as source of effectiveness and any difference (however uncertain) has potential to lead to a difference in whether abemaciclib is judged cost-effective versus the comparator appropriate to the subgroup.

⊙ *Is a difference in treatment effect for outcomes expected for premenopausal and postmenopausal women ?*

Issue 3: Generalisability of monarchE results to clinical practice for ET type

Background

- ET in monarchE given according to physician choice - might not be aligned with clinical practice
- Many premenopausal women received an aromatase inhibitor (AI) instead of tamoxifen contrary to NICE Guideline (NG101)

Company

- AI instead of tamoxifen is not contrary to NG101: may be contraindicated for tamoxifen and many premenopausal women become functionally postmenopausal
- UK based RWE - 1st adjuvant ET: [redacted] received an AI vs. [redacted] tamoxifen.
  - Cohort 1: 68% AI vs. 31% tamoxifen
- Costs of different ET similar & should be no differences in efficacy within same class of ET
  - discrepancies in types of ET used in monarchE and NHS is likely to have minimal impact on cost-effectiveness analyses
- IDFS and DRFS by menopausal status and first ET received (tamoxifen or AI) no statistically significant differences in terms of IDFS and DRFS between the subgroups.

ERG

- **Premenopausal at diagnosis**: % receiving an AI in would be >0 if subsequently become postmenopausal because of ovarian suppression by receiving GnRH agonists. However, % receiving GnRH agonists in premenopausal group ~ [redacted] and receiving AI is 41%
- IDFS and DRFS higher for abemaciclib with tamoxifen than with an AI, although there is overlap in the 95% CIs for the HRs

⊙ *Are any differences in ET used in the trial vs.in clinical practice? Is this likely to have an impact on treatment effect and cost-effectiveness estimates?*

Cost effectiveness

Key cost effectiveness issues

Issue	Impact
7. **Selection of IDFS survival curves for treatment and comparators**: *does the committee accept the uncertainty in the log-logistic IDFS extrapolation?*	
9. **Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning assumtions:** *is the assumed carry over benefit and treatment waning trajectory used by the company in its base case analysis sufficiently justified?*	
6. **Medication adherence not modelled**: *will non-adherence to adjuvant ET similarly impact both intervention and comparator arms?Is the pattern of non-adherence observed in monarchE representative of clinical practice?*	

Key

Model driver	
Unknown impact	

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Where do the QALY gains come from in the model?

The technology is modelled to affect QALYs by:

- An increase in invasive-free disease survival (IDFS) time
- A decrease in ET resistant and ET sensitive metastatic recurrences.

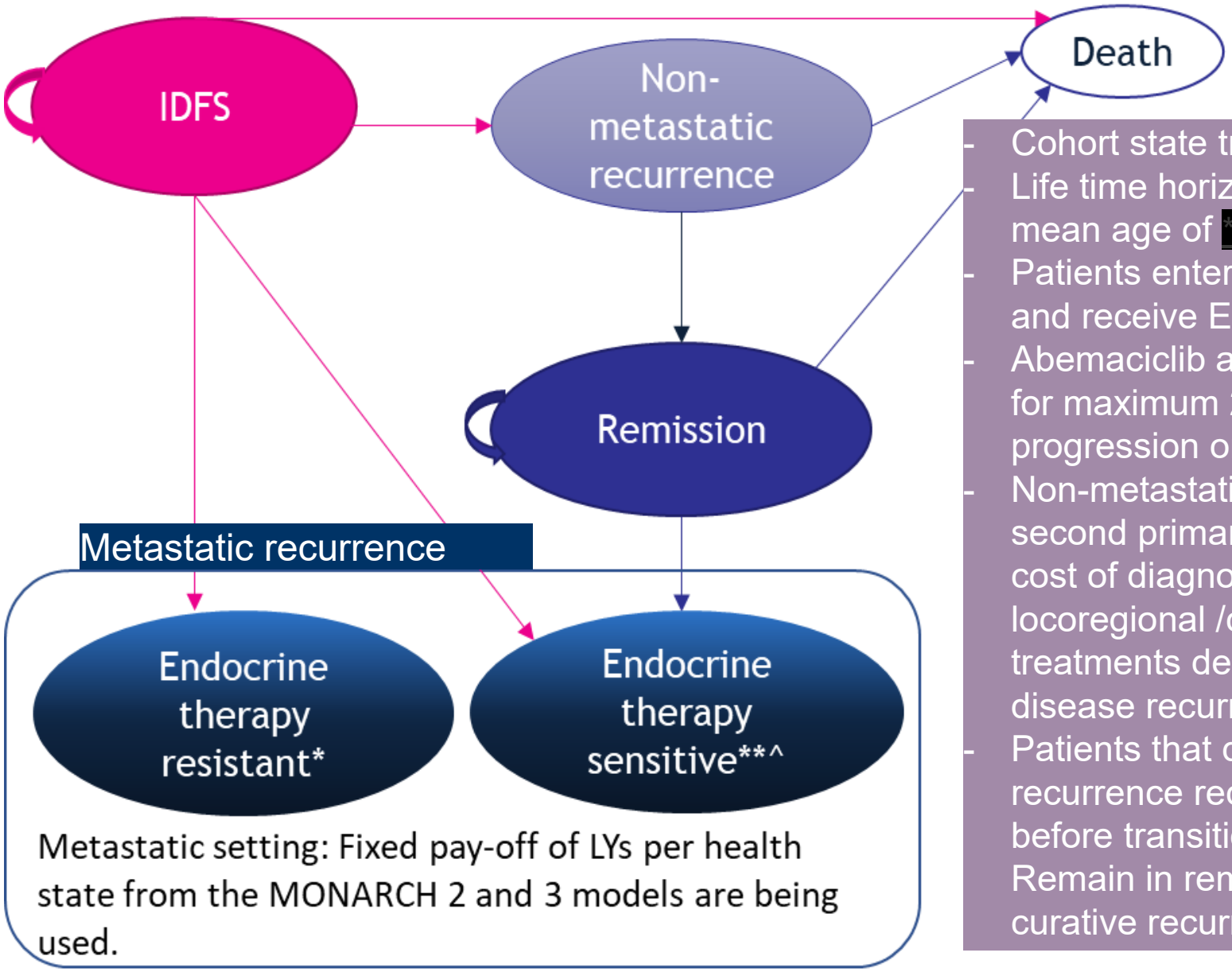
The technology is modelled to affect costs by:

- An increase in drug acquisition and treatment specific costs
- An increase in costs related to AEs
- A reduction in ET resistant and ET sensitive metastatic recurrences
- Eliminating the need of CDK inhibitors at the metastatic recurrence stage

Within the model the main assumptions that have a greater effect on the ICER are:

- The model used to extrapolate the IDFS curve beyond the treatment period
- Proportion of patients having a metastatic recurrence relative to a non-metastatic recurrence in each intervention arm
- Treatment costs in the metastatic recurrence state
- Treatment duration beyond 2 years and treatment waning.

Model structure



- Cohort state transition model with 5 states
- Life time horizon (49 years) from starting mean age of [redacted] years
- Patients enter IDFS progression-free state and receive ET for 5 years
- Abemaciclib arm receive additional treatment for maximum 2 years or until disease progression or toxicity
- Non-metastatic recurrence state split into 2 : second primary neoplasm (patients allocated cost of diagnosis then exit model) and locoregional /contralateral (tunnel state; treatments determined by type/location of disease recurrence
- Patients that don't die from non-metastatic recurrence receive 12 months treatment before transitioning to remission state. Remain in remission until another non curative recurrence occurs

*ET therapy resistant: Disease progression whilst receiving or within 12 months of completing prior adjuvant ET.
**ET therapy sensitive: Disease recurrence at least 12 months after completion of prior adjuvant ET.
^Includes treatment with tamoxifen.
Abbreviations: IDFS: invasive disease-free survival; LY: life year

Long-term IDFS extrapolations for abemaciclib + ET and ET alone in company base-case using log-logistic curve to extrapolate trial data with treatment effect lasting 8 years after which treatment effect begins to wane until year 27

- *Is the extrapolation of data for ET using the log-logistic curve clinically plausible?*
- *Given the relatively long extrapolation from the end of the trial KM data, how uncertain is the extrapolation?*
- *How plausible is the IDFS for the ET arm in this high risk population?*

Issue 7: invasive disease-free survival curve selection

Background

- Limited trial data available; considerable uncertainty in the long-term effectiveness of abemaciclib + ET compared with ET
- Company and ERG both use log-logistic curve in their base-cases to extrapolate IDFS trial data as best fit survival curve statistically but is the extrapolated curve clinically plausible?
  - Log-normal extrapolation for IDFS explored in a scenario analysis

Company

- Log-logistic curve - best statistical fit for extrapolation of IDFS
  - statistical fit alone not sufficient when considering immature data
- Extrapolations from monarchE underestimate 5-year IDFS rates for ET compared to literature
- External trials not directly comparable with monarchE as different definition of IDFS used and populations included with lower risks of recurrences
- Lognormal curve - worst statistical fit to first 3 years of KM data from monarchE than log-logistic curve

ERG

- Comparing patient characteristics between monarchE and [redacted] showed that despite lower degree of severity in monarchE, the log-logistic predicted a lower IDFS rates at 5 and 10 yrs
- Lognormal provides IDFS rate predictions closer to [redacted] only extrapolation that gives an overprediction
- Extrapolation of long-term IDFS is still a substantial source of uncertainty
- Scenario analysis shows that using an alternative extrapolation (log-normal) increases the ICER

⊙ *Does the committee accept the uncertainty in the log-logistic IDFS extrapolation used in both the company and ERG base-case?*

Issue 9: lack of evidence for assumed 'carryover benefit' and treatment waning assumptions in base-case analyses

	Treatment effect	Waning effect	Rationale
Company	Full treatment effect up to 8 years	19 years	Technology appraisal guidance [TA612]
ERG	Constant treatment effect duration 3 years	5 years **Note:** no treatment effect beyond year 8	3 years based on follow up of monarchE

Company

- monarchE demonstrates a treatment effect of abemaciclib + ET beyond discontinuation
  - Piecewise analysis for IDFS → treatment benefit of abemaciclib, in terms of the reduced risk of an IDFS event (ITT population)
    - continued to increase over time in follow-up period
  - HRs for Year 2+ (majority will have discontinued abemaciclib) suggests a lasting treatment effect beyond discontinuation
- Tamoxifen and AI arm of ATAC* trial:
  - Used as a proxy to inform plausible duration of treatment effect for abemaciclib
  - showed lasting treatment benefit up to 8 years for 1 ET over the other
- Colleoni et al. (2016) reporting annual hazard rates of recurrence for breast cancer with 24 year follow up supports long-term waning of treatment effect:
  - Risk of recurrence decreases over time - highest risk occurs in 1st 5 years after adjuvant therapy.
- ERG assumptions are more pessimistic than accepted in past NICE appraisals for early breast cancer treatments, including TA424, TA569 and TA612 (full treatment effect was assumed for a minimum of 4 years)

*Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial reported long term data for anastrazole and tamoxifen for up to 10 years

Issue 9: lack of evidence for assumed 'carryover benefit' and treatment waning assumptions in base-case analyses

ERG

- Recognises the widening hazard rates of IDFS between the arms at year 2+
  - Understand that it could suggest a treatment effect duration beyond the current follow up
  - However it is uncertain due to lack of data beyond current follow up
  - Acknowledging that it is a conservative scenario
- Less optimistic waning duration assumption still needs to be explored:
  - a waning duration defined by the timepoint where the hazard rate of IDFS and OS are equivalent (originally used in TA612 in the context of an advanced stage disease where the OS hazard rate was high) is optimistic in this context
- Comparison of trends in hazard rates between abemaciclib arm in the model and Colleoni et al. (2016) are difficult and should be considered cautiously due to differences in the populations, interventions and output definitions:
  - Results from Colleoni et al. show a substantial decrease in recurrence risks after 10 years after adjuvant therapy, while the recurrence risk in the extrapolated ET arm remains high
  - Ties in with key issue 7 where ERG is concerned that the model presents a pessimistic prediction of IDFS
- ERG explores different waning assumptions in scenario analyses and notes that this is one of the key drivers for the cost-effectiveness analyses

⊙ *Is the assumed carry over benefit and treatment waning assumptions used by the company in its base case analysis sufficiently justified ?*

Issue 6: Medication adherence not modelled

Background

- Non-adherence to adjuvant ET is a concern in clinical practice and its impact has not been modelled

Company

- Implicitly captured in trial efficacy outcomes and TTD extrapolations based on monarchE data
  - pattern of non-adherence observed in monarchE representative of clinical practice
- Any reduction in cost of ET is likely to have a small impact on the cost-effectiveness analysis as the overall costs for ET are relatively low.
- Non-adherence to ET can reduce efficacy of ET but impact will be similar in both intervention and comparator arms; no reason to suggest a larger impact on the abemaciclib + ET arm vs ET alone

ERG

- Scenario analyses accounting for non-adherence to adjuvant ET in a real-world setting would have been useful for decision-making
- Judgement by committee needed as to the applicability of monarchE adherence data to NHS clinical practice

Key cost effectiveness issues

Issue	Impact
7. **Selection of IDFS survival curves for treatment and comparators**: *does the committee accept the uncertainty in the log-logistic IDFS extrapolation?*	
9. **Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning assumtions:** *is the assumed carry over benefit and treatment waning trajectory used by the company in its base case analysis sufficiently justified?*	
6. **Medication adherence not modelled**: *will non-adherence to adjuvant ET similarly impact both intervention and comparator arms?Is the pattern of non-adherence observed in monarchE representative of clinical practice?*	

Key

Model driver	
Unknown impact	

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Company and ERG base case analyses assumptions

Assumption	Company base case	ERG base case
IDFS extrapolation	Log-logistic curve	Log-logistic curve
Constant treatment effect duration	8 years	3 years
Waning effect duration	19 years (years 8-27)	5 years (years 3-8)
Waning effect assumptions	Lasts until the hazard rate in the IDFS for ET is the same as the mortality rate for the general population	No treatment effect on IDFS beyond year 8

Note: ERG explored a scenario analysis where all patients in the abemaciclib arm who developed invasive disease would receive abemaciclib again

Cost-effectiveness results

ICERs are illustrative as they do not include all confidential discounts
ERG assumptions result in a higher level of cost-effectiveness compared to the company

	ICER (£/QALY)
Company base case	9,164
ERG Base case	17,809

Decision ICERs are reported in PART 2 slides because they include confidential discounts

ERG scenario analysis

ICERs are illustrative as they do not include all confidential discounts

Scenarios demonstrate the impact in changing assumptions

ERG base-case inputs	Alternative input	ICER (£/QALY)
Company base case		**9,164**
ERG base case		**17,809**
IDFS extrapolation: dependent log-logistic model	Dependent log-normal model	21,612
3-year constant treatment effect, waning from years 3-8	Constant life-long treatment effect duration	7,956
	8-year constant treatment effect, followed by no effect	12,902
	5-year constant treatment effect, waning from years 5-8	15,147
	3-year constant treatment effect, followed by no effect	31,734
	3-year constant treatment effect, linear waning from years 3-27	10,338
Percentage receiving subsequent CDK4 treatments to treat a metastatic disease: Market share information adapted from TA563 and TA725	Endocrine therapy resistant (ETR) pathway: both arms = ET arm in monarch2; Endocrine therapy sensitive (ETS) pathway: both arms = ET arm in monarch3	32,061
	monarch3 ET arm % applied to all arms	30,666

Decision ICERs are reported in PART 2 slides because they include confidential discounts

Equality and innovation

Equality

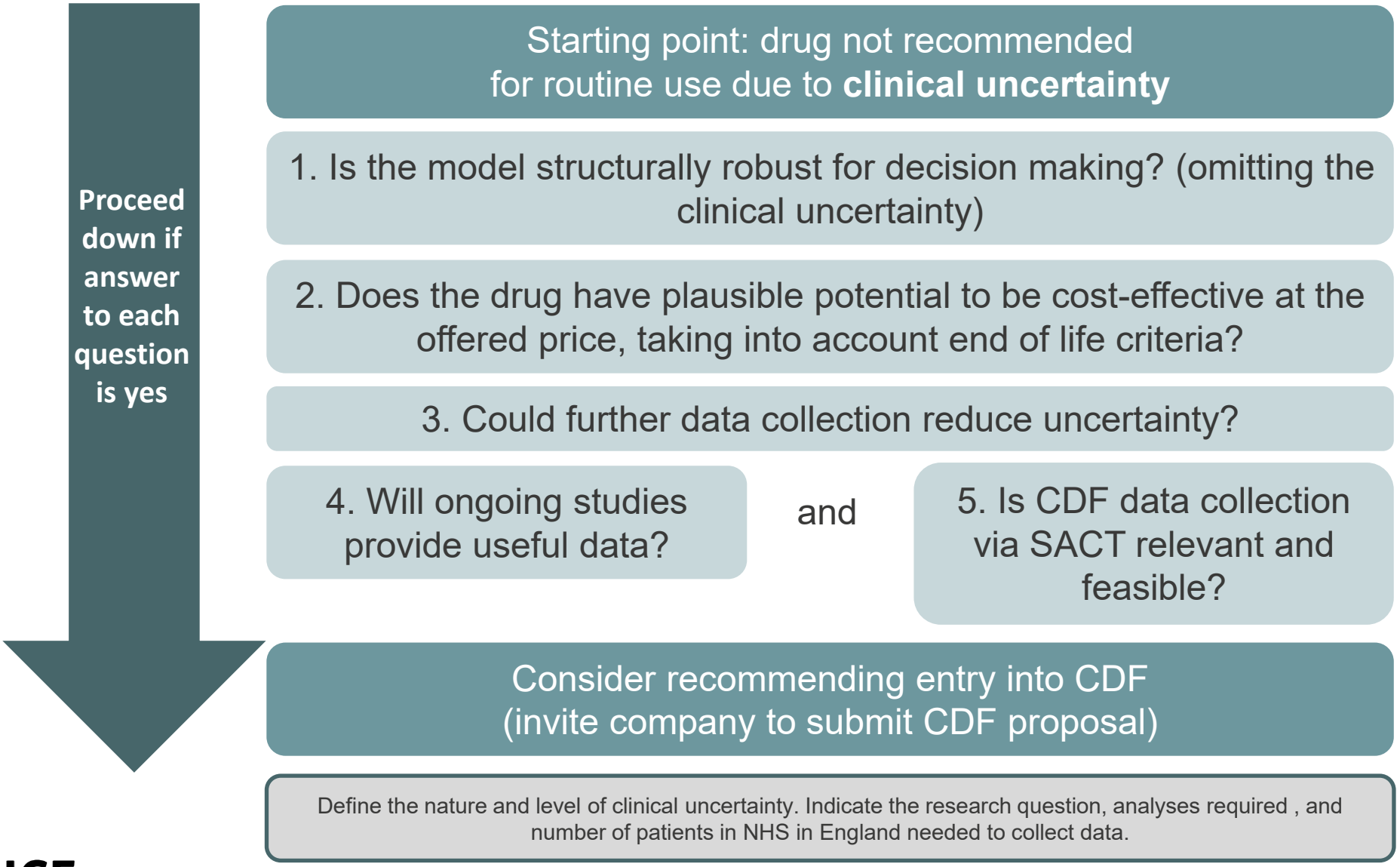
- No equality issues identified- MA anticipated to cover both women and men

Innovation

Company:

- Historical lack of innovation for patients with HR+, HER2− early breast cancer compared to other breast cancer subtypes:
  - cytotoxic chemotherapy and/or ET standard of care for many years
  - recent guideline recommendation for postmenopausal women to receive concomitant treatment with bisphosphonates
- Important to have effective treatment options as early in the disease as possible to reduce the likelihood of developing incurable advanced disease (and associated substantial reduction in quality of life and early death)
- Abemaciclib presents a step-change in the treatment pathway for early breast cancer setting

Committee decision making: CDF recommendation criteria



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Backup slides

Issues resolved after technical engagement

	Company's base case before technical engagement	Changes made after technical engagement
1	The Company included monarchE Cohort 1 population in the updated base case cost-effectiveness analysis	**Key issue 1:** addressing generalisability of trial results to NHS clinical practice given ambiguity in the definition of high risk of recurrence
2	The company used the Kaplan-Meier (KM) curve to model TTD for abemaciclib alone	**Matters of judgement 6:** KM curve to model TTD for abemaciclib alone was not used
3	The Company applied a value of £253.77	**Matters of judgement 7**: The cost of delivery of subsequent elements of a chemotherapy cycle deviated from the stated source of cost data. Updated cost to ERG preferred value of £341
4	Company applied pooled HSUVs for IDFS given lack of statistically significant EQ5D clinical results from monarchE Same utility values applied to both treatment and control arms in the IDFS setting	**Key issue 10:** updated pooled HSUVs ([redacted]) to reflect Cohort 1 given there was no difference found between treatment arms . **NOTE: ERG notes concern about use of pooled utility estimates and standard errors but notes small impact on results**
5	Probability of moving from IDFS health state to NMR and MR health states fixed throughout the model time horizon.	**Key issue 11:** included ERG's preferred method that the same treatment waning assumptions used for overall recurrences should apply to the probability of transitioning to the NMR and MR health states. In base case, waning is assumed to start at Year 8 and ends at Year 27.
6	Contained coding errors	**Key issue 13**: included ERG's proposed corrections for coding errors 1–4

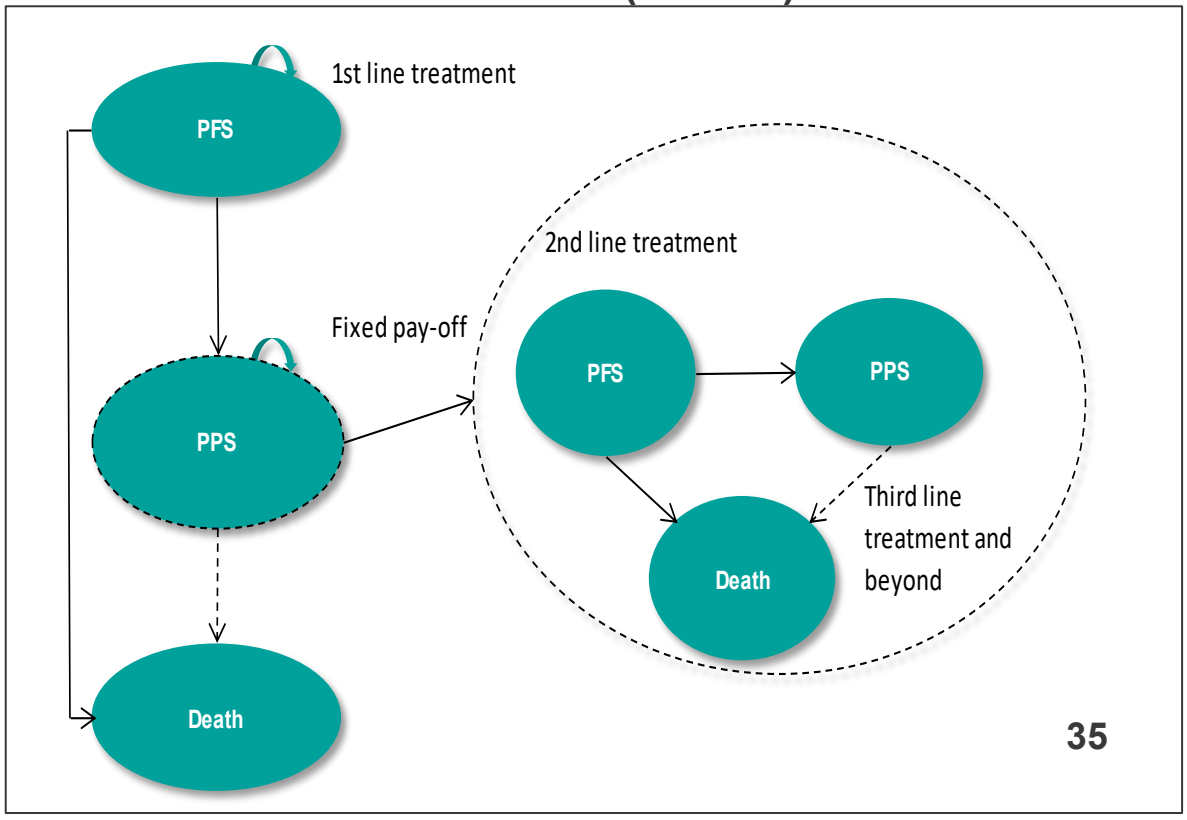
The metastatic recurrence health state

- Divided into two sub-states: **endocrine resistant**; and **endocrine sensitive**
- Transition to sub-states dependent on time to disease recurrence after completion of adjuvant ET
- Based on previous submissions for TA563 and TA725 (abemaciclib for metastatic disease), patients in these sub-states entered a partitioned survival model (PSM) with 3 survival states.
  - Entry to model in progression free survival (PFS) state with transitions to post-progression survival (PPS) or death
  - Death and metastatic recurrence modelled as absorbing states
- **TA563**: Key clinical evidence from Monarch3 trial. ET-sensitive metastatic setting modelled using a cohort state transition with three health states (PFS 1st line, PPS and death)
  - PFS state modelled as a Markov state. Following progression on advanced breast cancer ET treatment, patients allocated a fixed pay-off for PPS using costs and outcomes from Monarch2 model

ET-resistant metastatic setting modelled in TA725

[redacted]

Endocrine-sensitive metastatic breast cancer model (TA563)



Issue 4: Model structure and partitioned survival model (PSM) methodology

Background

- Debate between ERG and company whether model is a state transition model or a PSM

Company response to technical engagement:

- Model uses a Markov model structure (state transition model [STM] methodology). PSM methodology only used to calculate fixed payoffs associated with metastatic recurrence states, based on previously accepted PSM structures for metastatic indications in TA563 and TA725
- Current model different from a PSM as: 1) it uses transition probabilities between all states; ii) the structural relationship between non-metastatic recurrence and metastatic recurrence states; and iii) having OS dependent on metastatic recurrence (an intermediate endpoint) and OS without distant recurrence.

ERG critique of company technical engagement response:

- Important assumptions in model follow PSM structure: transitions between IDFS, non-metastatic recurrence and remission to a death (without distant recurrence) state dependent on same OS without distant recurrence curve and transition between IDFS and any recurrence states depends on shape of IDFS curve.
- Model best described as a hybrid or semi-Markov model; agree that cannot be categorised exclusively as a PSM

Issue 8: Overall survival (OS) survival curves

Background

- OS in model does not align with real-world OS estimates for patients in the same population
- Company's long term extrapolations of OS without distant recurrence show that ~97% of monarchE cohort will be alive at 5 years for both arms. NHS data shows 5 year survival is ~85% for people with stage III HR+, HER2-, breast cancer

Company

- OS extrapolations in model represent OS for patients **without distant recurrence (**including only patients who die in the IDFS, remission or NMR health state)
  - OS and OS without distant recurrence are **two distinct endpoints** and should not be used interchangeably
- However, OS estimates in model **not comparable to ~85%** estimate from NHS data (referring to people with HR+, HER2- breast cancer with an **initial stage III diagnosis**) as a substantial proportion of patients in monarchE were initially diagnosed with less advanced disease
- Considering above, and distinction between OS and OS without distant recurrence, no evidence to suggest discrepancy between OS predicted by model and survival expected in clinical practice

ERG

- Difficult to validate model predictions (of OS without distant recurrence) with external data
- Hazard rates of OS without distant recurrence extrapolated using monarchE data and capped by hazard rates from the UK general population using life tables:
  - As trial data is immature, the extrapolation of OS without distant recurrence starts using hazard rates from the general population i.e after a few cycles, the model assumes that the OS without distant recurrence at IDFS, non-metastatic recurrence and remission stage are equivalent to the general population survival.