Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Part 1 – redacted for screen

Technology appraisal committee A [01 April 2024]

Chair: Radha Todd

Lead Team: Richard Ballerand, Andrew Champion, Hugo Pedder

Evidence review group: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Harsimran Sarpal, Nigel Gumbleton, Ian Watson

Company: Novartis

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

- ✓ Key issues & decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Key issues for committee discussion


Unknown impact


Large impact


Small

Key issues for committee discussion		
Decision problem	1 & 7	• NATALEE trial populations and relevant comparators • Can population 1 results be used as a proxy for population 5?
	2	• What ET are used in NHS clinical practice? • Is NATALEE trial AI arm representative of ET used in NHS clinical practice?
	3	• Is DDFS a more appropriate proxy for OS than iDFS?
Clinical effectiveness	4 & 5	• Is it appropriate to assume equal efficacy for ribociclib + AI and abemaciclib + ET in population 4?
Cost effectiveness	6	• Is the company model structure appropriate?
	8, 9 & 10	• Is the company's approach of iDFS waning appropriate? • Is the company approach to modelling long-term iDFS estimates appropriate? • Is the company's or EAG's approach to iDFS event distribution more appropriate?
	11, 12 & 13	For ET-resistant and ET-sensitive distant relapse substates: • Are the company or EAG OS & PFS curves more appropriate for decision making? • What proportion of people in the substates would receive re-treatment with CDK4/6 inhibitor in clinical practice? • What PFS and progressed disease utility values are most appropriate?

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ET, endocrine therapy; DDFS, distant disease-free survival; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparisons

Background: Hormone receptor-positive, HER2-negative early breast cancer ~44,000 new case/year in the UK

Definition

- **Early -** cancer restricted to breast, or breast and nearby lymph nodes, has not spread to other parts of 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 ~68% of all breast cancers

Causes and diagnosis

- Genetic mutations, hormonal factors, lifestyle choices and environmental exposures
- All people can have HR+, HER2-negative early breast cancer, but incidence is higher in post menopausal women compared to premenopausal women
- Diagnosis involves triple assessment with breast examination, such as mammogram and/or ultrasound scan and biopsy

High risk of recurrence

- No universally accepted definition of high-risk early breast cancer
- NATALEE definition (slide 9): Anatomical Stage IIA: N0 with either: Grade 2/3, or N1. Stage IIB: N0 or N1. Stage III: N0, N1, N2 or N3

Equalities considerations

- No equality issueswere raised by the company and other stakeholders

Abbreviations: HER2:human epidermal growth factor receptor 2

Patient perspectives

Submissions from Breast Cancer Now and Independent Cancer Patient's Voice

Living with breast cancer

- Initial diagnosis shocking and people fear cancer returning or spreading to other parts of body
- Cause anxiety, and distress to people, friends and family members, affecting both physical and psychological well-being, with impacts that can last years

Unmet need and current treatments

- Treatment landscape has not moved for 30 years. Fearful of disease recurrence and question whether they are receiving optimal treatment
- People experience menopausal symptoms, diarrhoea, joint/muscle pain and fatigue, vaginal dryness and loss of libido

Ribociclib

- Convenient administration route: tablet can be taken at home and no need for hospital visit and a lower dose with reduced toxicities may support adherence
- Adjuvant ribociclib could reduce risk of recurrence and delay metastases which will reduce anxiety and improve quality of life of people and family members
- Adjuvant ribociclib could potentially enable a wider group (node-negative) to access a CDK4/6 inhibitor than are currently eligible for adjuvant abemaciclib

"Feeling like a 'sitting duck' following her treatment for primary breast cancer"

"I feel my future has been stolen" .."That fear of reoccurrence never truly leaves any of us"

"The treatments haven't moved on for many years the same drugs they were using 30 years ago. Things are a bit stagnant"

Regarding ribociclib: *"Safety blanket to catch anything. I feel lucky to be able to access it."…"I don't have to go into hospital, to go for an infusion"*

Abbreviations: CDK, Cyclin-dependent kinase

Clinical perspectives

Submissions from British Oncology Pharmacy Association & clinical expert

Aim of treatment

- Is to cure and reduce/delay the risk of recurrence of disease

Unmet need/current treatment options

- HR+, HER2- contributes to most deaths from early breast cancer
- Treatments include hormonal manipulation, bisphosphonates (and abemaciclib if patient fits NHS England criteria)

Ribociclib

- New line of therapy in adjuvant setting, will be offered to more people with node negative; better patient choice
- Increased disease-free survival and delayed recurrence

Resource use issues

- Longer treatment duration (3-years) compared with abemaciclib (2-years), may be intrusive and people may need extra blood tests
- More people would be eligible which will increase workload of cancer services

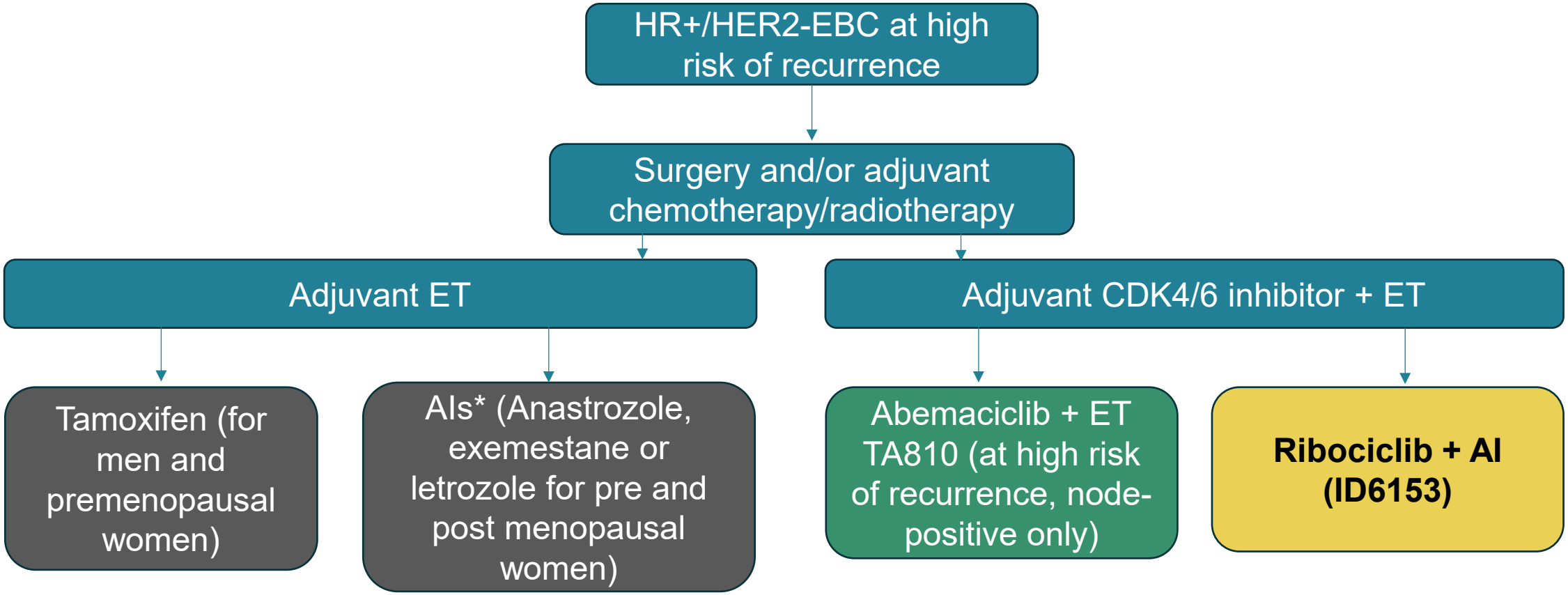
Abbreviations: AI, aromatase inhibitor; HER2:human epidermal growth factor receptor 2; HR, hormone receptor

Ribociclib (Kisqali, Novartis)

Technology details

Marketing authorisation	'Ribociclib in combination with an aromatase inhibitor (AI) for the adjuvant treatment of adult patients with hormone receptor (HR) positive (+)/human epidermal growth factor receptor 2 (HER2) negative (–) early breast cancer (EBC) at high risk of recurrence'
Mechanism of action	• Selective inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6) • By preventing interaction between CDK4/6 and cyclin D, ribociclib inhibits the phosphorylation of retinoblastoma tumour suppressor protein thereby blocking the progression from the G1 to the S phase of the cell cycle
Administration	• Oral: 400 mg tablet once daily for 21 days followed by 7 days off treatment • Maximum treatment duration 3 years or until disease recurrence or unacceptable toxicity occur
Price	• List price: £1,966.67 for 42 tablets (200 mg) • There is an existing simple patient access scheme (PAS) discount for ribociclib

Treatment pathway: Hormone receptor-positive, HER2-negative early breast cancer



***Only ET in NATALEE permitted were AI's anastrozole and letrozole**

Is the treatment pathway reflective of NHS clinical practice?

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Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intention-to-treat; TA technology appraisal

Key clinical trial: NATALEE

	NATALEE
Design	Phase III, multi-centre, open-label, randomised controlled trial
Location	International: 387 centres across 20 countries (83 people from UK)
Population	• Pre- and postmenopausal women and men with hormone receptor-positive HER2-negative early breast cancer at high risk* of recurrence (n = 5,101)
Intervention	• Ribociclib 400mg oral once daily for first 21 days of a 28-day treatment cycle for up to 36 months plus AI as outlined in comparator arm
Comparator	• 2.5mg once daily letrozole or 1mg once daily anastrozole continuously (+3.6mg goserelin once every 28-day treatment cycle for premenopausal women and men) for 60 months
Outcomes	**Primary**: iDFS; **Secondary**: RFS, DDFS, OS, PROs and safety and pharmacokinetics

***High risk in NATALEE defined by:**

- Anatomical Stage IIA:
  - N0 with either: Grade 3, or Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
  - N1
- Anatomical Stage IIB: N0 or N1
- Anatomical Stage III: N0, N1, N2 or N3

Abbreviations: AI, aromatase inhibitor; DDFS, distant disease-free survival; iDFS, invasive disease-free survival; OS, overall survival; PRO, patient-reported outcomes; RFS, recurrence-free survival

NATALEE trial: relevant populations

Population (% NATALEE)	Description	Comparator
1 – ITT (100%)	Node-negative or node-positive, HR-positive, HER2-negative EBC at high risk of recurrence	ET
NATALEE subgroups provided by company (all HR-positive, HER2-negative EBC at high risk of recurrence)		
2 (88%)	Node-positive abemaciclib eligible and ineligible	ET
3 (12%)	Node-negative, abemaciclib ineligible	ET
4 ([redacted]%)	Node-positive, abemaciclib eligible – unweighted (4a) and reweighted to match monarchE (4b)	Abemaciclib +ET and ET
5 EAG requested ([redacted]%)	Abemaciclib ineligible	ET

EAG

- People who are not eligible for abemaciclib + ET are treated with ET regardless of nodal status
- NATALEE ITT population problematic because comparator was only ET but most people in clinical practice will have abemaciclib + ET
- Consider population 4 and 5 most representative of NHS clinical practice

Abbreviations: ET, endocrine therapy; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; HR, hormone receptor

Unknown Impact ?

Issue 1 & 7: NATALEE populations and relevant comparator

Background

- NATALEE ITT population in line with MA but includes people eligible for abemaciclib + ET (population 4) and not eligible for abemaciclib + ET (population 5), however only comparator in NATALEE was AI

Company

- Efficacy of ribociclib + AI vs. AI was same irrespective if people are eligible or ineligible for abemaciclib + ET
- So only provided clinical data for population 5 but not cost-effectiveness results

iDFS HR (95%,CI);p-value	Population		
	NATALEE ITT (population 1) [n=5,101]	Node positive, abemaciclib eligible (population 4) [n = [redacted]]	Abemaciclib ineligible (population 5) [n= [redacted]]
Ribociclib + AI vs AI	0.715 (0.609 to 0.840); p<0.0001	[redacted]	[redacted]

EAG

- NATALEE comparator was only AI (anastrozole & letrozole) but most people in NHS clinical practice will be eligible for and receive abemaciclib + ET not ET
- Used population 1 clinical data to generate cost-effectiveness results for population 5 (ineligible for abemaciclib) but highlighted that the cost-effectiveness results may be conservative

Abbreviations: AI, aromatase inhibitor, CI, confidence intervals; ET, endocrine therapy; HR: hazard ratio; ITT, intention-to-treat; MA, marketing authorisation

Can population 1 results be used as a proxy for population 5?

Issue 2: NATALEE trial AI arm

Unknown Impact ?

Background

- In NATALEE, the only permitted ETs were the AIs, anastrozole and letrozole

Company

- Clinical advice to the company is that [redacted] of receive letrozole, [redacted] receive anastrozole and the remainder are likely to receive exemestane ([redacted]) or tamoxifen ([redacted]) in NHS practice - modelled as basket of comparators

EAG

- Clinical advice to the EAG is that, in NHS clinical practice, ET can include: anastrozole, letrozole, exemestane and tamoxifen (and ovarian suppression) however, as most people in NHS with HR-positive, HER2-negative early breast cancer receive either anastrozole or letrozole it was reasonable that letrozole and anastrozole were the only permitted ETs in the NATALEE
- Model assumes outcomes are equal across all AI's modelled, but as AI arm of NATALEE did not include tamoxifen, company also applied an adjusted HR for tamoxifen

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What ET are used in NHS clinical practice? Is NATALEE trial AI arm representative of ET used in NHS clinical practice?

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; HER2: human epidermal growth factor receptor 2; HR; hormone receptor/hazard ratio

Unknown Impact ?

Issue 3: iDFS or DDFS as a proxy for OS

Company

- NATALEE primary endpoint is iDFS
- iDFS is considered a clinically meaningful surrogate endpoint for OS, as disease recurrence is associated with breast cancer mortality
- Observed improvements in these endpoints [iDFS and DDFS] are anticipated, in the long-term, to translate into improvements in OS

EAG

- Clinical advice to the EAG is that DDFS is a more appropriate proxy for OS than iDFS

Clinical experts

- Consider statistical improvement in distant recurrence free survival a clinically significant treatment response; as even in patients with recurrence, death may be delayed a long time and so improvement in overall survival may not yet be apparent

Is DDFS a more appropriate proxy for OS than iDFS?

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Abbreviations: DDFS, distant disease-free survival; iDFS, invasive disease-free survival; OS, overall survival

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Results: NATALEE (ITT and subgroups)

EAG: 10% IFDS events in ITT population, long term impact remains uncertain

Outcomes (n),% 95(CI), p-value		NATALEE ITT (population 1)		Node positive, abemaciclib+ET eligible (population 4)		Abemaciclib+ET ineligible (population 5)	
		Rib + AI (n=2,549)	AI (n=2,552)	Rib + AI (n=[redacted])	AI (n=[redacted])	Rib + AI (n=[redacted])	AI(n=[redacted])
iDFS	Events (%)	263 (10.3)	340 (13.3)	[redacted]	[redacted]	[redacted]	[redacted]
	HR	0.715 (0.609 to 0.840); p<0.0001		[redacted]		[redacted]	
RFS	Events (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HR	[redacted]		[redacted]		[redacted]	
DDFS	Events (%)	240 (9.4)	311 (12.2)	[redacted]	[redacted]	[redacted]	[redacted]
	HR	0.715 (0.604 to 0.847); p<0.0001		[redacted]		[redacted]	
OS	Events (%)	105 (4.1)	121 (4.7)	[redacted]	[redacted]	[redacted]	[redacted]
	HR	0.827 (0.636 to 1.074); p=0.0766		[redacted]		[redacted]	

Abbreviations: AI, aromatase inhibitor; CI, confidence intervals; DDFS, distant disease-free survival; ET, endocrine therapy; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; HR, hazard ratio; Rib, ribociclib; RFS, recurrence-free survival

Issue 4 and 5 : ITC methodology (population 4)

Background

- NATALEE provided direct evidence for ribociclib + AI vs. AI only (iDFS from NATALEE used directly to inform efficacy for populations 1/5, 2 & 3). No direct evidence for ribociclib + AI compared with abemaciclib + ET
- For node-positive, HR-positive, HER2-negative EBC at high risk of recurrence and abemaciclib eligible population, company conducted MAICs to compare clinical effectiveness of ribociclib + AI vs. abemaciclib + ET for outcomes iDFS, OS & grade ≥3 TEAEs (see slides 38, 39 & 40 for results)

Company

- Conducted unanchored MAIC because NATALEE control arm = AI only (letrozole + anastrozole) and monarchE control arm = ET (consisting of AI's and tamoxifen). Considered monarchE and NATALEE control arms not equivalent
- For the comparison of ribociclib + AI vs. abemaciclib + ET (population 4):
  - selected people in NATALEE ribociclib+AI and AI arms who met monarchE inclusion criteria
  - weighted NATALEE ribociclib+AI IPD to match monarchE abemaciclib+ET arm baseline characteristics
- For the comparison of ribociclib + AI versus ET only (population 4)
  - selected people in NATALEE ribociclib+AI and AI arms who met monarchE inclusion criteria
  - NATALEE ribociclib + AI and AI arms were then weighted to match monarchE abemaciclib+ET and ET arms, respectively
- In model, company assume equal efficacy between ribociclib + AI and abemaciclib + ET based on MAIC results (except for TEAE's)

Abbreviations: AI, aromatase inhibitor; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparisons; TEAE, Treatment-emergent adverse event

Issue 4 & 5: ITC methodology: MAIC v STC (population 4)

EAG

- Unanchored comparisons rely on strong assumption of conditional constancy of absolute effects, results may be biased by residual confounding, extent of bias is unknown
- Ribociclib + AI vs. ET not strictly based on ITC; rather, a re-weighted NATALEE IPD analysis as only uses outcome data from NATALEE.
- Reweighting reduces the ESS, resulting in uncertain treatment effect
- EAG considered STC more appropriate, at clarification requested STCs for iDFS, DDFS and OS for comparison of ribociclib + AI vs. abemaciclib + ET

	Ribociclib+AI	AI
N	[redacted]	[redacted]
ESS (n)	[redacted]	[redacted]
ESS reduction (%)	[redacted]	[redacted]

Company (clarification response)

- Maintains MAIC approach appropriate to estimate the comparative efficacy of ribociclib plus AI and abemaciclib plus ET
- ESS in line with reasonable reductions in NICE DSU TSD18
- Provided STC as requested (DDFS not available from monarchE, so provided DRFS instead)

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; ESS, effective sample size; DDFS, distant disease-free survival; DRFS; distant relapse-free survival; DSU, decision support unit; iDFS, invasive disease-free survival; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparisons; TSD, technical support document

Unknown Impact ?

Issue 4 & 5: OS STC and OS MAIC results inconsistent (population 4)

EAG

- For comparison versus abemaciclib + ET:
  - Company iDFS STC and MAIC results are consistent – [redacted] (see slides 38 & 39)
  - Company OS MAIC and STC provide inconsistent results - OS STC results are [redacted] whereas the OS MAIC results are [redacted]

Analysis (Ribociclib+AI vs. abemaciclib + ET) population 4	HR (95% CI)	p-value
OS STC	[redacted]	[redacted]
OS MAIC	[redacted]	[redacted]

- STC not impacted by a reduction in ESS: so more reliable than MAIC but still are limited due to parametric distribution chosen by company, selecting a different model may lead to varying results

Is it appropriate to assume equal efficacy for ribociclib + AI and abemaciclib + ET in population 4?

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Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; DDFS, distant disease-free survival; HR, hazard ratio; invasive disease-free survival; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparisons

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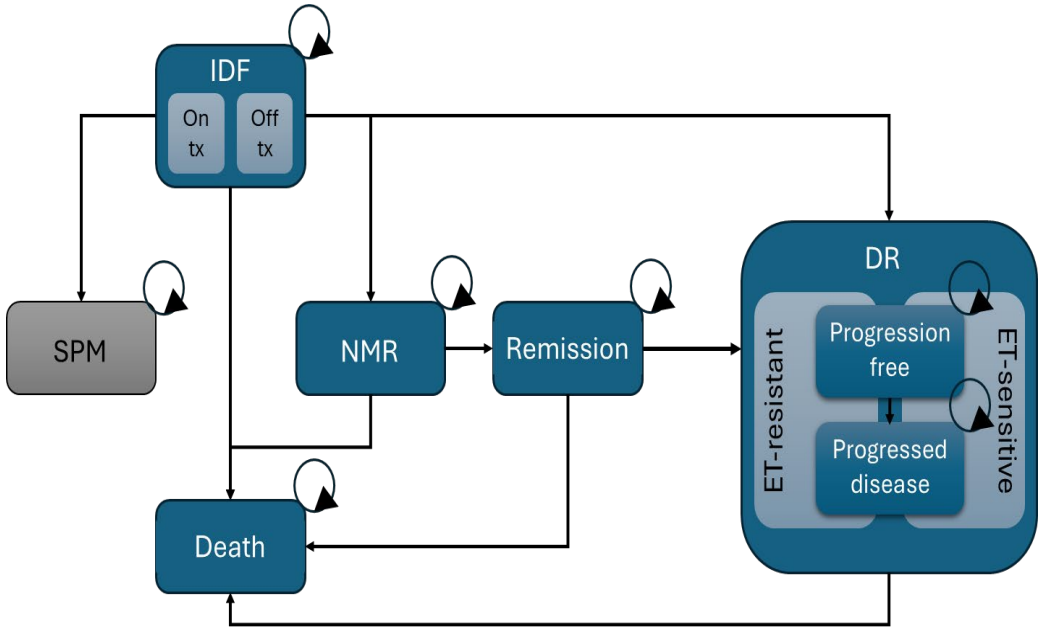
Company's model overview

Issue 6: EAG: company's model OS results may not be robust

Unknown Impact ?



Company

- Semi-Markov model with de novo partitioned survival sub-model for DR health states. Structure in line with previous TA and clinical experts agreed with proposed structure:
- 6 – mutually exclusive states (IDF, SPM, NMR, remission, DR and death)
- IDF split in 2 sub states: on-treatment and off-treatment
- DR split in 2 sub states: ET-resistant and ET-sensitive
- People enter the model in iDFS health state and are at risk of moving to SPM, NMR, DR and death health states
- Model assumed equal effectiveness of ribociclib+ AI and abemaciclib + ET based on ITC except AEs

EAG

- Broadly agree with model structure. EAG unable to directly estimate OS in the model due to the approach used to calculate life years in DR health state
- People transitioning to SPM exit the model without deaths being included in life-year calculations and was not included in any OS estimates for ribociclib + AI vs. ET

Is the company model structure appropriate?

Abbreviations; AI, aromatase inhibitor; AEs, adverse events; DR, distant recurrence; ET, endocrine therapy; IDF, invasive disease-free survival; ITC, indirect treatment comparison; NMR, non-metastatic recurrence; OS: overall survival; SPM, second primary malignancy; TA, technology appraisal

Large impact

Issue 8: iDFS treatment effect waning

Background

- Treatment effect waning applied for ribociclib + AI and abemaciclib + ET to represent reduction in treatment benefit versus ET over time

Company

- Treatment effect waning for ribociclib+AI and abemaciclib + ET based on evidence of carryover benefit in ATAC
- ATAC suggested risk of recurrence was lower in anastrozole vs. tamoxifen even after stopping treatment up until 8 years
- Company base case implemented iDFS treatment effect waning from 8 years until the point where iDFS reaches general population mortality

EAG

- Company iDFS treatment effect waning not supported by evidence & is arbitrary
- Acknowledged clinical advice that carry over period of between 5- and 10-year was clinically plausible following treatment
- 2 scenarios: 1) treatment effect waning removed entirely, and constant iDFS treatment effect assumed over model time horizon and 2) treatment effect assumed constant from 0 to 5 years and then waned over years 5 to 8, after which iDFS transition probabilities are equal for ribociclib + AI (and abemaciclib + ET) and ET

Is the company's approach of iDFS waning appropriate?

Abbreviations; AI, aromatase inhibitor; ATAC, arimidex, tamoxifen, alone or in combination trial; CE, cost-effectiveness; CDK, Cyclin-dependent kinase; ET, endocrine therapy; iDFS, invasive disease-free survival

Issue 9: iDFS modelling

Unknown Impact ?

Background

- NATALEE iDFS data immature and long-term (10 year +) iDFS estimates subject to substantial uncertainty

Company

- Explored iDFS curves using visual fit and statistical goodness-of-fit, but primarily based on clinical plausibility
- All parametric curves have similar validity versus trial K-M data and AIC/BIC similar
- Curves vary substantially after end of trial data and remainder of model time horizon
- Base case: exponential distribution for ribociclib + AI, abemaciclib + ET and ET, validated by expert opinion

EAG

- Literature search identified Martin 2023, that reported 5- and 10-year iDFS (75.2% and 57.0% respectively) for a population with node-positive, high risk HR-positive, HER2-negative EBC eligible for abemaciclib
- Company base case exponential curve provides 5- and 10-year iDFS estimates within [redacted] of Martin 2023
- Published iDFS data is only available for 10 years, and cannot be used to validate company extrapolations beyond 10 years
- EAG not made any changes to company base case iDFS curves
- Cautions NATALEE trial iDFS data are immature and long-term iDFS estimates subject to substantial uncertainty

Is the company approach to modelling long-term iDFS estimates appropriate?

Company fitted iDFS curves (slide 42)

Abbreviations; AI, aromatase inhibitor; ET, endocrine therapy; iDFS, invasive disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

Issue 10: iDFS event distribution

Small Impact

Background

- Company model assumed proportions of iDFS event types such as death, SPM, NMR or DR differ for ribociclib + AI and ET, but assumed to be the same for abemaciclib + ET as ribociclib + AI

EAG

- In ITT population for each health state, 95% CI overlapped substantially (table below), indicating insufficient statistical evidence of difference between iDFS distributions based on treatment

Treatment	Events (n)	NMR (95% CI)	Death (95% CI)	DR (95% CI)	SPM (95% CI)
Ribociclib+AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Preferred iDFS event distributions pooled across treatments to ensure similar iDFS event proportions for ribociclib + AI and ET
- EAG base case: set iDFS event proportions for all treatments equal to those for ribociclib + AI
- Setting iDFS event proportions equal does not result in equal transition probabilities aligning with clinical advice

Treatment EAG base case transition probabilities	iDFS to iDFS	iDFS to NMR	iDFS to death	iDFS to DR	iDFS to SPM
Ribociclib + AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE Is the company or EAG's approach to iDFS distribution more appropriate?

Abbreviations; AI, aromatase inhibitor; CI, confidence intervals; DR, distant recurrence; ET, endocrine therapy; iDFS, invasive disease-free survival; ITT, Intention-to-treat; NMR, non-metastatic recurrence; SPM, second primary malignancy

Issue 11: ET-resistant and ET-sensitive DR substate: PFS and OS

Small Impact

Company

- Used weighted basket of treatment to estimate PFS and OS in ET-resistant/ sensitive DR substates
- Estimated PFS and OS for treatment baskets by fitting parametric lognormal PFS and loglogistic OS curves for ribociclib + fulvestrant (ET-resistant DR substate) or ribociclib+ NSAI (ET-sensitive DR substate) to IPD data from MONALEESA-2 & 3

EAG

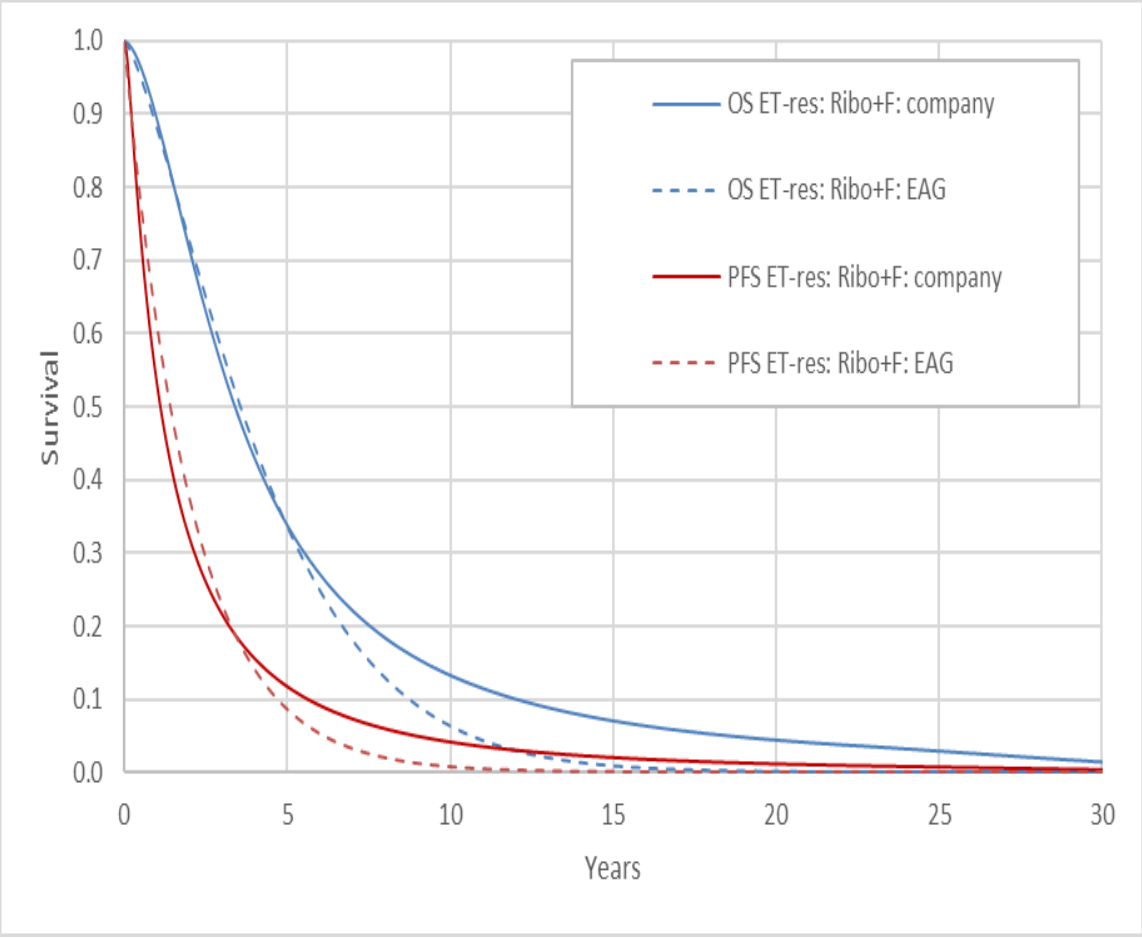
- Loglogistic (OS) and lognormal (PFS) curves are accelerated failure time parametric curves – Consider technically incorrect to apply HRs
- Long-term PH assumptions have not been justified for comparison of ribociclib + AI vs. basket of treatments
- Based on clinical advice, for ribociclib + AI, EAG prefer exponential PFS and Gamma OS curves in ET-sensitive DR, and exponential PFS and Weibull OS curves in ET-resistant DR substates

Abbreviations; AI, aromatase inhibitor; DR, distant recurrence; ET, endocrine therapy; HR, hazard ratios; NMA, network-meta-analysis; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival, PH, proportional hazard

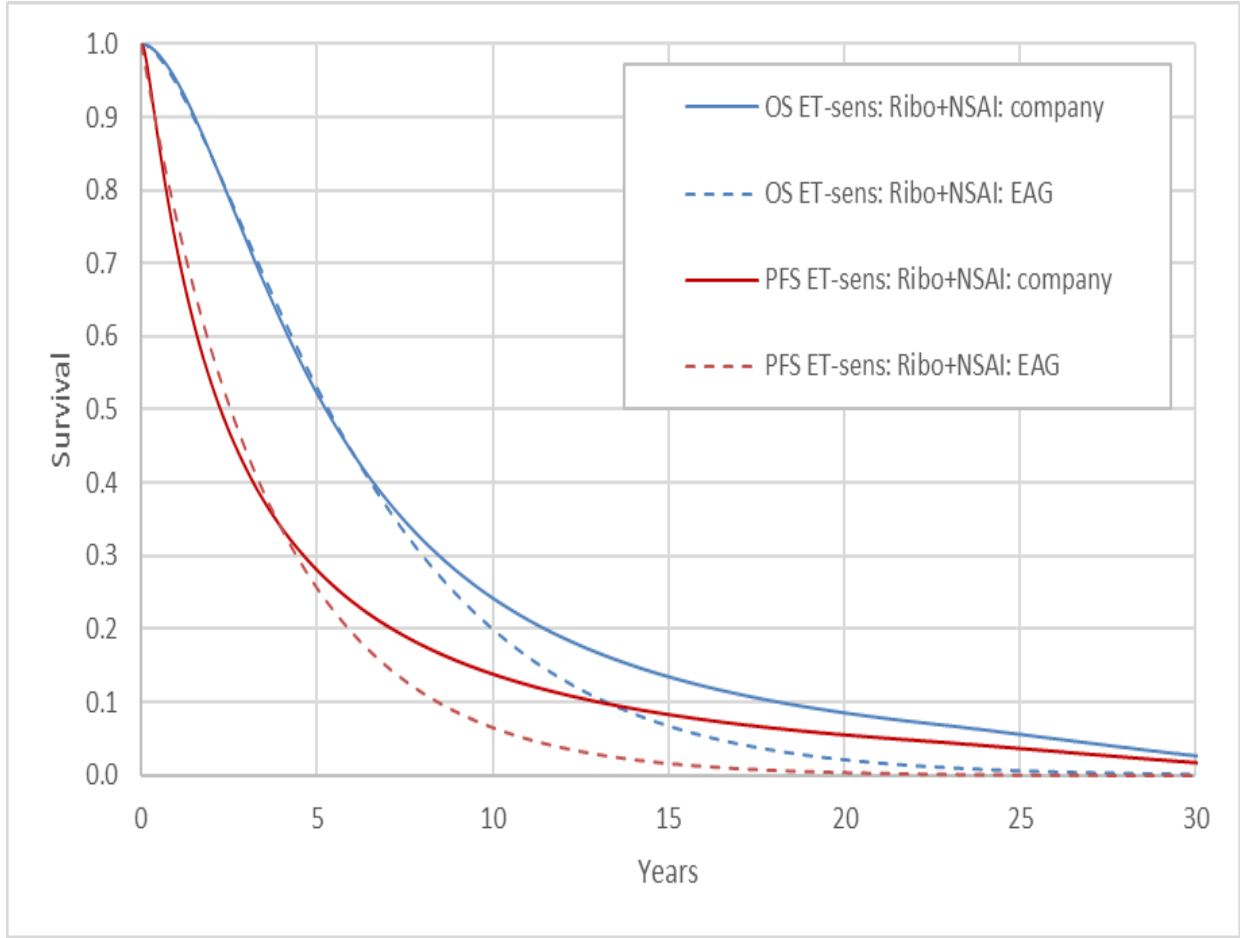
Small Impact

Issue 11: Company and EAG PFS and OS curves

Company and EAG PFS and OS curves for the ET-resistant DR substate



Company and EAG PFS and OS curves for the ET-sensitive DR substate



Are the company or EAG OS & PFS curves more appropriate for decision making?

Slide 43 for 5-30 year PFS and OS %

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Abbreviations; AI, aromatase inhibitor; DR, distant recurrence; ET, endocrine therapy; PFS, progression-free survival, NSAI, non-steroidal aromatase inhibitor; OS, overall survival

Issue 12: ET-resistant and ET-sensitive DR substate: treatment mix

Small Impact

Background

- Proportion of ET-resistant and ET-sensitive population previously treated with a CDK4/6 inhibitor and likely to receive subsequent CDK4/6 inhibitor is uncertain in clinical practice

Company

- For ET-resistant CDK4/6 inhibitor-sensitive people, assumed 30% would receive subsequent CDK4/6 inhibitor treatment, based on expert opinion that a lower proportion would be re-treated than those who received adjuvant ET alone
- For ET-sensitive CDK4/6 inhibitor-sensitive who had adjuvant treatment with a CDK4/6 inhibitor, assumed 45% would be retreated with a CDK4/6 inhibitor when entering the ET-sensitive DR substate versus 90% of people who receive adjuvant ET alone

EAG

- Consider company's modelled proportions not in line with clinical advice it received
- For ET-resistant and ET sensitive used 90% people who had CDK4/6 inhibitor-sensitive are retreated with a CDK4/6 inhibitor

What proportion of people in ET-resistant and ET-sensitive DR substates would receive re-treatment with CDK4/6 inhibitor in clinical practice?

Abbreviations; DR, distant recurrence; CDK; cyclin-dependent kinase ET, endocrine therapy;

Issue 13: Utility values- ET-resistant and ET-sensitive DR substate

Small Impact

Background

- PFS utility values assumed equal for both ET-resistant and ET-sensitive DR substates while progressed disease utilities differ

Company

- ET-resistant is more aggressive than ET-sensitive so it would expect lower HRQoL associated with it

EAG:

- HRQoL differs between ET-resistant and ET-sensitive from time of relapse, so expect ET-resistant progression-free utilities lower than ET-sensitive progression-free utilities
- Reasonable to use NMR state utility value to differentiate progression-free HRQoL between ET-sensitive and ET-resistant
- Provided scenarios using NMR health state utility value from NATALEE as the ET sensitive PFS utility value. Progressed disease utility values calculated from MONALEESA-2 and 3 trials

DR substate	Company base case		EAG base case	
	Progression free	Progressed disease	Progression free	Progressed disease
ET-resistant	[redacted]	[redacted]	[redacted]	[redacted]
ET-sensitive	[redacted]	[redacted]	[redacted]	[redacted]

What PFS & progressed disease utility values are most appropriate for ET-resistant & ET-sensitive DR substates?

Abbreviations; DR, disease recurrence; ET, endocrine therapy; HRQoL, health-related quality of life; NMR, non-metastatic recurrence; PFS, progression-free survival

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

- ❑ Key issues & decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ Other considerations
- ❑ Summary

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Other considerations

Severity

- Company: ribociclib + AI in HR+/HER2- EBC at high risk of recurrence does not meet NICE severity modifier criteria

Uncaptured benefits

- Clinical experts: Urgency of diarrhoea experienced with abemaciclib by some people may not be captured by indirect comparison and in QALY calculation

Managed access

- Company has not submitted a managed access proposal

Abbreviations: AI, aromatase inhibitor; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; QALY, quality-adjusted life year

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

- ❑ Key issues & decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ Summary

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Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption			Company base case	EAG base case
IDFS event distribution			Differ according to treatment	ET = Ribociclib + AI
Survival in DR substate	**ET-resistant**	**PFS**	Lognormal	Exponential
		OS	Loglogistic	Weibull
	ET-sensitive	**PFS**	Lognormal	Exponential
		OS	Loglogistic	Gamma
% CDK4/6 retreated DR substate	**ET-resistant**		30%	90%
	ET-sensitive		45%	90%
PFS utility values in DR substate			ET-resistant = ET-sensitive	ET-sensitive PFS utility values = NMR utilities
Treatment waning			After 8 years	Scenario 1: start: 5 year; end, 8 years Scenario 2: No treatment effect waning
AE costs			Grade ≥3 AEs	Grade ≥3 AEs according to severity

Abbreviations; AI, aromatase inhibitor; AE, adverse events; DR, distant recurrence; ET, endocrine therapy; iDFS, invasive disease-free survival; PFS, progression-free survival, NMR non-metastatic recurrence, OS, overall survival

Key issues for committee discussion


Unknown impact


Large impact


Small

Key issues for committee discussion			
Decision problem	1 & 7	• NATALEE trial populations and relevant comparators • Can population 1 results be used as a proxy for population 5?	
	2	• What ET are used in NHS clinical practice? • Is NATALEE trial AI arm representative of ET used in NHS clinical practice?	
	3	• Is DDFS a more appropriate proxy for OS than iDFS?	
Clinical effectiveness	4 & 5	• Is it appropriate to assume equal efficacy for ribociclib + AI and abemaciclib + ET in population 4?	
Cost effectiveness	6	• Is the company model structure appropriate?	
	8, 9 & 10	• Is the company's approach of iDFS waning appropriate? • Is the company approach to modelling long-term iDFS estimates appropriate? • Is the company's or EAG's approach to iDFS event distribution more appropriate?	  
	11, 12 & 13	For ET-resistant and ET-sensitive distant relapse substates: • Are the company or EAG OS & PFS curves more appropriate for decision making? • What proportion of people in the substates would receive re-treatment with CDK4/6 inhibitor in clinical practice? • What PFS and progressed disease utility values are most appropriate?	  

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ET, endocrine therapy; DDFS, distant disease-free survival; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparisons

Cost-effectiveness results

All ICERs are reported in PART 2 slides due to confidential prices

Base case

- Company base case
- EAG base case

EAG scenarios

- Changes to iDFS distribution
- Alternative PFS & OS in DR substates
- Changing proportion of people retreated with CDK4/6 inhibitor in ET-resistant/sensitive DR substate
- Alternative utility values for ET- sensitive
- Adverse events units according to severity
- Treatment effect waning for ribociclib + AI: 5 to 8 years
- Remove treatment effect waning for ribociclib +AI

Under £20,000/QALY

Some scenarios under £20,000/QALY gained, some over £20,000 QALY

Abbreviations: AE, adverse events; DR, distant recurrence; ET, endocrine therapy; ICER, ICER, incremental cost-effectiveness ratio; iDFS, invasive disease-free survival; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

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Thank you.

Supplementary appendix

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Decision problem – Issue 3: iDFS v DDFS proxy for OS

	Final scope	EAG comments
Population	Adults with HR-positive, HER2-negative early breast cancer after surgery of primary breast tumour	Adults with HR-positive, HER2-negative early breast cancer **at high risk of recurrence** after surgery of the primary breast tumour. **Company's definition of high risk appropriate**
Intervention	Ribociclib + AI	Appropriate
Comparators	• Full population: **Standard ET** • For node-positive early breast cancer at high risk of recurrence: **abemaciclib (+ET)**	EAG agrees that abemaciclib + ET and ET alone: relevant comparators
Outcomes	• iDFS, DDFS, OS, AEs & HRQoL	**Company** • iDFS a clinically meaningful surrogate endpoint for OS as disease recurrence is associated mortality • Improvements in iDFS and DDFS translate to improvements in OS **EAG:** DDFS more appropriate proxy for OS than iDFS
Subgroups	• Node positive/negative disease • Risk of recurrence • Presence of germline BRCA1 or 2 mutations	EAG: node-positive high-risk eligible for abemaciclib and high risk ineligible for abemaciclib are most representative of people seen in NHS

Abbreviations: AI, aromatase inhibitor; BRCA, breast cancer gene; DDFS, distant disease-free survival; ET endocrine therapy; iDFS, invasive disease-free survival; HRQoL, health-related quality of life; OS, overall survival; RFS, recurrence-free survival;

Baseline characteristics: NATALEE (population 1, 4 and 5)

Outcomes (n),% 95(CI), p-value		NATALEE ITT (population 1)		Node positive, abemaciclib+ET eligible (population 4)		Abemaciclib+ET ineligible (population 5)	
		Rib + AI (n=2,549)	AI (n=2,552)	Rib + AI (n=[redacted])	AI (n=[redacted])	Rib + AI (n=[redacted])	AI(n=[redacted])
Female, n (%)		2538 (99.6)	2543 (99.6)	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N stage at diagnosis	N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	N3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T stage at diagnosis	T3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AJCC stage	III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG:

- Baseline characteristics balanced across populations but population 4 included higher proportion of people:
  - T3 and T4 stage disease at diagnosis; N2 and N3 stage disease at diagnosis
  - American Joint Committee on Cancer (AJCC) stage III disease

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; ITT, intention-to-treat; Rib, ribociclib; SD, standard deviation

monarchE: trial

		monarchE
Design		Phase III, multi-centre, open-label, randomised controlled trial
Location		International: 603 centres across 38 countries (including UK)
Population		• Adults with with HR-positive, HER2-negative, node-positive, early breast cancer at a high-risk of recurrence; ECOG PS 0 to 1 **Cohort 1 (n=5120);** Pathological tumour involvement in: • ≥4 positive ALNs, or • 1 to 3 positive ALNs, and at least one of the following criteria: • grade 3 disease (defined as ≥8 points on the modified Bloom–Richardson grading system or equivalent), or • primary tumour size ≥5cm
Intervention		• Abemaciclib 150mg BID continuously for ≤24 months AND • ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5 to 10 years
Comparator		• ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5 to 10 years
Outcomes	**Primary**	• iDFS
	Secondary	• DRFS, OS, PROs (EQ-5D-5L FACT-B, FACT-ES, FACIT- F), safety and pharmacokinetics/pharmacodynamics

Abbreviations: ALN, axillary lymph node; BID, twice per day; DRFS, distant relapse-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; ET, endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Subscale; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; 3; Idfs,invasive disease-free survival; OS, overall survival; PROs, patient-reported outcomes

ITC results: iDFS and OS (MAIC)

iDFS and reweighted IPD analysis results (Population 4)

Comparison	Before matching	After matching
Ribociclib + AI vs. Abemaciclib + ET	[redacted]	[redacted]
Ribociclib + AI vs. ET (reweighted IPD)	[redacted]	[redacted]

OS MAIC and reweighted IPD analysis results (Population 4)

Comparison	Before matching	After matching
Ribociclib + AI vs. Abemaciclib + ET	[redacted]	[redacted]
Ribociclib + AI vs. ET (reweighted IPD)	[redacted]	[redacted]

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Abbreviations; AI, aromatase inhibitor; DR, distant recurrence; ET, endocrine therapy; IPD, individual patient data; MAIC, Matching-adjusted indirect comparison

Main slide

ITC results: iDFS, DRFS and OS (STC)

iDFS result (Population 4)

Comparison	HR (95%CI)	P-value
Ribociclib + AI vs. Abemaciclib + ET	[redacted]	[redacted]

DRFS result (Population 4)

Comparison	HR (95%CI)	P-value
Ribociclib + AI vs. Abemaciclib + ET	[redacted]	[redacted]

OS result (Population 4)

Comparison	HR (95%CI)	P-value
Ribociclib + AI vs. Abemaciclib + ET	[redacted]	[redacted]

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Abbreviations; AI, aromatase inhibitor; CI, confidence interval, DRFS, distant recurrence-free survival; ET, endocrine therapy; HR, hazard ratio; OS, overall survival

Main slide

ITC results: Grade ≥3 TEAE results (MAIC)

Grade ≥3 TEAE MAIC results: ribociclib+AI versus abemaciclib+ET (Population 4)

Outcome	Unweighted OR (95% CI)	Primary MAIC analysis weighted OR (95% CI)	Sensitivity MAIC analysis weighted OR (95% CI)
ALT increased	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]

Compared with abemaciclib + ET, both prior to and after matching, ribociclib+AI was associated with [redacted] odds of Grade ≥3 diarrhoea, leukopenia, and lymphopenia, and [redacted] odds of Grade ≥3 increased ALT and neutropenia

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Abbreviations; AI, aromatase inhibitor; ALT, alanine transaminase; CI, confidence intervals; ET, endocrine therapy; MAIC, Matching-adjusted indirect comparison; OR, odds ratio; TEAE, treatment-emergent adverse event

Main slide

How company incorporated evidence into model

	Assumptions and evidence source
Model Structure	• Semi Markov model cohort state transition model with partitioned survival structure for DR health state
Baseline characteristics	• NATALEE
Time horizon	• 50 years
Cycle length	• 28 days
Intervention efficacy	• NATALEE
Comparator efficacy	• NATALEE & monarchE
Utilities	• NATALEE and literature
Costs	• National Schedule of NHS Costs 2022/23, eMIT and BNF
Perspective	• NHS and PSS

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Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit

Main slide

Issue 9: company fitted iDFS curves

[redacted]

Abbreviations; AI, aromatase inhibitor; DR, distant recurrence; ET, endocrine therapy; MAIC, Matching-adjusted indirect comparison

Main slide

Issue 11: Company and EAG PFS and OS landmark efficacy

Health state	Outcome	Company/ EAG	Distribution	Landmark efficacy			
				5 years	10 years	20 years	30 years
ET-resistant	PFS	Company	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	OS	Company	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
ET-sensitive	PFS	Company	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	OS	Company	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Gamma	[redacted]	[redacted]	[redacted]	[redacted]

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Abbreviations; ET, endocrine therapy; PFS, progression-free survival; OS, overall survival

Main slide

Issue: ET-resistant and ET-sensitive DR substate: PFS and OS

Health state	Subsequent treatment	Proportion of people receiving subsequent therapy		
		Ribociclib plus AI (populations 1–4)	ET (populations 1–4)	Abemaciclib plus ET (population 4 only)
DR ET-resistant	Ribociclib + fulvestrant	[redacted]	[redacted]	[redacted]
	Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]
	Abemaciclib + fulvestrant	[redacted]	[redacted]	[redacted]
	Everolimus + exemestane	[redacted]	[redacted]	[redacted]
	Capecitabine	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]
	Alpelisib	[redacted]	[redacted]	[redacted]

Abbreviations; AI, aromatase inhibitor; ET, endocrine therapy; distant recurrence

Main slide

Issue 12: ET-resistant and ET-sensitive DR substate: treatment mix

DR Substate	CDK eligibility	Treatment	ET	Ribociclib+AI		Abemaciclib + ET
			Company	Company	EAG	Company
ET-resistant	Sensitive	Ribo+F	[redacted]	[redacted]	[redacted]	[redacted]
		Palbo+F	[redacted]	[redacted]	[redacted]	[redacted]
		Abema+F	[redacted]	[redacted]	[redacted]	[redacted]
		Eve+Exe	[redacted]	[redacted]	[redacted]	[redacted]
		Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
		Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
		Alpelisib	[redacted]	[redacted]	[redacted]	[redacted]

DR Substate	CDK eligibility	Treatment	ET	Ribociclib+AI		Abemaciclib + ET
			Company	Company	EAG	Company
ET-sensitive	Sensitive	Ribo+NSAI	[redacted]	[redacted]	[redacted]	[redacted]
		Palbo+NSAI	[redacted]	[redacted]	[redacted]	[redacted]
		Abe+NSAI	[redacted]	[redacted]	[redacted]	[redacted]
		Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
		Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
		Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations; abeam, abemaciclib; AI, aromatase inhibitor; DR, distant recurrence; EAG, External Assessment Group; ET, endocrine therapy; eve, everolimus; exe, exemestane; F, fulvestrant; palbo, palbociclib; ribo, ribociclib

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Thank you.