Inavolisib with palbociclib and fulvestrant for treating recurrent hormone receptor-positive HER2-negative PIK3CA-positive advanced breast cancer after adjuvant endocrine treatment [ID6425]

For screen – contains redacted confidential information

Technology appraisal committee A [10th February 2026]

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Company: Roche

Inavolisib with palbociclib and fulvestrant for treating recurrent hormone receptor-positive HER2-negative PIK3CA-positive advanced breast cancer after adjuvant endocrine treatment

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

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Background on locally advanced/metastatic breast cancer (hormone receptor positive, HER2-negative PIK3CA-mutated)

Breast cancer arises from tissues of the ducts or lobules of the breast; advanced breast cancer has spread to other parts of the body or grown in nearby tissues and cannot be surgically removed

Epidemiology

- 50,980 breast cancer diagnoses in England in 2022
- Approx. 15% of breast cancer in England in 2022 was advanced stage disease (stage 3 or 4) when diagnosed
- ~35% with early or locally advanced breast cancer progress to metastatic within 10 years of diagnosis
- 1-year survival rate for adults diagnosed at stage 4 (metastatic breast cancer) in England is 67%

Diagnosis and classification

- Tumour subtype guides treatment – e.g. oestrogen receptor, progesterone receptor, HER2 status
- Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative is most prevalent
- PIK3CA gene mutations are in 30%-40% of oestrogen receptor positive, HER2-negative tumours
- People with PIK3CA mutated breast cancer are likely to have a poorer prognosis than wild-type

Abbreviations: PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Patient perspectives

Targeted treatment would delay chemotherapy and improve quality of life

Submissions from patient expert, METUPUK, Breast Cancer Now

- Many with ER+/HER2-/PIK3CA-mutated metastatic breast cancer have repeated progression, cumulative side effects, anxiety, and uncertainty during treatment
- Quality of life is affected by fatigue, cognitive impacts, emotional burden, treatment logistics
- Molecular testing for mutations (PIK3CA, ESR1) is often delayed and varies regionally – if approved, testing needs to be available for timely access
- Strong preference for targeted treatments and oral medications that can be taken at home, over chemotherapy – new treatments extending life give hope and more time
- Inavolisib is targeted option earlier in pathway – helps delay chemotherapy and maintain independent, functioning, daily life
- Consider: Added toxicity and monitoring burden, unequal access, fulvestrant in 1st-line may prevent access to some 2nd-line treatments

"Metastatic breast cancer is the forgotten type…there's very little available once metastatic."

"Living with oestrogen positive breast cancer means living with the knowledge that your treatment will eventually fail. More lines of treatment means more options and more time."

"…every single treatment option means so much to me…they all mean time with my son…"

"…newly diagnosed patients can be given a treatment which increases how long they stay on their first line. That can only be a good thing."

Abbreviations: ER: Oestrogen receptor; ESR1: Oestrogen receptor 1; HER2: Human epidermal growth factor receptor 2; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Clinical perspectives

Unmet need for targeted treatment

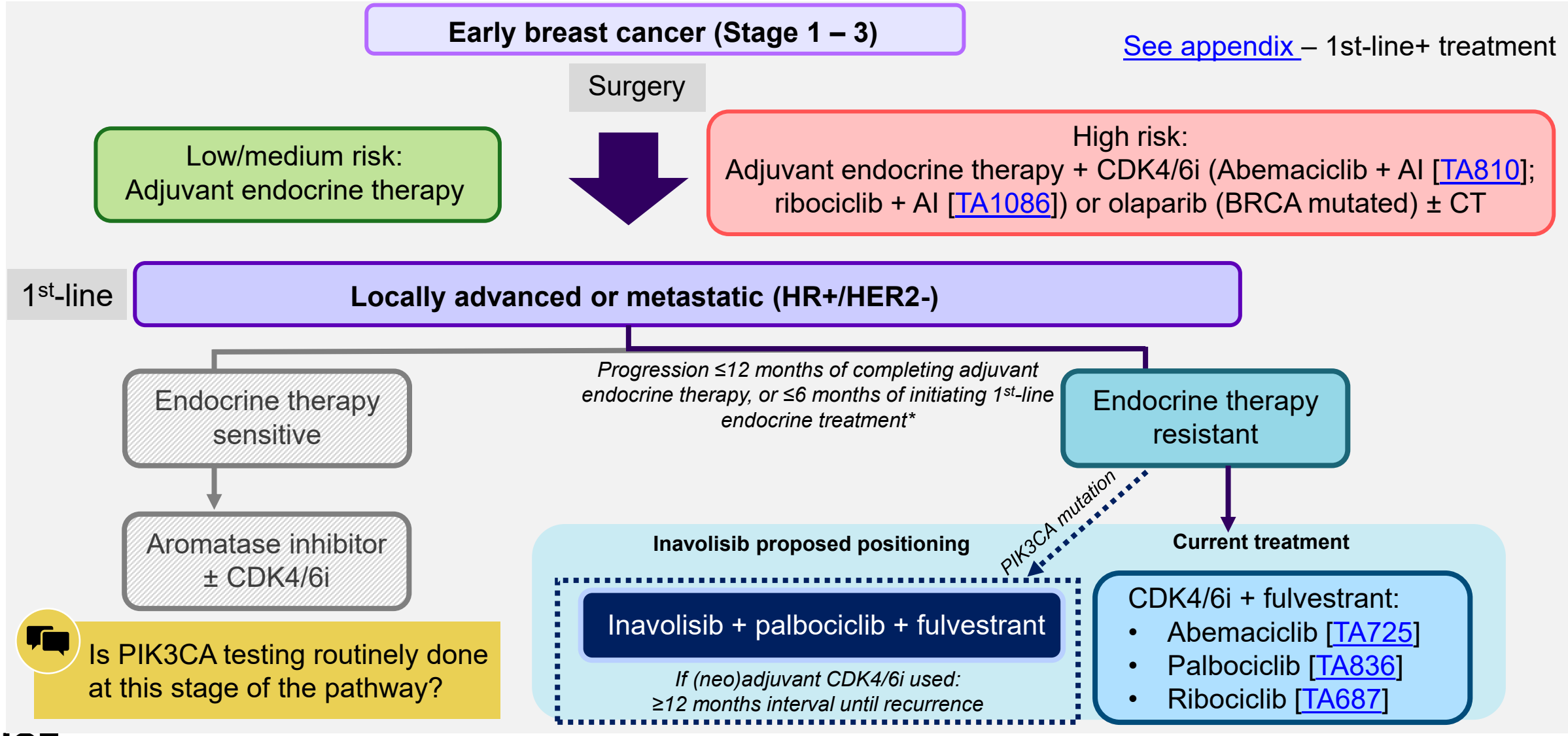
Ribociclib with fulvestrant (TA687)/ abemaciclib with fulvestrant (TA725)/ palbociclib with fulvestrant (TA836) – for hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy

Submission from clinical expert

- Aim of treatment: Prolong OS and PFS, whilst minimising side effects and maintaining quality of life
- Clinically significant treatment response: 30% reduction per RECIST 1.1; extending PFS and OS ≥6 months
- First-line treatment with fulvestrant and CDK4/6i (PAL/RIB/ABE); 2nd-line has multiple options
- Unmet need: New treatments needed; PIK3CA mutations expressed in ~1/3 people, resulting in less sensitivity to endocrine therapies
- Inavolisib would replace TA687, TA725, TA836 for people eligible for CDK4/6i+FUL and PIK3CA mutation – at the same time precluding later line treatment of alpelisib (TA816) and capivasertib (TA1063) [see appendix]
- Modest increase in healthcare resource needed – inavolisib needs more clinic visits to monitor and treat adverse effects than PAL and FUL, expect small increase in acute hospital admissions, but similar to alpelisib
- Not suitable for people with diabetes mellitus on treatment or people with poor glycaemic control
- PIK3CA mutation testing will be needed at time of relapse

Abbreviations: CDK: Cyclin-Dependent Kinase; FUL: fulvestrant; OS: Overall survival; PAL: palbociclib; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Treatment pathway – locally advanced/metastatic (HR+/HER2-) breast cancer, endocrine resistant



Abbreviations: AI: aromatase inhibitor; CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; CT: computed tomography; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Inavolisib (Itovebi, Roche)

Marketing authorisation – granted November 2025	Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence ≤12 months of completing adjuvant endocrine treatment • Interval of ≥12 months between termination of CDK4/6i treatment and detection of recurrence for those treated with a CDK4/6i in (neo)adjuvant setting • Combine endocrine therapy with an LHRH agonist in pre/perimenopausal setting
Mechanism of action	• Inhibits PI3K catalytic subunit protein (p110α; encoded by PIK3CA gene) and promotes degradation of mutated p110α • Dual mechanism of action inhibits downstream PI3K signalling, including AKT, resulting in less cell proliferation and inducing apoptosis in PIK3CA-mutated breast cancer cell lines
Administration	**Inavolisib:** 9 mg, once daily, oral tablet (dose reduction to 6 mg or 3 mg possible) **Palbociclib:** 125 mg, once daily, oral tablet, with 21 days on treatment then 7 days off **Fulvestrant:** 500 mg, intramuscularly, on days 1, 15, and 29, then once monthly Pre/perimenopausal: Include LHRH agonist
Price	• Inavolisib list price (28 tablets): £5,418 (3 mg); £10,836 (9 mg) • Mean total cost of inavolisib + palbociclib + fulvestrant: £296,166 (list price) • There are confidential commercial arrangements for inavolisib and palbociclib

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Abbreviations: CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; LHRH: luteinising hormone-releasing hormone; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Key issues

Issue	Slide	Appendix	ICER impact
1. Generalisability of INAVO120 results to NHS	11	41, 42, 43	Unknown
2. Indirect treatment comparison results	13, 14	44, 45	Unknown
3. PFS and PFS2 parametric extrapolation modelling	17, 18, 19	46, 49	Medium
4. Applying PFS and PFS2 distributions	20	-	Large
5. Consistency of PFS, PFS2, OS survival modelling	21, 22, 23	-	Small
6. Treatment duration modelling	24, 25	-	Large
7. Modelling efficacy of ABE+FUL and RIB+FUL comparators	26	-	Large
8. Relative dose intensity multipliers applied in the model	27	53	Medium
9. Subsequent treatment modelling	28	54	Medium
10. Age used in severity modifier	29	55	Large

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; RIB: ribociclib

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Key clinical trial – INAVO120 (NCT04191499)

Design	Phase 3, multicentre, double-blind, randomised, placebo-controlled
Population	People ≥18 years of age with locally advanced or metastatic PIK3CA-mutated, HR+, HER2-, breast cancer, whose cancer progressed either on, or within 12 months of completing adjuvant endocrine therapy
Interventions	Inavolisib (9 mg once daily) + palbociclib (125 mg once daily; 21 days on, 7 days off) + fulvestrant (500 mg intramuscularly; days 1 and 15, then day 1 of each 28-day cycle)
Comparator	Placebo + palbociclib + fulvestrant
Study duration	2020 to 2023 (primary outcome completion); estimated study completion is 2027
Median follow-up	34.2 months (intervention); 32.3 months (placebo)
Key outcomes	PFS (primary & updated clinical cut off); OS; response rate; duration of response; TTOT; adverse effects
Locations	123 centres across 28 countries (UK: n=5)
Key inclusion criteria	• No prior systemic therapy for locally advanced/metastatic tumour • Progression during adjuvant endocrine therapy or ≤12 months of completing adjuvant endocrine therapy with AI or tamoxifen ○ If include (neo)adjuvant CDK4/6, progression must be >12 months since completing CDK4/6i

See appendix for more on INAVO120 trial design

NICE Abbreviations: AI: aromatase inhibitor; CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; OS: overall survival; PFS: progression-free survival; TTOT: time to off-treatment

Key issues: Generalisability of INAVO120 results

EAG question generalisability of INAVO120 baseline characteristics to those treated in NHS

Unknown

EAG: Only 0.9% (n=3) had prior adjuvant treatment with CDK4/6i* – expected to increase for early breast cancer (high risk) due to NICE recommendations for ABE+AI (TA810; 2022) and RIB+AI (TA1086; 2025)

- Unclear if results from trial will be generalisable to NHS – need to establish relative effectiveness of INA+PAL+FUL and CDK4/6i+FUL regimens with prior CDK4/6i+AI adjuvant therapy

- Other differences in trial population vs NHS: Younger, fitter (ECOG PS), weighed less, and larger proportion were Asian, and only 2 were Black or African American

Early breast cancer (stage 1-3) treatment options post-surgery:

Low/medium risk:

- Adjuvant endocrine therapy

High risk:

- Adjuvant endocrine therapy + CDK4/6i (ABE + AI [TA810]; RIB + AI (TA1086]) ± CT
- Olaparib (BRCA mutated) ± CT

What is the likely impact of prior CDK4/6i+AI adjuvant endocrine therapy on clinical effectiveness?

- Does the trial reflect NHS in this population?

*All progressed ≤ 12 months so endocrine-resistant

Baseline characteristic		INA+PAL+FUL (n=161)	PBO+PAL+FUL (n=164)
Age, mean years (SD)		53.8 (10.9)	54.1 (11.2)
Race, n (%)	Asian	61 (37.9)	63 (38.4)
	Black or African American	1 (0.6)	1 (0.6)
Weight (kg), mean (SD)		66.2 (15.9)	65.4 (14.3)
ECOG PS, n (%)	0; 1	100 (62.1); 60 (37.3)	106 (64.6); 58 (35.4)
Prior (neo)-adjuvant treatment	**CDK4/6i***	**2 (1.2)**	**1 (0.6)**

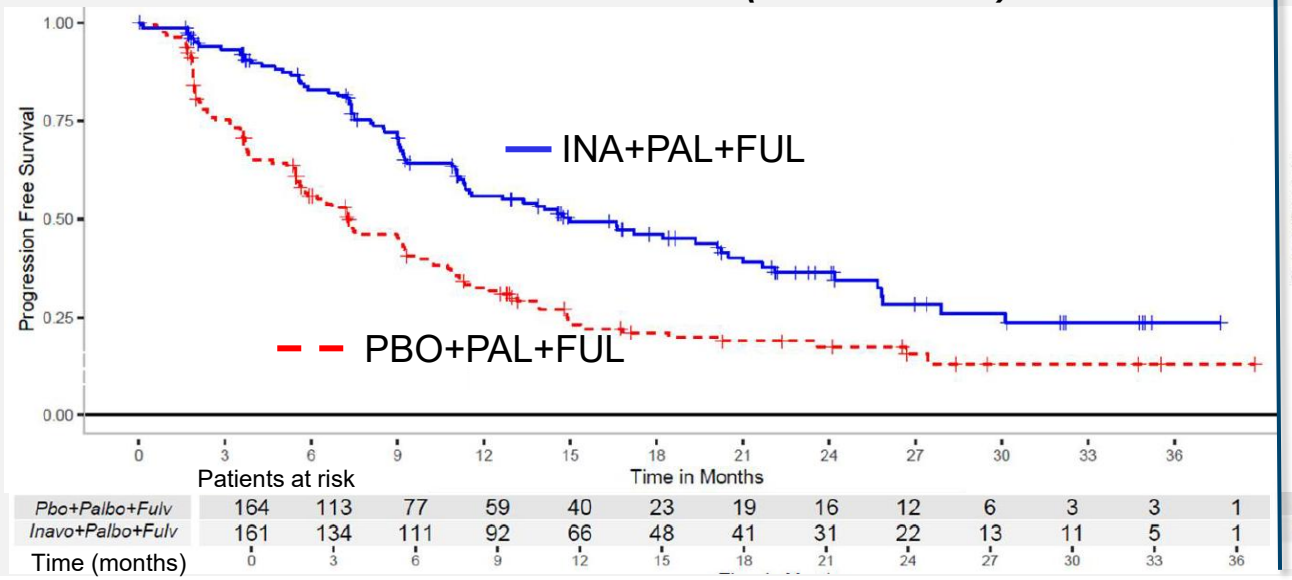
See appendix: Further baseline characteristics

Abbreviations: ABE: abemaciclib; AI: aromatase inhibitor; CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group performance score; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; RIB: ribociclib; SD: standard deviation

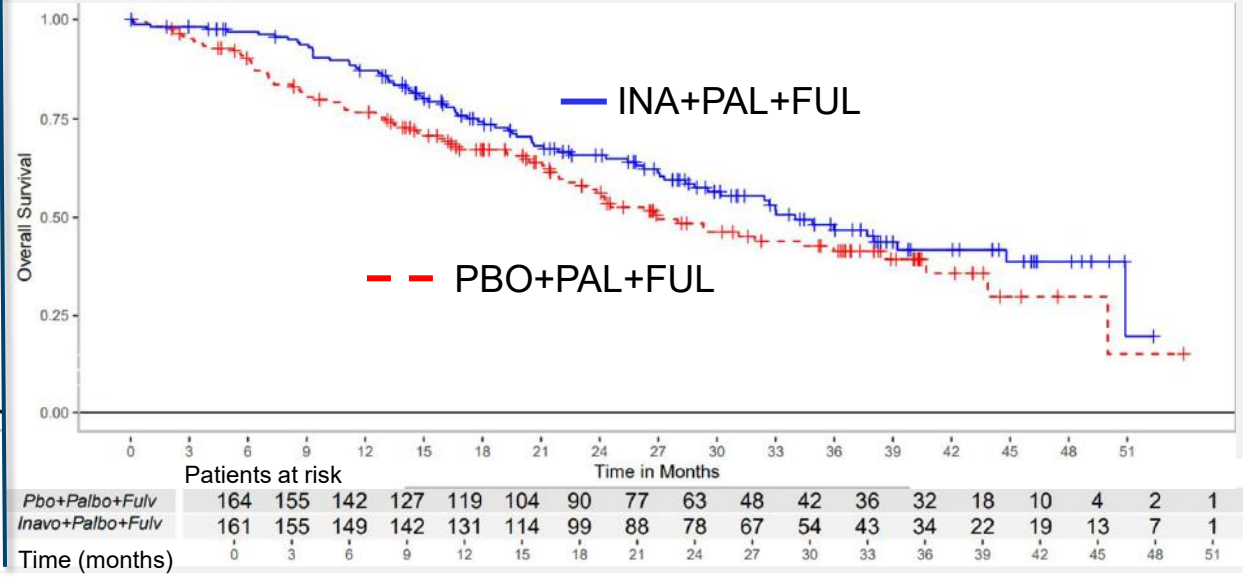
INAVO120 trial results – PFS and OS results

A statistically significant improvement in PFS and OS for INA+PAL+FUL vs PBO+PAL+FUL

Progression-free survival, full-analysis set, Sept 2023 PFS clinical cut-off date (≥194 events)



Overall survival, full-analysis set, Nov 2024 OS clinical cut-off date (≥153 events)



Sept 2023	INA+PAL+FUL (n=161)	PBO+PAL+FUL (n=164)
n (%)	82 (50.9)	113 (68.9)
Median, months (95% CI)	15 (11.3, 20.5)	7.3 (6.6, 9.3)
HR (95% CI), p-value	0.43 (0.32, 0.59), p<0.0001	

Nov 2024	INA+PAL+FUL (n=161)	PBO+PAL+FUL (n=164)
n (%)	72 (44.7)	82 (50)
Median, months (95% CI)	34 (28.4, 44.8)	27 (22.8, 38.7)
HR (95% CI), p-value	0.67 (0.48, 0.94), p = 0.019	

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Abbreviations: CI: confidence interval; HR: hazard ratio; INA: inavolisib; FUL: fulvestrant; OS: overall survival; PAL: palbociclib; PBO: placebo; PFS: progression-free survival

Network meta-analysis – efficacy results

Company: No direct evidence comparing INA+PAL+FUL vs ABE+FUL or RIB+FUL

- Conduct PFS and OS NMAs for indirect treatment comparison (vs INA+PAL+FUL)
  1. Mixed endocrine resistance (7 RCTs) – used in base case
  2. Endocrine-resistant (5 RCTs; exclude MONALEESA-3 and FLIPPER)
- Results show INA+PAL+FUL is more effective vs ABE+FUL than RIB+FUL
- Clinical benefit of ABE- or RIB+FUL may be overestimated because of poorer outcomes associated with PIK3CA mutations than wild-type (unconfirmed PIK3CA mutation status in comparator trials)

	NMA	ABE+FUL	RIB+FUL	PAL+FUL
PFS HR (95%CI)	Mixed	0.4 (0.2, 0.9)	0.4 (0.2, 0.8)	0.4 (0.3, 0.7)
	Endocrine resistant	0.5 (0.2, 1.3)	N/A	0.4 (0.2, 0.7)
OS HR (95%CI)	Mixed	0.6 (0.2, 1.4)	0.7 (0.3, 1.8)	0.7 (0.4, 1.2)
	Endocrine resistant	0.5 (0.2, 1.3)	N/A	0.7 (0.4, 1.1

See appendix for NMA overview and study inclusion criteria

EAG: Clinical advice: CDK4/6i+FUL regimens are considered to have similar efficacy

- TA836 conclude PAL-, ABE-, RIB+FUL are likely to provide similar health benefits of PFS and OS
- Prefer assuming ABE-, PAL-, RIB+FUL have equal efficacy in economic model
- Endocrine-resistant NMA more relevant to scope population
  - No results for RIB+FUL from endocrine-resistant NMA – important limitation

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Abbreviations: ABE: abemaciclib; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; CI: confidence interval; INA: inavolisib; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RCT: randomised controlled trial; RIB; ribociclib

Key issues: Network meta-analysis reliability

Potential treatment effect modifiers affecting reliability of network meta-analysis

Unknown

Heterogeneity between baseline characteristics of studies within NMA:

- **Median age:** 53-64 years of age
- **Asian:** 38%-90%
- **Visceral disease:** 56%-82%
- **Post-menopausal status:** 57%-100%
- **ECOG PS 0:** 52%-65%
- **Primary resistance to endocrine therapy:** 27%-36%
- **Prior (neo)adjuvant treatment:**
  - Chemotherapy: ~45% to ~85%
  - Endocrine therapy: ~55% to >90%
  - Aromatase inhibitor: <45% to ~80%

See appendix for differences in NMA baseline characteristics

EAG: NMA is limited by differences in potential treatment effect modifiers (TEM)

- Baseline characteristics with heterogeneity between studies align with previously identified potential TEM of CDK4/6i+FUL regimens for HR+/HER2- advanced breast cancer

- PIK3CA mutation may be TEM (comparator trials had mixed/unknown PIK3CA status)
  - Company's subgroup analysis by PIK3CA mutation status (2 trials) difficult to interpret – no p-values, mixed treatment lines, and conflicting results (similar or better PFS HR for wild-type over mutated PIK3CA; but similar or better OS HR for mutated over wild-type)
- Endocrine-resistant NMA is more comparable in terms of potential treatment effect modifiers

How important are the potential treatment effect modifiers that differed across trials?
Does PIK3CA mutation affect the relative effectiveness of CDK4/6i?
Are mixed endocrine status or endocrine resistant NMA results more appropriate to consider?
Is it appropriate to assume the CDK4/6i + FUL have equal or different efficacy? (in terms of PFS and OS)

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Abbreviations: ABE: abemaciclib; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; CI: confidence interval; FUL: fulvestrant; HR: hazard ratio; INA: inavolisib; NMA: network meta-analysis; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RIB; ribociclib

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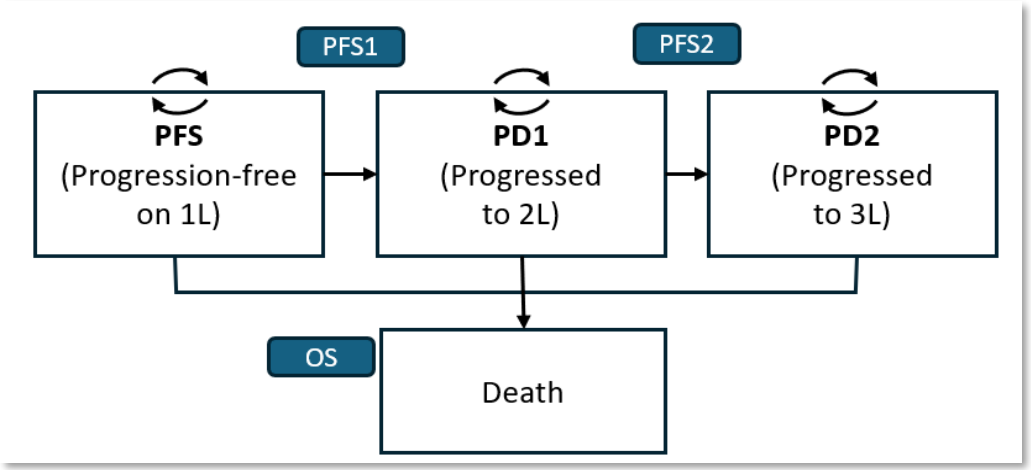
Company's model overview



Costs affected by:

- Increasing treatment costs by remaining progression-free

QALYs affected by:

- Increasing time remaining progression-free and survival

Assumptions with greatest ICER effect:

- Constraints applied to INAVO120 trial PFS and PFS2 curves
  - ➢ Parametric distribution modelling INAVO120 TTOT data
  - ➢ ABE+FUL and RIB+FUL treatment efficacy modelling

Partitioned survival model with 4 mutually exclusive health states:

- PFS (all enter model)
- First progressive disease (PD1)
- Second progressive disease (PD2)
- Death

- Each cycle, can remain in PFS or transition to PD1 or death states
- Transition to PD1 risks further progression (to PD2) or death
- PD2 state: Remain until death
- 7-day cycles with half-cycle correction to health outcomes and costs
- Time horizon: 40 years (lifetime)

Abbreviations: ABE; abemaciclib; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; RIB: ribociclib; TTOT: time to off-treatment

Key Issue: PFS and PFS2 parametric modelling

Medium

Company prefer log-normal distribution for PFS(2); EAG prefer log-logistic distribution

Company: INAVO120 used to estimate PFS and PFS2* for INA+PAL+FUL and PAL+FUL

- Consider hazards are non-proportional (curves cross and non-random pattern of Schoenfeld residuals against time) – fit independent parametric models for PFS across treatment arms
- Best visual fit: Log-normal and log-logistic for both arms
- Best statistical fit: Log-logistic for INA+PAL+FUL and log-normal for PAL+FUL
- UK clinical experts: Log-logistic or log-normal – both estimate 5% PFS at 10 years (most clinically plausible)
- Log-normal in base case for PFS and PFS2 (clinicians: no reason for PFS and PFS2 distributions to differ)

*PFS2 not available from INAVO120 – use time to end of next-line treatment as proxy

		AIC (Rank /7)	BIC (Rank /7)
INA+PAL+FUL	Log-normal	891 (7)	897 (7)
	Log-logistic	883 (1)	889 (1)
PAL+FUL	Log-normal	979 (1)	985 (1)
	Log-logistic	979 (2)	986 (2)

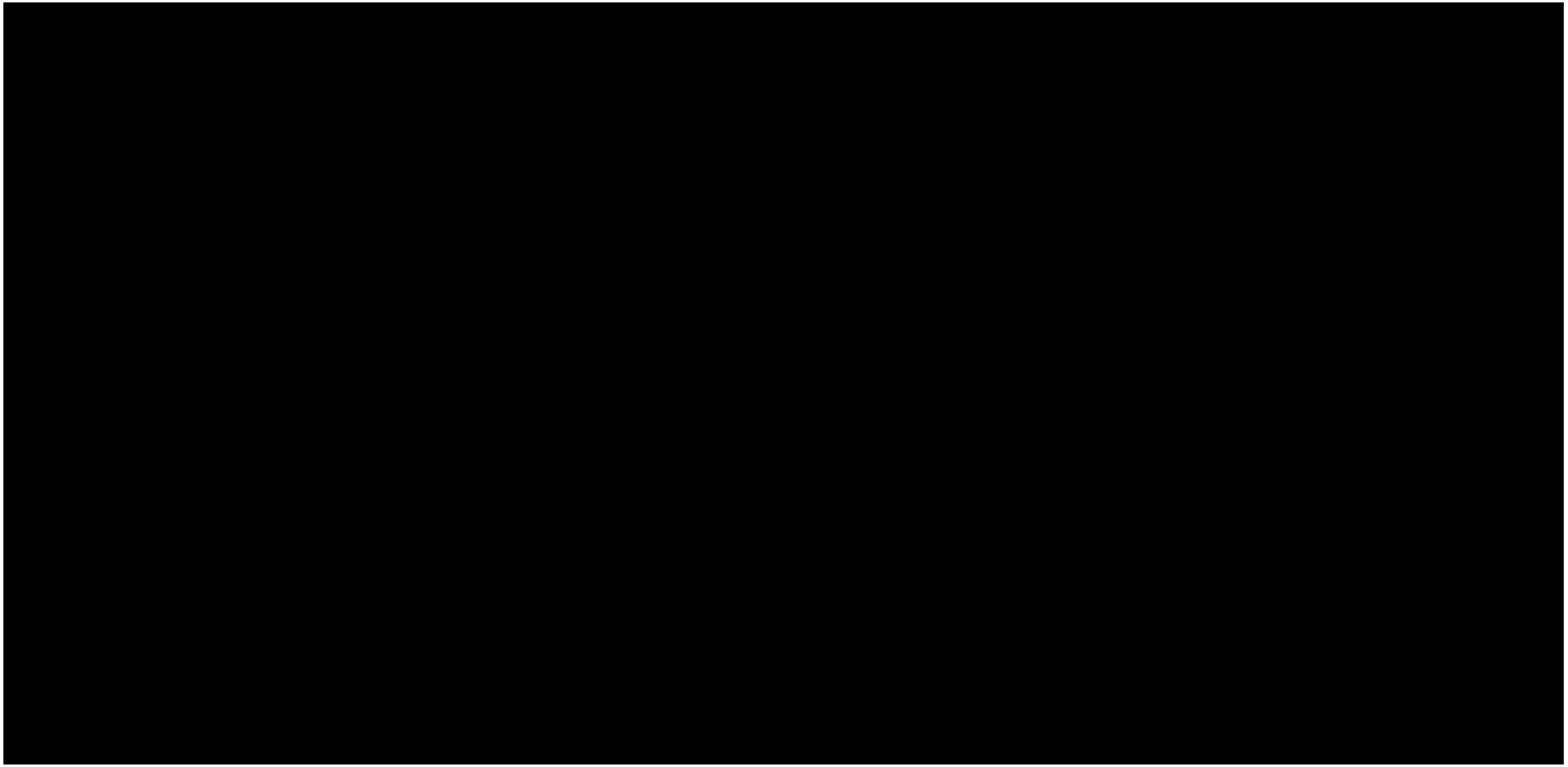
EAG: Prefer log-logistic – good statistical and visual fit to KM data, most plausible according to clinical experts, and appropriate for both arms

- [redacted] company's clinical experts prefer [redacted]
- Log-normal has lowest statistical fit for INA+PAL+FUL
- PFS revisions apply to PFS2 – where most expected to have chemotherapy as subsequent treatment, with relatively shorter PFS than first-line

Which distribution is appropriate to model PFS and PFS2?

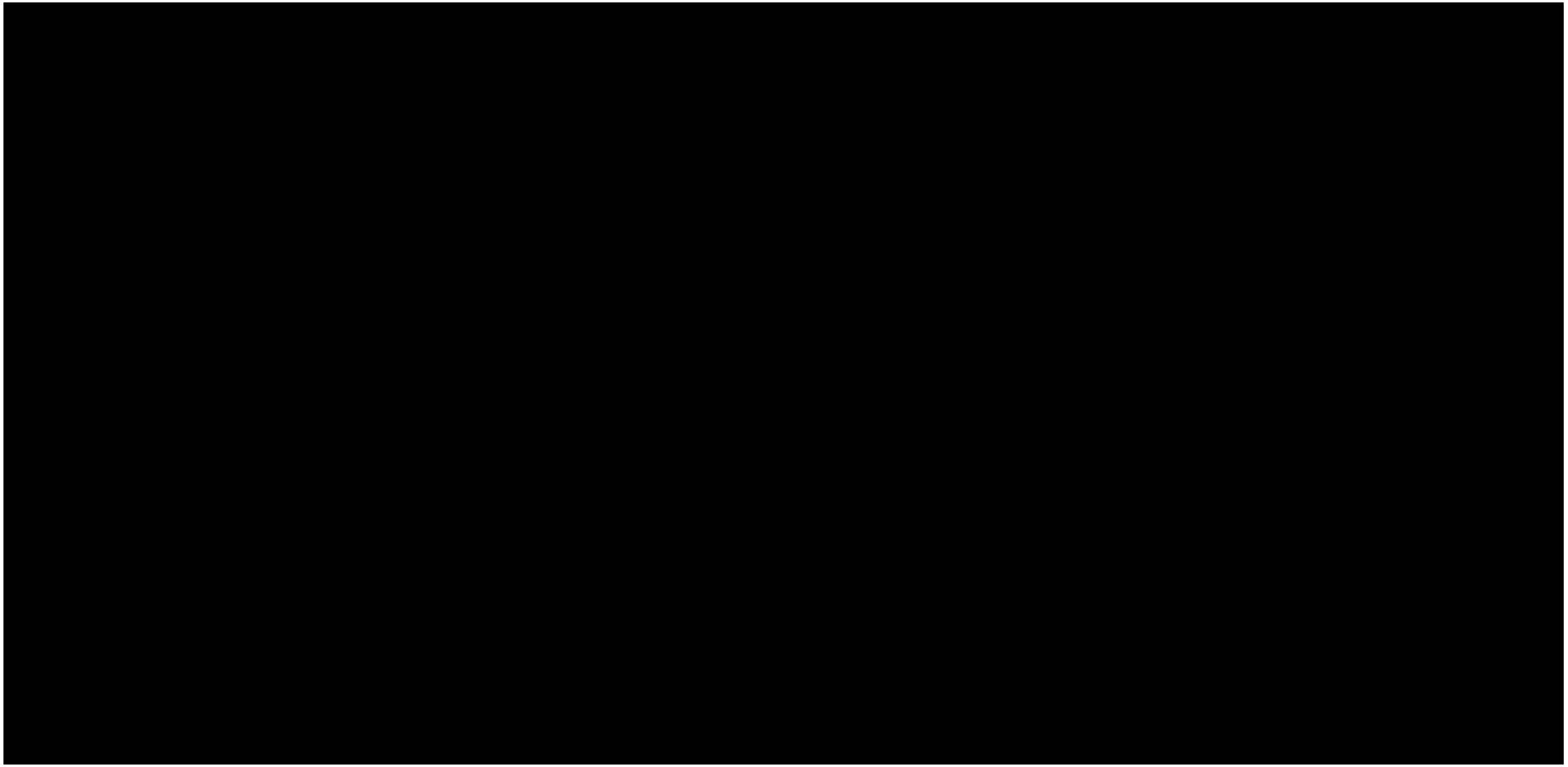
Abbreviations: ABE: abemaciclib; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival; RIB; ribociclib

PFS and PFS2 extrapolations for INA+PAL+FUL



Abbreviations: INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

PFS and PFS2 extrapolations for PAL+FUL



Abbreviations: FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

Key issue: Applying the parametric distributions

Large

Company: KM+ log-normal distribution at specific timepoint; EAG: Log-logistic from model start

Company: Piecewise approach using INAVO120 PFS KM data up to a timepoint then extrapolate survival

- KM data used for initial observed period of PFS – to accurately reflect trial outcomes and avoid any potential over- or underestimation from parametric distributions
- Parametric extrapolations applied only beyond trial follow-up: Log-normal distribution applied once ~20% people remained at risk (aligned with Pocock, Clayton, and Altman (2002) recommendations)

EAG: Question piecewise approach:

  - All parametric distributions give good visual fit to KM data in both arms
  - Converted monthly hazard rates to weekly and found it unclear if there are statistically and clinically significant turning points in hazards
- Using AIC/BIC is inappropriate if company fit parametric curves to KM data from time 0, but only apply distribution to tail of KM curve (AIC/BIC largely reflect data fit at earlier timepoints where more are at risk)
- 20% patient-at-risk threshold is arbitrary – Pocock et al. suggest 10-20% and note is debateable
  - ICER is sensitive to timepoint parametric distribution is applied (10% patient-at-risk threshold for PFS increases ICER by ~£7K)
- Prefer log-logistic distribution applied from the start of the model:
  - Appropriate for both trial arms, good statistical and visual fit to KM and most clinically plausible

Should the parametric distribution be applied from the start of the model or at a specific patient-at-risk threshold?

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; FUL: fulvestrant; PFS: progression-free survival;

Key issue: Consistency of OS, PFS, and PFS2 extrapolations

Small

Company: Cap PFS(2) curves by OS; EAG: constrain PFS(2) hazards by mortality hazard to ensure clinical plausibility

Company:
- PFS and PFS2 curves are capped by OS in model to prevent illogical survival estimates

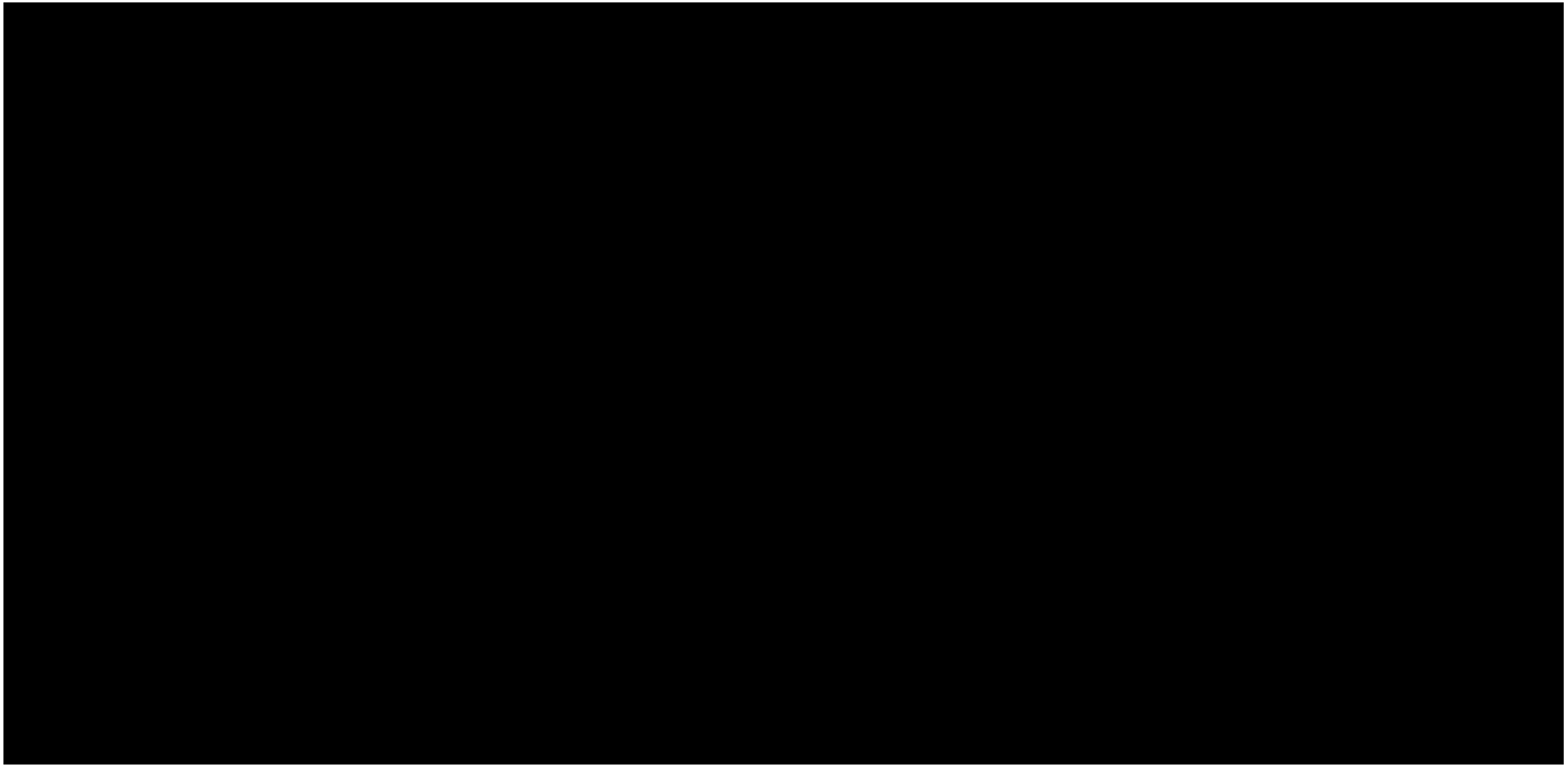
EAG: INA+PAL+FUL PFS curves cross OS curve at ~8.97 years for PFS and ~6.21 years for PFS2
- Company's cap in the model causes kinks in the curves which may not be clinically plausible because:
  - OS curve gradient is steeper than PFS and PFS2 when intersected – implies sharp change in hazard
- Consider this issue is limitation of partitioned survival model structure where survival endpoints are modelled independently, particularly with more than 1 progressed disease health state
- More appropriate to constrain PFS and PFS2 hazards so they cannot fall below mortality hazard estimated from OS curve
- Apply constraint to both trial arms for consistency (even though curves do not cross for PAL+FUL)
- Constraining PFS and PFS2 hazards by mortality hazard shifts tail of survival curve downwards – ensures extrapolations are logically consistent and clinically plausible

See next slides for survival curves

Is the company or EAG approach more appropriate?

Abbreviations: INA: inavolisib; KM: FUL: fulvestrant; OS: overall survival; PAL: palbociclib; PFS: progression-free survival;

Survival curves (company)



Abbreviations: INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; OS: overall survival; PAL: palbociclib; PFS: progression-free survival

Survival curves (EAG)

[redacted]

Abbreviations: INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; OS: overall survival; PAL: palbociclib; PFS: progression-free survival

Key issue: Treatment duration (1/2)

Large

Company: extrapolate TTOT using gamma distribution; EAG align TTOT with PFS distribution (log-logistic) to reflect decreasing toxicity over time

Company: TTOT data from trial used to model treatment duration for both arms

- Use different parametric distribution (gamma) than PFS because ~17% discontinued treatment for non-progression reasons; clinical experts prefer gamma distribution
- Estimate treatment duration separately for each drug (people can discontinue 1 drug and continue others)
- TTOT is capped by PFS in model (as administered until progression or unacceptable toxicity)
- In both arms, KM TTOT curves were similar for each drug – same parametric distribution applied
- Gamma distribution to extrapolate TTOT when 20% people remain at risk, avoiding reliance on tail data

EAG: Separation between TTOT and PFS curves largely driven by discontinuation from toxicity or AEs

- Company state mean TTOT in INA+PAL+FUL was lower (24 months) than mean PFS (32.5 months) because people can stop treatment for many reasons and remain progression-free
- Mean TTOT and PFS estimates are sensitive to curve extrapolations
  - KM estimates for TTOT and PFS at 27 months is similar (~[redacted]% vs ~[redacted]%)
- Company's model implies treatment discontinuation due to toxicity increases over time when progression-free (TTOT and PFS diverge)
- Clinical advice: Most toxicity discontinuations likely occur early, and drug-associated AEs can be well managed – expect negligible discontinuation rate after 2 to 3 years
- Model TTOT for each drug using same distribution as PFS (log-logistic) applied from the start of model

Abbreviations: AE: adverse effects; INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival; TTOT: time to off-treatment

Key issue: Treatment duration (2/2)

Large

Company base case

EAG base case

EAG: Log-logistic has best relative statistical fit for all drugs in both trial arms; gamma has relatively poor fit

- EAG base case still has gap between TTOT and PFS over trial period, but for people remaining PF:
  - EAG base case: Rate of treatment discontinuation due to toxicity expected to decrease over time
  - Company: Rate of treatment discontinuation due to toxicity expected to increase over time

Clinical expert: Excess of hypoglycaemia, stomatitis and dry eyes with using INA+PAL+FUL but low discontinuation rate due to toxicity

How should the rate of treatment discontinuation due to toxicity be modelled to change over time?

Abbreviations: INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; OS: overall survival; PAL: palbociclib; PF(S): progression-free (survival); TTOT: time to off-treatment

Key issue: Efficacy estimation for ABE+FUL and RIB+FUL

Large

Company: Apply NMA HRs for ABE+/RIB+FUL; EAG: Align all comparator efficacy to trial data

Company: Efficacy for ABE+FUL and RIB+FUL comparators modelled by applying PFS and OS HRs from mixed endocrine-resistant NMA to PFS, PFS2, OS curves for INA+PAL+FUL

- Assume PFS2 HR = PFS HR (NMA did not report PFS2)
- Model may overestimate clinical benefit of RIB+FUL or ABE+FUL because people with PIK3CA mutations have poorer outcomes than wild-type when treated with CDK4/6i
- Treatment duration for RIB+FUL and ABE+FUL estimated by applying PFS HRs to PAL and FUL TTOT curves for the INA+PAL+FUL regimen

EAG: Company's base case: Mean survival for ABE+FUL is lower than PAL+FUL or RIB+FUL

  - Undiscounted life years: 2.4 (ABE+FUL); 3.2 (PAL+FUL); 2.9 (RIB+FUL)
  - Reflects NMA → INA+PAL+FUL is more effective vs ABE+FUL than RIB+FUL
- Differences in survival estimates from using trial IPD (PAL+FUL) and NMA HRs (ABE+FUL and RIB+FUL)
- Assume ABE-, PAL-, RIB+FUL have equal efficacy – so match PFS, TTOT, PFS2, OS with PAL+FUL (using INAVO120 results)
- Minimises impact of statistical and modelling issues associated with NMA methods and results

How should the relative efficacy of PAL+FUL with ABE+FUL and RIB+FUL be modelled?

NICE

Abbreviations: ABE: abemaciclib; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; INA: inavolisib; FUL: fulvestrant; IPD: individual patient data; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RIB: ribociclib; TTOT: time to off-treatment

Key issue: Relative dose intensity

Medium

Company: Use trial RDI or assume 100% RDI; EAG: Adjust RDI for dose reductions affecting costs

Company: Apply RDI in the model to account for dose reductions and interruptions on treatment costs

- INA+PAL+FUL and PAL+FUL: Mean RDI sourced from INAVO120
- ABE+FUL: Assume RDI 100% - because 100% RDI assumed in TA725
- RIB+FUL: Assume RDI 100% - because RDI redacted in TA687

EAG: Apply adjusted RDI for INA and PAL to avoid overestimating treatment cost savings, by excluding:

  - INA 9 mg → 6 mg dose reductions (as both doses cost same)
  - All PAL dose reductions (as flat price across tablet strengths)

- 100% RDI for ABE-/RIB+FUL is inappropriate
  - Clinical advice: ABE and RIB have more toxicity than PAL (RDI likely lower)
  - RDI estimates for ABE and RIB from NMA trials is not suitable

Instead, apply RDI from INAVO120 control arm:

  - RIB: Mean unadjusted PAL RDI (all dose changes impact costs): [redacted]
  - ABE: Mean adjusted PAL RDI (only dose interruptions/missed doses impact costs): [redacted]
  - FUL: Use mean FUL RDI: [redacted]

- Likely lower RDI for ABE and RIB than PAL, so treatment costs may be overestimated and incremental costs for INA+PAL+FUL vs ABE-/RIB+ FUL may be underestimated

See appendix for company and EAG RDI assumptions

Which RDI values are most appropriate to use in the model?

Abbreviations: ABE: abemaciclib; INA: inavolisib; FUL: fulvestrant; NMA: network meta-analysis; PAL: palbociclib; RDI: relative dose intensity RIB: ribociclib

*elacestrant eligibility: ≥12 months treatment with CDK4/6i (TA1036)

Medium

Key issue: Subsequent treatment modelling

Company: Vary subsequent treatment by 1st-line; EAG: align distributions with clinical opinion

Company: Subsequent treatment in PD1 and PD2 health states informed by clinical advisory board
→ capecitabine; everolimus + exemestane; elacestrant (ESR1 mutation); paclitaxel; BSC (PD2 only)

			vs INA+PAL+FUL	vs CDK4/6i	Comment
Elacestrant	Company	PD1	[redacted]	[redacted]	Assume fewer have elacestrant after INA+PAL+FUL than CDK4/6i's
		PD2	[redacted]	[redacted]	
	EAG	PD1	[redacted]	[redacted]	Assume distributions only differ if progression is before or after 12 months • If <12 months, elacestrant = 0%
		PD2	[redacted]	[redacted]	
Everolimus + exemestane	Company	PD1	[redacted]	[redacted]	Assume fewer after INA+PAL+FUL than CDK4/6i's because less benefit from further endocrine-based therapy than after a CDK4/6i
		PD2	[redacted]	[redacted]	
	EAG	PD1	[redacted]	[redacted]	Assume distributions only differ if progression is before or after 12 months for PD1 • If <12 months, = [redacted] for PD1
		PD2	[redacted]	[redacted]	

EAG: Fewer progressed in intervention (42%) than control (69%) arm at 12 months in INAVO120 – clinicians expect more elacestrant eligibility* after INA+PAL+FUL than CDK4/6i

- Clinicians expect subsequent endocrine therapy unlikely to vary by 1L (similar across INAVO120 arms)

Which proportions of subsequent treatment distributions are appropriate to apply in the model?

Abbreviations: 1L: 1st-line; BSC: best supportive care; CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; PD: progressed disease

Key issue: Severity modifier

Company and EAG apply 1.2 QALY weighting; sensitive to mean starting age used

Large

Company: 1.2x severity modifier applied for all comparisons vs INA+FUL+PAL
- General population QALYs from INAVO120 baseline characteristics (54 years mean age; 1.8% male)

EAG: Preferences with largest impact on QALY estimates:
  - Assuming ABE+FUL and RIB+FUL efficacies = PAL+FUL
  - Using mapped EQ-5D-3L health state utilities (company use EQ-5D-5L – see appendix)
- Expected general population QALYs are sensitive to starting age – median age for first-line PAL+FUL was 66 years (TA836) and for RIB+FUL was 64 years (TA687)
- Age used should be consistent with evidence used in cost-effectiveness model to estimate QALYs for standard care
  - EAG base case: 54 years of age is appropriate because all treatment efficacies are from INAVO120
  - Company base case: As NMA HRs used to estimate ABE+FUL and RIB+FUL efficacies, the average age of all participants in the network should be used to calculate general population QALYs – but would need information about the relative contribution of each study to treatment effect estimates

See appendix for QALY shortfall calculations

Is a 1.2 QALY weighting appropriate to apply?

Abbreviations: ABE: abemaciclib; INA: inavolisib; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; PAL: palbociclib; QALY: quality-adjusted life year; RIB: ribociclib

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Survival analysis approach	Piecewise approach	Parametric distributions applied from start of model time horizon
PFS/PFS2 extrapolation	Log-normal distribution	Log-logistic distribution
PFS, PFS2, and OS	Cap PFS and PFS2 by OS	Constrain PFS and PFS2 by OS hazards
Treatment duration	Gamma distribution	Log-logistic (same distribution as PFS)
Efficacy and treatment duration ABE+FUL and RIB+FUL	Derived from company network meta-analysis hazard ratios	Assume PFS, PFS2, OS, TTOT are equivalent to PAL+FUL (INAVO12)
Utility	EQ-5D-5L	Mapped EQ-5D-3L
RDI (INA+PLA+FUL)	INAVO120 RDI	Adjusted INAVO120 RDI excluding effect of dose reductions
RDI (ABE+FUL, RIB+FUL)	100% RDI	Apply INAVO120 RDI values
Subsequent treatment	Lower proportion people assumed to have elacestrant as subsequent treatment after INA+PAL+FUL compared with CDK4/6i+FUL	Can only have elacestrant if disease progression is ≥12 months
Severity modifier	x1.2 QALY weighting	x1.2 QALY weighting

NICE Abbreviations: ABE: abemaciclib; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; FUL: fulvestrant; INA: inavolisib; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; QALY: quality-adjusted life year; RDI: relative dose intensity; RIB: ribociclib; TTOT: time to off treatment

Other issues: EAG additional changes

EAG model corrections to company base case	
Generic prices	Use eMIT prices rather than list prices for generic drugs
Drug administration costs	• Inflation of administration cost for subsequent fulvestrant doses inflated from 2019 value in TA816 to 2025 • Complex chemotherapy at first attendance (SB14z NHS reference cost) applied for paclitaxel as there is only 1 drug administration per treatment cycle
Drug acquisition costs	Calculated costs for INA, PAL, ABE, RIB in each weekly model cycle, rather than each 28-day cycle
Probabilistic mean parameter values	Amended sampling method for log-logistic distribution so probabilistic mean parameter values more closely align with deterministic values, ensuring clinically plausible results
Utility	Applied mapped EQ-5D-3L utility values rather than EQ-5D-5L

Does the committee accept the EAG's model corrections?

Abbreviations: ABE: abemaciclib; eMIT: Drugs and pharmaceutical electronic market information tool; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; RIB: ribociclib

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

- Company's fully incremental base case ICERs before and after EAG corrections are above £30,000/QALY
- EAG's fully incremental base case ICERs are substantially above £30,000 per QALY gained

EAG scenarios:

1. Gamma distribution for PFS and PFS2 (INA+PAL+FUL)
2. Generalised gamma distribution for PFS and PFS2 (PAL+FUL)
3. Weibull (INA+PAL+FUL) and Gompertz (PAL+FUL) distribution for OS
4. Include PIK3CA testing costs

NICE

Inavolisib with palbociclib and fulvestrant for treating recurrent hormone receptor-positive HER2-negative PIK3CA-positive advanced breast cancer after adjuvant endocrine treatment

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

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company: No managed access proposal
- If routine commissioning not possible, open to managed access consideration
- Note: Final data cut has been used in the analysis, no further data from INAVO120 trial

Additional considerations

Equality considerations:

- No equality issues raised at scoping or in company submission

Uncaptured benefits:

- **Company:** Clinical and cost-effectiveness of INA is not fully captured:
  - Comparator trials in NMA include people with mixed PIK3CA mutation status – efficacy of ABE+FUL and RIB+FUL in PIK3CA-mutated population may be overestimated in cost-effectiveness model
- **EAG:** NMA results may be biased in favour of CDK4/6i+FUL only if positive PIK3CA mutation status reduces relative efficacy of CDK4/6i+FUL vs FUL
  - Evidence whether PIK3CA mutation status is a treatment effect modifier is inconclusive

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

Abbreviations: ABE: abemaciclib; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; INA: inavolisib; FUL: fulvestrant; NMA: network meta-analysis; PAL: palbociclib; RIB: ribociclib

Inavolisib with palbociclib and fulvestrant for treating recurrent hormone receptor-positive HER2-negative PIK3CA-positive advanced breast cancer after adjuvant endocrine treatment

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

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Key issues

Issue	Slide	Appendix	ICER impact
1. Generalisability of INAVO120 results to NHS	11	41, 42, 43	Unknown
2. Indirect treatment comparison results	13, 14	44, 45	Unknown
3. PFS and PFS2 parametric extrapolation modelling	17, 18, 19	46, 49	Medium
4. Applying PFS and PFS2 distributions	20	-	Large
5. Consistency of PFS, PFS2, OS survival modelling	21, 22, 23	-	Small
6. Treatment duration modelling	24, 25	-	Large
7. Modelling efficacy of ABE+FUL and RIB+FUL comparators	26	-	Large
8. Relative dose intensity multipliers applied in the model	27	53	Medium
9. Subsequent treatment modelling	28	54	Medium
10. Age used in severity modifier	29	55	Large

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Abbreviations: ABE: abemaciclib; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; RIB: ribociclib

Inavolisib with palbociclib and fulvestrant for treating recurrent hormone receptor-positive HER2-negative PIK3CA-positive advanced breast cancer after adjuvant endocrine treatment

Supplementary appendix

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Relevant technology appraisals

TA421	Everolimus with exemestane for advanced breast cancer after endocrine therapy
TA687	Ribociclib with fulvestrant for hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA725	Abemaciclib with fulvestrant for hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA810	Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence
TA816	Alpelisib with fulvestrant for hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer
TA836	Palbociclib with fulvestrant for hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA1036	Elacestrant for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment
TA1063	Capivasertib with fulvestrant for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment
TA1086	Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive HER2-negative early breast cancer at high risk of recurrence

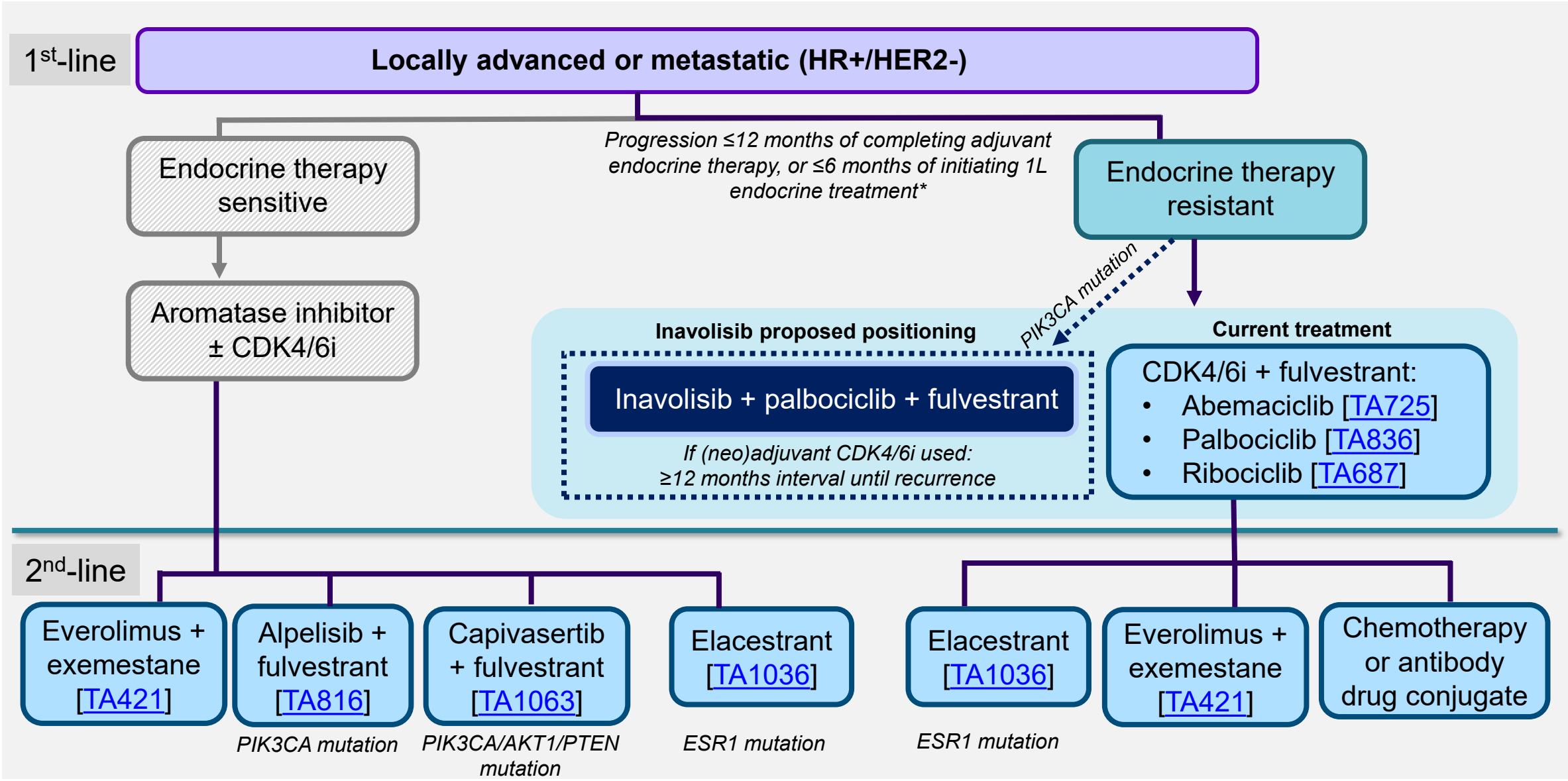
Abbreviations: ESR1: oestrogen receptor 1; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Decision problem

	Final scope	Company	EAG comments
Population	HR-positive HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer that has progressed ≤12 months after completing adjuvant endocrine therapy		Unclear if trial results will be representative of NHS in the future based on proportion with prior CDK4/6i
Intervention	INA+PAL+FUL		-
Comparators	CDK 4/6 inhibitors with fulvestrant: • RIB+FUL • ABE+FUL • PAL+FUL		Direct evidence from INAVO120 for INA+PAL+FUL vs PBO+PAL+FUL; PFS and OS NMAs for comparison with RIB+FUL and ABE+FUL
Outcomes	• OS • PFS • response rate • Duration of response • AEs of treatment • HRQoL	Include time to end of next-line treatment (PFS2 proxy) and TTOT to inform model	No clinical effectiveness results for TTOT from company; TTOT not a pre-specified outcome in INAVO120

Abbreviations: ABE: abemaciclib; AE: adverse effects; CDK4/6i: cyclin-dependent 4 and 6 inhibitor; FUL: fulvestrant; HER2: human epidermal growth factor receptor 2; HR: hormone-receptor; HRQoL: health-related quality of life; INA: inavolisib; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RIB: ribociclib; TTOT: time to off treatment

Treatment pathway – 1st-line+ locally advanced/metastatic



Abbreviations: ABE: abemaciclib; AI: aromatase inhibitor; CDK: Cyclin-Dependent Kinase; CT: computed tomography; ESR1: oestrogen receptor 1; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

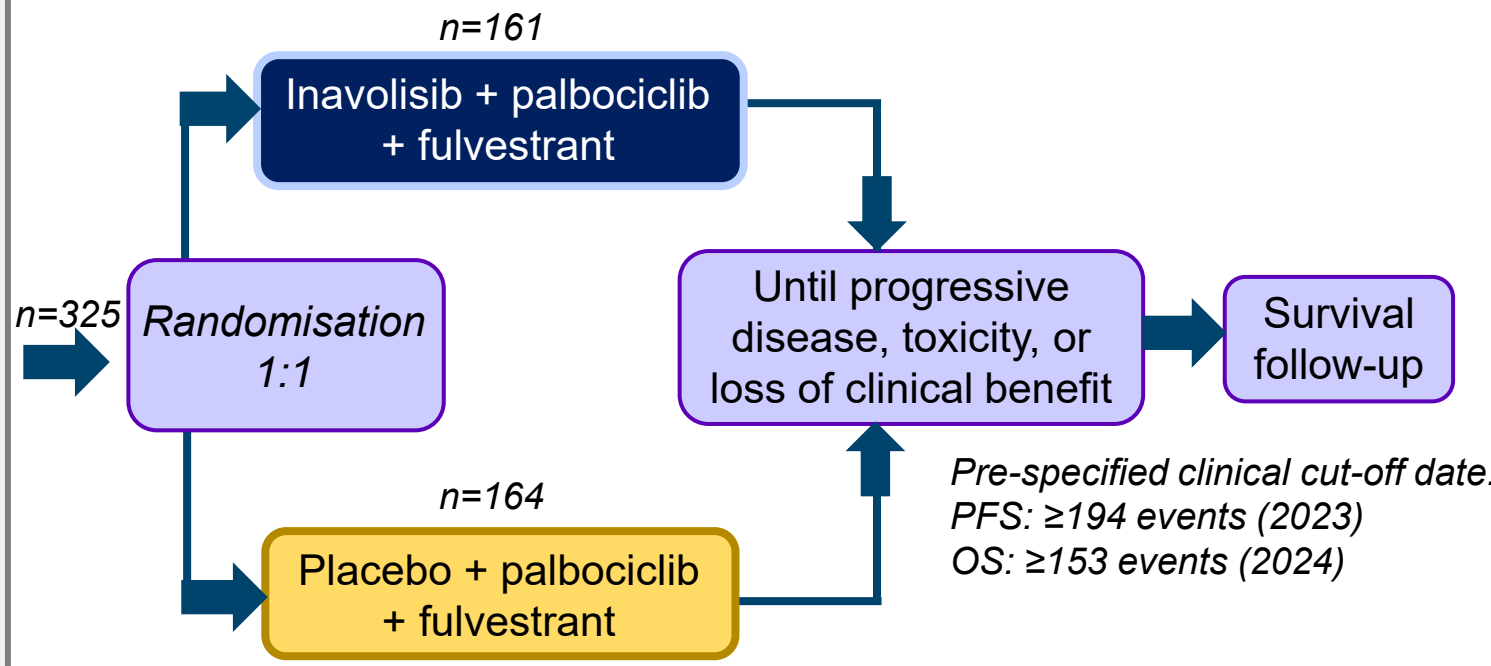
Key clinical trial – INAVO120

INAVO120 – primary source of direct clinical effectiveness evidence for INA+PAL+FUL vs PBO+PAL+FUL

Inclusion criteria

- ≥18 years of age
- Locally advanced or metastatic, ER+ and/or PR+, HER2-, PIK3CA-mutated, adenocarcinoma not amenable to surgical or radiation therapy with curative intent
- No prior systemic therapy for locally advanced/metastatic tumour
- LHRH agonist therapy before and during study if pre-/peri- menopausal
- Progression during adjuvant endocrine therapy or ≤12 months of completing adjuvant endocrine therapy with AI or tamoxifen
  - If include (neo)adjuvant CDK4/6, progression must be >12 months since completing CDK4/6i part of treatment
- Fasting glucose <126 mg/dL and HbA1c <6.0%

Phase 3, multicentre, double-blind, randomised, placebo-controlled
123 centres across 28 countries (UK: n=5)



- **Primary outcome:** PFS
- **Secondary outcomes:** OS, objective response (OR) rate, best OR, clinical benefit rate, time to confirmed deterioration (TTCD) in pain, TTCD in role functioning, TTCD in global health status/QoL

Abbreviations: AI: aromatase inhibitor; CDK4/6i: cyclin-dependent 4 and 6 inhibitor; dL: decilitre; FUL: fulvestrant; HbA1c: haemoglobin A1C; HER2: human epidermal growth factor receptor 2; INA: inavolisib; LHRH: luteinising hormone-releasing hormone; mg: milligram; OS: overall survival; PAL: palbociclib; PBO: placebo; PFS: progression-free survival; QoL: quality of life

INAVO120 baseline characteristics

Baseline characteristic		INA+PAL+FUL (n=161)	PBO+PAL+FUL (n=164)
Female, n (%)		156 (96.9)	163 (99.4)
Age, mean years (SD)		53.8 (10.9)	54.1 (11.2)
Race, n (%)	Asian	61 (37.9)	63 (38.4)
	Black or African American	1 (0.6)	1 (0.6)
	White	94 (58.4)	97 (59.1)
Weight (kg), mean (SD)		66.2 (15.9)	65.4 (14.3)
ECOG PS, n (%)	0; 1	100 (62.1); 60 (37.3)	106 (64.6); 58 (35.4)
Breast cancer stage, n (%)	Locally advanced; Metastatic	1 (0.6); 160 (99.4)	2 (1.2); 162 (98.8)
Organ sites, n (%)	1; 2; ≥3	21 (13); 58 (36); 82 (50.9)	32 (19.5); 46 (28); 86 (52.4)
Prior (neo)-adjuvant treatment	Chemotherapy	132 (82)	137 (83.5)
	CDK4/6i	2 (1.2)	1 (0.6)
	Endocrine therapy • Aromatase inhibitor (AI) • Tamoxifen • AI and tamoxifen	160 (99.4) • 60 (37.3) • 82 (50.9) • 18 (11.2)	163 (99.4) • 71 (43.3) • 73 (44.5) • 19 (11.6)

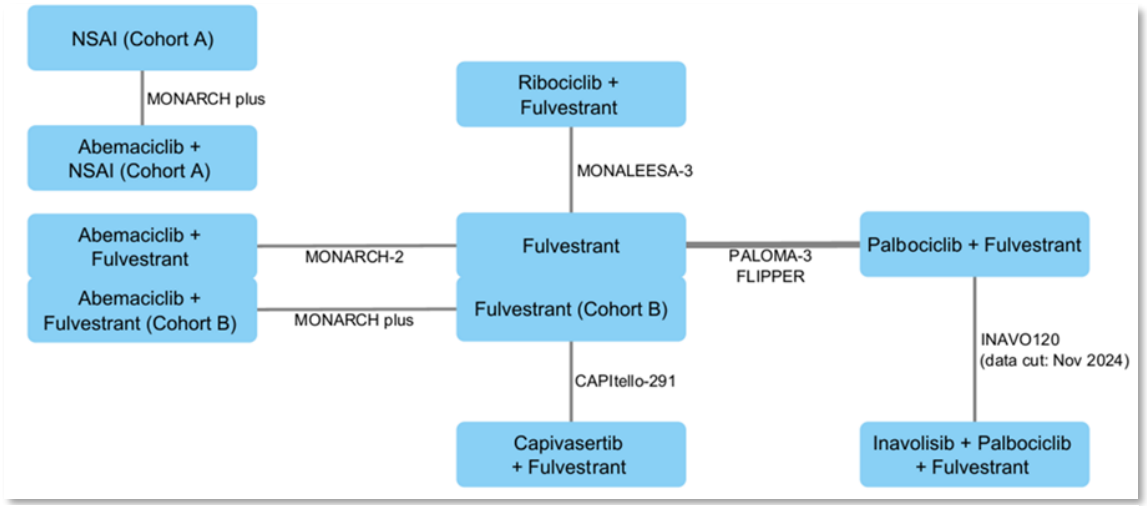
NICE Abbreviations: CDK4/6i: cyclin-dependent 4 and 6 inhibitor; ECOG PS: eastern cooperative oncology group performance score; FUL: fulvestrant; INA: inavolisib; PAL: palbociclib; PBO: placebo;

Indirect treatment comparison overview

ITC overview and trial characteristics

Overview of studies in network meta-analysis

- All studies are multi-centre, international, randomised controlled trials
- FLIPPER is phase 2; all other studies are phase 3



*Company consider this study as having no prior treatment

Network study	Intervention	PIK3CA mutation+ criteria? (mutation positive)	Endocrine-resistant?	Prior treatment?
INAVO120 (n=325)	INA+PAL+FUL	Yes (100%)	Yes	No
MONARCH-2 (n=669)	ABE+FUL	No (43.8%)	Yes	Mixed (untreated subgroup)
MONARCH plus (n=157)	ABE+FUL	No (NR)	Yes (subgroup)	Mixed (>75% untreated)*
FLIPPER (n=189)	PAL+FUL	No (NR)	No	No
PALOMA-3 (n=521)	PAL+FUL	No (16.6%)	Yes	Mixed (untreated subgroup)
MONALEESA-3 (n=726)	RIB+FUL	No (NR)	Mixed	Mixed (untreated subgroup)
CAPItello-291 (n=708)	CAP+FUL	No (36.4%)	Yes	Mixed (untreated subgroup)

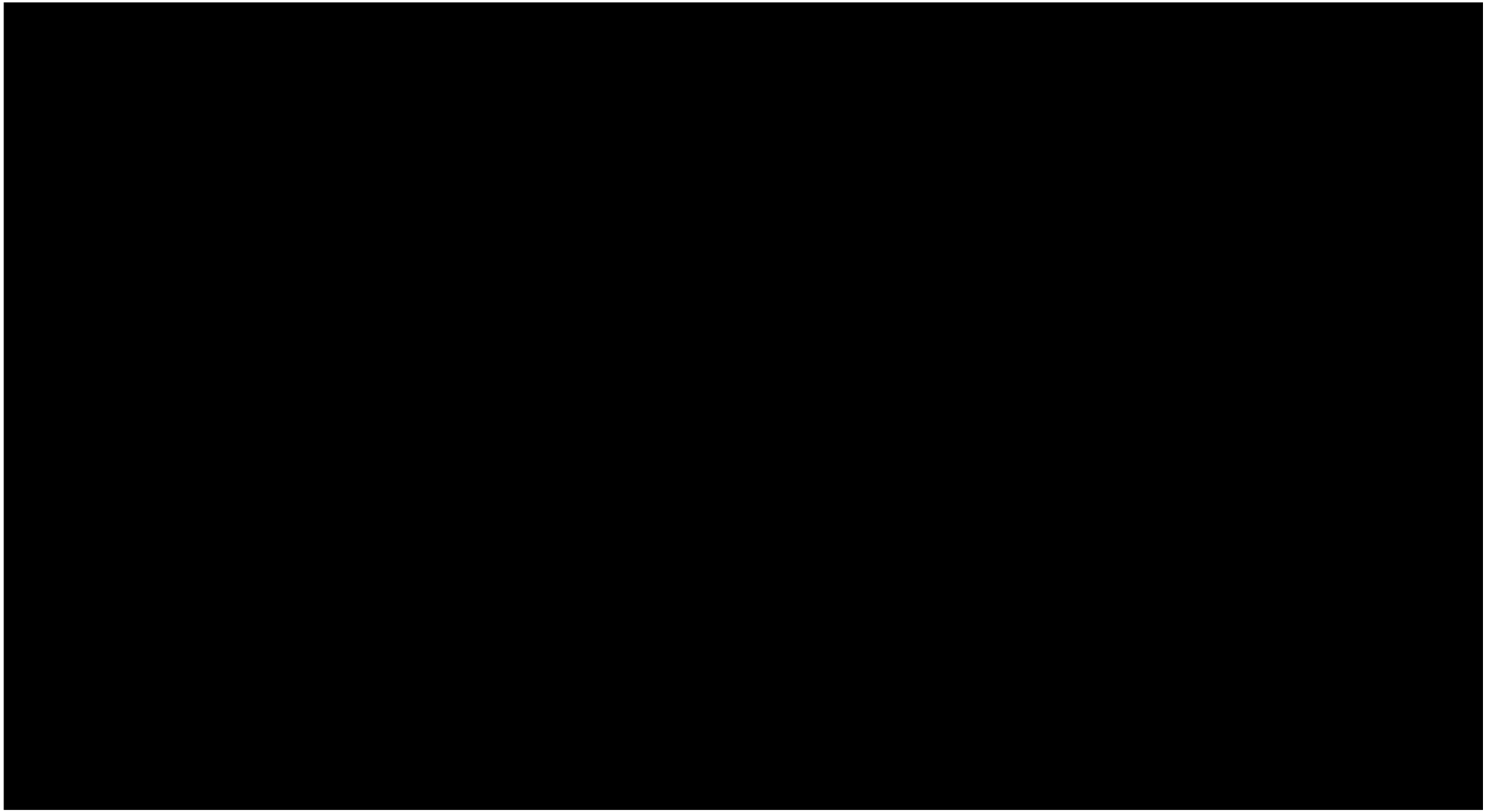
Abbreviations: ABE: abemaciclib; CAP: capivasertib; INA: inavolisib; FUL: fulvestrant; NR: not reported; PAL: palbociclib; RIB; ribociclib

Network meta-analysis baseline characteristics

Differences in baseline characteristics across trials in network meta-analysis (potentially treatment effect modifiers)

Characteristic	Trials	EAG comment
Median age	3	Lower in INAVO120 (53 years) than MONARCH plus (60 years) and FLIPPER (64 years)
Proportion Asian	2	Large variation from 38% (INAVO120) to 90% (MONARCH plus)
Proportion with visceral disease	4	Range from 56% (MONARCH-2) to 82% (INAVO120)
Proportion post-menopausal status	3	Range 57% (INAVO120) to 100% (MONARCH plus and FLIPPER)
Proportion with ECOG PS 0	2	Range from 52% (FLIPPER) to 65% (INAVO120)
Proportion with primary resistance to endocrine therapy	3	27% (MONARCH-2) to 36% (MONARCH plus)
Prior (neo)adjuvant) treatment	2-4	Chemotherapy: Lower in FLIPPER (~45%) than INAVO120 and MONARCH plus (~85%) Endocrine therapy: Lower in FLIPPER (~55%) than INAVO120 and MONARCH plus (>90%) Aromatase inhibitor: Lower in INAVO120 (<45%) than MONARCH plus (~80%)

PFS KM+ log-normal fit for INA+PAL+FUL vs PAL+FUL



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Abbreviations: INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PBO: placebo

Visual fit: PFS extrapolation for INA+PAL+FUL

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

Visual fit: PFS extrapolation for PAL+FUL

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

Proxy to PFS2 KM+ log-normal fit for INA+PAL+FUL vs PAL+FUL

Abbreviations: INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PBO: placebo; PFS: progression-free survival

Visual fit: Proxy to PFS2 extrapolation for INA+PAL+FUL

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; INA: inavolisib; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

Visual fit: Proxy to PFS2 extrapolation for PAL+FUL

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; FUL: fulvestrant; PAL: palbociclib; PFS: progression-free survival

Utility

Company: EQ-5D-5L utility from INAVO120; EAG: Utility mapped to EQ-5D-3L

Company: EQ-5D-5L used to collate HRQoL data in INAVO120

- EQ-5D-5L data pooled across trial arms to estimate mean health state utilities
- Progressed disease-2 health state: Use value from Lloyd 2006 – only small number of people in INAVO120 provide HRQoL data and trial utility was higher than other values found in literature
- Health state utility adjusted to account for decrease in HRQoL occurring with age (Ara and Brazier 2010)

EAG: EQ-5D-5L value set does not align with NICE reference case

- Company provided mapped EQ-5D-3L utility values but progression-free utility < progressed-disease utility across all analyses (assume typo)
- Using mapped EQ-5D-3L utility increases ICER

Model health state	Company		EAG	
	Utility	Source	Utility	Source
Progression-free	0.849	EQ-5D-5L data pooled across treatment arms in INAVO120	0.787	Pooled INAVO120 EQ-5D-5L data mapped to EQ-5D-3L
Progressed disease-1	0.777		0.703	
Progressed disease-2	0.505	Lloyd, 2006	0.505	Lloyd, 2006

Abbreviations: HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio

Relative dose intensity

Treatment regimen	Drug	Company		EAG	
		RDI	Source	RDI	Source
INA+PAL+FUL	INA	[redacted]	INAVO120	[redacted]	INAVO120 intervention arm excluding single dose reductions
	PAL	[redacted]		[redacted]	
	FUL	[redacted]		[redacted]	INAVO120 intervention arm
PAL+FUL	PAL	[redacted]	INAVO120	[redacted]	INAVO120 control arm excluding al dose reductions
	FUL	[redacted]		[redacted]	INAVO120 control arm
ABE+FUL	ABE	100%	Assumption	[redacted]	Assumption: Equivalent to adjusted INAVO120 PAL RDI (control arm)
	FUL	100%	Assumption	[redacted]	Assumption: Equivalent to INAVO120 FUL RDI (control arm)
RIB+FUL	RIB	100%	Assumption	[redacted]	Assumption: Equivalent to unadjusted INAVO PAL RDI (control arm)
	FUL	100%	Assumption	[redacted]	Assumption: Equivalent to INAVO120 FUL RDI (control arm)

Abbreviations: ABE: abemaciclib; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; RDI: relative dose intensity RIB: ribociclib

Subsequent treatment modelling

EAG1: For progression <12 months; EAG2: For progression ≥12 months

	1st- line treatment regimen											
	INA+PAL+FUL			PAL+FUL			ABE+FUL			RIB+FUL		
	Company	EAG1	EAG2	Company	EAG1	EAG2	Company	EAG1	EAG2	Company	EAG1	EAG2
PD1												
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus+ exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elacestrant	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD2												
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus+ exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elacestrant	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; BSC: best supportive care; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; PD: progressed disease; RIB: ribociclib

Severity modifier

x1.2: 12-18
x1.7: ≥18

x1.2: 85%-95%
x1.7: ≥95%

	Treatment	Expected QALYs		Absolute shortfall	Proportional shortfall	QALY weighting
		General population	With condition			
Company base case	PAL+FUL	14.8	[redacted]	[redacted]	[redacted]	1.2
	ABE+FUL		[redacted]	[redacted]	[redacted]	1.2
	RIB+FUL		[redacted]	[redacted]	[redacted]	1.2
EAG base case	PAL+FUL	14.8	[redacted]	[redacted]	[redacted]	1.2
	ABE+FUL		[redacted]	[redacted]	[redacted]	1.2
	RIB+FUL		[redacted]	[redacted]	[redacted]	1.2
EAG scenario (age: 64 years)	PAL+FUL	11.5	[redacted]	[redacted]	[redacted]	1
	ABE+FUL		[redacted]	[redacted]	[redacted]	1
	RIB+FUL		[redacted]	[redacted]	[redacted]	1
EAG scenario (age: 66 years)	PAL+FUL	10.8	[redacted]	[redacted]	[redacted]	1
	ABE+FUL		[redacted]	[redacted]	[redacted]	1
	RIB+FUL		[redacted]	[redacted]	[redacted]	1

Abbreviations: ABE: abemaciclib; BSC: best supportive care; INA: inavolisib; FUL: fulvestrant; PAL: palbociclib; QALY: quality-adjusted life year; RIB: ribociclib