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NICE National Institute for Health and Care Excellence

Palbociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer

Lead team presentation

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ERG: LRiG

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Company: Pfizer

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Key clinical issues

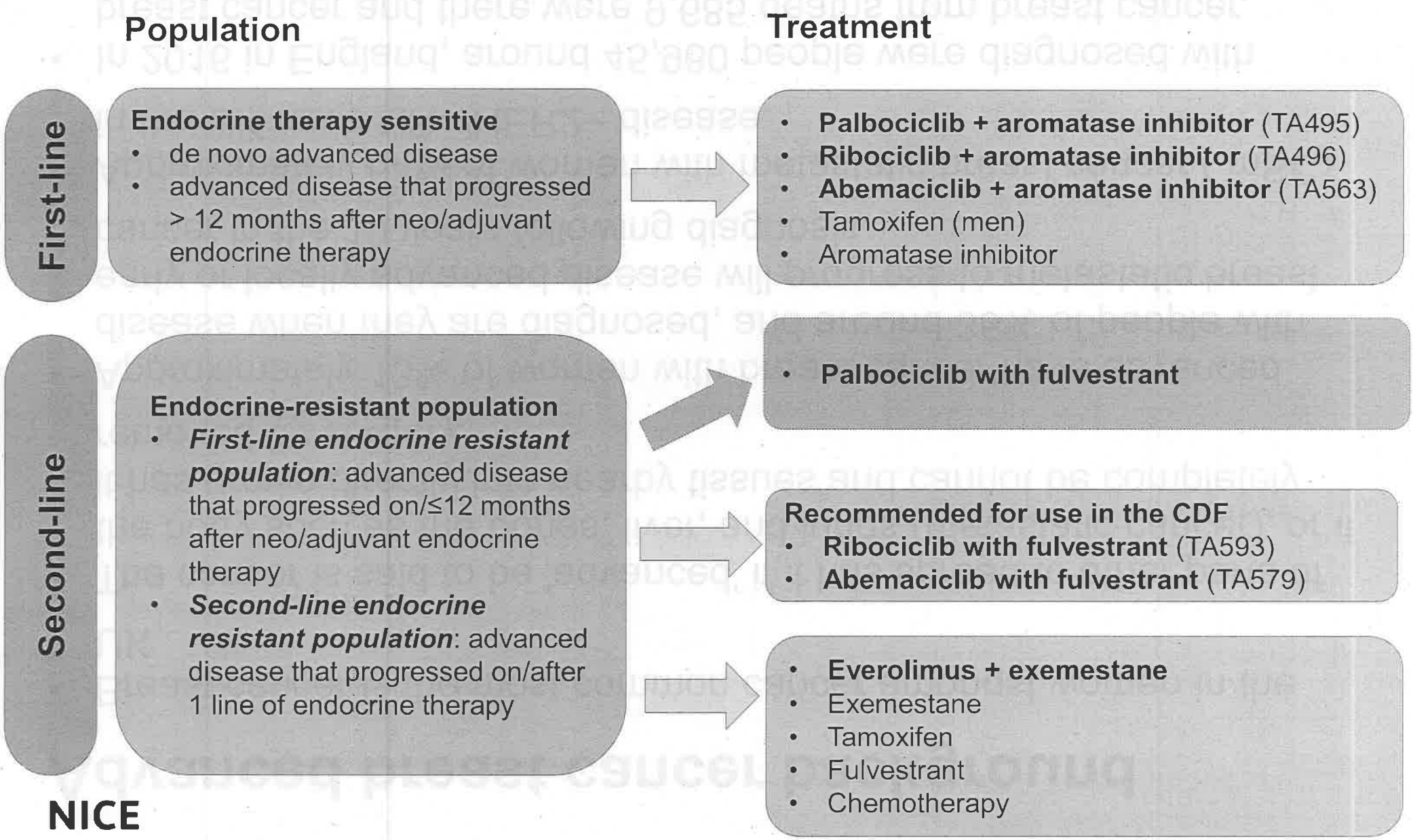
- Is palbociclib plus fulvestrant likely to be similar in efficacy to other CDK 4/6 inhibitors plus fulvestrant combinations?
- How would this treatment be used in the NHS?
- The trial included [redacted] of patients who had already received chemotherapy for advanced disease, how does this relate to how it might be used in clinical practice? Would a subgroup excluding these be appropriate?
- Exemestane plus everolimus (EE) was considered the most appropriate comparator and an indirect comparison was carried out with fractional polynomial NMA by the company, is this reasonable?
- The ERG considered this unreliable, and used the placebo plus fulvestrant arm from the trial for PFS, and the pooled data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms for OS, as a proxy for EE efficacy (suggesting that EE would be no worse than that estimate), and the trial data was more reliable than the NMA.
- Will there be further follow up OS data available?

Advanced breast cancer background

- Breast cancer is the most common cancer amongst women in the UK
- The cancer is said to be 'advanced' if it has spread to other parts of the body such as the bones, liver, and lungs (metastatic cancer), or if it has grown directly into nearby tissues and cannot be completely removed by surgery.
- Approximately 13% of women with breast cancer have advanced disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.
- Approximately 64% of women with metastatic breast cancer (mBC) in the UK have HR+/HER2− disease.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer and there were 9,685 deaths from breast cancer.

Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Treatment pathway



NICE

Palbociclib (Ibrance, Pfizer)

- Selective cyclin-dependent-kinase 4 and 6 (CDK4/6) inhibitor. When either of these two proteins are activated they can cause the cancer cells to grow and divide too quickly.

Marketing authorisation November 2016	…is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (mBC): • in combination with an aromatase inhibitor*; • **in combination with fulvestrant in women who have received prior endocrine therapy** In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
Administration	**Palbociclib:** 125 mg oral tablet once daily for 21 consecutive days followed by 7 days off treatment . **Fulvestrant:** 500 mg intramuscular injections on day 1 of each cycle (with an additional dose on day 15 of cycle 1 only).

NICE * palbociclib plus aromatase inhibitor previously appraised by NICE and recommended in routine commissioning.

Decision problem

	Final scope	Company
Population	Palbociclib (PAL) in combination with fulvestrant (FUL), in women with disease that progressed during or soon after completing the endocrine therapy they received in the (neo)adjuvant or advanced/metastatic setting.	Same as NICE scope
Intervention	Palbociclib in combination with fulvestrant (PAL + FUL)	Same as NICE scope
Comparators	• Fulvestrant monotherapy • Everolimus and exemestane (EE) • Exemestane • Tamoxifen • Chemotherapy	• Everolimus plus exemestane (EE)
Outcomes	PFS,OS, RR, AE, HRQoL	Same as NICE scope

Company: EE is the most relevant comparator in the endocrine resistant population. This opinion aligned with committee conclusions in recent appraisals for ribociclib (TA593) and abemaciclib (TA579) with fulvestrant for treating HR-positive, HER2-negative advanced breast cancer after endocrine therapy.

ERG: The company considers that EE is the treatment most commonly used in clinical practice which has been confirmed by clinical advice to ERG

Patient and carer perspectives

- Diagnosis of incurable metastatic breast cancer is difficult to accept
- Huge impact on mental and physical health, and Quality of Life
- Main advantages of this treatment:
  "Negligible"major side effects; improved patient choice; increased PFS; could delay starting systemic chemotherapy; 1 pill a day; 21 day cycle
- Disadvantages (which may be outweighed by increased PFS) include:
  -Fulvestrant administered by injection requiring hospital/ GP visits
  -Potential side effects (neutropenia, fatigue, nausea, infections & anaemia)
- "It has caused some of my metastases to disappear radiologically… I have not had to alter my lifestyle or cut down on my activities while on this treatment… I feel desperately sorry for those women …who will not have had access to these benefits" *(as treatment not currently available on NHS)*

NHS England comments

- NHS England considers the 3 CDK 4/6 inhibitors to be equally efficacious. NICE has recommended for routine commissioning all 3 CDK 4/6 inhibitors when used in combination with an aromatase inhibitor. NICE has recommended abemaciclib plus fulvestrant and ribociclib plus fulvestrant to the CDF. NHS England considers that there is a strong case for palbociclib plus fulvestrant also being recommended to the CDF if there is a plausible cost effective ICER on which to base a CDF recommendation on.
- NHS England notes that a further planned interim analysis is due in [redacted] and the final analysis is due in [redacted].

Clinical evidence: PALOMA-3

Design	Phase III, multi-centre, placebo-controlled, randomised, double-blinded (n=511)
Location	International: 144 sites & 17 countries; [redacted]
Population	Adult women of any menopausal status, with HR-positive, HER2-negative unresectable or metastatic advanced breast cancer, whose disease progressed during or soon after completion of prior endocrine therapy received in the (neo)adjuvant or advanced setting
Intervention	Palbociclib in combination with fulvestrant (n=347)
Comparator	Placebo in combination with fulvestrant (n=174)
Outcomes	**Primary: Investigator-assessed PFS** **Secondary:** OS, RRs (OR,CBR, DoR), TEAE, EORTC QLQ-C30, EQ-5D-5L

Abbreviations: RR: response rate, OR: objective response, CBR: clinical benefit response, DoR: duration of response, TEAE: treatment emergent adverse events

PALOMA-3: selected baseline characteristics

Baseline characteristics	ERG comments on trial baseline characteristics comparison with clinical practice in England and Wales
Age	Median age 56-57 years. Most people (75.2%) aged <65 years which is a higher proportion than proportion of patients aged <65 years in clinical practice (51.7%).
Menopausal status	Postmenopausal proportion 79.3% similar to expected proportion in clinical practice in UK
Disease at presentation	All patients had advanced cancer (locally advanced: 14.2% or metastatic: 85.8%). [redacted] proportion of patients had Stage IV disease at initial diagnosis [redacted] than typically seen in clinical practice in England (5%)
Prior chemotherapy	40.9% had received neoadjuvant chemotherapy 34.0%. had received chemotherapy for advanced disease* [redacted] received two or more regimens prior to trial entry. Purpose of the most recent treatment was more often for treating advanced disease (77.9%) than early disease (21.9%). *Not uncommon for endocrine resistant disease to receive chemotherapy for advanced disease in clinical practice.

*unlike trials for abemaciclib plus FUL (MONARCH 2) and ribociclib plus FUL (MONALEESA 3)

PALOMA-3 results

- Results for investigator assessed PFS (primary outcome) from 23 Oct 2015 data-cut
- Results for OS and time to subsequent chemotherapy from latest data-cut of 13th April 2018

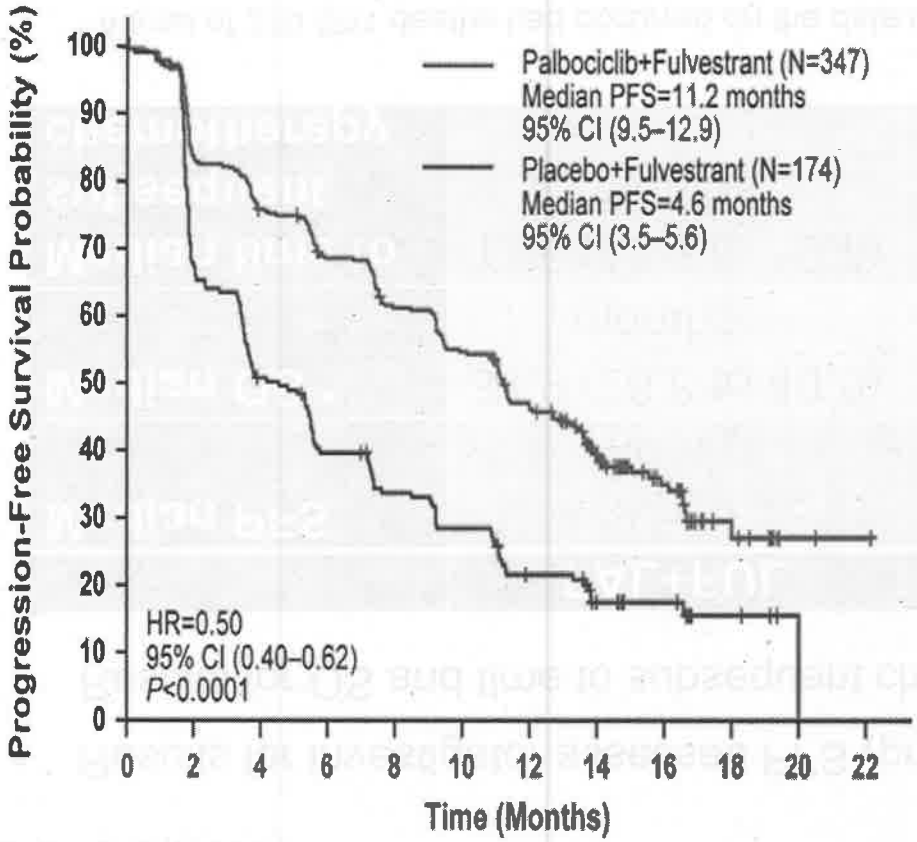
	PAL+FUL	Placebo+ FUL	Effect estimate
Median PFS	11.2 (9.5 to 12.9) months	4.6 (3.5 to 5.6) months	HR 0.497 (95% CI 0.398 to 0.620)
Median OS *	34.9 (28.8 to 40.0) months	28.0 (23.6 to 34.6) months	HR 0.81 (95% CI 0.64 to 1.03)
Median time to subsequent chemotherapy	17.6 (15.2 to 19.7) months	8.8 (7.3 to 12.7) months	HR 0.58 (95% CI 0.47 TO 0.73)

* A total of 310 /511 deaths had occurred on the data cut of 13 April 2018, permitting the planned final analysis of OS

PALOMA-3 Kaplan-Meier data

PFS:

intention to treat trial population (23 Oct 2015 data-cut)

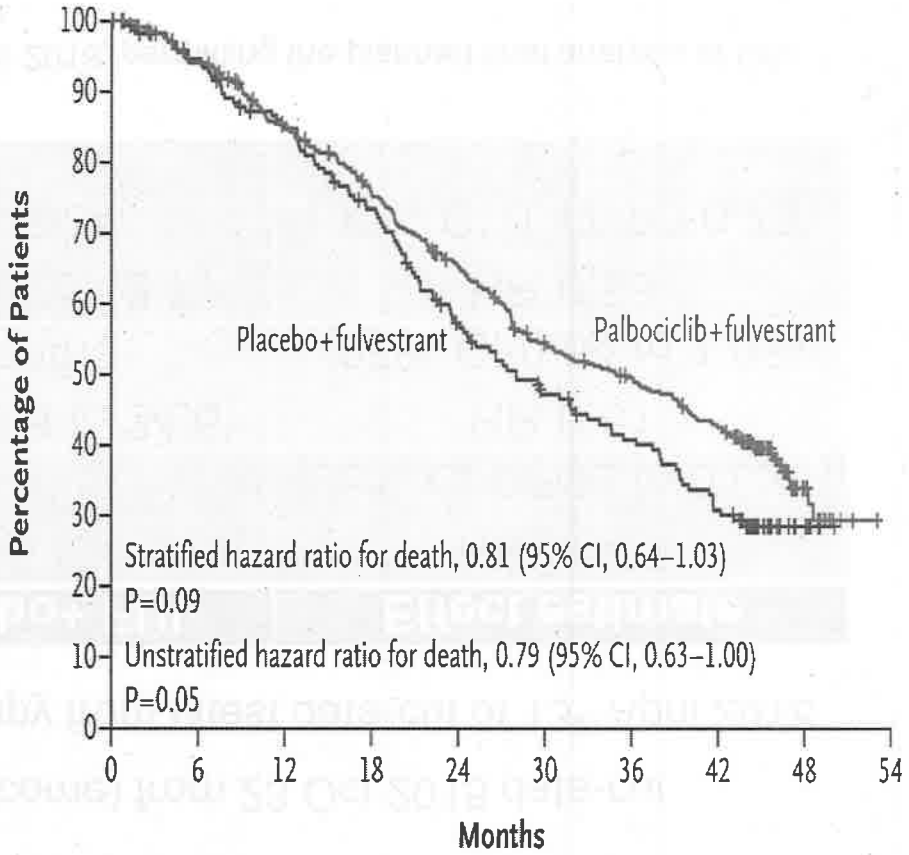


Number of patients at risk

PAL+FUL	347	276	245	215	189	168	137	69	38	12	2	1
PBO+FUL	174	112	83	62	51	43	29	15	11	4	1	

OS:

Intention to treat trial population(13 April 2018 data-cut)



No. at Risk

Palbociclib+fulvestrant	347	321	286	247	209	165	148	126	17	—
Placebo+fulvestrant	174	155	135	115	86	68	57	43	7	—

Adverse events (AE)

PALOMA-3 trial

- 49.8% neutropenia in the PAL + FUL arm, 0% in the placebo plus FUL arm
- Proportions of patients experiencing a serious AE were [redacted]
- Frequency of treatment-related Grade ≥3 AEs was [redacted] and treatment discontinuation [redacted] in PAL+ FUL arm of PALOMA-3
- [redacted] treatment-related deaths [redacted]

Adverse events from BOLERO-2 for people treated with everolimus plus exemestane

- Frequencies of treatment-related Grade ≥3 AEs were 40.9% and treatment discontinuation 29.0%. Most common Grade ≥3 treatment-related AE was pneumonitis (5.6%) and stomatitis (2.7%)
- AE-related deaths reported to be 1.7%

ERG: treatment discontinuation from PAL + FUL arm of PALOMA-3 was much lower than from the EE arm of BOLERO-2. Agrees that PAL + FUL is generally well-tolerated and resulted in very few permanent treatment discontinuations

Key issue 1: Generalisability of trial results to clinical practice in the NHS (1)

- Around [redacted] of the population in PALOMA-3 had previously been treated with chemotherapy in the advanced setting.

Response from engagement

Clinical expert:

- Substantial evidence now that CDK4/6 inhibitors improve OS. Use in 1st line in advanced setting will increase. For people who relapse on endocrine therapy or who progress on 1st line endocrine therapy alone, CDK4/6 inhibitor and FUL will be the standard of care (SoC) for these patients.

Company:

- 40-50% of patients receive chemotherapy as 1st line metastatic treatment in UK clinical practice. PALOMA-3 results show clinical benefit for these patients from PAL+FUL after chemotherapy. There is current unmet need for patients previously treated with chemotherapy upfront for advanced disease that cannot access treatment with a CDK4/6 inhibitor to delay further lines of chemotherapy.
- This sub-group likely to diminish over the next 2-3 years as number of people who receive chemotherapy 1st line reduces and use of CDK 4/6 inhibitors is established as first line SoC. NHS population will match more closely with chemotherapy-naïve sub-group in PALOMA-3

CDF clinical lead:

- Exclusion of 34% of people who had already received chemotherapy and patients who had failed 2 or more hormonal therapies for treatment of their advanced disease would reduce patient numbers and would count as post hoc manipulations of data.

Key issue 1: Clinical results of the ITT and chemotherapy-naïve populations (2)

	PAL + FUL	Placebo+ FUL	Effect estimate
Median PFS (ITT population)	11.2 (9.5 to 12.9) months	4.6 (3.5 to 5.6) months	HR 0.497 (95% CI 0.398 to 0.620)
Median PFS (No previous chemotherapy)	[redacted]	[redacted]	[redacted]
Median OS (ITT population)	34.9 (28.8 to 40.0) months	28.0 (23.6 to 34.6) months	HR 0.81 (95% CI 0.64 to 1.03)
Median OS (No previous chemotherapy)	[redacted]	[redacted]	[redacted]

ITT population
PAL + FUL(n=347)
PAL + FUL(n=174)

Chemotherapy naïve subgroup
Placebo+ FUL (n=[redacted])
Placebo + FUL(n=[redacted])

- Chemotherapy-naïve subgroup analysis includes people who have never received chemotherapy in the adjuvant or neoadjuvant and/or metastatic setting from PALOMA-3.

Key issue 1: Generalisability of trial population to clinical practice in the NHS (3)

ERG:

- Patient population in PALOMA-3 is representative of people who are currently likely to be treated with PAL + FUL in clinical practice in England and Wales.

Technical team:

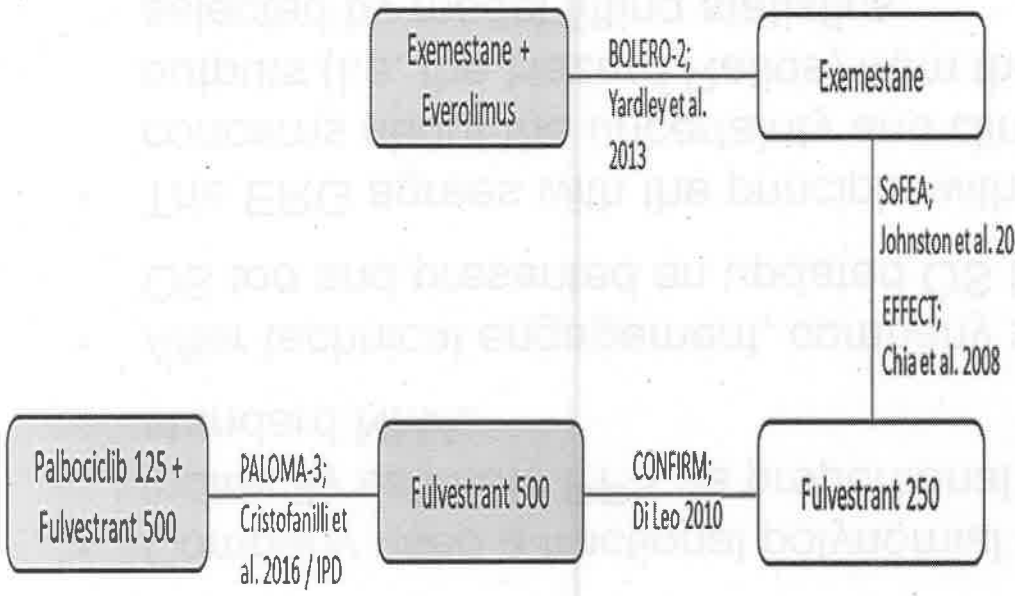
- It would seem that in the future, patients who have not had chemotherapy in the advanced setting, which is approximately 2/3 of the PALOMA-3 population may be more applicable to clinical practice in the NHS. However the company were unable to produce results for this population for the purpose of decision-making, only a population excluding all people who had had chemotherapy either in the early, or advanced setting.

⊙ *Should clinical results for the overall ITT population or the chemotherapy-naïve subpopulation from PALOMA-3 be used in analyses for decision-making?*

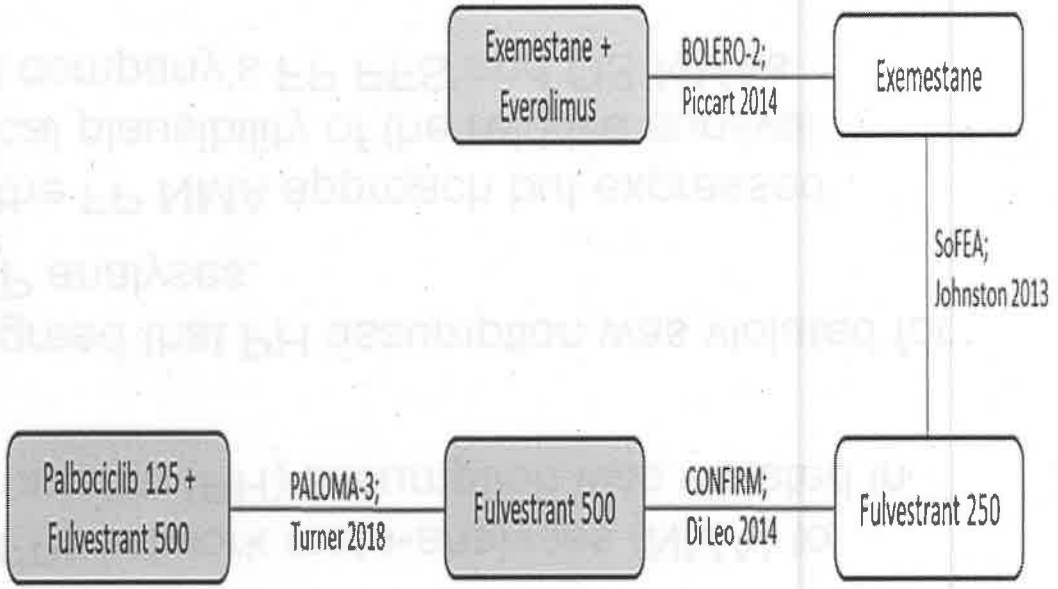
Key issue 2: NMA versus ERG proxy approach (1)

Company's indirect treatment comparisons(ITC) for comparison with EE

Network diagram for PFS



Network diagram for OS



Key issue 2: NMA versus ERG proxy approach (2)

- Company used a fractional polynomial (FP) network meta-analyses (NMA) to indirectly estimate PFS as proportional hazards (PH) assumption was violated in standard NMA.
- After technical engagement, company agreed that PH assumption was violated for OS too and presented an updated OS FP analyses.
- The ERG agrees with the principle with the FP NMA approach but expressed concerns about the uncertainty and clinical plausibility of the relative survival outputs (i.e. the Hazard Ratios) from the company's FP PFS and OS NMAs selected by model fitting statistics.
- Due to these concerns and the variability of results produced by the company's different FP PFS and OS NMAs, the ERG was unable to confidently select suitable FP models for each NMA.
- ERG instead used the PFS data from the placebo plus fulvestrant arm, and the OS data pooled from the PAL plus FUL and placebo plus FUL arms from PALOMA 3 to generate lower bound estimates of the clinical effectiveness of EE

Key issue 2: NMA versus ERG proxy approach (3)

Response from engagement:

Clinical expert:

- Likely that EE has slightly longer PFS than FUL monotherapy from cross-study comparisons

Company:

- Efficacy of EE compared to FUL has never been assessed in head to head studies. 1 study comparing EE plus FUL with FUL alone showed superiority of the combination treatment Without head to head data, PFS and OS outputs are uncertain.
- Everolimus and FUL are different drugs, with different side effect profiles. Assuming outcomes for EE and FUL to be same have no basis on clinical assumptions of the way the drugs are used.
- An ITC using clinical data for EE from BOLERO-2 to estimate the relative clinical effectiveness of PAL + FUL with EE is therefore important.

CDF clinical Lead:

- NHS England does not agree with ERG position of using the outcomes of fulvestrant monotherapy as being a proxy for those of EE. Clinicians consider EE to be more efficacious than fulvestrant monotherapy (supported by a meta-analysis).

Key issue 2: NMA versus ERG proxy approach (4)

ERG comment:

- ERG assumes clinical effectiveness of EE is no worse than the clinical effectiveness of FUL; this is not the same as assuming clinical equivalency for EE and FUL.
- No evidence to support company claim that EE is clinically superior to FUL in terms of PFS and OS. ERG accepts that EE is generally considered to be more effective than FUL by clinicians but no data presented to support this opinion
- To enable alternative cost effectiveness estimates to be produced, PFS and OS data from the FUL arm of PALOMA-3 to generate lower bound estimates of the effectiveness of EE.

Technical team:

- Both approaches are uncertain. As there is no suitable data to support the assumption that outcomes with EE would be no worse than with FUL, is it preferable to use results from an ITC based on clinical data?

⊙ Is fulvestrant monotherapy a clinically plausible proxy for everolimus and exemestane in clinical practice?

Key clinical issues

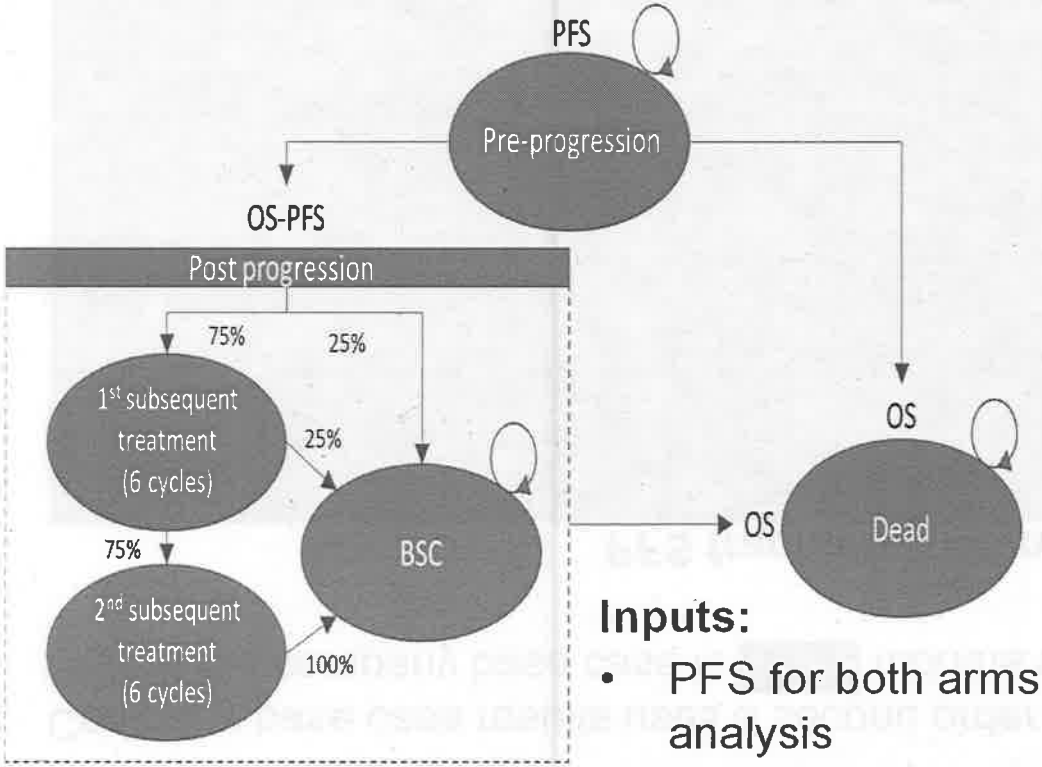
- Is palbociclib plus fulvestrant likely to be similar in efficacy to other CDK 4/6 inhibitors plus fulvestrant combinations?
- How would this treatment be used in the NHS?
- The trial included [redacted] of patients who had already received chemotherapy for advanced disease, how does this relate to how it might be used in clinical practice? Would a subgroup excluding these be appropriate?
- Exemestane plus everolimus (EE) was considered the most appropriate comparator and an indirect comparison was carried out with fractional polynomial NMA by the company, is this reasonable?
- The ERG considered this unreliable, and used the placebo plus fulvestrant arm from the trial for PFS, and the pooled data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms for OS, as a proxy for EE efficacy (suggesting that EE would be no worse than that estimate), and the trial data was more reliable than the NMA.
- Will there be further follow up OS data available?

Key cost issues

- Should the company approach for PFS, OS and TTD or ERG's PFS, OS and TTD estimates be used in the model?
  - Company used NMA
  - ERG used placebo plus fulvestrant estimates from PALOMA-3 to inform EE efficacy
- Which assumption for subsequent treatments should be used in the model?
- Does committee agree that patients would see an oncologist once every 2 months?

Company model

- Partitioned survival model with 3 states. Post-progression state subdivided into subsequent treatment lines
- Life time horizon (40 years) with mean age of 56.9 years at baseline



Assumptions:

- Patients entering post-progression state receive either 6 cycles of 1st active subsequent therapy (75%) or move immediately to BSC (25%)
- After 6 cycles of 1st active subsequent therapy, patients either move to second subsequent therapy (75%) or to BSC (25%).
- After 6 cycles of second subsequent therapy, all patients move to BSC.

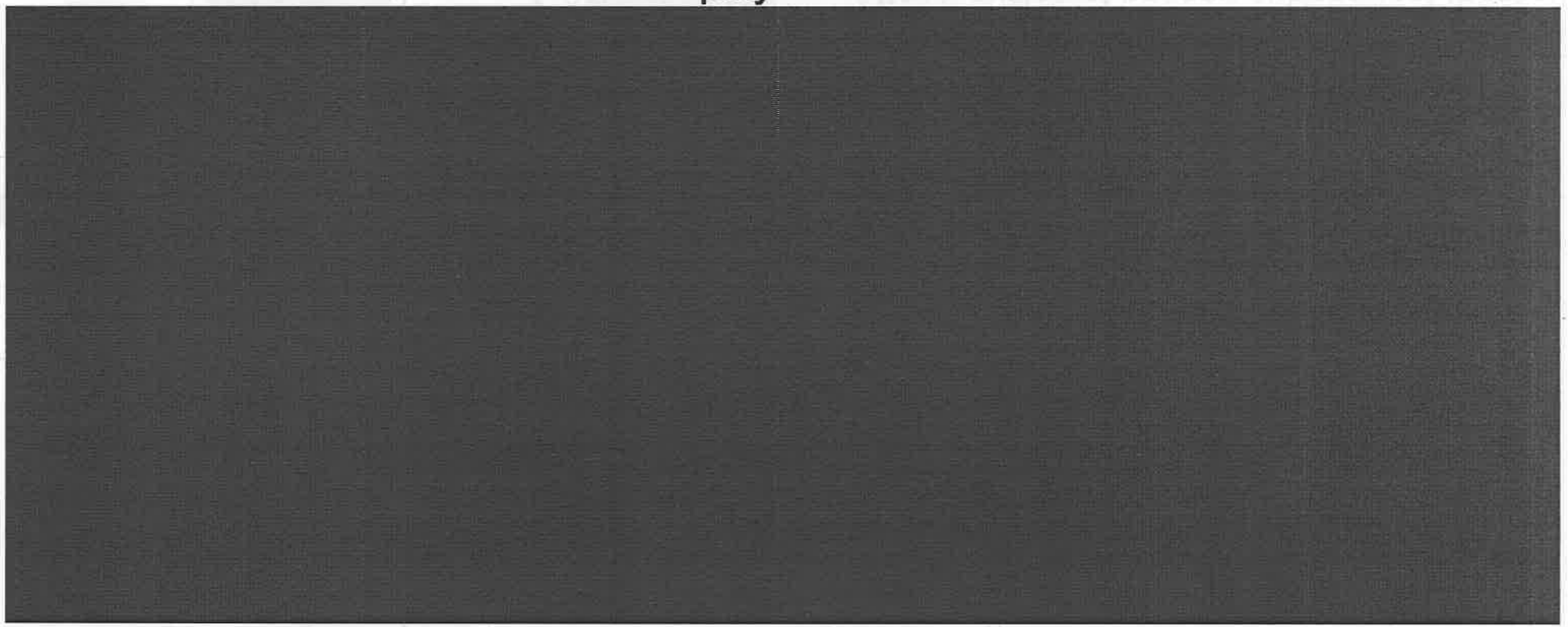
Inputs:

- PFS for both arms and OS for EE from fractional polynomial NMA analysis
- TTD, OS for for treatment with PAL + FUL and utility values, AEs for PAL + FUL from PALOMA-3
- Baseline utility for everolimus with exemestane assumed to be same as FUL EQ-5D value
- Subsequent treatment costs from TA563

Key issue 3: Impact of company and ERG approaches on PFS outputs (1)

- Company base case results uses a second order model (fixed effects) with powers -1 and -1. Mean PFS in the company base case is [redacted] months with PAL + FUL and [redacted] months with EE

PFS fractional polynomial NMA results



Key issue 3: Impact of company and ERG approaches on PFS outputs (2)

Everolimus plus exemestane PFS:

ERG results mean PFS is [redacted] months for PAL+FUL and [redacted] months for EE

- ERG approach predicts worse PFS outcomes for EE than the company approach

[redacted]

Key issue 3: Impact of company and ERG approaches on PFS outputs (3)

- **Company:** mean PFS [redacted] months with PAL+FUL and [redacted] months with EE (**gain=** [redacted] **months**)
- ERG used PFS data from the placebo + FUL arm of PALOMA-3 as a proxy for EE based on clinical advice that EE is generally more effective than FUL but acknowledged this was a conservative approach. Approach implies PFS with EE is **no worse** than with placebo+ FUL.
- **ERG**: mean PFS is [redacted] months for PAL+FUL and [redacted] months for EE (**gain=** [redacted] **months)**

- ***ERG approach produced greater PFS gain***

Response from engagement:

Clinical expert:

- ERG approach appears to generate more clinically plausible assumptions of PFS

Company:

- Efficacy of EE compared to FUL not been assessed in head to head trials. Without data, PFS and OS outputs are uncertain.
- An ITC using clinical data for EE from BOLERO-2 to estimate the relative clinical effectiveness of PAL+FUL with EE is based on best available data.

CDF Clinical Lead:

- Mean PFS of [redacted] months for EE used by the ERG is conservative although both company and ERG approaches produce suitable conclusions.

Key issue 3: Impact of company and ERG approaches on PFS outputs (4)

ERG:

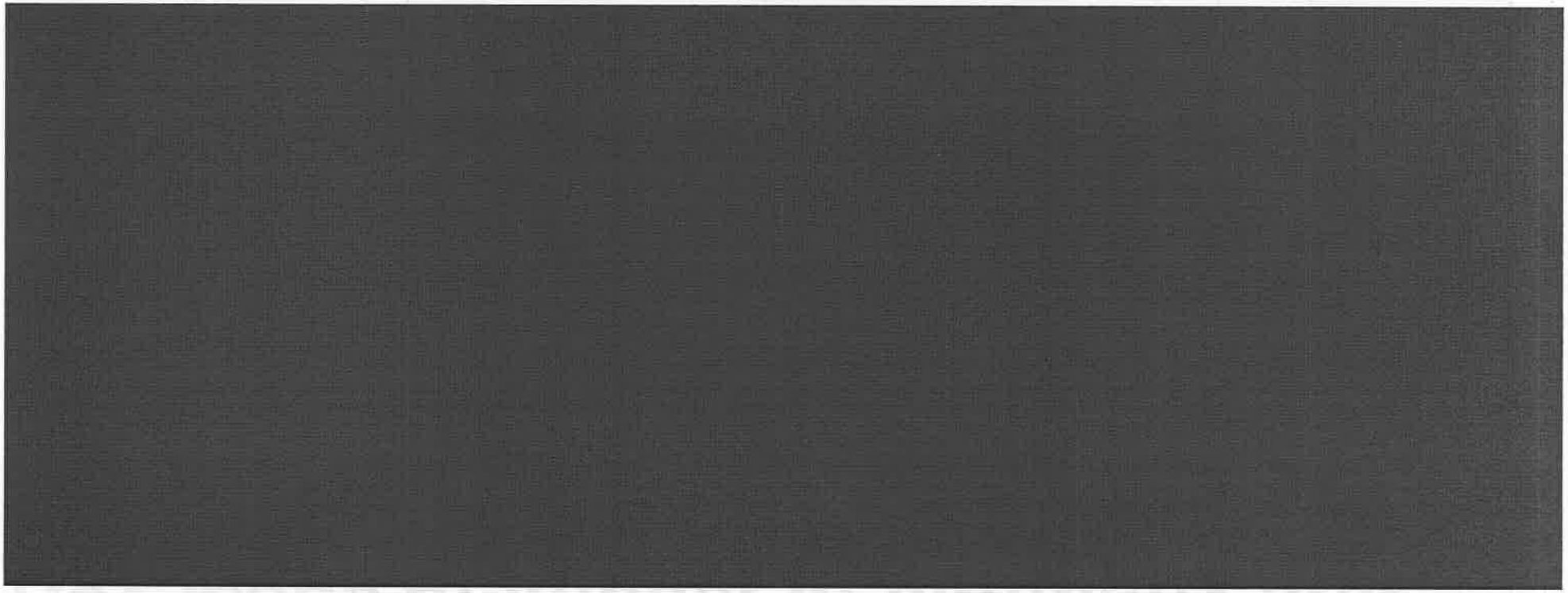
- The ERG cannot select a suitable FP model with any degree of confidence to inform the relative comparison of the clinical effectiveness of PAL+FUL versus EE for PFS.
  - Company's 3 'best fitting' 2nd order FP models [redacted]
- Main reason for performing an NMA is to avoid breaking randomisation by modelling the relationships between arms of trials and adjusting outcomes accordingly to maintain relative treatment effects. Comparing EE BOLERO-2 PFS K-M data with company and ERG estimates is meaningless.

⊙ Which approach does committee consider produces more plausible results?

Key issue 4: Impact of company and ERG approaches on OS outputs (1)

- Company's updated base case results uses a second order model (fixed effects) with powers 0 and 0.5.
- Mean OS in the company base case is [redacted] months with PAL + FUL and [redacted] months with EE (gain= [redacted] months)

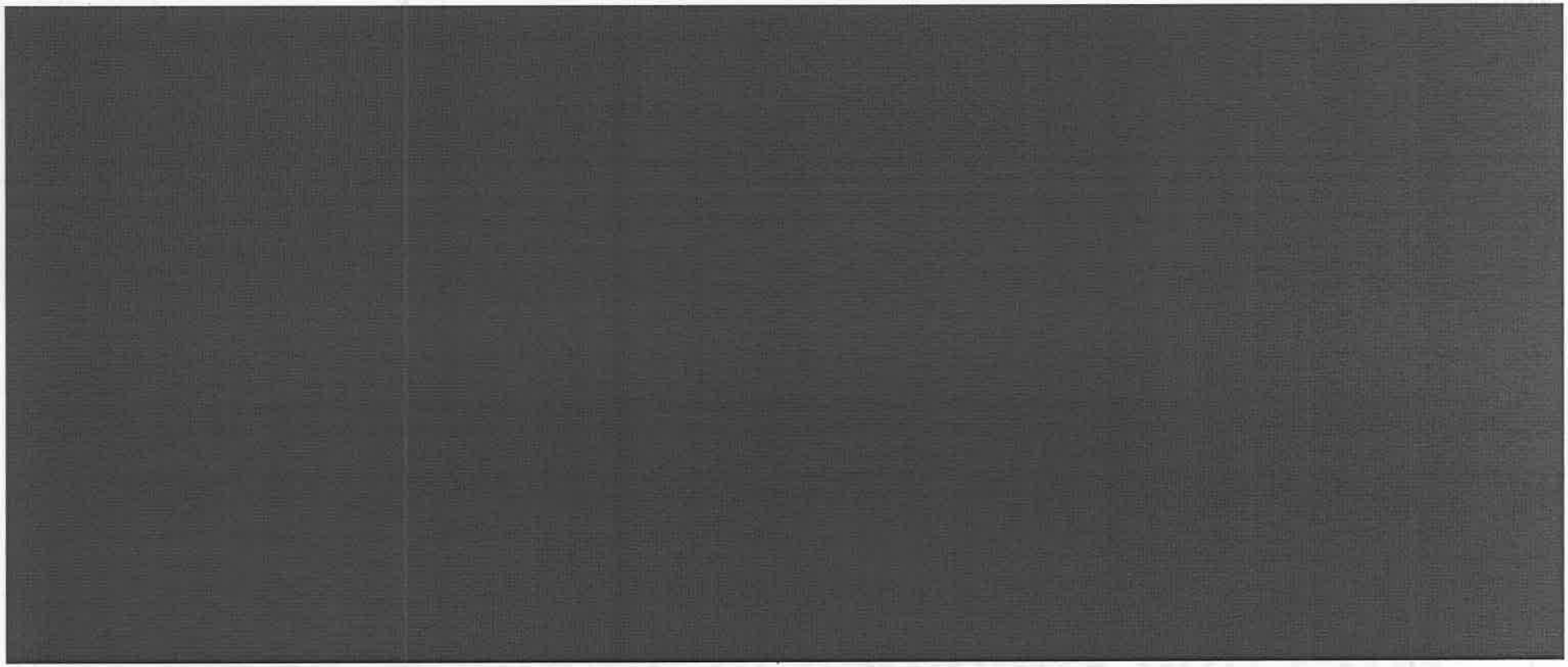
OS fractional polynomial NMA results



Key issue 4: Impact of company and ERG approaches on OS outputs (2)

Everolimus plus exemestane OS

- ERG approach predicts better OS outcomes for EE than the company approach



Key issue 4: Impact of company and ERG approaches on OS outputs (3)

- ERG pooled data from both arms of PALOMA-3 trial till 40 months and used this data to model OS for both PAL+FUL and EE. An exponential curve was appended to pooled OS Kaplan-Meir data. Using this approach, mean OS, irrespective of treatment, is [redacted] months
- ERG approach predicts there is no OS gain with PAL+FUL compared with EE.

Response from engagement:

Clinical expert:

- Trials show statistically significant improvements in OS for CDK4/6 inhibitors. EE did not show OS improvement in BOLERO-2
- Model that generates no difference in OS between PAL+FUL versus EE does not appear clinically plausible

Company:

- PALOMA-3 was not powered to detect an effect in OS. Pooling survival data from the trial and assuming equivalence based on the lack of OS statistical significance is not appropriate.
- After technical engagement, a FP analysis was conducted replacing the original Bayesian NMA providing updated OS estimates for EE.

CDF Clinical Lead:

- Very likely that there will be an advantage to OS with PAL+FUL in PALOMA-3 had the trial been powered for survival, therefore company outputs more plausible.

Key issue 4: Impact of company and ERG approaches on OS outputs (4)

ERG:

- The Deviance Information Criterion (DIC) is a measure of statistical model fit and should not be used alone to select, or rule out an FP model when model outputs are intended to be used to inform cost-effectiveness analysis.
- Some of the company FP models with very similar DIC values [redacted]
- The ERG cannot select a suitable FP model with any degree of confidence to inform the relative comparison of the clinical effectiveness of PAL+FUL versus EE for OS.

⊙ Which approach does committee consider produces more plausible results?

Key issue 5:Time-to-treatment discontinuation modelling (1)

- Company TTD for PAL+FUL is estimated by applying a HR to PFS data from PALOMA-3. This meant TTD was ***less*** than PFS.
- As no TTD data for EE, company assumed TTD was ***equal*** *to* PFS (using results of PFS FP NMA).
- The ERG used TTD data from the PAL+FUL and placebo plus FUL arms of PALOMA-3 to model TTD for patients receiving PAL+FUL and EE respectively instead (in absence of TTD data for EE)

Response from engagement:

Clinical expert:

- Majority of patients on PAL+FUL continue treatment until disease progression. EE is likely discontinued more frequently than FUL monotherapy prior to progression
- ERG approach is potentially more plausible

Company:

- Not unusual for TTD to be less than PFS as patients can discontinue treatment due to AEs, treatment breaks etc. People can continue to derive benefit from treatment whilst off therapy as PFS in a clinical setting is based on RECIST criteria.
- Median PFS for EE reported in BOLERO-2 is 7.8 months, while median duration of exposure is 5.98 months. In SMC, final PFS analysis conducted when median everolimus treatment duration was ~7.5 months compared with 14 weeks for placebo. Comparing ERG estimates to reported medians indicates ERG approach underestimates TTD for EE.

CDF Clinical Lead:

- Company uses PFS value for EE when comparing respective times to discontinuation which is inappropriate as cost of everolimus in the modelling is significantly inflated. ERG uses treatment duration for FUL to model for EE which is also inappropriate as EE is more efficacious than FUL monotherapy. Scenario analyses of differing treatment durations for EE should be explored.

Key issue 5:Time-to-treatment discontinuation modelling (2)

EE time to discontinuation	ERG approach	Company approach
Mean TTD (months)	8.93	[redacted]
Median TTD (months)	4.60	[redacted]

Key issue 5:Time-to-treatment discontinuation modelling (3)

ERG:

- Company approach of using TTD for PAL+ FUL and PFS data to represent TTD for EE is arbitrary and unfair.
- Using two different approaches to model the same effect is inconsistent.

⊙ Does the ERG's approach reduce uncertainty and produce more clinically plausible TTD estimates than the **company's** approach using a ratio of TTD to PFS from PALOMA-3 for PAL+ FUL arm and assuming TTD=PFS for the EE arm?

Key issue 6: Subsequent therapy assumptions (1)

- Company base case includes 2 active lines of subsequent therapy following progression based on basket of therapies taken from TA563 (abemaciclib)

Subsequent therapy	% split in first/second subsequent therapy in post-progression state	
	PAL + FUL	EE
Capecitabine	25%	40%
Paclitaxel	25%	20%
Everolimus plus exemestane	15%	0%
Exemestane	5%	0%
Fulvestrant	0%	10%
Tamoxifen	25%	20%
Vinorelbine	5%	10%

- In company model subsequent therapy options differ between people treated with PAL+FUL and EE. Patients who received PAL+FUL are assumed to be able to receive EE as a later line of treatment.
- In company model, people spend near 5 months receiving subsequent treatments and 16 to 18 months in the BSC health state
- ERG considers that mean time spent receiving subsequent therapies is an underestimate (prefer [redacted] months) and the mean time spent in BSC is an overestimate in the company's model
- Model also assumes that 75% of patients would proceed to receive BSC when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy. ERG considers 100% is more plausible.

Key issue 6: Subsequent therapy assumptions (2)

Response from engagement:

Company:

- Scenario analysis presented assuming same subsequent therapy costs for both arms.
- 5 months is a more accurate estimate (not changed after technical engagement).
- 25% of patients would not switch to a subsequent line (not changed after technical engagement).
- Not clinically plausible for 100% of patients to progress to a 2nd subsequent therapy. These patients instead progress to BSC.

Clinical expert:

- Patients receive subsequent treatments for longer than both company and ERG estimates in clinical practice. Patients receive multiple subsequent therapies in clinical practice

CDF Clinical Lead:

- Subsequent therapies after PAL+FUL, FUL monotherapy or EE include further hormonal therapy and various options of chemotherapy. Patients will have at least 2 lines of further treatment with most having more.
  - treatment rate for further therapy likely to be between 75%-100% with steady falls following each line of therapy. In PALOMA-3, 39% and 49% had 3 or more subsequent lines of treatment in PAL+FUL and FUL arms respectively.

Key issue 6: Subsequent therapy assumptions (3)

ERG comment:

- Clinical advice to ERG suggests people who receive PAL+FUL will receive EE as a subsequent therapy in clinical practice. Patients in PALOMA-3 also received EE as a later line of treatment after PAL+FUL.
- Scenario assuming same subsequent therapies for PAL+FUL and EE does not reflect clinical practice as the proportion of patients treated with EE or exemestane monotherapy as later lines of treatment are excluded
- Estimate of 25% of patients unable to proceed at each subsequent therapy line is too high.
- Structure of model limited ERG's ability to extend maximum duration of subsequent therapy beyond [redacted] months. Assuming 100% proceeding to BSC was only way to further influence duration of subsequent therapy to explore impact on ICER.

⊙ Which assumption, the 75% (company) or 100% (ERG), for people receiving BSC when max duration of 1st line subsequent therapy reached, is appropriate?

Key issue 7: number of appointments with a consultant oncologist

- It is important to include the correct number of consultant oncologist meetings annually as this has an impact on the costs of treatment included in the economic model.

Response from engagement

Clinical expert:

- Patients see a consultant every 2-3 months once established on PAL+FUL

Company:

- Estimate of one appointment every 2 months is used by company

CDF Clinical Lead:

- Company's assumption of consultant appointment every 6 months in the PFS state is wrong although being seen in the post progression state every 2 months is reasonable. Monthly consultant visits by the ERG is inappropriate for the BSC period.

ERG:

- One appointment per month, irrespective of health state reflect NHS clinical practice
- In the company model, a consultant appointment every 2 months is used in the first subsequent therapy health state. In the second subsequent therapy health state, an estimation one appointment per month is used. However, in the pre-progression health state this is assumed to be once every 6 months.

⊙ How frequently does a patient see a consultant oncologist?

ERG cost effectiveness results (PAS price for palbociclib, list price for everolimus)

ERG revision	PAL+FUL			EVE+EXE			Incremental			*ICER*
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY	£/QALY
Company revised base case	[redacted]									£8,176
R1) Estimating OS (pooled) from PALOMA-3	[redacted]									Dominates
R2) Estimating PFS from the PALOMA-3 trial	[redacted]									£19,272
R3) Estimating TTD from the PALOMA-3 trial	[redacted]									£19,832
R4) Amend subsequent therapy assumptions	[redacted]									£9,831
R5) Remove daily oral drug wastage	[redacted]									£11,335
R6) Include monthly oncologist consultation in every health state	[redacted]									£9,222
ERG preferred modelling of effectiveness R1) +R2) +R3)	[redacted]									**Dominates**
Company preferred modelling of effectiveness + ERG amendments R4) + R5) + R6)	[redacted]									**£13,867**
ERG preferred modelling of effectiveness + ERG amendments R1) to R6)	[redacted]									**Dominates**

Company scenario 2 received after technical engagement applied to revised company base exploring same subsequent therapies in both arms produced an ICER of £6,291 when considering PAS price for palbociclib and list price for everolimus.

Key cost issues

- Should the company approach for PFS, OS and TTD or ERG's PFS, OS and TTD estimates be used in the model?
  - Company used NMA
  - ERG used placebo plus fulvestrant estimates from PALOMA-3 to inform EE efficacy
- Which assumption for subsequent treatments should be used in the model?
- Does committee agree that patients would see an oncologist once every 2 months?