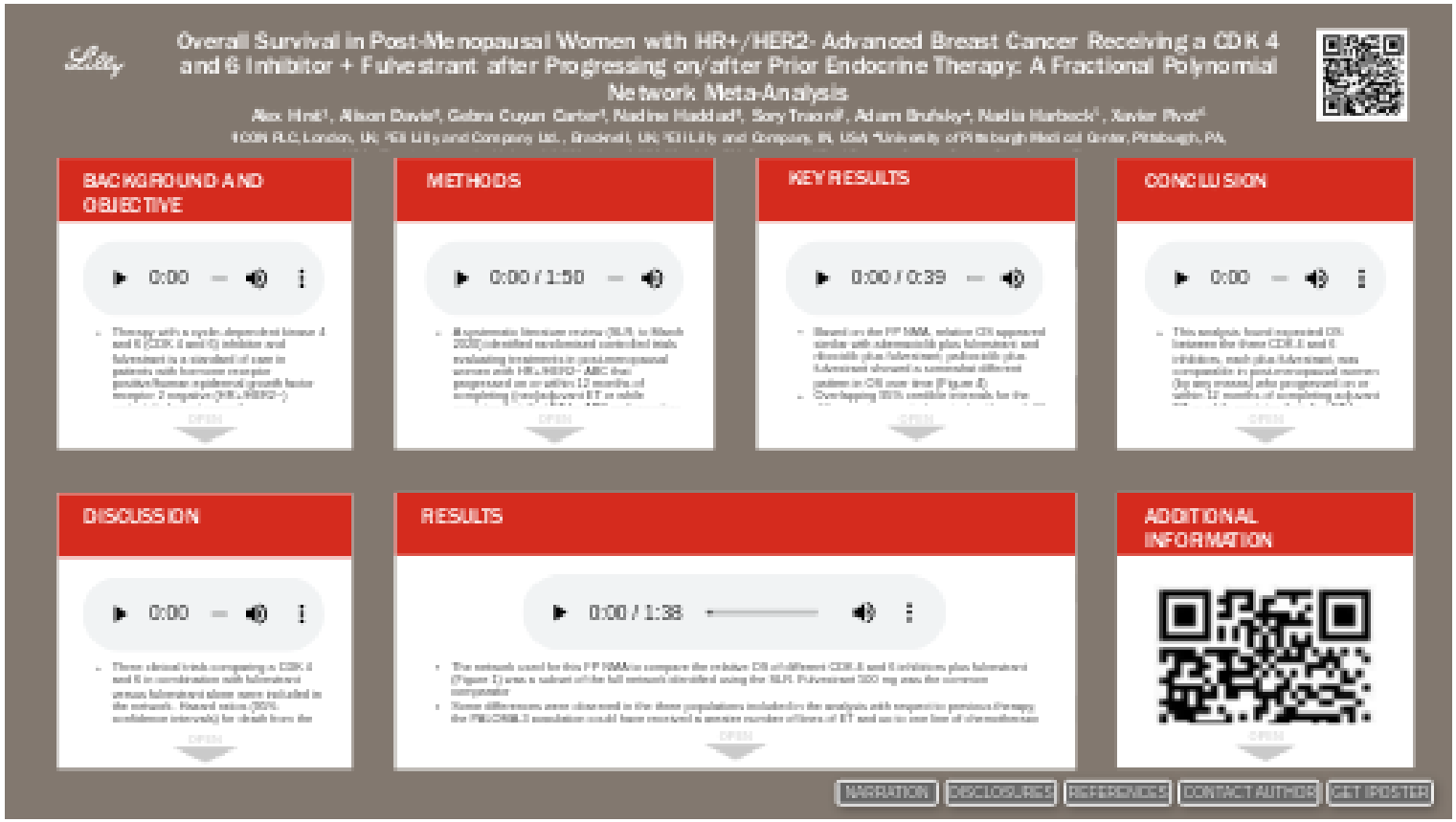
Overall Survival in Post-Menopausal Women with HR+/HER2- Advanced Breast Cancer Receiving a CDK 4 and 6 Inhibitor + Fulvestrant after Progressing on/after Prior Endocrine Therapy: A Fractional Polynomial Network Meta-Analysis



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BACKGROUND AND OBJECTIVE

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- Therapy with a cyclin-dependent kinase 4 and 6 (CDK 4 and 6) inhibitor and fulvestrant is a standard of care in patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) metastatic breast cancer[1]
- This combination therapy improved progression-free survival (PFS) compared with fulvestrant alone in post-menopausal women (pre- or peri-menopausal women also received ovarian suppression) with HR+/HER2− advanced breast cancer (ABC) who had progressed on or after previous endocrine therapy (ET) in three trials[2–4]
- Overall survival (OS) data from these trials have now been reported[5–7]: Abemaciclib plus fulvestrant[5] and ribociclib plus fulvestrant[7] significantly improved median OS versus fulvestrant in the intention-to-treat (ITT) populations, while palbociclib plus fulvestrant numerically prolonged median OS relative to fulvestrant, the improvement was not significant in the ITT population[6]

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- In the absence of head-to-head clinical trials, indirect treatment comparison (ITC) methods, such as network meta-analysis (NMA), are often used to compare treatments of interest
- Several ITCs examining the efficacy of CDK 4 and 6 inhibitors have been published[8–15]. These used hazard ratio-based methodology that assumes the hazard ratio is constant between arms (proportional hazards [PH] assumption) and provides comparative data at a fixed time. None of these ITCs reported testing the PH assumption

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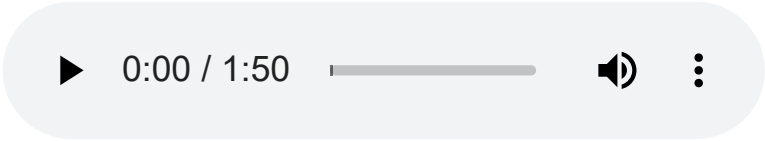
- **The objective of this NMA was to compare relative OS over time with different CDK 4 and 6 inhibitors plus fulvestrant in post-menopausal women (pre- or peri-menopausal women received ovarian suppression) who**

progressed on or within 12 months of completing (neo)adjuvant ET or while receiving their first ET for ABC

METHODS



- A systematic literature review (SLR; to March 2020) identified randomised controlled trials evaluating treatments in post-menopausal women with HR+/HER2− ABC that progressed on or within 12 months of completing (neo)adjuvant ET or while receiving their first ET for ABC and reporting efficacy, safety and quality of life data (Table 1)

    1. Best practice from multiple guidelines was used[16–18]
    2. Searches were performed in MEDLINE®, MEDLINE® In-process, EMBASE and the Cochrane Central Register of Controlled Trials and databases from major conference proceedings
    3. The population of interest was that of the MONARCH 2 trial, but due to the specificity of the MONARCH 2 population and reporting heterogeneity in published studies, it was anticipated that few trials would be identified if the SLR used the same eligibility criteria as MONARCH 2. Thus, the SLR was designed to identify studies in broader populations comparable to that for which abemaciclib plus fulvestrant is indicated

- Data from the ITT populations and pre-defined subgroups meeting criteria for the population of interest (Table 1) were extracted and analysed as follows:

    1. Baseline patient characteristics, specifically potential treatment effect modifiers, were summarised
    2. Original study Kaplan-Meier OS curves were digitised and generated based on the methods of Guyot et al.[19]. The initial survival curves generated were compared with the original Kaplan-Meier curves to document the accuracy of the digitisation

Table 1. Baseline patient characteristics of interest for the SLR

Adult females (18 years and older)
Post-menopausal by any means, including but not limited to natural, surgical or ovarian suppression methods (pre- and peri-menopausal included if there was a clear indication that they received treatment to induce menopause)
HR+ (at least 50% of study population reported as HR+)
Locally advanced disease not amenable to curative treatment by surgery or metastatic breast cancer
Patients must fulfil one of the following criteria:
• Relapsed with progression while receiving (neo)adjuvant ET, with no subsequent ET received following progression
• Relapsed with progression within 12 months from completion of adjuvant ET, with no subsequent ET received following progression
• Relapsed with progression more than 1 year from completion of adjuvant ET and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease; patients may not have received more than one line of ET or chemotherapy for metastatic disease
• Presented de novo with metastatic disease and then relapsed with progression after receiving treatment with either an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease; patients may not have received more than one line of ET or chemotherapy for metastatic disease

Patient characteristics of interest were selected based on the MONARCH 2 eligibility criteria. However, due to the specificity of the MONARCH 2 population the following deviations from the MONARCH 2 requirements were allowed to ensure studies conducted in patients largely comparable to MONARCH 2 participants and aligned with the indicated population were captured: at least 50% of population HR+, HER2- status not considered, menopausal status not necessarily reported (100% pre-menopausal not allowed), extent of prior ET not specifically reported (assuming that standard treatment would require exhaustion of ET options prior to subsequent chemotherapy regimens), and patients were permitted to receive ≤1 line of chemotherapy in the advanced setting. PALOMA-3 was included although patients could have received more than one line of ET for advanced breast cancer
ET, endocrine therapy; HR, hormone receptor; SLR, systematic literature review

NMA statistical analyses

- For the full NMA based on SLR results, feasibility assessment and visual inspection of plausibility showed that the PH assumption did not hold for a number of studies (e.g. BOLERO-2, CONFIRM, SoFEA [these three not included in this analysis], MONARCH 2, PALOMA-3). A method allowing for time-varying hazard ratios was needed
- The relative efficacy of treatments were assessed via a time-to-event NMA based on fractional polynomials (FP), as proposed by Jansen (2011)20, and conducted in a Bayesian framework

1. This did not require that the PH assumption holds
2. A range of first and second order FP were considered
3. A FP function of first or second order were utilised to estimate the natural logarithm of the hazard function per treatment arm in each study, defined as ln(h(t))=β_0+ ⟦β_1 t⟧ ^p1 and ln(h(t))=β_0+ ⟦β_1 t⟧ ^p1+ ⟦β_2 t⟧ ^p2 with t0=log t. If p1=p2=p, the model becomes a repeated powers model, defined as ln(h(t))=β_0+ ⟦β_1 t⟧ ^p+ ⟦β_2 t⟧ ^p logt
4. For each FP, random effects (RE) and fixed effects (FE) models, as used by Jansen (2011), were fitted to the data representing the powers (P) -2, -1, -0.5, 0, 0.5, 1, 2, 3

5. The best fitting model was selected as the model with the lowest deviance information criteria
6. A NMA was performed on the parameters of the FP from each study using the best fitting model to obtain an overall set of estimated parameters for each treatment
7. Survival curves were generated showing the NMA data presynthesis (with fitted survival functions) using the selected power or combination of powers. These were compared with original study Kaplan-Meier OS data to ensure appropriateness of the analyses at a study level
8. The estimated parameters were used to generate and display survival curves for each treatment and these were compared with Kaplan-Meier OS data
9. The differences in expected survival (with 95% credible intervals) at month 80 between abemaciclib plus fulvestrant and ribociclib plus fulvestrant or abemaciclib plus fulvestrant and palbociclib plus fulvestrant were estimated. Month 80 was aligned with the longest observed data within the wider network
10. Analyses were conducted using OpenBUGS version 3.2.3, and R version 3.4.4

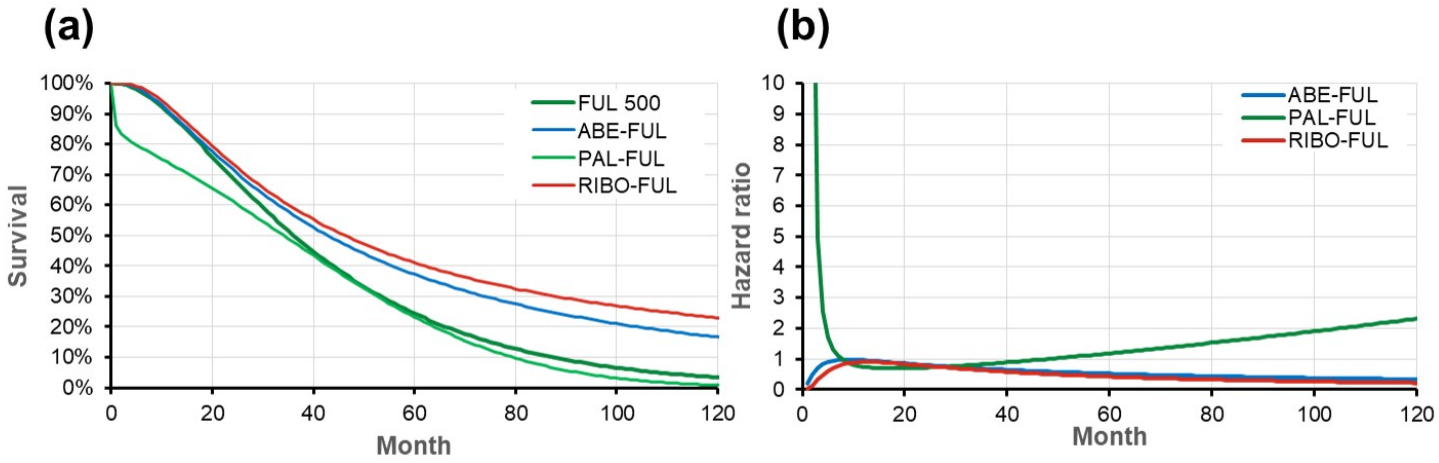
- The SLR identified a total of 39 publications. 10 trials, involving 10 comparator regimens, could be included in the full NMA
- The current analysis focused on the subset of studies (n=3) that evaluated a CDK 4 and 6 inhibitor and fulvestrant in comparison with fulvestrant 500 mg monotherapy in the population of interest and were found to be feasible for the FP NMA

1. MONARCH 2[5]
2. PALOMA-3[6]
3. Pre-defined subgroup of MONALEESA-3 since the full intention-to-treat population did not meet the SLR/NMA criteria[7]

KEY RESULTS

- Based on the FP NMA, relative OS appeared similar with abemaciclib plus fulvestrant and ribociclib plus fulvestrant; palbociclib plus fulvestrant showed a somewhat different pattern in OS over time (Figure 4)
- Overlapping 95% credible intervals for the difference in expected survival until month 80 indicate no significant differences between palbociclib plus fulvestrant vs abemaciclib plus fulvestrant and ribociclib plus fulvestrant vs abemaciclib plus fulvestrant (Table 3)

Figure 4. FP NMA of (a) relative OS and (b) OS hazard ratio for fulvestrant, abemaciclib plus fulvestrant, ribociclib plus fulvestrant and palbociclib plus fulvestrant



OS for each combination treatment is relative to fulvestrant 500mg therapy.
ABE, abemaciclib; FUL, fulvestrant 500 mg; FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; PAL, palbociclib; RIBO, ribociclib

Table 3. Relative overall survival (months) with each CDK 4 and 6 inhibitor plus fulvestrant

	ABE+FUL	PAL+FUL	RIBO+FUL
Expected survival (until 80 months)	45.86	34.89	48.01
Difference in expected survival (months)	–	-11.44	2.16
Credible interval	–	(-21.86 to 2.85)	(-6.70 to 10.65)

Overall survival for each combination treatment is relative to fulvestrant 500mg therapy.
ABE, abemaciclib; CDK, cyclin-dependent kinase; FUL, fulvestrant 500 mg; PAL, palbociclib; RIBO, ribociclib

CONCLUSION

- This analysis found expected OS between the three CDK 4 and 6 inhibitors, each plus fulvestrant, was comparable in post-menopausal women (by any means) who progressed on or within 12 months of completing adjuvant ET or while receiving their first ET for advanced disease
- While PH NMA capture treatment effect within one estimate that remains constant over time, use of a FP NMA approach has revealed subtle differences in OS patterns over time between the CDK 4 and 6 inhibitors abemaciclib, ribociclib and palbociclib, when administered in combination with fulvestrant, that have not previously been identified
- Future research should explore potential differences between the CDK 4 and 6 inhibitors across different subgroups of patients, such as those with varying degrees of endocrine sensitivity

DISCUSSION

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- Three clinical trials comparing a CDK 4 and 6 in combination with fulvestrant versus fulvestrant alone were included in the network. Hazard ratios (95% confidence intervals) for death from the three trials were as follows: abemaciclib plus fulvestrant (ITT) 0.757 (0.606–0.945), p=0.01;[5] ribociclib plus fulvestrant (ITT) 0.72 (0.57–0.92), p=0.005, ([subgroup for current analysis] 0.73 [0.53–1.00])[7] and palbociclib plus fulvestrant (ITT) 0.81 (0.64–1.03), p=0.09[6]
- The FP NMA showed no significant differences in expected OS between the three CDK 4 and 6 inhibitors when combined with fulvestrant 500 mg. OS was numerically prolonged with abemaciclib plus fulvestrant and ribociclib plus fulvestrant compared with fulvestrant 500 mg monotherapy from about 30 months onwards
- This finding of no significant difference in relative efficacy between the three CDK 4 and 6 inhibitors is supported by the results of other published ITCs that used hazard ratio-based methodology to compare relative OS or PFS with these agents[8–15]

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- The constructed curves for the FP analysis generally showed survival functions to be a good representation of the original study data and the trends between the two treatment arms (CDK 4 and 6 inhibitor plus fulvestrant vs fulvestrant). However, for the PALOMA-3 trial, the generated survival data were consistently higher than the observed study data
- Use of the FP approach revealed subtle differences in OS over time between the three CDK 4 and 6 inhibitors when combined with fulvestrant 500 mg:

    1. Abemaciclib plus fulvestrant and ribociclib plus fulvestrant similarly showed comparable survival to fulvestrant alone initially, but over time, increasingly provided a survival advantage over the monotherapy
    2. The OS curve for palbociclib plus fulvestrant initially dropped considerably; subsequently, long-term projections showed OS to trend toward, but remain numerically lower than that observed with fulvestrant

- Differences in the study populations in the current NMA may have impacted results. Patients in the PALOMA-3 trial could have received >1 ET and one line of chemotherapy in the advanced setting, whereas those in MONARCH 2 had received ≤1 ET and no chemotherapy in the advanced setting. Post-hoc analysis of PALOMA-3 revealed that prior ET sensitivity (i.e., secondary ET resistance) and no prior chemotherapy for ABC were prognostic for OS[21]

- Strengths

    1. This NMA was based on the results of a robust SLR
    2. Other published NMAs comparing available CDK 4 and 6 inhibitors generally consider the hazard ratio approach but this analysis is the first to address possible violations of the PH assumption
    3. The study populations were as similar as possible, as a result of the inclusion of a MONALEESA-3 sub-population instead of the ITT population

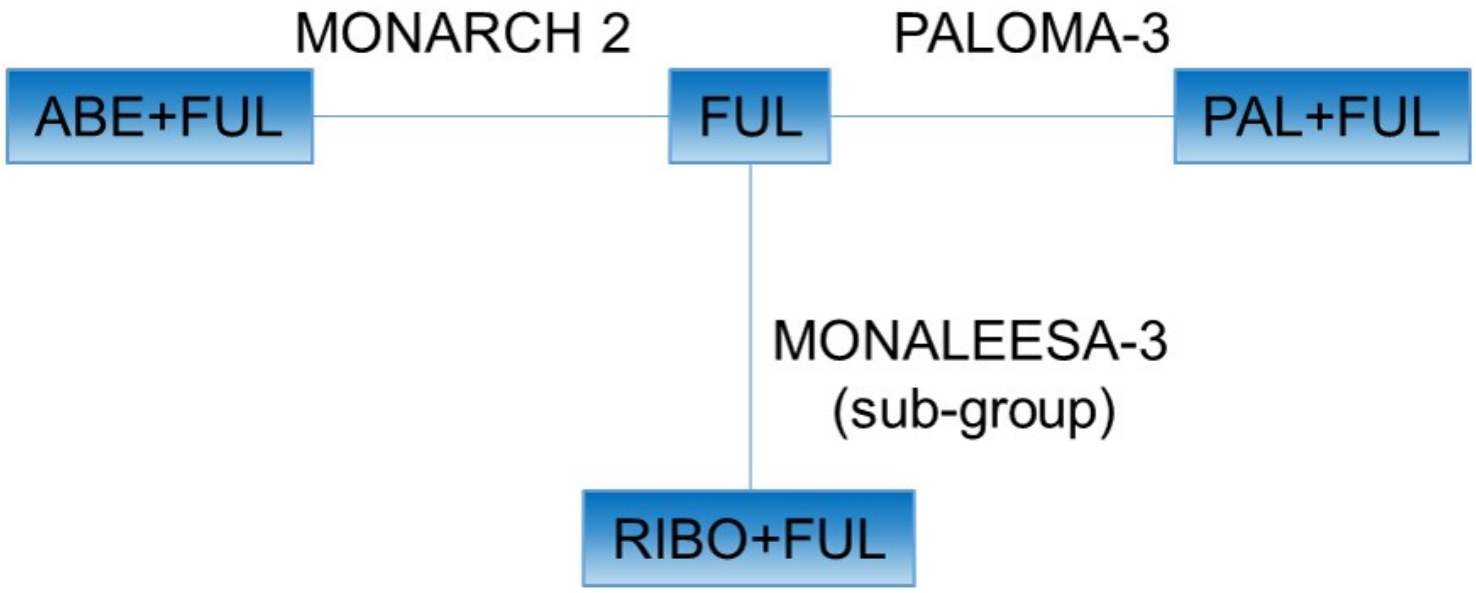
- Limitations

    1. Although all three CDK 4 and 6 inhibitors are indicated for use in the same patient groups, and we strove to identify similar target populations for each treatment, some heterogeneity remained between the study populations reflecting the heterogeneity of patients with HR+/HER2- ABC in the real world. Patients in PALOMA-3 could have received more ET and chemotherapy in the advanced setting than patients in the other trials
    2. Use of FP NMA methodology means that there was no single measure of treatment effect, observed individual patient data were not used, and although the primary effect measure for the included trials was stratified HR, analyses based on KM data are, by definition, non-stratified and unadjusted

RESULTS

- The network used for this FP NMA to compare the relative OS of different CDK 4 and 6 inhibitors plus fulvestrant (Figure 1) was a subset of the full network identified using the SLR. Fulvestrant 500 mg was the common comparator
- Some differences were observed in the three populations included in the analysis with respect to previous therapy; the PALOMA-3 population could have received a greater number of lines of ET and up to one line of chemotherapy for ABC compared with the MONARCH 2 and MONALEESA-3 analysis populations (Table 2)
- A FE model with P1 = -0.5 and P2 = 0 was the best fitting model for this network
- Generated Kaplan-Meier curves for the individual trials show good data fit relative to the original study Kaplan-Meier data (Figure 2)
- When only data from the fulvestrant 500 mg monotherapy groups from each study were considered, data from the MONARCH 2 trial best aligned to the combined and fitted data (Figure 3)
- The MONALEESA-3 fulvestrant 500 mg subgroup data were also in general alignment with the combined and fitted data, but at approximately month 40 decreased considerably compared with these latter data, possibly due to the lack of maturity of data and small number of patients at risk
- The PALOMA-3 data followed a lower but at times an approximately parallel trajectory compared with the the combined and fitted data, possibly due to the fact that patients could have received more than one prior ET or one line of prior chemotherapy in the advanced setting

Figure 1. Restricted evidence network



ABE, abemaciclib; FUL, fulvestrant 500 mg; PAL, palbociclib; RIBO, ribociclib

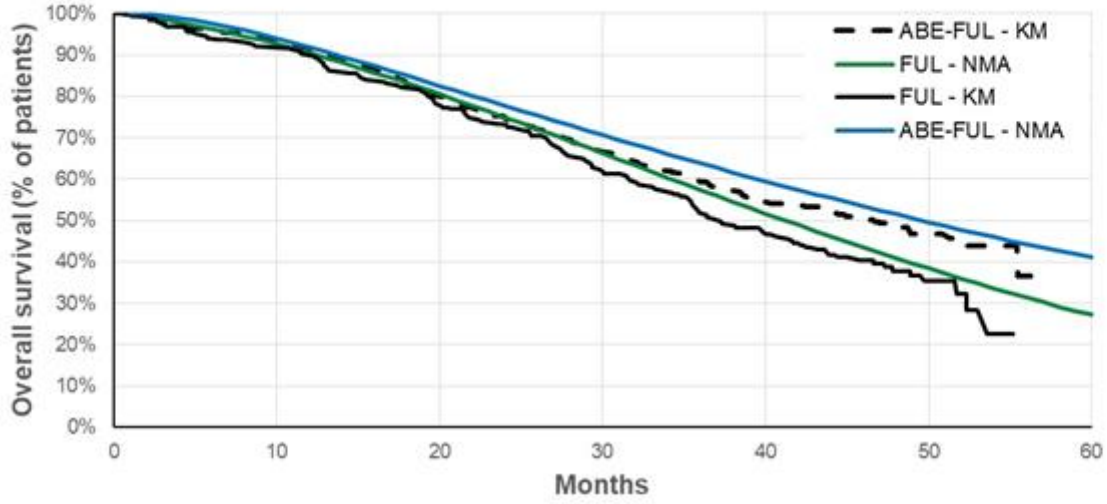
Table 2. Patient characteristics in studies evaluating overall survival in post-menopausal women with HR+/HER2− ABC receiving a CDK 4 and 6 inhibitor + fulvestrant after progressing on or after prior ET

Study	Previous ET	Definition of post-menopausal	Previous chemotherapy for ABC	Previous adjuvant therapy
MONARCH 2 (ITT)[3,5] (Abemaciclib)	All progressed on or ≤12 months after completing (neo)adjuvant treatment, or on first-line ET for ABC 73.1% secondary ET resistance[a]	Surgical/natural menopause or ovarian suppression with a GnRH agonist[b]	None	ET + chemotherapy
PALOMA-3 (ITT)[4,6] (Palbociclib)	All progressed on or ≤12 months after completing adjuvant treatment, or on or ≤1 month after ≥1 ET for ABC 78.7% secondary ET resistance[c]	Surgical/natural menopause or ovarian suppression with a GnRH agonist[b]	≤1	ET + chemotherapy
MONALEESA-3 (Subgroup[d])[2,7] (Ribociclib)	≤1 line of (neo)adjuvant and/or first-line ET for ABC (MONALESSA-3 subgroups 3 to 5)[d]	Post-menopausal (no further definition)	None	≤1 ET + chemotherapy

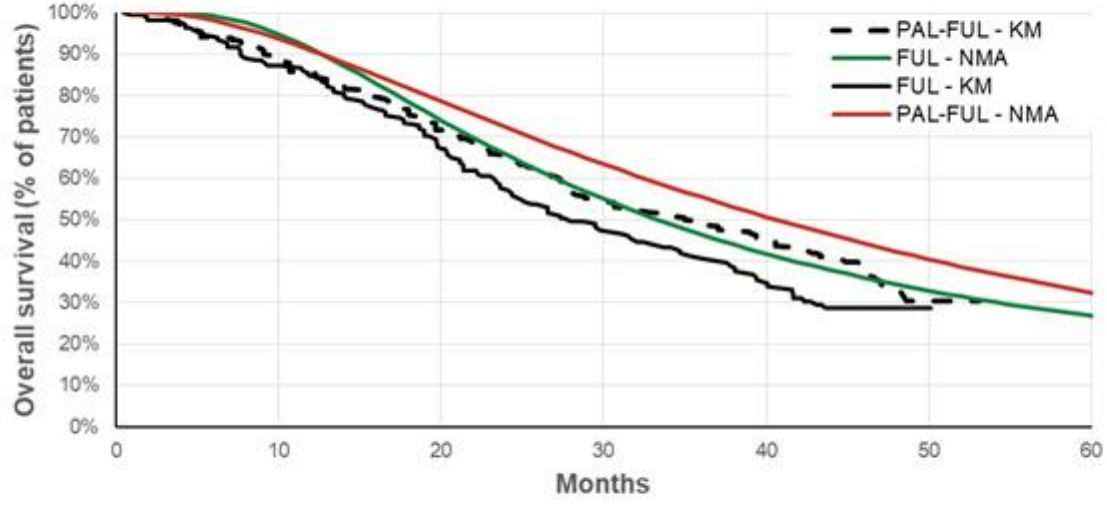
[a] Patients were considered to have secondary ET resistance if they did not have primary ET resistance, as defined by European Society for Medical Oncology guidelines (includes patients whose disease relapsed while receiving the first 2 years of neoadjuvant or adjuvant ET or progressed while receiving the first 6 months of ET for ABC).[5]
[b] Pre- or peri-menopausal women received a GnRH agonist.
[c] Patients were considered to have secondary ET resistance if they were initially sensitive to ET, defined as either a documented clinical benefit (complete response, partial response, or stable disease for ≥24 weeks) from at least one previous ET in the context of metastatic disease or the receipt of at least 24 months of adjuvant ET before recurrence.[5]
[d] The MONALEESA-3 population included in the NMA was a prespecified subgroup of the ITT population. The ITT population included patients (1) with newly diagnosed ABC, (2) who relapsed >12 months after completing (neo)adjuvant ET with no treatment for ABC, (3) who relapsed on or ≤12 months after completing (neo)adjuvant ET with no treatment for ABC, (4) who relapsed >12 months after completing (neo)adjuvant therapy with progression after first-line ET for ABC, and (5) with ABC at diagnosis that progressed after first-line ET for ABC with no prior (neo)adjuvant treatment for early disease.
ABC, advanced breast cancer; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intention-to-treat.

Figure 2. Constructed KM OS curves with presynthesis NMA data

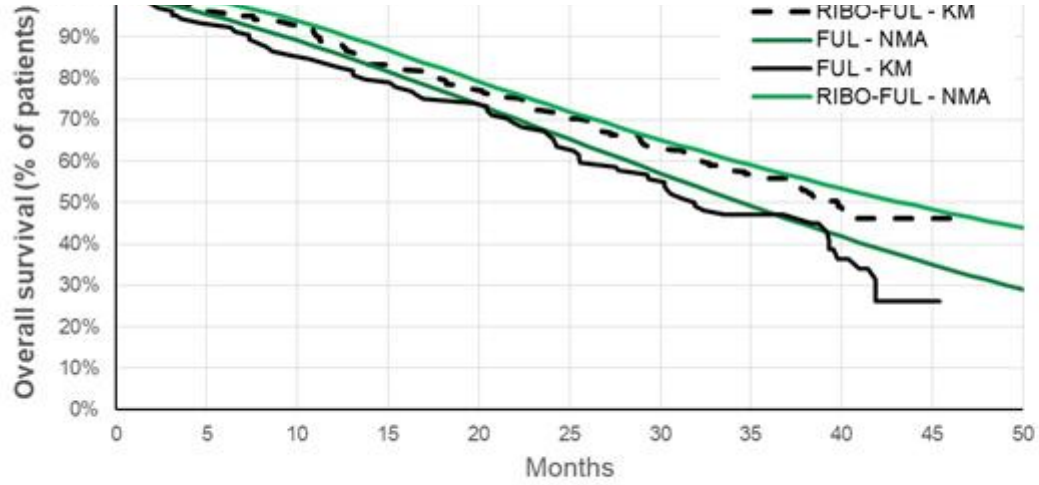
(a) MONARCH 2



(b) PALOMA-3

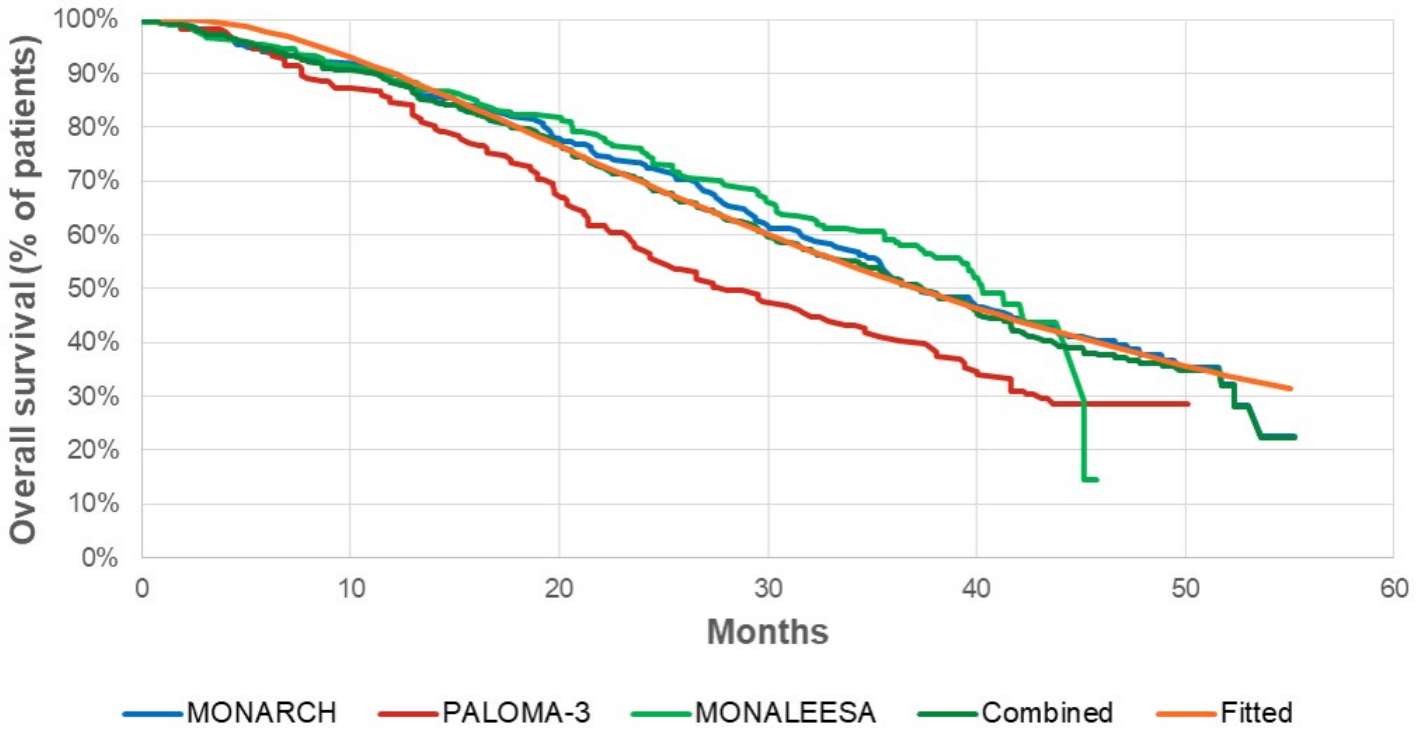


(c) MONALEESA-3 subgroup



ABE, abemaciclib; FUL, fulvestrant 500 mg; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; PAL, palbociclib; RIBO, ribociclib

Figure 3. Constructed KM OS curves with NMA output for fulvestrant 500mg monotherapy data – for each study and for the combined and fitted data



KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival

ADDITIONAL INFORMATION

DISCLOSURES

- We would like to thank Peter O'Donovan and the ICON GHTA-HERO team for their work and assistance on the SLR and supporting analyses. This study was sponsored by Eli Lilly and Company. Medical writing services were provided by Caroline Spencer and Dr Claire Lavin (Rx Communications, Mold, UK), and were funded by Eli Lilly and Company

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