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Endocrine-based strategies after CDK4/6 inhibitors in biomarker-selected subgroup of hormone receptor positive advanced breast cancer: A systematic review and network *meta*-analysis

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ABSTRACT

Background: Several endocrine-based strategies have been evaluated following CDK4/6 inhibition (CDK4/6i) in hormone receptor–positive advanced breast cancer. However, the absence of head-to-head comparisons leave uncertainty regarding the optimal treatment selection.
Methods: A systematic literature search was performed to identify randomized controlled trials (RCTs) evaluating endocrine-based strategies after CDK4/6i for hormone receptor-positive advanced breast cancer. A network *meta*-analysis was used to compare overall treatment strategies, rather than individual treatments. In addition, an extracted individual patient data *meta*-analysis was conducted. The primary endpoint was progression-free survival (PFS) evaluated independently in tumors with PI3K-AKT-PTEN alterations, *ESR1*-mutated and wild-type tumors.
Results: A total of 20 RCTs including 4,716 patients were included. In *ESR1*-mutated tumors, oral SERD/SERM/PROTAC showed numerically better PFS compared with switching CDK4/6i plus fulvestrant (HR = 0.67, 95 % CI

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0.45–1.00). In this population, the addition of i) CDK4/6i or ii) mTORi to oral SERDs improved PFS compared with oral SERD/SERM/PROTAC alone (HR = 0.44, 95 % CI 0.27–0.72 and HR = 0.45, 95 % CI 0.23–0.89, respectively). In PI3K-AKT-PTEN altered tumors, the greatest benefit was observed with PI3K/AKT/mTORi plus fulvestrant and oral SERDs plus CDK4/6i (P-scores > 0.75). In *ESR1* and PI3K/AKT/PTEN wild-type tumors, several treatment combinations outperformed fulvestrant. The use of PI3K/AKT/mTORi plus fulvestrant was associated with the highest incidence of grade ≥ 3 adverse events (66.0 %).
Conclusion: This *meta*-analysis reinforces the importance of molecular stratification in treatment decisions after CDK4/6i progression, highlighting the need for efficacy and safety assessments across biomarker-selected subgroups.

Introduction

Hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer represents the most common subtype of advanced breast cancer [1]. In this setting, the combination of endocrine therapy and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) is the current first-line standard of care in most cases, with multiple randomized trials and real-world studies demonstrating consistent improvements in survival outcomes [2]. However, despite these benefits, disease progression is inevitable due to primary or secondary resistance to the treatment.

After progression on CDK4/6i-based therapy, selecting the optimal next-line treatment remains a clinical challenge due to the absence of a defined standard of care. Although tumors often develop resistance to prior endocrine therapy, many retain dependency on estrogen receptor (ER) signaling, offering the potential for subsequent endocrine-based strategies before transitioning to chemotherapy. Current international guidelines recommend considering further endocrine therapy, alone or in combination with targeted agents, based on clinical, biological and molecular factors, including prior treatment response, tumor burden, mutational profile (e.g. *ESR1*, *PIK3CA*), and patient preferences [3–5].

Several therapeutic strategies have emerged in this post-CDK4/6i setting, including: i) selective ER degraders (SERDs), selective ER modulators (SERMs) and oral proteolysis-targeting chimera ER degrader (PROTAC), with growing evidence of activity in tumors harboring *ESR1* mutations [6–10]; ii) inhibitors of the PI3K/AKT/mTOR pathway, especially in tumors with activating mutations or pathway activation [11–13]; iii) or continuation or rechallenge with CDK4/6i in selected patients [8,14,15]. Although these options reflect a significant advance in the therapeutic armamentarium, the absence of direct head-to-head randomized comparisons and the heterogeneity of the available trials limit direct evidence-based treatment sequencing. In this context, additional analyses are needed to quantify the absolute and relative differences among the various potential therapeutic strategies, as well as their respective safety profiles.

To address this unmet need, we conducted a systematic review and network *meta*-analysis of randomized clinical trials (RCTs) evaluating endocrine-based strategies after progression on CDK4/6i in HR+/HER2– advanced breast cancer. The aim of the study was to focus on clinically relevant biomarker-defined subgroups of patients, quantify the efficacy and safety of available treatment strategies, and provide guidance for treatment selection in the increasingly complex landscape of precision oncology.

Methods

A systematic review of the literature was performed to identify RCTs that investigate endocrine-based strategies for HR+/HER2- advanced breast cancer after progression on a CDK4/6i containing regimen. A network *meta*-analysis was conducted to compare the efficacy and safety of all identify treatment options. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and the PRISMA extension for network *meta*-analyses [16]. The study was registered in the International Prospective Register for Systematic Reviews (PROSPERO), with registration number CRD420251114707.

Selection criteria, search strategy and data extraction

To be included in the systematic review, potentially eligible studies had to satisfy the following criteria: (i) RCTs that evaluate endocrine-based treatment in patients who had HR+/HER2- advanced breast cancer, (ii) that include patients who had experienced disease progression following a CDK4/6i containing regimen, (iii) the control arm included fulvestrant as one of the available treatment option (iv) with available information on survival outcomes and (v) publication available in English. All studies that met the inclusion criteria were selected for the analysis. Exclusion criteria included studies that did not report outcomes in patients previously treated with CDK4/6i, or in which fulvestrant was absent from the control arm.

The literature search included two electronic databases: MEDLINE and Embase to identify all potentially eligible published studies on 14th July 2025. Additionally, abstracts from major oncology conference were reviewed to identify eligible unpublished data. The search was updated on 8th November 2025. For studies in which not all patients had received prior CDK4/6i treatment, data were extracted specifically for the subgroup of patients with previous CDK4/6i in almost all cases (Supplementary Table 1). Likewise, in studies where fulvestrant was not the only control treatment option, results from the comparison with fulvestrant were extracted when available. When multiple publications from the same trial were available, relevant data were extracted from all sources to ensure maximal coverage and the most recent publication for each relevant endpoint was selected for the analysis.

The search strategy, and the complete list of information extracted in each of the selected studies is available in the Supplementary Materials. Kaplan-Meier curves from existing publications were used to reconstruct individual patient data and to conduct a pooled analysis of survival outcomes in clinically relevant comparison [17,18]. More information regarding the process of creating the extracted individual patient data can be found in the Supplementary Materials. The risk of bias of eligible studies was assessed comprehensively according to the Cochrane Collaboration's Risk of Bias tool [19].

Outcomes and treatment classification

The primary outcome was progression-free survival (PFS), which was also the primary endpoint in most trials. PFS was defined according to each study's criteria, which were generally consistent in capturing radiologically confirmed disease progression or death from any cause, in line with RECIST-based assessments and standard clinical trial methodology. PFS was evaluated independently in tumors with PI3K-AKT-PTEN signaling pathway alterations, *ESR1*-mutated tumors, wild-type tumors (Supplementary Tables 3–4), and in the intention-to-treat (ITT) population. Secondary outcomes included overall survival (OS) and safety outcomes such as all-grade and grade ≥ 3 adverse events, as well as the frequency of specific adverse events.

To enable clinically meaningful comparisons and preserve network connectivity, treatment strategies were pre-specified and grouped into biologically and clinically coherent categories. Oral SERDs, SERM, and

PROTAC ER degraders were clustered into a single ER-directed therapy category ("oral SERD/SERM/PROTAC"), as all suppress ER signaling through degradation and/or antagonism, share overlapping indications in ESR1-mutated and endocrine-resistant HR+/HER2 − disease and are evaluated in comparable post-CDK4/6i populations. Similarly, PI3K, AKT, and mTORi were combined into a PI3K/AKT/mTORi plus fulvestrant category, reflecting their action on sequential nodes of the same signaling axis, their use in biomarker-defined populations with PI3K-pathway activation, and their shared therapeutic intent. This strategy-level classification aligns with clinical decision-making in current guidelines [20,21]. More detailed information on the classification of treatments in individual studies is provided in Supplementary Table 2.

Statistical analysis

A trial-level network *meta*-analysis with a frequentist framework was performed to simultaneously compare all treatment strategies. The network *meta*-analysis incorporates i) direct estimations (traditional pairwise *meta*-analysis) and ii) indirect estimations, estimations of treatments that have been never compared head-to-head but have been evaluated in separate trials in comparison with a common control arm [22,23]. To summarize efficacy endpoints, hazard ratios (HR) with 95 % confidence intervals (95 %CI) were calculated for survival outcomes, with HR less than 1 indicating a risk reduction in the treatment defined as experimental arm. For the safety analysis, a penalized likelihood regression model was used to deal with adverse events with low frequency [24]; results were reported as percentages. Random-effects models were fitted for all the analysis. The ranking of treatments for each outcome was performed using the P-score. The P-score measures the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. Possible values of the P-score are between 0 and 1. The I^2 statistic was used to quantify the amount of heterogeneity in the context of the network *meta*-analysis. To evaluate the transitivity assumption, we examine the network using the net-splitting method to compare the direct and indirect evidence [25].

Additionally, an individual patient data *meta*-analysis was performed using reconstructed data extracted from published Kaplan–Meier curves. Relevant comparisons were identified, and corresponding survival curves were digitized and reconstructed. A pooled analysis was then conducted by combining patient-level data according to treatment strategy. Adjusted survival curves were generated using the conditional approach from Cox proportional hazards models to estimate absolute differences between treatments [26]. Further methodological details are provided in the Supplementary Material. No imputation was performed, and no p-values were reported to avoid multiple comparison and over-reporting of p-values. All analyses were conducted in R version 4.4.1 using the packages *meta*, *netmeta*, *ggplot2*, and *survival*.

Ethics

This study is a *meta*-analysis of published clinical trial data and did not involve individual patient consent or require institutional ethical approval. Ethical approvals for each included study are referenced in the respective original publications.

Results

The literature search identified 1443 records, out of which 20 RCT [6–11,14,15,27–40] met the eligibility criteria [Supplementary Fig. 1]. Information related to study design and trial characteristics are summarized in Table 1. The risk of bias of included trials were graphically summarized in Supplementary Fig. 2 with no or little concern for bias, other than the open-label design in some studies.

In the 20 selected RCTs, a total of 4716 patients with HR+/HER2- advanced breast cancer were included in the present *meta*-analysis and ten different types of treatment strategies were evaluated. Overall, 1,906 (40.4 %) of patients received fulvestrant alone, 964 (20.4 %) received an oral SERD/SERM/PROTAC, 746 (15.8 %) received PI3K/AKT/mTORi plus fulvestrant, 462 (9.8 %) received CDK4/6i plus fulvestrant (either by switching to a different CDK4/6i or by continuing the same agent), 183 (3.9 %) oral SERDs plus mTORi, 151 (3.2 %) oral SERDs plus CDK4/6i, 131 (2.8 %) CDK4/6i plus PI3K//mTORi plus fulvestrant, 92 (2.0 %) CDK4/6i and immunotherapy plus fulvestrant, 51 (1.1 %) BCL2 inhibitors plus fulvestrant and 30 (0.6 %) received immunotherapy plus fulvestrant. Seven different types of oral SERD/SERM/PROTAC treatments (elacestrant, giredestrant, amcenestrant, camizestrant, imlunestrant, lasofoxifene and vepdegestrant), six PI3K/AKT/mTORi (capivasertib, alpelisib, ipatasertib, sapanisertib, gedatolisib and taselisib), and three different types of CDK4/6i (palbociclib, ribociclib, and abemaciclib) were identified in the selected RCTs.

In the available data the percentage of patients classified as *ESR1*-mutated and PI3K-AKT-PTEN altered were 42.7 % and 40.1 %, respectively (Supplementary Table 3–4). The co-occurrence of ESR1 and PI3K-pathway mutations was reported in the EMBER-3 trial, with a prevalence of 24.4 %, whereas in the EMERALD trial, co-occurrence of ESR1 and PIK3CA mutations was reported only in the subgroup with ≥ 12 months duration of prior ET + CDK4/6i, with a prevalence of 39 %. All the studies evaluated treatment strategies following progression on endocrine therapy, although not all required prior progression on CDK4/6i as an inclusion criterion (Supplementary Table 1). The percentage of patients who had received previous chemotherapy (below 33 % across all studies) are represented in Supplementary Table 5. Fulvestrant was the only control arm in 13 studies (65.0 %) (Supplementary Table 6). The primary endpoint for all the studies was PFS except for the MORPHEUS HR + BC and VERONICA trials that used the overall response rate and clinical benefit rate, respectively.

Efficacy of treatment regimens in the ITT population

Fig. 1A shows the overall network graph for PFS endpoint that includes a total of 4,716 patients, with ten different treatment strategies being compared (I^2 = 1.8 %). Six strategies were associated with a statistically improvement in PFS compared with fulvestrant alone: i) CDK4/6i plus PI3K/mTORi plus fulvestrant, ii) oral SERDs plus mTORi, iii) oral SERDs plus CDK4/6i, iv) PI3K/AKT/mTORi plus fulvestrant, v) switching CDK4/6i plus fulvestrant and vi) oral SERD/SERM/PROTAC as monotherapy (Supplementary Table 7). Similar PFS outcomes were observed in the subgroup of patients who had not received previous chemotherapy (Supplementary Table 8). No evidence of inconsistency was observed in the network *meta*-analysis and no evidence of publication bias was found (Supplementary Fig. 3).

Efficacy outcomes in patients with ESR1-mutated tumors

A separate analysis was conducted within patients with *ESR1*-mutated tumors (Fig. 1B, n = 1,591; I^2=14.0 %). Oral SERD/SERM/PROTAC in monotherapy were associated with better PFS (HR = 0.59, 95 % CI 0.50–0.69) and OS (HR = 0.57, 95 % CI 0.41–0.79) compared to fulvestrant (Fig. 2A and Supplementary Fig. 4). As a sensitivity analysis Supplementary Fig. 5 presents the PFS outcomes for each treatment separately. Additionally, oral SERD/SERM/PROTAC showed similar PFS than the combination of AKTi plus fulvestrant and a numerically better PFS compared with the strategy of CDK4/6i plus fulvestrant; both when switching to a different CDK4/6i (HR = 0.67, 95 % CI 0.45–1.00) and when continuing the same one (HR = 0.87, 95 % CI 0.51–1.48) (Fig. 2A). In the comparison of oral SERDs plus CDK4/6i versus SERD/SERM/PROTAC in monotherapy, the addition of CDK4/6i improved PFS (HR = 0.44, 95 % CI 0.27–0.71) with an 18.7 % difference in the 12-month PFS rates. Similar outcomes were observed when oral SERDs were used in combination with either CDK4/6i or mTORi (HR = 0.97) (Fig. 2B). The P-scores also favored the use of the combinations (Supplementary Table 9). Outcomes from the comparison between oral SERD/SERM/

Table 1
. Main characteristics of the studies included in the systematic review: results in the postCDK4/6 population.

Clinical Trial (name and NCT)	Year	Total sample size (prior CDK4/6)	Study design	Key inclusion criteria	Stratification Factors	Experimental treatment	Control treatment	Primary endpoint	Primary results
EvERA (NCT05306340)	2025	373 (373)	Phase III, two-arm, randomized, open-label (R: 1:1)	− Pre-/ postmenopausal women and men. − Disease recurrence or progression on a CDK4/6i plus ET. − ≤2 lines of prior ET and no prior CT for ABC.	− Prior treatment with fulvestrant (Y/N) − ESR1m (Y/N or indeterminate) − Visceral desease (Y/N)	Giredestrant + everolimus	SOC ET (Fulvestrant; 21.6 %) + everolimus	PFS in ESR1mand in ITT (co-primary endpoint)	PFS HR ESR1m 0.38 (95 % CI, 0.27—0.54) PFS HR ITT 0.56 (9 %5 CI, 0.44–0.71)
VIKTORIA-1STUDY 1 (PIK3CA-WT) (NCT05501886)	2025	392 (392)	Phase III, three-arm, randomized, open-label (R: 1:1:1)	− Pre-/ postmenopausal women and men. − Disease progression on/ after systemic treatment with CDK4/6i and AI. − ≤2 lines of prior ET and no prior CT for ABC. − No prior mTOR, PI3K, or AKT inhibitors.	− Lung/liver metastases (Y/N) − Time to progression on immediate prior therapy (≤ or > 6 months) − Region (US/ Canada or rest of world)	Gedatolisib + palbociclib + fulvestrant or Gedatolisib + fulvestrant	Fulvestrant	PFS in gedatolisib triplet vs fulvestrant and PFS in gedatolisib doublet vs fulvestrant (co-primary endpoint)	PFS HR (gedatolisib triplet vs fulvestrant): 0.24 (95 % CI, 0.17–0.35) PFS HR (gedatolisib doublet vs fulvestrant): 0.33 (95 % CI, 0.24–0.48)
FINER (NCT04650581)	2025	250 (250)	Phase III, two-arm, randomized, double-blind (R: 1:1)	− Pre-/ postmenopausal women and men. − Disease progression on first line of systemic treatment with CDK4/6i and AI. − No prior fulvestrant or CT for ABC. − No prior mTOR, PI3K, or AKT inhibitors.	−PI3KCA/AKT/ PTEN altered vs wildtype − Primary vs secondary endocrine resistence	Ipatasertib + fulvestrant	Placebo + fulvestrant	PFS in ITT	PFS HR ITT 0.61 (95 % CI, 0.46–0.81)
EMBER-3 (NCT04975308)	2025	874 (523)	Phase III, three-arm, randomized, open-label (R: 1:1:1)	− Pre-/ postmenopausal women and men. − Disease recurrence or progression while receiving an AI (administered alone or with a CDK4/6i) as (neo) adjuvant treatment or within 12 months after adjuvant treatment or while receiving first-line treatment for ABC. − No prior fulvestrant.	− Prior CDK4/6i (Y/N) − Visceral metastases (Y/N) − Region (East Asia vs. North America or western Europe vs. other).	Imlunestrant + abemaciclib or Imlunestrant	SOC ET (Fulvestrant; 90.1 %)	PFS in ESR1m and in ITT (Imlunestrant vs SOC ET) PFS in ITT (Imlunestrant + abemaciclib vs imlunestrant)	PFS HR (95 % CI) (Imlunestrant vs fulvestrant) : − ESR1mut: 0.62 (0.46–0.82) − ITT: 0.87 (0.72–1.04) (Imlunestrant + abe. vs imlunestrant): 0.51 (0.38–0.68)
VERITAC-2 (NCT05654623)	2025	624 (624)	Phase III, two-arm, randomized, open-label (R: 1:1)	− Pre-/ postmenopausal women and men. − Disease recurrence or progression after one previous line of CDK4/6i plus ET; adjuvant therapy was	− Visceral metastasis (Y/N) − ERS1 mutation (Y/N)	Vepdegestrant	Fulvestrant	PFS in ESR1m and if positive PFS in ITT	PFS HR ESR1m 0.58 (95 % CI, 0.43–0.78) PFS HR ITT 0.83 (95 % CI, 0.69–1.01)

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Table 1 (*continued*)

Clinical Trial (name and NCT)	Year	Total sample size (prior CDK4/6)	Study design	Key inclusion criteria	Stratification Factors	Experimental treatment	Control treatment	Primary endpoint	Primary results
				counted as a line of therapy in the context of ABC if disease progression had occurred ≤ 12 months after the receipt of this therapy. − No prior fulvestrant or CT for ABC.					
PALMIRA (NCT03809988)	2025	198 (198)	Phase II, two-arm, randomized, open-label (R: 2:1)	− Pre-/postmenopausal women. − Disease progression on first-line palbociclib plus ET after having achieved a clinical benefit to this regimen. Palbociclib in the adjuvant setting was suitable for the study if disease recurrence was confirmed after ≥ 12 months from CDK4/6i start but ≤ 12 months after its completion. − No prior CT for ABC.	− Previous ET (fulvestrant/IA) − Visceral metastasis (Y/N)	Palbociclib + SOC ET	SOC ET (Fulvestrant; 89.9 %)	PFS in ITT	PFS HR ITT 0.86 (95 % CI, 0.67–1.11)
PostMONARCH (NCT05169567)	2025	368 (368)	Phase III, two-arm, randomized, double-blind (R: 1:1)	− Pre-/postmenopausal women and men. −Disease recurrence or progression on a CDK4/6i plus AI (adjuvant or ABC). − No prior fulvestrant or CT for ABC.	− Geography − Visceral metastasis (Y/N) − Duration of previous CDK4/6i therapy (greater/less than 12 months in ABC or recurrence during/after treatment in the adjuvant setting)	Abemaciclib + fulvestrant	Placebo + fulvestrant	PFS in ITT	PFS HR ITT 0.73 (95 % CI, 0.57–0.95)
SERENA-2 (NCT04214288)	2024	220 (112)	Phase II, three-arm, randomized, open-label (R: 1:1:1)	− Post-menopausal women. − Disease recurrence or progression on at least one line of ET and have received no more than one line of ET or CT for ABC. − No prior fulvestrant.	− Visceral metastatasis in lung/liver (Y/N) − Prior CDK4/6i (Y/N)	Camizestrant 75 mg or Camizestrant 150 mg	Fulvestrant	PFS in ITT	PFS HR (Camizestrant 75 mg vs fulvestrant) 0.49 (90 % CI, 0.31–0.75) PFS HR (Camizestrant 150 mg vs fulvestrant) 0.68 (90 % CI, 0.44–1.04)
AcelERA (NCT04576455)	2024	303 (125)	Phase II, two-arm, randomized, open-label (R: 1:1)	− Pre-/postmenopausal women and men. − Disease progression after 1 or 2 prior lines of	− Visceral metastases in lung/liver (Y/N) − Prior fulvestrant (Y/	Giredestrant	SOC ET (Fulvestrant; 75 %)	PFS in ITT	PFS HR ITT 0.80 (95 % CI, 0.52–1.23)

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Table 1 (*continued*)

Clinical Trial (name and NCT)	Year	Total sample size (prior CDK4/6)	Study design	Key inclusion criteria	Stratification Factors	Experimental treatment	Control treatment	Primary endpoint	Primary results
				systemic therapy (one of the prior lines must have been ET for ≥ 6 months; ≤1 targeted agent (including, but not limited to, CDK4/6i) and one of the lines may have included CT.	N) − Prior CDK4/6i (Y/N)				
PACE (NCT03147287)	2024	220 (220)	Phase II, three-arm, randomized, open-label (R: 1:2:1)	− Pre-/postmenopausal women and men. − Disease recurrence or progression on ET and any CDK4/6i after at least 6 months of therapy in the ABC or within 12 months of CDK4/6i exposure in the adjuvant setting. Up to one previous line of CT and up to two lines of ET for ABC was allowed. − No prior fulvestrant.	CT between previous CDK4/6i (Y/N)	Fulvestrant + palbociclib (FP) or Fulvestrant + palbociclib + avelumab (FPA).	Fulvestrant	PFS in patients treated with FP vs fulvestrant	PFS HR (FP vs fulvestrant) 1.11 (90 % CI, 0.79–1.55)
AMEERA-3 (NCT04059484)	2023	290 (230)	Phase II, two-arm, randomized, open-label (R: 1:1)	− Pre-/postmenopausal women and men. − ≤1 previous CT or targetedtherapy for ABC, pretreatment with CDK4/6i in countries where approved (CDK4/6i-naïve patients limited to ≤ 20 %), progression after ≥ 6 months of continuous ET or relapse while on adjuvant ET but after the first 2 years or within 12 months of completing adjuvant ET, and ≤ 2 previous lines of ET.	− Visceral metastatasis in lung/liver (Y/N) − Prior CDK4/6i (Y/N) − ECOG (0/1)	Amcenestrant	SOC ET (Fulvestant; 89.8 %)	PFS in ITT	PFS HR ITT 1.03 (95 % CI, 0.75–1.42)
ELAINE-1 (NCT03781063)	2023	103 (103)	Phase II, two-arm, randomized, open-label (R: 1:1)	− Pre-/postmenopausal women. − Disease progression on a prior AI plus CDK4/6i as their most recent ET; one or more ESR1mutations identified in ctDNA); prior sensitivity to ET	− Visceral metastasis (Y/N) − Y537S ESR1 mutation (Y/N)	Lasofoxifene	Fulvestrant	PFS in ITT (ESR1m)	PFS HR ITT 0.705 (95 % CI, 0.431–1.153)

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Table 1 (*continued*)

Clinical Trial (name and NCT)	Year	Total sample size (prior CDK4/6)	Study design	Key inclusion criteria	Stratification Factors	Experimental treatment	Control treatment	Primary endpoint	Primary results
				(recurrence or progression after ≥ 12 treatment months for ABC); and ≤ 1 lines of CT for ABC. − No prior fulvestrant.					
CAPItello-291 (NCT04305496)	2023	708 (496)	Phase III, two-arm, randomized, double-blind (R: 1:1)	− Pre-/ postmenopausal women and men. − Disease progression on an AI, with or without a CDK4/6i in the context of ABC or as recurrence ≤ 12 months after the end of (neo) adjuvant treatment. Up to two previous lines of ET and one of CT for ABC was allowed. − No prior fulvestrant. − No prior mTOR, PI3K, or AKT inhibitors.	− Liver metastases (Y/N) − Prior CDK4/6i (Y/N) − Geographic region.	Capivasertib + fulvestrant	Placebo + fulvestrant	PFS in ITT and AKT pathway–altered (PIK3CA, AKT1, or PTEN) tumors (dual primary endpoint)	PFS HR ITT 0.62 (95 % CI, 0.51–0.75) PFS HR AKT pathway–altered 0.40 (95 % CI, 0.36–0.66)
MAINTAIN (NCT02632045)	2023	119 (119)	Phase II, two-arm, randomized, double-blind (R: 1:1)	− Pre-/ postmenopausal women and men. − Disease progression on previous CDK4/6i and ≤ 1 previous line of CT for ABC was allowed.	− Previous ET	Ribociclib + SOC ET *SOC ET (Fulvestrant 83.2 %)	Placebo + SOC ET	PFS in ITT	PFS HR ITT 0.61 (95 % CI, 0.40–0.94)
MORPHEUS HR + BC (NCT03280563)	2023	88 (88)	Phase Ib/II, three-arm, randomized, open-label, umbrella study	− Postmenopausal women. −Disease recurrence or progression on a CDK4/6i plus ET. − No prior fulvestrant or CT for ABC.	−None.	Fulvestrant + atezolizumab (FA) or Fulvestrant + abemaciclib + atezolizumab (FAA)	Fulvestrant	ORR, safety	ORR FA 10 %, ORR FAA 26,3% ORR fulvestrant 10 %
EMERALD (NCT03778931)	2022	477 (477)	Phase III, two-arm, randomized, open-label (R: 1:1)	− Postmenopausal women and men. − Disease progression after 1 or 2 prior lines of ET for ABC, including progression on previous CDK4/6i. Recurrence during or within 12 months of adjuvant ET was included as a line of ET for ABC. One CT regimen in the ABC setting was permitted.	− ESR1m (Y/N) − Visceral metastases (Y/N) − Prior fulvestrant (Y/N)	Elacestrant	SOC ET (Fulvestrant; 69.3 %)	PFS in ITT and PFS in ESR1m (co-primary endpoint)	PFS HR ITT 0.68 (95 % CI, 0.52–0.90) PFS HR ESR1m 0.50 (95 % CI, 0.34–0.74)

(*continued on next page*)

Table 1 (*continued*)

Clinical Trial (name and NCT)	Year	Total sample size (prior CDK4/6)	Study design	Key inclusion criteria	Stratification Factors	Experimental treatment	Control treatment	Primary endpoint	Primary results
VERONICA (NCT03584009)	2022	103 (103)	Phase II, two-arm, randomized, open-label (R: 1:1)	− Pre-/postmenopausal women. − ≤2 prior lines of ET with no prior CT for ABC and disease recurrence or progression during/after CDK4/6i. − No prior fulvestrant.	− Prior lines of therapy for ABC (one vs. two) − BCL2 clinical status (high vs. low)	Venetoclax + fulvestrant	Fulvestrant	CBR	11.8 % vs 13.7 % (risk difference: −1.96 % (−16.86 to 12.94)).
García-Sáenz, JA (NCT02756364)	2022	141 (48)	Phase II, three-arm, randomized, open-label (R: 1:1:1)	− Postmenopausal women. − Disease recurrence or progression on prior AI therapy (recurrence during or within 12 months after discontinuation of adjuvant therapy or progression during treatment for ABC). − No prior fulvestrant. − No prior mTOR, PI3K, or AKT inhibitors.	− Visceral metastases (Y/N) − Primary endocrine resistance (Y/N) − Prior CDK4/6i (Y/N)	Sapanisertib 4 mg + fulvestrant or Sapanisertib 30 mg + fulvestrant	Fulvestrant	PFS in ITT	PFS HR (Sapa.4 mg + Ful) 0.34 (95 % CI, 0.14–0.82) PFS HR (Sapa.30 mg + Ful) 0.48 (95 % CI, 0.21–1.12)
SANDPIPER (NCT02340221)	2021	516 (15)	Phase III, two-arm, randomized, double-blind (R: 2:1)	− Postmenopausal women. − Disease recurrence or progression on prior AI therapy (recurrence during or within 12 months after discontinuation of adjuvant therapy or progression during treatment for ABC). − No prior fulvestrant. − No prior mTOR, PI3K, or AKT inhibitors.	− Visceral disease (Y/N) − Endocrine sensitivity − Geographic region	Taselisib + fulvestrant	Placebo + fulvestrant	PFS in PIK3CAm	PFS HR PIK3CAm 0.62 (95 % CI, 0.15–2.49)
SOLAR-1 (NCT02437318)	2019	572 (35)	Phase III, two-arm, randomized, double-blind (R: 1:1)	− Postmenopausal women and men. − Disease progression on an AI in the context of ABC or relapse during/after (neo) adjuvant therapy. − No prior fulvestrant or CT for ABC. − No prior mTOR, PI3K, or AKT inhibitors.	− Visceral metastases in lung/liver (Y/N) − Prior CDK4/6i (Y/N)	Alpelisib + fulvestrant	Placebo + fulvestrant	PFS in PIK3CAm	PFS HR PIK3CAm 0.48 (95 % CI, 0.17–1.36)

Legend: Estrogen receptor positivity was defined as ≥1 % staining by immunohistochemistry in these studies. ABC: advanced/metastatic breast cancer; AI: aromatase inhibitor; AKT: protein kinase B; CBR: clinical benefit rate; CDK4/6i: Cyclin-Dependent Kinase 4 and 6 inhibitor; CT: chemotherapy; ctDNA: cell-free circulating tumor DNA; ESR1m: estrogen receptor alpha mutated population; ET: endocrine therapy; HR: hazard ratio; ITT: intention to treat population; mTOR: mechanistic target of rapamycin; ORR: overall response rate; PFS: progression free survival; PI3K: phosphoinositide 3-kinase; PIK3CAm: alpha isoform of phosphatidylinositol 3-kinase mutated. SOC: standard of care; Y/N: yes or no.

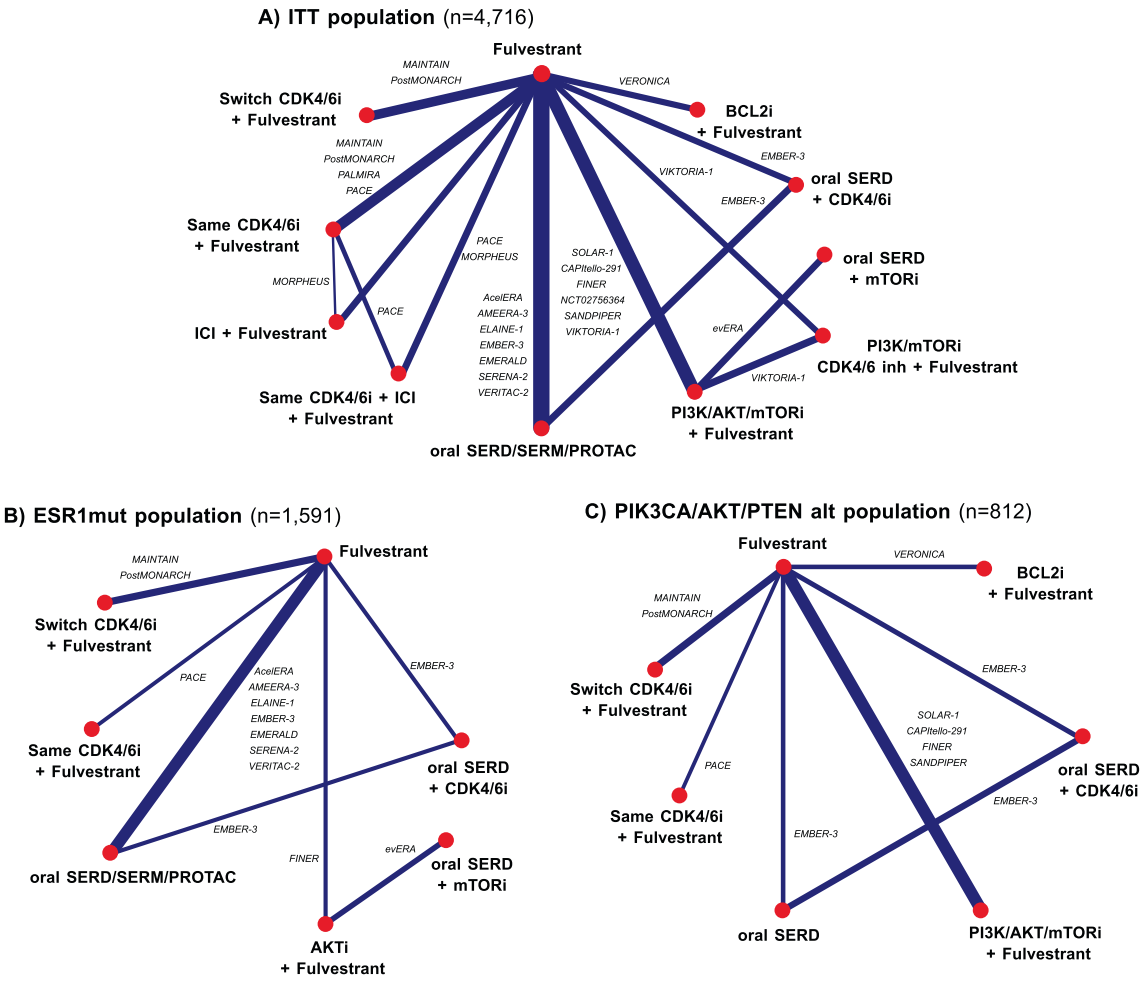

Fig. 1. Network graph of the endocrine-based treatments after progression on a CDK4/6i containing regimen in HR+/HER2- advanced breast cancer tumors. (A) PFS in the ITT population. (B) PFS in the ESR1 mutated population. (C) PFS in the PIK3CA/AKT/PTEN altered population. The lines connect treatments that have been comparted head-to-head and the width of lines is proportional to the number of studies that evaluated this pairwise comparison. ITT: intention-to-treat; PFS: progression-free survival; I: inhibitor; ICI: immune checkpoint inhibitor; Mut: mutated; Alt: altered.

PROTAC and fulvestrant were also presented: (i) in the population without previous chemotherapy, and (ii) according to the duration of prior CDK4/6i treatment (Supplementary Table 10). The benefit of this strategy was bigger in the subgroup of patients previously treated with CDK4/6i for more than 12 months (HR = 0.25, 95 % CI 0.12–0.52).

Efficacy outcomes in patients with PI3K-AKT-PTEN-pathway mutated tumors

Either PI3K/AKT/mTORi plus fulvestrant or oral SERDs with or without CDK4/6i was associated with better PFS compared to fulvestrant in population with PI3K-AKT-PTEN-pathway altered tumors (Fig. 1C, n = 812; I^2=0%). However, switching CDK4/6i plus fulvestrant did not statistically improve PFS outcomes in comparison to fulvestrant (HR = 0.88, 95 % CI 0.63–1.23) (Fig. 3). PI3K/AKT/mTORi plus fulvestrant outperformed the switch of CDK4/6i plus fulvestrant (HR = 0.56, 95 % CI 0.37–0.86) but did not show statistically significant difference against i) oral SERDs and ii) oral SERDs plus CDK4/6i. The highest P-scores were achieved by oral SERDs plus CDK4/6i and PI3K/AKT/mTORi plus fulvestrant (Supplementary Table 9). Notably, the combination of PI3K/AKT/mTORi and fulvestrant is the only strategy with mature OS data (HR = 0.69, 95 % CI 0.46–1.02 in comparison with fulvestrant).

Efficacy outcomes in patients with wild-type tumors

The efficacy of the evaluated treatment strategies cannot be assessed in the wild-type population for both *ESR1* and the PI3K–AKT–PTEN pathway due to a paucity of data. However, a pooled analysis could be conducted in the *ESR1*– and PI3K–AKT–PTEN wild-type population, separately. In the subgroup of patients with *ESR1* wild-type tumors, SERDs as monotherapy showed no PFS benefit compared with fulvestrant (HR 0.96; 95 % CI, 0.83–1.11) (Supplementary Fig. 6). In contrast, (i) oral SERDs in combination with either mTORi or CDK4/6i, (ii) PI3K/AKT/mTORi plus fulvestrant, and (iii) switching CDK4/6i plus fulvestrant statistically improved PFS compared with fulvestrant, showing similar hazard ratios (Supplementary Fig. 7). In the PI3K-AKT-PTEN wild-type population, (i) CDK4/6i plus PI3K/mTORi plus fulvestrant and (ii) oral SERDs plus CDK4/6i showed the best results in comparison with fulvestrant alone (Supplementary Fig. 8).

Safety outcomes in the entire original trial population

The use of PI3K/AKT/mTORi plus fulvestrant was associated with a higher incidence of grade ≥ 3 adverse events (66.0 %) compared with other treatment strategies: SERDs plus CDK4/6i (48.6 %), CDK4/6i plus fulvestrant (45.9 %), SERDs alone (18.9 %), and fulvestrant monotherapy (16.4 %). The rate of permanent treatment discontinuation was higher with PI3K/AKT/mTORi plus fulvestrant (20.9 %), followed by

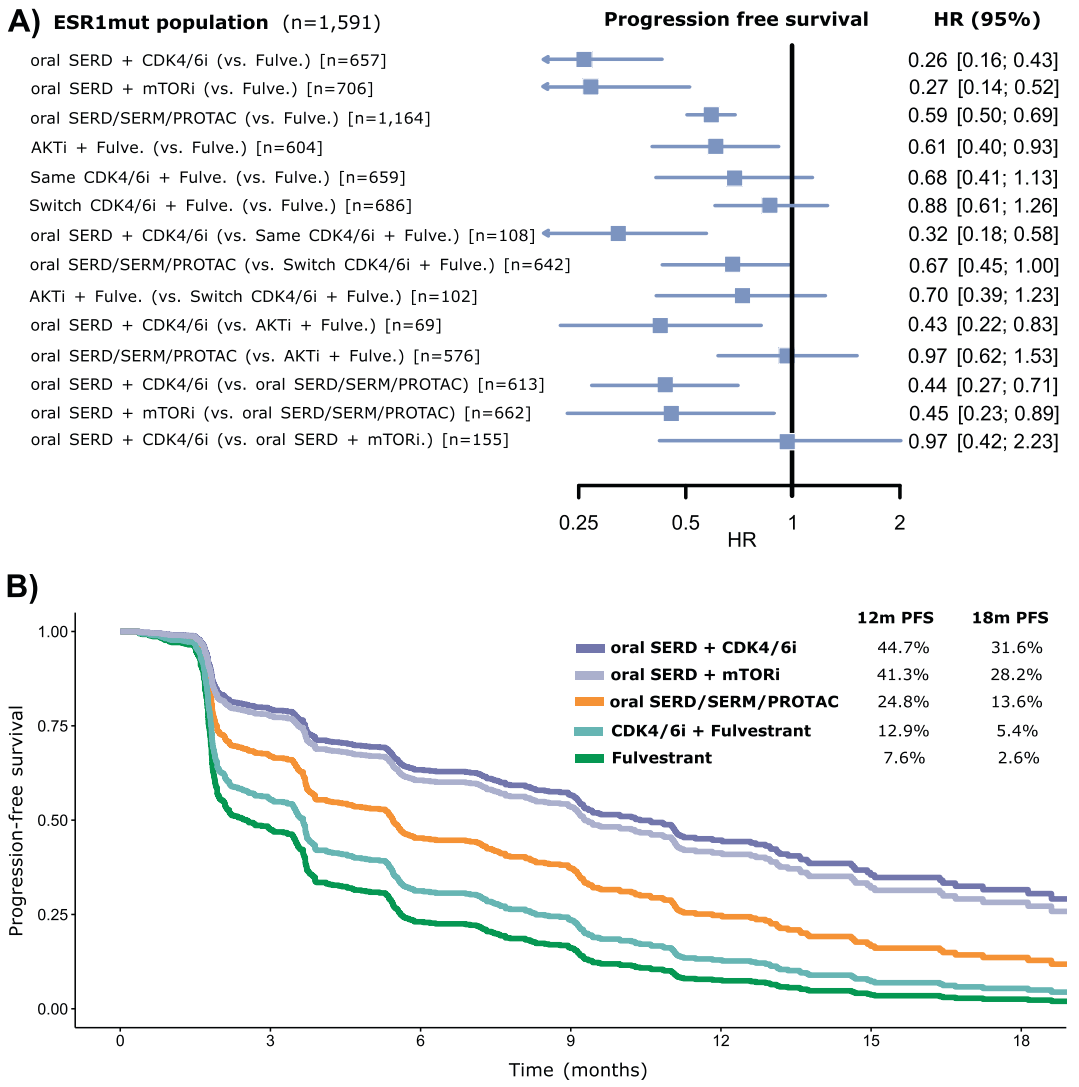

Fig. 2. Comparison of treatment strategies in the ESR1 mutated population. (A) Forest plot with the pairwise results of the trial-level network *meta*-analysis for the progression-free survival endpoint. (B) Kaplan-Meier curves for progression-free survival, generated with extracted individual patient data, comparing four treatment strategies: i) oral SERD plus CDK4/6i, ii) oral SERD/SERM/PROTAC, iii) CDK4/6i plus fulvestrant and iv) fulvestrant. The curves were generated with the extracted individual patient data from the EMERALD, AcelERA, AMEERA-3, SERENA-2, EMBER-3, PACE and MAINTAIN. HR: hazard ratio; PFS: progression-free survival; 12 m: 12-months; 18 m: 18-months.

SERDs plus CDK4/6i (6.3 %), CDK4/6i plus fulvestrant (6.1 %), SERDs (2.8 %) and fulvestrant (1.9 %). Grade 5 events were less than 3 % with all treatment strategies. In Fig. 4, we present the toxicity profiles of the different treatment strategies, ranked according to the P-score. Treatments with CDK4/6i had the worst score for grade $\geq$ 3 neutropenia (P-score $\leq$ 0.20), while PI3K/AKT/mTORi were associated with a higher probability of hyperglycemia and rash. The combination of SERDs plus CDK4/6i showed high risk of diarrhea and nausea. Overall, the best safety profiles were observed with fulvestrant and oral SERDs as monotherapy.

Discussion

The landscape of second line therapy for HR+/HER2- advanced breast cancer after progression on CDK4/6i encompasses multiple endocrine-based options. However, the absence of a defined standard of care and the considerable heterogeneity of the patient population poses a challenge in clinical practice. This systematic review and network *meta*-analysis pooled data from 20 RCTs involving 4716 patients integrates direct and indirect evidence to evaluate the efficacy and safety of endocrine-based treatment strategies across biomarker-specific subpopulations.

In *ESR1*-mutated tumors, oral SERDs/SERMs/PROTACs monotherapy showed superiority over fulvestrant, translating into improved PFS and OS. In contrast, the combination of CDK4/6i and fulvestrant—whether by maintaining or switching the CDK4/6i— did not show a statistically significant improvement in efficacy endpoints. These results are derived from pooled analyses across palbociclib, ribociclib, and abemaciclib, precluding firm conclusions about individual CDK4/6i. The addition of CDK4/6i or mTORi to SERDs further enhances outcomes in this population, although the incremental benefit must be weighed against toxicity, costs, and the lack of mature OS data. Recently, results from the SERENA-6 trial have provided further support for the effectiveness of oral SERDs in the *ESR1*-mutated setting [41]. However, the long-term efficacy of this early-switch strategy remains uncertain, and the lack of a direct comparison with the "switch-at-progression" approach leave this clinically relevant question unanswered.

Several ongoing phase III trials are expected to further define the role of oral SERDs and novel combinations in the post-CDK4/6 setting. The OPERA-01 trial (NCT06016738) aims to evaluate whether the next-

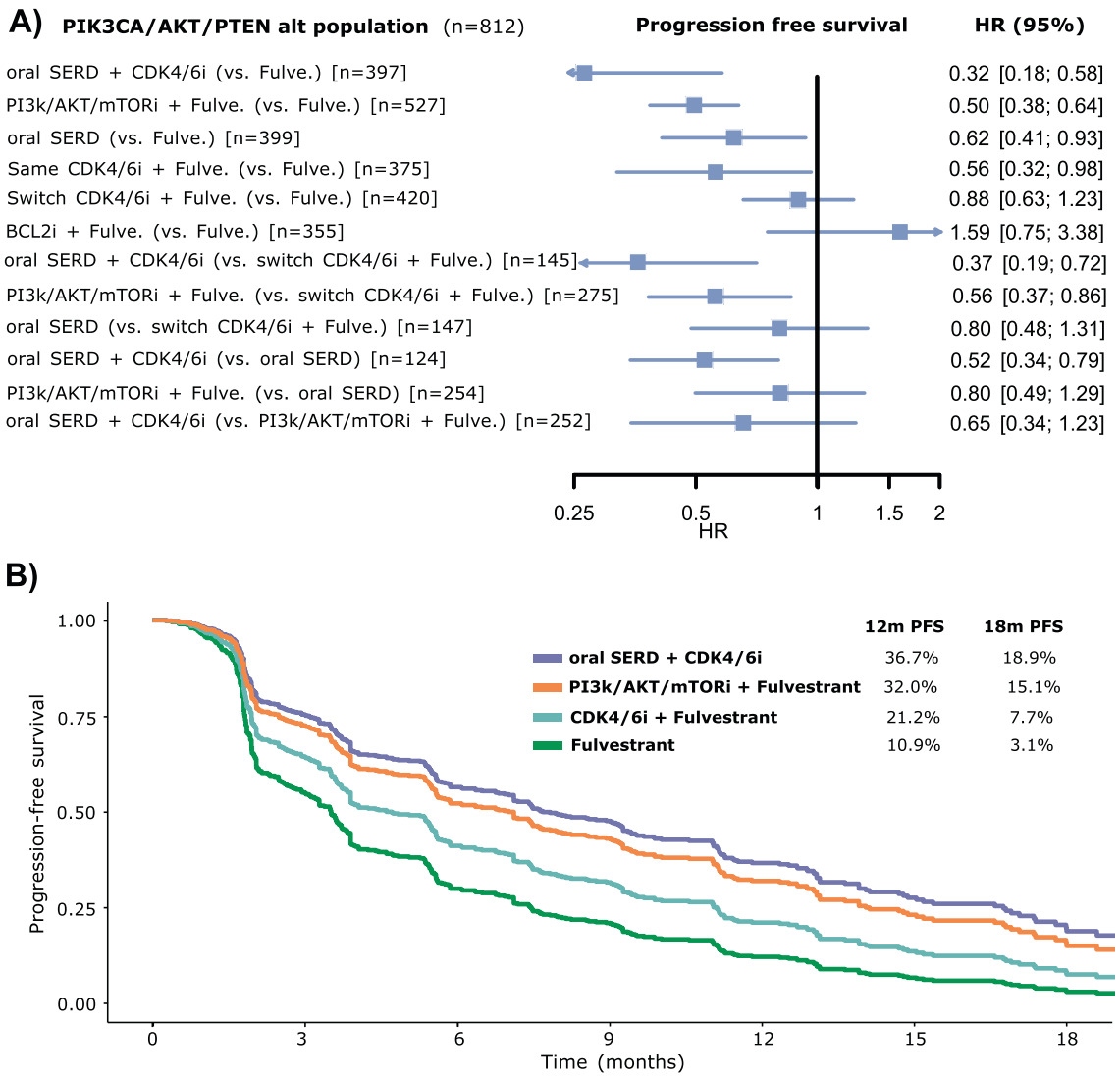

Fig. 3. Comparison of treatment strategies in the PIK3CA/AKT/PTEN altered population. (A) Forest plot with the pairwise results of the trial-level network *meta*-analysis for the progression-free survival endpoint. (B) Kaplan-Meier curves for progression-free survival, generated with extracted individual patient data, comparing four treatment strategies: i) oral SERD plus CDK4/6i, ii) PI3k/AKT/mTORi plus fulvestrant, iii) CDK4/6i plus fulvestrant and iv) fulvestrant. The curves were generated with the extracted individual patient data from the CAPITELLO-291, Finer, PACE, MAINTAIN and EMBER-3. HR: hazard ratio; PFS: progression-free survival; 12 m: 12-months; 18 m: 18-months.

generation CERAN (Complete Estrogen Receptor Antagonist)/SERD, can serve as an effective monotherapy backbone [42], while the ELAINE-3 trial (NCT05696626) will evaluate lasofoxifene plus abemaciclib, directly assessing whether a non-steroidal SERM/SERD hybrid can enhance efficacy while maintaining CDK4/6i [43]. Collectively, these ongoing trials will generate evidence to address outstanding questions regarding the management of *ESR1*-mutated tumors.

In tumors with PI3K-AKT-PTEN alterations, PI3K/AKT/mTORi in combination with fulvestrant improve efficacy outcomes, supporting pathway inhibition as a rational therapeutic strategy in this biomarker-defined subgroup. Interestingly, our analysis also suggests that oral SERDs combined with CDK4/6i achieve comparable efficacy; however, current evidence remains limited to the EMBER-3 trial and lacks mature OS data. These findings highlight two distinct but potentially complementary strategies in this biomarker-defined subgroup, such as vertical inhibition of the PI3K/AKT/mTOR pathway or intensified estrogen receptor blockade using a SERD in combination with CDK4/6i. Current research is positioning PI3K–AKT–PTEN pathway inhibition as a first-line strategy for advanced breast cancer. In the INAVO-120 trial, the addition of inavolisib to palbociclib and fulvestrant achieved clinically meaningful improvements in both PFS and OS in endocrine-resistant disease [44]. In the same setting, the CAPItello-292 trial (NCT04862663) is evaluating the addition of capivasertib to fulvestrant and CDK4/6i [45]. These studies are likely to influence the interpretation of existing results and reshape the therapeutic landscape.

For patients with tumors lacking *ESR1* and PI3K–AKT–PTEN alterations, evidence remains inconclusive. While some signals of activity were observed with switching CDK4/6i plus fulvestrant, SERDs plus CDK4/6i, or with PI3K/AKT/mTORi plus fulvestrant, heterogeneity and small sample sizes preclude solid conclusions. More recently, results from the VIKTORIA-1 trial have shown a remarkable improvement with the triplet combination of CDK4/6i plus PI3K/mTORi and fulvestrant in patients with PIK3CA- wild-type tumors [39]. These observations underscore the need to assess both *ESR1* and PI3K–AKT–PTEN status when selecting therapy and highlight the need for alternative therapeutic strategies and more robust data in molecularly unselected patients.

To support the translation of these results into clinical practice, we developed an evidence-based treatment pathway summarizing the

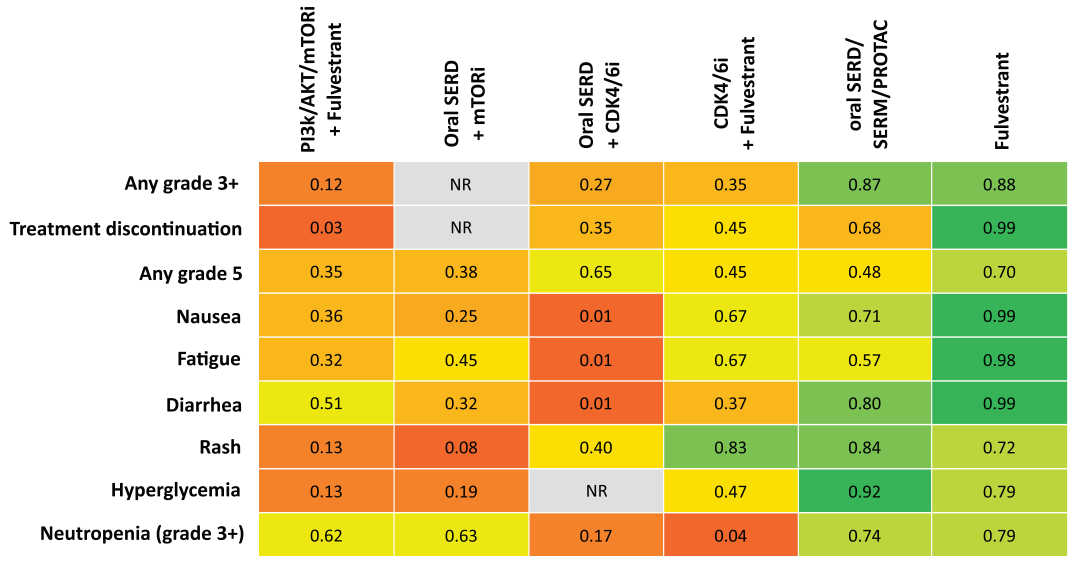

Fig. 4. Rank-heat plot for safety outcomes in endocrine-based treatments after progression on a CDK4/6i-containing regimen. Treatments are ranked by the P-score (ranging from 0 to 1) for each adverse event or safety measurement. Larger values are associated with a lower risk of adverse events. Greener shades correspond to higher P-scores and more favorable outcomes, while red tones indicate lower P-scores and poorer results. Evaluated adverse events were any grade ≥3, any grade 5, nausea, fatigue, diarrhea, rash, hyperglycemia, were neutropenia grade ≥3 and treatment discontinuation. Safety data from the VIKTORIA-1 trial were not included, as at the time of the analysis only treatment-related adverse events had been reported. Consequently, the overall safety profile of the combination of CDK4/6i plus PI3K/mTORi and fulvestrant could not be assessed.

relative performance of endocrine-based strategies in the post-CDK4/6i setting. The summary table (Supplementary Table 11) provides a practical overview intended to support treatment decision-making in routine clinical practice.

Taken together, these results suggest that better options than fulvestrant exist for most patients after progression on a CDK4/6i. This context is essential when interpreting the SONIA trial, in which no clinically meaningful advantage was demonstrated for the strategy of first-line CDK4/6i plus an aromatase inhibitor followed, upon progression, by fulvestrant, compared with second-line CDK4/6i combined with fulvestrant after progression on an aromatase inhibitor [46]. The consistently inferior outcomes associated with fulvestrant monotherapy following CDK4/6i progression—used as the control arm in SONIA—suggest that this approach is suboptimal for the majority of patients. Nevertheless, the SONIA strategy may remain a reasonable option for a select subgroup of patients who are not suitable candidates for targeted combinations due to comorbidities, toxicity considerations, or individual preferences. However, it does not represent the most effective therapeutic approach for the broader population with HR+/HER2– advanced breast cancer in contemporary clinical practice.

Safety analyses confirmed the expected toxicity profiles of targeted combinations. PI3K/AKT/mTORi were associated with a higher incidence of grade ≥ 3 adverse events and treatment discontinuations. Combining SERDs with CDK4/6i increased gastrointestinal and hematological toxicity, largely attributable to abemaciclib, suggesting the need for careful patient selection and proactive toxicity management. In contrast, oral SERDs in monotherapy exhibited a favorable safety profile, with discontinuation rates similar to fulvestrant and lower than targeted combinations. These results position SERDs as an attractive option, particularly for patients with frailty, comorbidities, or limited tolerance to toxic regimens. It is also important to consider that only 10–15 % of patients with advanced breast cancer participate in randomized clinical trials, and populations included in the studies underlying this network *meta*-analysis may not fully reflect real-world patients, particularly those with relevant comorbidities such as diabetes. This is especially relevant for PI3K/AKT inhibitors, whose metabolic toxicity frequently results in the exclusion of patients with diabetes or impaired glucose homeostasis from clinical trials. As a result, the real-world applicability and tolerability of these regimens may differ from trial-based estimates.

Emerging data also emphasize the biological complexity of resistance. Following CDK4/6i, estrogen signaling is downregulated and a shift in intrinsic subtype occurs, with enrichment of HER2-enriched and basal-like phenotypes, which are associated with poorer clinical outcomes [47]. These observations suggest that treatment selection after CDK4/6i progression should not rely exclusively on single-gene biomarkers, but also account for broader tumor biology, including dynamic profiling with ctDNA and reassessment of intrinsic subtype. Alterations in HER2, RB1 loss, and MAPK pathway activation further contribute to acquired resistance and may inform future therapeutic strategies [48,49]. Beyond endocrine-based strategies, ADCs are redefining the role of chemotherapy in heavily pretreated HR+/HER2– disease and are likely to reshape future sequencing algorithms. Data from DestinyBreast-06 highlight the activity of ADCs in this setting, particularly among patients with early progression on CDK4/6i (PFS < 6 months), a subgroup traditionally associated with endocrine resistance and poor prognosis [50]. Results from ASCENT-07 (NCT05840211), which also enrolled patients progressing within 6 months of CDK4/6i, will further clarify the role of ADCs in this high-risk population [51]. Collectively, these findings suggest that ADCs may soon move into earlier lines of therapy for endocrine-refractory patients, raising the critical question of how best to integrate them with emerging endocrine-based strategies, especially for those deriving limited benefit from SERDs or PI3K/AKT/mTORi.

Strengths of this network metanalysis include (1) a comprehensive evaluation of all available endocrine-based strategies in a patients with HR+/HER2– advanced breast cancer previously exposed to CDK4/6i; (2) its focus on post-CDK4/6i progression to better reflects the current treatment landscape; (3) its aim to provide the best to date available evidence to answer clinically relevant questions in biomarker-defined subgroups (*ESR1*-mutated, PI3K/AKT/PTEN-altered, and wild-type tumors); (4) the large sample size, which allowed for more precise subgroup analyses and increased statistical power; (5) the combination of trial-level and reconstructed individual patient data enables both relative and absolute benefit estimation to better quantify treatment effectiveness; and (6) it simultaneously evaluates efficacy and safety

outcomes, providing a balanced view of the overall risk–benefit ratio. This study also has limitations that need to be acknowledged. First, the absence of original individual patient data and the fact that some of the data used were unpublished. Second, the immaturity of OS data in most comparisons. Third, some subgroup analyses for *ESR1*-mutated and *ESR1*–wild-type tumors had small sample sizes and included patients who had not previously received CDK4/6i. Fourth, the fact the pooling of treatments that are not identical, such as oral SERDs, novel SERMs, and PROTACs, may introduce heterogeneity. Fifth, the absence of data for patients with co-occurring *ESR1* mutations and PI3K-pathway alterations, or with *ESR1* wild-type/PIK3CA wild-type tumors. Sixth, while other pooled analyses have been conducted in this field [52–55], this is the first to focus on therapeutic strategies rather than individual agents, and to incorporate extracted patient-level data to estimate absolute differences. Seventh, variability in biomarker testing strategies for *ESR1* mutations and PI3K/AKT/PTEN pathway alterations across trials; including differences in sample type (ctDNA vs. tissue), sequencing platforms, and variant allele frequency thresholds that limited the comparability of subgroup analyses. And lastly, the lack of current evidence supporting the use of PARP inhibitors in the post-CDK4/6i setting [56].

In conclusion, this network *meta*-analysis offers a framework for decision-making by facilitating indirect comparisons of the efficacy and safety of treatments lacking direct head-to-head evidence. The results reinforce the importance of molecular stratification when selecting treatment after progression on CDK4/6i. In ESR1-mutated tumors, oral SERDs, either in combination with CDK4/6i or mTORi presented the better efficacy results. PI3K/AKT/mTORi combined with fulvestrant, or SERD plus CDK4/6i, yielded meaningful clinical benefit in patients with tumors carrying pathway alterations, although toxicity remains a major challenge with PI3K/AKT/mTORi-based combinations. Further work is needed to understand the optimal strategy in the absence of ESR1 or PI3K–AKT–PTEN alterations and for patients who fall outside the eligibility criteria for RCTs. Future research should prioritize biomarker-enriched, with head-to-head trial designs, ideally incorporating liquid biopsies for real-time monitoring of resistance mechanisms.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **A.Escudero** reports speaker, educational events and travel/accommodation expenses from Pfizer and Novartis. **M. Bellet** declares other support from Pfizer, Lilly, Novartis, and Menarini Stemline and personal fees from Pfizer, Roche, Novartis, and Menarini Stemline outside the submitted work. No disclosures were reported by the other authors. **Cristina Saura** has received honoraria: AstraZéneca, Daiichi Sankyo/Astra Zeneca, Eisai Europe, Ltd, Zymeworks, Puma Biotechnology, Roche Pharma AG, Seagen, Solti, Phillips Health Works, Pfizer, Pierre Fabre, Exeter Pharmaceuticals. Consulting or Advisory Role: AstraZeneca, Daiichi Sankyo, Eisai, MediTech, Novartis, Pfizer, Philips Healthcare, Pierre Fabre, Puma Biotechnology, SeaGen, Gilead Sciences, Pint Pharma, Synthon, Zymeworks, PharmaLex, Lilly, Menarini, F. Hoffmann LaRoche. 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Expert Testimony: AX's consulting SARL, Boehringer Ingelheim, Bristol Myers Squibb/Sanofi, Genentech, InnoUp, Merck Sharp and Dohme Spain, Novartis, Sanofi. Travel, Accommodations, Expenses: Pfizer, Novartis, Roche, AstraZeneca, Puma Biotechnology, Daiichi Sankyo, Eisai Europe, Gilead Sciences, Lilly, Pierre Fabre, Seagen. **A.Papakonstantinou** declares no conflict of interest. **P.Tolosa** has held a consultant or advisory role with AstraZeneca, Daiichi-Sankyo, Novartis, Roche, Adamed and Seagen, has received a speaker's fee from Pfizer, MSD, Novartis, Lilly, AstraZeneca, Daiichi-Sankyo and Seagen, and travel grants from Pfizer, AstraZeneca, Novartis and GSK. **JA.García-Sáenz** declares consultant/advisor fees from Seagen, AstraZeneca, Daiichi Sankyo, Novartis, Gilead, Menarini Stemline, Jazz Pharmaceuticals. 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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2025.103063.

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