# Efficacy and safety of systemic therapies following progression on CDK4/6 inhibitors in patients with HR+/HER2– metastatic breast cancer: a systematic review and network meta-analysis

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## Summary

**Background** In the absence of head-to-head trials, optimal treatment sequencing following disease progression on a CDK4/6 inhibitor (CDK4/6i) combined with endocrine therapy (ET) in hormone receptor-positive, HER2-negative (HR+/HER2–) metastatic breast cancer (mBC) remains challenging. To address this gap, we conducted a systematic review and network meta-analysis (NMA) to provide evidence-based guidance for treatment selection in this setting.

**Methods** We identified randomized phase II–III trials involving HR+/HER2– mBC patients whose tumors progressed on CDK4/6i-based therapy, published between January 1, 2014 and June 6, 2025 (PROSPERO n° CRD42024604417). Hazard ratios (HRs) for progression-free survival (PFS) were extracted from published data and analyzed using a frequentist random-effects model. Subgroup analyses were performed based on the duration of CDK4/6i treatment and the presence of ESR1 or PI3K/PTEN/AKT pathway alterations. Treatments were compared with conventional ET or chemotherapy and ranked using the P-score metric. Confidence in network estimates was evaluated using the CINeMA framework. Safety data, including grade ≥3 adverse events (AEs) and treatment discontinuation, were descriptively analyzed.

**Findings** Twenty-eight randomized trials (n = 6544) were included in the NMA. Sapanisertib plus fulvestrant provided the greatest PFS benefit (HR 0.34, 95% CI 0.14–0.82) but had a high discontinuation rate (>15%). Among the approved therapies, ribociclib plus ET (HR 0.57, 95% CI 0.39–0.84), capivasertib plus fulvestrant (HR 0.62, 95% CI

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0.51–0.75), and elacestrant (HR 0.70, 95% CI 0.55–0.89) demonstrated superior efficacy. Elacestrant was most effective in patients with *ESR1*-mutant tumors and among patients with prolonged prior CDK4/6i exposure. Ipatasertib and alpelisib showed the greatest benefits in patients with PI3K/PTEN/AKT alterations. Antibody–drug conjugates (ADCs), such as trastuzumab deruxtecan and sacituzumab govitecan, outperformed standard chemotherapy, albeit with higher toxicity.

**Interpretation** Combinations of targeted agents with ET or novel endocrine agents such as oral selective estrogen receptor degraders (SERDs) demonstrated favorable efficacy and safety profiles in biomarker-selected populations, supporting a shift toward biomarker-driven treatment algorithms. In endocrine-resistant diseases that require chemotherapy, ADCs are the most effective therapeutic option.

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**Keywords:** HR+/HER2– metastatic breast cancer; CDK4/6 inhibitor resistance; Systematic review; Network meta-analysis; Biomarker-driven therapy; Antibody–drug conjugates

### Research in context

#### Evidence before this study

Several systemic therapies, including targeted agents, novel endocrine drugs, and antibody–drug conjugates (ADCs), have demonstrated efficacy in HR+/HER2– metastatic breast cancer progressing after endocrine therapy (ET) plus CDK4/6 inhibitors. However, the optimal treatment strategy following CDK4/6 inhibitor therapy remains uncertain due to the lack of head-to-head trials and the rapidly evolving therapeutic landscape. To address this gap, we conducted a systematic search of PubMed, Embase, and the Cochrane Library (January 1, 2014–June 6, 2025) for phase II–III randomized trials, extracted hazard ratios for progression-free survival (PFS) in the overall population and biomarker-defined subgroups, and analyzed the data using a network meta-analytic framework.

#### Added value of this study

Among the available therapies, ribociclib plus ET, capivasertib plus fulvestrant, and elacestrant showed the most favorable PFS outcomes in the overall population. In biomarker-defined subgroups, elacestrant showed particularly efficacy in ESR1-mutant disease and after prolonged exposure to CDK4/6 inhibitors, while PI3K-targeted agents (ipatasertib, alpelisib, capivasertib) provided benefits in PI3K pathway-altered tumors. ADCs, such as trastuzumab deruxtecan and sacituzumab govitecan, outperformed standard chemotherapy in endocrine-resistant cases requiring cytotoxic treatment.

#### Implications of all the available evidence

These results highlight the importance of biomarker-driven treatment selection in HR+/HER2– mBC after progression on CDK4/6 inhibitors therapy. Our findings provide an evidence-based framework to guide individualized therapeutic decisions across both unselected and molecularly defined subgroups. This approach may improve outcomes by optimizing post-CDK4/6i management.

## Introduction

The combination of the cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), namely palbociclib, ribociclib, or abemaciclib, with endocrine therapy (ET) has significantly improved clinical outcomes in patients with hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) when compared to ET alone.[1–6] This combination is now considered the standard-of-care first-line treatment in this clinical setting.[7,8] Despite the efficacy of ET plus CDK4/6i and a non-negligible proportion (~20%) of patients with long-term disease control at five years after treatment initiation, resistance to CDK4/6i ultimately develops in most patients,[9] leading to disease progression and CDK4/6i discontinuation. Therapeutic decision-making following progression on CDK4/6i remains a major clinical challenge,[10] as it involves numerous variables and lacks standardized

algorithms. Available treatment options upon progression to ET plus CDK4/6i encompass different ET and chemotherapy drugs,[11–13] but also novel targeted agents. These include PI3K and AKT inhibitors (i.e., alpelisib and capivasertib),[14–16] the oral selective estrogen receptor degrader (SERD) elacestrant,[17–19] poly(ADP-ribose) polymerase inhibitors (PARPi) (i.e., talazoparib and olaparib),[20,21] and the antibody–drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd),[22,23] sacituzumab govitecan (SG)[24] and datopotamab deruxtecan (Dato-DXd).[25] Current treatment selection upon tumor progression to first-line ET plus CDK4/6i is typically guided by a combination of clinical factors, including endocrine sensitivity, disease burden, duration of prior CDK4/6i therapy and drug toxicity profile, and molecular biomarkers, such as *Estrogen Receptor 1* (*ESR1*) gene mutations, alterations in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, germline pathogenic variants in *BRCA1/2* genes, and HER2-low tumor status.[26] International guidelines recommend utilizing specific targeted therapies when predictive molecular biomarkers are identified.[7,8] However, the detection of such biomarkers does not preclude the potential efficacy of alternative treatments. For instance, T-DXd and SG have shown to be effective across various biomarker-defined subgroups. Trastuzumab deruxtecan has shown consistent efficacy in patients with *ESR1* or *PIK3CA* mutations,[27] as well as in those harboring *BRCA1/2* germline mutations or alteration in homologous recombination repair (*HRR*) genes.[28] Similarly, SG has provided durable clinical benefit in HER2-low tumors[29] and in patients with alterations in DNA damage response (*DDR*) pathways.[30] These findings underscore the importance of a comprehensive approach that integrates both molecular and clinical features when selecting post-CDK4/6i therapies. Nevertheless, in the absence of direct head-to-head comparisons among an increasing number of available therapeutic approaches, treatment decisions are frequently driven by regulatory and reimbursement policies rather than by robust comparative evidence. Within this context, we conducted a systematic review and a frequentist network meta-analysis (NMA) to comprehensively assess and compare the efficacy of available post-CDK4/6i therapeutic strategies in HR+/HER2– mBC. This analysis was performed both in the overall population and within clinically and biologically relevant subgroups to inform evidence-based treatment selection.

## Methods

### Search strategy

This study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-Analyses (PRISMA-NMA) guidelines (Supplementary Material), and it was prospectively registered in PROSPERO (CRD42024604417). A comprehensive systematic literature search was performed across PubMed, Cochrane, and Embase databases between January 1st, 2014 and June 6th, 2025, using the following search terms: "Metastatic breast cancer" "Hormone receptor positive" "HER2 negative". In addition, abstracts and proceedings from major international oncology conferences held within the past five years were reviewed including the American Society for Clinical Oncology (ASCO) Annual Meeting, the European Society for Medical Oncology (ESMO) Congress, the ESMO Breast Cancer congress, and the San Antonio Breast Cancer Symposium (SABCS).

### Inclusion and exclusion criteria

Eligible studies for systematic review included phase II or phase III randomized controlled trials (RCTs) enrolling patients with HR+/HER2– mBC who had experienced tumor progression on prior ET plus CDK4/6i. We included trials in which prior ET plus CDK4/6i therapy was either mandated or allowed. In cases of multiple publications from the same trial, the most recent and complete version (up to June 6th,2025) was considered for inclusion in the analysis. Phase I trials or trials assessing the addition of locoregional treatments to systemic therapy were excluded.

### Data extraction

Two independent investigators (RB and AC) screened the retrieved studies in a blinded manner, using the Rayyan platform to facilitate the title and abstract screening process.[31] Discrepancies between investigators were resolved through consensus discussion or, when required, by assessment from a second-level independent investigator (CDA). For each eligible study, methodological and clinical characteristics, including study design, patient population and treatment details, were systematically extracted. The number of patients treated with CDK4/6i in the experimental and control arms was also collected. Hazard ratios (HRs) with 95% confidence intervals (CIs) for progression-free survival (PFS) in the overall CDK4/6i-pretreated population were systematically collected. To assess the impact of potential effect modifiers, HRs and 95% CIs were also extracted, whenever reported, for predefined subgroups defined by the presence of *ESR1* or *PIK3CA-AKT-PTEN* alterations, or to the duration of prior CDK4/6i treatment ($\geq$12 or $\leq$12 months). Additionally, data on adverse events (AEs) of any grade, grade $\geq$3 AEs, and AEs leading to treatment discontinuation or death were retrieved.

### Risk of bias

A comprehensive risk of bias (RoB) assessment was conducted for each trial included in the NMA and for

the overall network. The Cochrane Collaboration's tool (RoB-2) was used to evaluate the following five domains: randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result.[32] Judgements (low risk, some concerns, or high risk) were independently assigned by two reviewers (RB and AC), with discrepancies resolved through consensus or adjudication by a third reviewer (CDA). Assessment was based on the earliest available primary publication and trial protocol (when available), following the RoB-2 algorithm. The overall network RoB was further evaluated using the CINeMA (Confidence in Network Meta-Analysis) domains, including within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[33] CINeMA assessments were guided by GRADE[34] principles and based on the full body of evidence contributing to each comparison.

### Statistical analysis

The NMA was conducted using the frequentist method.[35] Direct and indirect evidence comparisons were integrated through a common comparator. A random-effects model was applied to estimate HRs for PFS, accounting for potential heterogeneity. Hazard ratios were analyzed on the logarithmic scale, and the resulting coefficients were exponentiated to derive interpretable HR estimates. However, estimation of between-study heterogeneity ($\tau^2$) was not feasible, as each treatment comparison was informed by a single study only. The absence of replicated comparisons limited the ability to assess variability across studies and thus precluded a meaningful estimation of heterogeneity. Consequently, no formal tests for global heterogeneity or inconsistency were performed. League tables and heat maps of efficacy were constructed based on indirect comparisons. Treatments were ranked according to their relative efficacy using P-scores values.[36] Although formal testing for inconsistency was not feasible due to the star-shaped structure of the network, the assumption of transitivity was assessed by examining the distribution of potential effect modifiers across studies. These included median age, prior exposure to endocrine and chemotherapy, and the proportion of patients with visceral metastases. The distribution of these characteristics appeared broadly comparable across treatment arms, supporting the validity of the transitivity assumption and indicating that the included trials enrolled sufficiently similar patient populations (Supplementary Tables S1–S3). All analyses were performed using R software (version 4.4.2) employing the netmeta (version 2.9.1) and ggplot2 (version 3.5.1) packages.

### Role of the funding source

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## Results

### Study selection

A total of 1793 reports were identified. After the removal of duplicates (n = 709) and the application of eligibility criteria, fifty-six studies were included in the systematic review (Fig. 1). The characteristics of the study populations are summarized in Table 1. Twenty-nine studies reported HR data for PFS following progression on ET plus CDK4/6i and were considered for the NMA. However, the REVERT trial[65] was excluded due to its non-comparative design, early termination, and the descriptive nature of the PFS data. As a result, twenty-eight studies were included in the final analysis. A detailed overview of the study selection process is provided in the PRISMA flowchart (Fig. 1).

#### *Efficacy analysis*

A total of 6544 patients were included in the NMA. The primary analysis compared different investigational treatments with conventional ET, such as fulvestrant or aromatase inhibitors, in an unselected population of patients previously treated with ET plus CDK4/6i (Fig. 2a). The same comparisons were also performed in specific patient subgroups, including patients with *ESR1*-mutated tumors, patients with tumor alterations in the PI3K/PTEN/AKT pathway, or patients with different durations of prior CDK4/6i treatment ($\leq$12 vs. $\geq$12 months) (Fig. 2b–e). A separate network included clinical trials comparing ADCs and novel chemotherapy-based combinations with standard single-agent chemotherapy (including capecitabine, eribulin, vinorelbine, paclitaxel, nab-paclitaxel and gemcitabine) (Fig. 2f). Finally, an additional analysis included trials evaluating giredestrant-based combinations (Supplementary Fig. S1). Forest Plot results are summarized in Fig. 3. When compared to conventional ET, the combination of the mTORC1/2 inhibitor sapanisertib 4 mg plus fulvestrant (NCT02756364)[66] demonstrated the most favorable HR (HR 0.34; 95% CI 0.14–0.82), followed by atezolizumab plus abemaciclib plus fulvestrant[75] (MORPHEUS HR + BC, HR 0.43; 95% CI 0.22–0.86), and sapanisertib 30 mg plus fulvestrant[66] (NCT02756364, HR 0.48; 95% CI 0.21–1.19). Among approved agents, the most effective treatments were ribociclib plus ET[37] (MAINTAIN, HR 0.57; 95% CI 0.39–0.84), capivasertib plus fulvestrant[16] (CAPItello-291, HR 0.62; 95% CI 0.51–0.75), and elacestrant[17] (EMERALD, HR 0.70; 95% CI 0.55–0.89). In contrast, palbociclib plus fulvestrant showed the least favorable outcome[39] (PACE, HR 1.10; 95% CI 0.79–1.55).

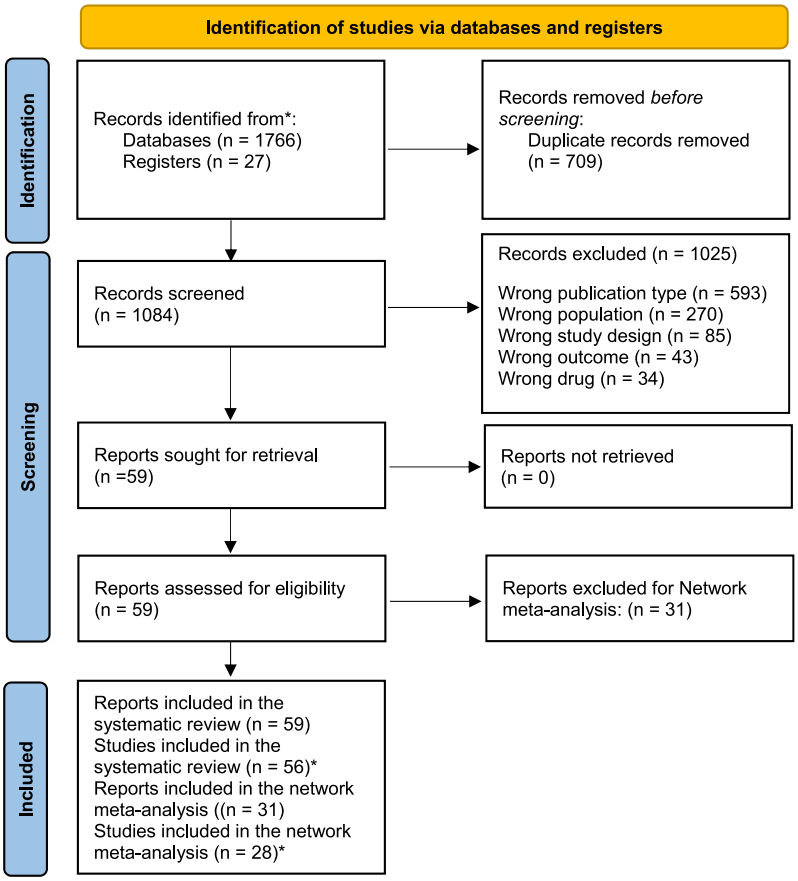


***Fig. 1:*** PRISMA flow chart diagram of study selection. *The Morpheus BC trial was reported in four separate publications, each presenting results from a distinct treatment arm.

In the *ESR1*-mutant subgroup, novel endocrine agents, such as elacestrant[17] (HR 0.55, 95% CI 0.39–0.77), and vepdegestrant[57] (HR 0.57, 95% CI 0.42–0.77) were associated with the most favorable HRs when compared to conventional ET (Fig. 3b). In patients with PI3K/AKT pathway alterations, the most favorable HRs were observed with ipatasertib plus fulvestrant[60] (FINER, HR 0.47; 95% CI 0.31–0.72), alpelisib plus fulvestrant[14] (SOLAR-1, HR 0.48; 95% CI 0.17–1.36), and capivasertib plus fulvestrant[16] (CAPItello-291, HR 0.49; 95% CI 0.36–0.66). Among patients who had received prior ET plus CDK4/6i for more than 12 months, elacestrant was the most effective treatment when compared to standard ET[87] (HR 0.41; 95% CI 0.26–0.64), while ribociclib plus ET was the only regimen significantly superior to ET in patients treated with ET plus CDK4/6i for ≤12 months[37] (HR 0.36; 95% CI 0.17–0.75).

In comparisons with standard chemotherapy regimens, the most effective interventions were T-DXd[27](DESTINY-Breast04, HR 0.55; 95% CI 0.42–0.73) and SG[45] (EVER-132-002, HR 0.55; 95% CI 0.39–0.81) (Fig. 3f). Conversely, combinations of chemotherapy plus targeted agents and/or immunotherapy, such as ipatasertib plus paclitaxel[64] (IPATunity-130), pegylated liposomal doxorubicin plus cyclophosphamide plus ipatasertib plus nivolumab[70] (ICON), or paclitaxel plus eftilagimod[77] (AIPAC), did not demonstrate superior efficacy over conventional single-agent chemotherapy (Fig. 3f).

Treatment rankings based on P-scores were consistent with HR estimates, although minor discrepancies were noted. In the overall network, the highest-ranking therapies were sapanisertib 4 mg plus fulvestrant (P-score = 0.901), atezolizumab plus abemaciclib plus fulvestrant (0.840), and camizestrant 75 mg (0.813). In the *ESR1*-mutant subgroup, elacestrant ranked the highest (0.803) followed by vepdegestrant (0.769) and ipatasertib plus fulvestrant (0.676). Among patients with PI3K/PTEN/AKT pathway alterations, ipatasertib plus fulvestrant achieved the highest ranking (0.789), whereas ribociclib plus ET and elacestrant were associated with the best performance in patients treated with CDK4/6i for ≤12 months (0.975) and ≥12 months

| Therapeutic strategies | Trials | Year | Phase | Experimental arm | Number of patients (ITT) | Number of patients treated with CDK4/6i (exp) | Control arm | Number of patients (ITT) | Number of patients treated with CDK4/6 inhibitor (cont) | CDK4/6 inhibitor Permitted/ Required | PFS HR (95% CI) ITT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CDK4/6 inhibitor beyond progression on prior CDK4/6 inhibitor | MAINTAIN[37] | 2023 | II | Ribociclib + Fulvestrant | 59 | 59 | Fulvestrant | 60 | 60 | Required | 0.59 (95% CI 0.39–0.95) |
| | PALMIRA[38] | 2023 | II | Palbociclib + Letrozole or Fulvestrant | 136 | 136 | AI or Fulvestrant | 62 | 62 | Required | 0.84 (95% CI 0.66–1.07) |
| | PACE[39] | 2024 | II | Palbociclib + Fulvestrant | 55 | 55 | Fulvestrant | 111 | 111 | Required | 1.11 (95% CI 0.74–1.66) |
| | postMONARCH[40] | 2024 | II | Abemaciclib + Fulvestrant | 182 | 182 | Fulvestrant | 186 | 186 | Required | 0.73 (95% CI 0.57–0.95) |
| | PADA-1[41] | 2022 | III | Fulvestrant + Palbociclib | 88 | 88 | AI + Palbociclib | 84 | 84 | Required | 0.63 (95% CI 0.39–1.02) |
| | MORPHEUS BC (1)[42] | 2023 | IB/II | Giredestrant + Ribociclib | 17 | 17 | Giredestrant | 11 | 11 | Required | 0.62 (95% CI 0.25–1.55) |
| | MORPHEUS BC (2)[42] | 2023 | IB/II | Giredestrant + Abemaciclib | 15 | 15 | Giredestrant | 11 | 11 | Required | 0.65 (95% CI 0.28–1.55) |
| Antibody-drug conjugates | DESTINY-Breast04[27] | 2023 | III | Trastuzumab-DXd | 331 | 233 | Chemotherapy | 163 | 115 | Permitted | 0.50 (95% CI 0.40–0.63) |
| | DESTINY-Breast06[23] | 2024 | III | Trastuzumab-DXd | 436 | 388 | Chemotherapy | 430 | 385 | Permitted | 0.64 (95% CI 0.54–0.76) |
| | TROPiCS-02[24,29] | 2022/ 2023 | III | Sacituzumab govitecan | 272 | 272 | Chemotherapy | 271 | 271 | Required | 0.66 (95% CI 0.53–0.83) |
| | NCT06105008[43]] | 2024 | II | Disitamab vedotin + Toripalimab | / | / | Disitamab vedotin | / | / | Permitted | Ongoing |
| | NCT05904964[44] | 2023 | III | Disitamab vedotin | / | / | AI or Fulvestrant | / | / | Permitted | Ongoing |
| | EVER-132-002[45] | 2024 | III | Sacituzumab govitecan | 166 | 81 | Chemotherapy | 165 | 79 | Permitted | 0.69 (95% CI 0.54–0.89) |
| | ASCENT-07[46] | 2024 | III | Sacituzumab govitecan | 267 | / | Chemotherapy | 262 | / | Permitted | 0.41 (95% CI 0.33–0.52) |
| | DYNASTY-Breast02[47] | 2023 | III | DB-1303/BNT323 | / | / | Chemotherapy | / | / | Permitted | 0.36 (95% CI 0.28–0.45) |
| | TROPION-Breast01[25] | 2023 | III | Datopotomab-DXd | 365 | 299 | Chemotherapy | 367 | 286 | Permitted | 0.63 (95% CI 0.52–0.76) |
| | SACI-IO HR +[48] | 2024 | II | Sacituzumab govitecan + Pembrolizumab | 52 | / | Sacituzumab govitecan | 52 | / | Permitted | 0.76 (95% CI 0.47–1.23) |
| Novel endocrine agents (SERDS, PROTACs, SERMs) | EMERALD[17] | 2023 | III | Elacestrant | 239 | 239 | AI or Fulvestrant | 238 | 238 | Required | 0.55 (95% CI 0.39–0.77) |
| | acelERA[49] | 2024 | II | Giredestrant | 151 | 65 | AI or Fulvestrant | 152 | 62 | Permitted | 0.81 (95% CI 0.65–1.01) |
| | SERENA-2[18] | 2023 | II | Camizestrant 75 mg/150 mg | 147 | 75 | AI or Fulvestrant | 73 | 37 | Permitted | 0.55 (95% CI 0.39–0.77) |
| | OPERA-01[50] | 2024 | III | Palazestrant | / | / | AI or Fulvestrant | / | / | Required | Ongoing |
| | AMEERA-3[51] | 2023 | II | Amcenestrant | 143 | 114 | AI or Fulvestrant | 147 | 115 | Permitted | 1.05 (95% CI 0.789–1.4) |
| | MORPHEUS BC (3)[52] | 2024 | IB/II | Giredestrant + Everolimus | 14 | 14 | Giredestrant | 11 | 11 | Required | 0.59 (95% CI 0.25–1.43) |
| | evERA[53] | 2023 | III | Giredestrant + Everolimus | / | / | Exemestane + Everolimus | / | / | Required | 0.80 (95% CI 0.60–1.06) |
| | ADELA[54] | 2024 | III | Elacestrant + Everolimus | / | / | Elacestrant + Placebo | / | / | Required | 0.68 (95% CI 0.38–1.21) |
| | EMBER-3[55] | 2023 | III | Imlunestrant/Imlunestrant + Abemaciclib | 331/213 | 93/138 | Exemestane or Fulvestrant | 330 | 188 | Required | 0.87 (95% CI 0.72–1.04) |
| | ELAINE 1[56] | 2023 | II | Lasofoxifene | 52 | 52 | Fulvestrant | 51 | 51 | Required | 0.61 (95% CI 0.39–0.95) |
| | VERITAC-2[57] | 2023 | III | Vepdegestrant | 313 | 313 | Fulvestrant | 311 | 311 | Required | 0.83 (95% CI 0.68–1.02) |
| PIK3CA/AKT inhibitors | SOLAR-1[14] | 2021 | III | Alpelisib + Fulvestrant | 169 | 9 | Fulvestrant + Placebo | 172 | 11 | Permitted | 0.65 (95% CI 0.50–0.85) |
| | SANDPIPER[58] | 2022 | III | Taselisib + Fulvestrant | 340 | 12 | Fulvestrant + Placebo | 176 | 3 | Permitted | 0.70 (95% CI 0.56–0.89) |
| | MORPHEUS BC (4)[59] | 2023 | IB/II | Giredestrant + Ipatasertib | 24 | 24 | Giredestrant | 8 | 8 | Required | 0.91 (95% CI 0.38–2.20) |
| | FINER[60] | 2023 | III | Ipatasertib + Fulvestrant | 125 | 125 | Fulvestrant + Placebo | 125 | 125 | Required | 0.61 (95% CI 0.46–0.81) |
| | EPIK-B5[61] | 2021 | III | Alpelisib + Fulvestrant | / | / | Fulvestrant + Placebo | / | / | Required | Ongoing |
| | VIKTORIA-1[62] | 2022 | III | Gedatolisib + Fulvestrant ± Palbociclib | / | / | Gedatolisib + Fulvestrant/ Fulvestrant | / | / | Required | Ongoing |
| | INAVO-121[63] | 2023 | III | Inavolisib + Fulvestrant | / | / | Fulvestrant + Alpelisib | / | / | Required | Ongoing |
| | CAPItello-291[16] | 2023 | III | Capivasertib + Fulvestrant | 355 | 247 | AI or Fulvestrant | 353 | 249 | Permitted | 0.60 (95% CI 0.51–0.71) |
| | IPATunity130[64] | 2024 | III | Ipatasertib + Paclitaxel | 144 | 36 | Paclitaxel + Placebo | 76 | 21 | Permitted | 1.00 (95% CI 0.71–1.40) |

(Table 1 continues on next page)

| Therapeutic strategies | Trials | Year | Phase | Experimental arm | Number of patients (ITT) | Number of patients treated with CDK4/6i (exp) | Control arm | Number of patients (ITT) | Number of patients treated with CDK4/6 inhibitor (cont) | CDK4/6 inhibitor Permitted/ Required | PFS HR (95% CI) ITT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | | | | |
| Chemotherapy | METEORA[13] | 2023 | II | VEX | 70 | 29 | Paclitaxel | 63 | 26 | Permitted | 0.67 (95% CI 0.46–0.96) |
| | REVERT[65] | 2022 | II | Eribulin + aromatase inhibitor | 15 | 8 | Eribulin | 7 | 4 | Permitted | 0.96 (95% CI 0.2–3.9) |
| | NCT02756364[66] | 2021 | II | Sapanisertinib 4 mg/30 mg + Fulvestrant | 47/48 | 16/16 | Fulvestrant | 46 | 16 | Permitted | 0.77 (95% CI 0.47–1.26)/ 0.88 (95% CI 0.53–1.45) |
| | CONTESSA 2[67] | 2021 | III | Tesetaxel + reduced dose of capecitabine | 343 | 168 | Capecitabine | 342 | 174 | Permitted | 0.72 (95% CI 0.57–0.89) |
| | AIPAC-003[68] | 2024 | III | Paclitaxel + Eftilagimod | / | / | Paclitaxel + Placebo | / | / | Permitted | |
| | XENERA-1[69] | 2023 | II | Xentuzumab + Everolimus + Exemestane | 52 | 39 | Everolimus + Exemestane | 51 | 39 | Permitted | 1.19 (95% CI 0.55–2.59) |
| Immune-based strategies | NCT03409198 (ICON)[70] | 2023 | II | Pegylated liposomal doxorubicin + cyclophosphamide + IPI + NIVO | 49 | 22 | Chemotherapy | 33 | 13 | Permitted | 1.05 (95% CI 0.77–1.43) |
| | NCT03051659[71] | 2020 | II | Eribulin + Pembrolizumab | 44 | 34 | Eribulin | 44 | 33 | Permitted | 0.80 (95% CI 0.50–1.26) |
| | Young-PALETTA, KCSG BR21-09[72] | 2024 | II | Talazoparib + Atezolizumab | / | / | Talazoparib | / | / | Required | Ongoing |
| | AMBITION[73] | 2021 | III | Bevacizumab + Paclitaxel + Atezolizumab | / | / | Bevacizumab + Paclitaxel | / | / | Permitted | Ongoing |
| | KEYNOTE B-49[74] | 2021 | III | Pembrolizumab + Chemotherapy | / | / | Chemotherapy + Placebo | / | / | Permitted | Ongoing |
| | MORPHEUS HR + BC[75] | 2024 | IB/II | Atezolizumab + Fulvestrant ± Abemaciclib | 40/31 | 40/31 | Fulvestrant | 25 | 25 | Required | 0.43 (95% CI 0.24–0.78) |
| Other strategies | TBCCRC041[76] | 2023 | II | Alisertib + Fulvestrant | 46 | 46 | Fulvestrant | 45 | 45 | Permitted | 0.57 (95% CI 0.44–0.74) |
| | AIPAC[77] | 2023 | III | Eftilagimod alpha + paclitaxel | 114 | 50 | Paclitaxel + Placebo | 112 | 50 | Permitted | 0.93 (95% CI 0.67–1.30) |
| | ENABLAR-2[78] | 2024 | III | Enobosarm ± Abemaciclib | / | / | NSAI or SAI (±Everolimus) or Fulvestrant | / | / | Required | Ongoing |
| | FORTRESS[79] | 2020 | III | Balixafortide + Eribulin | 162 | / | Eribulin | 168 | / | Permitted | 1.07 (95% CI 0.81–1.41) |
| | NCT03538171[80] | 2023 | III | Entinostat + Exemestane | 235 | 15 | Exemestane | 119 | 8 | Permitted | 0.76 (95% CI 0.58–0.98) |
| | E2112[81] | 2021 | III | Entinostat + Exemestane | 305 | 113 | Exemestane | 303 | 101 | Permitted | 0.87 (95% CI 0.67–1.13) |
| | SUMIT-BC[82] | 2024 | II | Samuraciclib + Fulvestrant | / | / | Fulvestrant | / | / | Required | Ongoing |
| | VERONICA[83] | 2022 | II | Venetroclax + Fulvestrant | 51 | 51 | Fulvestrant | 52 | 52 | Required | 0.94 (95% CI 0.61–1.45) |
| | NCT06374459[84] | 2025 | Ib/II | Zunsemetinib + Capecitabine | / | / | Capecitabine + Standard of care anti-resorptive | / | / | Required | Ongoing |
| | NCT05181033[85] | 2021 | II | Lenvatinib + Letrozole | / | / | Fulvestrant | / | / | Required | Ongoing |
| | MORPHEUS BC (5)[86] | 2024 | IB/II | Giredestrant + Samuraciclib | 15 | 15 | Giredestrant | 18 | 18 | Required | 0.68 (95% CI 0.31–1.46) |

exp = experimental; cont = control; ITT = Intent-To-Treat; PFS = progression-free survival; / = not available (ongoing trial).

***Table 1:*** **Key study characteristics of randomized phase II-III trials included in the systematic review.**

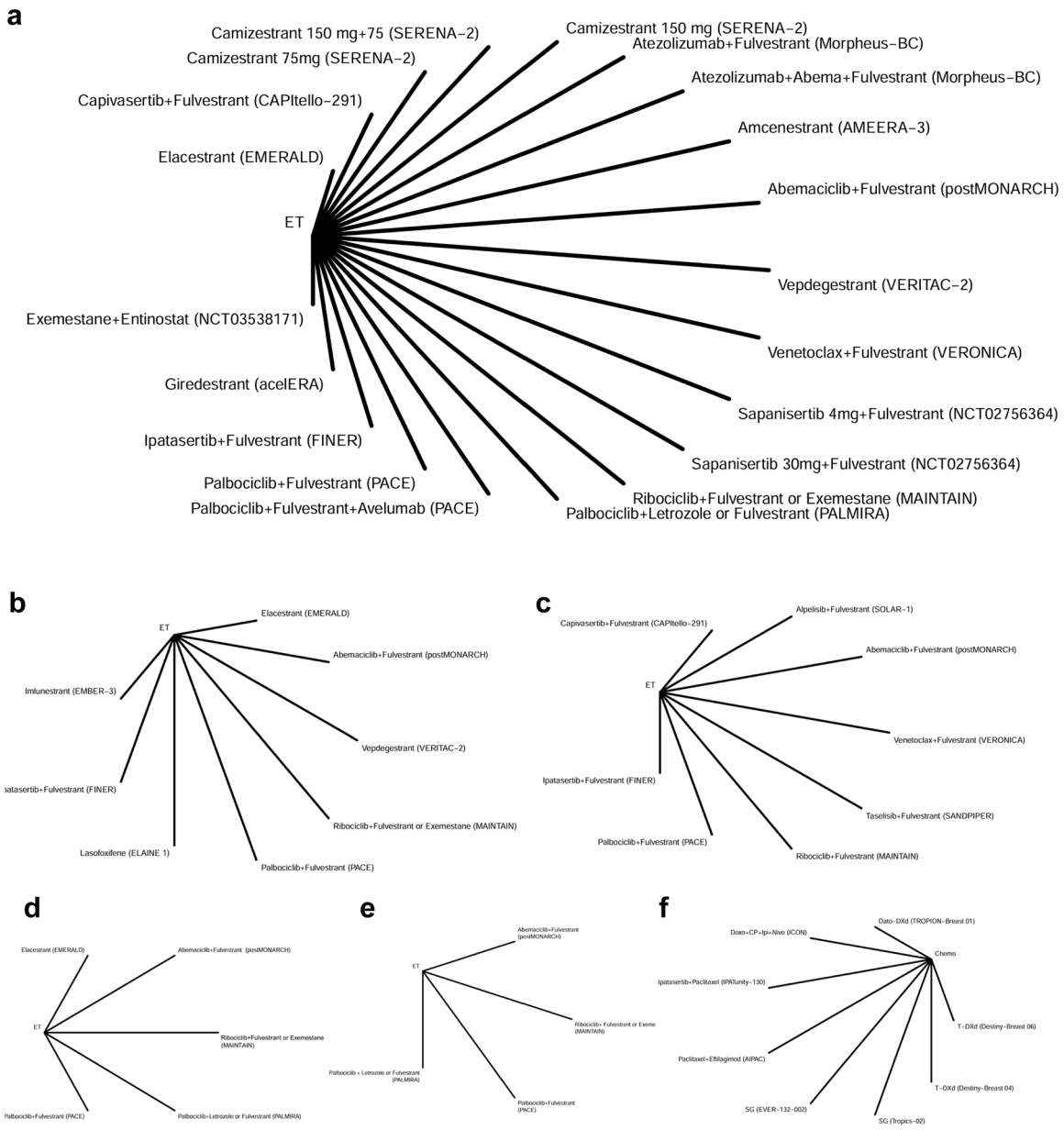


***Fig. 2:*** Network plot for PFS in the overall population (a) and across molecular and clinical subgroups (b–f). (b) ESR1 mutated group; (c) PI3K/AKT altered pathway group; (d) CDK4/6i ≥ 12 months group; (e) CDK4/6i ≤ 12 months group; (f) chemo-related group.

(0.988), respectively. Within the chemotherapy-based network, T-DXd (0.830) and SG (0.789) showed the highest P-scores. Full P-scores values for all treatments across networks, league tables, and heatmaps for pairwise treatment comparisons are provided in the Supplementary Material (Supplementary Figs. S2 and S3, and Table S4).

*Safety*

A descriptive analysis of AEs was further performed, including all-grade AEs, grade ≥3 AEs, and AEs leading to study drug discontinuation or death. Notably, there was substantial inconsistency in AEs reporting across studies. AEs were variably described as treatment-related, treatment-emergent, or simply reported without a standardized classification, which limits direct comparability of safety outcomes (Table 2).

The incidence of grade ≥3 AEs in the experimental arms of included trials ranged from 4% (giredestrant, acelERA)[49] to 82% (SG, EVER-132-002).[45] Neutropenia was the most frequently reported grade ≥3 AE, especially in trials involving ADCs–EVER-132-002[45] (82%),

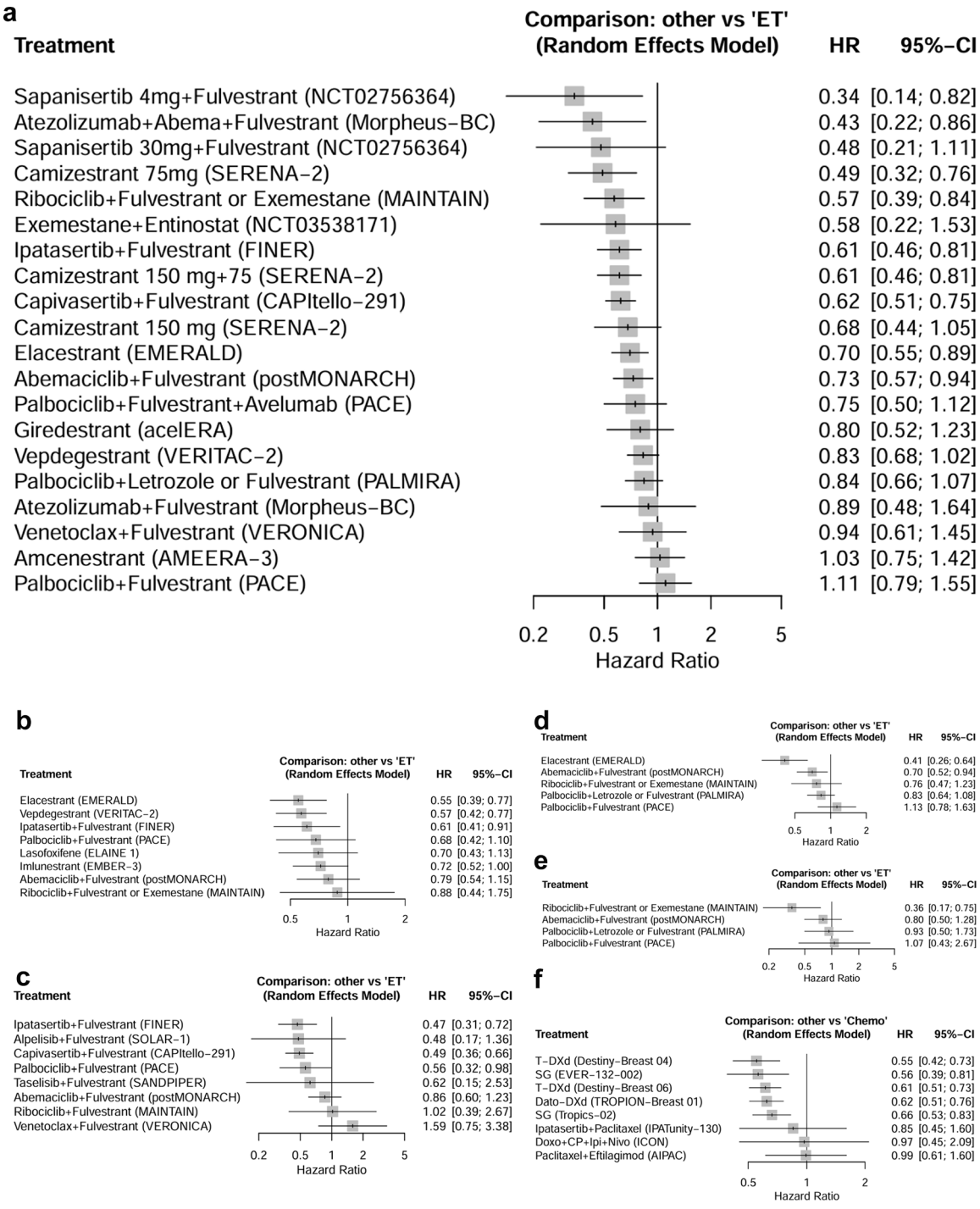


***Fig. 3:*** Forest plot of PFS in the overall population (a) and across molecular and clinical subgroups (b–f). (b) *ESR1* mutated group; (c) PI3K/AKT altered pathway group; (d) CDK4/6i $\geq$ 12 months group; (e) CDK4/6i $\leq$ 12 months group; (f) chemo-related group.

TROPiCS-02[29] (74%), and DESTINY-Breast04[22] (54%)–as well as experimental chemotherapy-based regimens such those evaluated in the CONTESSA[67] (71%) and ICON[70] (73%) trials.

The combination of sapanisertib plus fulvestrant (NCT02756364)[66] was associated with a high incidence of grade $\geq$3 vomiting and skin rash (>60%) and reported the highest treatment discontinuation rate (>30%)

| Trials | Phase | Discontinuation exp (%) | Discontinuation cont (%) | G5 AE exp (%) | G5 AE cont (%) | G ≥ 3 AE exp (%) | G ≥ 3 AE cont (%) | Most common G ≥ 3 AE exp | Most common G ≥ 3 AE cont | Most common Any Grade AE exp | Most common Any Grade AE cont |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MAINTAIN[37] | II | 8.3° | 1.7° | 3.33 | 1.69 | – | – | Neutropenia° | AST increase° | Neutropenia° | Fatigue° |
| PALMIRA[38] | II | NA | NA | 0 | 0 | 45.2° | 8.3° | NA | NA | NA | NA |
| PACE[39] | II | NA | NA | 0 | 0 | 41.8 | 1.9 | Neutropenia | None | Neutropenia | Fatigue |
| postMONARCH[40] | II | 6° | 0° | 0.6 | 0 | 30.4° | 10.8° | Neutropenia° | Anemia° | Diarrhea° | Fatigue° |
| PADA-1[41] | III | 0° | 1.19° | 0 | 0 | 44.3° | 41.7° | Neutropenia° | Neutropenia° | NA | NA |
| MORPHEUS BC (1)[42] | IB/II | 7* | 0* | 0° | 0° | 43 | 0 | NA | NA | Nausea, fatigue, neutropenia, asthenia, QT interval prolongation | Fatigue |
| MORPHEUS BC (2)[42] | IB/II | 0* | 0* | 0° | 0° | 60 | 0 | NA | NA | Diarrhea, nausea, abdominal pain, fatigue, neutropenia, vomiting, decreased appetite | Fatigue |
| DESTINY-Breast04[27] | III | 16.2° | 8.1° | 2.1 | 0 | 52.6° | 67.4° | Neutropenia | Neutropenia | Nausea | Fatigue |
| DESTINY-Breast06[23] | III | 14.3° | 9.4° | 1.2 | 0 | 52.8° | 44.4° | Neutropenia° | Neutropenia° | Nausea | Fatigue |
| TROPiCS-02[24,29] | III | 6^ | 4^ | 0.4 | 0 | 74^ | 60^ | Neutropenia | Neutropenia | Neutropenia | Neutropenia |
| NCT06105008[43] | II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NCT05904964[44] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| DYNASTY-Breast02[47] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| TROPION-Breast01[25] | III | 2.5 | 2.7 | 0 | 0.3 | 20.8 | 44.7 | Stomatitis | Neutropenia | Nausea | Neutropenia |
| EMERALD[17] | III | 3.4 | 0.9 | 0 | 0 | 7.2 | 3.1 | Nausea, back pain° | Nausea, fatigue, diarrhea, AST increase° | Nausea° | Nausea, fatigue° |
| acelERA[49] | II | 1.3° | 2° | 0.7° | 0.7° | 4 | 2.6 | AST increase° | Anemia° | Hepatotoxicity° | Musculoskeletal pain° |
| SERENA-2[18] | II | 3 (75 mg) - 0 (150 mg) | 0 | 0 (75 mg) – 0 (150 mg) | 0 | 1 (75 mg) - 3 (150 mg) | 0 | None (75 mg)^ - fatigue, hypertension (150 mg)^ | Anemia, pleural effusion^ | Photopsia (75 mg)^ Photopsia (150 mg)^ | AST increase^ |
| AMEERA-3[51] | II | 3.5° | 1.4° | 3.5^ | 1.4^ | – | – | Nausea^ | Back pain^ | Nausea^ | Fatigue^ |
| EMBER-3[55] | III | 4 (I)- 6 (I + A)° | 1° | NA | NA | 17 (I) - 49 (I + A) | 21 | Anemia (I) - Neutropenia (I + A) | Anemia | Fatigue (I) - Diarrhea (I + A) | Arthralgia |
| ELAINE-1[56] | II | 0 | 2.1 | 0 | 0 | 19.6 | 20.8 | Anemia/ Hypertension | Anemia | Nausea | Fatigue |
| VERITAC-2[57] | III | 1.6 | 0.3 | 0 | 0 | 7.7 | 2.9 | Neutropenia | Fatigue | Fatigue | Fatigue |
| SOLAR-1[14] | III | 3°,*** | 1.7°,*** | NA | NA | – | – | NA | NA | Hyperglycemia | Nausea |
| SANDPIPER[58] | III | 16.8° | 2.3° | 1.9 | 0.5 | 49.5 | 16.4 | Diarrhea | Hypertension | Diarrhea | Nausea |
| MORPHEUS-BC (4) [86] | IB/II | 8.3 | 0 | NA | NA | 37.5 | 12.5 | NA | NA | Diarrhea | Fatigue |
| EPIK-B5[61] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| VIKTORIA-1[62] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| INAVO-121 [88] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| CAPitello-291[16] | III | 13° | 2.3° | NA | NA | – | – | Rash | NA | Diarrhea | Diarrhea |
| METEORA[13] | II | 21.4° | 25.4° | NA | NA | 42.9 | 28.6 | NA | NA | NA | NA |
| NCT02756364[66] | II | 31.9 (4 mg/die) - 36.2 (30 mg/die) | 4.3 | NA | NA | 74.5 (4 mg/die) - 66 (30 mg/die) | 30.4 | Rash (4 mg/die) - Vomiting (30 mg/die) | None | Hyperglycemia (4 mg/die) - Nausea (30 mg/die) | Headache |
| XENERA-1[69] | II | 14° | 19.6° | 0 | 0 | 56 | 54.9 | Fatigue | Stomatitis | Diarrhea | Diarrhea, fatigue, decreased appetite |
| MORPHEUS BC (3)[52] | IB/II | 6.7 | NA | NA | NA | 5 | NA | NA | NA | Dysgeusia | NA |

(Table 2 continues on next page)

| Trials | Phase | Discontinuation exp (%) | Discontinuation cont (%) | G5 AE exp (%) | G5 AE cont (%) | G ≥ 3 AE exp (%) | G ≥ 3 AE cont (%) | Most common G ≥ 3 AE exp | Most common G ≥ 3 AE cont | Most common Any Grade AE exp | Most common Any Grade AE cont |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | | | | |
| MORPHEUS HR + BC[75] | IB/II | 20.5° (Abemaciclib) – 6.7° | 0 | NA | NA | 82.1 (Abemaciclib) - 26.7 | 15 | NA | NA | 0 | Diarrhea (+Abemaciclib) - Fatigue |
| evERA[53] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ADELA[54] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NCT03409198 (ICON)[70] | II | 22° | NA | NA | NA | 73 | 39 | Lymphopenia | Lymphopenia | Lymphopenia | Constipation |
| AMBITION[73] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| KEYNOTE B-49[74] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| TBCCRC041[76] | II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| AIPAC-003[68] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ENABLAR-2[78] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| FORTRESS[79] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NCT03538171[80] | III | 14 | 6 | 1.3 | 0 | 65.5° | 19.3° | Neutropenia, AST increase | GGT increase | Neutropenia | AST increase |
| E2112[81] | III | 16 | 8 | NA | NA | 51° | 16° | Neutropenia | Anemia | NA | NA |
| SUMIT-BC[82] | II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| VERONICA[83] | II | NA | NA | 2 (% leading to death) | NA | 12° | 2° | Neutropenia | Fatigue | Nausea | Fatigue/ Headache |
| EVER-132-002[45] | III | NA | NA | NA | NA | 82^ | 70^ | Neutropenia | Neutropenia | Neutropenia | Neutropenia |
| NCT06374459[84] | Ib/II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NCT05181033[85] | II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| CONTESSA 2[67] | III | 23.1 | 11.9 | NA | NA | NA | NA | Neutropenia | Hand-foot syndrome | NA | NA |
| OPERA-01[50] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ASCENT-07[46] | III | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Young-PALETTA, KCSG BR21-09[72] | II | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| FINER[60] | III | 6.5 | 0.8 | 0 | 0 | 37.1 | 27.4 | Diarrhea | Nausea/ Vomiting | Diarrhea | Hyperglycemia |
| NCT03051659[71] | II | NA | NA | 5 | NA | 68° | 61° | Neutropenia | Neutropenia | Fatigue | Fatigue |
| REVERT[65] | II | 6.7 | 14.3 | NA | NA | 53.3 | 28.6 | Neutropenia | Neutropenia, Febrile neutropenia | Fatigue | Alopecia |
| AIPAC[77] | IIb | 6.1 | 8 | 2.7 | 1.8 | 68.4° | 65.2° | Anemia | GGT increase | Fatigue | Alopecia |
| SACI-IO HR +[48] | II | 5.8 | 1.9 | NA | NA | NA | NA | Neutropenia | Neutropenia | NA | NA |
| MORPHEUS BC (5)[86] | IB/II | 13.3° | 0* | NA | NA | NA | NA | NA | NA | Diarrhea | Fatigue/Diarrhea |
| IPATunity130[64] | III | 30 | 13 | 3 | 1 | 55 | 47 | Diarrhea | Neutropenia | Diarrhea | Alopecia |

exp = experimental; cont = control; GGT = gamma-glutamyl transferase; AST = aspartate aminotransferase; - = not reported for overall G ≥ 3; NA = not available; ° = AE; * = AE/TRAE;^= treatment-emergent adverse events; I = Imlunestrant; I + A = Imlunestrant + Abemaciclib; *** = *PIK3CA* mutated cohort.

***Table 2:*** **Reported adverse events in phase II-III trials including patients pre-treated with CDK4/6 inhibitors.**

among all regimens, followed by vinorelbine, cyclophosphamide, and capecitabine (VEX) regimen[13] (21,4%, METEORA-II trial) and taselisib plus fulvestrant[58] (16.8%, SANDPIPER). Grade 5 AEs were generally uncommon (Table 2). However, their highest incidence was observed with entinostat plus exemestane[81] (6%, E2112), followed by T-DXd[22] (3.66%, DESTINY-Breast04), amcenestrant[51] (3%, AMEERA-3), and eribulin plus pembrolizumab[71] (5%, NCT03051659). Additional details regarding the incidence and type of AEs are provided in Table 2.

### Risk of bias

The distribution of risk of bias (RoB) across the included studies was visualized using a traffic light plot and a contribution analysis matrix (Fig. 4a and b). The traffic light plot revealed that the majority of randomized controlled trials exhibited an overall low risk of bias. Specifically, twenty-one out of twenty-eight studies (75%) were classified as having a low RoB, whereas only five (18%) and two trials (7%) were classified as a high and moderate risk, respectively. The most frequently identified sources of bias included: deviations from intended interventions, missing outcome data, and outcome measurement. In contrast, other domains such as randomization process and selection of the reported result were generally well addressed, with a predominance of low concern RoB. The contribution matrix further quantified the impact of each domain on the overall estimates. Bias due to missing outcome data and measurement of outcome contributed the most to the overall bias. Conversely, domains such as the randomization process, deviations from intended interventions, and selection in results reporting, had a limited impact, with over 70% of the studies rated as low-risk. The CINeMA framework[33] was employed to assess the certainty of evidence across the primary network comparisons. The main factors limiting the robustness of the evidence were heterogeneity, imprecision, and incoherence. In contrast, within-study bias, reporting bias, and indirectness were found to have minimal impact on the overall assessment. Of two hundred and ten pairwise comparisons evaluated, one hundred and one (48%) were rated as moderate-certainty evidence, while one hundred and seven (52%) were judged to be of low certainty. No comparisons were classified as having very low certainty. Additional details are provided in Supplementary Table S5.

## Discussion

In this study, we conducted a systematic review and frequentist NMA of phase II–III RCTs evaluating therapeutic strategies for patients with HR+/HER2– mBC following progression on CDK4/6i. We found that oral SERDs or combinations of ET and targeted biological agents selected based on genomic biomarkers are associated with the highest clinical benefit when compared to prior ET treatments. We also found that T-DXd and SG are associated with higher efficacy when compared to old chemotherapy regimens. Our findings corroborate recommendations on treatment selection provided by international guidelines and offer additional insights into the optimization of therapeutic sequencing in the post-CDK4/6i setting.

Despite the latest advances in mBC treatment landscape, among the fifty-six identified trials, only 29 (52%) reported PFS outcomes specifically for CDK4/6i-pretreated patients. This reflects a major limitation in the available clinical evidence, especially because ET plus CDK4/6i is now the standard-of-care first-line setting for most patients diagnosed with HR+/HER2– mBC. Notably, pivotal trials supporting guideline-recommended second-line therapies, such as BOLERO-2 (everolimus plus exemestane),[11] EMBRACA (talazoparib),[21] and OLYMPIAD (olaparib),[20] enrolled exclusively CDK4/6i-naïve patients. Therefore, the use of these treatments in the post-CDK4/6i setting is primarily supported by retrospective analyses,[12,88] real-world evidence[89] and small non-randomized trials.[90,91] A recent multicentre retrospective cohort study[92] including five hundred and six patients with HR +/HER2– mBC progressing on ET plus CDK4/6i reported lower PFS with ET plus everolimus or ET alone when compared to oral chemotherapy. Furthermore, intravenous chemotherapy was associated with shorter PFS and overall survival (OS) than oral chemotherapy, particularly in patients with visceral metastases.[92] These findings align with the results of the METEORA-II study,[13] which was excluded from our NMA as outcomes were not reported for the subgroup of patients previously treated with CDK4/6i. Firstly, we conducted a NMA to compare treatment efficacy in the post-CDK4/6i setting in unselected patient populations. Sapanisertib plus fulvestrant (NCT02756364)[66] ranked as the most effective regimen in the overall network analysis (HR 0.34; P-score 0.901), but it was associated with high toxicity and a 36% treatment discontinuation rate, ultimately leading to the discontinuation of the clinical development of this combination. Among investigational regimens, the triplet combination of atezolizumab plus abemaciclib plus fulvestrant (MORPHEUS HR + BC),[75] showed promising results (HR 0.43; P-score 0.840), although efficacy data were derived from an interim analysis of which PFS was a secondary endpoint.[75] Therefore, the robustness of these results remains limited and warrants cautious interpretation. Among currently available options, ribociclib plus fulvestrant (MAINTAIN)[37] showed the most favorable efficacy profile, followed by capivasertib plus fulvestrant (CAPItello-291)[16] and elacestrant (EMERALD).[17] However, cross-trial comparisons are limited by differences in study design and patient

a Risk of Bias Assessment for Each Trial Included in the NMA (Unselected population)


*Fig. 4:* Risk of bias: Traffic Light Plot (a) and contribution matrix (b).

eligibility, such as prior CDK4/6i or chemotherapy exposure. Prior CDK4/6i therapy was required in both EMERALD[17] and MAINTAIN,[37] whereas CAPItello-291 enrolled both patients with (69%) and without prior exposure to CDK4/6i[16] (Table 1). In addition, prior chemotherapy was permitted in EMERALD[17] and CAPItello-291,[16] but not in MAINTAIN.[37] It is important to note that the EMBER-3 trial[55] was not included in the primary network meta-analysis, as efficacy results in the post-CDK4/6 inhibitor population were only available for the comparison between imlunestrant plus abemaciclib vs. imlunestrant alone, and not against

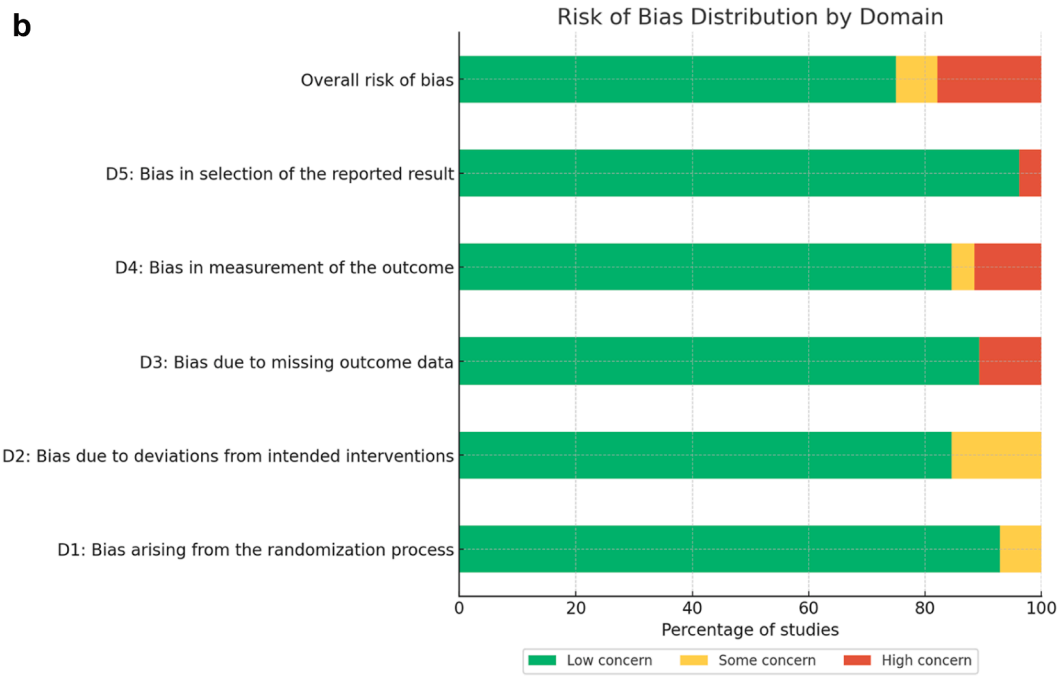


*Fig. 4:* Continued.

standard endocrine therapy. However, EMBER-3 was included in the *ESR1*-mutant subgroup network meta-analysis, as relevant efficacy data were available in the CDK4/6i-pretreated population.

Secondly, we performed subgroup analyses to evaluate the efficacy of available treatments in specific, and clinically relevant patient populations. Among patients with *ESR1*-mutated tumors, the oral SERD elacestrant (EMERALD) demonstrated the most pronounced clinical benefit when compared to conventional ET. These findings strengthen current international guideline recommendations[7,8] which favor elacestrant for patients with *ESR1*-mutant HR+/HER2– mBC, and more broadly support the conclusion that PFS benefit associated with oral SERDs is primarily driven by tumors harboring *ESR1* mutations.[7,8,93] Notably, the AMEERA-3,[51] SERENA-2,[18] and acelERA[60] trials, which evaluated oral SERDs, did not report outcomes stratified by prior CDK4/6i exposure in patients with *ESR1* mutations and were therefore excluded from the analysis.

In the PI3K/PTEN/AKT pathway-altered group, the combinations of ipatasertib plus fulvestrant (FINER),[60] alpelisib plus fulvestrant (SOLAR-1 trial),[14] and capivasertib plus fulvestrant (CAPItello-291 trial)[16] were associated with the most favorable hazard ratios. Among these treatment combinations, ipatasertib plus fulvestrant achieved the highest P-score (0.789). Notably, the FINER study[60] included only patients previously treated with CDK4/6i, of whom one hundred and one (45%) had alterations in the PI3K/PTEN/AKT pathway. On the contrary, the SOLAR-1 trial,[14] included a negligible proportion of patients previously treated with CDK4/6i (n = 20) in the *PIK3CA*-mutant cohort, thus preventing any reliable conclusion in this setting. The multi-cohort phase II BYLieve trial[94] confirmed the efficacy of alpelisib plus fulvestrant in patients previously exposed to CDK4/6i, but it was excluded from this NMA due to its non-comparative design. The ongoing EPIK-B5 trial,[61] which is evaluating alpelisib plus fulvestrant vs. fulvestrant alone in CDK4/6i-pretreated *PIK3CA*-mutant disease, is expected to provide more definitive evidence. In contrast, in the phase III CAPItello-291[16] a clinically meaningful proportion of patients with altered PI3K/PTEN/AKT pathway was previously exposed to CDK4/6i (72%, n = 208). Capivasertib plus fulvestrant combination has emerged as the current standard of care for HR+/HER2– mBC harboring alterations not only in *PIK3CA*, but also in *AKT1* or *PTEN* genes. Interestingly, the combination of palbociclib plus fulvestrant showed a PFS benefit in *PIK3CA*-mutant mBC (HR 0,56; P score 0.715), as observed in the phase II PACE trial.[39] However, the clinical relevance of these findings is low, especially in the light of the recent FDA approval of the palbociclib plus fulvestrant plus inavolisib regimen as a first-line treatment option for *PIK3CA*-mutant HR+/HER2– mBC.[95] Combinations involving ribociclib (MAINTAIN)[37] or abemaciclib (postMONARCH)[40] upon tumor progression to prior ET plus CDK4/6i did not replicate this benefit, raising questions about the efficacy of

CDK4/6 inhibition beyond progression in *PIK3CA*-mutant disease. On the other hand, ribociclib plus fulvestrant (MAINTAIN)[37] demonstrated the greatest benefit in patients with ≤12 months of prior CDK4/6i therapy (HR 0.36); however, the limited representation of this subgroup, together with the absence of key comparators such as ADCs and chemotherapy, both of which are effective strategies in endocrine-resistant disease, limit the clinical applicability of these findings. Conversely, elacestrant showed the most favorable outcome (HR 0.41) in patients who experienced a sustained benefit from CDK4/6i therapy (≥12 months).[87] These results align with the emerging treatment paradigm, which identifies patients with *ESR1* mutations and prolonged sensitivity to CDK4/6i as optimal candidates for elacestrant. However, drawing definitive conclusions regarding treatment sensitivity based on the duration of prior CDK4/6i exposure remains challenging, as these subgroups were not consistently pre-specified across trials and exhibited substantial heterogeneity in both their definition and reporting (Supplementary Table S4).

Thirdly, a separate network using conventional chemotherapy as the common comparator showed that ADCs–particularly T-DXd (DESTINY-Breast04)[22] and SG (EVER 132 002)[45]–consistently ranked as the most effective treatments. However, efficacy estimates were influenced by differences in trial design, patient selection and prior treatment exposure. As an example, prior chemotherapy for mBC was not permitted in the DESTINY-Breast06 trial,[96] whereas patients enrolled in the DESTINY-Breast04[22] and TROPION-Breast01[25] received 1–2 prior chemotherapy lines; finally, a minimum of two, and a maximum of four prior chemotherapy lines were needed for patient enrollment in the EVER-132-002[45] and TROPiCS-02 trials.[29] Conventional chemotherapy and experimental chemotherapy-based combinations demonstrated limited clinical benefit, further underscoring the progressive displacement of conventional chemotherapy by next generation ADCs in the post-CDK4/6i treatment setting.

We finally performed a descriptive analysis of treatment-related toxicities. AE reporting varied substantially across studies, thus complicating cross-trial comparisons. Nausea and asthenia were the most common AEs observed across treatment classes. As expected, chemotherapy and ADCs were associated with the highest incidence of grade ≥3 AEs and treatment discontinuation rates. Notably, T-DXd was associated with a 14% discontinuation rate and with 52.6% incidence of grade ≥3 AEs (DESTINY-Breast04).[22] Everolimus plus exemestane (XENERA-1)[69] and capivasertib plus fulvestrant (CAPItello-291)[16] were also associated with significant toxicities, with grade ≥3 cutaneous rash and stomatitis occurring in 12% and 56% of cases, respectively, and discontinuation rates exceeding 10%, highlighting the need for individualized treatment selection and careful toxicity monitoring.

Previous studies have investigated the efficacy of systemic therapies in patients with HR+/HER2– metastatic breast cancer who experienced disease progression on CDK4/6 inhibitors, using trial-level aggregate data[97,98] or individual patient data reconstructed from Kaplan–Meier curves.[99] In line with our findings, these analyses demonstrated a significant benefit from continuing a CDK4/6 inhibitor in combination with ET, compared to ET monotherapy, even among patients with visceral metastases or ESR1 mutations.[98] Additionally, one study reported superior outcomes with capivasertib over alpelisib in patients with PI3K/AKT/mTOR pathway alterations.[97] Differences between our results and those of previous studies may be attributed to the greater number and more recent inclusion of randomized trials in our analysis. To the best of our knowledge, our study represents the most comprehensive and up-to-date synthesis of randomized evidence in this setting, incorporating 28 trials. Furthermore, unlike previous metanalyses that aggregated agents within the same therapeutic class, our network meta-analysis assessed individual treatments, thereby capturing distinct efficacy and safety profiles for each therapeutic option. Lastly, the inclusion of biomarker-defined subgroup analyses further enhanced the clinical relevance of our findings, supporting a more personalized and biomarker-driven approach to treatment selection.

Our study has several limitations. First, the NMA relied on a star-shaped configuration, which limited the number of direct head-to-head comparisons; this may have reduced the robustness of certain indirect estimates. Second, heterogeneity in inclusion criteria and prior therapies across trials may have impacted comparability of treatment effects. Third, RoB assessment and application of the CINeMA framework revealed methodological concerns related to missing outcome data and outcome measurement, which may reduce the reliability of some estimates. Furthermore, it is important to acknowledge that indirect comparisons within the network meta-analysis are exploratory and hypothesis-generating rather than confirmatory. As such, the results should be interpreted with appropriate caution. Finally, other important clinical or molecular variables, such as genomic alterations or the presence of visceral metastases or imminent organ failure, could not be evaluated due to limited reporting. The therapeutic landscape following progression on first-line CDK4/6i in HR+/HER2– mBC is rapidly evolving, yet selecting the most appropriate treatment option remains challenging. Current endocrine-based therapies and their combinations with targeted agents have yielded only modest improvements in PFS, with no consistent OS benefit reported to date. Nevertheless, clinical research in the second-line setting play a pivotal role in informing the development of future first-line strategies. This transition is already underway for several investigational agents; for instance, the

SERENA-6 trial[38] recently demonstrated that camizestrant may be effective in patients with emerging *ESR1* mutations during first-line endocrine therapy plus CDK4/6 inhibition, suggesting that *ESR1* mutations are becoming actionable earlier in the disease course. Pending results from ongoing clinical trials that are expected to redefine early-line therapeutic options for patients with HR+/HER2– mBC, this study provides, to our knowledge, the most comprehensive systematic review and NMA to date comparing the efficacy and toxicity profiles of currently available post-CDK4/6i treatment strategies. Our findings highlight substantial heterogeneity in treatment outcomes across clinical and molecular subgroups, reinforcing the importance of biomarker-driven therapeutic decision-making. Overall, our results suggest that combinations of targeted agents with endocrine therapy, or novel endocrine agents, offer favorable efficacy and safety profiles, particularly in the presence of actionable molecular alterations, underscoring the need to transition toward biomarker-driven treatment algorithms. In cases where tumors exhibit features of endocrine resistance and a chemotherapy-based approach is deemed necessary; ADCs have shown the highest efficacy compared to standard single-agent chemotherapy. As the treatment armamentarium continues to expand, the integration of emerging comparative data will be critical to refine prognostic models and support personalized treatment strategies in the post-CDK4/6i setting.

#### Contributors

Carmine De Angelis, Roberto Buonaiuto, and Michelino De Laurentiis were responsible for the conception and design of the study. Carmine De Angelis, Roberto Buonaiuto, Mario Fordellone, Paolo Chiodini, Aldo Caltavituro, Mario Giuliano, and Michelino De Laurentiis contributed to data analysis. All authors participated in the interpretation of the data, critically revised the manuscript, and approved the final version for submission.

#### Data sharing statement

All data used in this network meta-analysis are publicly available from the original publications. No individual patient data were accessed, and therefore no raw data can be shared. The study was prospectively registered in PROSPERO (CRD42024604417). For any further information, requests can be addressed to the corresponding author by email.

#### Declaration of interests

Carmen Criscitiello: Consultancy, advisory roles, or speaker bureau participation with Pfizer, MSD, Roche, Novartis, Lilly, Gilead, Seagen, Daiichi Sankyo, AstraZeneca, and Stemline. Maria Vittoria Dieci: Personal fees for consultancy, speaker honoraria or advisory roles from Eli Lilly, Pfizer, Novartis, Roche, MSD, AstraZeneca, Daiichi Sankyo, Gilead, Seagen, and Exact Sciences research funding from Roche (Institution); travel grant from Gilead, Daiichi Sankyo, Roche, EliLilly, AstraZeneca; MVD is also listed as an inventor on patent applications for the HER2DX assay. Matteo Lambertini: advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, Menarini; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Menarini, AstraZeneca; travel Grants from Gilead, Daiichi Sankyo, Roche; research funding (to the Institution) from Gilead all outside the submitted work. Andrea Botticelli: Personal fees for consultancy and advisory roles from EliLilly, Novartis, Pfizer, Roche, BMS, AstraZeneca, MSD, Daiichi Sankyo, Gilead and Seagen. Mario Giuliano: advisory role and honoraria from AstraZeneca, Daichii Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Menarini Stemline; MSD, Novartis, Pfizer, Roche, Seagen. Support for travels and accommodations from Lilly, Pfizer, AstraZeneca. Research funding to the institution from AstraZeneca. Antonio Giordano: personal fees from Pfizer and Novartis outside the submitted work. Roberta Caputo: advisory roles with Roche, Lilly, Novartis, MSD, Gilead, Daiichi Sankyo, and Pierre-Fabre. Martina Pagliuca: research grant from Gilead (to Institution), travel and accommodation support from Ipsen. Lorenzo Gerratana: Consulting or advisory roles with AstraZeneca, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Incyte, Novartis, Pfizer, Merck Sharp & Dohme, Menarini Stemline, and AbbVie; travel expenses covered by Menarini Stemline and Novartis. Luca Malorni: Honoraria received from Pfizer, Novartis, and Seagen; consulting or advisory roles with Pfizer, Novartis, Seagen, Roche, and Menarini Group; research funding from Pfizer and Novartis; travel, accommodations, and expenses covered by Roche, Janssen, Gilead Sciences, and Menarini Group. Novartis. Grazia Arpino: consulting fees from Roche, AstraZeneca, Novartis, Lilly, MSD, Pfizer; honoraria from Roche, AstraZeneca, Novartis, Lilly, MSD, Pfizer; travel accommodations from Roche, AstraZeneca, Novartis, Lilly, MSD, Pfizer. Michelino De Laurentiis: advisory boards, activities as a speaker, travel grants, consultancy: Eli Lilly, Novartis, Seagen, Takeda, Roche, Daiichi Sankyo, Tomalab, Gilead, Genetic, Menarini, Sophos, AstraZeneca, Pfizer, Sanofi, Ipsen, Pierre Fabre, GSK. Carmine De Angelis: advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Gilead, Daiichi Sankyo and GSK; speaker honoraria from Roche, Lilly, Novartis, Pfizer, and GSK; Travel Grants from Gilead and research support (to the Institution) from Novartis, GILEAD and Daiichi Sankyo outside the submitted work. Claudio Vernieri: grants from Roche, Daiichi Sankyo, Astra Zeneca; consulting fees from Pfizer, Novartis, Eli Lilly, Gilead; honoraria from Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, AstraZeneca, Istituto Gentili, MSD, Menarini Stemline, Accademia Nazionale di Medicina; support for attending meetings from Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, AstraZeneca, Istituto Gentili, MSD, Menarini Stemline, Accademia Nazionale di Medicina; advisory board from Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, AstraZeneca, Menarini Stemline. Aldo Caltavituro: honoraria from Eli Lilly, Accademia Nazionale di Medicina, XENIA, Uvet Congress and Learning Srl, Andromeda; receipt of drugs, medical writing: Genetic farma spa, Gentili s. r.l The remaining authors declare that they have no conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103535.

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