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Unmet clinical need in patients with pre-treated hormone receptor-positive/HER2-negative (HR+/HER2–) metastatic breast cancer in routine care: a targeted literature review

Laura Spring[1], Simon M Collin[2], Inderjit K Dhillon[2], Gráinne Long[2], Evelina Bertranou[2], Komal Jhaveri[3], Aditya Bardia[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Oncology Business Unit, AstraZeneca Pharmaceuticals, Cambridge, UK; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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Background

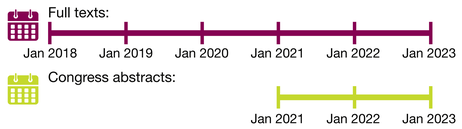
- Patients with HR+/HER2– MBC for whom ET has failed, either with or without the use of CDK4/6i or PI3K pathway inhibitors, have limited targeted treatment options.
- Traditionally, post-ET management has relied on CT, which is associated with low response rates that diminish with subsequent therapy lines.
- We reviewed published literature to understand real-world outcomes for patients with HR+/HER2– MBC, including ET resistance, survival with CT, tolerability, and discontinuation.

Methods

Search

- MEDLINE, Embase, and the Cochrane Library were searched via Ovid for observational studies, supplemented by hand searching for congress abstracts.
- All screening was performed by one reviewer, and any uncertainties were resolved by a senior reviewer.

Date restrictions



PICOS

- Studies were included based on pre-defined criteria.
  - Patients with HR+/HER2– MBC (N ≥ 50 patients).
  - ≥ 1 prior systemic therapy in the metastatic setting.
  - Outcomes: diagnostic testing, treatment sequencing, demographic characteristics, clinical burden of illness, safety, humanistic burden of disease, incidence, and management of stomatitis.
  - Publications in English.

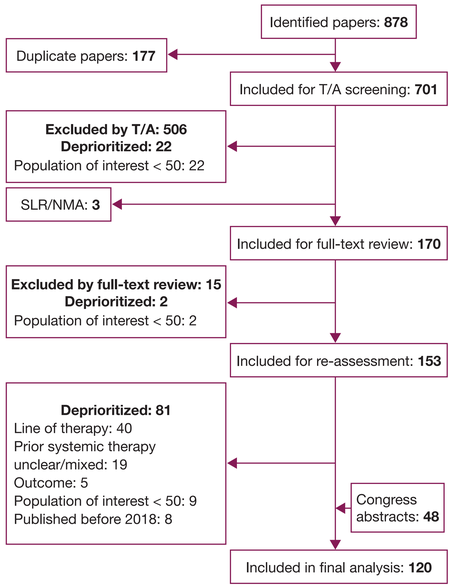
Supplementary material

Results

1. Included studies

- We included 72 full-text publications and 48 congress abstracts (**Figure 1**).
- Most publications were from the USA (39%), followed by Europe (28%), and Asia (23%).

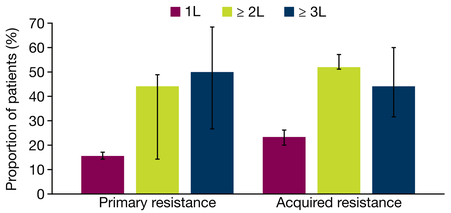
Figure 1. PRISMA flow diagram



2. Treatment characteristics

- Median treatment duration was 1.9–16.2 months for ET (7 studies) and 2.0–24.5 months for ET combination therapy (5 studies).
- Exceptional responders (10% of patients treated for the longest time) received ET for ≥ 43.6 months (1 study, N = 4195).
- The frequency of ET resistance ranged widely (3–100%; 22 studies) and increased by the line of therapy in which CDK4/6i + ET was used (2 studies; **Figure 2**).
- After one or two cycles of ET-based regimens, CT is the current standard of care (**Figure 3**).
- The proportion of patients who did not reach next line of therapy following 1L, 2L, and 3L therapy was 2.2–36.4% (6 studies), 13.7–39.0% (4 studies), and 32.1–37.3% (2 studies), respectively.

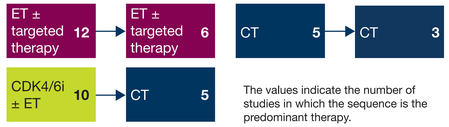
Figure 2. Frequency of ET resistance increased by line of CDK4/6i + ET



The bars show the frequency of ET resistance when the patient populations from the 2 studies were combined. Error bars represent the range of patients with ET resistance reported across the 2 studies.

- Time to ET and/or CDK4/6i discontinuation and time to ET and/or CDK4/6i failure were 4.7–12.4 months (4 studies) and 6.3–8.3 months (2 studies), respectively.
- Time to next treatment following ET and/or CDK4/6i was 4.8–24.6 months (4 studies). Time to CT was 11.5–44.1 months (4 studies).

Figure 3. Most common treatment sequences for main 1L drug classes

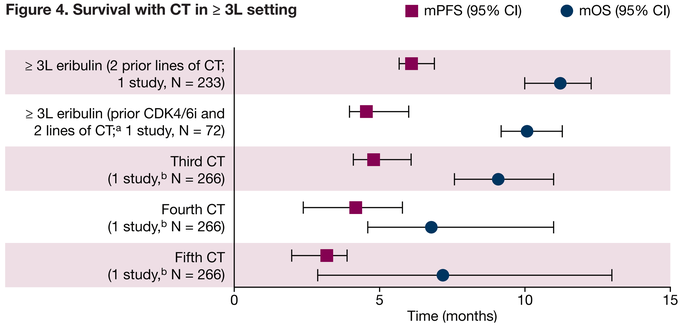


The values indicate the number of studies in which the sequence is the predominant therapy.

3. Clinical outcomes

- Consecutive CT cycles steadily lost clinical benefit in later lines of therapy (**Figure 4**).

Figure 4. Survival with CT in ≥ 3L setting



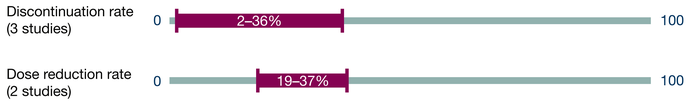
[a]Prior CT includes the adjuvant and metastatic settings. [b]The study also reported survival outcomes for second CT.

- Patients treated between 2014[a] and 2021 whose best response to CDK4/6i was progression, or who had an mPFS of < 6 months on ET, benefited more from CT than ET in the ≥ 2L setting (2 studies):
  - mPFS was 7.1–8.1 months with CT and 1.7–3.9 months with ET.

[a]The TLR excluded studies published before 2018; however, reported data collection periods include earlier time points.

- Most studies reported that one or more prior lines of CT had a negative impact on mOS (5 studies) and mPFS (11 studies) in subsequent lines of therapy, regardless of the chosen treatment.
- CT was associated with significant toxicity (**Figure 5**).
  - Grade 3/4 AEs with CT included leukopenia (17%), neutropenia (7%), thrombocytopenia (3%), and pneumonitis (1–3%) (3 studies).

Figure 5. CT is associated with a significant toxicity burden



Conclusions

- **In patients with HR+/HER2– MBC, the frequency of primary and acquired ET resistance increases steeply after 1L, with patients requiring treatments with an alternative mechanism of action.**
- **Our review of real-world evidence highlights the limited efficacy of repeated CT, characterized by diminishing clinical benefit in later lines.**
- **The results are limited by treatment and study population heterogeneity.**
- **Clinical outcomes are expected to improve with the use of new, more tolerable therapies, for which real-world evidence has yet to accrue.**

Abbreviations

1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; CDK4/6i, inhibitor of cyclin-dependent kinase 4/6; CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; MBC, metastatic breast cancer; mOS, median overall survival; mPFS, median progression-free survival; NMA, network meta-analysis; PI3K, phosphoinositide 3-kinase; PICOS, Population, Intervention, Comparator, Outcome, Study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; T/A, title/abstract.

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Disclosures

SC, GL, and EB are employees of AstraZeneca, and own stock or stock options. ID is a former employee of AstraZeneca. AB: AstraZeneca, Daiichi Sankyo, Eli Lilly, Foundation Medicine, Genentech, Immunomedics/Gilead, Merck, Novartis, Pfizer, Phillips, Radius Health, and Sanofi. LS: AstraZeneca, Daiichi Sankyo, Eli Lilly, G1 Therapeutics, Genentech, Gilead, Merck, Novartis, Phillips, and Puma Biotechnology. KJ: AbbVie, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Context Therapeutics, Daiichi Sankyo, Debio Pharmaceuticals, Eisai, Genentech/Roche, Gilead, Jounce Therapeutics, Lilly Pharmaceuticals/Loxo Oncology, Menarini/Stemline, Merck, Novartis, Olema Pharmaceuticals, Pfizer, Puma Biotechnology, Scorpion Therapeutics, Seattle Genetics, Sun Pharma Advanced Research Company, Taiho Oncology, and Zymeworks.