Unmet Needs in Second-Line Therapy for ER-Positive, HER2-Negative Advanced Breast Cancer

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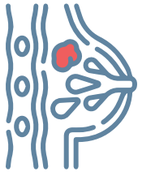
1) First-Line Standard of Care Treatment



First-line standard of care treatment for ER+/HER2- advanced breast cancer is endocrine therapy plus a CDK4/6 inhibitor[1,2]

- The median duration of treatment with endocrine therapy plus a CDK4/6 inhibitor based on pivotal trials is 15-21 months[3-9]

However, most patients will eventually develop resistance to endocrine therapy[7-11]

- Resistance can be classified by clinical and molecular variables[1] [Fig 1]

Figure 1: Mechanisms of resistance to endocrine therapy in ER+/HER2- advanced breast cancer[1,12-16]

Molecular	Clinical
Intrinsic **Alterations to the PI3K/AKT/mTOR pathway, RB1 downregulation, or TP53 activation**	**Primary** **Disease progression within the first 6 months of first-line ET** for aBC
Acquired Mechanisms of resistance **occuring after prior endocrine therapy in aBC**	**Secondary** **Disease progression ≥6 months after initiating ET** for aBC

***ESR1* mutation is a key mechanism of acquired resistance**

Mutation of the **ER** ligand-binding domain causes it to be **constitutively active,** and therefore **ligand independent**

***ESR1* mutations** affect up to **40%** of ER+ aBC cases **previously treated with ET**[17]

2) Second-Line Treatment Options after ET+CD4/6i

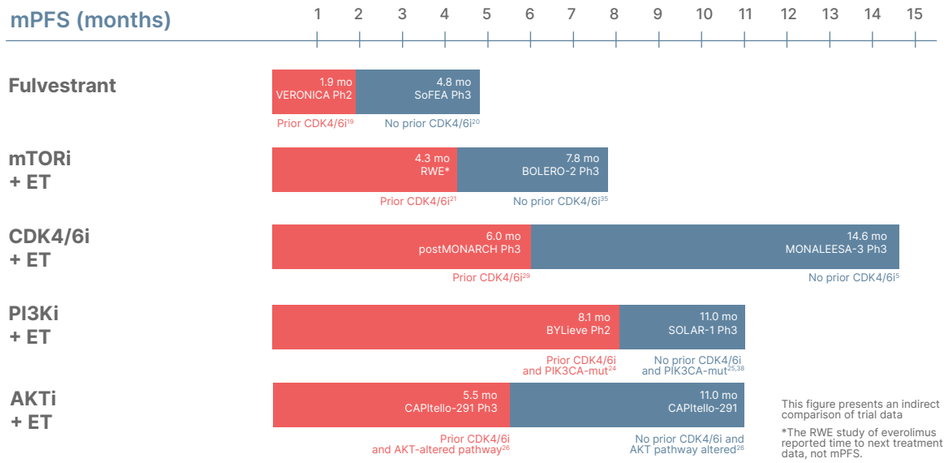
Guidelines recommend exhausting sequential endocrine therapy options following first-line treatment with ETs and CDK4/6 inhibitors[1,2,18]

However:

- Available regimens are far less efficacious in patients with prior CDK4/6 inhibitor exposure[5,19-26] [Fig 2]*
- Most regimens are less efficacious in patients with prior CDK4/6 inhibitor exposure and PIK3CA or *ESR1* mutations than in those without[5,17,20-30] [Fig 3]*
- Combination therapy with CDK4/6 inhibitors is associated with Grade 3/4 AEs of diarrhoea, rash, and hyperglycaemia, and combinations with PI3K/AKT/mTOR pathway inhibitors are associated with myelosuppression and diarrhoea[7,10,31-42] [Fig 4]

* based on indirect comparisons of trial data

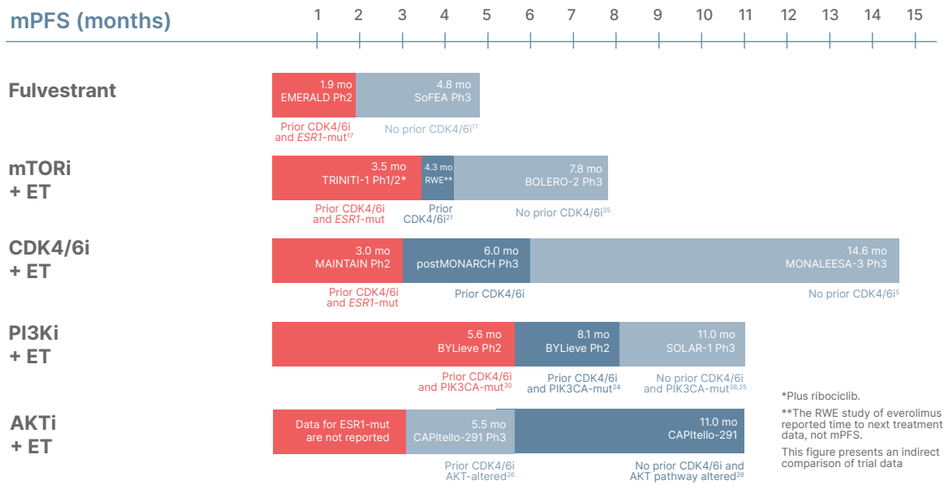
Figure 2: Efficacy of second-line therapy in ER+/HER2- advanced breast cancer with prior CDK4/6 inhibitor therapy



This figure presents an indirect comparison of trial data

*The RWE study of everolimus reported time to next treatment data, not mPFS.

Figure 3: Efficacy of second-line therapy in ER+/HER2- advanced breast cancer with prior CDK4/6 inhibitor therapy and *ESR1* mutation



*Plus ribociclib.

**The RWE study of everolimus reported time to next treatment data, not mPFS.

This figure presents an indirect comparison of trial data

Figure 4: ET combinations with CDK4/6 inhibitors and PI3K/AKT/mTOR inhibitors[7,10,31-42]

AEs and discontinuation rates

CDK4/6 inhibitors

- E.g. neutropenia, leukopenia, infections, and diarrhoea
- Discontinuation due to AEs in up to 19% of patients

PI3K/AKT/mTOR inhibitors

- E.g. diarrhoea, rash, and hyperglycaemia
- Discontinuation due to AEs in up to 24% of patients

Intramuscular injection

Combinations with fulvestrant require intramuscular injection

3) Conclusion

- Treatment of patients who experience disease progression on ET plus CDK4/6 inhibitors is challenging[43]
- Despite the promise shown by multiple targeted and endocrine therapies in this setting, outcomes remain suboptimal, and combination therapies are often associated with AEs[7,10,31-42]
- Resistance mechanisms can be acquired during first-line therapy (i.e., *ESR1*-mut) Testing should be done at each progression (if not detected previously). Blood ctDNA is the preferred methodology[2,18]

Abbreviations

aBC: advanced breast cancer; AE: adverse event; AKT: protein kinase B; CDK4/6: cyclin-dependent kinase 4/6; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; ER: oestrogen receptor; ET: endocrine therapy; FGFR1: fibroblast growth factor receptor 1; HER2: human epidermal growth factor receptor 2; mo: months; mPFS: median progression-free survival; mTOR: mechanistic target of rapamycin; mut: mutation; PARP: poly ADP ribose polymerase; Ph: Phase; PFS: progression-free survival; PI3K: phosphoinositide 3-kinase; RAS-MAPK: rat sarcoma-mitogen-activated protein kinase; RB1: retinoblastoma protein; RWE: real-world evidence; TP53: tumour protein p53.

See references on next page.

References

1. Gennari A et al.; ESMO Guidelines Committee. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95.
2. Burstein HJ et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline Update. J Clin Oncol. 2021;39(35):3959-77.
3. Finn RS et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/ human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2. Abstract LBA1003. ASCO Annual Meeting II, 3-7 June, 2022.
4. Eli Lily and Company. VERZENIO (abemaciclib). FDA prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/ label/2023/208716s010s011lbl.pdf. Last accessed: 3 April 2024.
5. Slamon DJ et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med. 2020;382:514-24.
6. Im SA et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med. 2019;381:307-16.
7. Pfizer. Ibrance (palbociclib). Prescribing information. 2022. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207103s015lbl.pdf. Last accessed: 3 April 2024.
8. Pfizer. Ibrance (palbociclib). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf. Last accessed: 9 July 2024.
9. Hortobagyi GN et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29(7):1541-7.
10. Tripathy D et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-15.
11. Johnston S et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019:5:5.
12. Patel R et al. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ Breast Cancer. 2023;9(1):20.
13. Rani A et al. Endocrine resistance in hormone receptor positive breast cancer-from mechanism to therapy. Front Endocrinol (Lausanne). 2019;10:245.
14. Xu X-Q et al. Intrinsic and acquired resistance to CDK4/6 inhibitors and potential overcoming strategies. Acta Pharmacol Sin. 2021;42(2):171-8.
15. Belachew EB, Sewaseq DT. Molecular mechanisms of endocrine resistance in estrogen-receptor-positive breast cancer. Front Endocrinol. 2021;12:599586.
16. Lei JT et al. Endocrine therapy resistance: new insights. Breast. 2019;48(Suppl 1):S26-30.
17. Bidard F-C et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol. 2022;40(28):3246-56.
18. ESMO. ESMO Metastatic Breast Cancer Living Guideline – ER-positive HER2-negative Breast Cancer. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancerliving-guideline/er-positive-her2-negative-breast-cancer. Last accessed 03 April 2024'
19. Lindeman GJ et al. VERONICA: randomized phase II study of fulvestrant and venetoclax in ER-positive metastatic breast cancer post-CDK4/6 inhibitors - efficacy, safety, and biomarker results. Clin Cancer Res. 2022:28(15):3256-67.
20. Johnston SR et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 2013;14:989–98.
21. Rozenblit M et al. Patterns of treatment with everolimus exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy. Breast Cancer Res. 2021;23(1):14.
22. Yardley DA et al. Everolimus plus exemestane in postmenopausal patients with hr+ breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870–884.
23. Data on file. Presented at ASCO 2024.
24. Chia S et al. Alpelisib + endocrine therapy in patients with PIK3CA-mutated, hormone receptor–positive, human epidermal growth factor receptor 2–negative, advanced breast cancer: Analysis of all 3 cohorts of the BYLieve study. ASCO 2023. P1078.
25. André F, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med 2019;380:1929–40.
26. Turner NC et al. Capivasertib in hormone receptor-positive advanced breast cancer. N Engl J Med 2023;388:2058–70.
27. Bidard F-C et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol. 2022;40(28):3246–56.
28. Hurvitz SA et al. Abstract PD13-03: Ribociclib, everolimus, exemestane triplet therapy in HR+/HER2− advanced breast cancer after progression on a CDK4/6 inhibitor: Final efficacy, safety, and biomarker results from TRINITI-1. Cancer Res. 2022;82(4_Supplement):PD13-03.
29. Kalinsky K et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN Trial. J Clin Oncol. 2023;41:4004–4013.
30. Turner S et al. Abstract PD15-01: Impact of ESR1 mutations on endocrine therapy (ET) plus alpelisib benefit in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced breast cancer (ABC) who progressed on or after prior cyclin-dependent kinase inhibitor (CDK4/6i) therapy in the BYLieve trial. Cancer Res. 2022;82(4_Supplement):PD15-01
31. Novartis. Kisqali (ribociclib). Prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209092s016lbl.pdf. Last accessed: 3 April 2024.
32. Novartis. Kisqali (ribociclib). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_en.pdf. Last accessed: 9 July 2024.
33. Eli Lilly and Company. Verzenio (abemaciclib). Prescribing information. 2023. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208716s010s011lbl.pdf. Last accessed: 3 April 2024.
34. Eli Lilly and Company. Verzenios (abemaciclib). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf. Last accessed: 9 July 2024.
35. Novartis. Afinitor (everolimus). Prescribing information. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203985s023,022334s051lbl.pdf. Last accessed: 3 April 2024.
36. Novartis. Afinitor (everolimus). Summary of product characteristics. 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/afinitor-epar-product-information_en.pdf. Last accessed: 9 July 2024.
37. Novartis. Piqray (alpelisib). Prescribing information. 2024. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf. Last accessed: 3 April 2024.
38. Novartis. Piqray (alpelisib). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf. Last accessed: 9 July 2024.
39. AstraZeneca. Truqap (capivasertib). Prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf. Last accessed: 3 April 2024.
40. AstraZeneca. Truqap (capivasertib). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/truqap-epar-product-information_en.pdf. Last accessed: 17 July 2024.
41. AstraZeneca. Faslodex (fulvestrant) Prescribing Information. 2021. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021344s044lbl.pdf. Last accessed: 3 April 2024.
42. AstraZeneca. Faslodex (fulvestrant). Summary of product characteristics. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/faslodex-epar-product-information_en.pdf. Last accessed: 9 July 2024.
43. Mittal A et al. Filling the gap after CDK4/6 inhibitors: novel endocrine and biologic treatment options for metastatic hormone receptor positive breast cancer. Cancers. 2023;15(7):2015.