Poster 335P

Chemotherapy outcomes in human epidermal growth factor receptor 2 (HER2)-low, hormone receptor positive (HR+) metastatic breast cancer (mBC): Insights from the French multicenter ESME database

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Objectives

- To examine demographic and clinical characteristics and treatment patterns of a real-world cohort of HER2-low, HR+ mBC patients in France who initiated a chemotherapy-based regimen after ≥1 qualifying line(s) of endocrine therapy (ET).
- To describe real-world median time-to-event (TTE) estimates and TTE distributions in the target population for all-cause mortality, progression-free survival, discontinuation of treatment, and start of next line of therapy (LOT).

Conclusions

- This real-world study of a French cohort with HER2-low, HR+ mBC suggests a limited long-term efficacy of chemotherapy-based treatments and emphasizes the high unmet clinical need in the post-ET setting for these patients.
- A substantial proportion of patients (38%) in this real-world cohort had rapidly progressing disease and poor outcomes, suggesting the need for earlier and more effective interventions in these patients.
- This study provided detailed information on patients' site(s) of metastases, highlighting the diverse presentation of mBC in this population and warranting further assessment of treatment outcomes in these sub-populations.

Plain Language Summary

Why did we perform this research?

- Some patients with breast cancer that spreads express hormone receptor (HR) proteins but not a lot of the human epidermal growth factor 2 receptor protein (HER2), a breast cancer type referred to as HER2-low, HR-positive(+) metastatic breast cancer (mBC).
- For this cancer type, the first treatment is commonly endocrine therapy (ET); however, ET frequently stops working and results in the use of chemotherapy.
- Recent clinical studies suggest that other types of targeted treatments may be more effective than chemotherapy for HER2-low, HR+ mBC that has not responded to ET. To determine the best treatment choices after ET, it is important to know how patients are currently treated and what the outcomes of such treatment are.

How did we perform this research?

- We analyzed patients' treatments and outcomes after they received ET and chemotherapy for HER2-low, HR+ mBC from a French database of health records between January 2008 and March 2024.

What were the findings and implications of this research?

- Our results illustrate that HER2-low, HR+ mBC patients who receive chemotherapy after ET soon require other treatments or die, highlighting the need for better therapies earlier in their care. Our results suggest that this is especially true for patients who quickly progress on ET.

Where can I access more information?

- Please reach out to Dr. William Jacot at William.Jacot@icm.unicancer.fr

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below.

https://bit.ly/DSESMOBC25

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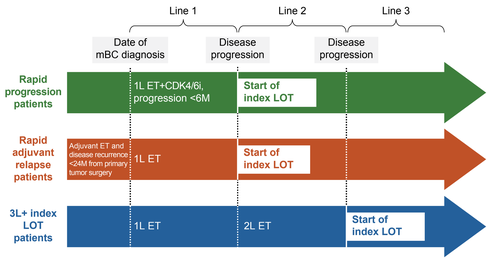
Introduction

- Standard of care (SOC) for the initial treatment of HER2-negative (immunohistochemistry [IHC] 0, 1+, or 2+ without gene amplification), HR+ mBC is ET ± cyclin-dependent kinase 4/6 inhibitors (CDK4/6i); however, systemic chemotherapy is recommended upon visceral crisis or the development of endocrine resistance.[1]
- Over half of HER2-negative mBCs express low levels of HER2 (IHC 1+ or IHC 2+ without gene amplification [HER2-low]).[2]
- The HER2-directed antibody drug conjugate trastuzumab-deruxtecan (T-DXd) as monotherapy has been approved in the European Union for the treatment of adult patients with unresectable or metastatic HR+, HER2-low or HER2-ultralow breast cancer who have received at least one ET in the metastatic setting and who are not considered suitable for ET as the next line of treatment.[3]
- Data are needed to understand the real-world, long-term SOC treatment patterns and outcomes for patients with HER2-low, HR+ mBC who initiated a chemotherapy-based regimen after ≥1 qualifying line(s) of ET.

Methods

- Retrospective, observational study of patients with HER2-low, HR+ mBC whose first metastasis was treated at a contributing site (18 French Comprehensive Cancer Centers spread over 20 sites) from 1 January 2008 to 8 March 2024.
- Eligible patients initiated chemotherapy-based regimen (index LOT) after ≥1 qualifying line of ET and met other inclusion and exclusion criteria (Figure 1).
- Real-world overall survival (rwOS): time from start of index LOT to death for any cause; patients without endpoint were censored at date of last medical information (MI).
- Real-world progression-free survival (rwPFS): time from start of index LOT to first disease progression or death, whichever occurred first; patients without progression after start of index LOT or with death >9 months after date of last MI were censored at date of last MI.
  - Progression was defined as a new metastatic site, progression of a previously diagnosed metastatic site, diagnosis of local or loco-regional recurrence of a primary tumor, end of chemotherapy or targeted therapy or immunotherapy or endocrine therapy due to progression.
- Real-world time to treatment discontinuation or death (rwTTD/D): time from start of index LOT to treatment discontinuation in index LOT or death, whichever occurred first.
  - Patients alive without discontinuation or subsequent LOT were censored at date of last MI.
  - Patients without discontinuation or subsequent LOT and with death reported >9 months after date of last MI were censored at date of last MI.
- Real-world time to next treatment or death (rwTTNT/D): time from start of index LOT to start date of first subsequent LOT or death, whichever occurred first; patients who did not receive subsequent LOT or with death reported >9 months after date of last MI were censored at date of last MI.
- All analyses were exploratory in nature. Descriptive analyses were performed for patient characteristics and treatment patterns.
- TTE analyses were performed for the study endpoints (rwOS, rwPFS, rwTTD/D, rwTTNT/D) using Kaplan-Meier estimation for the overall cohort and stratified by progression status (rapid adjuvant relapse, rapid progression, 3L+ index) and index chemotherapy type.

Figure 1. Study Cohort



Additional inclusion criteria:
- ECOG status 0 or 1 within 30 days prior or up to 15 days after index treatment date
- Index treatment date ≥90 days prior to 8 March 2024

Exclusion criteria:
- HER2-positive test result prior to or on the index treatment date
- T-DXd received at any time prior to or in the index LOT
- Received clinical study drug in the metastatic setting prior to or in the index LOT
- Received ET in the index LOT
- Prior cancer within 3 years from the index LOT

The index LOT is the first chemotherapy provided after qualifying line(s) of ET. 1L=first-line, 2L=second-line, 3L=third-line; ECOG=Eastern Cooperative Oncology Group; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; LOT=line of therapy; M=months; mBC=metastatic breast cancer; T-DXd=trastuzumab-deruxtecan.

Results and Interpretation

Table 1. Clinical Characteristics at Start of Index LOT

Characteristic	Participants, (N=326)
Age, median (Q1, Q3)	**66 (57, 74)**
Female, n (%)	**321 (98.5)**
ECOG performance-status score, n (%)	
0	**112 (34.4)**
1	**214 (65.6)**
Setting at mBC diagnosis, n (%)	
Recurrent	**251 (77.0)**
De novo	**75 (23.0)**
Number of metastatic sites at index, median (Q1, Q3)	**2 (2, 3)**
Type of metastatic disease at index*, n (%)	
Visceral	**210 (64.4)**
Central nervous system	**16 (4.9)**
Bone	**269 (82.5)**
Bone-only	**51 (15.6)**
Other	**177 (54.3)**
Number of ET lines before index, median (Q1, Q3)	**2 (1, 2)**
Index LOT number, n (%)**	
2	**124 (38.0)**
≥3	**202 (62.0)**
Calendar year of index LOT, n (%)	
2008–2016	**57 (17.5)**
2017–2019†	**73 (22.4)**
2020–2024	**196 (60.1)**

*Patients could have more than one type of metastatic disease; **The index LOT is the first chemotherapy provided after qualifying line(s) of ET; †The first CDK4/6i received European Medicines Agency reimbursement decisions from 2017–2019.[4] CDK4/6i=cyclin dependent kinase 4/6 inhibitors; ECOG=Eastern Cooperative Oncology Group; ET=endocrine therapy; LOT=line of therapy; mBC=metastatic breast cancer; Q=quartile.

Table 2. Clinical Outcomes

Cohort	Median TTE, months (95% CI)			
	rwOS	rwPFS	rwTTD/D	rwTTNT/D
Overall (N=326)	**23.1 (19.7–27.5)**	**5.1 (4.8–5.7)**	**5.7 (5.1–6.2)**	**6.7 (6.3–7.4)**
Rapid adjuvant relapse (n=23)	**17.9 (10.5–30.5)**	**4.6 (2.4–6.2)**	**4.0 (2.8–5.3)**	**6.2 (4.1–6.9)**
Rapid progression (n=101)	**18.6 (14.3–23.0)**	**5.6 (4.6–6.3)**	**5.8 (4.8–6.7)**	**7.2 (6.2–7.9)**
3L+ index LOT (n=202)	**27.6 (22.7–31.3)**	**5.2 (4.7–6.0)**	**6.0 (5.1–6.4)**	**6.7 (6.2–8.0)**
By index chemotherapy				
Capecitabine (n=162)	**27.6 (22.7–34.0)**	**5.8 (4.8–6.4)**	**6.5 (6.0–8.2)**	**7.8 (6.7–9.0)**
Paclitaxel (n=79)	**18.2 (13.4–28.3)**	**4.6 (3.0–5.1)**	**4.6 (3.2–5.1)**	**6.0 (5.2–6.6)**
Other (n=85)	**21.0 (15.8–25.7)**	**5.6 (4.7–7.1)**	**5.6 (4.7–6.7)**	**6.7 (6.0–8.4)**

3L+third-line; CI=confidence interval; rwOS=real-world overall survival; rwPFS=real-world progression-free survival; rwTTD/D=real-world time to discontinuation or death; rwTTNT/D=real-world time to next treatment or death; TTE=time to event.

Patient Characteristics and Treatment Patterns:

- A total of 326 patients were included in the study and index LOT was 3L+ for 202 (62.0%) patients and 2L for 124 (38.0%) patients; patient characteristics at the start of the index LOT are presented in Table 1.
- First choice index chemotherapy was capecitabine in 162 (49.7%) patients, followed by paclitaxel in 79 (24.2%) patients.
- Among the 251 (77.0%) patients who received a subsequent LOT after their first chemotherapy, 203 (80.9%) received a subsequent chemotherapy-based LOT and 24 (9.6%) returned to an ET-based regimen (Figure 2).

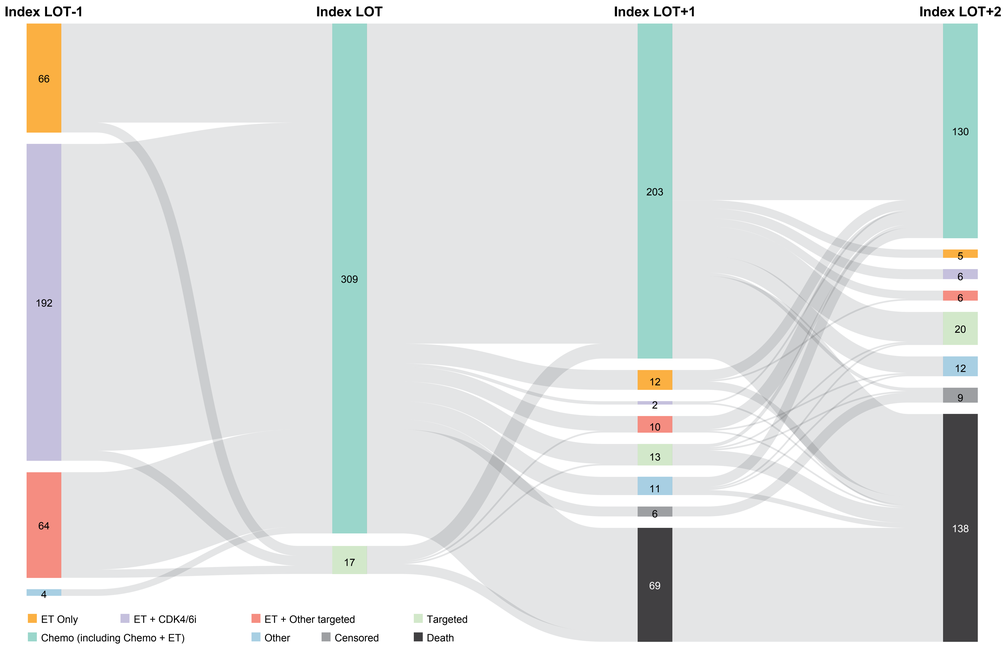
Clinical Outcomes:

- Median follow-up time by reverse Kaplan-Meier method for the overall cohort was 39.7 months (95% CI: 32.2–53.0). Clinical outcomes by cohort and overall are presented in Table 2 and Figure 3.

Strengths and Limitations:

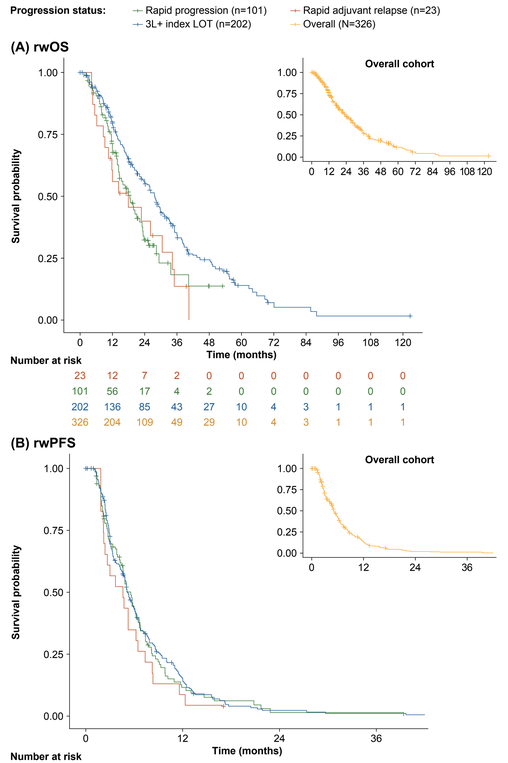
- This large study of a robust real-world cancer care database provides a needed analysis of HER2-low, HR+ treatment patterns and outcomes in a French cohort.
- Patient characteristics among the groups stratified by progression status may be different and no comparison between groups should be performed.
- The results may not reflect the broader population of patients with mBC treated in other countries or non-specialist centers.
- Therapies and treatment approaches for mBC evolved over the study period (e.g., the approvals of CDK4/6i from 2016–2018[4]), and this may make it more complex to draw conclusions specific to individual therapies or strategies.

Figure 2. Treatment Patterns Before and After Index LOT in the Overall Cohort



Sankey diagram where the numbers represent the number of patients within each category. CDK4/6i=cyclin dependent kinase 4/6 inhibitor; Chemo=chemotherapy; ET=endocrine therapy; LOT=line of therapy.

Figure 3. Clinical Outcomes



(A) rwOS and (B) rwPFS outcomes stratified by progression status and in the overall cohort (insets). 3L+third-line; CI=confidence interval; LOT=line of therapy; rwOS=real-world overall survival; rwPFS=real-world progression-free survival.

References

1. Gennari A, et al. Ann Oncol. 2021;32(12):1475–1495; **2.** Viale G, et al. ESMO Open. 2023;8(4):101615; **3.** ENHERTU® Approved in the EU as First HER2 Directed Therapy for Patients with HR Positive, HER2 Low or HER2 Ultralow Metastatic Breast Cancer Following at Least One Endocrine Therapy. Press release. Daiichi Sankyo. April 4 2025. Accessed on April 4 2025. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202504/20250404_E.pdf; **4.** Luyendijk M, et al. JAMA Netw Open. 2023;6(2):e2256170.

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