Treatment patterns and clinical outcomes following progression on first-line ET + CDK4/6i among patients with HR+/HER2− metastatic breast cancer (mBC) in the US

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PURPOSE

- This study aimed to assess real-world treatment patterns and clinical outcomes in patients in the US with HR+/HER2− mBC that progressed during therapy with 1L ET + CDK4/6i

DISCUSSION

- Of 1415 US patients included in this study, most were older (median age, 65 y) and White (66%)
- 57% of patients who initiated 2L treatment experienced real-world progression within 12 mo during 1L ET + CDK4/6i therapy
- Following disease progression during 1L ET + CDK4/6i therapy, the predominant 2L therapy was a further ET-based regimen (64%), followed by CT-based regimens (27%)
  - Patients who experienced earlier disease progression during 1L ET + CDK4/6i therapy more frequently received 2L CT-based regimens (patients receiving 2L CT monotherapy; time to 1L progression: ≤6 mo, 33.3%; >6 and ≤12 mo, 26.2%; >12 mo, 15.1%)
  - The opposite relationship was observed for ET-based regimen use, with patients more likely to receive further 2L ET-based regimens when disease progression during 1L ET-based regimens was delayed (patients receiving 2L ET-based regimens; time to 1L progression: ≤6 mo, 52.2%; >6 and ≤12 mo, 62.4%; >12 mo, 73.2%)

CONCLUSIONS

- In this study of patients with HR+/HER2− mBC who had evidence of real-world disease progression during 1L ET + CDK4/6i and initiated 2L therapy, 57% had 1L disease progression within 12 mo of treatment initiation, and 27% received CT in a subsequent treatment line
- Median rwPFS with 2L therapy was shorter among those who were using CT in the 2L or had early real-world progression (≤12 months) on 1L ET + CDK4/6i, highlighting the emergence of ET resistance and a need for more effective therapeutic alternatives to improve patient outcomes

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BACKGROUND

- BC remains one of the most frequently diagnosed cancers globally, with HR+/HER2− BC representing 68% of all cases in the US[1]
- ET in combination with a CDK4/6i is a preferred 1L treatment for patients with HR+/HER2− mBC[2-6]; however, patients may experience disease progression on 1L treatment, and many receive subsequent CT or other targeted regimens[2-5]
- There is an evidence gap regarding real-world treatment patterns and outcomes in patients on 2L therapy following disease progression during 1L ET + CDK4/6i therapy
- This study aimed to assess real-world population characteristics, treatment patterns, and clinical outcomes in patients with real-world disease progression during 1L ET + CDK4/6i who initiated 2L therapy

METHODS

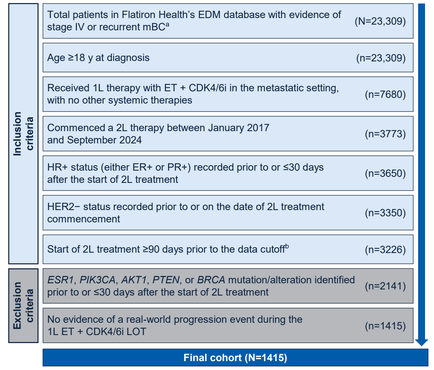
- This noninterventional, retrospective, observational cohort study obtained data for patients with HR+/HER2− mBC with evidence of real-world progression during 1L treatment with ET + CDK4/6i and initiated 2L therapy
  - Data from the nationwide US Flatiron Health EDM mBC database between 1 January 2017 and 30 September 2024 (data cutoff) were used[7]; see **Figure 1** for inclusion and exclusion criteria
- The 2L therapy was the subsequent LOT following progression during ET + CDK4/6i
- Treatment data were recorded as documented by physicians and may reflect off-label use
- The follow-up period included the start of 2L treatment to the earliest of the following: the data cutoff or the date of death or the last documented nondeath activity in the database
- Key subgroups for analysis: time to first real-world progression during 1L treatment and 2L treatment category
- Primary endpoint: rwPFS from 2L start
- Secondary endpoints:
  - rwOS, rwTTD/D, and rwTTNT/D from 2L start
- Kaplan-Meier methods were used to estimate real-world time-to-event outcomes

RESULTS

Patient Selection

- Of 23,309 patients with stage IV or recurrent mBC identified from the Flatiron Health's EDM database, **a total of 1415 patients met the inclusion/exclusion criteria for this study** (**Figure 1**)

Figure 1. Inclusion and Exclusion Criteria



[a] Metastatic diagnosis on or after 1 January 2017. [b] Data cutoff, 30 September 2024.

RESULTS

Patient Selection (continued)

- Patients were predominantly older (median age, 65 y), White (66%), and female (99%) and had treatment administered in a community setting (70%) and no or minimal restriction to activity (ECOG performance status of 0/1: 68%) (**Table 1**)
- The majority of patients (57%) had evidence of real-world disease progression in ≤1 y during 1L ET + CDK4/6i therapy; 17% had 1L real-world disease progression at >2 y
  - All patients in this study had experienced real-world progression during 1L ET + CDK4/6i therapy; therefore, these data should not be interpreted as typical time to progression on 1L ET + CDK4/6i
- Primary endocrine resistance (see footnote a below Table 1) was more frequent among patients who received 2L CT (CT monotherapy, 47%; multiagent CT, 72%) than among the full population (33%)
  - The median time from start of 1L to initiation of 2L treatment was shorter among patients who received 2L CT (CT monotherapy, 8.7 months; multiagent CT, 4.4 months) than among the full population (13.4 months)

Table 1. Baseline Demographics and Clinical Characteristics at Initiation of 2L Therapy

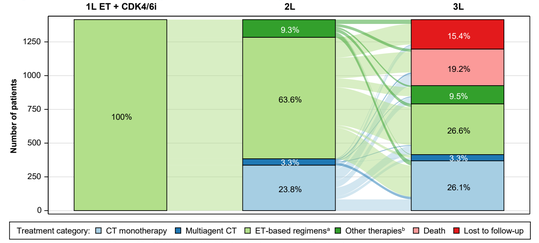
Characteristic		All patients (N=1415)	2L CT monotherapy (n=337)	2L Multiagent CT (n=47)
Age, y	Median (Q1-Q3)	65.0 (57.0-74.0)	63.0 (55.0-71.0)	61.0 (52.0-68.0)
Sex, n (%)	Female	1400 (98.9)	334 (99.1)	45 (95.7)
	Male	15 (1.1)	3 (0.9)	2 (4.3)
Race, n (%)	Asian	34 (2.4)	9 (2.7)	0
	Black or African American	164 (11.6)	42 (12.5)	6 (12.8)
	White	937 (66.2)	222 (65.9)	27 (57.4)
	Other	110 (7.8)	28 (8.3)	5 (10.6)
	Unknown	170 (12.0)	36 (10.7)	9 (19.1)
Practice type, n (%)	Academic	377 (26.6)	98 (29.1)	11 (23.4)
	Community	993 (70.2)	221 (65.6)	36 (76.6)
	Both	45 (3.2)	18 (5.3)	0
Year of initial BC diagnosis, n (%)	Before 2000	51 (3.6)	9 (2.7)	0
	2000-2009	227 (16.0)	44 (13.1)	6 (12.8)
	2010-2019	897 (63.4)	241 (71.5)	33 (70.2)
	In or after 2020	238 (16.8)	43 (12.8)	8 (17.0)
	Unknown	2 (0.1)	0	0
Endocrine resistance, n (%)[a]	Primary	471 (33.3)	157 (46.6)	34 (72.3)
	Secondary	944 (66.7)	180 (53.4)	13 (27.7)
Year of mBC diagnosis, n (%)	2017-2020	1028 (72.7)	240 (71.2)	35 (74.5)
	2021-2024	387 (27.3)	97 (28.8)	12 (25.5)
De novo stage IV, n (%)	Yes	440 (31.1)	68 (20.2)	11 (23.4)
	No	854 (60.4)	239 (70.9)	31 (66.0)
	Unknown	121 (8.6)	30 (8.9)	5 (10.6)
Time from mBC diagnosis to start of 2L LOT, mo	Median (Q1-Q3)	15.1 (8.1-25.6)	10.3 (5.4-18.6)	6.2 (4.0-14.1)
ECOG performance status, n (%)	0/1	965 (68.2)	206 (61.1)	35 (74.5)
	2-4	198 (14.0)	61 (18.1)	8 (17.0)
	Unknown	252 (17.8)	70 (20.8)	4 (8.5)
HER2-negative category, n (%)	IHC 0	416 (29.4)	106 (31.5)	13 (27.7)
	Low[a]	718 (50.7)	165 (49.0)	25 (53.2)
	Negative NOS	281 (19.9)	66 (19.6)	9 (19.1)
Time from start of 1L to initiation of 2L treatment, mo	Median (Q1-Q3)	13.4 (6.9-23.4)	8.7 (4.5-16.9)	4.4 (2.6-11.5)
Time from start of 1L to first real-world progression during 1L, n (%)	≤6 mo	471 (33.3)	157 (46.6)	34 (72.3)
	>6 to ≤12 mo	340 (24.0)	89 (26.4)	6 (12.8)
	>12 to ≤18 mo	214 (15.1)	38 (11.3)	1 (2.1)
	>18 to ≤24 mo	147 (10.4)	23 (6.8)	2 (4.3)
	>24 mo	243 (17.2)	30 (8.9)	4 (8.5)
Follow-up from start of 2L treatment, mo	Median (Q1-Q3)	14.6 (6.8-25.8)	12.5 (6.1-21.5)	10.9 (5.6-17.5)

[a] Primary ET resistance based on real-world progression data, rather than being identified by clinicians. Primary ET resistance defined as disease progression ≤6 months from starting 1L ET and secondary endocrine resistance defined as disease progression >6 months from starting ET, as per the ESMO Clinical Practice Guideline for metastatic breast cancer.[4, 5] "Low" defined as IHC 1+ or IHC 2+ (equivocal) and an ISH test within ±14 days of an IHC test with status "ISH negative/not amplified."

Treatment Categories

- Among patients receiving 2L therapy following disease progression during 1L ET + CDK4/6i, 63.6% received an ET-based regimen, 27.1% received CT (monotherapy, 23.8%; multiagent, 3.3%), and 9.3% received other therapies (**Figure 2**)

Figure 2. Treatment Use by 2L Treatment Category



[a] ET-based regimens included ET only, ET + CDK4/6i, ET + CT, ET + targeted therapies, and ET + other therapies.
[b] Other therapies include AKT inhibitor, PARP inhibitor, and the ADCs sacituzumab govitecan or T-DXd.

- **Patients with earlier disease progression during 1L ET + CDK4/6i used 2L CT-based regimens more frequently** than those with later disease progression (**Table 2**)
  - The opposite relationship was observed for patients receiving 2L ET

Table 2. 2L Treatment Categories by Time to Disease Progression During 1L ET + CDK4/6i

2L Treatment category, n (%)	All patients (N=1415)	Time to first real-world progression during 1L treatment, n (%)				
		≤6 mo (n=471)	>6 to ≤12 mo (n=340)	>12 to ≤18 mo (n=214)	>18 to ≤24 mo (n=147)	>24 mo (n=243)
CT monotherapy	337 (23.8)	157 (33.3)	89 (26.2)	38 (17.8)	23 (15.6)	30 (12.3)
Multiagent CT	47 (3.3)	34 (7.2)	6 (1.8)	1 (0.4)	2 (1.4)	4 (1.6)
ET-based regimens[a]	900 (63.6)	246 (52.2)	212 (62.4)	154 (72.0)	105 (71.4)	183 (75.3)
Other therapies[b]	131 (9.3)	34 (7.2)	33 (9.7)	21 (9.8)	17 (11.6)	26 (10.7)

[a] ET-based regimens included ET only, ET + CDK4/6i, ET + CT, ET + targeted therapies, and ET + other therapies.
[b] Other therapies include AKT inhibitor, PARP inhibitor, and the ADCs sacituzumab govitecan or T-DXd.

Real-World Clinical Outcomes

- Real-world clinical outcomes with 2L therapy were generally poor, with **worse outcomes observed in patients receiving CT** than in those receiving ET-based or other therapies (**Table 3**)

Table 3. Real-World Clinical Outcomes by 2L Therapy Regimen Among Patients Who Experienced Disease Progression During 1L ET + CDK4/6i

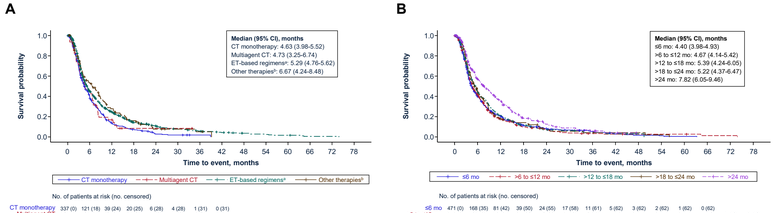
	2L therapy				
	All patients (N=1415)	ET-based regimens[a] (n=900)	CT monotherapy (n=337)	Multiagent CT (n=47)	Other therapies[b] (n=131)
Median rwPFS (95% CI), mo	5.1 (4.7-5.6)	5.3 (4.8-5.6)	4.6 (4.0-5.5)	4.7 (3.3-6.7)	6.7 (4.2-8.5)
Median rwOS (95% CI), mo	21.0 (19.2-22.7)	25.2 (22.7-27.7)	16.5 (13.2-17.3)	14.4 (9.7-17.5)	18.6 (16.4-24.5)
Median rwTTD/D (95% CI), mo	5.2 (4.9-5.6)	5.6 (5.1-6.1)	4.7 (3.9-5.3)	3.5 (2.1-4.4)	6.7 (4.0-8.3)
Median rwTTNT/D (95% CI), mo	5.8 (5.5-6.2)	6.1 (5.6-6.7)	5.5 (4.8-6.1)	4.4 (3.0-4.9)	7.3 (4.6-9.1)

[a] ET-based regimens included ET only, ET + CDK4/6i, ET + CT, ET + targeted therapies, and ET + other therapies.
[b] Other therapies include AKT inhibitor, PARP inhibitor, and the ADCs sacituzumab govitecan or T-DXd.

Real-World Clinical Outcomes (continued)

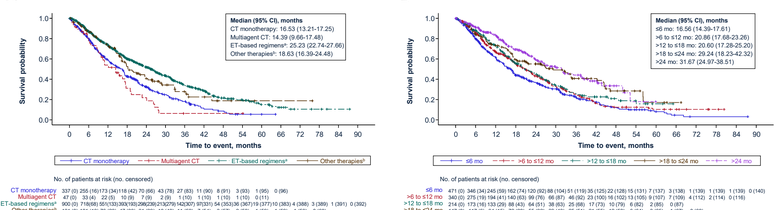
- 12-month survival rates for both rwPFS and rwOS were higher among patients who received 2L ET-based regimens vs 2L CT monotherapy (12-month rwPFS: 24.8% vs 13.8%, respectively; 12-month rwOS: 73.8% vs 59.1%, respectively) (**Figures 3A and 4A**)
- Patients with later real-world disease progression during 1L ET + CDK4/6i had longer rwPFS and rwOS from the start of 2L treatment (**Figures 3B and 4B**)
- Patients who experienced earlier progression during 1L ET + CDK4/6i generally demonstrated worse real-world clinical outcomes than patients who had later disease progression during 1L therapy (**Table 4**)

Figure 3. Kaplan-Meier Analysis of rwPFS From the Start of 2L Treatment Following Disease Progression on 1L ET + CDK4/6i by Treatment Category (A) and Time to 1L Progression (B)



[a] ET-based regimens included ET only, ET + CDK4/6i, ET + CT, ET + targeted therapies, and ET + other therapies.
[b] Other therapies include AKT inhibitor, PARP inhibitor, and the ADCs sacituzumab govitecan or T-DXd.

Figure 4. Kaplan-Meier Analysis of rwOS From the Start of 2L Treatment Following Disease Progression on 1L ET + CDK4/6i by Treatment Category (A) and Time to 1L Progression (B)



[a] ET-based regimens included ET only, ET + CDK4/6i, ET + CT, ET + targeted therapies, and ET + other therapies.
[b] Other therapies include AKT inhibitor, PARP inhibitor, and the ADCs sacituzumab govitecan or T-DXd.

Table 4. Real-World Clinical Outcomes of 2L Therapy by Time to Disease Progression During 1L ET + CDK4/6i

	Time to real-world progression from the start of 1L treatment				
	≤6 mo (n=471)	>6 mo to ≤12 mo (n=340)	>12 mo to ≤18 mo (n=214)	>18 mo to ≤24 mo (n=147)	>24 mo (n=243)
Median rwPFS (95% CI), mo	4.4 (4.0-4.9)	4.7 (4.1-5.4)	5.4 (4.2-6.1)	5.2 (4.4-6.5)	7.8 (6.1-9.5)
Median rwOS (95% CI), mo	16.6 (14.4-17.6)	20.9 (17.7-23.3)	20.6 (17.3-25.2)	29.2 (18.2-42.3)	31.7 (25.0-38.5)
Median rwTTD/D (95% CI), mo	4.6 (4.0-5.3)	5.3 (4.7-5.9)	5.1 (4.5-5.9)	4.9 (3.7-6.5)	7.9 (6.0-9.2)
Median rwTTNT/D (95% CI), mo	5.2 (4.7-5.7)	5.6 (5.1-6.5)	5.8 (4.9-6.8)	5.7 (4.4-7.5)	8.4 (6.9-9.5)

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ABBREVIATIONS

1L, first line; 2L, second line; 3L; third line; ADC, antibody-drug conjugate; AKT, AKT serine/threonine kinase; BC, breast cancer; BRCA, breast cancer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EDM, Enhanced Datamart; ER, estrogen receptor; ESMO, European Society for Medical Oncology; ESR1, estrogen receptor 1; ET, endocrine therapy; FISH, fluorescence in situ hybridization; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; LOT, line of therapy; mBC, metastatic breast cancer; NOS, not otherwise specified; PARP, poly(ADP-ribose) polymerase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; Q, quartile; 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; T-DXd, trastuzumab deruxtecan; TROP2, trophoblast cell-surface antigen 2.

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