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

Virginia G. Kaklamani,[1] Samantha Valliant,[2] Shannon Hunter,[2] Olga Tymejczyk,[2] Agnes Weixuan Yu,[3] Jagadeswara Rao Earla,[3] Sandhya Mehta,[2] Esther Pang[2]

[1]UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX, USA; [2]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [3]Merck & Co., Inc., Rahway, NJ, USA

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

Corresponding author: Virginia G. Kaklamani
Contact: kaklamani@uthscsa.edu

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

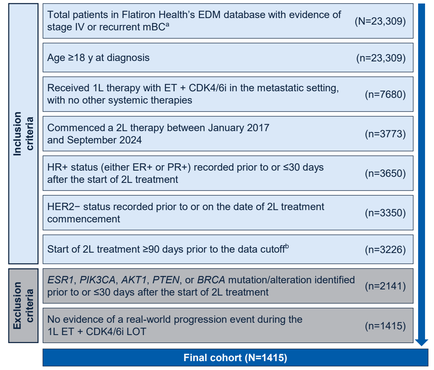
- This noninterventional, retrospective, observational cohort study obtained data for patients with HR+/HER2− mBC with evidence of real-world progression during 1L treatment with ET + CDK4/6i and initiated 2L therapy
  - Data from the nationwide US Flatiron Health EDM mBC database between 1 January 2017 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

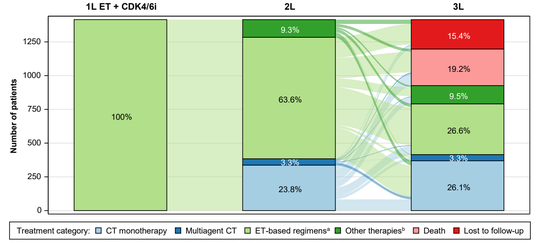
Characteristic		All patients (N=1415)	2L CT monotherapy (n=337)	2L Multiagent CT (n=47)
Age, y	Median (Q1-Q3)	65.0 (57.0-74.0)	63.0 (55.0-71.0)	61.0 (52.0-68.0)
Sex, n (%)	Female	1400 (98.9)	334 (99.1)	45 (95.7)
	Male	15 (1.1)	3 (0.9)	2 (4.3)
Race, n (%)	Asian	34 (2.4)	9 (2.7)	0
	Black or African American	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

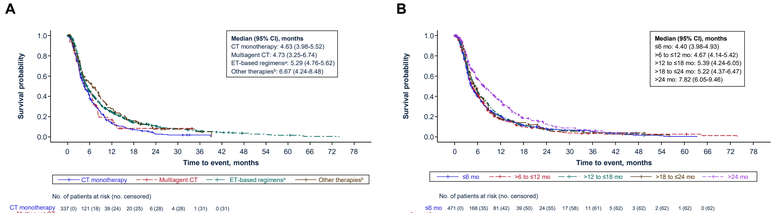
	2L therapy				
	All patients (N=1415)	ET-based regimens[a] (n=900)	CT monotherapy (n=337)	Multiagent CT (n=47)	Other therapies[b] (n=131)
Median rwPFS (95% CI), mo	5.1 (4.7-5.6)	5.3 (4.8-5.6)	4.6 (4.0-5.5)	4.7 (3.3-6.7)	6.7 (4.2-8.5)
Median rwOS (95% CI), mo	21.0 (19.2-22.7)	25.2 (22.7-27.7)	16.5 (13.2-17.3)	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)

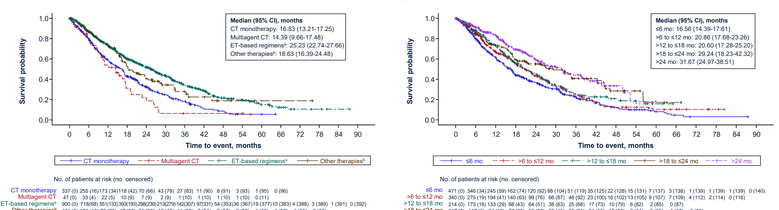
- 12-month survival rates for both rwPFS and rwOS were higher among patients who received 2L ET-based regimens vs 2L CT monotherapy (12-month rwPFS: 24.8% vs 13.8%, respectively; 12-month rwOS: 73.8% vs 59.1%, respectively) (**Figures 3A and 4A**)
- Patients with later real-world disease progression 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)

REFERENCES

1. Giaquinto AN, et al. *CA Cancer J Clin*. 2022;72(6):524-541.
2. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649.
3. Gao Y, et al. *Front Oncol*. 2024;14:1448687.
4. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495.
5. Gennari A, et al. ESMO Living Guideline: Metastatic Breast Cancer, v1.2 2025. Accessed 16 October 2025. https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-breast-cancer.
6. Reinert T, Barrios C. *Ther Adv Med Oncol*. 2015;7(6):304-320.
7. Flatiron Health. Accessed 17 October 2025. https://flatiron.com/database-characterization.

ACKNOWLEDGMENTS

- Funding for this study was provided by Daiichi Sankyo Company, Limited, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
- Medical writing support was provided by Simon Foale, PhD (Nucleus Global, an Inizio company), and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (https://ismpp.org/gpp-2022).

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.

Presented at: San Antonio Breast Cancer Symposium 2025; 9-12 December 2025; San Antonio, Texas.