HSD89

Endocrine Resistance and Real-World Treatment Patterns After First-Line (1L) Endocrine Therapy (ET) + CDK4/6i in HR+/HER2- Metastatic Breast Cancer

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Background

- Approximately 70% of breast cancer cases are hormone receptor–positive and HER2-negative (HR+/HER2-) at diagnosis[1]
- For metastatic patients (pts) with HR+/HER2- breast cancer, standard first-line (1L) treatment consists of endocrine therapy (ET) combined with a CDK4/6 inhibitor (CDK4/6i)
- Most pts with HR+/HER2- metastatic breast cancer (mBC) will develop endocrine resistance, categorized as primary (PR) or secondary (SR), as follows:
  - PR is defined as a relapse during the first 2 years of adjuvant ET or disease progression within the first 12 months of 1L ET for mBC
  - SR is defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or disease progression >12 months after initiating ET for mBC

Objective

- To describe patient characteristics and treatment patterns among pts with mBC and disease progression or death on 1L ET + CDK4/6i, by second-line (2L) treatment and resistance status

Methods

- **Study design:** Retrospective, observational cohort study
- **Data source:** Structured and unstructured data from iKnowMed, an oncology-specific electronic health record system that captures outpatient encounters across the US Oncology Network
- **Study population:** Adult pts with HR+/HER2- mBC whose cancer progressed on 1L ET + CDK4/6 inhibitor (initiated between 02/2015 and 01/2023)
  - Pts were selected based on a stratified random sample of their 2L treatment, aiming for 125 each for the following cohorts: *No 2L*, any exposure to 2L chemotherapy or antibody drug conjugate (*2L CT/ADC*), *2L ET* (mono-) therapy only, *Other 2L*.
- **Statistical analysis:** Patient characteristics and treatment patterns were assessed descriptively, by endocrine resistance status, overall and further stratified by 2L treatment status

Results

Tables 1 and 2

- In general, SR patients have a higher proportion of de novo metastatic disease than PR patients
- Regardless of resistance status:
  - Pts treated with *2L CT/ADC* were the youngest, whereas those with *No 2L* were oldest
  - Pts treated with *2L ET* were more likely to have de novo metastasis than their 2L treatment counterparts
  - Pts treated with 2L ET-containing regimens (ie, *2L ET* or *Other 2L*) had longer median duration of follow-up
- Visceral disease was most common among PR pts treated with *2L CT* and SR pts treated with *2L ET*
- Postmenopausal status was least common in PR pts with *Other 2L* treatments and SR pts treated with *2L ET*

Tables 3 and 4

- In general, PR pts have more frequent exposure to adjuvant therapy, shorter duration of 1L CDK, and more frequent use of 3L CT/ADC. In contrast, SR pts have more frequent exposure to *Other 2L* treatments, especially ET-containing combinations
- Regardless of resistance status:
  - Pts receiving *2L CT* or *Other 2L* treatment were more likely to have prior adjuvant exposure than their 2L treatment counterparts
  - Pts with *Other 2L* treatment (ie, mostly ET combinations) have the longest exposure to 1L CDK

Conclusions

- Real-world data demonstrate distinct clinical characteristics and treatment patterns among pts with HR+/HER2- mBC based on ET resistance status
- Primary resistance was associated with shorter 1L CDK duration, more frequent exposure to adjuvant treatment, and earlier transition to 3L CT/ADC. Secondary resistance was more common among pts with de novo metastatic disease and was associated with greater use of *Other 2L* treatment, primarily ET-based combinations with targeted therapies
- These findings provide resistance-informed treatment sequencing data to help guide treatment utilization in HR+/HER2- mBC

Table 1. Demographics and clinical characteristics among patients with primary resistance

Variable	Overall (N=220)	Primary resistance			
		No 2L treatment (n=72)	2L CT/ADC[a] (n=82)	2L ET (n=22)	Other 2L[b] (n=44)
Age (years), median (IQR)	66 (57, 75)	71 (61, 76)	63 (55, 71)	70 (62, 80)	65 (55, 74)
Race, n (%)					
White	151 (68.6)	47 (65.3)	59 (72.0)	13 (59.1)	32 (72.7)
Black/Asian/Other	31 (14.1)	8 (11.1)	10 (12.2)	5 (22.7)	8 (18.2)
Not documented	38 (17.3)	17 (23.6)	13 (15.9)	<5	<5
Menopausal status, n (%)					
Premenopausal	23 (10.5)	4 (5.6)	12 (14.6)	1 (4.5)	6 (13.6)
Postmenopausal	156 (70.9)	54 (75.0)	59 (72.0)	17 (77.3)	26 (59.1)
Other/not documented	41 (18.4)	14 (19.4)	11 (13.4)	4 (18.2)	12 (27.3)
De novo mBC, n (%)	77 (35.0)	26 (36.1)	23 (28.0)	11 (50.0)	17 (38.6)
Visceral disease, n (%)[c]	120 (54.5)	38 (52.8)	52 (63.4)	9 (40.9)	21 (47.7)
Duration of follow-up (months), median (IQR)[d]	13.4 (6.0, 23.6)	4.6 (2.2, 8.3)	16.6 (11.4, 24.7)	21.5 (10.3, 32.8)	21.8 (15.7, 30.8)

[a]No patients received 2L ADC during the study observation period. [b]Other 2L primarily includes ET combinations such as ET + CDK4/6i (57%), mTOR + ET (23%), and PIK3CA + ET (11%). [c]Visceral disease includes metastasis to the brain/CNS, head/neck, lung, chest/thorax, liver, abdomen-other, fluid/pleura, or pelvis. [d]Calculated from mBC diagnosis date.

Table 2. Demographics and clinical characteristics among patients with secondary resistance

Variable	Overall (N=210)	Secondary resistance			
		No 2L treatment (n=53)	2L CT/ADC[a] (n=40)	2L ET (n=35)	Other 2L[b] (n=82)
Age (years), median (IQR)	68 (59, 76)	72 (64, 81)	63 (57, 74)	67 (57, 77)	68 (60, 75)
Race, n (%)					
White	151 (71.9)	39 (73.6)	26 (65.0)	24 (68.6)	62 (75.6)
Black/Asian/Other	34 (16.2)	7 (13.2)	7 (17.5)	5 (14.3)	14 (17.1)
Not documented	25 (11.9)	7 (13.2)	7 (17.5)	5 (14.3)	6 (7.3)
Menopausal status, n (%)					
Premenopausal	16 (7.6)	2 (3.8)	5 (12.5)	3 (8.6)	6 (7.3)
Postmenopausal	161 (76.7)	46 (86.8)	29 (72.5)	22 (62.9)	64 (78.0)
Other/not documented	33 (15.7)	5 (9.4)	6 (15.0)	10 (28.6)	12 (14.6)
De novo mBC, n (%)	114 (54.3)	30 (56.6)	21 (52.5)	23 (65.7)	40 (48.8)
Visceral disease, n (%)[c]	111 (52.9)	31 (58.5)	20 (50.0)	22 (62.9)	38 (46.3)
Duration of follow-up (months), median (IQR)[d]	35.1 (24.2, 47.8)	23.9 (14.5, 33.2)	33.2 (15.8, 74.7)	38.8 (26.6, 57.9)	41.8 (30.6, 58.6)

[a]No patients received 2L ADC during the study observation period. [b]Other 2L primarily includes ET combinations such as ET + CDK4/6i (57%), mTOR + ET (20%), and PIK3CA + ET (15%). [c]Visceral disease includes metastasis to the brain/CNS, head/neck, lung, chest/thorax, liver, abdomen-other, fluid/pleura, or pelvis. [d]Calculated from mBC diagnosis date.

Table 3. Treatment patterns among patients with primary resistance

Variable	Overall (N=220)	Primary resistance			
		No 2L treatment (n=72)	2L CT/ADC[a] (n=82)	2L ET (n=22)	Other 2L (n=44)
Neoadjuvant treatment, n (%)[b]	18 (8.2)	5 (6.9)	9 (11.0)	0 (0.0)	4 (9.1)
Adjuvant treatment, n (%)[b]	51 (23.2)	10 (13.9)	28 (34.1)	3 (13.6)	10 (22.7)
ET-based adjuvant treatment, n (%)[c]	44 (86.3)	9 (90.0)	23 (82.1)	2 (66.7)	10 (100.0)
1L, duration (months), median (IQR)	5.4 (2.9, 9.5)	4.3 (2.0, 6.9)	4.5 (2.8, 8.3)	8.0 (5.0, 11.2)	8.9 (5.6, 11.7)
1L CDK4/6i, duration (months), median (IQR)	4.8 (2.5, 9.1)	3.9 (1.7, 6.6)	4.0 (2.3, 8.1)	6.0 (3.7, 10.3)	8.8 (4.8, 11.5)
2L (all regimens), n (%)	148 (67.3)	–	–	–	–
CT/ADC[a]	82 (37.3)	–	82 (100.0)	0 (0.0)	0 (0.0)
ET	30 (13.6)	–	4 (4.9)	22 (100.0)	4 (9.1)
Other	54 (24.5)	–	10 (12.2)	0 (0.0)	44 (100.0)
ET-containing 2L therapy, n (%)	83 (37.7)	–	0 (0.0)	17 (77.3)	22 (50.0)
2L, duration (months), median (IQR)	4.5 (2.6, 9.7)	–	4.7 (2.5, 10.1)	3.1 (1.6, 4.7)	5.1 (3.2, 12.4)
3L (all regimens), n (%)	84 (38.2)	–	45 (54.9)	14 (63.6)	25 (56.8)
CT/ADC	59 (26.8)	–	31 (37.8)	8 (36.4)	20 (45.5)
ET	4 (1.8)	–	3 (3.7)	0 (0.0)	1 (2.3)
Other	27 (12.3)	–	13 (15.9)	8 (36.4)	6 (13.6)

[a]No patients received 2L ADC during the study observation period. [b]Calculated among patients who progressed from early-stage disease to metastatic disease. [c]Calculated among patients who received adjuvant treatment.

Table 4. Treatment patterns among patients with secondary resistance

Variable	Overall (N=210)	Secondary resistance			
		No 2L treatment (n=53)	2L CT/ADC[a] (n=40)	2L ET (n=35)	Other 2L (n=82)
Neoadjuvant treatment, n (%)[b]	8 (3.8)	2 (3.8)	3 (7.5)	0 (0.0)	3 (3.7)
Adjuvant treatment, n (%)[b]	25 (11.9)	3 (5.7)	8 (20.0)	1 (2.9)	13 (15.9)
ET-based adjuvant treatment, n (%)[c]	23 (92.0)	2 (66.7)	7 (87.5)	1 (100.0)	13 (100.0)
1L, duration (months), median (IQR)	22.8 (16.1, 31.5)	23.5 (15.0, 33.3)	18.9 (16.1, 25.6)	22.8 (16.1, 33.9)	24.6 (17.3, 35.7)
1L CDK4/6i, duration (months), median (IQR)	20.3 (14.0, 29.7)	15.2 (12.1, 29.7)	18.9 (15.5, 25.6)	20.5 (12.4, 33.9)	22.2 (15.4, 31.3)
2L (all regimens), n (%)	157 (74.8)	–	40 (100.0)	35 (100.0)	82 (100.0)
CT/ADC[a]	40 (19.0)	–	40 (100.0)	0 (0.0)	0 (0.0)
ET	37 (17.6)	–	0 (0.0)	35 (100.0)	2 (2.4)
Other	84 (40.0)	–	2 (5.0)	0 (0.0)	82 (100.0)
ET-containing 2L therapy, n (%)	118 (56.2)	–	6 (15.0)	35 (100.0)	77 (93.9)
2L, duration (months), median (IQR)	5.1 (2.4, 10.6)	–	5.8 (2.9, 10.1)	3.0 (1.9, 7.6)	6.0 (3.0, 13.6)
3L (all regimens), n (%)	81 (38.6)	–	21 (52.5)	23 (65.7)	37 (45.1)
CT/ADC	39 (18.6)	–	11 (27.5)	9 (25.7)	19 (23.2)
ET	15 (7.1)	–	3 (7.5)	6 (17.1)	6 (7.3)
Other	32 (15.2)	–	9 (22.5)	9 (25.7)	14 (17.1)

[a]No patients received 2L ADC during the study observation period. [b]Calculated among patients who received adjuvant treatment. [c]Calculated among patients who received adjuvant treatment.

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