The significance of HER2 Low status on clinical outcomes of breast cancer patients with metastatic hormone-receptor positive tumors treated in the CDK4/6 inhibitor era

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BACKGROUND

- HER2 classification was revised in 2023, with HER2-low (IHC 1+ or 2+/ISH-) as a new entity in HER2 non-amplified tumors.
- We describe the characteristics and clinical outcomes of patients with hormone-receptor positive (HR+) metastatic BC (mBC) with HER2-low and HER2 IHC 0 tumors, treated with CDK4/6 inhibitors (CDK4/6i) prior to inclusion of trastuzumab-deruxtecan in the national formulary, in a 2.8-million-member Healthcare Organization.

METHODS

- This retrospective cohort study used de-identified data from patients aged ≥18 years who initiated endocrine therapy combined with a CDK4/6 inhibitor for metastatic breast cancer (mBC) between 1 January 2018 and 31 December 2022, with follow-up continuing until 31 December 2023.
- Patients with HER2 non-amplified tumors were classified into HER2 IHC 0 and HER2-low.
- Kaplan-Meier analysis was used to describe time-on-treatment (TOT, as a surrogate for progression-free-survival) and overall survival (OS).

RESULTS

- A total of 1,067 patients were identified with a median age of 63 years, 60.7% were HER2-low, 31.4% were HER2 IHC 0 and 7.9% with missing data.
- A total of 705 patients received first-line CDK4/6i with an aromatase inhibitor (AI), with a median follow-up of 27.6 months, and 362 received CDK4/6i with fulvestrant (F), with a median follow-up of 23.0 months.
- For the group of patients receiving CDK4/6i & AI, median TOT was 27.0 (95%CI: 23.5-34.4) and 22.6 (95%CI: 17.5,32.7) months for patients with HER2-low and HER2 IHC 0 respectively, and median OS was 67.0 (95%CI: 58.0, NR) months and 52.4 (95%CI:47.4, NR) months, respectively (P=0.056).
- For the group of patients receiving CDK4/6i & F (in second or further lines), median TOT was 11.2 (95%CI: 7.8, 15.6) and 13.0 (95%CI:11.4, 20.4) months for patients with HER2-low and HER2 IHC 0 respectively, and median OS was 36.4 (95%CI: 30.9, 44.0) months and 37.8 (95%CI:28.7, 43.1) months, respectively.
- A total of 523 patients (49%) received at least one subsequent line after CDK4/6i initial treatment and 346 (32.4%) continued to a further line, with TOT around 4 months.

Table 1

Baseline demographic and clinical characteristics of patients diagnosed with metastatic HER2 non-amplifed breast cancer from 1st January 2018 to 31st December 2022, that initiated first-line treatment with CDK4/6 inhibitor treatment, n=1067

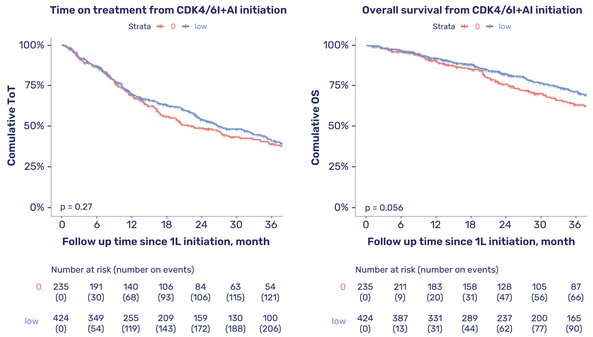
	Total, n=1067	HER2=0, n=335 (31.4%)	HER2=low, n=648 (60.7%)	Unknown HER2, n=84 (7.9%)	P-Value
Age, median [IQR]	63.00 [52.00, 72.00]	64.00 [53.00, 73.00]	62.00 [52.00, 71.00]	65.50 [56.75, 73.00]	0.131
Deyo-Charlson co-morbidity index, mean (SD)[a]	6.33 (2.27)	6.46 (2.35)	6.20 (2.26)	6.90 (1.81)	0.012
0	61 (5.7)	20 (6.0)	41 (6.3)	0 (0.0)	0.243
1-5	43 (4.0)	11 (3.3)	29 (4.5)	3 (3.6)	
6	515 (48.3)	155 (46.3)	318 (49.1)	42 (50.0)	
>=7	448 (42.0)	149 (44.5)	260 (40.1)	39 (46.4)	
Diabetes mellitus	257 (24.1)	82 (24.5)	152 (23.5)	23 (27.4)	0.716
Cardiovascular disease	126 (11.8)	49 (14.6)	68 (10.5)	9 (10.7)	0.155
Hypertension	473 (44.3)	161 (48.1)	268 (41.4)	44 (52.4)	0.040
Body mass index, median [IQR]	27.92 [24.16, 31.83]	28.10 [24.66, 32.32]	27.76 [23.81, 31.25]	27.79 [25.23, 31.88]	0.299
Histology					<0.001
Invasive ductal	773 (72.4)	228 (68.1)	501 (77.3)	44 (52.4)	
Invasive lobular	174 (16.3)	63 (18.8)	94 (14.5)	17 (20.2)	
Lobular and ductal	26 (2.4)	5 (1.5)	21 (3.2)	0 (0.0)	
Other	15 (1.4)	7 (2.1)	8 (1.2)	0 (0.0)	
Unknown/missing	79 (7.4)	32 (9.6)	24 (3.7)	23 (27.4)	
Metastases[b]					<0.001
Bone only	205 (19.2)	83 (24.8)	95 (14.7)	27 (32.1)	
Brain	16 (1.5)	3 (0.9)	10 (1.5)	3 (3.6)	0.194

[a] Not including malignancy or HIV

[b] We suspect that there is a lot of missing data here

Figure 1

Time on treatment and overall survival from CDK4/6i + AI initiation, stratified by HER2 result

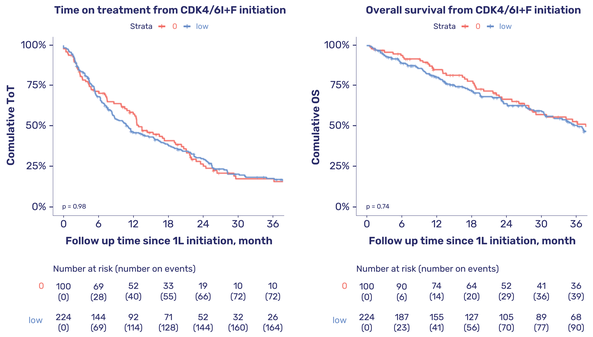


	HER2 Result	N	Discontinued, n(%)	Median ToT (95%CI)	% treated at 6 months	% treated at 12 months	% treated at 24 months	% treated at 36 months
TOT	0	235	143 (60.9%)	22.6 (17.5, 32.7)	86.90%	68.80%	48.90%	39.00%
	low	424	234 (55.2%)	27.0 (23.5, 34.4)	87.00%	70.00%	53.90%	41.10%

	HER2 Result	N	Died n(%)	Median OS (95%CI)	% OS at 6 months	% OS at 12 months	% OS at 24 months	% OS at 36 months
OS	0	235	89 (37.9%)	52.4 (47.4, NR)	96.00%	90.80%	76.10%	63.50%
	low	424	123 (29.0%)	67.0 (58.0, NR)	96.80%	92.10%	82.50%	71.70%

Figure 2

Time on treatment and overall survival from CDK4/6i + F initiation, stratified by HER2 result



	HER2 Result	N	Discontinued, n(%)	Median ToT (95%CI)	% treated at 6 months	% treated at 12 months	% treated at 24 months	% treated at 36 months
TOT	0	100	78 (78.0%)	13.0 (11.4, 20.4)	71.60%	58.70%	26.90%	17.60%
	low	224	175 (78.1%)	11.2 (8.8, 15.6)	68.40%	46.60%	30.00%	17.90%

	HER2 Result	N	Died n(%)	Median OS (95%CI)	% OS at 6 months	% OS at 12 months	% OS at 24 months	% OS at 36 months
OS	0	100	57 (57.0%)	37.8 (28.7, 43.1)	93.90%	85.10%	66.80%	53.00%
	low	224	117 (52.2%)	36.4 (30.9, 44.0)	89.40%	80.50%	64.00%	50.60%

CONCLUSION

- This study shows that HR+/HER2- metastatic breast cancer is a mixed population of IHC scores, with 60-65% of cases being HER2-low, consistent with prior studies.
- **The limited real-world TOT duration at post-CDK4/6i progression highlights a critical unmet need for new and more efficacious treatments for patients progressing on this modern endocrine-biologic regimen.**
- **In this real-world analysis, first-line CDK4/6i & AI treatment showed numerically higher, not statistically significant OS by 14.6 months in HER2-low patients compared to HER2 IHC 0 tumors whereas in patients who received CDK4/6i/F at more advanced setting of their metastatic disease, OS did not differ by HER2 status.**
- **Those results stand in line with recent retrospective analysis of PALOMA-2 and PALOMA-3 trials, where HER2-low patients showed higher benefit from CDK4/6i in the 1st line setting compared with HER2 IHC 0, whereas in later treatment-lines adding CDK4/6i to endocrine therapy benefited all patients similarly.**
- Additional studies are encouraged to support this retrospective observation.

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