Association of weight changes compared to baseline with time on CDK 4/6 inhibitor in women with de novo Stage IV HR+HER2- breast cancer.

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Background and Objectives

- Overweight and obesity are associated with worse outcomes in breast cancer (BC), while weight loss can delay the onset of endocrine therapy resistance in pre-clinical models.
- Weight gain is a common side-effect of endocrine therapy.
- We explored if weight loss delays resistance to endocrine therapy with CDK 4/6 inhibitors in women with de novo hormone-receptor positive (HR+) /HER2- metastatic breast cancer

Methods

- We analyzed patients with de novo HR+/HER2- metastatic breast cancer treated at MD Anderson Cancer Center with CDK4/6 inhibitors and endocrine therapy from January 2015 to December 2024 who experienced disease progression.
- Body weight and BMI were tracked at baseline (CDK4/6 inhibitor initiation) and 3, 6, and 12 months from CDK4/6 inhibitor start.
- Mixed-effects models assessed associations between treatment duration and weight/BMI change.
- Cox proportional hazards models evaluated factors associated with overall survival (OS).

Results

- 488 patients progressed on CDK 4/6i and ET
- Palbociclib was the most used drug (86.3%).
- Of 488, 80 (16.4%) experienced weight gain and 48 (9.8%) experienced weight loss at 12 months compared to baseline. Similar proportions were observed for change in BMI. (Figure 1)
- Mixed-effects univariate and multivariate models showed that increases in absolute weight and BMI from baseline over time were associated with longer CDK4/6i therapy duration (p=0.010 and p=0.005, respectively). (Tables 1 and 2)
- In univariate Cox analysis, longer CDK4/6i use was associated with improved OS (HR 0.50, 95% CI 0.44-0.57, p<0.001), while higher tumor grade and presence of BRCA mutations correlated with poorer OS. (Table 3)

Based on the result of mixed effect model, absolute weight change/BMI increased significantly over time with continued CDK4/6 therapy, indicating a significant association between treatment duration and changes in weight/BMI.

Contrary to our hypothesis, absolute weight and BMI increase from baseline was associated with longer CDK 4/6i use in de novo HR+/HER2- breast cancer.

Weight trends and tumor biology may offer prognostic insight into the obesity paradox (increase in weight associated with better outcomes) and warrant further study in prospective settings.

Results

Figure 1: Box plot of median absolute weight change at 3,6, and 12 months

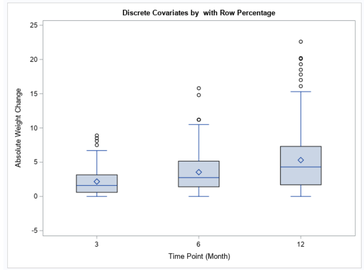


Table 1: Univariate and independent association between absolute weight change and patient characteristics (mixed effects model, random intercept)

Variable	Category	Estimate	p-value	95% CI
Univariate regression				
CDK4 use duration		0.48	0.008	0.13, 0.83
Age	>50 vs <=50	0.08	0.856	-0.83, 1.00
Race	Asian vs white	-1.72	0.029	-3.26, -0.17
	Black vs white	0.66	0.403	-0.88, 2.19
	Hispanic vs white	-0.11	0.875	-1.51, 1.28
PR Primary	Positive vs negative	0.04	0.952	-1.13, 1.20
HER2 IHC	1+ vs 0	-0.09	0.860	-1.20, 1.00
	2+ vs 0	-0.30	0.649	-1.62-1.00
Grade Primary	II vs I	-0.74	0.413	-2.51, 1.03
	III vs I	-1.33	0.165	-3.21, 0.55
Lymphatic invasion	Pos vs Neg	-0.01	0.992	-1.17, 1.16
Vascular Invasion	Pos vs Neg	-0.01	0.992	-1.17, 1.16
BRCA	BRCA2 vs BRCA negative	-1.15	0.362	-3.64, 1.33
	BRCA vs no testing	-0.003	0.994	-0.93, 0.92
Multivariate regression				
CDK4 use duration		0.46	0.010	0.11, 0.81
Race	Asian vs white	-1.59	0.043	-3.13, -0.06
	Black vs white	0.71	0.362	-0.81, 2.23
	Hispanic vs white	-0.18	0.803	-1.56, 1.21

Results

Table 2: Independent association between absolute BMI and patient and treatment characteristics (mixed effects model, random intercept)

Variable	Category	Estimate	p-value	95% CI
CDK4 use duration		0.19	0.005	0.06, 0.33
Race	Asian vs white	-0.53	0.081	-1.12, 0.07
	Black vs white	0.25	0.398	-0.33, 0.84
	Hispanic vs white	0.03	0.918	-0.51, 0.56

Table 3: OS univariate / multivariate (if included) models

Variable	Category	P value	HR	95% CI
Age	>50 vs <=50	0.252	1.15	0.90-1.48
Race	Asian vs white	0.725	0.92	0.55-1.50
	Black vs white	0.106	1.37	0.93-2.01
	Hispanic vs white	0.926	0.98	0.65-1.48
Clinical T stage	T1 vs T0	0.693	1.15	0.57-2.34
	T2 vs T0	0.867	1.06	0.55-2.02
	T3 vs T0	0.948	0.98	0.48-1.99
	T4 vs T0	0.318	1.41	0.72-2.76
Clinical N stage	N1 vs N0	0.302	0.84	0.59-1.18
	N2 vs N0	0.928	1.03	0.59-1.76
	N3 vs N0	0.837	1.03	0.69-1.53
PR Primary	Pos vs Neg	0.498	0.90	0.66-1.23
HER2 IHC	1+ vs 0	0.492	1.12	0.82-1.52
	2+ vs 0	0.533	1.12	0.78-1.60
Grade Primary	II vs I	0.031 / 0.121	1.83 / 1.53	1.06-3.16 / 0.89-3.52
	III vs I	0.013 / 0.0165	2.07 / 1.27	1.16-3.68 / 1.13-3.52
Lymphatic invasion	Pos vs Neg	0.985	1.00	0.75-1.33
Vascular Invasion	Pos vs Neg	0.985	1.00	0.75-1.33
BRCA	BRCA1 vs BRCA-	0.388 / 0.037	0.29 / 0.04	0.02-4.82 / 0.002 – 0.821
	BRCA2 vs BRCA-	0.307 / 0.565	1.48 / 1.35	0.70-3.16 / 0.56 – 2.86
	BRCA vs no testing	0.002 / 0.042	1.54 / 1.35	1.16-2.02 / 1.01-1.79
CDK4 use duration		<0.001 / = < 0.001	0.50 / .43	0.44-0.57 / 0.37-0.50

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