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Genomic Landscape of ER+/HER2- Metastatic Breast Cancer as a Function of Prior Treatment With a CDK4/6 Inhibitor

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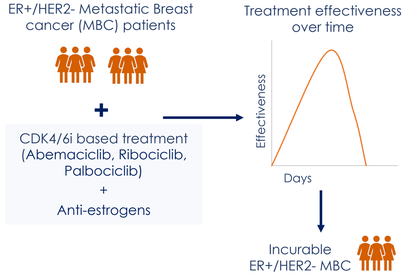
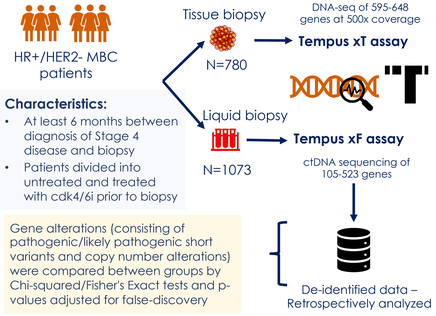
INTRODUCTION



The landscape of acquired somatic alterations causal to CDK4/6i resistance remains unknown so there is an urgent need to understand molecular basis of resistance

In this study, we report differences in mutational landscapes between ER+ HER2- MBC patients treated with and without CDK4/6i

METHODS



Characteristics:

- At least 6 months between diagnosis of Stage 4 disease and biopsy
- Patients divided into untreated and treated with cdk4/6i prior to biopsy

Gene alterations (consisting of pathogenic/likely pathogenic short variants and copy number alterations) were compared between groups by Chi-squared/Fisher's Exact tests and p-values adjusted for false-discovery

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RESULTS

Characteristic	Overall, N = 1,853[1]	Without CDK4/6i, N = 371[1]	With CDK4/6i, N = 1,482[1]	p-value[2]
Age at diagnosis (yrs, IQR)	54 (45, 63)	53 (44, 63)	55 (45, 63)	**0.7**
Unknown	5	1	4	
Gender				**0.4**
Female	1,835 (99%)	366 (99%)	1,469 (99%)	
Male	18 (1.0%)	5 (1.3%)	13 (0.9%)	
Race				**0.085**
White	997 (80%)	193 (75%)	804 (81%)	
Black /African American	142 (11%)	38 (15%)	104 (11%)	
Asian	52 (4.2%)	11 (4.3%)	41 (4.1%)	
Other Race	50 (4.0%)	13 (5.0%)	37 (3.7%)	
Native Hawaiian or Other Pacific Islander	4 (0.3%)	1 (0.4%)	3 (0.3%)	
American Indian/Alaskan	3 (0.2%)	2 (0.8%)	1 (0.1%)	
Unknown	605	113	492	
Ethnicity				**0.2**
Not Hispanic or Latino	622 (86%)	115 (83%)	507 (87%)	
Hispanic or Latino	100 (14%)	24 (17%)	76 (13%)	
Unknown	1,131	232	899	
Assay				**0.007**
xF	1,073 (58%)	192 (52%)	881 (59%)	
xT	780 (42%)	179 (48%)	601 (41%)	
HR/HER2 Status				**0.019**
ER+, PR+, HER2-	1,558 (84%)	297 (80%)	1,261 (85%)	
ER+, PR-, HER2-	248 (13%)	66 (18%)	182 (12%)	
ER+, HER2-	47 (2.5%)	8 (2.2%)	39 (2.6%)	
Receipt of AI	1,584 (88%)	223 (70%)	1,361 (92%)	**<0.001**
No	213 (12%)	94 (30%)	119 (8%)	
Unknown	56	54	2	

[1]Median (IQR); n (%)
[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Table 1. Cohort characteristics

RB1 Alteration Types	Overall, N = 62[1]	Without CDK4/6i, N = 12[1]	With CDK4/6i, N = 50[1]
Copy Number Loss	18 (29%)	4 (33.3%)	14 (28%)
Disruptive Inframe Deletion	1 (1.6%)	0 (0%)	1 (2%)
Frameshift Variant	9 (14.5%)	2 (16.7%)	7 (14%)
Inframe Deletion	1 (1.6%)	0 (0%)	1 (2%)
Intron Variant	16 (25.8%)	4 (33.3%)	12 (24%)
Missense Variant	2 (3.2%)	0 (0%)	2 (4%)
Splice Acceptor Variant	6 (9.7%)	2 (16.7%)	4 (8%)
Splice Donor Variant	10 (16.1%)	2 (16.7%)	8 (16%)
Splice Region Variant	5 (8.1%)	0 (0%)	5 (10%)
Stop Gained	24 (38.7%)	3 (25%)	21 (42%)

[1] n (%) of patients

Table 2. Types of *RB1* alterations in patients treated with and without CDK4/6i

PTEN Alteration Types	Overall, N = 82[1]	Without CDK4/6i, N = 11[1]	With CDK4/6i, N = 71[1]
Copy Number Loss	39 (47.6%)	8 (72.7%)	31 (43.7%)
Disruptive Inframe Deletion	1 (1.2%)	0 (0%)	1(1.4%)
Frameshift Variant	22 (26.8%)	0 (0%)	22 (31%)
Intron Variant	2 (2.4%)	0 (0%)	2 (2.8%)
Missense Variant	11 (13.4%)	2 (18.2%)	9 (12.7%)
Splice Acceptor Variant	1 (1.2%)	0 (0%)	1 (1.4%)
Splice Donor Variant	1 (1.2%)	0 (0%)	1 (1.4%)
Stop Gained	9 (11%)	1 (9.1%)	8 (11.3%)

[1] n (%) of patients

Table 3. Types of *PTEN* alterations in patients treated with and without CDK4/6i

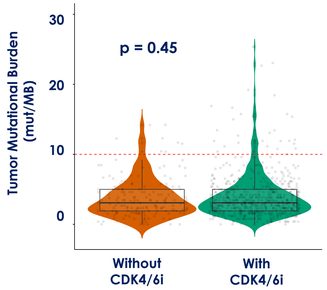

Figure 1. A comparison of the Tumor Mutational Burden status between patients treated with and without CDK4/6i

KEY TAKEAWAYS

- **Patients with prior CDK4/6i therapy harbored significantly more *ESR1* somatic alterations**, at a similar rate in both solid tissue (xT) and liquid biopsies (xF).
- In **tissue biopsy (xT)**, patients with prior CDK4/6i therapy harbored **more *CCND1*, *FGF3*, *FGF4*, and *GATA3* alterations** and **fewer *TP53* alterations**, although these findings were non-significant after false-discovery adjustment.
- ***CCND1*, *FGF3*, *FGF4*** and ***FGF19*** alterations were copy number amplifications, which may be consistent with 11q13 amplification.

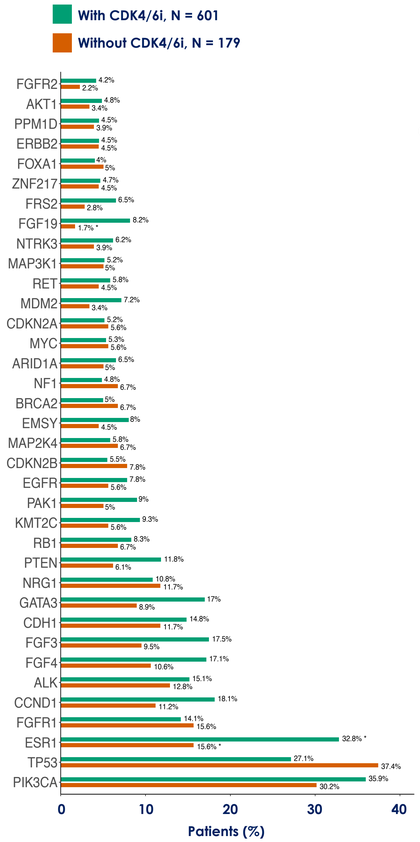

Figure 2. Somatic mutations in Tempus tissue (xT) sequencing population. *notates genes significant after false discovery. Note - Gene list was abridged to genes present in >=4% of CDK4/6i treated population and genes annotated in OncoKB

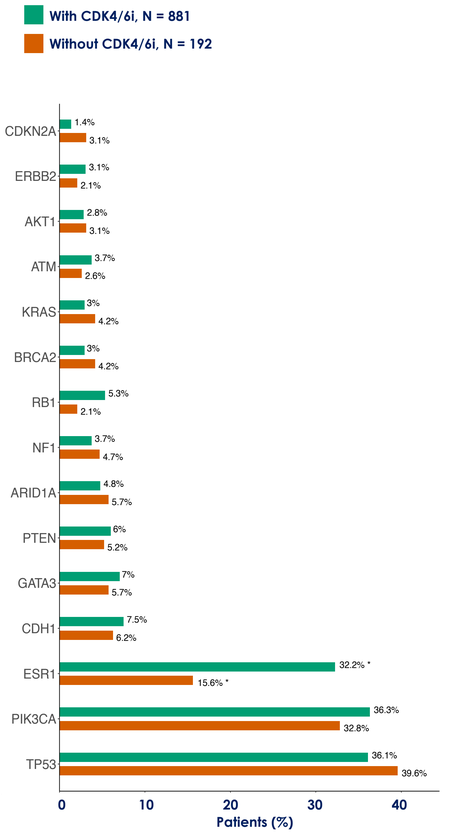

Figure 3. Somatic mutations in Tempus liquid biopsy (xF) sequencing population. *notates genes significant after false discovery.
Note. -Genes listed here was altered in >=3% of overall xF population

Note - Analyses reflect a convenience sample and only bivariate analyses were performed without adjustment for confounding factors between groups (i.e. selection bias for receipt of CDK4/6i and immortal time bias). Therefore, findings serve as exploratory and hypothesis-generating.