Genomic Profiles of Early Progressors vs Exceptional Responders on CDK4/6i in ER+ HER2- Advanced Breast Cancer

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San Antonio Breast Cancer Symposium
December 10-13, 2024
P4-10-09

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Introduction

- CDK4/6 inhibitors (CDK4/6i) paired with endocrine therapy (ET) are common first-line (1L) therapy for patients (pts) with hormone receptor positive (HR+) HER2 negative (HER2-) advanced breast cancer (aBC).
- A subset of pts will demonstrate primary resistance to CDK4/6i, as characterized by early progression, while other patients will remain on CDK4/6i for an extended duration prior to progression.
- The underlying genomic landscapes mediating response is still unclear.
- Guardant360 CDx (blood ctDNA) and Tempus (xT: tumor with normal matched sample; xF: blood ctDNA) are panel-based platforms detecting genomic alterations and copy number variation of commonly-mutated genes.

Objectives

- To investigate clinical and genomic differences between cohorts of early progressors and exceptional responders (late progressors).

Methods

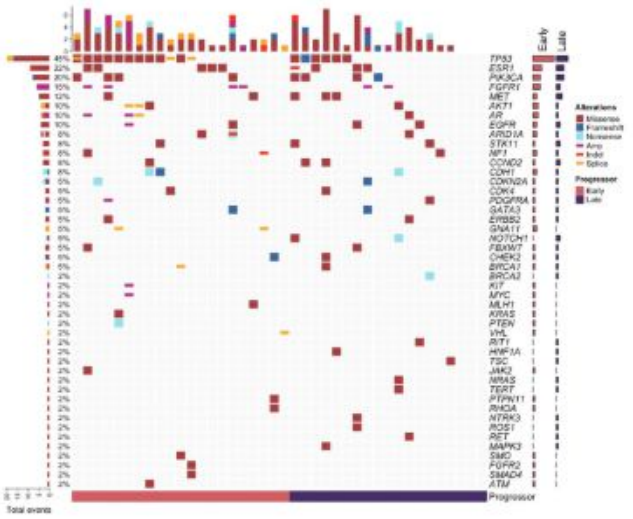
- Clinical information, including treatment start and stop dates, was collected from the electronic medical record. Progression-free survival (PFS) was estimated by the treatment duration on a specified treatment regimen. Overall survival (OS) was defined as time to death from the initiation of CDK4/6i.
- NGS testing was performed using the Guardant360 CDx (sample: peripheral blood) or Tempus (sample: tissue in 43/45 pts) platforms per standard-of-care at time points per the treating physician's discretion in the retrospective CDK4/6i study patients and Whole Exome Sequencing (WES) of circulatiang tumor DNA was performed on the palbo alt dosing trial (NCT3007979) patients at baseline and progression.
- For early progressors, only patients who discontinued therapy due to progression were included.
- Guardant360 cohort: Early progression (EP) on CDK4/6i was defined as PFS < 6 months; late progression (LP) was defined as PFS > 18 months. Patients who received 1st or 2nd line therapy with guardant360 CDx performed prior to or within 60 days of starting therapy, were included.
- Tempus cohort: Early progression (EP) on CDK4/6i was defined as PFS < 12 months; late progression (LP) was defined as PFS > 12 months for Tempus testing. Patients who received CDK4/6i as 1st line and Tempus testing pre-treatment were included.
- Tumor samples from TCGA BRCA cohort was analyzed to evaluate the consequence of *AR*-alterations in the treatment-naïve setting.

Results

Guardant360 CDx clinical/patient demographics

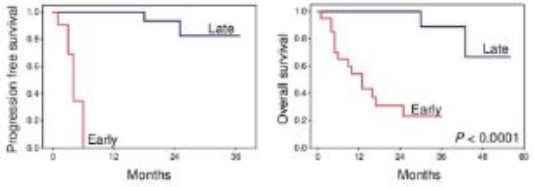
Variable	Level	Overall (n = 40)	Early progressor (n = 21)	Late progressor (n = 19)
Age (med, SD)		63 (12.0)	60 (10.2)	72 (12.8)
Race	White	26 (70.0%)	11 (52.4%)	17 (89.5%)
	Black	11 (27.5%)	10 (47.6%)	1 (5.3%)
	Other	1 (2.5%)	0 (0%)	1 (5.3%)
Line of therapy	First	23 (57.5%)	8 (38.1%)	15 (78.9%)
	Second	17 (42.5%)	13 (61.9%)	4 (21.1%)
Endocrine therapy partner	AI	19 (47.5%)	10 (47.6%)	9 (47.4%)
	Fulvestrant/SERD	21 (52.5%)	11 (52.4%)	10 (52.6%)
Site of disease	Visceral	18 (45.0%)	12 (57.1%)	6 (31.6%)
	Non-visceral	22 (55.0%)	5 (23.8%)	5 (26.3%)
	Bone only	10 (25.0%)	4 (19.0%)	8 (42.1%)

Guardant360 CDx ctDNA profiling



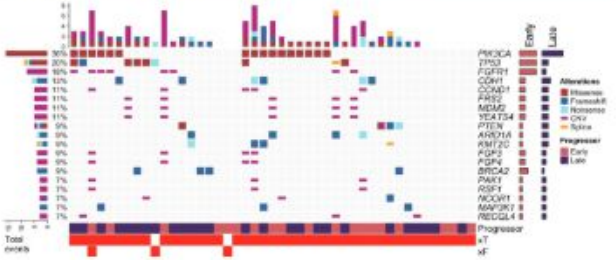
- *TP53* enrichment in early progressors (12/21) compared to late progressors (6/19).
- *AR* and *AKT1* enrichment in early progressors (3/21) compared to late progressors (1/19).
- *FGFR1* enrichment in early progressors (4/21) compared to late progressors (2/19).

Guardant progression free/overall survival



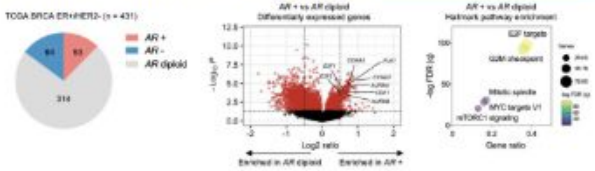
- Median PFS of early progressors was 4 months and OS was 13 months.

Tempus xT/xF profiling



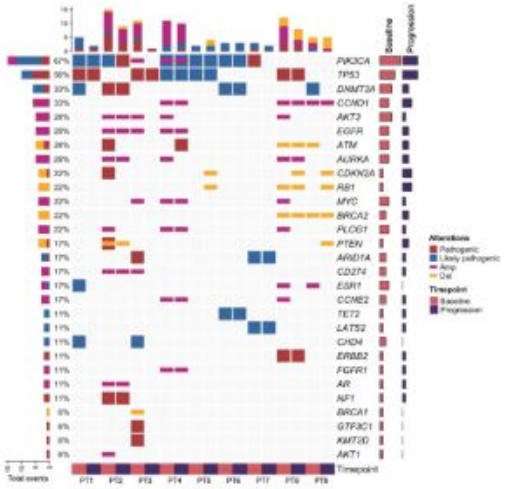
- *TP53* enrichment in early progressors (6/19) compared to late progressors (3/26).
- *FGFR1* enrichment in early progressors (6/19) compared to late progressors (2/26).
- Lack of *ESR1* or *AR* alterations detected.

AR alterations in TCGA BRCA



- Potential cell cycle and oncogenic pathway enrichment in *AR*-altered ER+/HER- breast cancers.

Whole exome sequencing Early progressors in the Alt Dosing Trial



- Median PFS of early progressors was 3.0 months and OS was 13.0 months.
- Median of 2.83 months between baseline and progression WES.
- No significant differences in mutational profiles at baseline versus progression.

Conclusions

- Enriched alteration incidence in *TP53* and *FGFR1* consistent with the literature.
- Increased *AR* alteration incidence in early progressors should be validated in larger cohorts.
- Gain-of-function alterations in *AR* associated with enhanced cell cycle and other oncogenic pathways
- Varying degrees of mutation detection sensitivity in peripheral blood ctDNA and tissue (undetected *ESR1* and *AR* in our cohort by tissue biopsy).