Genomic Insights in Metastatic Invasive Lobular Carcinoma: a Real-world Study

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Introduction

- Invasive lobular carcinoma (ILC) has distinct genomic alterations that can bypass estrogen and CDK4/6 dependence, but there is limited systematic data linking specific alterations to treatment response.
- This gap is critical as ILC represents 10-15% of breast cancers with unique biology and treatment resistance compared to ductal carcinoma.
- The study aimed to identify how individual genomic alterations affect clinical outcomes in metastatic ILC patients.

Methods

❑ Study Design and Data Source:

- Retrospective observational study using the nationwide Flatiron Health–Foundation Medicine Clinicogenomics Database with patient-level electronic health record data from approximately 280 cancer clinics across ~800 sites of care

❑ Study population:

- Inclusion criteria: Adult patients (≥18 years) with hormone receptor–positive, HER2-negative metastatic ILC (Jan 2015–Sep 2022) who underwent genomic profiling between 90 days before metastatic diagnosis and 90 days after first-line therapy initiation
- Exclusion criteria: Patients without documented Hormone Receptor (HR)/HER2 status, those who participated in clinical trials, and those with less than six months of follow-up

❑ Biomarker Assessment:

- To determine alteration status, only variant classified as pathogenic or likely pathogenic were included.
- ERBB2 assessed only in tumors with HER2-negative status confirmed by both IHC and FISH

❑ Statistical Analysis:

- Demographic and clinical characteristics were summarized using descriptive statistics, while overall survival (OS) and time-to-treatment-discontinuation (TTD) were evaluated using Kaplan-Meier analysis and multivariable Cox proportional hazards models adjusted for patients' demographic and clinical characteristics.

Result and Interpretation

Table 1: Baseline Characteristics

Characteristic, n (%)	N= 256
Age, Median (IQR)	65 (58, 73)
Race	
White	195 (76%)
Black	49 (19%)
Other	12 (5%)
Tumor Grade	
Grade 1-2	226 (88%)
Grade 3-4	30 (12%)
ECOG Status	
0-1	200 (78%)
2-4	31 (12%)
Missing	25 (10%)
First-line Treatment	
CDK4/6 + ET	144 (56%)
Chemotherapy	62 (24%)
Endocrine Therapy	27 (11%)
Other	23 (9%)
Metastasis Sites	
Bone Metastasis	170 (66%)
Brain Metastasis	10 (4%)
Liver Metastasis	75 (29%)
Lung Metastasis	42 (16%)

Figure 1: Biomarker Status

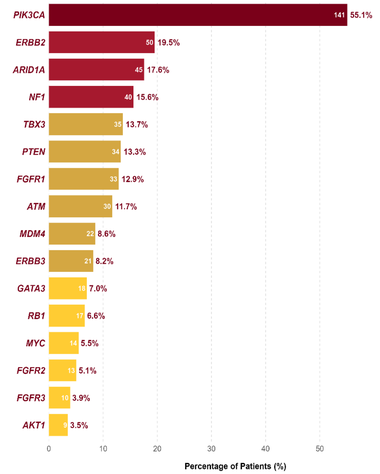

Figure 2: OS and TTD by *ARIDIA1* status

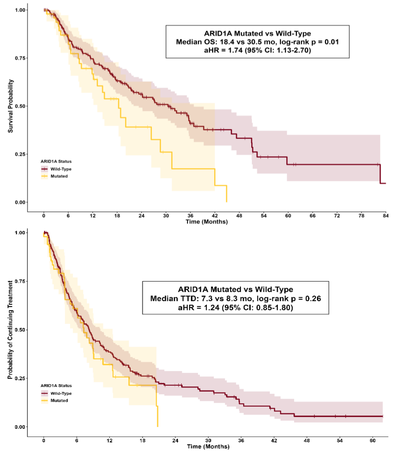

Figure 3: OS and TTD by *GATA3* status

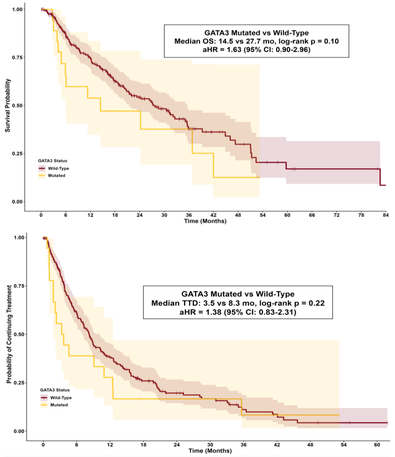

Figure 4: OS and TTD by *NF1* status

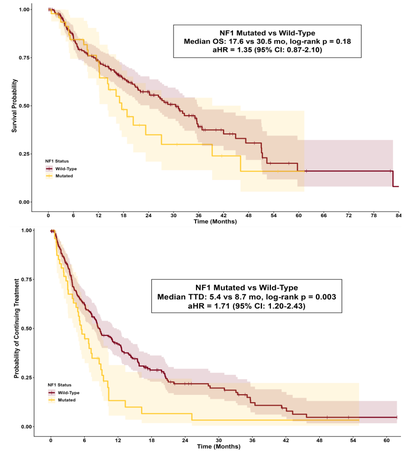

Figure 5: OS and TTD by *RB1* status

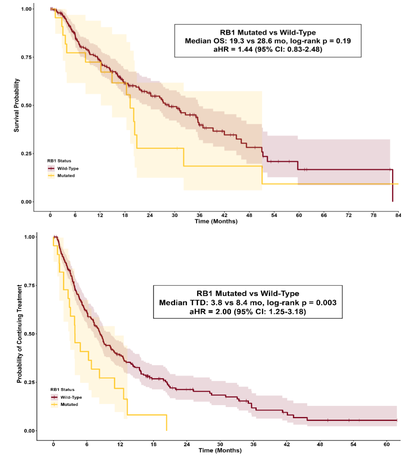

Table 2: Survival Analysis in CDK4/6 inhibitors cohort

- *ERBB2,PTEN , ATM , PIK3CA , ERBB3 , TBX3 , MDM4 , FGFR1 , FGFR2.AKT1 ,* and *MYC* did not demonstrate statistically significant impact on survival outcomes.

Gene	Metric	Status	Median (95% CI)	P-value	HR (95% CI)
ARID1A	OS	Wild-Type	35.6 (24.2-44.5)	0.22	1.51 (0.78-2.94)
		Mutated	31.4 (13.1-NR)		
	TTD	Wild-Type	11.0 (8.5-15.7)	0.65	1.13 (0.67-1.91)
		Mutated	9.1 (6.2-NR)		
GATA3	**OS**	**Wild-Type**	**35.6 (27.1-49.3)**	**0.003**	**3.24 (1.45-7.27)**
		Mutated	**11.3 (4.9-NR)**		
	TTD	**Wild-Type**	**11.8 (8.7-15.8)**	**0.003**	**2.65 (1.37-5.12)**
		Mutated	**3.7 (2.2-NR)**		
NF1	OS	**Wild-Type**	**44.9 (30.5-55.1)**	**0.01**	**2.30 (1.18-4.49)**
		Mutated	**17.6 (11.5-29.3)**		
	TTD	**Wild-Type**	**12.6 (8.9-15.8)**	**< 0.01**	**2.95 (1.72-5.09)**
		Mutated	**5.1 (3.1-10.3)**		
RB1	OS	Wild-Type	35.6 (27.1-49.2)	0.20	1.74 (0.74-4.08)
		Mutated	20.3 (19.3-NR)		
	TTD	**Wild-Type**	**12.2 (8.7-15.5)**	**0.02**	**2.29 (1.11-4.75)**
		Mutated	**3.8 (3.0-NR)**		

Conclusion

- **This large-scale analysis identifies *NF1, RB1, GATA3*, and *ARID1A* alterations as potential predictors of treatment resistance in metastatic ILC.**
- **Patients harboring these genomic alterations demonstrate reduced benefit from standard therapies and may require alternative treatment strategies.**
- **Routine genomic profiling is essential to identify high-risk patients and guide personalized therapeutic decisions.**
- **Further studies are needed to validate these findings and develop targeted approaches to overcome genomic-driven resistance mechanisms.**

References:
1 McCart Reed, A. E., Foong, S., Kutasovic, J. R., Nones, K., Waddell, N., Lakhani, S. R., & Simpson, P. T. (2021). The Genomic Landscape of Lobular Breast Cancer. Cancers, 13(8), 1950. https://doi.org/10.3390/cancers1308195
2 Batra, H.; Mouabbi, J.A.; Ding, Q.; Sahin, A.A.; Raso, M.G. Lobular Carcinoma of the Breast: A Comprehensive Review with Translational Insights. Cancers 2023, 15, 5491. https://doi.org/10.3390/cancers15225491

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