Impact of *RB1* alteration on Clinical Outcomes in Metastatic Breast Cancer: A Real-World Subtype-Dependent Survival Analysis

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Introduction

- *RB1* is a master cell cycle regulator that controls the G1–S transition and influences hormone-receptor signaling and tumor immunity.
- The prognostic impact of *RB1* loss across breast cancer subtypes remains unclear despite its known tumor-suppressor functions.
- This study compares *RB1* loss effects in HR+/HER2– versus triple-negative metastatic breast cancer (TNBC) to clarify subtype-specific clinical outcomes.

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 metastatic breast cancer diagnosis(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.

❑ 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

HR+/ HER2-

Table 1: Baseline Characteristics

Characteristic, n(%)	Mutated (N = 83)	Wild-Type (N = 1,630)	p-value
Age, Median (IQR)	62 (54, 69)	61 (52, 70)	0.9
Race			
White	55 (67%)	1,057 (65%)	
Black	13 (16%)	153 (9.4%)	
Other	14 (17%)	410 (25%)	
Tumor Grade			0.060
Grade 1-2	15 (55%)	897 (66%)	
Grade 3	29 (45%)	356 (54%)	
Unknown	19	577	
ECOG Status			
0-1	65 (78%)	1,272 (78%)	
2-4	10 (12%)	188 (12%)	
Missing	8 (9.6%)	170 (10%)	
First-line Treatment			0.2
CDK4/6 + ET	38 (46%)	978 (60%)	
Chemotherapy	25 (30%)	326 (20%)	
Endocrine Therapy	14 (17%)	245 (15%)	
Other	6 (7%)	70 (4%)	
Metastatic Sites			
Bone Metastasis	54 (65%)	1,145 (70%)	0.3
Brain Metastasis	5 (6%)	101 (6%)	0.9
Liver Metastasis	36 (43%)	489 (30%)	0.010
Lung Metastasis	32 (39%)	519 (32%)	0.2
Genomic Alterations			
PIK3CA Mutation	41 (49%)	703 (43%)	0.3
PTEN Mutation	22 (27%)	158 (9.7%)	<0.001
AKT1 Mutation	5 (6.0%)	84 (5.8%)	0.2
ESR1 Mutation	19 (23%)	216 (13%)	0.013
TP53 Mutation	49 (59%)	520 (32%)	<0.001
NF1 Mutation	13 (16%)	179 (11%)	0.2

Figure 2: OS and TTD by *RB1* status

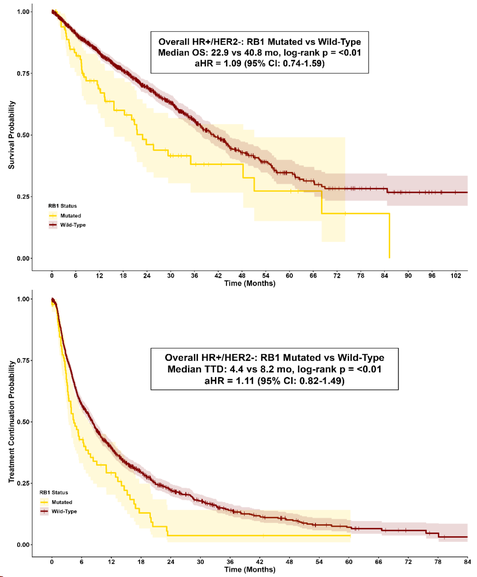


Table 2: Survival Analysis based on 1L treatment

Treatment	Outcome	*RB1* Status	Median (95% CI)	P-value	aHR (95% CI)
CDK4/6i + ET	OS	Mutated	46.4 (38.7-66.2)	0.22	1.22 (0.65–2.30)
		Wild-Type	51.1 (20.9-NR)		
	TTD	Mutated	10.9 (5.0-19.8)	0.02	1.28 (0.84–1.97)
		Wild-Type	13.3 (12.1-15.1)		
Chemotherapy	OS	Mutated	13.3 (5.7-NR)	0.06	1.18 (0.86–1.97)
		Wild-Type	24.9 (20.2-31.2)		
	TTD	Mutated	3.3 (2.7-6.3)	0.11	1.13 (0.67–1.86)
		Wild-Type	4.3 (4.0-4.8)		

TNBC

Table 3: Baseline Characteristics

Characteristic, n(%)	Mutated (N = 46)	Wild-Type (N 240)	p-value
Age, Median (IQR)	54 (49, 67)	60 (49, 69)	0.2
Race			0.4
White	29 (63%)	132 (55%)	
Black	9 (20%)	48 (20%)	
Other	7 (16%)	61 (25%)	
Tumor Grade			0.4
Grade 1-2	3 (9%)	21 (8.6%)	
Grade 3	30 (65%)	132 (55%)	
Unknown	13 (29%)	88 (36%)	
ECOG Status			
0-1	36 (78%)	183 (76%)	
2-4	5 (10%)	28 (11%)	
Missing	6 (12%)	29 (12%)	
First-line Treatment			0.2
Chemotherapy	27 (59%)	135 (56%)	
Immunotherapy	13 (29%)	77 (32%)	
Other	6 (12%)	29 (12%)	
Metastatic Sites			
Bone Metastasis	13 (29%)	102 (43%)	0.06
Brain Metastasis	4 (8.9%)	24 (10%)	0.9
Liver Metastasis	11 (24%)	76 (32%)	0.3
Lung Metastasis	22 (47%)	134 (56%)	0.3
Genomic Alterations			
PIK3CA Mutation	7 (16%)	43 (18%)	0.8
PTEN Mutation	7 (16%)	38 (16%)	0.9
AKT1 Mutation	5 (10%)	14 (5.7%)	0.3
BRCA Mutation	9 (20%)	50 (21%)	0.9
TP53 Mutation	46 (100%)	216 (90%)	0.011
NF1 Mutation	9 (20%)	29 (12%)	0.13

Figure 3: OS and TTD by *RB1* status

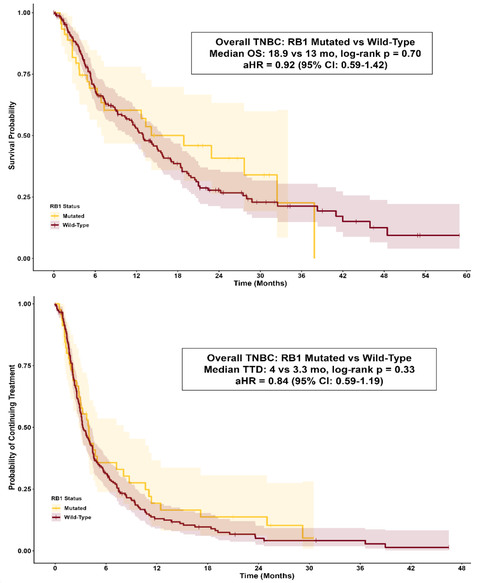


Table 4: Survival Analysis based on 1L treatment

Treatment	Outcome	*RB1* Status	Median (95% CI)	P-value	aHR (95% CI)
Immunotherapy	OS	Mutated	12.3 (8.6-NR)	0.9	1.1 (0.4–2.23)
		Wild-Type	12.6 (7.5-15.8)		
	TTD	Mutated	2.8 (2.1-NR)	0.5	1.3 (0.67–2.16)
		Wild-Type	3.6 (2.5-6.2)		
Chemotherapy	OS	Mutated	14.2 (7.8-20.1)	0.61	0.85 (0.55–1.62)
		Wild-Type	11.5 (7.4-16.9)		
	TTD	Mutated	4.6 (3.8-11.4)	0.33	0.88 (0.57–1.35)
		Wild-Type	3.3 (3.1-4.2)		

Conclusion

- **This real-world analysis demonstrates that *RB1* mutations have subtype-dependent clinical impact: in TNBC, *RB1* loss does not affect treatment response or survival, whereas in HR+/HER2- disease, *RB1* mutations are associated with poor prognosis and reduced benefit from CDK4/6 inhibitors.**
- **Co-occurring mutations with resistance drivers including *PTEN* and *ESR1* further compound treatment resistance, suggesting *RB1* mutation status may guide precision medicine therapeutic strategies.**

References:
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