Molecular Characteristics of TNBC and pathologic response to chemoimmunotherapy: a focus on racial disparities

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Introduction

Triple-negative breast cancer (TNBC) is characterized by aggressive clinical behavior with limited targeted therapies. The addition of pembrolizumab to neoadjuvant chemotherapy (NACT) has improved pathologic complete response (pCR) rates in early-stage TNBC; however, racial disparities in outcomes remain. Limited data exist on how these disparities may impact pathologic response to chemoimmunotherapy. This study evaluates genomic differences among TNBC patients treated with a pembrolizumab-based NACT regimen at a regional health system, aiming to identify genetic markers that may predict treatment response and provide insight into observed racial disparities.

Methods

Patient records from Ochsner Health, a regional healthcare network, were reviewed to identify individuals with early-stage TNBC treated with pembrolizumab-based NACT between 2020 and 2024. Exclusion criteria included unknown receptor status and age <18 years. Eligible patients were required to have archived formalin-fixed paraffin-embedded (FFPE) biopsy samples available at the main campus. Consented participants underwent tumor DNA sequencing performed by Tempus using their archived diagnostic tissue.

Results

Archived FFPE tumor samples were obtained from 50 TNBC patients treated with NACT and pembrolizumab. Of these, 43 samples passed Tempus quality control measures, and 40 were included in the final analysis (excluding one patient who identified as "Other" race and two without definitive surgery or pCR data). Among the 40 analyzed patients, 25 identified as AA and 15 as White. The average number of mutations detected per patient was 16.5 with an average of 18 mutations/patient in AA patients and 13 mutations/patient in White patients (Table 1).

Results

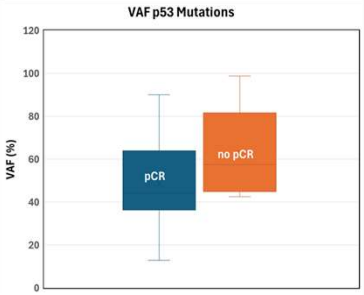
White Subjects													
Mutation	TP53	RB1	CKS1B	LRP1B	RANBP2	FAS	KMT-2C/D	ARID1A	PTEN	SYNE1	NOTCH2	MYC	MCL1
% Present	93	33	33	33	27	20	33	13	13	7	13	13	13
pCR	11	4	5	5	3	2	5	2	2	1	1	1	2
No PCR	3	1	0	0	1	1	0	0	0	0	1	1	0
Total	14	5	5	5	4	3	5	2	2	1	2	2	2
Total PCR %	78	80	100	100	75	66	100	100	100	100	50	50	100
AA Subjects													
Mutation	TP53	RB1	CKS1B	LRP1B	RANBP2	FAS	KMT-2C/D	ARID1A	PTEN	SYNE1	NOTCH2	MYC	MCL1
% Present	96	32	28	16	4	8	60	20	20	24	12	20	36
pCR	16	6	6	3	1	1	14	2	3	5	3	2	6
No PCR	8	2	1	1	0	1	1	3	2	1	0	3	3
Total	24	8	7	4	1	2	15	5	5	6	3	5	9
Total PCR %	66	75	85	75	100	50	93	40	60	83	100	40	66

Table 1. Mutation frequencies and PCR response by race in TNBC patients

	pCR		no pCR		p-value	Race	Mutation	No Mutation	p-value
KMT2CD	mutation	16	mutation	1	0.005	AA	12	1	0.512
	no mutation	12	no mutation	11		White	5	10	
LRP1B	mutation	8	mutation	1	0.233	AA	4	21	0.255
	no mutation	20	no mutation	11		White	5	10	
RANBP2	mutation	4	mutation	1	1	AA	1	24	0.056
	no mutation	24	no mutation	12		White	4	11	
MCL1	mutation	8	mutation	3	1	AA	9	16	0.158
	no mutation	20	no mutation	9		White	2	13	
CKS1B	mutation	11	mutation	1	0.067	AA	7	18	0.736
	no mutation	17	no mutation	11		White	5	10	

Table 2. Mutations significantly associated with pCR vs no pCR

Results



95% (38/40) of patients harbored mutations in the TP53 gene—substantially higher than reported in broader breast cancer cohorts. A correlation was observed between variant allele frequency (VAF) of TP53 mutations and pCR status (p=0.047).

Conclusion

Because of the small sample size, most frequently mutated genes did not reach statistical significance, except for KMT2C/D. These methyltransferase mutations may serve as biomarkers for immunotherapy response in TNBC, given the high pCR rates observed across races—consistent with findings in other cancer types. Higher TP53 VAF was associated with poorer pCR rates, suggesting that mutation burden may affect treatment response. As additional data accumulates, it may reveal racially distinct genomic signatures that predict response to NACT with immunotherapy.

Reference

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- Meric-Bernstam F, Zheng X, Shariati M, Damodaran S, Wathoo C, Brusco L, Demirhan ME, Tapia C, Eterovic AK, Basho RK, Ueno NT, Janku F, Sahin A, Rodon J, Broaddus R, Kim TB, Mendelsohn J, Mills Shaw KR, Tripathy D, Mills GB, Chen K. Survival Outcomes by TP53 Mutation Status in Metastatic Breast Cancer. JCO Precis Oncol. 2018;2018:PO.17.00245.

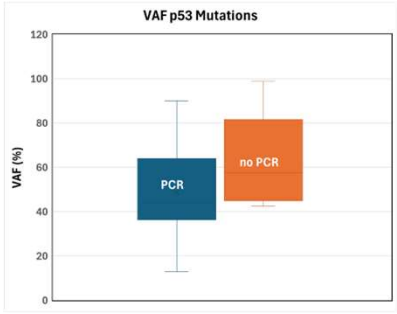
Contacts

Questions/ Inquiry: melanie.sheen@ochsner.org

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VAF p53 Mutations
120
100
80
60
40
20
0
VAF (%)
PCR
no PCR