Differences in Genomic Landscape Between Younger and Older Women with Advanced Breast Cancer

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Background

- Despite underrepresentation in clinical trials, the treatment of premenopausal breast cancer is extrapolated from trials focusing on postmenopausal women. [1]
- Clinical trials also are less likely to include older women.
- The same therapeutic benefit may not translate given differences in tumor biology, grade, and need for ovarian function suppression. [1]
- In both younger and older breast cancer patients, there is a need to enhance our understanding of predictive biomarkers for response to targeted therapies.
- The goal was to evaluate genomic differences between women < 50 years of age compared to women and > 60 years of age with advanced breast cancer.

Methods

- FFPE blocks of 1,144 advanced breast cancer cases among women < 50 and > 60 were analyzed by FoundationOne®CDx comprehensive genomic profiling that evaluated for mutations, insertions/deletions, amplifications, homozygous deletions, rearrangements, and fusions.
- Microsatellite instability-high (MSI-H) status, tumor mutational burden (TMB), and homologous recombination deficiency signature (HRDsig)° were determined from sequencing data. PD-L1 status was determined by IHC (Ventana SP142 assay, % of immunocyte/inflammatory cell staining).
- Genomic alterations were compared using Fisher's exact test with the Benjamini-Hochberg multiplicity adjustment.

° HRDsig provided as a professional service and is not reviewed or approved by the FDA

Results

- Of the 1,144 cases, 787 were hormone receptor positive (HR+) breast cancer and 368 were triple negative breast cancer (TNBC).
- In HR+ and TNBC cohorts, non-European genetic ancestry was more prevalent in women < 50 vs > 60 (HR+ 38.87% vs 15.41% p=<0.001; TNBC 42.14% vs 22.73%, p=0.004).
- In HR+ and TNBC cohorts, *CDH1* alterations were more frequent in those > 60 than < 50 (HR+ 22.41% vs 8.2% p=0.002; TNBC 10.4% vs. 2.41% p=0.09).
- In the HR+ group, *ESR1* alterations were more common in the > 60 group vs < 50 (18.64% vs 8.98% p=0.06).
- In the TNBC and HR+ groups, *PIK3CA* genomic alterations (GA) were more common in > 60 than < 50 (TNBC 31.68% vs 10.84% p=0.007; HR+ 49.34% vs < 50 36.33%, p=0.18).
- *BRCA1* and *BRCA2* alterations were more common in < 50 vs > 60 in the HR+ cohort (*BRCA1* 3.52% vs 0.56%, p=0.07; *BRCA2* 9.38% vs 3.01% p=0.03).
- *BRCA1* alterations were more frequent in < 50 vs > 60 with TNBC (15.66% vs 4.95%, p=0.06).
- HRDsig+ was significantly more common < 50 vs > 60 (HR+ 15.54% vs 6.24% p<0.001; TNBC 45.68% vs 23.74% p=0.002).

- ***Older women*** **> 60 were more likely to have targetable alterations in *ESR1*, *PIK3CA*, and TMB ≥ 10 mut/Mb.**
- ***Older women* were also more likely to have *CDH1* alterations.**
- ***Younger women*** **< 50 had a higher prevalence of *BRCA1* and *BRCA2* alterations.**
- ***Younger women* also had a higher prevalence of PD-L1+, HRDsig+, and *TP53* alterations.**

Table 1: Genomic Alterations by Age and HR status

	HR+/HER2-				TNBC				
	< 50 (n=256)	> 60 (n=531)	P-value*	OR		< 50 (n=166)	> 60 (n=202)	P-value*	OR
Median age (range)	43 (38-46)	69 (64-74)	-	-	Median age (range)	41 (37-46)	69 (64-74)	-	-
Median GA	3 (5-8)	3 (5-8)	0.3	-	Median GA	3 (5-7)	4 (6-8)	0.006	-
Genetic Ancestry									
European	61.13% (151)	84.59% (439)	0.006	0.71	European	57.86% (92)	77.27% (153)	0.066	0.73
African	16.60% (41)	7.90% (41)	0.002	2.07	African	23.90% (38)	16.16% (32)	0.19	1.45
Admixed American	13.77% (34)	3.66% (19)	<0.001	3.71	Admixed American	13.21% (21)	3.54% (7)	0.003	3.65
Eastern Asian	6.07% (15)	2.50% (13)	0.02	1.39	Eastern Asian	3.14% (5)	2.02% (4)	0.7	1.52
South Asian	2.43% (6)	1.35% (7)	0.37	1.77	South Asian	1.89% (3)	1.01% (2)	0.66	1.83
Non-European	38.87% (96)	15.41% (80)	<0.001	2.52	Non-European	42.14% (67)	22.73% (45)	0.004	1.85
Genomic Alterations									
CDH1	**8.2% (21)**	**22.41% (119)**	**0.002**	**0.37**	*CDH1*	2.41% (4)	10.4% (21)	0.09	0.23
IGF1R	**4.69% (12)**	**0.56% (3)**	**0.01**	**8.3**	*PIK3CA*	**10.84% (18)**	**31.68% (64)**	**0.007**	**0.34**
BRCA2	**9.38% (24)**	**3.01% (16)**	**0.03**	**3.11**	*TERT*	0% (0)	3.96% (8)	0.1	0
ESR1	8.98% (23)	18.64% (99)	0.06	0.48	*NTRK1*	7.23% (12)	1.49% (3)	0.1	4.87
BRCA1	3.52% (9)	0.56% (3)	0.07	6.22	*BRCA1*	15.66% (26)	4.95% (10)	0.06	3.16
TP53	39.84% (102)	27.5% (146)	0.14	1.45	*TP53*	93.98% (156)	85.64% (173)	0.7	1.1
PIK3CA	36.33% (93)	49.34% (262)	0.18	0.74	*ERBB3*	0% (0)	3.47% (7)	0.1	0
ERBB2	1.56% (5)	3.58% (19)	0.17	0.44	*ERBB2*	1.2% (2)	4.46% (9)	0.12	0.27
Multiple *PIK3CA*	15.05% (14/93)	19.47% (51/262)	-	-	Multiple *PIK3CA*	5.55% (1/18)	10.94% (7/64)	-	-

*False discovery rate (FDR) corrected using Benjamini/Hochberg adjustment †Mann Whitney

Results

- Younger patients were more frequently PD-L1+ compared to older patients (HR+ 40.14% vs 30.18% p=0.15; TNBC 73.39% vs 57.04%, p=0.2).
- TMB ≥ 10 mut/Mb was more common in > 60 vs < 50 (HR+ 8.22% vs 4.15% p=0.062; TNBC 11.68% vs 2.47% p=0.002).

Table 2: Additional Genomic Alterations by Age and HR status

	HR+/HER2-				TNBC				
	<50 (n=256)	> 60 (n=531)	P-value*	OR†		<50 (n=166)	> 60 (n=202)	P-value*	OR†
Median TMB (IQR)	**2.50 (1.25-3.75)**	**2.50 (1.25-5)**	**0.018**	-	Median TMB (IQR)	**2.50 (1.25-5)**	**3.75 (1.25-6.25)**	**<0.001**	-
TMB ≥ 10 Mu/Mb	4.15% (10)	8.22% (42)	0.062	0.51	TMB ≥ 10 Mu/Mb	**2.47% (4)**	**11.68% (23)**	**0.002**	0.21
TMB ≥ 20 Mu/Mb	1.24% (3)	2.74% (14)	0.29	0.45	TMB ≥ 20 Mu/Mb	**0**	**3.05% (6)**	**0.036**	0
HRDSig									
N	251	513	-	-	N	162	198	-	-
HRDsig+	**15.54% (39)**	**6.24% (32)**	**<0.001**	**2.49**	HRDsig+	**45.68% (74)**	**23.74% (47)**	**0.002**	**1.92**
PD-L1									
N	142	275	-	-	N	109	142	-	-
PD-L1+	40.14% (57)	30.18% (83)	0.15	1.33	PD-L1+	73.39% (80)	57.04% (81)	0.22	1.29
APOBEC									
N	13	43	-	-	N	2	20	-	-
APOBEC+	100% (13)	79.07% (34)	0.6	1.27	APOBEC+	100% (2)	65% (13)	1.0	1.54

Discussion

- Older women were more likely to have targetable genomic alterations including *ESR1*, *PIK3CA*, and TMB ≥ 10 mut/Mb.
- Higher prevalence of *ESR1* GA in older women may reflect longer history of endocrine therapy use.
- Higher prevalence of *CDH1* GA in older women likely represents the increased prevalence of invasive lobular carcinoma in this population.
- The prevalence of *PIK3CA* alterations in older women with TNBC is a potential area for therapeutic investigation.
- Younger women had a higher prevalence of *BRCA1* and *BRCA2* alterations, likely reflecting germline alterations and benefit of PARP inhibitors. [2, 3]

References

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