Real-world data Outcomes of HR+/HER2- metastatic Breast Cancer (mBC) with High Tumor Mutational Burden (hTMB) Treated with Immune Checkpoint Inhibitors (ICI)

S Sammons[1,2], L Alder[1,2], E Sokol[3], N Danzinger[3], K Raskina[3], AB Schrock[3], JM Venstrom[3], T Snow[4], E Castellanos[4], E Ochuonyo[4], J Snider[4], K McGregor3, S Chumsri[5]

Duke University Hospital, Durham, NC[1], Duke Cancer Institute, Durham, NC[2] , Foundation Medicine[3], Flatiron Health[4], Jacoby Center for Breast Health, Mayo Clinic, Jacksonville, FL[5]

Background

Immune checkpoint inhibitor (ICI) has shown benefit in PDL-1+ metastatic triple negative breast cancer and solid tumors with hTMB (≥10 mut/Mb). Pembrolizumab is FDA approved based on the Keynote-158 study in advanced solid tumors with hTMB (1). However, there is limited data on ICI efficacy specifically in hTMB HR+/HER2- mBC. Prior work has shown that 7% of HR+/HER2- BC has hTMB with enrichment in lobular carcinoma (15%) and most harboring APOBEC signatures (70%) (2). The purpose of this study was to describe efficacy data by evaluating real-world time-to-treatment discontinuation (rwTTD) for hTMB HR+/HER2- mBC patients treated with ICI monotherapy or combined with chemotherapy.

Methods

hTMB was defined as ≥10 mut/Mb utilizing FoundationOne/FoundationOne® CDx.

CGDB cohort: Patients with HR+/HER2- metastatic breast cancer from the nationwide (US-based) de-identified Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic database (CGDB) with genomic profiling by FMI between January 2011 – September 2020 and ICI initiation ≥ 6 months and at least 2 documented clinic visits prior to cutoff date were eligible. rwTTD was measured as the difference between the last and first drug episode within a given line of treatment (LOT). LOTs were derived based on FH algorithms. The de-identified electronic health record (EHR) data came from ~280 US cancer clinics.

Duke/Mayo Cohort: Eligible patients from Mayo Clinic and Duke University with HR+/HER2- mBC and hTMB tested via FMI between September 2013 – July 2020. Clinical data were manually extracted from Mayo and Duke EHRs. rwTTD was measured as the difference between the last and first date ICI was received.

Results

	Duke/Mayo (N=8)	CGDB (N=20)
Median Age (range)	69.4 (60.0, 70.1)	53.0 (46.5, 63.0)
Stage at Diagnosis		
- I-III	6 (75%)	15 (75%)
- IV	2 (25%)	5 (25%)
Tumor Type		
- Invasive ductal carcinoma	4 (50.0%)	1 (5.0%)
- Invasive lobular carcinoma	3 (37.5%)	10 (50.0%)
- Other/Unknown	1 (12.5%)	9 (45.0%)
Median TMB (range)	32.5 (23.2, 47.5)	20.9 (13.8, 33.8)
MSI		
- MSI-H	0 (0.0%)	3 (15.0%)
- MSS	8 (100.0%)	16 (80.0%)
- Not documented	0 (0.0%)	1 (5.0%)

Results

	Duke/Mayo (N=8)	CGDB (N=20)
BRCA (germline or somatic)	2 (25.0%)	3 (15.0%)
PIK3CA mutation	7 (87.5%)	14 (70.0%)
ICI		
- Atezolizumab	1 (12.5%)	4 (20.0%)
- Nivolumab	2 (25.0%)	0 (0.0%)
- Pembrolizumab	5 (62.5%)	16 (80.0%)
ICI monotherapy	2 (25%)	14 (70%)
Line ICI started		
- 1-2	3 (37.5%)	1 (5.0%)
- 3+	5 (62.5%)	19 (95.0%)
Deceased	2 (25.0%)	8 (40.0%)

Table 1: Clinical characteristics of CGDB and Duke/Mayo patients with hTMB HR+/HER2- mBC treated with ICI. 6389 eligible pts in CGDB, 3955 HR+/HER2- of which 99 received ICI. Of these, 20/99 had hTMB. Eight (8) pts with HR+/HER2- hTMB mBC treated with ICI at Duke/Mayo. PDL-1 status unknown for most patients.

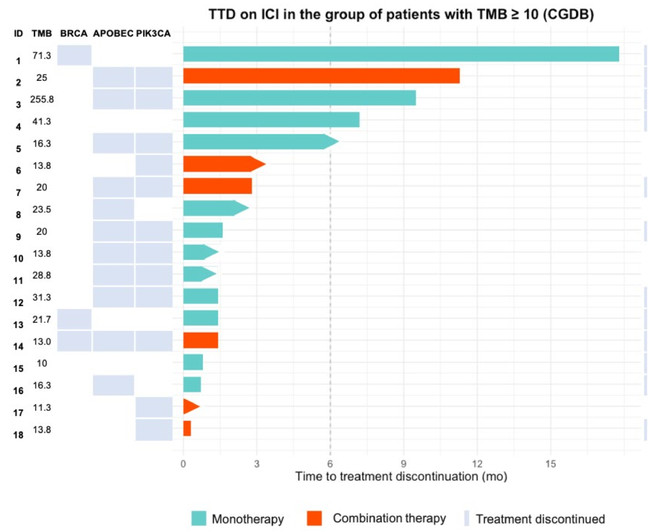

Figure 1: (CGDB Cohort): ICI rwTTD in hTMB HR+/HER2- mBC. CGDB cohort contained 20 patients with HR+/HER2- hTMB breast cancer that received ICI. 2 patients were excluded as only one therapy visit was recorded. Median rwTTD was 2.8 months (range 0.3 - 17.8 months). 5/18 (28%) patients had rwTTD ≥ 6 months 11/18 (61%) patients had APOBEC signature. 4/5 (80%) patients with TTD ≥ 6 months had TMB higher than median (21 mut/Mb).

Results

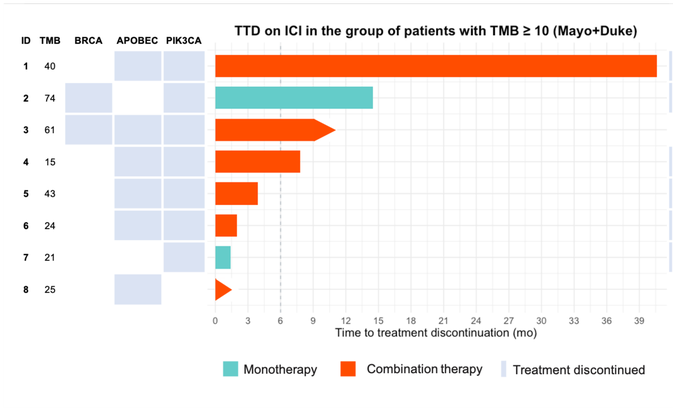

Figure 2: (Duke/Mayo Cohort):) ICI rwTTD in hTMB HR+/HER2- mBC. Median rwTTD 5.8 months (range 0.9-40.6 months); with 2 patients ongoing as of 8/1/2021. 4/8 (50%) patients rwTTD > 6 mo. 75% of patients had APOBEC signature. 75% of patients with rwTTD >6 mo had TMB higher than median (32.5 mut/Mb).

Conclusions

- Both RWD cohorts with hTMB HR+/HER2- metastatic breast cancer had subsets of patients with time-to-treatment discontinuation ≥ 6 months (28% and 50%).
- hTMB cohort in HR+/HER2- breast cancer is enriched for invasive lobular carcinoma and APOBEC signature.
- Patients with durable response tended to have very high TMB with 6/9 (66%) ≥ 40 mut/Mb.
- Further studies are needed to further identify subsets of HR+/HER2- mBC patients with hTMB who are more likely to have prolonged benefit from ICI.

Citations

1. Chumsri, S., *et al.* Durable Complete Response With Immune Checkpoint Inhibitor in Breast Cancer With High Tumor Mutational Burden and APOBEC Signature. *J Natl Compr Canc Netw* **18**, 517-521 (2020).
2. Marabelle, A., *et al.* Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* **21**, 1353-1365 (2020).