TPS1140 **Poster Session**

A phase II trial to assess the impact of β2 adrenergic receptor (β2-AR) blockade in metastatic triple negative breast cancer (mTNBC).

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Background: In PD-L1+ mTNBC patients (pts), the standard of care treatment is chemotherapy and pembrolizumab (P) in the first-line setting. Our group and others have demonstrated that chronic β2-AR signaling suppresses $CD8^+$ cytotoxic T lymphocytes (CTL) function, drives their exhaustion, and increases the number of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in the tumor microenvironment (TME), thus supporting tumor proliferation. Consequently, abrogation of β-AR signaling using the pan β-blocker propranolol or $\beta\text{-AR}^{-/-}$ knockout mice increased the intratumoral frequency of CTLs and elevated the CTL:Treg ratio (Bucsek et al. Cancer Res. 2017; PMID: 28819022). Similarly, mouse tumor models also demonstrated decreased exhaustion markers (PD1, TIM3, LAG3) on CTLs when β-AR was blocked, via propranolol (Qiao G et al. Cancer Immunol Res. 2021, PMID: 33762351). Confirming this phenomenon, we have shown, in a prospective clinical trial in metastatic melanoma, that β-AR blockade with propranolol significantly increased response to P with an objective response rate (ORR) of 78%, as opposed to 30-40% with P alone (Gandhi et al. Clin Cancer Res 2021, PMID: 33127652). Moreover, clinical β-AR blockade was associated with higher immune infiltration in the TME (Hiller JG, Clin Cancer Res 2020, PMID: 31754048). Therefore, we hypothesize that using propranolol with chemotherapy and P should improve response for pts with newly metastatic PD-L1+ TNBC. **Methods:** This is a phase II single-arm, non-randomized multi-center study. Pts are women ≥18 yrs with PD-L1+ mTNBC, who will receive propranolol, chemotherapy (paclitaxel, nab-paclitaxel, gemcitabine-carboplatin) and P in the upfront setting: chemotherapy on days 1, 8 and P on day 1 every 3 weeks in addition to propranolol 30 mg BID, with intra-pt propranolol dose-escalation by 10 mg BID weekly to a total of 80 mg BID as tolerated by blood pressure and heart rate as natural biomarkers for dose. Treatment will continue until disease progression per RECIST. The primary endpoint is ORR, defined as complete or partial response. The secondary endpoint is safety, 6-month progression-free and overall survival. As an exploratory endpoint, changes in TME and blood immune markers will be assessed. In stage 1, n1=23 evaluable pts will be enrolled. If ≥ 13/23 responses are observed, then the study will continue to enroll another n2=14 pts for a total of n=37, otherwise will be suspended for futility. If ≥ 24/37 responses are observed, then the proposed therapy will be considered promising. Pre- and 6-week post-treatment tumor biopsies and blood samples will be analyzed for changes in stress-induced biomarkers (epinephrine, norepinephrine, and frequency of CTL, MDSC, Treg) and exhaustion markers (PD1, TIM3, LAG3). The study is currently open and has accrued one patient. Clinical trial information: NCT05741164. Research Sponsor: NIH (NCI).