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CD47 EXPRESSION IS UPREGULATED IN SOLID TUMORS AND CORRELATES WITH PHAGOCYTIC TUMOR-ASSOCIATED MACROPHAGE GENE SIGNATURE

¹Nick van Buuren*, ²Kelli Boyd, ²Mengshu Xu, ²Azadeh Madjidi, ²Christina Moon, ²Shiva Zabolli, ²Iris Liu, ²Ruidong Li, ²Kai-Hui Sun, ²Abhishek Aggarwal, ¹Jared Odegard. ¹Gilead Sciences, Seattle, WA, USA; ²Gilead Sciences, Foster City, CA, USA

Background Immune checkpoint blockade targeting the PD-1/PD-L1 axis has revolutionized the treatment of many solid tumors. PD-L1 expression is known to be modulated by both infiltrating T cells and by tumor intrinsic mechanisms. Therapeutics targeting the macrophage checkpoints CD47 and SIRP α are now being evaluated clinically, but little is known about how CD47 expression is influenced by tumor molecular subtypes or the presence of immune cells, particularly macrophages.

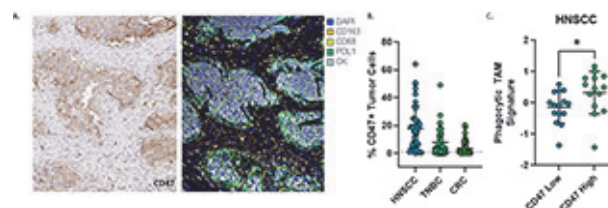
Methods Formalin fixed and paraffin embedded samples of primary, resectable tumors from patients with HNSCC (N=44), TNBC (N=48) and CRC (N=48) were commercially procured and evaluated for CD47 (Abcam clone EPR21794) and SIRP α (LSBio LS-B551) expression by IHC. DNA/RNA were extracted from all samples and subjected to RNA-Seq and whole exome sequencing (WES). Multiplex immunofluorescence (mIF) was performed on 26 samples from each indication utilizing two custom 4-plex immunofluorescence assays. A macrophage panel evaluated CD68, CD163, PD-L1 and cytokeratin and a tissue resident memory T cell panel evaluated CD3, CD8, CD103 and cytokeratin.

Results CD47 expression was upregulated in the tumor versus the surrounding stroma in all three indications and was highest in HNSCC, followed by TNBC and CRC (figure 1). CD47 expression as measured by IHC was used to subdivide samples into high and low CD47 expression categories using the median within each indication. A phagocytic tumor associated macrophage (TAM) gene signature¹ was significantly higher in the high CD47 samples from HNSCC and CRC (figure 1). Characterization of macrophages (mIF panel) indicated that CD163+/CD68- macrophages were the most abundant macrophages in all three indications, demonstrated increased prevalence within the tumor stroma, and correlated strongly with the phagocytic TAM gene signature. PD-L1 expression was predominantly found on CD68+/CD163- macrophages in all tumor indications. We classified samples using molecular subtyping for CRC,² and unsupervised clustering for HNSCC and TNBC. CD47 expression was generally not differentiated across the CRC molecular subtypes.

Conclusions CD47 targeting therapies are currently being evaluated in clinical trials in multiple solid tumor indications. Here we demonstrate that CD47 expression is higher in tumor compared to stroma in HNSCC, TNBC and CRC and correlates with an increased phagocytic TAM signature. These data suggest that some tumors may avoid immune surveillance by upregulating CD47 in the presence of phagocytic macrophages, and that tumors with these characteristics could be rationale candidates for evaluation of CD47 based therapies.

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