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Comprehensive transcriptomic analysis of immune checkpoint markers in a pan-cancer cohort: Implications for response and resistance

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Background/Methods:

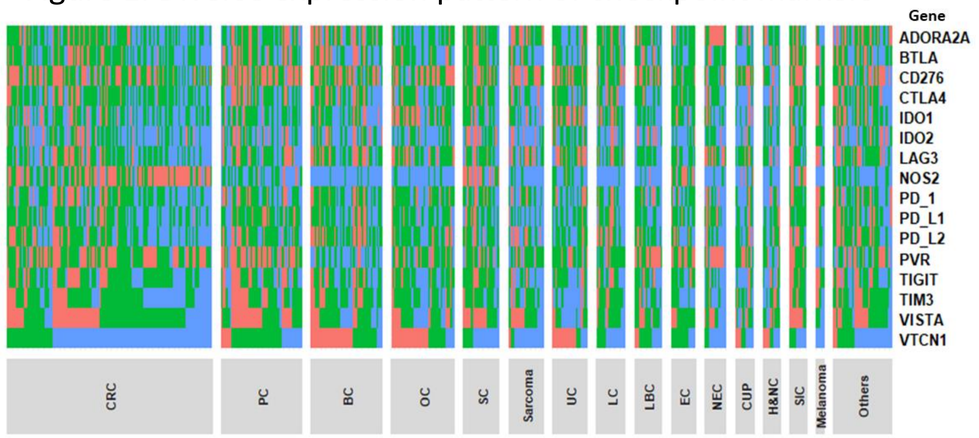
- Although immune checkpoint blockades (ICBs) have improved cancer treatment outcomes, not all patients with cancer can benefit from ICBs.
- The next step to improve the efficacy of ICBs can be analyzing the immunomic profile using RNA sequencing to determine the ICBs to be given.
- We analyzed the expression of multiple proteins related to immune checkpoints among diverse cancers

Methods:

- 514 patients with various types of solid tumors seen at the University of San Diego (UCSD), Moors Cancer Center for personalized therapy were included in this study.
- The expression of 16 genes related to the immune checkpoint, including ADORA2A, BTLA, CD276, CTLA4, IDO1, IDO2, LAG3, NOS2, PD-1, PD-L1, PD-L2, PVR, TIGIT, TIM3, VISTA, and VTCN were analyzed.
- The expressions of each checkpoint marker were correlated with cancer types, microsatellite instability (MSI), tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) status on immunohistochemistry.

Due to the *extremely various expression* of immune checkpoint markers, clinical trials with patient selection *based on the expression level of checkpoint markers* matched to the corresponding ICB drug are warranted.

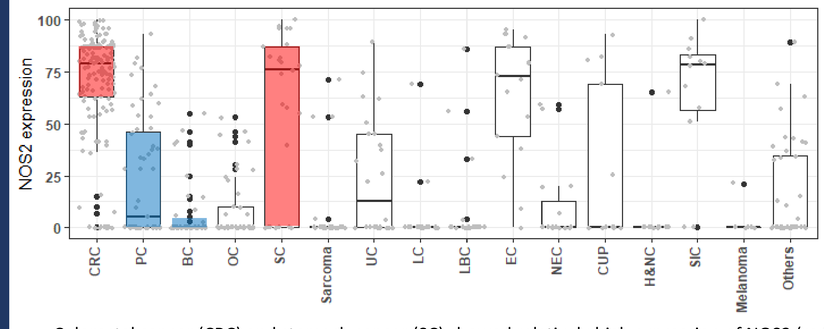
Figure 1. Diverse expression pattern of checkpoint markers



BC: breast cancer, CRC: colorectal cancer, CUP: cancer of unknown primary, EC: esophageal cancer, H&NC: head and neck cancer, LBC: liver and bile duct cancer, LC: lung cancer, NEC: neuroendocrine cancer, OC: ovarian cancer, PC: pancreatic cancer, SC: stomach cancer, SIC: small intestine cancer, UC: uterine cancer

Red, green and blue means high (>74), intermediate (25-74) and high (<25) expression

Figure 2. Expression of NOS2 per cancer types



Colorectal cancer (CRC) and stomach cancer (SC) showed relatively high expression of NOS2 (red boxes) while pancreatic cancer (PC) and breast cancer (BC) showed low expression (blue boxes).

Results

- Each patient had a distinctive portfolio of the categorical expression levels of 16 checkpoint markers.
- Several checkpoint markers, especially NOS2, showed a significant correlation with cancer type. (median rank values in colorectal, stomach, pancreatic, and breast cancer were 79, 76, 5 and 0 respectively, $p < 0.001$)
- Five markers (IDO1, LAG3, PD-1, PD-L1, and TIGIT) showed significant correlation with MSI, while seven markers (CTLA4, IDO1, LAG3, PD-1, PD-L1, PD-L2, and TIGIT) were significantly associated with positive PD-L1 status.
- No significant association was seen based on TMB or tissue-specific grouping of patients.