Abstract # 2561

LAG3 transcriptomic expression correlates with high levels of PD-1, PD-L1, PD-L2, and CTLA-4 checkpoints and with high tumor mutational burden across cancers

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Background

- Lymphocyte Activation Gene 3 (LAG3) or CD223 is an immune checkpoint that can be found on various T cells: CD4+, CD8+, regulatory T cells (Tregs), natural killer T cells, natural killer cells, and plasmacytoid dendritic cells
- Expression of LAG3 molecule acts to increase T-cell exhaustion, leading to decreased tumor killing as well as an increase in immune suppressive cytokine release
- Many clinical trials of LAG3 inhibitors have had modest effects
- Recent data suggests that the LAG3 antibody relatlimab together with nivolumab (anti-PD1) provided greater benefit than nivolumab alone in patients with melanoma

Methods

- RNA expression levels of 397 genes in various types of solid tumors from 514 patients seen at the UCSD Moores Cancer Center were analyzed at a CLIA-licensed laboratory, OmniSeq
- Following removal of germline variants, synonymous variants, indels and SNVs with <5% VAF, TMB is reported as mutations/megabase
- Transcript abundance was normalized to internal housekeeping gene profiles and ranked (0-100 percentile) in a standardized manner to a reference population of 735 tumors spanning 35 histologies
- Odds ratio for high LAG3 expression was calculated and Bonferroni corrected for multiple genes and cancer histologies with >40 samples

Conclusions

- High LAG3 was found in almost a quarter of tumor samples and significantly associated with other immune checkpoints with FDA-approved drugs
- Multiple ongoing studies are investigating the utility of LAG3 inhibitors in combination with other checkpoint inhibitors
- Ongoing studies combining LAG3 inhibitors and specific immune checkpoint inhibitors may yield more clinical benefit if individualized immunomic transcript interrogation is undertaken rather than population-based approaches without employment of rationally combined agents matched to each patient's cancer

High LAG3 expression correlates to high immune checkpoints and TMB in pan-cancers

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Results

Table 1. Patient Characteristics

All cancers	N = 514
Median Age (range) years	61 (24-93) years
Men	40% (N = 203)
Women	60% (N = 310) (1 patient "unspecified gender")
Tumor Histology	Number of patients (%)
Breast cancer	49 (10%)
Colorectal cancer	140 (27%)
Lung cancer	20 (4%)
Neuroendocrine cancer	15 (3%)
Ovarian cancer	43 (8%)
Pancreatic cancer	55 (11%)
Sarcoma	24 (5%)
Stomach cancer	25 (5%)
Uterine cancer	23 (4%)
All others <10 samples per histology	120 (23%)

Figure 1: Expression of LAG-3 among diverse cancers

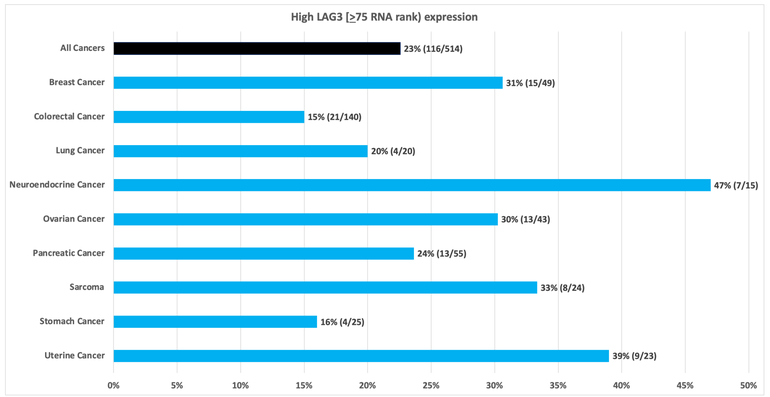

Table 2: Univariate analysis table of significant

Feature	N (%) of patients with high LAG3	Odds ratio for High LAG3 (95% CI)	P value uncorrected	Adjusted P value (Bonferroni corrected)
High PD-L1 (n = 67) Low PD-L1* (n = 447)	42 (63%) 74 (17%)	8.468 (4.9 -14.7) 0.1181 (0.0678 – 0.2056)	P < 0.0001	adj P < 0.0014
High PD-1 (n = 93) Low PD-1 (n = 421)	58 (62%) 58 (14%)	10.4 (6.2730 - 17.1476) 0.0964 (0.0583 – 0.1594)	P < 0.0001	adj P < 0.0014
High PD-L2 (n = 100) Low PD-L2 (n = 414)	46 (46%) 70 (17%)	4.19 (2.62 - 6.7) 0.2389 (0.1493 – 0.3821)	P < 0.0001	adj P < 0.0014
High CTLA-4 (n = 87) Low CTLA-4 (n = 427)	47 (54%) 69 (16%)	6.1 (3.72 - 9.99) 0.164 (0.1001 – 0.2689)	P < 0.0001	adj P < 0.0014
TMB ≥10 mutations/mb (n = 33) TMB<10 mutations/mb (n = 417)**	14 (42%) 83 (20%)	2.97 (1.428 - 6.16) 0.3373 (0.1624 – 0.7005)	P = 0.0036	adj P = 0.0504

*High LAG3 or PD-L1 or PD-1 or PD-L2 or CTLA4 means ≥75 transcript expression percentile rank; low LAG3 or PD-L1 or PD-1 or PD-L2 or CTLA-4 means<75 percentile rank.
**Total number of patients are less in TMB because data was not available on all patients