Abstract # 4703

PD-L1 expression is strongly associated with TIGIT, FOXP3 and LAG3 across advanced cancers, but not OX40, TIM3 and IDO

CONTRIBUTING RESEARCHERS

Sumanta K. Pal, M.D.[1], Ari M. Vanderwalde, M.D.[2], Christopher W. Szeto, Ph.D.[3], Sandeep K. Reddy, M.D. [4], Omid Hamid, M.D.[5]

[1]City of Hope Cancer Center, Duarte, CA; [2]West Cancer Center, Germantown, TN; [3]NantOmics LLC., Santa Cruz, CA; [4]NantHealth LLC., Culver City, CA; [5]The Angeles Clinic, Los Angeles, CA;

BACKGROUND

- Agents that target programmed death-1 (PD-1) and its cognate ligand programmed death-ligand 1 (PD-L1) have shown activity in multiple cancer types - monotherapy with these agents tends to elicit responses in the minority of patients, however
- Multiple strategies have been attempted, including combinations of PD-1 inhibitors with chemotherapy (approved in lung cancer) and combinations with antiangiogenic targeted therapy (with encouraging data in renal cell carcinoma)
- Combinations with other immunotherapeutic strategies have also been attempted – PD-1 inhibition with CTLA4 inhibition appears to be an effective approach in advanced renal cell carcinoma, for instance, where nivolumab/ipilimumab has recently shown improved survival relative to sunitinib
- Combinations of PD-1/PD-L1 with other checkpoint inhibitors have produced more sobering results – for example, a recent trial comparing pembrolizumab to pembrolizumab with epacadostat failed to meet its primary endpoint
- These results inspired us to look for biologic data to support rationale combinations of checkpoint inhibition

METHODS

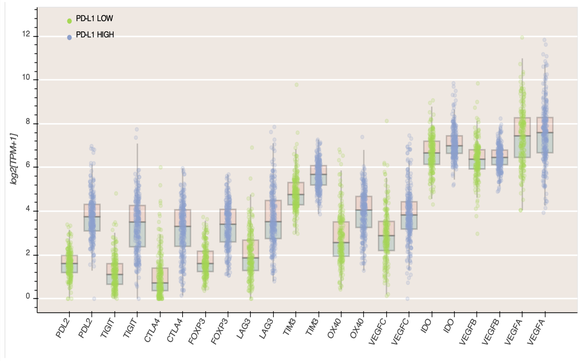
- We assessed FFPE slides or tissue blocks from patients with advanced cancer who had genomic testing in the course of routine clinical care
- A total of **1,467 unselected clinical cases** were analyzed, including breast (18.4%), colon (9.5%), lung (7.6%) and sarcoma (7.6%)
- Patients had histologically confirmation of diagnosis from an internal pathologist
- RNA-seq libraries were prepared from tumor tissue using the KAPA Stranded RNA-Seq kit with RiboErase (Wilmington, MA) and sequenced on the Illumina HiSeq platform (San Diego, CA)
- Cases were categorized as PD-L1-low, PD-L1-normal and PD-L1-high by cutoffs at the 15th percentile of expression
- **Expression and co-expression (with PD-L1) of 6 checkpoint markers (PD-L2, CTLA4, TIGIT, FOXP3, LAG3, OX40, TIM3 and IDO) were analyzed for tissue-specific enrichment; an exploratory analysis of TMB was performed**

RESULTS

Table 1. Distribution of histologies included in the current analysis with accompanying gender distribution and PD-L1/TMB data.

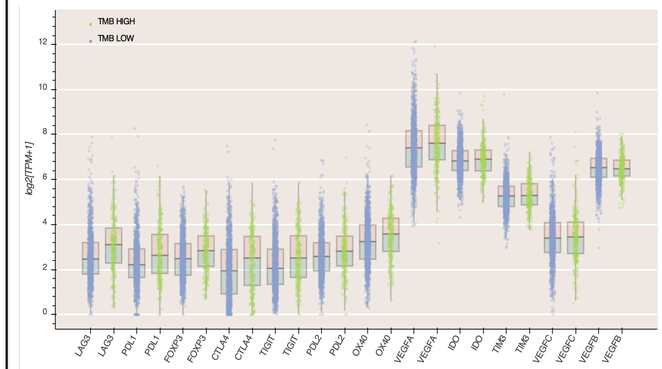
	N	% of cases	% Female	TMB avg.	TMB med.	Age med.	% low PDL1	% high PDL1
Breast	270	18.40	99.26	129.54	92	56	10.37	13.70
Colon	140	9.54	55.40	269.81	129	58	17.14	7.14
Lung	112	7.63	53.57	260.13	179	65	8.93	41.07
Sarcoma	111	7.57	45.95	135.41	68	51	27.03	12.61
Pancreatic	93	6.34	44.09	71.39	58	63	8.60	11.83
Ovarian	77	5.25	100.00	91.94	86	58	22.08	9.09
Brain	76	5.18	40.79	96.83	68	47	17.11	13.16
Other Cancer	60	4.09	45.00	114.27	84	63	11.67	23.33
None	48	3.27	41.67	602.50	75	60	18.75	14.58
Prostate	36	2.45	0.00	99.86	61	65	27.78	0.00
Gastric	34	2.32	38.24	124.26	68	61	0.00	20.59
Melanoma	33	2.25	30.30	598.00	231	64	6.06	30.30
Esophageal	33	2.25	27.27	172.21	123	64	18.18	18.18
Head and Neck	32	2.18	21.88	102.63	95	64	9.38	46.88
Kidney	29	1.98	31.03	406.38	74	58	10.34	20.69
Liver	28	1.91	32.14	182.04	103	65	25.00	14.29
Oral	28	1.91	39.29	143.89	88	61	3.57	32.14
Rectal	27	1.84	29.63	251.74	112	57	3.70	18.52
Bladder	22	1.50	45.45	255.55	125	71	4.55	45.45
Unknown Primary	22	1.50	59.09	181.59	86	53	9.09	31.82
Uterine	22	1.50	100.00	188.00	107	67	27.27	4.55
Soft Tissue	20	1.36	30.00	101.55	67	18	40.00	15.00
Overall	1467	100.00	56.99	201.93	91	60	14.38	18.81

Figure 1. Expression of checkpoint molecules based on PD-L1 status. PD-L1 high and low characterized by top and bottom 15th percentiles of expression.



	t	p	adj. p
PDL2	27.2	1.35E-99	1.48E-98
TIGIT	22.2	1.13E-75	6.23E-75
CTLA4	20.6	4.98E-68	1.82E-67
FOXP3	19.4	1.24E-62	3.41E-62
LAG3	15.0	3.59E-42	7.90E-42
TIM3	12.0	3.88E-29	7.12E-29
OX40	11.8	2.20E-28	3.46E-28
VEGFC	8.3	7.53E-16	1.04E-15
IDO	6.7	5.53E-11	6.76E-11
VEGFB	1.8	0.0728	8.01E-02
VEGFA	1.0	0.3374	3.37E-01

Figure 2. Expression of checkpoint molecules based on TMB status. High TMB characterized as greater than or equal to 200 exonic nonsynonymous somatic mutations.



	t	p	adj. p
LAG3	6.4	2.24E-10	2.69E-09
PDL1	5.3	1.21E-07	7.23E-07
FOXP3	4.7	3.47E-06	1.39E-05
CTLA4	4.5	8.68E-06	2.08E-05
TIGIT	4.5	8.15E-06	2.08E-05
PDL2	3.6	3.51E-04	7.02E-04
OX40	3.3	1.15E-03	1.97E-03
VEGFA	2.3	2.33E-02	3.50E-02
IDO	1.4	1.66E-01	1.99E-01
TIM3	1.4	1.63E-01	1.99E-01
VEGFC	1.0	3.05E-01	3.33E-01
VEGFB	0.1	9.45E-01	9.45E-01

KEY FINDINGS

- In patients demonstrating the highest PD-L1 expression, higher expression of CTLA4, TIGIT, FOXP3 and LAG3 were also observed
- For other checkpoint molecules, however, including TIM3 and IDO, no variation in expression was observed at the extremes of PD-L1 expression
- TMB did not vary based on expression of immune checkpoint markers

CONCLUSIONS

In the era of targeted therapy, it was quickly recognized that agents directed at HER2 or EGFR would optimally function in the context of patients with salient molecular alterations. In the era of checkpoint inhibition, the same premise may warrant testing. Many investigators have proposed biomarker driven pathways for application of checkpoint inhibitors – here, we provide a readily available assay to facilitate this approach.

1. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. The New England journal of medicine 2013;369:134-44.
2. Langer CJ, Gadgeel SM, Borghaei H et al Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology 2016 17 (11):1497-1508.
3. Motzer RJ, Tannir NM, McDermott DF et al Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. The New England journal of medicine 2018 378 (14):1277-1290.

ESMO 2018 Congress October 19-23, 2018 Munich, Germany