Abstract #2614: Pan-cancer analysis of IDO1 transcriptome expression and its impact on outcome in patients treated with immune checkpoint inhibitors.

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Background:

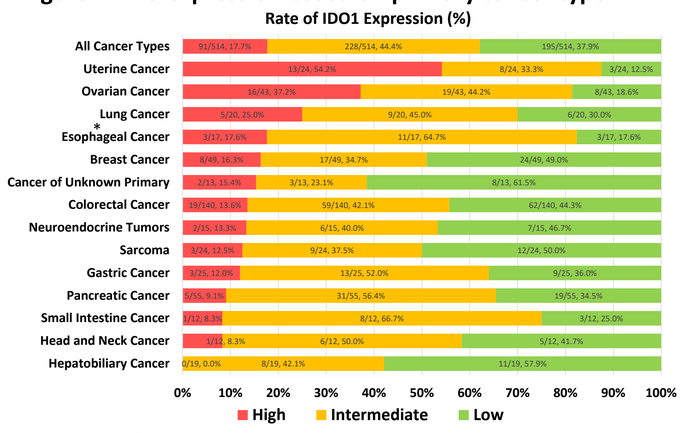
- The immunosuppressive tumor microenvironment (TME) is a major component of resistance to immune checkpoint inhibitors (ICIs).
- Tryptophan catabolism leads to immunosuppression, and indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme catabolizing tryptophan to kynurenine, has been investigated as a potential target to overcome ICI resistance.
- Analyzing the association of IDO1 and immune molecules in the TME could better elucidate the role of IDO1 as an immunotherapeutic strategy.
- Little is known about the impact of IDO1 on the efficacy of ICIs.

Methods:

- We performed comprehensive transcriptome analysis of IDO1 and selected immune markers in 514 patients with advanced solid tumors at the Moores Cancer Center, the University of California San Diego.
- “High” (75-100percentile), “Intermediate” (25-74), and “Low” (0-24) RNA expression of IDO1 and selected immune markers was calculated for each patient (rank compared to 735 controls).
- The rate of “High”, “Intermediate”, and “Low” IDO1 expression was evaluated based on cancer types.
- RNA expression of targetable checkpoint (PD-1, PD-L1, CTLA-4, and LAG-3) were illustrated by IDO1 expression groups.
- Univariate and multivariate analyses of the odds ratio (OR) for high IDO1 expression were conducted.
- Progression-free survival (PFS) and overall survival (OS) from the time of ICI therapy was compared between IDO1 expression groups by the Kaplan-Meier method, and multivariate survival analysis was performed using the Cox proportional hazards model.

Results:

Figure 1. IDO expression based on primary cancer type



High IDO1 expression is seen in uterine and ovarian cancer.

* Lung cancer type (Number of patients: High IDO1/Overall): Adenocarcinoma (4/13), SCLC (1/2), NSCLC NOS (1/1), Squamous carcinoma (0/2), Sarcomatoid (0/1), Mesothelioma (0/1)

Conclusions

- IDO1 RNA levels are high in uterine and ovarian cancers.
- High IDO1 RNA levels are associated with high targetable checkpoint RNA levels.
- High IDO1 levels correspond with longer PFS and OS from start of ICI therapy.
- These results suggest the importance of patient selection through pan-cancer analysis and the potential role of IDO1 as a predictive marker for ICI therapy.

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Table 1. Associations between IDO1 and immune markers

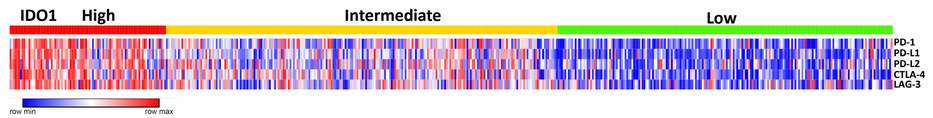
		IDO1 group, N of patients (%)		OR (95% CI), univariate		Adjusted OR (95% CI) *	
		H (≧75), N=91	I/L (<75), N=423		p value		p value
Age	≥ 61	56 (61.5)	200 (47.3)	1.78 (1.12-2.84)	**0.015**	1.52 (0.60-3.87)	0.379
	< 60	35 (38.5)	223 (52.7)				
Sex	M	18 (19.8)	186 (44.0)	0.31 (0.18-0.54)	**<0.001**	0.33 (0.09-1.26)	0.091
	F	73 (80.2)	237 (56.0)				
CTLA-4	H	38 (41.8)	49 (11.6)	5.47 (3.28-9.13)	**<0.001**	2.78 (0.53-14.48)	0.226
	I/L	53 (58.2)	374 (88.4)				
LAG-3	H	54 (59.3)	62 (14.7)	8.50 (5.17-13.98)	**<0.001**	1.45 (0.47-4.48)	0.516
	I/L	37 (40.7)	361 (85.3)				
PD-1	H	43 (47.3)	50 (11.8)	6.68 (4.03-11.09)	**<0.001**	2.78 (0.53-14.45)	0.225
	I/L	48 (52.7)	373 (88.2)				
PD-L1	H	39 (42.9)	28 (6.6)	10.58 (6.01-18.62)	**<0.001**	3.58 (0.79-16.31)	0.099
	I/L	52 (57.1)	395 (93.4)				
PD-L2	H	37 (40.7)	63 (14.9)	3.92 (2.38-6.43)	**<0.001**	0.75 (0.16-3.44)	0.714
	I/L	54 (59.3)	360 (85.1)				
STAT1	H	59 (64.8)	44 (10.4)	15.88 (9.33-27.02)	**<0.001**	17.87 (5.08-62.81)	**<0.001**
	I/L	32 (35.2)	379 (89.6)				
MSI	H	8 (9.3)	7 (2.0)	5.08 (1.79-14.44)	**0.003**	15.19 (0.67-345.94)	0.079
	L	78 (90.7)	347 (98.0)				
TMB	H	17 (24.3)	31 (9.6)	3.01 (1.56-5.83)	**0.002**	0.80 (0.13-5.04)	0.807
	L	53 (75.7)	291 (90.4)				
Ovarian	Yes	16 (17.6)	27 (6.4)	3.13 (1.61-6.09)	**0.001**	8.28 (2.05-33.40)	**0.003**
	No	75 (82.4)	396 (93.6)				
Uterine	Yes	13 (14.3)	11 (2.6)	6.24 (2.70-14.44)	**<0.001**	45.20 (7.80-261.88)	**<0.001**
	No	78 (85.7)	412 (97.4)				

H:High, I/L: Intermediate/Low. Cutoff of TMB is 10 mutation/mb.

Selected factors were shown in the table.
Variables used for multivariate analysis include inhibitory and co-stimulatory checkpoint, factors associated with angiogenesis, Tregs, Myeloid-derived suppressive cells, tumor-associated macrophage, IDO1 pathway, JAK-STAT pathway, IL-6, MSI, TMB, and chemokines related to immunosuppression in the TME.

High STAT1 expression, ovarian cancer, and uterine cancer were associated with high IDO1 expression in multivariate analysis.

Figure 2. Expression of immune checkpoint markers based on IDO1 expression groups



The heatmap showed that RNA levels of targetable checkpoint (PD-1, PD-L1, CTLA-4, and LAG-3) correspond to the levels of IDO1 expression

Figure 3. PFS (A) and OS (B) based on IDO1 expression (High vs Intermediate/Low) in patients treated with ICIs

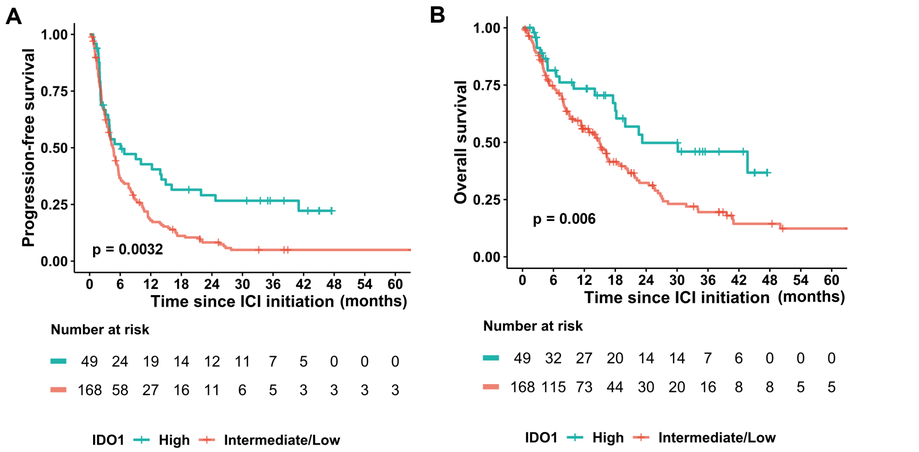


Table 2. Univariate and multivariate analysis of OS from start of ICIs

	Univariate (n=217)			Multivariate with TMB/MSI n=137		
Variable*	HR	95%CI	P value	HR	95%CI	P value
Age, > 60 (n=116)	1.05	0.75-1.49	0.768	1.09	0.66-1.82	0.734
Sex, male (n=95)	1.10	0.78-1.55	0.607	1.19	0.69-2.04	0.531
IDO1 , high (n=49)	0.52	0.32-0.83	**0.006**	0.28	0.11-0.69	**0.006**
PD1, high (n=44)	0.47	0.28-0.79	**0.003**	0.24	0.09-0.65	**0.005**
PDL1, high (n=36)	0.58	0.33-1.01	0.051	1.49	0.64-3.45	0.355
PDL2, high (n=51)	0.59	0.38-0.92	**0.019**	0.90	0.40-2.02	0.795
CTLA4, high (n=41)	0.44	0.26-0.74	**0.002**	0.90	0.36-2.26	0.814
LAG3, high (n=51)	0.50	0.32-0.79	**0.003**	0.98	0.49-1.95	0.955
Uterine (n=12)	0.72	0.31-1.63	0.421	1.64	0.50-5.33	0.413
Ovarian (n=18)	1.05	0.59-1.85	0.882	1.76	0.68-4.53	0.242
TMB, high** (n=32/165)	0.57	0.34-0.95	**0.031**	0.61	0.29-1.27	0.186
MSI, unstable (n=9/186)	0.35	0.11-1.11	0.061	0.50	0.13-1.94	0.317

(Figure 3 and Table 2). High IDO1 levels were associated with better PFS and OS. Multivariate analysis showed high IDO1 and PD1 expression were associated with better OS in 137 patients treated with ICIs and TMB/MSI data being available.
* Not all variables are shown here. Only selected factors are listed. **Cutoff of TMB is 10 mutation/mb.