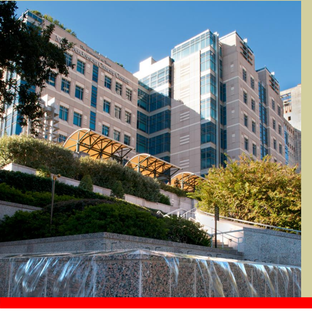

Tumor Content Is Not Linked To Pembrolizumab Response In Rare Tumors

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Introduction

- Immune checkpoint inhibitors (ICIs) have shown promise in the treatment of several cancer subtypes.[1]
- Efficacy in solid tumors, however, ranges from 10-40%.[2]
- There is a lack of biomarkers that can predict response to treatment, particularly in rare tumors.[1]
- This study sought to determine whether histological analysis of tumor content in biopsies can be utilized to predict clinical response.

Methods

- 232 biopsies (121 at baseline and 111 on-treatment) from 39 patients with 9 different rare solid tumors undergoing treatment in a phase II pembrolizumab clinical trial were analyzed.
- H&E-stained slides were scanned into Aperio Digital Scanner and then tumor content (TC), necrosis, and proliferative fibrosis (PF) were quantified utilizing ImageScope digital software.
- TC and necrosis were classified as “high” or “low” according to a 10% cut-off while PF was classified as “present” or “absent.”
- These classifications as well as the shift in TC from baseline to on-treatment were correlated with patient clinical response.
- Clinical response was defined in accordance with RECIST1.1.

Results

- Patients' characteristics are described in Table 1.
- At baseline, 3 patients had low TC while 6 patients had low TC on-treatment (Table 1).
- A majority of tumors displayed PF and necrosis.
- A high TC at baseline was associated with an increased time-to-progression (TTP; Table 2).
- 10% of the patients had a decrease in TC from baseline (Fig. 1; Table 1).
- There is no association between a decrease in TC from baseline to on-treatment and objective response rate (ORR; Table 3).

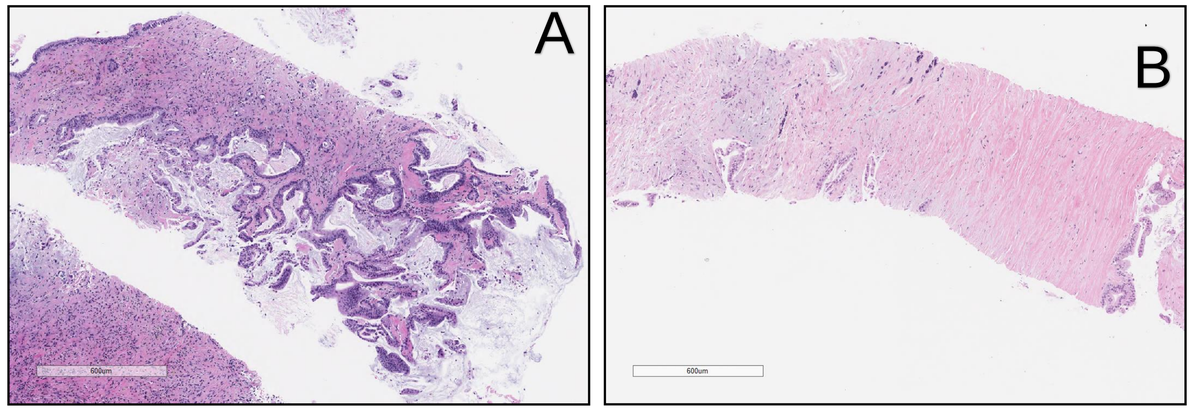

Fig. 1 Example of a biopsy from a patient with a decrease in TC from baseline to on-treatment. (A) Baseline biopsy specimen with high tumor content. (B) On-treatment biopsy specimen with low tumor content.

Table 1 Summary of Patient Characteristics, Cohorts, Response Data, and TC (N=39)

Feature	Category	Total Cohort n=39 (100%)	Baseline		On-treatment	
			Low TC n=3 (7%)	High TC n=36 (92%)	Low TC n=6 (15%)	High TC n=33 (85%)
Sex	Female	22 (56%)	1 (3%)	21 (58%)	4 (67%)	18 (55%)
	Male	17 (44%)	2 (67%)	15 (42%)	2 (33%)	15 (45%)
Age (years)	Mean	54	36	55	45	55
	Range	22 - 78	22 - 46	23 - 78	22 - 73	23 - 78
Trial cohorts	Carcinoma of unknown primary	11 (28%)	2 (67%)	9 (25%)	3 (50%)	8 (24%)
	Squamous cell carcinoma	4 (10%)	0	4 (11%)	0 (0%)	4 (12%)
	Germ cell tumor	2 (5%)	1 (3%)	1 (3%)	1 (17%)	1 (3%)
	Adrenocortical carcinoma	5 (13%)	0	5 (14%)	0	5 (15%)
	Paraganglioma	3 (8%)	0	3 (8%)	0	3 (9%)
	Small cell (non-pulmonary)	3 (8%)	0	3 (8%)	1 (17%)	2 (6%)
	Medullary RCC	2 (5%)	0	2 (6%)	0	2 (6%)
	Vascular sarcoma	5 (13%)	0	5 (14%)	1 (17%)	4 (12%)
	Other rare tumors	4 (10%)	0	4 (11%)	0	4 (12%)
Response	CR	0	0	0	0	0
	PR	4 (10%)	0	4 (11%)	1 (17%)	3 (9%)
	SD (≥6 months)	1 (3%)	0	1 (3%)	0 (0%)	1 (3%)
	SD (<6 months)	11 (28%)	1 (3%)	10 (28%)	1 (17%)	10 (30%)
	PD	23 (59%)	2 (67%)	21 (58%)	4 (67%)	19 (58%)
	Objective response rate (PR)	4 (10%)	0	4 (11%)	1 (17%)	3 (9%)
	Clinical benefit rate	5 (13%)	0	5 (14%)	1 (17%)	4 (12%)
Change in TC	No change from baseline	34 (87%)				
	Increased from baseline	1 (3%)				
	Decreased from baseline	4 (10%)				

Table 2 Association between TC and Risk Events (Cox Proportional Hazards Regression Analysis)

Covariate	Level	Hazard Ratio (HR)	95% CI	P-value
Death	Low TC at baseline (referent)	1		
	High TC at baseline	0.542	(0.159 - 1.855)	0.330
	Low TC on-treatment (referent)	1		
	High TC at on-treatment	0.97	(0.36 - 2.58)	0.947
Progression	Low TC at baseline (referent)	1		
	High TC at baseline	0.242	(0.070 - 0.836)	0.025
	Low TC on-treatment (referent)	1		
	High TC at on-treatment	0.920	(0.355 - 2.389)	0.865

Table 3 Association between Change in TC from Baseline and Response (Univariate Logistic Regression Analysis)

Covariate	Level	Odds Ratio (OR)	95% CI	P-value
Objective response rate (ORR)	No change and Increase in TC from baseline combined (referent)	1		
	Decrease in TC from baseline	3.556	(0.277 - 45.72)	0.330

Discussion

- The results of this experiment negate our hypothesis that histological analysis of biopsy specimens can be utilized to predict patient response to immunotherapy as a decrease in TC was not associated with an ORR.
- A prior study, however, showed that decreases in TC from baseline to on-treatment predicts response to immunotherapy and increased progression-free survival.[3]
- This incongruence can likely be explained by the power of this cohort, as the overall cohort was relatively small (n=39) and there was only a small number of patients that were determined to have a low TC (n=3 at baseline and n=6 on-treatment).
- We intend to initiate additional experiments to increase our study power.

Conclusions

At this time, we can not conclude that histological analyses of TC predict patient response to immunotherapy. However, this study had the significant limitation of a small cohort size. Therefore, it is reasonable to conduct similar analyses with larger cohorts.

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