Confirmatory study of the IO Score, a tumor immune microenvironment (TIME) classifier, demonstrates efficacy in a real-world cohort of metastatic urothelial cancer (mUC) patients treated with immune checkpoint inhibitors (ICIs)

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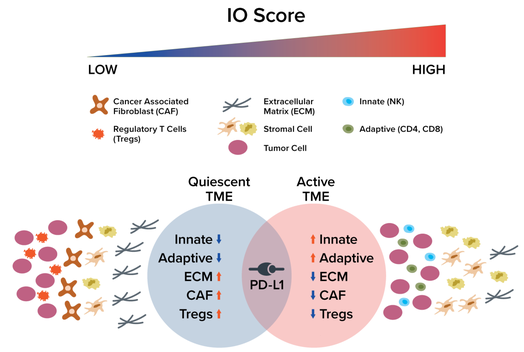
Abstract# 1272

Background

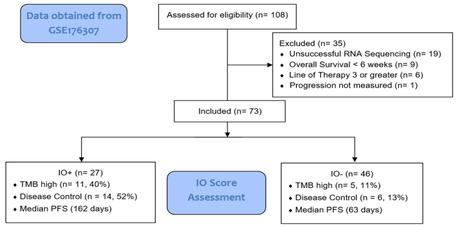
- Prognosis for patients with mUC is poor with fewer than 10% surviving two years after diagnosis.
- Approximately 17% of patients receive a subsequent therapy, emphasizing the importance of therapeutic sequencing, despite multiple approved targeted therapies[1].
- Tumor mutational burden (TMB) has been shown to be an effective biomarker for predicting ICI therapy, but relatively few patients are TMB high.
- The 27-gene IO assay (IO Score) is a gene expression panel which has recently been described as a classifier of the tumor immune microenvironment (TIME) and has demonstrated ability to predict response to immune checkpoint inhibitors (ICIs) across multiple indications. [2,3] The IO score produces a continuous result, from which a threshold of positivity has been prospectively set and remains consistent across NSCLC, TNBC, and UC.
- A more accurate predictor of response to ICIs in UC could better help direct patients to appropriate therapy earlier in their treatment.
- Therefore, we sought to expand the IMvigor210 findings of the utility of the IO Score as a biomarker for ICI efficacy in bladder cancer and suggest a new biomarker paradigm to aid in therapeutic sequencing for mUC.[4]



Methods

- The IO score was calculated using the 27-genes as previously described and defined as IO+/IO- based on an existing established threshold.[2]
- TMB high was determined as ≥ 10 mutations/MB and a composite biomarker of IO+ or TMB high was calculated (IO/TMB).
- Survival was estimated using Kaplan-Meier (K-M) plots and Cox proportional hazard ratios (HRs) were calculated for IO score, TMB high, and IO/TMB.

Figure 2: CONSORT diagram for sample inclusion.



Cohort Demographics

	Cohort (n=73)	IO+ (n=27)	IO- (n=46)	Chi-Square IO+/-
Age at IO Therapy (years)				p=0.88
≤50	3 (4%)	1 (4%)	2 (4%)	
51-60	12 (16%)	5 (19%)	7 (15%)	
61-70	24 (33%)	10 (37%)	14 (30%)	
> 70	34 (47%)	11 (41%)	23 (50%)	
Sex				p=0.41
Female	28 (38%)	12 (44%)	16 (35%)	
Male	45 (62%)	15 (56%)	30 (65%)	
Race				p=0.53
African American	18 (25%)	5 (19%)	13 (28%)	
Caucasian	51 (70%)	21 (78%)	30 (65%)	
Other	4 (5%)	1 (4%)	3 (7%)	
Disease Stage at Dx				p=0.70
Stage 1	6 (8%)	3 (11%)	3 (7%)	
Stage 2	47 (64%)	19 (70%)	28 (61%)	
Stage 3	15 (21%)	4 (15%)	11 (24%)	
Stage 4	4 (5%)	1 (4%)	3 (7%)	
Unavailable	1 (1%)	0	1 (2%)	
Histology				p=0.38
TCC	51 (70%)	20 (74%)	31 (67%)	
TCC w/ Squamous	10 (14%)	5 (19%)	5 (115)	
TCC with Other	11 (15%)	2 (7%)	9 (20%)	
non-TCC	1 (1%)	0	1 (2%)	
FGFR3 Status				p=0.61
Mutated	14 (19%)	6 (22%)	8 (17%)	
Wild-Type	59 (81%)	21 (78%)	38 (83%)	
ECOG Performance Status				p=0.23
0	18 (25%)	5 (19%)	13 (28%)	
1	28 (38%)	9 (33%)	19 (41%)	
2	11 (15%)	4 (15%)	7 (15%)	
3	2 (3%)	2 (7%)	0	
Unavailable	14 (19%)	7 (26%)	7 (15%)	
ICI Therapy Received				p=0.15
Atezolizumab	26 (36%)	9 (33%)	17 (37%)	
Durvalumab	2 (3%)	0	2 (4%)	
Nivolumab	5 (7%)	0	5 (11%)	
Pembrolizumab	40 (55%)	18 (67%)	22 (48%)	

Results

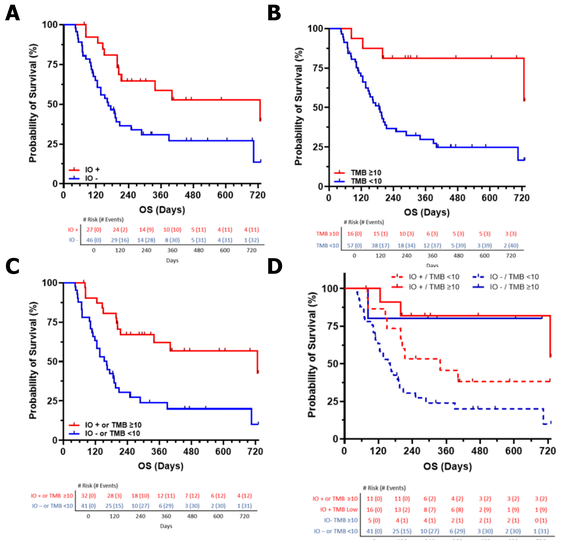


Figure 3: A-C) K-M curve of IO score, TMB, and IO/TMB for up to 2-year overall survival, respectively **D)** K-M curve of IO score and TMB in bivariate equation.

Results

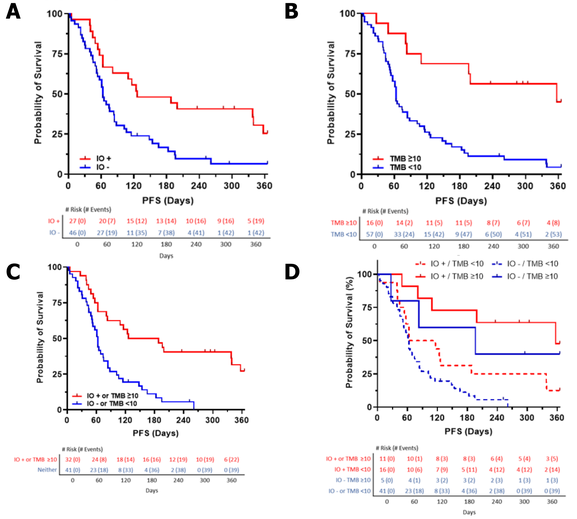


Figure 4: A-C) K-M curve of IO score, TMB, and IO/TMB for up to 1-year PFS, respectively **D)** K-M curve of IO score and TMB in bivariate equation.

Measure	IO Score	TMB (10 mut/MB)	IO Score or TMB
Biomarker Positive	27 (37%)	16 (22%)	32 (44%)
2-year OS	HR = 0.40; p=0.007	HR = 0.22; p=0.004	HR = 0.31; p=0.0005
1-year PFS	HR = 0.41; p=0.003	HR = 0.32; p=0.0001	HR = 0.32; p=0.0001
Disease Control Odds Ratio	7.18; p=0.007	11.73; p=0.0002	14.36; p=0.0001
PPV / NPV	52% / 87%	69% / 84%	53% / 93%

Table 2: Summary of therapeutic outcome for each of the three biomarkers tested. All three markers were independent of choice of ICI therapy.

Gene	IO+ (n=176)	IO- (n=257)	p=
NECTIN4	57.0	76.4	0.000023
FGFR3	49.3	59.7	0.0068
FGFR1	3.6	4.7	0.056

Table 3: Distribution of *FGFR3, FGFR1,* and *NECTIN4* upper quartile from TCGA-BLCA FPKM *data. Higher* FGFR3 and NECTIN4 expression is strongly and FGFR1 is weakly associated with an IO- TIME.

Conclusion

IO score has demonstrated ability to predict response to ICI therapy in mUC from both the IMvigor210 clinical trial and now confirmed in this real-world cohort.[4]

- IO score is independent and incremental to TMB in predicting response to ICI. Thus, an IO/TMB model would be a rational biomarker.
- Considering the reported 40% ORR with erdafitinib[1] and observed 93% NPV for IO/TMB in ICI therapy; a rational therapeutic paradigm for IO/TMB negative and FGFR altered patients is presented.

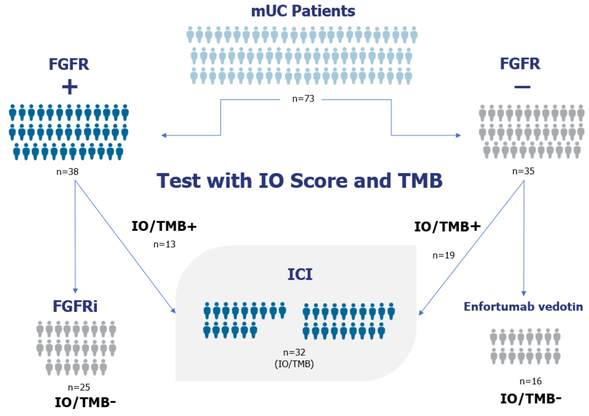


Figure 6: Proposed therapeutic management of platinum ineligible mUC patients.

References

1. Rose, T.L.; et. al. Fibroblast growth factor receptor 3 alternations and response to immune checkpoint inhibition in metastatic urothelial cancer: a real-world experience. *BJC.* 2021.
2. Nielsen, T.J.; et. al. A novel immuno-oncology algorithm measuring tumor microenvironment to predict response to immunotherapies. *Heliyon.* 2021.
3. Iwase, T; et. al. A Novel Immunomodulatory 27-Gene Signature to Predict Response to Neoadjuvant Immunochemotherapy for Primary Triple-Negative Breast Cancer. *Cancers.* 2021.
4. Seitz, R; et. al. Validation of a 27-gene immuno-oncology algorithm in metastatic urothelial carcinoma treated with an immune checkpoint inhibitor. ASCO. 2021.

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