RNAseq and Mutation Analysis Reveal Novel Response Signatures to IO Treatment in Muscle Invasive Bladder Cancer (MIBC) Patients

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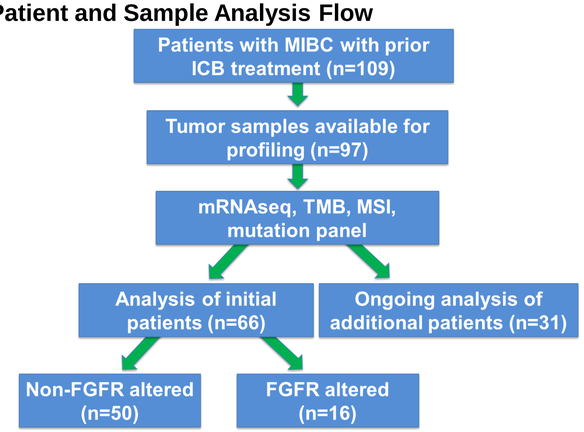
BACKGROUND

- Five-year survival for metastatic bladder cancer is poor (~5%).(1)
- Immuno-Oncology (IO) agents such as immune checkpoint Blockade (ICB) provide a survival advantage over traditional chemotherapy in patients with advanced muscle invasive bladder cancer (MIBC) but only ~20% respond to such agents.(2,3)
- The luminal molecular subtype is less immune infiltrated but is enriched for fibroblast growth factor receptor (FGFR)-alterations.
- New FGFR-targeting agents offer promising approaches for treatment of metastatic bladder cancers with FGFR alterations.
- The overall goal of this ongoing study is to examine the genomic characteristics of MIBC patients treated ICB and to assess the possible implications of those characteristics on treatment responses and outcomes.
- Another focus of the current analysis is to assess the role of FGFR alterations on survival.

METHODS

- De-identified clinical history and treatment outcomes were collected on patients who underwent prior ICB (Figure 1/Table 1).
- Comprehensive genomic analyses were performed on archived FFPE samples.
- Tumor/immune profiling analysis was performed in the context of ICB treatments and RECIST 1.1 outcomes.
- A 60-gene MIBC 4-class expression subtyper and other response associated predictors were used to stratify and identify positive/negative ICB response indicators.
- An initial FGFR3 activation response signature was developed using publicly available MIBC TCGA data (4,5).
- Preliminary mutation analysis from the first 66 patients is presented herein.

Figure 1. Patient and Sample Analysis Flow



Initial results presented at the 2019 Genitourinary Cancers Symposium (Rose et al, 2019)

RESULTS

Table 1. Patient Characteristics at Time of ICP Initiation

Characteristic		All (n=109)
Age, years, median (range)		71 (44-89)
Sex, n (%)	Male	70 (64%)
	Female	39 (36%)
Race, n (%)	White	85 (78%)
	Black	19 (17%)
	Other	5 (5%)
Smoking status, n (%)	Current/Former	78 (72%)
	Never	31 (28%)
Primary site, n (%)	Bladder	91 (83%)
	Ureter/renal pelvis	18 (17%)
Lines of systemic therapy, n (%)	1	24 (22%)
	2	63 (58%)
	3	12 (11%)
	≥4	10 (9%)
Prior platinum-based chemo, n (%)	Yes	78 (72%)
Type of first-line chemo	Cisplatin	55 (55%)
	Carboplatin	17 (16%)
	Both Cisplatin and Carboplatin	6 (6%)
	Other	3 (3%)
	None	28(26%)
ECOG PS, n (%)	0	22 (20%)
	1	45 (41%)
	>=2	19 (17%)
	Unknown	23 (21%)
Hemoglobin, n (%)	>=10g/dL	72 (66%)
Liver metastases, n (%)	Yes	33 (30%)

Table 2. FGFR Alterations Were Present in 24% (16 of 66) of Patients

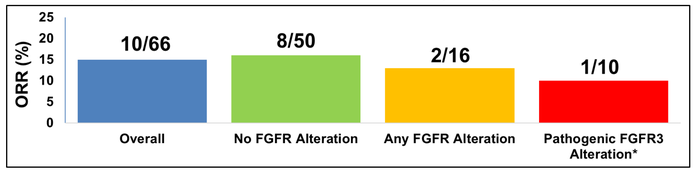
ID	Gene	Alteration	Best Response to ICB
1	FGFR3	Y373C	PD
2	FGFR3	S249C	SD
3	FGFR3	S249C	PD
4	FGFR3	D776EfsX41,R248C	PD
5	FGFR3	FGFR3-TACC3 fusion	PD
6	FGFR2	K660N	PD
7	FGFR3	R248C	PD
8	FGFR3	FGFR3-TACC3 fusion	PD
9	FGFR1	amplified-gain	PD
10	FGFR3	S249C	PR
11	FGFR3	S249C	PD
12	FGFR3	S249C	PD
13	FGFR1	amplified-gain	CR
14	FGFR3	S249C	PD
15	FGFR3	FGFR3-TACC3 fusion, FGFR3/4 amp	SD
16	FGFR3	S249C	PD

Table 3. Overall FGFR Alteration Status Does Not Impact ICB Response

Best Response	All (n=66)	No Known FGFR Alteration (n=50)	Any FGFR Alteration (n=16)
PD	49 (74%)	37 (74%)	12 (75%)
SD	7 (11%)	5 (10%)	2 (13%)
PR	7 (11%)	6 (12%)	1 (6%)
CR	3 (5%)	2 (4%)	1 (6%)

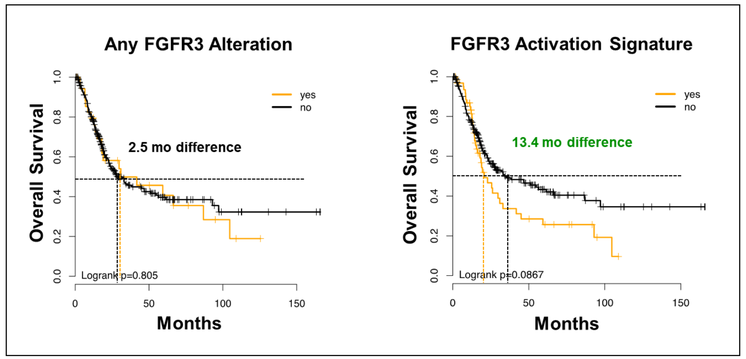
Response based upon RECIST 1.1

Figure 2. Pathogenic FGFR3 Alterations May Negatively Impact Response



*Pathogenic FGFR3 alterations include FGFR3-TACC3 fusions and S249C mutations; ORR = objective response rate

Figure 3. There is a Trend Towards Decreased Survival in Patients with FGFR3-Activated Tumors (TCGA Analysis)



TCGA analysis of n=318 patients with MIBC

- Signature based upon gene expression profile of FGFR3 mutant samples

SUMMARY AND CONCLUSIONS

- FGFR alterations were observed in 24% of tumor samples from the initial patients (n=66), which is consistent with previous studies.
- This preliminary analysis suggests that overall FGFR alteration status alone does not predict a lack of ICB responsiveness.
- An FGFR3 Predictive Response Signature based upon genes associated with FGFR3 activation may aid in selection of patients more suited for FGFR-targeted therapies such as the recently approved erdafitinib
- Full analysis of the complete dataset (n=97) will be presented at a future meeting.

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