Fibroblast Growth Factor Receptor Status and Response to Immune Checkpoint Inhibition in Metastatic Urothelial Cancer

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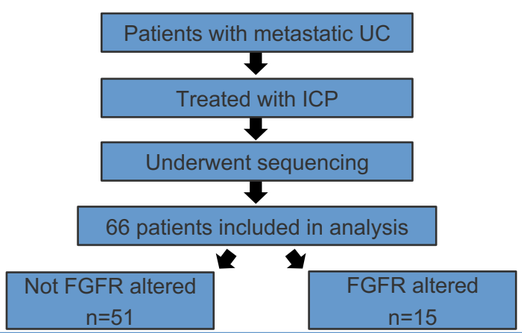
Background

- Urothelial cancer (UC) is a common malignancy with poor outcomes in patients with metastatic disease.
- Fibroblast growth factor receptor (FGFR) inhibitors are a promising new targeted therapy for patients with metastatic UC and FGFR alterations.
- FGFR-altered tumors are enriched in the luminal molecular subtype, which is less immune infiltrated, and may suggest differential response to immune checkpoint inhibitors (ICP).

Hypothesis: FGFR-altered tumors will have lower response rates to ICP than those without alterations.

Methods

- Metastatic UC patients at the University of North Carolina who underwent targeted exon sequencing (any CLIA-certified platform) and were treated with ICP since 2014 were identified.
- Patients with any FGFR alteration (mutations, fusions, and amplifications in FGFR1-4) were compared to patients without alterations.
- Overall response rates (ORR) to ICP were assessed by a radiologist (K.M.) per RECIST 1.1 and compared between FGFR-altered and unaltered tumors using Fisher's exact tests.
- Patients who died prior to radiologic assessment were considered non-responders.



Patient Characteristics at Time of ICP Initiation

Characteristic		FGFR-altered (n=15)	FGFR-unaltered (n=51)
Age, years	Median (range)	74 (52-90)	67 (44-82)
Sex, n (%)	Male	9 (60%)	34 (67%)
Race, n (%)	White	12 (80%)	38 (75%)
	Black	2 (13%)	12 (24%)
	Unknown	1 (7%)	1 (2%)
Smoking Status, n (%)	Current/Former	14 (93%)	32 (64%)
	Never	1 (7%)	18 (36%)
Primary Site, n (%)	Bladder	13 (87%)	43 (84%)
	Upper tract	2 (13%)	8 (16%)
Line of therapy, n (%)	1	7 (47%)	10 (20%)
	2	5 (33%)	35 (70%)
	>=3	3 (20%)	5 (10%)
ECOG PS, n (%)	0	3 (20%)	12 (24%)
	1	8 (53%)	19 (37%)
	>=2	2 (13%)	10 (20%)
	Unknown	2 (13%)	10 (20%)
Liver Mets, n (%)	Yes	5 (33%)	17 (33%)
Hgb, n (%)	>= 10 g/dL	12 (80%)	33 (64%)
Checkpoint Inhibitor Received, n (%)	Pembrolizumab	10 (67%)	30 (59%)
	Atezolizumab	4 (27%)	15 (29%)
	Nivolumab	0	4 (8%)
	Durvalumab	0	2 (4%)
	Avelumab	1 (7%)	0

Abbreviations: ECOG PS, European Cooperative Oncology Group performance status

Treatment Response By FGFR status

Best Response#	All (n=66)	FGFR-altered (n=15)	FGFR-unaltered (n=51)
PD	49 (74%)	10 (67%)	39 (76%)
SD	7 (11%)	3 (20%)	4 (8%)
PR	7 (11%)	1 (7%)	6 (12%)
CR	3 (5%)	1 (7%)	2 (4%)
ORR*	**15% (10/66)**	**13% (2/15)**	**16% (8/51)**

Based on RECIST 1.1
* Fisher's exact p = 1.0 for FGFR-altered vs unaltered patients

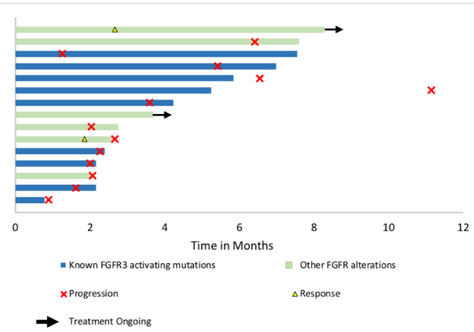
No patients (0/9, 0%) with known pathogenic mutations in FGFR3 responded to ICP compared to 10/57 (18%) of patients without these alterations (p=0.33).

Treatment Response by FGFR Status and Molecular Characterization

Specific FGFR Alterations by Patient

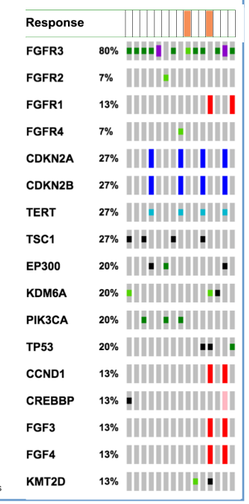
ID*	Gene	Alteration	Best Response To ICP
1	*FGFR3*	Y373C	PD
2	*FGFR3*	S249C	SD
3	*FGFR3*	S249C	PD
4	*FGFR3*	D776fs*41 R248C	PD
5	*FGFR3*	TACC3 fusion	PD
6	*FGFR2*	K660N	PD
7	*FGFR3*	R248C S249C	PD
8	*FGFR4*	G388R	SD
9	*FGFR3*	S785L	PR
10	*FGFR3*	S249C	PD
11	*FGFR3*	S249C	PD
12	*FGFR1*	amplification	CR
13	*FGFR3*	S249C	PD
14	*FGFR3*	TACC3 fusion	SD
15	*FGFR3* *FGFR1*	S249C *amplification*	PD

Treatment Duration in Patients with FGFR alterations



Note: Known FGFR3 activating mutations include Y373C, R248C, and S249C.

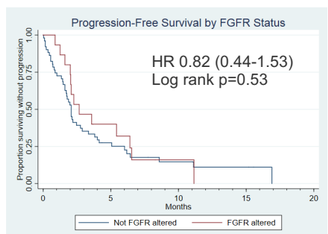
Common somatic mutations in patients with FGFR alterations

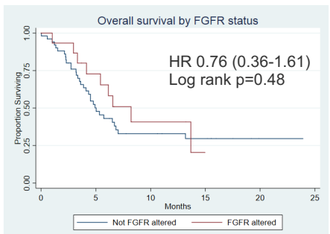


Reported alterations include all FGFR alterations and all other alterations in >10% of patients

Survival by FGFR status

Outcome	All (n=66)	FGFR-altered (n=15)	FGFR-unaltered (n=51)
PFS, median (95% CI), mos	2.1 (1.8-2.9)	2.7 (1.6-6.4)	2.1 (1.6-2.9)
OS, median (95% CI), mos	5.7 (4.3-7.0)	8.2 (3.3-NR)	5.0 (3.9-6.8)





- Median follow-up = 13.4 months
- 46% of FGFR-altered patients who stopped ICP due to progression received subsequent therapy

Conclusions

- There was no difference in ORR between FGFR-altered and unaltered patients.
- Although no patients with pathogenic FGFR3 mutations responded to ICP in our cohort, this difference did not reach statistical significance.
- Given low response rates overall, some FGFR-altered patients may benefit from treatment with FGFR inhibitors prior to ICP.
- Analysis of larger cohorts of patients as well as patients from clinical trials and more in-depth molecular profiling may add further clarity.

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