Infigratinib in upper tract urothelial carcinoma vs urothelial carcinoma of the bladder and association with comprehensive genomic profiling/cell-free DNA results

Dizman N,[1] Rosenberg J,[2] Hoffman-Censits J,[3] Quinn DI,[4] Petrylak D,[5] Galsky M,[6] Vaishampayan U,[7] De Giorgi U,[8] Gupta S,[9] Howard Burris H,[10] Soifer H,[11] Li G,[11] Dambkowski CL,[11] Moran S,[11] Ye Y,[11] Daneshmand S,[12] Bajorin D,[2] Pal SK[1]

[1]City of Hope Comprehensive Cancer Center, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; [4]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [5]Yale Cancer Center, Smilow Cancer Hospital, New Haven, CT; [6]Mount Sinai School of Medicine, New York, NY; [7]Wayne State University, Detroit, MI; [8]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy; [9]Huntsman Cancer Institute – University of Utah Health Care, Salt Lake City, UT; [10]Sarah Cannon Research Institute, Nashville, TN; [11]QED Therapeutics Inc, San Francisco, CA; [12]Keck School of Medicine of USC, Los Angeles, CA

#PD4510

Background

- Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor with significant activity in patients with advanced or metastatic urothelial carcinoma (mUC) bearing *FGFR3* alterations.[1]
- Given the distinct biologic characteristics of upper tract UC (UTUC) and urothelial carcinoma of the bladder (UCB), we sought to determine if infigratinib had varying activity in these settings.
- In addition, tumor tissue and cell-free DNA (cfDNA) was further characterized to determine if UTUC and UCB differed in their genomic profiles in patients with advanced or metastatic UC.[2,3]

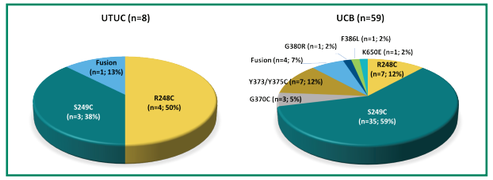
Study methods

- Eligible patients had mUC with activating *FGFR3* mutations/fusions and prior platinum-based chemotherapy, unless contraindicated.
- Patients received infigratinib 125 mg orally daily (3 weeks on/1 week off).
- Overall response rate (ORR: CR+PR) and disease control rate (DCR; CR+PR+SD) were characterized in UCB and UTUC patients.
- Genomic profiling of UCB and UTUC patients was performed with DNA isolated from FFPE tumor tissue and plasma (cfDNA) obtained prior to treatment:
  - Comprehensive genomic profiling of tumor tissue (Foundation Medicine; Cambridge, MA) was used to enroll patients with genetic alterations in *FGFR3*.
  - Cell-free DNA (cfDNA) obtained from blood prior to treatment was evaluated by next-generation sequencing using a 600-gene panel (Novartis Labs).

Table 1. Baseline characteristics

Characteristic	UTUC (n=8)	UCB (n=59)	Total (n=67)
Age			
<65 years	4 (50.0)	25 (42.4)	29 (43.3)
≥65 years	4 (50.0)	34 (57.6)	38 (56.7)
Gender, n (%)			
Male	7 (87.5)	39 (66.1)	46 (68.7)
Female	1 (12.5)	20 (33.9)	21 (31.3)
WHO PS, n (%)			
0	2 (25.0)	19 (32.2)	21 (31.3)
1	6 (75.0)	30 (50.8)	36 (53.7)
2	0	10 (16.9)	10 (14.9)
Bellmunt criteria – risk group, n (%)			
0	2 (25.0)	10 (16.9)	12 (17.9)
1	3 (37.5)	24 (40.7)	27 (40.3)
2	3 (37.5)	22 (37.3)	25 (37.3)
3	0	3 (5.1)	3 (4.5)
Visceral disease, n (%)			
Lung	5 (62.5)	36 (61.0)	41 (61.2)
Liver	2 (25.0)	23 (39.0)	25 (37.3)
Lymph node metastases, n (%)			
Yes	2 (25.0)	26 (44.1)	19 (28.4)
No	6 (75.0)	33 (55.9)	46 (68.7)
Bony metastases, n (%)			
Yes	3 (37.5)	23 (39.0)	25 (37.3)
No	5 (62.5)	36 (61.0)	40 (59.7)

Figure 1. Proportion of *FGFR3* alterations in UCB vs UTUC



- A different frequency of mutations R248C and S249C in the *FGFR3* extracellular Ig-like domains was observed in UTUC vs UCB.
- Mutations outside of the Ig-like domains were observed in UCB but not UTUC.

Table 2. Prior anti-cancer therapies

	UTUC (n=8)	UCB (n=59)	Total (n=67)
Total number of lines of prior therapies, n (%)			
0	0	13 (22.0)	13 (19.4)
1	5 (62.5)	19 (32.2)	24 (35.8)
≥2	3 (37.5)	27 (45.7)	30 (44.8)
Total number of prior anticancer regimens, n (%)			
0	0	1 (1.7)	1 (1.5)
1	2 (25.0)	17 (28.8)	19 (28.4)
≥2	6 (75.0)	41 (67.8)	47 (70.1)
Best response to prior anticancer regimen, n (%)			
Complete response (confirmed)	0	1 (1.7)	1 (1.5)
Complete response (unconfirmed)	0	1 (1.7)	1 (1.5)
Partial response	2 (25.0)	8 (13.6)	10 (14.9)
Stable disease	2 (25.0)	21 (35.6)	23 (34.3)
Progressive disease	2 (25.0)	14 (23.7)	16 (23.9)
Missing	2 (25.0)	14 (23.7)	16 (23.9)

Table 3. Efficacy summary

	UTUC (n=8)	UCB (n=59)	Total (n=67)
Response assessment, n (%)			
Complete response (CR), confirmed	1 (12.5)	0	1 (1.5)
Partial response (PR), confirmed	3 (37.5)	13 (22.0)	16 (23.9)
Stable disease (SD)	4 (50.0)	22 (37.3)	26 (38.8)
CR/PR, unconfirmed	1 (12.5)	10 (16.9)	11 (16.4)
Progressive disease	0	18 (30.5)	18 (26.9)
Unknown/not done	0	6 (10.2)	6 (9.0)
Confirmed objective response (CR or PR), n (%)	**4 (50.0)**	**13 (22.0)**	**17 (25.4)**
95% CI	15.7–84.3	12.3–34.7	15.5–37.5
Best overall response (CR or PR, conf/unconf), n (%)	**5 (62.5)**	**23 (39.0)**	**28 (41.8)**
95% CI	24.5–91.5	26.5–52.6	29.8–54.5
Disease control rate (CR/PR or SD), n (%)	**8 (100.0)**	**35 (59.3)**	**43 (64.2)**
95% CI	63.1–100.0	45.7–71.9	51.5–75.5
Median duration of response, months	**6.77**	**5.04**	**5.62**
Range*	3.32[+] – 11.01	2.33[+] – 8.08	2.33[+] – 11.01

*+: patients who have a confirmed objective response without an assessment of disease progression/deaths are included as 'censored'

Figure 2. Progression-free survival

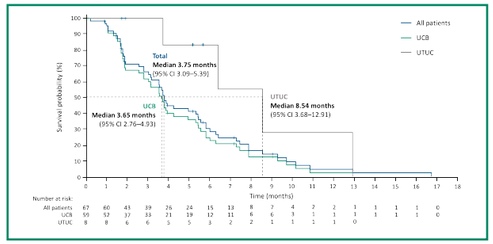


Figure 3. Overall survival

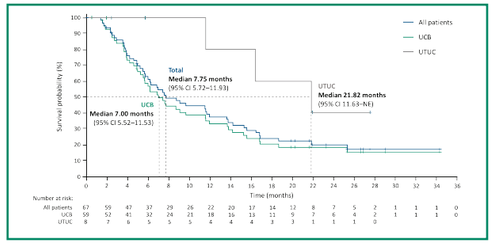


Figure 4. Tumor response with treatment exposure

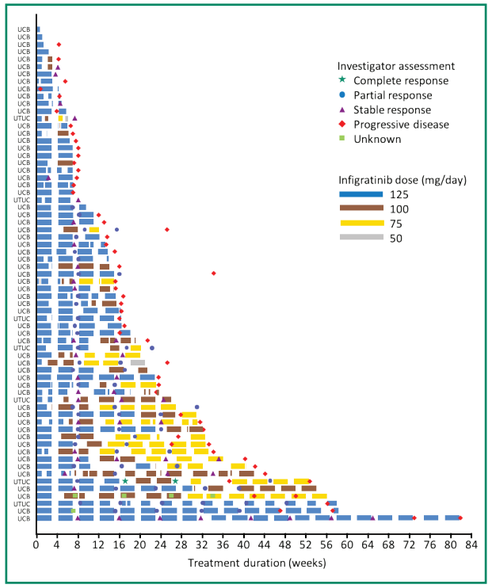


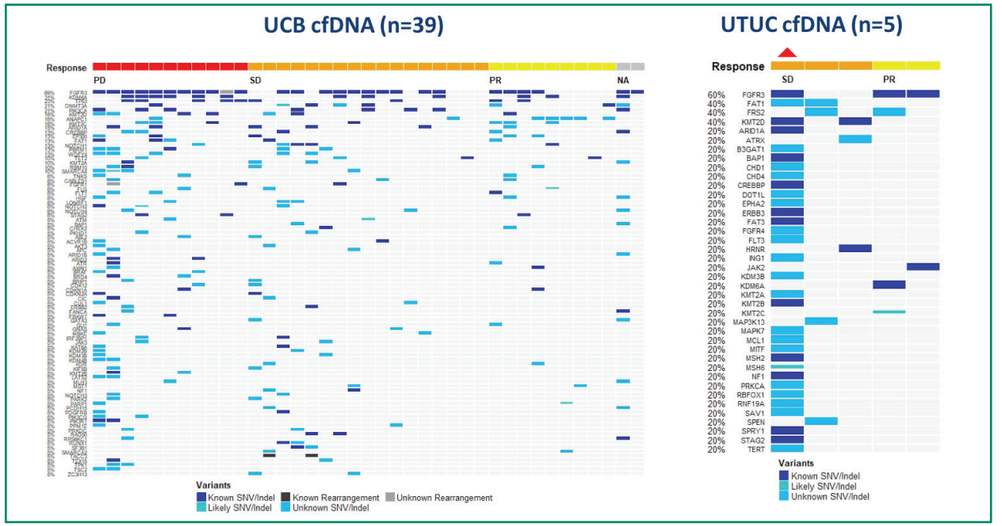
Table 4. TEAEs in >20% of patients (any grade)

n (%)	UTUC (n=8)	UCB (n=59)	Total (n=67)
Blood creatinine increased	5 (62.5)	22 (37.3)	27 (40.3)
Fatigue	1 (12.5)	25 (42.4)	26 (38.8)
Hyperphosphatemia	4 (50.0)	22 (37.3)	26 (38.8)
Constipation	5 (62.5)	20 (33.9)	25 (37.3)
Anemia	2 (25.0)	22 (37.3)	24 (35.8)
Decreased appetite	2 (25.0)	20 (33.9)	22 (32.8)
Alopecia	3 (37.5)	18 (30.5)	21 (31.3)
Dry mouth	3 (37.5)	18 (30.5)	21 (31.3)
Nausea	0	19 (32.2)	19 (28.4)
Stomatitis	4 (50.0)	14 (23.7)	18 (26.9)
Nail disorder	2 (25.0)	14 (23.7)	16 (23.9)
Dysgeusia	3 (37.5)	12 (20.3)	15 (22.5)
Mucosal inflammation	1 (12.5)	14 (23.7)	15 (22.4)

Table 5. TEAEs in >5% of patients (grade 3/4)

n (%)	UTUC (n=8)	UCB (n=59)	Total (n=67)
Lipase increased	1 (12.5)	6 (10.2)	7 (10.4)
Anemia	0	5 (8.5)	5 (7.5)
Fatigue	0	5 (8.5)	5 (7.5)
Hypophosphatemia	0	5 (8.5)	5 (7.5)
Hyponatremia	1 (12.5)	3 (5.1)	4 (6.0)

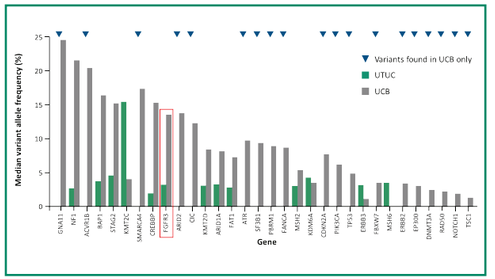
Figure 5. Oncoplots of cfDNA genomic profiles in UCB and UTUC



For UCB, only gene variants that were in at least 5% of patient samples are included in the oncoplot. For UTUC, all gene variants in patient samples are included in the oncoplot.

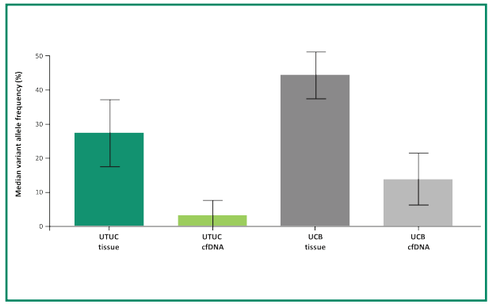
- *FGFR3* alterations were concordant in 30/38 (79%) of patients with both tumor tissue and cfDNA at screening.
- A more complex genomic profile with an increased mutational burden was observed in cfDNA from UCB patients vs UTUC.

Figure 6. The frequency of variants found in cfDNA differed in UCB vs UTUC



- Across the majority of genes the variant allele frequency (VAF) in cfDNA was higher in UCB than in UTUC.
- The higher VAF in cfDNA observed in UCB suggests that UCB patients may have higher disease burden or different mechanisms of metastasis compared with UTUC.

Figure 7. *FGFR3* variant allele frequency was higher in UCB vs UTUC



- The median VAF for *FGFR3* genomic alterations was higher in tumor tissue and cfDNA in UCB vs UTUC

References

1. Pal SK et al. Cancer Discov 2018;8:812–21.
2. Sfakianos JP et al. Eur Urol 2015;68:970–7.
3. Moss TJ et al. Eur Urol 2017;72:641–9.

Conclusions

- Different patterns of genomic alterations were observed between UCB and UTUC in this *FGFR3*-restricted experience, underscoring the distinct biology of these diseases.
- Results with infigratinib in UTUC support a planned phase III adjuvant study predominantly in this population.

Presented at the 2019 ASCO Annual Meeting, May 31 – June 4, Chicago, Illinois, USA