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

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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

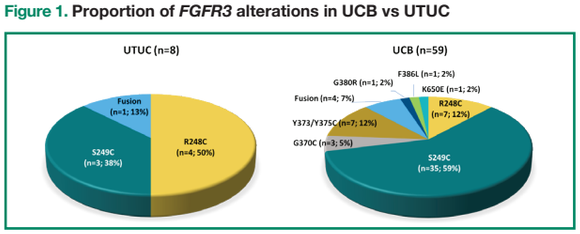


Table 2. Prior anti-cancer therapies

	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)

- 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.

Figure 2. Progression-free survival

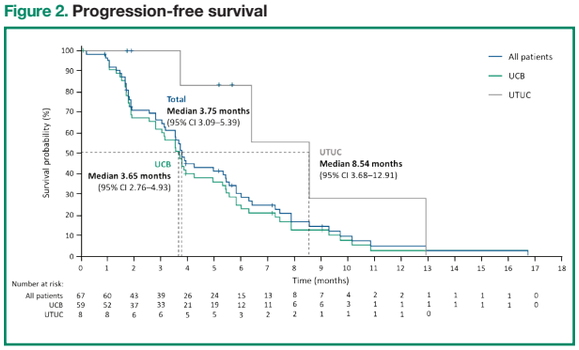


Figure 3. Overall survival

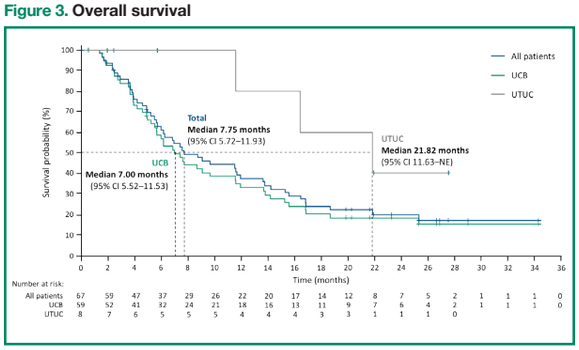


Table 3. Efficacy summary

	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'

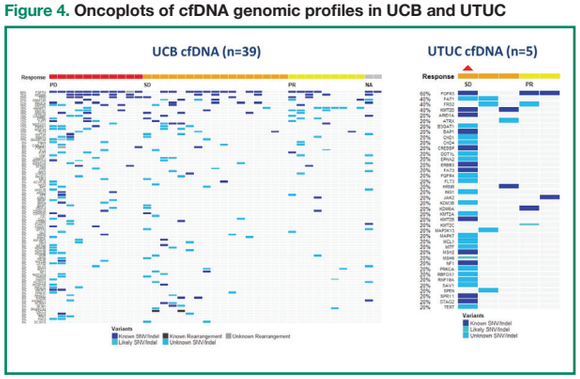
Table 4. TEAEs in >20% of patients (any grade)

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)

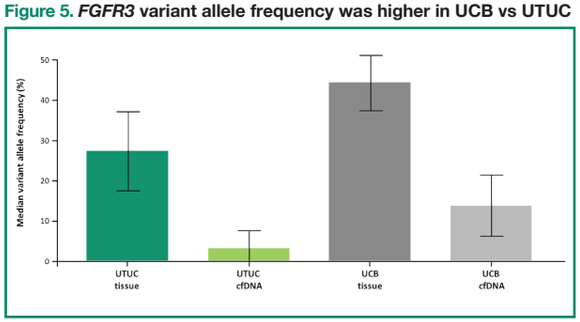
Figure 4. Oncoplots of cfDNA genomic profiles in UCB and UTUC



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.
- 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 5. *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

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.

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.

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