Activity of the FGFR1–3 inhibitor infigratinib in patients with upper tract urothelial carcinoma and urothelial carcinoma of the bladder: latest efficacy findings and comprehensive genomic profiling/cell-free DNA data

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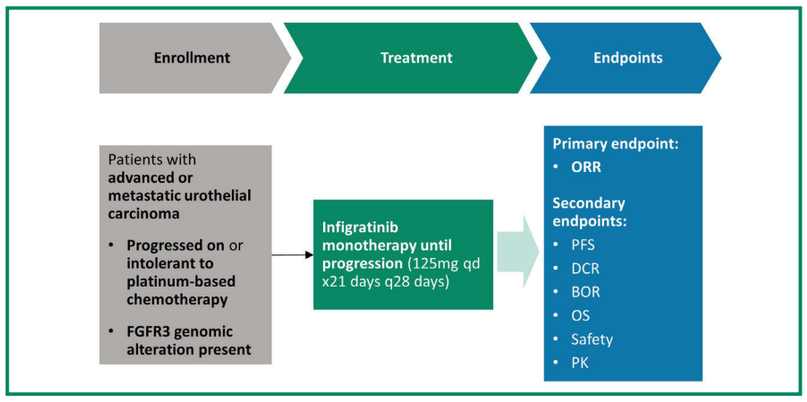
Background and methods

- Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor with significant activity in patients with advanced or metastatic urothelial carcinoma 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]
- 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.*
  - cfDNA obtained from blood prior to treatment was evaluated by next-generation sequencing using a 600-gene panel (Novartis Labs).

Figure 1. Phase 1 study CBGJ398X2101 design (expansion cohort)

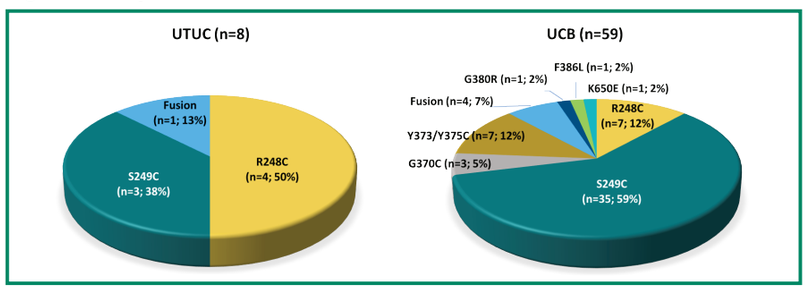


Results

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 2. 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)

Figure 3. Responses seen in urothelial patients

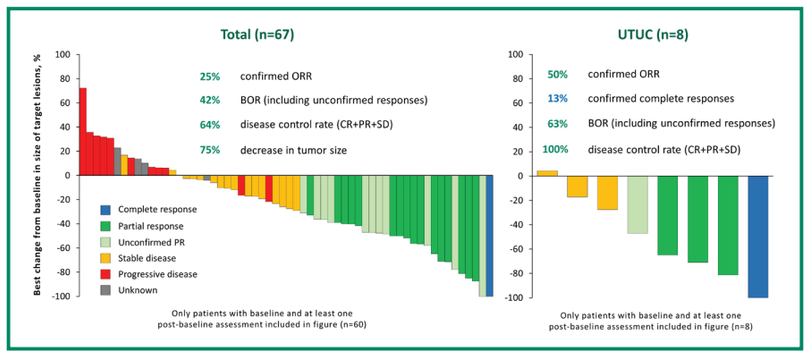


Figure 4. Progression-free survival

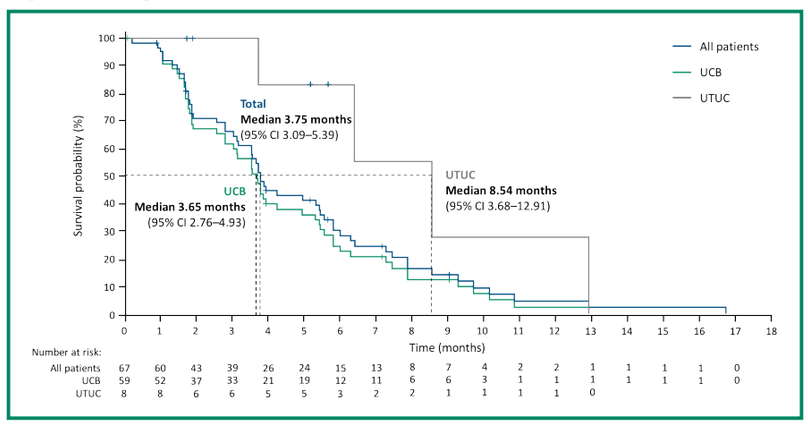
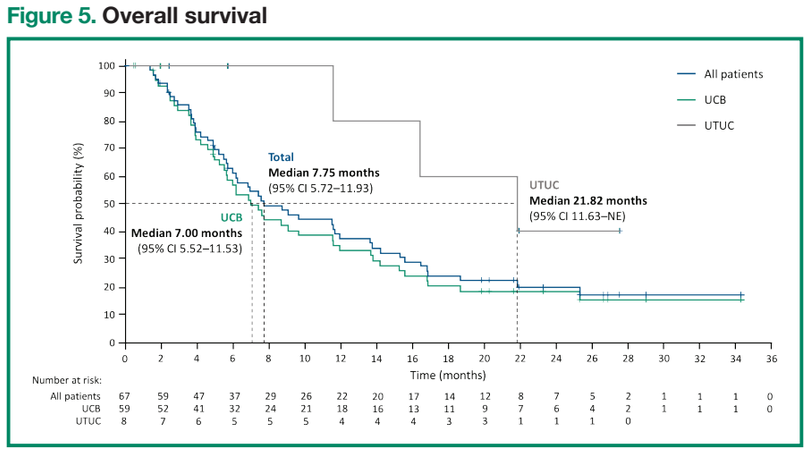


Figure 5. Overall survival



- One of the UTUC patients was a 61-year old male with a tumor bearing a *FGFR3-TACC3* fusion.
- Following receipt of infigratinib, he experienced a CR per central assessment on Day 55, which was later confirmed on Day 120.
- The CR continued until progressive disease developed on Day 260.

Table 3. 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)

Figure 6. Oncoplots of tumor genomic profiles in UCB and UTUC

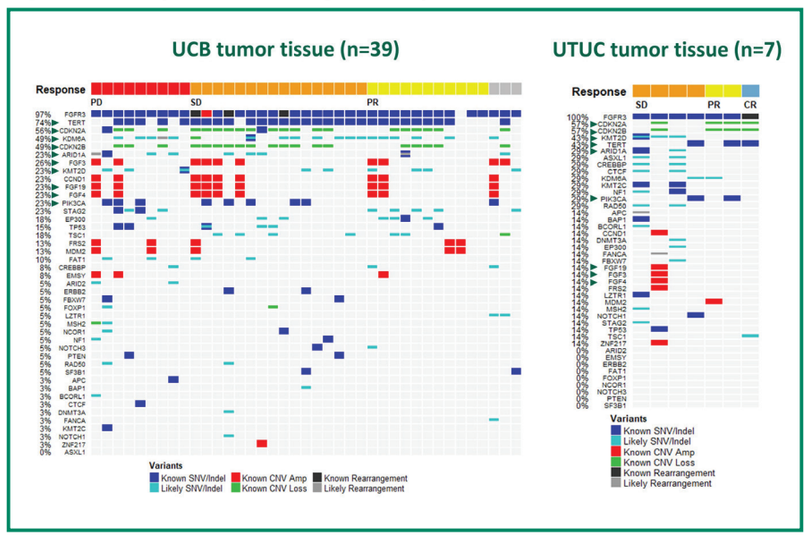
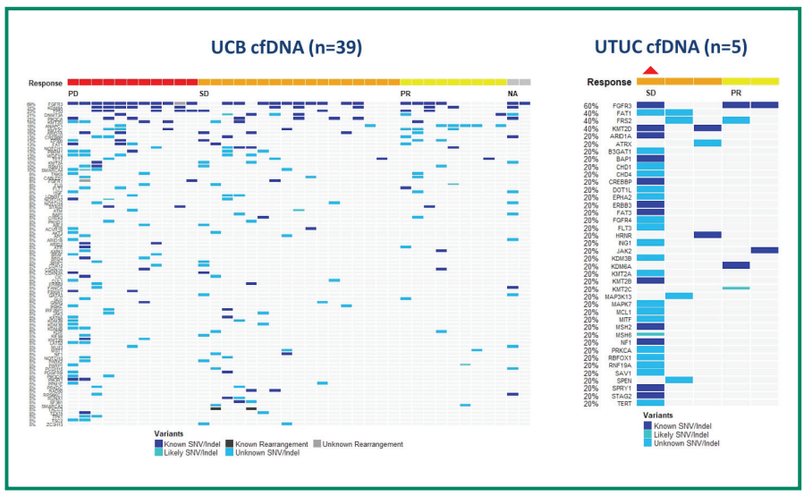


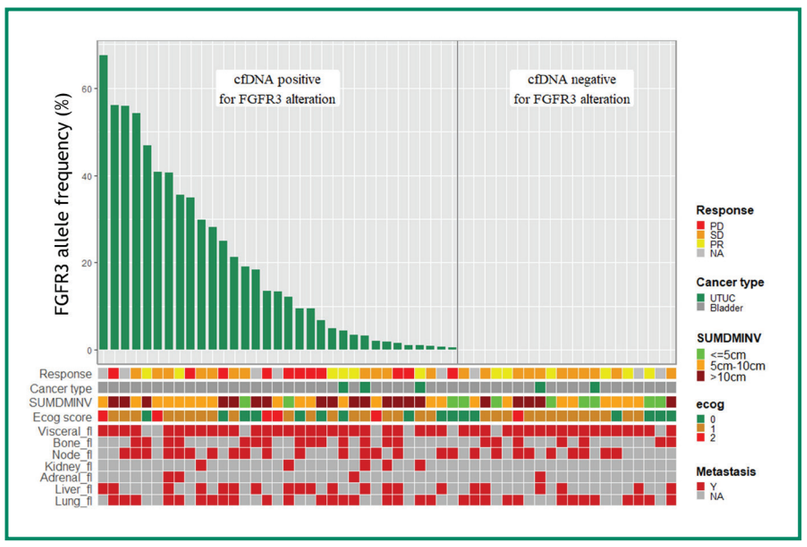
Figure 7. Oncoplots of cfDNA genomic profiles in UCB and UTUC



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

- Genomic alterations in genes involved in chromosome maintenance (*TERT*), cell cycle (*CDKN2A, CDKN2B*), FGFR signaling (*FGF3/4/19*) chromatin remodeling (*KMT2D, KDM6A*), transcription (*ARID1A*), and signal transduction (*PIK3CA*) were observed in both UTUC and UCB tumors.
- *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 patients.

Figure 8. FGFR3 allele frequency and clinical characteristics

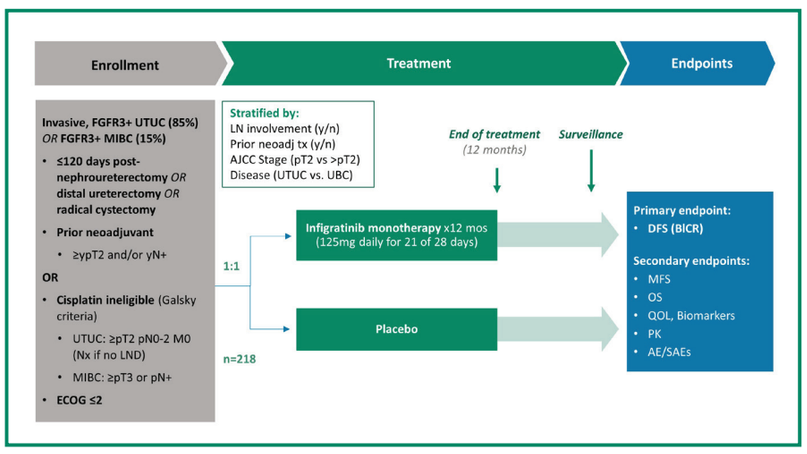


- All subjects in this plot have at least one genetic alteration in cfDNA. Subjects with no detectable cfDNA alterations were excluded.
- There was no observable correlation between FGFR3 allele frequency in cfDNA and clinical characteristics such as sum of longest dimension, ECOG score, and sites of metastasis.

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 (see Figure 9).

Figure 9. PROOF 302: adjuvant infigratinib vs. placebo for invasive urothelial carcinoma with susceptible *FGFR3* alterations



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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