Infigratinib in advanced/unresectable or metastatic urothelial carcinoma demonstrates consistent treatment response in both first-line and later-line treatment settings

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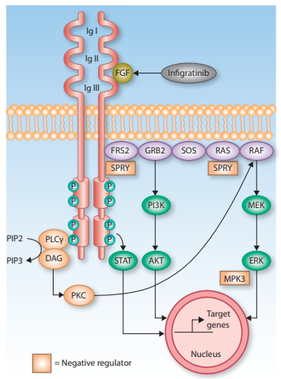
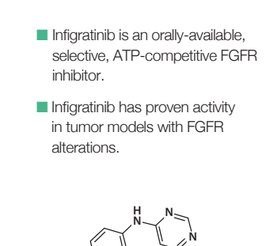
Background

- Advanced urothelial carcinoma (aUC) is an incurable disease for many patients.
- Platinum-based chemotherapy remains a cornerstone of therapy; a minority of patients (15–40%) respond to newer immune checkpoint inhibitors.[1–3]
- Activating mutations of *FGFR3*, which are altered in approximately 20% of patients with lower tract urothelial cancer, and in 40–75% of patients with upper tract disease,[4–6] are a target for novel therapies.
- Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor (Figure 1) previously reported to have significant clinical activity in a study of patients with aUC bearing *FGFR3* alterations.[7,8]
- However, this previous study (Figure 2) did not examine differences in infigratinib activity based on number of prior lines of treatment (LOT). TKIs studied in other indications (e.g. VEGFRis in renal cell carcinoma) have shown consistent activity in both the first and later LOT.
- Given the effect seen with other TKIs, we sought to determine if infigratinib showed consistent treatment responses in patients with aUC according to LOT.

Figure 1. Infigratinib: an oral FGFR1–3 selective kinase inhibitor



- Infigratinib is an orally-available, selective, ATP-competitive FGFR inhibitor.
- Infigratinib has proven activity in tumor models with FGFR alterations.



Methods

- Patients with aUC bearing FGFR3 alterations received oral infigratinib 125 mg orally once daily on days 1–21 every 28 days until disease progression or unacceptable toxicity (Figure 2).[7]
- **Primary objective:** compare the objective response rate (ORR) in patients receiving first-line therapy versus later-line therapy. Treatment response was characterized using RECIST 1.0 criteria.
- **Secondary objectives:** compare disease control rate (DCR) and progression-free survival (PFS) in the same groups.
- The chi-square test was used to compare response among subgroups, and the Kaplan-Meier method with log-rank test was used to compare PFS.
- Comparisons were also made across individual lines of therapy (e.g., first- versus second- versus third-line therapy, and thereafter) using descriptive statistics due to best fit the number of patients in each subgroup.
- Genomic assessment of tissue and blood specimens was conducted as described previously.[5]

Figure 2. Study design

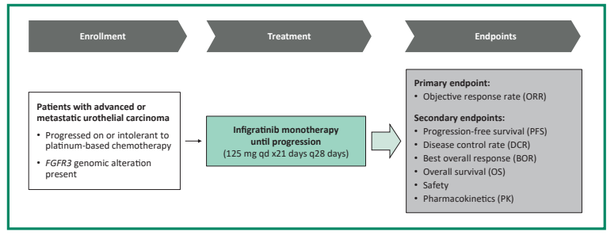


Table 1. Patient characteristics

Characteristic	Infigratinib as first-line therapy (n=13)	Infigratinib as second/later-line therapy (n=54)	Total (n=67)
Age			
<65 years	5 (38.5)	24 (44.4)	29 (43.3)
≥65 years	8 (61.5)	30 (55.6)	38 (56.7)
Gender, n (%)			
Male	7 (53.8)	39 (72.2)	46 (68.7)
Female	6 (46.2)	15 (27.8)	21 (31.3)
WHO PS, n (%)			
0	3 (23.1)	18 (33.3)	21 (31.3)
1	7 (53.8)	29 (53.7)	36 (53.7)
2	3 (23.1)	7 (13.0)	10 (14.9)
Bellmunt Criteria[a] – risk group, n (%)			
0	3 (23.1)	9 (16.7)	12 (17.9)
1	6 (46.2)	21 (38.9)	27 (40.3)
2	3 (23.1)	22 (40.7)	25 (37.3)
3	1 (7.7)	2 (3.7)	3 (4.5)
Type of cancer, n (%)			
UTUC	0	8 (14.8)	8 (11.9)
UBC	13 (100)	46 (85.2)	59 (88.1)
Visceral disease, n (%)			
Lung	9 (69.2)	32 (59.3)	41 (61.2)
Liver	4 (30.8)	21 (38.9)	25 (37.3)
Lymph node metastases, n (%)			
Yes	2 (15.4)	26 (48.1)	28 (41.8)
No	11 (84.6)	28 (51.9)	39 (58.2)
Bony metastases, n (%)			
Yes	5 (38.5)	21 (38.9)	26 (38.8)
No	8 (61.5)	33 (61.1)	41 (61.2)
Any prior immunotherapy			
Yes	2 (15.4)	11 (20.4)	13 (19.4)
No	11 (84.6)	43 (79.6)	54 (80.6)

[a]Bellmunt Criteria include ECOG>0, liver metastases, and hemoglobin <10 g/dL at baseline
UTUC: upper tract urothelial cancer
UBC: urothelial bladder cancer

Table 2. Efficacy findings – all patients

	Infigratinib as first-line therapy (n=13)	Infigratinib as second/later-line therapy (n=54)	Total (n=67)
Response assessment, n (%)			
Complete response (CR), confirmed	0	1 (1.9)	1 (1.5)
Partial response (PR), confirmed	4 (30.8)	12 (22.2)	16 (23.9)
Stable disease (SD)	2 (15.4)	24 (44.4)	26 (38.8)
CR/PR, unconfirmed	1 (7.7)	10 (18.5)	11 (16.4)
Progressive disease	6 (46.2)	12 (22.2)	18 (26.9)
Unknown/not done	1 (7.7)	5 (9.3)	6 (9)
Confirmed objective response (CR or PR), n (%)	4 (30.8)	13 (24.1)	17 (25.4)
95% CI	9.1–61.4	13.5–37.6	15.5–37.5
Best overall response (CR or PR, conf/unconf), n (%)	5 (38.5)	23 (42.6)	28 (41.8)
95% CI	13.9–68.4	29.2–56.8	29.8–54.5
Disease control rate (CR/PR or SD), n (%)	6 (46.2)	37 (68.5)	43 (64.2)
95% CI	19.2–74.9	54.4–80.5	51.5–75.5

Table 3. Efficacy findings – UBC patients

	Infigratinib as first-line therapy (n=13)	Infigratinib as second/later-line therapy (n=46)	Total (n=59)
Response assessment, n (%)			
Complete response (CR), confirmed	0	0	0
Partial response (PR), confirmed	4 (30.8)	9 (19.6)	13 (22.0)
Stable disease (SD)	2 (15.4)	20 (43.5)	22 (37.3)
CR/PR, unconfirmed	1 (7.7)	9 (19.6)	10 (16.9)
Progressive disease	6 (46.2)	12 (26.1)	18 (30.5)
Unknown/not done	1 (7.7)	5 (10.9)	6 (10.2)
Confirmed objective response (CR or PR), n (%)	4 (30.8)	9 (19.6)	13 (22.0)
95% CI	9.1–61.4	9.4–33.9	12.3–34.7
Best overall response (CR or PR, conf/unconf), n (%)	5 (38.5)	18 (39.1)	23 (39.0)
95% CI	13.9–68.4	25.1–54.6	26.5–52.6
Disease control rate (CR/PR or SD), n (%)	6 (46.2)	29 (63.0)	35 (59.3)
95% CI	19.2–74.9	47.5–76.8	45.7–71.9

UBC: urothelial bladder cancer

- All patients with UTUC (n=8) received infigratinib as second-/later-line therapy; the confirmed ORR was 50% (95% CI 15.7–84.3) and the DCR was 100%.[8]

Figure 3. Progression-free survival – all patients

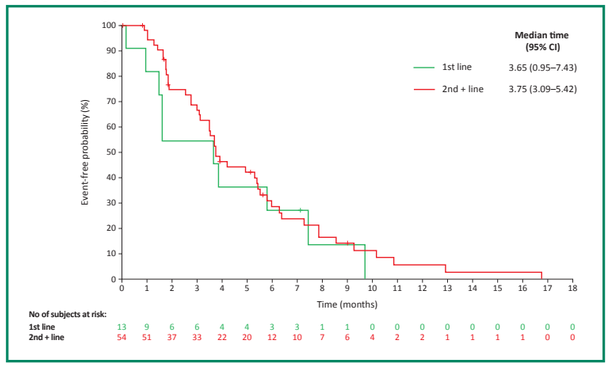


Figure 4. Overall survival – all patients

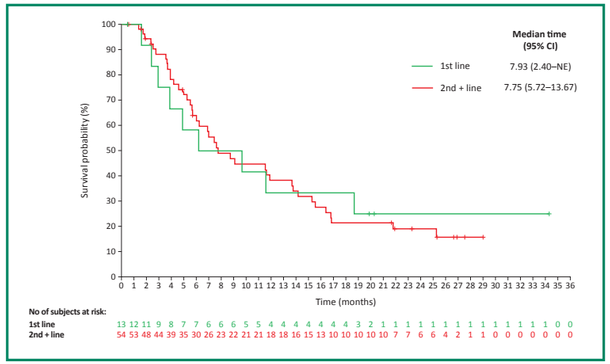


Table 4. TEAEs in ≥15% of patients with any AEs

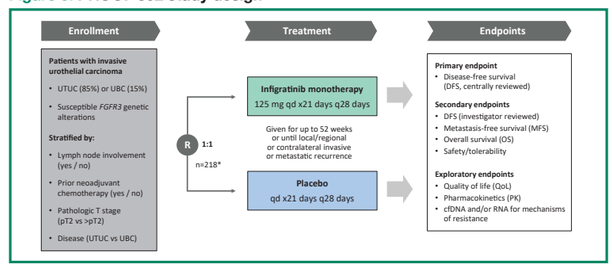
n (%)	All grades	Grade 3/4
All TEAEs	**66 (98.5)**	**46 (68.7)**
Hyperphosphatemia	31 (46.3)	1 (1.5)
Elevated creatinine	28 (41.8)	0
Fatigue	25 (37.3)	5 (7.5)
Constipation	25 (37.3)	0
Anemia	24 (35.8)	5 (7.5)
Decreased appetite	22 (32.8)	3 (4.5)
Dry mouth	21 (31.3)	1 (1.5)
Alopecia	21 (31.3)	0
Nausea	19 (28.4)	3 (4.5)
Stomatitis	17 (25.4)	2 (3.0)
Dysgeusia	14 (20.9)	0
Nail disorder	14 (20.9)	0
Vomiting	13 (19.4)	3 (4.5)
Diarrhea	13 (19.4)	2 (3.0)
Abdominal pain	12 (17.9)	1 (1.5)
Dyspepsia	12 (17.9)	1 (1.5)
Arthralgia	11 (16.4)	2 (3.0)
Dry eye	11 (16.4)	0

AEs: adverse events
TEAEs: treatment-emergent adverse events

Conclusions

- Our data suggests similar activity of infigratinib in patients receiving it in the first-line setting versus the subsequent lines for aUC.
- In addition, significant activity was seen in the subset of patients with an upper tract primary – a group enriched for *FGFR3*-driven disease.
- These results suggest that infigratinib has activity in patients with aUC regardless of LOT. Additionally, patients with UTUC showed a trend for improved ORR and DCR.
- Collectively, these results support the ongoing adjuvant PROOF 302 study comparing infigratinib with placebo in patients with resected disease, assessing infigratinib in an even earlier setting in a UTUC-enriched population (NCT04197986, Figure 5).
- Limitations of our study include the relatively small proportion of patients receiving infigratinib in the first-line setting. The current data also reflects an unplanned subset analysis, and thus our findings should be interpreted as hypothesis generating.

Figure 5. PROOF 302 study design



UTUC: upper tract urothelial cancer
UBC: urothelial bladder cancer

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References

1. Sharma P, et al. Lancet Oncol 2017;18:312–22.
2. Rosenberg JE, et al. Lancet 2016;387:1909–20.
3. Balar AV, et al. Lancet 2017;389:67–76.
4. Robertson AG, et al. Cell 2017;171:540–56.
5. Ross JS, et al. Cancer 2016;122:702–11.
6. Moss TJ, et al. Eur Urol 2017;72:641–9.
7. Pal SK, et al. Cancer Discov 2018;8:812–21.
8. Pal SK, et al. Cancer 2020;126:2597–606.