cfDNA is an acceptable but insufficient means of characterizing *FGFR3* mutation in patients with metastatic urothelial cancer

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Background

- Previous studies indicate that genomic alterations in cell-free (cf)DNA are found in >90% of patients with metastatic urothelial cancer (mUC).[1]
- The ease of collection of cfDNA makes it an attractive alternative to tumor tissue-based screening, but the equivalency of cfDNA and tumor tissue for biomarker testing has yet to be defined in a prospective trial in mUC.
- We examine this in a phase Ib trial of infigratinib (BGJ398), a potent and selective FGFR1–3 inhibitor, in patients with mUC bearing *FGFR3* alterations.[2]

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.
- Genomic profiling of 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).

Table 1. Baseline characteristics

Characteristic	Total (n=67)
Age	
<65 years	29 (43.3)
≥65 years	38 (56.7)
Gender, n (%)	
Male	46 (68.7)
Female	21 (31.3)
WHO PS, n (%)	
0	21 (31.3)
1	36 (53.7)
2	10 (14.9)
Bellmunt criteria – risk group, n (%)	
0	12 (17.9)
1	27 (40.3)
2	25 (37.3)
3	3 (4.5)
Visceral disease, n (%)	
Lung	41 (61.2)
Liver	25 (37.3)
Lymph node metastases, n (%)	
Yes	19 (28.4)
No	46 (68.7)
Bony metastases, n (%)	
Yes	25 (37.3)
No	40 (59.7)

Table 2. Prior anti-cancer therapies

	Total (n=67)
Total number of lines of prior therapies, n (%)	
0	13 (19.4)
1	24 (35.8)
≥2	30 (44.8)
Total number of prior anticancer regimens, n (%)	
0	1 (1.5)
1	19 (28.4)
≥2	47 (70.1)
Best response to prior anticancer regimen, n (%)	
Complete response (confirmed)	1 (1.5)
Complete response (unconfirmed)	1 (1.5)
Partial response	10 (14.9)
Stable disease	23 (34.3)
Progressive disease	16 (23.9)
Missing	16 (23.9)

Table 3. Efficacy summary

	Total (n=67)
Response assessment, n (%)	
Complete response (CR), confirmed	1 (1.5)
Partial response (PR), confirmed	16 (23.9)
Stable disease (SD)	26 (38.8)
CR/PR, unconfirmed	11 (16.4)
Progressive disease	18 (26.9)
Unknown/not done	6 (9.0)
Confirmed objective response (CR or PR), n (%)	**17 (25.4)**
95% CI	15.5–37.5
Best overall response (CR or PR, conf/unconf), n (%)	**28 (41.8)**
95% CI	29.8–54.5
Disease control rate (CR/PR or SD), n (%)	**43 (64.2)**
95% CI	51.5–75.5
Median duration of response, months	**5.62**
Range*	2.33+ – 11.01

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

Figure 1. Progression-free survival

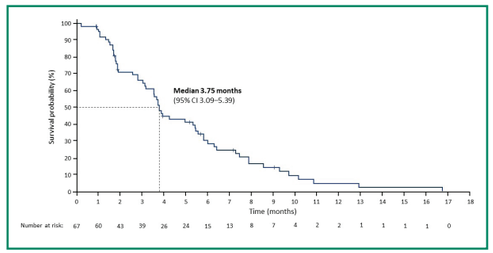


Figure 2. Overall survival

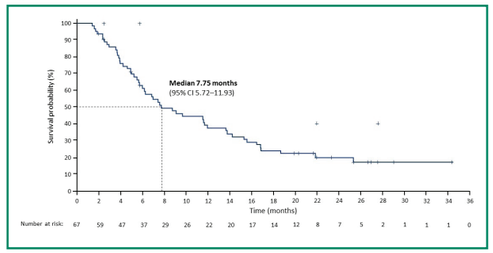


Table 4. TEAEs in >20% of patients (any grade)

n (%)	Total (n=67)
Blood creatinine increased	27 (40.3)
Fatigue	26 (38.8)
Hyperphosphatemia	26 (38.8)
Constipation	25 (37.3)
Anemia	24 (35.8)
Decreased appetite	22 (32.8)
Alopecia	21 (31.3)
Dry mouth	21 (31.3)
Nausea	19 (28.4)
Stomatitis	18 (26.9)
Nail disorder	16 (23.9)
Dysgeusia	15 (22.5)
Mucosal inflammation	15 (22.4)

Figure 3. Best change in tumor size (n=63)

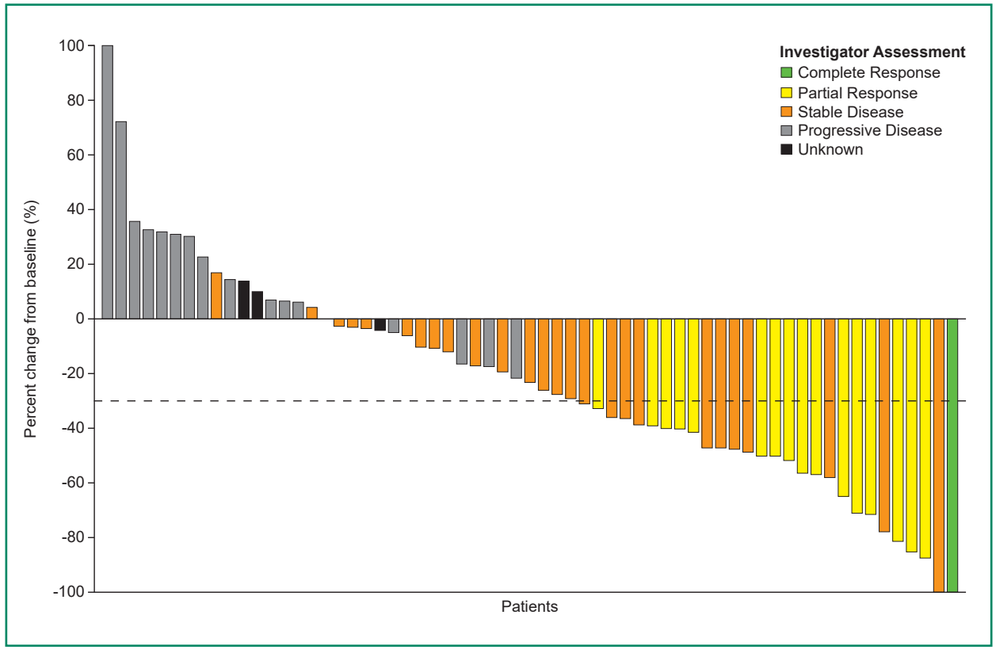
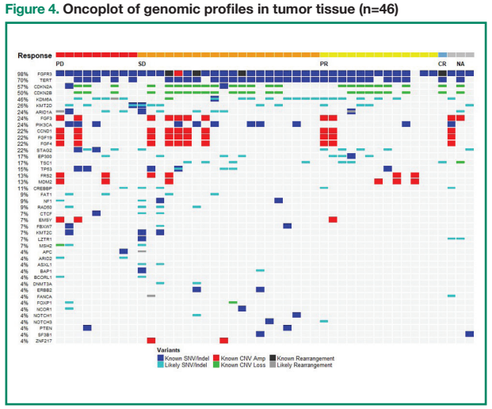
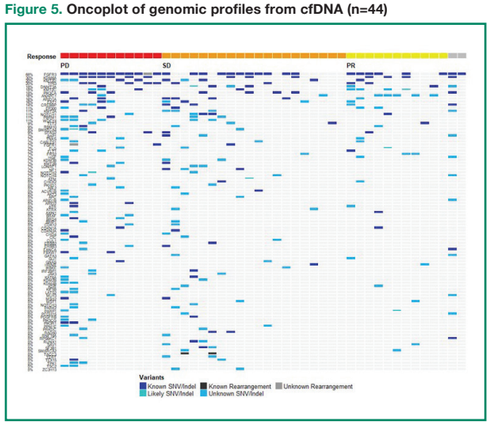


Figure 4. Oncoplot of genomic profiles in tumor tissue (n=46)



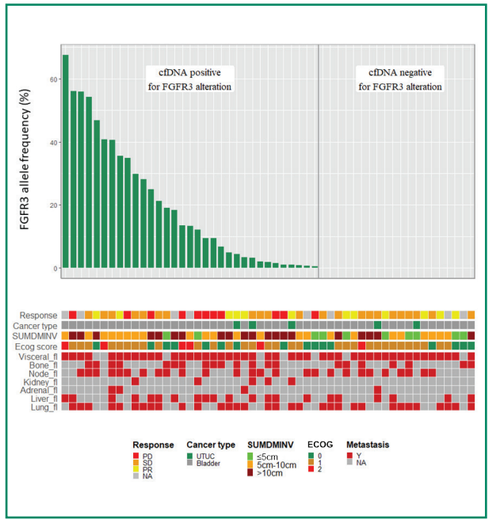
- Genomic alterations in genes involved in telomere maintenance (TERT), cell cycle (CDKN2A, CDKN2B), chromatin remodeling (KMT2D, KDM6A), transcription (ARID1A), and FGFR ligands (FGF3/4/19) were commonly observed.

Figure 5. Oncoplot of genomic profiles from cfDNA (n=44)



- *FGFR3* alterations were concordant in 30/38 (79%) of tumors with both tumor tissue and cfDNA at screening.

Figure 6. *FGFR3* allele frequency in cfDNA and clinical characteristics



- Correlative analysis of *FGFR3* allele frequency in cfDNA and clinical characteristics, including sum of longest dimension, ECOG score, and sites of tumor metastasis.

Conclusions

- The ORR of 25.4% with infigratinib compares favorably to response rates for other approved therapies in this setting, including PD-L1/PD-L1- and FGFR3-targeted therapies.
- The safety profile of infigratinib is predictable, manageable, and consistent with on-target inhibition of FGFR1–3.
- cfDNA identified *FGFR3* mutations in 79% of patients whose mutations were previously identified in tumor tissue, suggesting that cfDNA is a secondary screening option for trials assessing *FGFR3*-directed therapies.
- The higher rate of progressive disease in patients with detectable *FGFR3* mutations in cfDNA warrants further study.

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References

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2. Pal SK, et al. Cancer Discov 2018;8:812–21.