Published in final edited form as:

Clin Genitourin Cancer. 2022 February ; 20(1): 35–42. doi:10.1016/j.clgc.2021.10.004.

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Data Statement

The data supporting the findings in this study may be shared upon written request of qualified researchers for scientifically valid research proposals submitted to the author(s) of this publication. Data requests shall be considered beginning 6 months and ending 2 years after publication of the study, provided that any investigational drug discussed has been approved for at least 6 months. The scope and format of data provided to third parties will be determined by any legal, regulatory, contractual, or consent provisions or other practical considerations applicable to these data.

Previous Presentation

Presented in part at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (Virtual Meeting), May 29 to June 2, 2020.

Disclosure

Y. Lyou has received support for the present manuscript from QED Therapeutics, Inc.; grants or contracts from the American Cancer Society (Internal pilot award); and consulting fees from Pfizer and Seattle Genetics.
J. E. Rosenberg has received support for the present manuscript from QED Therapeutics, Inc.; institutional grants or contracts from QED Therapeutics, Inc. (Investigator-initiated clinical trial) and Novartis (Investigator-initiated clinical trial); consulting fees from Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, EMD-Serono, GSK, Janssen, Merck, Mirati, Lilly, Pharmacyclics, Pfizer, Roche/Genentech, Seagen, Tyra Biosciences; payments or honoraria from Medscape, MJH Lifesciences, Onclive, Research to Practice Clinical Care Options; support for attending meetings and/or travel from Bristol-Myers Squibb and Chugai; participation on a Data Safety Monitoring Board or Advisory Board for Bioclin; and stock or stock options for Merck (sold 2018).
J. Hoffman-Censits has received support for the present manuscript from QED Therapeutics, Inc.; consulting fees from Seattle Genetics (Advisory Board) and AstraZeneca (Consultant); and medical writing services from Genentech.
D. I. Quinn reports institutional payments for trials, medical writing, and article processing charges from Novartis; institutional payments for trials from Merck and Pfizer; personal payments for consulting from Astellas, AstraZeneca, Bristol-Myers Squibb, Bayer, EMD Serono, Merck, Pfizer, and Seattle Genetics; payment for lectures and presentations from Astellas, Bristol-Myers Squibb, Bayer, EMD Serono, and Merck; support for trial-related travel from Bayer AG; support for travel for lectures and presentations from Bristol-Myers Squibb and Merck; payment for participation on Data Safety Monitoring Boards from US Biotest and Eisai.
D. Petrylak reports institutional grant funding from Ada Cap (Advanced Accelerator Applications), Agensys Inc., Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Bristol-Myers Squibb, Clovis Oncology, Eisai, Eli Lilly, Endocyte, Genentech, Innocrin, MedImmune, Medivation, Merck, Mirati, Novartis, Pfizer, Progenics, Replimune, Roche, Sanofi Aventis, Seattle Genetics; consulting fees from Ada Cap (Advanced Accelerator Applications), Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Mirati, Monopteros, Pfizer, Pharmacyclics, Roche, Seattle Genetics, Urogen; and stock or stock options for Bellicum (sold 7/2020), Tyme (sold 10/2019).
M. Galsky has received grants or contracts from AstraZeneca, Bristol-Myers Squibb, Genentech, Merck; consulting fees from Astellas, AstraZeneca, Bristol-Myers Squibb, EMD Serono, Genentech, Merck, Novartis, Pfizer, Seagen; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Bristol-Myers Squibb; and participation on a Data Safety Monitoring Board or Advisory Board for Incyte.
U. Vaishampayan's institution has received grants or contracts from BMS, Exelixis, Astellas, and Merck Inc. U. Vaishampayan has received consulting fees from Exelixis, Merck, Alkermes, AAA, and BMS, and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Pfizer, Bayer, BMS, and Exelixis.
U. De Giorgi has received consulting fees from Astellas, Janssen, Sanofi, Bayer, BMS, MSD, Ipsen, Pfizer, Novartis, and Pharmamar.
S. Gupta has received support for the present manuscript, attending meetings and/or travel, payment or honoraria, and institutional grants or contracts from QED Therapeutics, Inc.
H. Burris reports institutional payments from Agios, Arch, Array BioPharma, Arvinas, AstraZeneca, Bayer, BIND Therapeutics, BioAtla, BioMed Valley Discoveries, Boehringer Ingelheim, Bristol-Myers Squibb, CicloMed, CytomX Therapeutics, eFFECTOR Therapeutics, Foundation Medicine, Gilead Sciences, GlaxoSmithKline, Harpoon Therapeutics, Incyte, Janssen, Jounce Therapeutics, Kymab, Lilly, Macrogenics, MedImmune, Merck, miRNA Therapeutics, Moderna Therapeutics, Novartis, Pfizer, Revolution Medicine, Roche/Genentech, Seattle Genetics, Takeda/Millennium, TG Therapeutics, Tesaro, Verastem, Vertex.
J. Rearden is employed by QED Therapeutics, Inc.

Infigratinib in Early-Line and Salvage Therapy for *FGFR3*-Altered Metastatic Urothelial Carcinoma

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S. Daneshmand is a member of advisory boards for Janssen, Ferring, Photocure, Taris, Spectrum, Pacific Edge, QED, Abbvie, Johnson & Johnson, Seattle Genetics, Nucleix, Aduro, BMS. He has received consulting fees from the following companies: Janssen, Ferring, Photocure, Taris, Spectrum, Pacific Edge, QED, Abbvie, Johnson & Johnson, Seattle Genetics, Nucleix, Aduro, BMS. He has received institutional grants or contracts from Photocure, Janssen, Ferring, Taris, Pacific Edge, Johnson and Johnson, BMS. He currently holds investments in Taris.
D. Bajorin has received institutional grants or contracts from Bristol-Myers Squibb, Merck and Co, the NIH and NCI; consulting fees from Merck & Co, Bristol-Myers Squibb, and DragonFly; and has participated on Data Safety Monitoring Boards or Advisory Boards for Merck and Co, Bristol-Myers Squibb, and DragonFly.
S. K. Pal has received support for the present manuscript from QED Therapeutics, Inc.
P. Grivas has received support for the present manuscript from QED Therapeutics, Inc.; and in the last 3 years (unrelated to this manuscript) has provided consulting to AstraZeneca, Astellas Pharma, Bristol-Myers Squibb, Clovis Oncology, Dyania Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, Regeneron Pharmaceuticals, QED Therapeutics, Seattle Genetics, 4D Pharma PLC, UroGen; his institution has received research funding from Bavarian Nordic, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics.

Abstract

The optimal sequencing of systemic treatments for metastatic urothelial cancer (mUC) is unknown. We assessed the efficacy of infigratinib, a fibroblast growth factor receptor (FGFR) 1 to 3 inhibitor, in 67 patients with *FGFR3*-altered mUC by line of therapy. Objective response rates were 31% (early-line setting) and 24% (≥2nd-line setting). Infigratinib has notable activity in mUC regardless of line of therapy.

Introduction: To describe the efficacy of infigratinib, a potent, selective fibroblast growth factor receptor (FGFR) 1–3 tyrosine kinase inhibitor, across lines of therapy (LOT) in patients with metastatic urothelial cancer (mUC).

Patients and Methods: Eligible patients had mUC and prior platinum-based chemotherapy, unless contraindicated, and activating *FGFR3* mutation/fusion. Patients received infigratinib 125 mg orally daily (3 weeks on/1 week off) in a single-arm, open-label study. Primary endpoint: investigator-assessed confirmed objective response rate (ORR). Disease control rate (DCR), progression-free survival (PFS), best overall response (BOR) that included unconfirmed responses, and overall survival (OS) were also assessed. Subgroup analysis of efficacy and safety outcomes by LOT was performed.

Results: Sixty-seven patients were enrolled; 13 (19.4%) received infigratinib as early-line therapy for mUC due to ineligibility to receive platinum-based chemotherapy. Overall, ORR was 25.4% (95% CI 15.5–37.5) and DCR was 64.2% (95% CI 51.5–75.5). ORR was 30.8% (95% CI 9.1–61.4) with early-line infigratinib and 24.1% (95% CI 13.5–37.6) for ≥2 LOT. DCR was 46.2% (95% CI 19.2–74.9) for early-line and 68.5% (95% CI 54.4–80.5) for ≥2 LOT. PFS and OS appeared similar in both groups. Thirteen of 59 patients with a bladder primary tumor received early-line treatment with an ORR of 30.5% (95% CI 9.1–61.4), and 46 received ≥2 LOT with an ORR of 20.3% (95% CI 9.4–33.9); BOR was 38.5% (95% CI: 13.9–68.4%) and 42.6% (95% CI: 29.2–56.8%) in the early-line and salvage settings, respectively. Eight patients with upper tract urothelial carcinoma received salvage therapy (ORR, 50.0%; DCR, 100.0%). No significant differences in toxicities between LOT were observed.

Conclusion: Infigratinib has notable activity in patients with mUC regardless of LOT. The findings support the evaluation of infigratinib across different settings in mUC.

Keywords

Bladder cancer; FGFR inhibitors; Line of therapy; Efficacy; Safety

Introduction

Over the past 5 years, treatment of metastatic urothelial cancer (mUC) has evolved and expanded rapidly leading to new lines of therapies (LOT). Platinum-based chemotherapy combination regimens using cisplatin or carboplatin,[1,2] with avelumab switch maintenance for those with a response or stable disease to chemotherapy, is the preferred first-line systemic therapy as recommended in the National Comprehensive Cancer Network (NCCN, version 4, 2021)[3] and ESMO guidelines. For patients who progress on platinum-based chemotherapy, immune checkpoint inhibitors (ICPIs) that inhibit programmed death-1 (PD-1; nivolumab and pembrolizumab) and programmed death-ligand 1 (PD-L1;

atezolizumab, durvalumab and avelumab) have been FDA-approved (although atezolizumab and durvalumab were recently withdrawn from the platinum-refractory setting), with pembrolizumab having level I evidence in this particular setting.[4–9] Fibroblast growth factor receptor (FGFR) inhibitors, such as erdafitinib and infigratinib, have shown compelling anti-tumor activity in patients with mUC bearing *FGFR2* or *FGFR3* activating mutation or fusion.[10,11] Erdafitinib has received accelerated FDA approval for patients with platinum-refractory mUC and tumors with susceptible *FGFR2* or *FGFR3* mutation or fusion.[10] Furthermore, two antibody-drug conjugates, enfortumab vedotin and sacituzumab govitecan, which target Nectin-4 and Trop-2, respectively, have been FDA-approved as single agents for those patients who are refractory to platinum-based chemotherapy and ICPIs.[12] All the recently approved agents show notable activity in patients with treatment-refractory visceral metastases, which is usually associated with a poor prognosis.[10,12]

The expansion of treatment options for patients with mUC has led to the major question of how to optimally sequence and/or combine these therapies for maximum clinical benefit and tolerability. Recent studies found that in patients with mUC, activating *FGFR3* alterations may be associated with a T-cell–depleted phenotype.[13,14] These findings suggest that tumors with *FGFR3* alterations that have a T-cell–depleted phenotype may have a lower response rate to ICPIs and may benefit from earlier use of FGFR3 inhibitors.[13,14] On the other hand, studies suggest that the anti-tumor response to ICPIs may not be significantly different between those with and without *FGFR3* alterations.[15] Therefore, it is still unclear whether patients with mUC and such alterations should receive FGFR3 inhibitors earlier in the disease course.

In order to further inform ongoing broader discussions about therapy sequence, we assessed the activity of infigratinib, a potent and selective FGFR1–3 inhibitor, across different LOT in patients with mUC and an activating *FGFR3* mutation or fusion in the NCT01004224 trial of patients with mUC.[11] We hypothesized that infigratinib would be active both prior to platinum-based chemotherapy for mUC, defined hereafter as the “early-line” setting, and in the salvage setting in mUC, although a formal comparison between LOT could not be performed due to limited sample size.

Patients and Methods

Patient Selection

A subset of 67 patients from the expansion cohort of a multicenter phase Ib clinical trial (ClinicalTrials.gov Identifier: NCT01004224)[11] who had mUC and were refractory to or ineligible for platinum-based chemotherapy were included. Tumors had to harbor activating *FGFR3* mutation or fusion with presumed functional significance, identified using a Clinical Laboratory Improvement Amendments (CLIA)-certified comprehensive genomic profiling (CGP) platform (Foundation Medicine; Cambridge, MA).[11] Patients had World Health Organization (WHO) performance status 0 to 2, normal serum calcium and phosphate levels, and adequate hepatic, renal and bone marrow function. Patients with prior therapy with FGFR or MEK inhibitors were excluded. The informed consent form and protocol were approved by institutional review boards from each participating institution. All patients enrolled provided written informed consent, and the study was conducted in accordance

with the amended Declaration of Helsinki and Good Clinical Practice and International Conference on Harmonisation Guidelines.

Treatment Regimen and Study Assessments

All patients received open-label infigratinib, administered orally once daily, in a 28-day cycle (21 days on, 7 days off) at a starting dose of 125 mg per day, with permitted dose reductions to 100 mg and 75 mg per day. Treatment was continued until disease progression, intolerable toxicity or patient withdrawal. Patients received baseline imaging of the brain, chest, abdomen and pelvis (either computed tomography or magnetic resonance imaging) and 99^{m} technetium bone scan. Patients then received serial imaging every 8 weeks until end of study. Extensive correlative studies (including serial cell-free DNA and pharmacokinetic/pharmacodynamic assessments) were performed, as previously described.[11]

Genomic Assessment of Tissue Specimens

The methods used to perform CGP analysis for this study have been previously published in detail.[11] Briefly, available formalin fixed paraffin-embedded (FFPE) patient tissue samples derived from primary tumor or metastatic site, transurethral resection of bladder tumor, cystectomy, or (nephro)ureterectomy were collected for DNA extraction using standard established protocols. The functional significance of DNA alterations in *FGFR3* was determined through interrogation of the Catalogue Of Somatic Mutations In Cancer (COSMIC) database and review of published literature. Ultimately, the activating *FGFR3* DNA alterations included mutations in exon 7 (R248C, S249C), exon 10 (G372C, A393E, Y375C), exon 15 (K652M/T, K652E/Q) or *FGFR3* fusions, including, but not limited to, the FGFR3-TACC fusion.[11]

Statistical Analysis

The primary objective of this analysis was to describe objective response rate [ORR] (partial response [PR] + complete response [CR]) in patients receiving early-line and later lines of therapy. Early-line therapy was defined as given prior to platinum-based chemotherapy for mUC. Treatment response, evaluated by the investigator, was characterized using Response Evaluation Criteria In Solid Tumors (RECIST) 1.0. Secondary objectives included assessment of disease control rate [DCR] (CR + PR + stable disease), best overall response (CR or PR, confirmed and unconfirmed), progression-free survival (PFS), and overall survival (OS) in the same groups. In a pilot exploratory analysis, the chi-square test was used to compare ORR among subgroups, and the Kaplan-Meier method with log-rank test was used to compare PFS and OS.

Results

Patient Characteristics

A total of 67 patients with *FGFR3*-altered mUC were identified for this retrospective analysis using data from a previously published phase Ib clinical trial[11] (Table 1). Median age was 67 years (range 39–85) and 46 patients (69%) were men. Thirteen patients (19%) who were platinum-based chemotherapy ineligible were treated with infigratinib in the early-line setting, with 2 patients receiving prior ICPIs and 11 patients receiving

no prior ICPIs. Fifty-four patients (81%) had received 1 or more prior LOT (salvage setting). All previously treated patients had received platinum-based chemotherapy; of these, 45 patients (68%) received cisplatin while 26 patients (39%) received carboplatin (patients could have received more than one prior line of therapy). Beyond platinum-based chemotherapy, the most commonly administered treatments prior to infigratinib were taxane-based chemotherapy (17 patients, 26%) and ICPIs (11 patients, or 17%). Other treatments included gemcitabine, doxorubicin, and methotrexate in 44 (67%), 12 (18%), and 12 (18%) of patients, respectively.

Efficacy by Line of Therapy

The ORR (confirmed CR and PR; unconfirmed responses not included) among all 67 patients treated with infigratinib was 25.4% (95% confidence interval [CI]: 15.5–37.5%) with a DCR of 64.2% (95% CI: 51.5–75.5%; Table 2). The ORR was 30.8% (95% CI: 9.1–61.4%) and 24.1% (95% CI: 13.5–37.6%) in the early-line and salvage settings, respectively. DCR was 46.2% (95% CI: 19.2–74.9%) in the early-line setting and 68.5% (95% CI: 54.4–80.5) in the salvage setting. Interestingly, as previously reported,[16] all eight patients who had an upper urinary tract primary tumor had received another prior therapy, and the ORR and DCR in these patients were 50.0% and 100.0%, respectively. In patients who had a bladder primary tumor (n = 59), the ORR was 30.5% (95% CI: 9.1–61.4%) in the early-line setting and 20.3% (95% CI: 9.4–33.9%) in the salvage setting. BOR (including unconfirmed responses) was 38.5% (95% CI: 13.9–68.4%) in the early-line setting and 42.6% (95% CI: 29.2–56.8%) in the salvage setting, respectively. No significant differences were observed in median PFS and OS times in the early-line and salvage settings among all 67 patients treated with infigratinib (Figure 1).

Treatment-Emergent Toxicities by Line of Therapy

The most common treatment-emergent adverse events (all grades) were as follows: increased serum creatinine (40.3%), fatigue (38.8%) and hyperphosphatemia (38.8%). The most common grade 3/4 treatment-emergent adverse events were as follows: hyperlipasemia (10.4%), anemia (7.5%) and hyperphosphatemia (7.5%). No substantial differences were observed among patients receiving infigratinib in the early-line vs the salvage setting (Table 3). The rate of hyperphosphatemia, which is associated with the mechanism of action of and response to FGFR inhibitors, in the early-line setting (38.5%) was similar to that in the salvage setting (38.9%; Table 3).

Discussion

Our data suggest clinically relevant activity of infigratinib in the early-line and salvage settings in patients with mUC. In addition, significant activity was seen in the subset of eight patients with upper urinary tract primary tumors, a tumor type that is enriched for *FGFR3*-driven biology,[16] all of whom were receiving infigratinib as salvage therapy. Also of note was that the rate of hyperphosphatemia, which is an “on-target” mechanism-based toxicity correlated with treatment efficacy,[17] was similar in both groups in the current study (38.9% vs 38.5%). These findings suggest that not only can infigratinib have consistent activity across different LOT but might lead one to hypothesize that the agent may

possibly have efficacy across treatment settings. To that end, infigratinib is being explored in a placebo-controlled, double-blind, randomized phase III adjuvant trial (PROOF 302, NCT04197986), including patients with radically resected locally advanced disease with high risk of recurrence who are ineligible for cisplatin-based (neo)adjuvant chemotherapy or who have residual disease after neoadjuvant therapy; however, this trial is not in the metastatic setting.

Current NCCN guidelines (version 4, 2021)[3] for mUC recommend that first-line systemic therapy should include platinum-based chemotherapy for eligible patients, followed by switch maintenance avelumab in those with response or stable disease following chemotherapy. Platinum-based chemotherapy in the first-line setting is not always feasible due to advanced age, performance status, medical comorbidities, organ function, potential toxicity and patient preference. The criteria to define platinum-ineligibility still need to be further defined.[18] Since this patient population can be variable and overall frail, it is possible that the patient phenotype and baseline features may impact safety and efficacy of infigratinib in the few platinum-ineligible patients in our trial and may introduce selection bias when we compare results between early and salvage LOT. First-line immune checkpoint inhibition can be used in platinum-unfit patients in the US based on existing FDA approval as of the time of writing this manuscript. Targeted therapy with FGFR inhibitors may potentially represent an alternate first-line option in patients who cannot tolerate chemotherapy and have tumors with *FGFR*-activating alterations, especially if they have a contraindication to ICPIs. For those patients who progress on platinum-based chemotherapy, the recommended subsequent therapies involve the use of either ICPIs (pembrolizumab has level I evidence) or an FGFR3 inhibitor if they have a targetable activating *FGFR3* mutation or fusion, or participation in a clinical trial (eg, phase III THOR trial; NCT03390504). In other malignancies, such as metastatic non-small cell lung cancer and melanoma, the earlier use of targeted therapies for eligible patients has become standard of care based on data from large phase III clinical trials, and is recommended per NCCN guidelines.[19,20] However, for mUC there have not been enough studies to determine whether the earlier use of targeted therapies prior to ICPIs or chemotherapy for eligible patients would be more beneficial or not. It is possible that, in the near future, clinical trials with other FGFR inhibitors (ie, rogaratinib, pemigatinib, vofatamab) could help answer such questions.[21–23] Moreover, our findings can contribute to this dialogue and may support evaluation of infigratinib in properly designed clinical trials in earlier LOT in mUC.

Limitations of our study include the small proportion of patients receiving infigratinib in the early-line setting, overall small sample size, and number of events for PFS and OS, which limited our ability to perform formal comparisons. All eight patients with upper urinary tract primary tumors had received prior therapy; therefore, this analysis did not include data on infigratinib in the early-line setting. “Platinum-ineligibility” is a loosely defined term broadly used to identify a group of individuals with presumed intolerance to platinum-based chemotherapy. The protocol preceded a presentation of an attempted consensus definition of “unfit” for platinum-based chemotherapy[18] and did not collect data on the reason for platinum ineligibility. The lack of randomization or stratification is another major limitation inherent to the study design, while there can be a number of selection and confounding biases that may have impacted our findings. Our results emanated from an unplanned

exploratory analysis and, consequently are hypothesis-generating and should certainly be interpreted with caution. However, these data can inform clinical trial design in earlier LOT, including in the early-line setting in patients with mUC.

Conclusions

Our results suggest that infigratinib had notable activity in patients with mUC, regardless of the LOT, and further support evaluation of this agent in earlier therapy settings in mUC.

Acknowledgments

This work was supported by QED Therapeutics Inc., an affiliate of BridgeBio. The funder compiled and analyzed the data in collaboration with the lead authors, and interpreted data in collaboration with all authors. Editorial support was provided by Miller Medical Communications which was funded by QED Therapeutics Inc. and Helsinn Healthcare SA. All authors reviewed and critically revised the manuscript and approved the final submitted version. The corresponding author had final responsibility for the decision to submit for publication.

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Clinical Practice Points

- For patients with metastatic urothelial cancer (mUC) who progress on first-line platinum-based chemotherapy, recommended systemic therapies include immune checkpoint inhibitors or fibroblast growth factor receptor (FGFR) inhibitors in patients with susceptible *FGFR2* or *FGFR3* genomic alterations, or enfortumab vedotin in cisplatin-ineligible patients as second-line therapy.
- The availability of expanded treatment options has led to questions about how to optimally sequence and/or combine these therapies, and whether patients with *FGFR2* or *FGFR3* alterations should receive an FGFR inhibitor earlier in the course of their disease.
- To inform discussions about therapy sequencing, the efficacy of infigratinib, a potent, selective FGFR1–3 tyrosine kinase inhibitor, was assessed across lines of therapy (LOT) in 67 patients with *FGFR3*-altered mUC from a multicenter phase Ib study.
- Thirteen patients were treated with infigratinib in the early-line setting, and 54 patients had received 1 or more prior LOT including platinum-based chemotherapy.
- ORR was 31% with early-line infigratinib and 24% with infigratinib after 1 or more prior LOT.
- No differences in toxicities with infigratinib were observed regardless of LOT.
- Infigratinib has notable activity in patients with mUC regardless of LOT, a finding that supports the further evaluation of infigratinib across different settings in mUC.

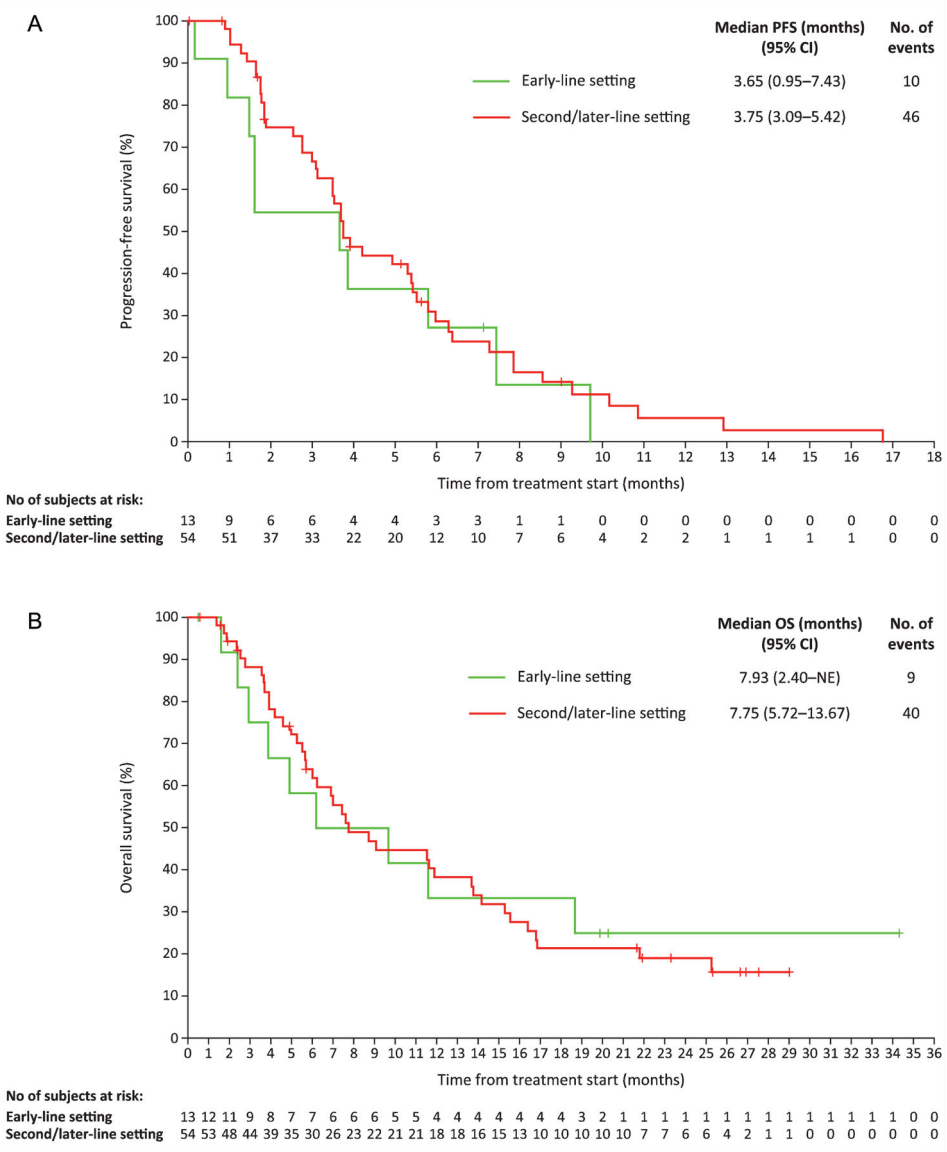

Figure 1.

Progression-free survival [PFS] (a) and overall survival [OS] (b) in patients with *FGFR3*-altered metastatic urothelial carcinoma according to line of therapy.

Note: Early-line therapy was defined as given prior to platinum-based chemotherapy for metastatic urothelial cancer.

Table 1

Baseline Patient and Disease Characteristics According to Line of Therapy

Characteristic	Infigratinib as Early-Line Therapy[a] (n = 13)	Infigratinib as Second/Later-Line Therapy (n = 54)
Age, n (%)		
<65 years	5 (38.5)	24 (44.4)
≥65 years	8 (61.5)	30 (55.6)
Sex, n (%)		
Male	7 (53.8)	39 (72.2)
Female	6 (46.2)	15 (27.8)
WHO performance status, n (%)		
0	3 (23.1)	18 (33.3)
1	7 (53.8)	29 (53.7)
2	3 (23.1)	7 (13.0)
Bellmunt criteria[b]—risk group, n (%)		
0	3 (23.1)	9 (16.7)
1	6 (46.2)	21 (38.9)
2	3 (23.1)	22 (40.7)
3	1 (7.7)	2 (3.7)
Type of cancer, n (%)		
Upper tract urothelial carcinoma	0	8 (14.8)
Urothelial carcinoma of the bladder	13 (100.0)	46 (85.2)
Visceral disease, n (%)		
Lung	9 (69.2)	32 (59.3)
Liver	4 (30.8)	21 (38.9)
Lymph node metastases, n (%)		
Yes	2 (15.4)	26 (48.1)
No	11 (84.6)	28 (51.9)
Bony metastases, n (%)		
Yes	5 (38.5)	21 (38.9)
No	8 (61.5)	33 (61.1)
Any prior immunotherapy, n (%)		

Characteristic	Infigratinib as Early-Line Therapy[a] (n = 13)	Infigratinib as Second/Later-Line Therapy (n = 54)
Yes	2 (15.4)	11 (20.4)
No	11 (84.6)	43 (79.6)

Abbreviation: WHO, World Health Organization.

[a] Early-line therapy was defined as given prior to platinum-based chemotherapy for metastatic urothelial cancer.

[b] Patients who had none of the following risk factors were in risk group 1: 1, hemoglobin level <100 g/L; 2, Eastern Cooperative Oncology Group performance status ≥1; 3, presence of liver metastases. Patients who had one, two, or three risk factors were placed in risk groups 1, 2, or 3, respectively.

Table 2

Efficacy Findings According to Line of Therapy

	Infigratinib as Early-Line Therapy[a] (n = 13)	Infigratinib as Second/Later-Line Therapy (n = 54)
Response assessment, n (%)		
Complete response (CR), confirmed	0	1 (1.9)
Partial response (PR), confirmed	4 (30.8)	12 (22.2)
Stable disease (SD)	2 (15.4)	24 (44.4)
CR/PR, unconfirmed	1 (7.7)	10 (18.5)
Progressive disease	6 (46.2)	12 (22.2)
Unknown/not done	1 (7.7)	5 (9.3)
Confirmed objective response (CR or PR), n (%)	4 (30.8)	13 (24.1)
95% CI	9.1–61.4	13.5–37.6
Best overall response (CR or PR, including unconfirmed), n (%)	5 (38.5)	23 (42.6)
95% CI	13.9–68.4	29.2–56.8
Disease control rate (CR, PR or SD), n (%)	6 (46.2)	37 (68.5)
95% CI	19.2–74.9	54.4–80.5

Abbreviation: CI, confidence interval.

[a]Early-line therapy was defined as given prior to platinum-based chemotherapy for metastatic urothelial cancer.

Table 3

Most Common All-Cause Treatment-Emergent Adverse Events According to Line of Therapy—All Grades (>20% of Total Patients)

	Infigratinib as Early-Line Therapy[a] (n = 13)	Infigratinib as Second/Later-Line Therapy (n = 54)
Any treatment-emergent adverse event, n (%)	13 (100.0)	53 (98.1)
Serum creatinine increased	4 (30.8)	23 (42.6)
Fatigue	7 (53.8)	19 (35.2)
Hyperphosphatemia	5 (38.5)	21 (38.9)
Constipation	2 (15.4)	23 (42.6)
Anemia	4 (30.8)	20 (37.0)
Decreased appetite	6 (46.2)	16 (29.6)
Alopecia	3 (23.1)	18 (33.3)
Dry mouth	4 (30.8)	17 (31.5)
Nausea	5 (38.5)	14 (25.9)
Stomatitis	4 (30.8)	14 (25.9)
Nail disorder	6 (46.2)	10 (18.5)
Dysgeusia	3 (23.1)	12 (22.2)
Mucosal inflammation	3 (23.1)	12 (22.2)

[a]Early-line therapy was defined as given prior to platinum-based chemotherapy for metastatic urothelial cancer.