Advanced urothelial carcinoma (UC) is an incurable disease for many patients. 

Methods

Patients

• Eligible patients had a history of activating FGFR2 mutations and had received prior platinum-based chemotherapy, unless contraindicated.

• Patients were pre-screened for FGFR2 alterations using a commercially available comprehensive genomic profiling (CGP) platform (Foundation Medicine; Cambridge, MA) from a phase Ib clinical trial (Figure 1).

• All patients provided separate consent to receive FGFR2 alterations (unless genetic testing was already done) and consent for therapy with infigratinib.

Efficacy was assessed by ORR and DCR based on RECIST 1.0 criteria.

• Patients with at least one evaluable PK parameter (AUC or Cmax) and serum phosphorus level at the same visit were included in the analysis.

• Patients were categorized as having hyperphosphatemia or not at the visit where a PK parameter was available.

Results

• A total of 77 patients with activating FGFR2 mutations were enrolled, of which 44 had hyperphosphatemia and 19 did not (Table 1).

• Blood samples were collected pre-dose and on 24 hour post-dose on days 1, 15, and 28. Samples were processed, and plasma was frozen at −80 °C until analysis, as described previously.

• Infigratinib plasma concentrations were measured using a validated liquid chromatography-tandem mass spectrometry method with a 1.0 ng/mL lower limit of quantification.

• PK parameters were calculated using noncompartmental methods with Phoenix (Pharsight, Mountain View, CA).

• Serum phosphorus was measured as part of the standard clinical chemistry panel for safety monitoring.

• Clinical chemistry was assessed at baseline, cycle 1 days 1, 2, 15 and 22, and on subsequent cycles on day 1 and day 15.

• Patients with at least one valid infigratinib concentration and a corresponding phosphorus level at the same visit were included in the analysis.

• Infigratinib concentration–phosphorus relationship was defined as a corresponding phosphorus value on the same visit and triplicate were included in the analysis.

• The hyperphosphatemia group had a higher rate of dose interruption and managed with diet and phosphate binders.

• The pre-dose concentration of infigratinib at steady state in patients from the phase I dose-escalation cohorts and dose-escalation cohort were included in this analysis (5–150 qd and 125–320 qd 3 weeks on/off cycle).

Background

• Platinum-based chemotherapy remains a cornerstone of treatment, with many patients (15%–40%) responding to newer immune checkpoint inhibitors.1–3

• Active mechanisms of resistance, which are associated with approximately 20% of patients with lower tract urothelial cancer, and 40–75% of patients with upper tract disease4 are a potential new target for novel therapies.

• Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor with significant clinical activity in AUC45-541 FGFR2–3–4–5–6

• A common adverse event with FGFR inhibitors is hyperphosphatemia, which is a clear mechanism associated with FGFR inhibition.

• We explored whether hyperphosphatemia could serve as a surrogate biomarker for infigratinib treatment response in patients with UC5 from a previously reported6–7 study.

Efficacy

• Patients with at least one evaluable PK parameter (AUC or Cmax) and serum phosphorus level at the same visit were included in the analysis.

• Patients were categorized as having hyperphosphatemia or not at the visit where a PK parameter was available.

• Infigratinib concentration–phosphorus relationship is defined as a corresponding phosphorus value on the same visit and triplicate were included in the analysis.

• Infigratinib concentration–phosphorus relationship was calculated by comparing patients with hyperphosphatemia defined as phosphorus ≥ 5 mg/dL and no dose interruption.

• Median and range of duration of response for patients with confirmed response (complete response [CR] or partial response [PR]) were also summarized.

• ORR and OS in patients with/without hyperphosphatemia and in the overall population were described by Kaplan-Meier (KM) plot.

• Landmark Analysis using a KM approach was also performed for the efficacy endpoints (ORR/OS) by comparing patients with/without hyperphosphatemia. This process enabled using the above-mentioned statistical analysis methods after excluding patients who discontinued infigratinib treatment in <50 days.

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Discussion

• A higher median exposure (AUC and Cmax

• Median OS (71.3 months vs 57.3 months) was similar between the two groups.

• Efficacy was assessed by ORR and DCR based on RECIST 1.0 criteria.

• Hyperphosphatemia was defined as serum phosphorus levels exceeding 5 mg/dL, which was consistent with the timepoints for dose achievement of the study.

• Follow-up serial imaging included CT of the chest, abdomen and pelvis, bone-magnetic resonance imaging [MRI] and thoracic bone scan.

• The pre-dose concentration of infigratinib at steady state in patients from the phase I dose-escalation cohorts and dose-escalation cohort were included in this analysis (5–150 qd and 125–320 qd 3 weeks on/off cycle).

• A higher median exposure (AUC and Cmax

• Medians were calculated (5% CI: 57.3–136.7) vs 1.13 months (5% CI: 2.53–13.55).

• Median DOR: 10.5 vs 7.5 months.

• Infigratinib was considered a well-tolerated agent with a low grade toxicity profile (Table 1).

• Phosphorus level numeric result in standard unit (mmol/L)

• Data in patients with hyperphosphatemia were: ORR: 37.5% (95% CI 22.7%–54.2%) vs 11.1% (95% CI 1.4%–34.7%).

• Safety

• Grade ≥ 2 adverse events (AEs) occurred at similar levels with 7% (95% CI 3.1%–11.1%) vs 15% (95% CI 5.2%–24.8%).

• The median phosphate level was 21.98 (95% CI 15.04–24.07) mg/dL in the hyperphosphatemia group and 11.25 (95% CI 9.64–12.9) mg/dL in the no hyperphosphatemia group, respectively.

• The hyperphosphatemia group had a higher rate of dose interruption and managed with diet and phosphate binders.

• The infigratinib group had a lower dose discontinuation rate than the non-hyperphosphatemia group due to treatment-related AEs (3.6% vs 38.5%).

• The pre-dose concentration of infigratinib at steady state in patients from dose-escalation cohorts was 48.7 ± 20.8 ng/mL/mg.

• The infigratinib group had a lower dose discontinuation rate than the non-hyperphosphatemia group due to treatment-related AEs (3.6% vs 38.5%).

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Conclusions

• Hyperphosphatemia is a well-described adverse effect and pharmacokinetic biomarker for FGFR2 inhibition, with a dose-dependent effect.

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