# Relationship between hyperphosphatemia with infigratinib (BGJ398) and efficacy in *FGFR3*-altered advanced/metastatic urothelial carcinoma

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## Background

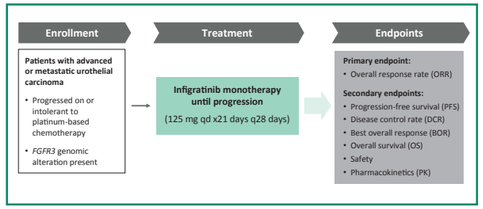
- Advanced urothelial carcinoma (aUC) is an incurable disease for many patients.
- Platinum-based chemotherapy remains a cornerstone of therapy; a minority of patients (15–40%) respond to newer immune checkpoint inhibitors.[1–3]
- Activating mutations of *FGFR3*, which are altered in approximately 20% of patients with lower tract urothelial cancer, and in 40–75% of patients with upper tract disease,[4–6] are a potential new target for novel therapies.
- Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor with significant clinical activity in aUC bearing *FGFR3* alterations.[7]
- A common adverse event with FGFR inhibitors is hyperphosphatemia, which is a class effect associated with FGFR1 inhibition.
- We explored whether hyperphosphatemia could serve as a surrogate biomarker for infigratinib treatment response in patients with aUC from a previously reported dataset.[7]

## Methods

### *Patients*

- Eligible patients had aUC with activating *FGFR3* mutations/fusions and had received prior platinum-based chemotherapy, unless contraindicated.
- Patients were pre-screened for *FGFR3* alterations using a commercially available comprehensive genomics profiling (CGP) platform (Foundation Medicine; Cambridge, MA) from a phase Ib clinical trial (Figure 1).[7]
- The protocol and consent for this international multicenter study was approved by each institution's institutional review board.
- All patients provided separate consent to screen for *FGFR3* alterations (unless genomic testing was already done) and for therapy with infigratinib.

**Figure 1. Study design**




### *Treatment*

- Patients received oral infigratinib 125 mg orally once daily on days 1–21 every 28 days until disease progression or unacceptable toxicity.
- Dose reductions to 100 mg/day followed by 75 mg/day were permitted, with further dose reductions allowed on an individual basis.
- All patients received hyperphosphatemia prophylaxis with the oral phosphate binder sevelamer hydrochloride.

### *Evaluations*

- Patients underwent baseline imaging, including CT of the chest, abdomen and pelvis, brain magnetic resonance imaging or CT, and technetium bone scan.
- Follow-up serial imaging included CT of the chest, abdomen and pelvis (along with bone scan if indicated) at 8-week intervals thereafter.
- Efficacy was assessed by ORR and DCR based on RECIST 1.0 criteria.
- Hyperphosphatemia was defined as serum phosphorus levels exceeding 5.5 mg/dL, which was consistent with the threshold for dose reduction or interruption in this study protocol.

### *Genomic assessment of tissue and blood specimens*

- Methods for CGP used in this study have been published previously.[8]

### *Pharmacokinetic/pharmacodynamic assessments*

- PK and pharmacodynamic (PD) data from the phase 1 dose-escalation cohorts and dose-expansion cohort were included in this analysis (doses: 5–150 mg QD and 125 mg 3 weeks on/1 week off).
- Blood samples were collected pre-dose and up to 24 hours post-dose on days 1,15 & 28 of cycle 1. Samples were processed, and plasma was frozen at ≤ –60°C until analysis, as described previously.[9]
- 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, 8, 15 and 22 and on subsequent cycles on day 1 and day 15.

### *Infigratinib pharmacokinetics–hyperphosphatemia relationship*

- Patients with at least one evaluable PK parameter (AUC or $C_{max}$) 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*

- Patients with at least one valid infigratinib concentration and a corresponding phosphorus value on the same visit and timepoints were included in the analysis.

### *Statistical analysis*

- ORR (partial response [PR] + complete response [CR]) and DCR (CR + PR + stable disease [SD]) and BOR were characterized in all patients (RECIST 1.0 criteria).
- ORR/DCR/BOR and the 95% confidence interval based on exact binomial method were calculated by comparing patients with hyperphosphatemia (defined as phosphate > 5.5 mg/dL post-dose) vs non-hyperphosphatemia.
- Median and range of duration of response for patients with confirmed responses (confirmed CR or PR) were also summarized.
- PFS and OS in patients with/without hyperphosphatemia and in the overall population were described by Kaplan-Meier (KM) plot.
- Landmark Analyses using a 1-month threshold were also performed for the efficacy endpoints (ORR/PFS/OS) by comparing patients with/without hyperphosphatemia. This process entailed using the above-mentioned statistical analysis methods after excluding patients who discontinued infigratinib treatment in <30 days.

## Results

### *Patient characteristics*

- A total of 67 patients with activating *FGFR3* mutations were enrolled, of which 48 had hyperphosphatemia and 19 did not (Table 1).

### *Efficacy*

- Efficacy findings in patients with/without hyperphosphatemia were:
  - ORR: 33.3% (95% CI 20.4–48.4) vs 5.3% (95% CI 0.1–26.0), p=0.027.
  - Median PFS: 4.93 months (95% CI 3.65–5.98) vs 1.84 months (95% CI 1.28–3.48).
  - Median OS: 8.74 months (95% CI 5.72–13.67) vs 7.62 months (95% CI 2.53–15.57).
  - Median DOR: 5.0 vs 3.7 months.
- A landmark analysis at the 1-month mark (excluding patients with <30 days of infigratinib treatment) showed that the differences in efficacy outcomes were still observed in the hyperphosphatemia vs no hyperphosphatemia groups:
  - ORR: 37.5% (95% CI 22.7%–54.2%) vs 11.1% (95% CI 1.4%–34.7%).
  - Median PFS: 5.42 months (95% CI 3.52–6.37) vs 3.68 months (95% CI 1.84–4.93).
  - Median OS: 9.66 months (95% CI 6.90–15.28) vs 6.24 months (95% CI 3.94–16.82).

**Figure 2. Progression-free survival and overall survival**

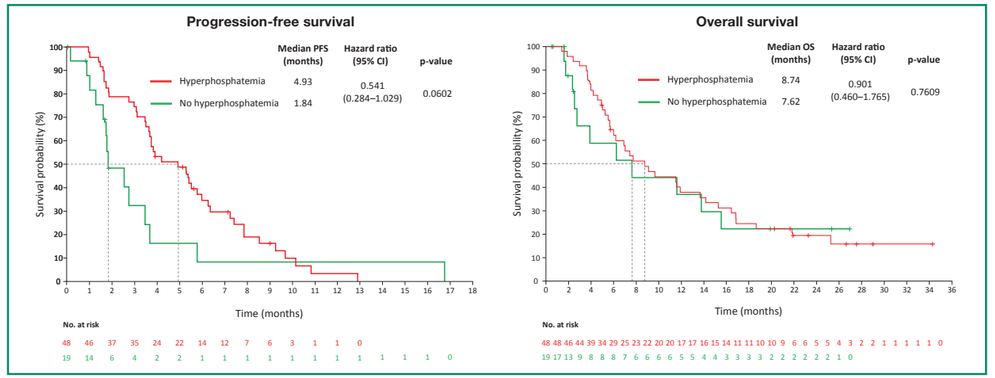



**Table 1. Patient characteristics**

| Characteristic | Hyperphosphatemia (n=48) | No hyperphosphatemia (n=19) | Total (n=67) |
|---|---|---|---|
| **Age** | | | |
| <65 years | 18 (37.5) | 11 (57.9) | 29 (43.4) |
| ≥65 years | 30 (62.5) | 8 (42.1) | 38 (56.7) |
| **Gender, n (%)** | | | |
| Male | 35 (72.9) | 11 (57.9) | 46 (68.7) |
| Female | 13 (27.1) | 8 (42.1) | 21 (31.3) |
| **WHO PS, n (%)** | | | |
| 0 | 13 (27.1) | 8 (42.1) | 21 (31.3) |
| 1 | 30 (62.5) | 6 (31.6) | 36 (53.7) |
| 2 | 5 (10.4) | 5 (26.3) | 10 (14.9) |
| **Bellmunt Criteria[a] – risk group, n (%)** | | | |
| 0 | 7 (14.6) | 5 (26.3) | 12 (17.9) |
| 1 | 21 (43.8) | 6 (31.6) | 27 (40.3) |
| 2 | 18 (37.5) | 7 (36.8) | 25 (37.3) |
| 3 | 2 (4.2) | 1 (5.3) | 3 (4.5) |
| **Visceral disease, n (%)** | | | |
| Lung | 30 (62.5) | 11 (57.9) | 41 (61.2) |
| Liver | 17 (35.4) | 8 (42.1) | 25 (37.3) |
| **Lymph node metastases, n (%)** | | | |
| Yes | 20 (41.7) | 8 (42.1) | 28 (41.8) |
| No | 28 (58.3) | 11 (57.9) | 39 (58.2) |
| **Bony metastases, n (%)** | | | |
| Yes | 16 (33.3) | 10 (52.6) | 26 (38.8) |
| No | 32 (66.7) | 9 (47.4) | 41 (61.2) |
| **Any prior immunotherapy** | | | |
| Yes | 8 (16.7) | 5 (26.3) | 13 (19.4) |
| No | 40 (83.3) | 14 (73.7) | 54 (80.6) |

[a]Bellmunt Criteria include ECOG>0, liver metastases, and hemoglobin <10 g/dL at baseline.

### *Safety*

- Grade 3/4 adverse events (AEs) occurred at similar levels with rates of 70.8% (n=34) and 63.2% (n=12) in the hyperphosphatemia and non-hyperphosphatemia groups, respectively.
- The hyperphosphatemia group had a higher rate of dose interruption and adjustments at 89% (n=43) vs 52.6% (n=10) in the non-hyperphosphatemia group.
- The hyperphosphatemia group had a lower discontinuation rate than the non-hyperphosphatemia group due to treatment-related AEs: 6.3% (n=3) vs 36.8% (n=7).

**Table 2. Efficacy findings**

| Characteristic | Hyperphosphatemia (n=48) | No hyperphosphatemia (n=19) | Total (n=67) |
|---|---|---|---|
| **Response assessment, n (%)** | | | |
| Complete response (CR), confirmed | 1 (2.1) | 0 | 1 (1.5) |
| Partial response (PR), confirmed | 15 (31.3) | 1 (5.3) | 16 (23.9) |
| Stable disease (SD) | 20 (41.7) | 6 (31.6) | 26 (38.8) |
| CR/PR, unconfirmed | 8 (16.7) | 3 (15.8) | 11 (16.4) |
| Progressive disease | 11 (22.9) | 7 (36.8) | 18 (26.9) |
| Unknown/not done | 1 (2.1) | 5 (26.3) | 6 (9) |
| **Confirmed objective response (CR or PR), n (%)** | 16 (33.3) | 1 (5.3) | 17 (25.4) |
| 95% CI | 20.4–48.4 | 0.1–26.0 | 15.5–37.5 |
| **Best overall response (CR or PR, conf/unconf), n (%)** | 24 (50.0) | 4 (21.1) | 28 (41.8) |
| 95% CI | 35.2–64.8 | 6.1–45.6 | 29.8–54.5 |
| **Disease control rate (CR/PR or SD), n (%)** | 36 (75.0) | 7 (36.8) | 43 (64.2) |
| 95% CI | 60.4–86.4 | 16.3–61.6 | 51.5–75.5 |

### *Relationship between hyperphosphatemia and drug exposure*

- Patients with hyperphosphatemia showed a similar median $AUC_{0-24}$ and $C_{max}$ value for infigratinib on cycle 1 day 1 relative to patients without hyperphosphatemia (Figure 3).
- On cycle 1 day 15, patients with hyperphosphatemia showed a higher median dose normalized exposure of infigratinib, with $AUC_{0-24}$ (27.5 ng*h/mL/mg) and $C_{max}$ (1.76 ng/mL/mg) compared to an $AUC_{0-24}$ (10.5 ng*h/mL/mg ) and $C_{max}$ (1.03 ng/mL/mg) in patients without hyperphosphatemia. Similar differences were observed on cycle 1 day 28.
- The pre-dose concentration of infigratinib at steady state in patients from dose-expansion cohort 4 showed a trend towards increasing phosphorus levels with increasing infigratinib concentration (Figure 4). This result was consistent with the trend observed in the dose-escalation and dose-expansion cohorts 1–3.

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**Figure 3. Bar graphs/scatter plots of AUC and $C_{max}$ (Y-axis)**

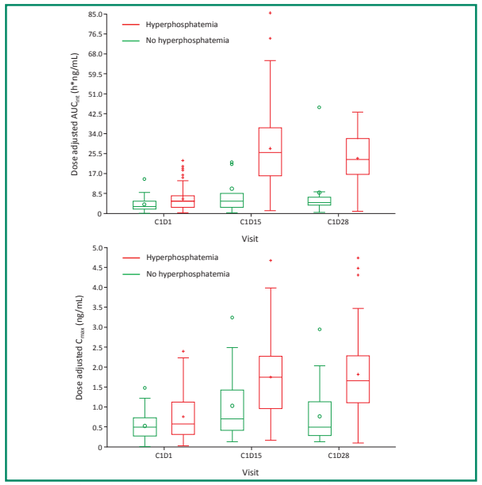


Figure shows data from patients in dose-escalation and dose-expansion cohorts 1–3.

**Figure 4. X-Y plot of pre-dose drug concentration (X) versus phosphorus level (Y)**

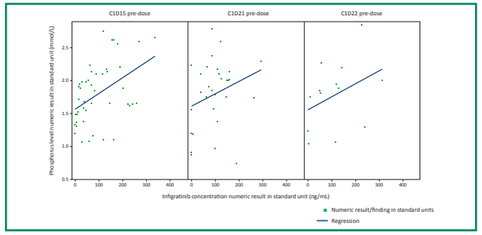


Figure shows data from dose-expansion cohort 4.

## Conclusions

- Hyperphosphatemia is a well-described class effect and pharmacodynamic biomarker for FGFR inhibitors, including infigratinib, and is generally reversible/easily managed with diet and phosphate binders.
- Mechanistically, it is a consequence of FGFR1 inhibition, which is inhibited by infigratinib at single nanomolar (nM) potency in biochemical assays. Inhibition of FGFR1 by infigratinib is similar to inhibition of FGFR3, where single nM potency is also observed.
- Our data support prior observations with FGFR inhibitors, suggesting that patients with aUC who are receiving infigratinib and develop hyperphosphatemia are more likely to show a response.
- Importantly, the correlative relationship between hyperphosphatemia on efficacy showed similar trends in the overall and landmark analysis.
- A higher median exposure (AUC and $C_{max}$) of infigratinib was observed in patients with hyperphosphatemia compared with those without hyperphosphatemia.
- This study suggests that hyperphosphatemia caused by FGFR inhibitors can be a surrogate biomarker for treatment response.

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