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Activity of the FGFR1–3 inhibitor infigratinib in patients with upper tract urothelial carcinoma and urothelial carcinoma of the bladder: Latest efficacy findings and comprehensive genomic profiling/cell-free DNA data

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Introduction & Objectives: Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor with significant activity in patients with advanced or metastatic urothelial carcinoma (mUC) bearing *FGFR3* alterations [Pal et al 2018]. Given the distinct biologic characteristics of upper tract UC (UTUC) and urothelial carcinoma of the bladder (UCB), we sought to determine if infigratinib had varying activity in these settings.

Materials & 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) and disease control rate (DCR) were characterized in UCB and UTUC patients. Comprehensive genomic profiling was performed on FFPE tissues in a CLIA-certified lab (Foundation Medicine; Cambridge, MA). Blood was collected for cell-free (cf)DNA analysis using a 600-gene panel on an Illumina HiSeq 2500 sequencer.

Results: 67 patients were enrolled; the majority (70.1%) had received ≥2 prior antineoplastic therapies. ORR was 25.4% and DCR was 64.2%. In the 8 patients with UTUC, 1 complete response (CR) and 3 partial responses (PRs) were observed (ORR 50%); the remainder had a best response of stable disease (SD; DCR 100%). One of the UTUC patients was a 61-year old male with a tumor bearing a *FGFR3-TACC3* fusion. Following receipt of infigratinib, he experienced a CR per central assessment on Day 55, which was later confirmed on Day 120. The CR continued until progressive disease (PD) developed on Day 260. UTUC patients were predominantly 2nd line (62.5%), with only 2 (25%) showing response to previous treatment. In patients with UCB, 13 PRs were observed (ORR 22%), and 22 patients had a best response of SD (DCR 59.3%). Notable

differences in genomic alterations between cohorts included a higher frequency of *FGFR3-TACC3* fusions (12.5% vs 5.8%) and *FGFR3 R248C* mutations (50% vs 11.5%), and a lower frequency of *FGFR3 S249C* mutations (25% vs 59.6%) in UTUC vs UCB. Consistent with previous reports [Sfakianos et al 2016], UTUC patients had a differential frequency of alterations in *HRAS*, *CDKN2B* and *ARID1A*. Sufficient cfDNA yield was obtained in UTUC and UCB patients; a comprehensive comparison of these data will be presented.

Conclusions: Differences in cumulative genomic profile were observed between UCB and UTUC in this *FGFR3*-restricted experience, underscoring the distinct biology of these diseases. Results with infigratinib in UTUC support a planned phase III adjuvant study predominantly in this population.