**Table S1.** Progression-free survival per investigator review using RANO criteria and the Kaplan-Meier method (Full analysis set)

|  | **Infigratinib****(N=26)** |
| --- | --- |
| Progression-free survival events, n (%) |  24 (92.3) |
| Progression | 20 (76.9) |
| Death |  4 (15.4) |
| Censored, n (%) |  2 (7.7) |
| Progression-free survival rate estimates, % [95% CI] |  |
| 6 months | 16.0 [5.0, 32.5] |
| 12 months | 16.0 [5.0, 32.5] |
| 18 months | 8.0 [1.4, 22.5] |
| 24 months | 4.0 [0.3; 17.0] |
| Progression-free survival, months [95% CI] |  |
| Median |  1.7 [1.1, 2.8] |

*Abbreviations:* CI, confidence interval; RANO, Response Assessment in Neuro-Oncology.

**Table S2.** Overall survival using the Kaplan-Meier method (Full analysis set)

|  | **Infigratinib****(N=26)** |
| --- | --- |
| Deaths, n (%) |  23 (88.5) |
| Censored, n (%) |  3 (11.5) |
| Overall survival rate, % [95% CI] |  |
| 6 months |  53.8 [33.3, 70.6] |
| 12 months |  29.6 [13.5, 47.7] |
| 18 months |  25.4 [10.6, 43.3] |
| 24 months |  10.2 [1.9; 26.9] |
| Overall survival, months  |  |
| Median [95% CI] |  6.7 [4.2, 11.7] |

*Abbreviation:* CI, confidence interval.

**Table S3.** Details of biomarker testing (*n* = 16)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Patient number | Local *FGFR* genotype | Local laboratory name | Local laboratory method | Quest *FGFR* genotype (by PCR) | Foundation Medicine *FGFR* genotype (by NGS) |
| 2 | N/A | N/A | N/A | *FGFR3* amplification | No *FGFR* alterations |
| 5 | N/A | N/A | N/A | N/A | *FGFR1-ARHGEF18* fusion |
| 8 | *FGFR3* amplification | Utrecht University | RT-PCR | N/A | No *FGFR* alterations |
| 10 | N/A | N/A | N/A | N/A | *FGFR3-TACC3* fusion |
| 11 | N/A | N/A | N/A | *FGFR*3 amplification | No *FGFR* alterations |
| 13 | *FGFR3-TACC3* fusion and *FGFR1* fusion | University of Washington | IHC | N/A | *FGFR3-TACC3* fusion |
| 14 | N/A | N/A | N/A | N/A | *FGFR3-TACC3* fusion |
| 15 | *FGFR3* amplification and *FGFR3-TACC3* fusion | Tulane University | Other, not specified | N/A | No *FGFR* alterations |
| 16 | N/A | N/A | N/A | *FGFR*3 amplification | *FGFR3-TACC3* fusion |
| 17 | *FGFR3* amplification and *FGFR3-TACC3* fusion | Brigham and Women's Hospital | Other, not specified  | N/A | *FGFR3* amplification (equivocal) and *FGFR3* rearrangement (N/A partner) |
| 19 | N/A | N/A | N/A | N/A | *FGFR3-TACC3* fusion |
| 20 | N/A | N/A | N/A | N/A | *FGFR3-TACC3* fusion |
| 22 | N/A | N/A | N/A | *FGFR3* amplification | No FGFR alterations |
| 23 | N/A | N/A | N/A | N/A | *FGFR3* K650E |
| 25 | N/A | N/A | N/A | N/A | *FGFR1* K656E |
| 26 | N/A | N/A | N/A | N/A | *FGFR3-TACC3* fusion |

*Abbreviations:* FGFR, fibroblast growth factor receptor; IHC, immunohistochemistry; N/A, not applicable: NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction.

*FGFR* abnormalities in red are those which were used to fulfil eligibility (except case 16 with amplification detected during screening and fusion detected on post-hoc analysis of pre-treatment tissue) and are shown in the Oncoplot (Supplementary Fig. S3).

Molecular testing methodology and the types of *FGFR* alterations allowed for eligibility evolved over the lifespan of the clinical trial. First, the understanding of FGFR biology in brain and other solid tumors advanced, such as the recognition that amplification was poorly predictive of benefit from infigratinib and a poor surrogate for fusion (resulting in a protocol amendment excluding amplification alone as sufficient for eligibility as described in the manuscript Methods; see also Table A12 in report by Nogova et al. of a concurrently conducted multi-histology study that followed an analogous process of amendments as the science and available assays evolved1). Second, use of next-generation sequencing (NGS) assays that could detect various types of *FGFR* alterations, particularly *FGFR* fusions, became more widespread.

Therefore, the protocol allowed for 3 testing options to identify allowable *FGFR* alterations for eligibility: 1) a “local” assay performed by an academic institution, such as that of the participating investigator; 2) a commercial assay, such as NGS (e.g. FoundationOne) ordered as part of routine care; or 3) a “central” laboratory option if neither a local institutional assay nor commercial assay were performed as part of routine care. Initially, a quantitative polymerase chain reaction (PCR) assay (Quest Diagnostics) for *FGFR* amplification and *FGFR3* point mutations, but not fusions, was the centrally available assay for screening patients whose *FGFR* status were otherwise unknown. As the technology advanced, and it emerged that amplification alone was neither a surrogate for fusion nor likely to predict response to infigratinib, the qPCR assay was abandoned in favor of the FoundationOne NGS test that could identify amplification, point mutations, and fusions. In addition, the protocol requested that additional archival tumor tissue (which could have been from a different surgical procedure in location or date than the tissue assayed for eligibility), if available, be submitted for post-hoc FoundationOne NGS to support exploratory analysis of biomarkers associated with response. Although such post-hoc analyses were exploratory rather than pre-specified or explicitly mandated to confirm (or refute) prospectively detected *FGFR* alterations that fulfilled eligibility criteria in real time, they represent an opportunity to compare *FGFR* results among different assays.

To that end, there were a total of 16 cases (Supplementary Table S3 above, Fig. S1 and Fig. S3 below) with both response assessments and informative NGS analysis (either during screening or post-hoc); among these, 8 were also subjected to another assay (either locally at an academic institution with a variety of methods, or centrally by Quest using qPCR) during screening. Results were discordant in 6 of the 8 cases.

In 4 cases (2, 11, 16, 22), , the FoundationOne assay did not report the *FGFR3* amplification despite *FGFR3* amplification detection by the Quest qPCR assay as part of molecular screening for trial eligibility. (Of note, the FoundationOne assay detected an *FGFR3-TACC3* fusion, but no concomitant amplification, in one of these cases (16) that was identified by qPCR as *FGFR3*-amplified; thus, presence of fusion does not appear to depend on concomitant detection of amplification; see also Supplementary Fig. S2).

In the other 4 cases, assays performed at local academic institutions (University of Washington, Tulane University, Brigham and Women’s Hospital, and Utrecht University; *n* = 1 each) were used for molecular screening and trial eligibility. In 2 (13 and 17) of these 4, *FGFR3* fusions were detected by both the local institution and NGS; in the other 2 (8 and 15), *FGFR3* amplification and/or fusion was reported by the local institution but not identified by NGS.

Differences in assay methodology (qPCR vs RT-PCR vs NGS), discrepancies in the amplification threshold, tumor heterogeneity, and testing of different tissue samples (from different surgical dates or tumor foci) are factors that likely contribute to the observed discordance in *FGFR* alterations among assays.

Perhaps most importantly, it is now clear the presence of *FGFR* amplification alone neither predicts response to infigratinib, nor is a good surrogate marker for tumors that are likely to harbor an *FGFR* fusion gene. Therefore, use of local (or commercial) assays capable of detecting only gene amplification and not fusion/rearrangements (or activating point mutations, see Supplementary Fig. S2, S9 and S10) is not a recommended screening strategy for biomarkers predictive of response to infigratinib, both because of discordance in identifying amplification among assays but more so because a test for amplification alone is not an effective screening method for capturing of cases of fusion or point mutation, and because amplification alone does not enrich for response to infigratinib.

1. Nogova L, Sequist LV, Perez Garcia JM, et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. J Clin Oncol 2017;**35**(2):157-65.

**Table S4.** Overview of treatment-emergent adverse events (TEAE) [Safety set]

| **Parameter, n (%)** | **Infigratinib (N=26)** |
| --- | --- |
| Any TEAE | 26 (100) |
| Grade 3 or 4 TEAE | 14 (53.8)a |
| Serious TEAE | 9 (34.6) |
| Treatment-related TEAE | 22 (84.6) |
| Serious treatment-related TEAE | 1 (3.8) |
| TEAE leading to treatment discontinuation | 1 (3.8) |
| TEAE leading to dose interruption/dose adjustment | 14 (53.8) |
| TEAE leading to concomitant medications or other therapy | 24 (92.3) |

aNo grade 4 treatment-emergent adverse events were reported.

**Table S5.** Details of 2 additional patients with recurrent glioblastoma and *FGFR* alterations treated with infigratinib who were enrolled in a separate phase II study (NCT02160041)\*

|  |  |  |
| --- | --- | --- |
| **Variable** | **Patient #1** | **Patient #2** |
| Age, years | 45 | 50 |
| Sex | Female | Female |
| WHO performance status | 1 | 1 |
| Prior treatment (time on treatment) | Temozolomide (14 months)Radiotherapy | Temozolomide/bevacizumab (9 months)Radiotherapy |
| *FGFR* status | *FGFR3* amplification and FGFR3 fusion | *FGFR3* fusion |
| Duration of exposure to infigratinib, days | 561 | 40 |
| Overall response | Partial response | Stable disease |
| Tumor response | –64% | +18% |
| Progression-free survival, days | 540 | 59 |
| Overall survival, days | 650 | 116 |

*Abbreviations:* FGFR, fibroblast growth factor receptor; WHO, World Health Organization.

\*Note: These were the only patients with glioblastoma enrolled into the study.