A Phase 2, open-label, single-arm study of lirafugratinib in patients with previously treated, unresectable, locally advanced, or metastatic solid tumors (excluding cholangiocarcinoma) with FGFR2 fusion or rearrangement

Richard Kim[1], Antoine Hollebecque[2], Kristin Ryan[3], Alison Schram[4]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Gustave Roussy Cancer Center, Villejuif, France; [3]Elevar Therapeutics, Fort Lee, NJ, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract #TPS4251

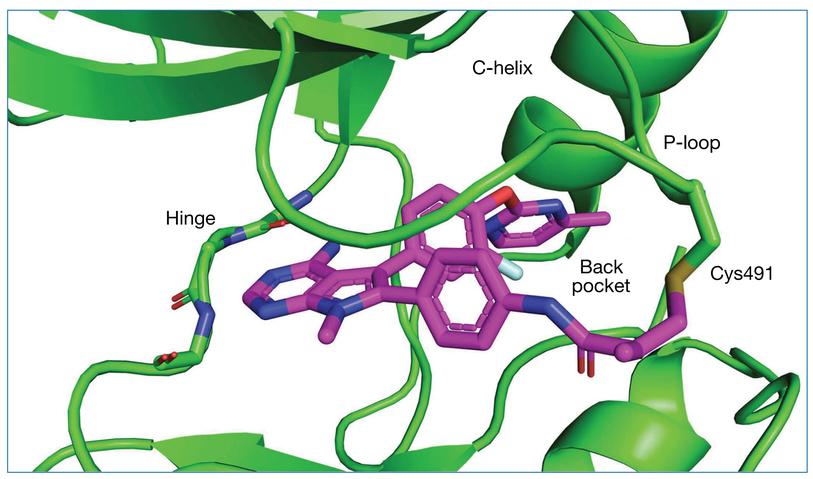
Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting

May 29-June 2, 2026

BACKGROUND

- Tissue agnostic cancer therapies offer the potential to markedly change the treatment landscape by targeting oncogenic drivers rather than the tumor's site of origin.[1]
- Lirafugratinib is the first highly selective, irreversible inhibitor designed to target oncogenic fibroblast growth factor receptor (FGFR)2 driver alterations and resistance mutations (**Figure 1**).[2]
- In the phase 1/2 ReFocus Trial (RLY-4008-101; NCT04526106), 46 patients (Group 3) with non-cholangiocarcinoma (CCA) solid tumors harboring FGFR2 fusion/rearrangements (f/r) received lirafugratinib 70 mg once daily. The ORR was 33.3% (95% CI 19.6 - 49.5).[3] However, this sample size was insufficient to support regulatory approval of lirafugratinib for a tissue agnostic indication.
- The ELE-4008-202, phase 2, open-label, single-arm study (NCT07359820) is designed to further evaluate the efficacy and safety of lirafugratinib 70 mg in patients with FGFR2 f/r, previously treated, unresectable, locally advanced or metastatic, non-CCA solid tumors who have not received prior FGFR inhibitor therapy.

Figure 1. Lirafugratinib Mechanism of Action[4]

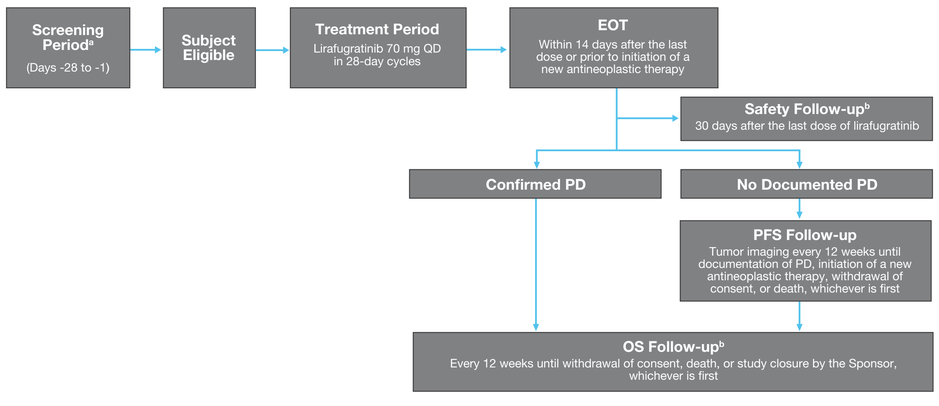


Crystal structure of lirafugratinib in complex with FGFR2 (PDB: 8STG). Protein is shown in green, and inhibitor carbons are shown in magenta. The Cys491 sulfur is shown in gold and as a covalent adduct with lirafugratinib.[4]

METHODS

- Approximately 20 to 30 patients will be enrolled in this study to reach the target patient population for the proposed interim analysis (i.e., at least 7 tumor types with ≥5 patients in each tumor type when pooled with 46 patients from Group 3 of Study RLY-4008-101).

Study Design



Abbreviations: EOT=End of Treatment; OS=overall survival; PD= progressive disease; PFS=progression-free survival; QD=once daily.
Note: See the Schedule of Assessments (Table 1) for the complete schedule and details of study procedures.
[a] Informed consent should be provided before any Screening study procedures are performed.
[b] Safety Follow-up and Overall Survival Follow-up Visits can be completed via telephone.

Statistical Analysis

- Statistical analyses of efficacy, safety, pharmacokinetic, and pharmacodynamic endpoints will be primarily descriptive in nature.
- Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).
- Categorical variables will be summarized showing the number and percentage (n [%]) of patients within each classification. Appropriate CIs will also be presented.
- All data from Study ELE-4008-202 will be pooled with the data of 46 patients from Group 3 of Study RLY-4008-101 for analysis.

METHODS, continued

Objectives

Primary Objective

- To evaluate the efficacy of lirafugratinib by ORR assessed by IRC

Key Secondary Objective

- Determine the duration of response of lirafugratinib assessed by IRC

Additional Secondary Objectives

- Evaluate safety and tolerability of lirafugratinib
- Evaluate additional antitumor activity of lirafugratinib including ORR, DOR, DCR, PFS, OS, PFS/OS rates at 6, 9, and 12 months, TTR, and TTP, as assessed by Investigator and/or IRC per RECIST v1.1.
- Evaluate pharmacokinetics of lirafugratinib
- Evaluate exposure response of lirafugratinib for efficacy and safety
- Evaluate quality of life

Exploratory Objectives

- Correlate FGFR2 genotype by central tissue assessment with the ORR
- Identify potential new blood and tumor tissue biomarkers (e.g., DNA, RNA, and/or protein markers) of pharmacodynamic activity, antineoplastic activity, resistance, and/or toxicity

DCR, disease control rate; DNA, deoxyribonucleic acid; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RNA, ribonucleic acid; TTP, time to progression; TTR, time to response.

Eligibility Criteria

Key Inclusion Criteria

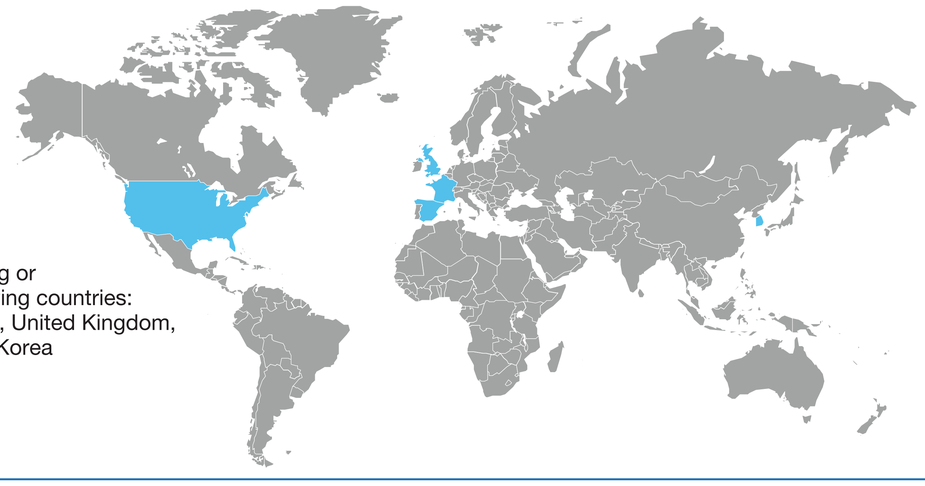
- Adults ≥18 years of age
- Measurable disease per RECIST v1.1
- Unresectable, locally advanced, or metastatic solid tumor (other than CCA) with FGFR2 f/r as detected by DNA or RNA sequencing or break-apart fluorescence in situ hybridization, per local assessment of blood and/or tumor
- Previously (>30 days) treated with ≥1 line of systemic therapy including chemotherapy (e.g., gemcitabine/cisplatin), immunotherapy, radiation therapy, or other approved therapies
- No prior treatment with an FGFRi
- ECOG performance status of 0 or 1

Key Exclusion Criteria

- Uncontrolled comorbidity
- Cancer other than FGFR2 f/r and has a known primary driver alteration that is amenable to approved targeted therapy (e.g., EGFR, ALK, ROS1, RET, HER2, BRAF, IDH1, KRAS). However, the subject may be eligible after consultation with the Sponsor
- Inadequate organ function assessments within 7 days prior to the first dose of lirafugratinib
- Active infection, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infection
- QT interval corrected using Fridericia's formula >480 msec or a history of prolonged QT syndrome or Torsade de Pointes or a family history of prolonged QT syndrome
- Clinically significant, uncontrolled cardiovascular disease
- CNS metastases or primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease
- Received anticancer therapy (including both systemic therapy and radiotherapy) within 14 days or 5 half-lives (whichever is shorter) and immunotherapy or other antibody therapy within 28 days prior to the first dose of lirafugratinib
- Received locoregional hepatic therapy (e.g., transcatheter arterial chemoembolization or yttrium-90) within 4 weeks prior to C1D1
- Received neutrophil growth factor support within 14 days of the first dose of lirafugratinib
- Requires treatment with a prohibited medication that cannot be discontinued at least 5 half-lives or 2 weeks (whichever is shorter) before the initiation of lirafugratinib
- Major surgical procedure within 14 days of the first dose of lirafugratinib (procedures such as central venous catheter placement and tumor needle biopsy are not considered major surgical procedures). Study centers should discuss other minor surgeries with the Sponsor
- History of another primary malignancy that has been diagnosed or required therapy within the past year. The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate or breast cancer, curatively treated localized thyroid cancer, and completely resected carcinoma in situ of any site. Adjuvant hormonal therapy for previously treated breast cancer, prostate cancer, or another hormone-dependent solid tumor is not exclusionary

Current Status

Enrollment is ongoing or planned in the following countries: United States, Spain, United Kingdom, France, Republic of Korea



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