TPS3173 **Poster Session**

Trial in progress: First-in-human study of PFL-721/STX-721 in participants with locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations.

Anas Gazzah, Chia-Chi Lin, Gerrina Ruiter, Pilar Garrido, Julien Mazieres, Enriqueta Felip, Yung-Hung Luo, David R. Spigel, Sandrine Hiret, Ki Hyeong Lee, Allegra Mondillo, Marie Bernardo, Ming Lin, Bill Bradley, Simon Roberts, Raymond Pagliarini, Jin Xu, Mark Chao, Danny Nguyen, Alex Spira; Gustave Roussy, Villejuif, France; National Taiwan University Cancer Center, Taipei, Taiwan; Netherlands Cancer Institute, Amsterdam, Netherlands; Ramón y Cajal University Hospital, Madrid, Spain; CHU de Toulouse, Université Paul Sabatier, Toulouse, France; Vall d'Hebron University Hospital, Barcelona, Spain; Division of Thoracic Oncology, Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; Sarah Cannon Research Institute Oncology Partners, Nashville, TN; Institut de Cancérologie de l'Ouest, Saint-Herblain, France; Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University School of Medicine, Cheongju-Si, South Korea; Scorpion Therapeutics, Boston, MA; Scorpion Therapeutics, Inc., Boston, MA; City of Hope- Long Beach Elm, Long Beach, CA; NEXT Oncology Virginia, Fairfax, VA

Background: Mutations in exon 20 of the *EGFR* gene account for approximately 4% to 10% of all EGFR mutations in Non-Small Cell Lung Cancer (NSCLC). Most of these mutations are insertions (EGFR ex20ins) that reduce the binding of first, second, and third generation tyrosine kinase inhibitors (TKI) to the ATP-binding pocket of the EGFR. Amivantamab, a bispecific anti-EGFR/c-MET-receptor antibody, is approved for the treatment of NSCLC with EGFR ex20ins mutations. However, there is significant unmet need for new oral agents that lack the limitations of intravenous administration and associated infusion-related toxicities and possess improved target engagement, mutant selectivity, and tolerability. PFL-721/STX-721 is an orally bioavailable, irreversible small-molecule inhibitor targeting a broad range of EGFR- and HER2-activating ex20ins mutations. PFL-721/STX-721 is highly selective for EGFR ex20ins mutations compared to wild type EGFR and exhibits greater selectivity compared to other EGFR mutant inhibitors. In addition, PFL-721/STX-721 has demonstrated superior anti-proliferation and antitumor effects compared to other investigational anti-EGFR ex20ins agents in relevant tumor models *in vitro* and *in vivo.* These observations suggest a more robust clinical risk-to-benefit profile and support further clinical investigation of PFL-721/STX-721. **Methods:** PFL-721/STX-721-101 (NCT06043817) is an open-label, first-in-human (FIH), Phase 1/2 study evaluating the safety, tolerability, pharmacokinetic (PK) exposure, and preliminary antitumor activity of PFL-721/STX-721 in participants with locally advanced or metastatic NSCLC harboring EGFR/HER2 ex20ins mutations. It consists of 3 parts: Part 1 Dose Escalation, Part 2 Recommended Phase 2 Dose (RP2D) selection, and Part 3 Dose Expansion. In Part 1, participants with NSCLC harboring EGFR or HER2 ex20ins mutations will be enrolled into sequential cohorts to receive ascending oral doses of PFL-721/STX-721 administered daily in 28-day treatment cycles. The main goal is to identify the maximum tolerated dose (MTD) and optimal biological dose (OBD) of PFL-721/STX-721. In Part 2, participants with NSCLC harboring EGFR ex20ins mutations who have received 1 to 2 prior lines of treatment, including a platinum-containing chemotherapy regimen and excluding EGFR targeted therapies with the exception of amivantamab, will be randomized 1:1 to receive PFL-721/STX-721 at the MTD or OBD in order to determine the optimal RP2D. Finally, Part 3 will further test the anticancer efficacy of PFL-721/STX-721 is administered at the RP2D. PFL-721/STX-721-101 is actively enrolling at 18 sites in 7 countries globally. Clinical trial information: NCT06043817. Research Sponsor: Scorpion Therapeutics, Inc.