NEWS RELEASE

FORE Biotherapeutics to Present Promising New Data from Phase 1/2a Trial Evaluating Plixorafenib (FORE8394) in Patients With BRAF-Altered Advanced Solid and Central Nervous System Tumors at ASCO 2023

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- Positive data support the potential of plixorafenib to induce deep and durable benefit for patients with BRAF-mutated (V600+) cancers
- In the V600+ population benefit was observed in both MAPK-inhibitor (MAPKi) naïve and pre-treated patients, with an overall response rate (ORR) of 37.5% and 16.7% and median duration of response (mDOR) of 32.3 months and 12.9 months, respectively
- Plixorafenib demonstrated evidence of durable activity with median progression free survival (mPFS) of more than 2 years in MAPKi-naïve V600+patients
- With a favorable benefit/risk profile and measurable clinical responses, 900 mg once daily of plixorafenib with cobicistat has been selected as the recommended Phase 2 dose (RP2D)

PHILADELPHIA--(BUSINESS WIRE)-- FORE Biotherapeutics today announced new clinical data from the Phase 1/2a clinical trial for plixorafenib (FORE8394), a novel, investigational, small-molecule, next-generation, orally available selective inhibitor of BRAF alterations. The results demonstrate promising single-agent activity against BRAF-altered tumors, including primary central nervous system (CNS) tumors, and will be featured in presentations at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, being held June 2-6, 2023, in Chicago, IL.

“The updated data from our Phase 1/2a study further reinforces plixorafenib’s differentiated clinical profile,” said Stacie Shepherd, MD, PhD, and Chief Medical Officer of FORE. “Plixorafenib has demonstrated both promising antitumor activity with durable responses and favorable tolerability as a single agent in patients with advanced BRAF-altered tumors. Notably, plixorafenib has a striking safety profile as compared to the currently approved BRAF/MEK and investigational pan-raf inhibitors.”

“In addition, our results demonstrate that targeted efficacious exposures are achieved at the recommended Phase 2 dose of 900mg a day with cobicistat in patients greater than 10 years of age, and that this dose provides the most favorable efficacy and safety profile,” continued Shepherd. “We look forward to advancing plixorafenib in our ongoing, global FORTE Phase 2 clinical basket study in patients with V600E-mutated primary recurrent CNS malignancies and in patients with advanced solid and CNS tumors with non-V600 alterations.”

Updated safety and efficacy data from the Phase 1/2a study will be highlighted during an oral presentation, with dose optimization results presented in a poster session. As of the data cutoff date of March 31, 2023, 113 adults and children have received ≥1 dose of plixorafenib under continuous dosing and fasting conditions on 28-day cycles until disease progression and are included in the safety population. Forty-two adults (≥18 years) met the criteria for the V600+ efficacy analysis with an ORR of 28.6%, based upon confirmed responses, and a mDOR of 17.8 months. An additional analysis was conducted in the MAPKi-naïve subset (N=24). Both analyses excluded patients with colorectal cancer, due to known intrinsic resistance pathways. A wide range of doses (900–3600 mg/d) and schedules with and without cobicistat, a novel CYP3A inhibitor, were explored.

Key Findings from the Ongoing Phase 1/2a Study

Efficacy Highlights:

- MAPKi-naïve adult V600+ population (N=24, excluding CRC):
    - Confirmed and durable responses and disease control were seen across multiple tumor types.
    - Clinical activity observed in this population includes nine confirmed partial responses (PR) for a 37.5% ORR, mDOR was 32.2 months and mPFS was 28.6 months.
        - In primary CNS tumors, six of ten efficacy-evaluable patients experienced a PR, with durable responses in both high grade and low grade glioma

    - Patients experienced long term benefit and tolerability:
        - Three V600+ patients with papillary thyroid cancer are ongoing after more than six years of treatment
        - Four of the ten with primary CNS tumor have remained on treatment for over a year, including a

patient with glioblastoma on treatment for 34 months

- MAPKi pre-treated adult V600+ population (N=18, excluding CRC):
    - Clinical activity observed in this population includes three confirmed PRs for a 16.7% ORR, mDOR was 12.9 months
    - Responses were observed in two of two patients with V600+ ovarian cancer, both of whom had prior MAPKi treatment and one with multiple regimens and documented progression of disease (PD)
- BRAF fusion population (N=14):
    - Clinical activity continued to be observed in patients with tumors harboring BRAF non-V600 alterations, including a patient with metastatic melanoma with complete response who continues on plixorafenib after five years of treatment with a DOR of 55+ months
    - Eight patients experienced stable disease (up to 9.2+ months)
    - Four patients are ongoing with plixorafenib treatment

Safety and Tolerability Highlights

- Plixorafenib demonstrated a favorable safety profile with a low frequency and grade of treatment-emergent adverse events (TEAEs) that are frequently seen with MAPKi therapies, including approved BRAF/MEK inhibitor combinations
    - Only one participant discontinued treatment due to treatment-related adverse event
- Symptomatic adverse events (AEs) were predominantly low grade (Grade 1 or 2) and included fatigue, nausea, diarrhea & vomiting
- No secondary cutaneous skin malignancies occurred, in contrast to the early single agent data with the approved BRAF inhibitors

“These results demonstrate that plixorafenib has promising activity against V600 & non-V600 BRAF mutant tumors, and in particular, primary CNS tumors,” shared Macarena de la Fuente, MD, Associate Professor and Chief of Neuro-oncology at the University of Miami Sylvester Comprehensive Cancer Center. “With no signs of paradoxical activation of the MAPK pathway and plixorafenib’s long term tolerability, this investigational agent is ideally suited for continued investigation in recurrent primary CNS tumors harboring BRAF V600E mutations and unresectable, locally advanced/metastatic solid tumors/primary CNS tumors harboring BRAF fusions.”

Dose Optimization Results

- Twelve patients (10.6%) are still on treatment as of the data cutoff; overall experience with plixorafenib represents 80 patient-years of exposure, including patients with over seven years of treatment.
- The most common reasons for discontinuation are progressive disease (n=65 [57.5%]) and clinical

progression (n=18 [15.9%]); one discontinuation due to plixorafenib treatment-related AE occurred with 3600 mg/day + cobicistat.

- Measurable clinical responses were observed across all doses, with a wide therapeutic window
- ORR was greatest with total daily doses of plixorafenib 900 mg + cobicistat, with three of four V600+ MAPKi-naïve patients having confirmed PR at this dose once daily; no increase in efficacy was observed at higher doses or exposures
- This dose provided favorable tolerability, maximizing dose intensity, with pharmacodynamically active exposures. As such plixorafenib 900 mg QD + cobicistat was declared the optimal dose and RP2D for further development

"The plixorafenib Phase 1/2a trial results demonstrate that the 900mg QD with cobicistat is the optimal monotherapy dose and schedule for this novel inhibitor of mutated BRAF," added Eric Sherman, MD, Associate Attending Physician at Memorial Sloan Kettering Cancer Center. "With responses observed in both MAP-kinase naïve treated and previously treated patients and its depth of durable remissions, plixorafenib has shown both promising tolerability as a single agent and has achieved durable responses and long-term benefit across a variety of patients harboring both V600 and nonV600 alterations. I look forward to the further study of plixorafenib to address patients where high unmet needs remain."

Plixorafenib was granted Orphan Drug Designation by the U.S. Food and Drug Administration in March 2023 for the treatment of primary CNS malignancies. In September 2022, the Agency granted plixorafenib Fast Track Designation for the treatment of patients with cancers harboring BRAF Class 1 (V600) and Class 2 alterations (including fusions) who have exhausted prior therapies.

Details for the ASCO 2023 presentations are as follows:

Oral Presentation

Title: Safety and efficacy of the novel BRAF inhibitor FORE8394 in patients with advanced solid and CNS tumors: Results from a phase 1/2a study
Presenter: Macarena de la Fuente, MD, University of Miami Sylvester Comprehensive Cancer Center
Session Title: Developmental Therapeutics – Molecularly Targeted Agents and Tumor Biology
Presentation Date and Time: Monday, June 5, 2023, 8:00a.m. – 11:00 a.m. CDT
Abstract Number: 3006

Poster Presentation

Title: Dose optimization of novel BRAF inhibitor FORE8394 based on PK and efficacy results
Presenter: Eric Sherman, MD, Memorial Sloan-Kettering Cancer Center
Session Title: Developmental Therapeutics – Molecularly Targeted Agents and Tumor Biology

Presentation Date and Time: Saturday, June 3, 2023, from 8:00a.m. – 11:00 a.m. CDT
Abstract Number: 3106

About Plixorafenib (FORE8394)

Plixorafenib is an investigational, novel, small-molecule, next-generation, orally available selective inhibitor of mutated BRAF. It was designed to target a wide range of BRAF mutations while sparing wild-type forms of RAF. Preclinical studies and clinical trials have shown that its unique mechanism of action effectively inhibits not only the constitutively active BRAFV600 monomers targeted by first-generation RAF inhibitors but also disrupts constitutively active dimeric BRAF class 2 mutants, fusions, splice variants and others. Unlike first-generation RAF inhibitors, plixorafenib does not induce paradoxical activation of the RAF/MEK/ERK pathway. As a "paradox breaker," plixorafenib could therefore treat acquired resistance to current RAF inhibitors and, more generally, yield improved safety and more durable efficacy than first-generation RAF inhibitors.

About FORE Biotherapeutics

FORE Bio is a precision oncology company dedicated to developing innovative treatments that provide a better outcome for cancer patients. Its lead asset plixorafenib is a Class 1/V600 and 2 BRAF inhibitor with demonstrated clinical safety and early efficacy signals in an ongoing Phase 1/2a clinical trial. Leveraging a proprietary functional genomics platform that can screen a wide range of known mutations for cancer-driving genes, the Fore R&D team is optimizing drug development by identifying existing compounds with known clinical profiles and a clear path through clinical development to advance new medicines for patients without treatment options. For more information, please visit **www.fore.bio** or follow us on Twitter and LinkedIn.

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