C4 Therapeutics Presents Monotherapy Data Demonstrating Proof of Mechanism and Early Evidence of Proof of Concept From Ongoing CFT1946 Phase 1 Trial in BRAF V600 Mutant Solid Tumors at the European Society for Medical Oncology (ESMO) Congress 2024

September 13, 2024 2:00 PM EDT

CFT1946 Is Well-Tolerated at All Dose Levels; No Dose-Limiting Toxicities

CFT1946 Achieves Dose Proportional Pharmacokinetic Exposure; Successfully Degrades BRAF V600 Mutant Protein

Early Evidence of CFT1946 Monotherapy Anti-Tumor Activity in Patients Who Have Progressed on or After BRAF Inhibitor Therapies; Majority of Patients Demonstrated Tumor Reduction Across V600 Mutation Types

CFT1946 Global Phase 1 Trial Continues to Enroll; Monotherapy and Combination Expansion Cohorts Advancing With Additional Data Expected in 2025

C4T To Host Webcast Today at 12:00 pm ET; Webcast Link Available Here

WATERTOWN, Mass., Sept. 13, 2024 (GLOBE NEWSWIRE) -- C4 Therapeutics, Inc. (C4T) (Nasdaq: CCCC), a clinical-stage biopharmaceutical company dedicated to advancing targeted protein degradation science, today announced initial clinical data from the ongoing clinical trial of CFT1946, an orally bioavailable small molecule degrader of BRAF V600 mutations in solid tumors. These data, the first clinical results for a BRAF V600X degrader, were shared as a proffered paper in an oral presentation by Maria Vieito, M.D., MSc, medical oncologist at Vall d'Hebron University Hospital, Barcelona, Spain, at the European Society for Medical Oncology (ESMO) Congress 2024, being held September 13 – 17 in Barcelona, Spain.

"We are thrilled to share initial CFT1946 monotherapy data and highlight how this molecule, the first and only clinical-stage degrader of BRAF V600 mutants, may disrupt the current treatment landscape as it quickly progresses through clinical development," said Andrew Hirsch, president and chief executive officer of C4 Therapeutics. "In addition to addressing the needs of patients with BRAF V600 mutant solid tumors, we believe these clinical data further reinforce the potential of our TORPEDO® platform to design innovative small molecule degraders that excite the medical community and have the potential to improve patients' lives."

"The data presented at the ESMO Congress 2024 are impressive given the early stage of development of CFT1946 and the novel modality," said Dr. Vieito. "I am especially encouraged by the safety and tolerability of CFT1946, which may allow for additional monotherapy exploration as well as combination approaches to better understand how this oral degrader medicine may support the needs of patients refractory to BRAF inhibitor therapies."

"We are pleased with the safety profile CFT1946 has demonstrated over a range of doses, as well as its pharmacokinetics, pharmacodynamics and initial anti-tumor activity. Taken together, these data support our hypothesis that degradation may offer a new therapeutic option over inhibition for BRAF V600 mutant solid tumors," said Len Reyno, M.D., chief medical officer of C4 Therapeutics. "We are deeply appreciative of the contributions from patients, caregivers and the oncology community that have enabled us to deliver this preliminary monotherapy data and we look forward to continuing these important relationships as we progress CFT1946 toward additional milestones in 2025 and beyond."

At the ESMO Congress 2024, C4T reported initial monotherapy data from the ongoing dose escalation Phase 1 clinical trial evaluating twice daily oral dosing of CFT1946, a degrader of BRAF V600 mutants, in patients with BRAF V600X solid tumors who have received at least one prior standard of care therapy for unresectable locally advanced or metastatic disease. Prior therapy must include a BRAF inhibitor, unless access is limited by regional regulatory approvals or reimbursement. As of the data cutoff date of July 19, 2024, a total of 36 patients received CFT1946 monotherapy across five dose escalation cohorts (20 mg BID, 80 mg BID, 160 mg BID, 320 mg BID and 640 mg BID). Patients received a median of three prior therapies; 35 patients (97 percent) had received prior BRAF inhibitor therapy. Thirty-three patients (92 percent) had a BRAF V600E mutation, two patients (six percent) had a BRAF V600K mutation and one patient (two percent) had a BRAF V600R mutation. Fourteen patients (39 percent) had melanoma, 14 patients (39 percent) had colorectal cancer, two patients (six percent) had non-small cell lung cancer and six patients (17 percent) had other cancers. All patients had unresectable, locally advanced or metastatic disease, and 32 patients (89 percent) entered the study with Stage IV cancer.

Safety and Tolerability: CFT1946 has a well-tolerated safety profile that supports further clinical development as monotherapy and in combination with MEK and EGFR inhibitors.

- There were no dose-limiting toxicities and no treatment-related serious adverse events.
- Adverse events occurring in more than 10 percent of patients were all Grade 1 or Grade 2.
- No patients discontinued therapy or experienced treatment interruptions due to treatment-related adverse events.
- No patients receiving CFT1946 monotherapy experienced a Grade 3 or higher treatment-related cutaneous adverse event. These cutaneous adverse events, which are related to BRAF wild-type inhibition, are commonly seen with BRAF inhibitors.

Pharmacokinetics (PK) and Pharmacodynamics (PD): Initial data demonstrating dose-dependent bioavailability and degradation of BRAF

V600E protein support CFT1946 proof of mechanism.

- CFT1946 exhibits dose-dependent bioavailability in the five dose levels explored to date.
- In all available post-treatment biopsies collected to date, degradation of BRAF V600E protein is observed.

Anti-Tumor Activity: CFT1946 demonstrates evidence of monotherapy anti-tumor activity, supportive of early proof of degrader concept.

- At data cutoff, 27 patients were evaluable for anti-tumor activity, which is measured by RECIST 1.1 criteria.
  - 16 patients demonstrated reduction of target metastatic lesions.
  - Two patients achieved a confirmed Partial Response.
- Reduction of target lesion tumors was observed across histologies. Of the 27 patients evaluable for anti-tumor activity:
  - Eleven patients had melanoma, eight of whom had evidence of tumor reduction. One patient with Stage IV BRAF V600K melanoma enrolled in the 320 mg BID cohort achieved a 67 percent decrease in target lesions as measured by RECIST 1.1 criteria. This patient remains on CFT1946 treatment and in response.
  - Nine patients had colorectal cancer, three of whom had evidence of tumor reduction.
  - Seven patients have other tumor histologies, three of whom had evidence of tumor reduction. One patient with Stage IV BRAF V600E pancreatic cancer, who has liver metastases, enrolled in the 640 mg BID cohort achieved a 55 percent decrease in target lesion as measured by RECIST 1.1 criteria. This patient remains on CFT1946 treatment and in response.
- As of data cutoff, 11 of the patients who were evaluable for anti-tumor activity remain on therapy.

Next Steps and Future Milestones for CFT1946
The CFT1946 Phase 1 trial is ongoing and multiple indication-specific cohorts are advancing. Next steps and related milestones for CFT1946 include:

- **Complete Phase 1 monotherapy dose escalation** – This portion of the trial is enrolling patients with BRAF V600X mutations across solid tumor indications. Patients are currently enrolling in the 640 mg BID PD backfill cohort as this dose level was recently declared safe. The full monotherapy dose escalation data are expected in 2025.
- **Complete expansion cohort exploring CFT1946 monotherapy in melanoma** – This Phase 1 exploratory expansion cohort is evaluating the potential of CFT1946 monotherapy for melanoma patients refractory to BRAF inhibitor therapies. Enrollment for the 320 mg BID dose level is complete, and enrollment is ongoing for the 640 mg BID dose level. Data from these dose levels are expected in 2025.
- **Complete dose escalation cohort exploring CFT1946 in combination with cetuximab in colorectal cancer** – This Phase 1b dose escalation cohort is enrolling patients at the 160 mg BID dose level to explore safety and tolerability, PK, PD and anti-tumor activity of CFT1946 in combination with cetuximab. These data are expected in 2025.
- **Initiate dose escalation cohort exploring CFT1946 in combination with trametinib in melanoma** – This Phase 1b dose escalation cohort will explore safety and tolerability, PK, PD and anti-tumor activity of CFT1946 in combination with trametinib. C4T expects to initiate this cohort by year-end 2024.

C4T Webcast for Analysts and Investors
C4T will host an investor webcast today, September 13, 2024, at 12:00 pm ET. To join the webcast, please visit this link or the "Events & Presentations" page of the Investors section on the company's website at www.c4therapeutics.com. A replay of the webcast will be archived and available following the event.

About BRAF V600 Mutant Solid Tumors
BRAF mutations are found in approximately five percent of all cancers, including melanoma, colorectal cancer (CRC), non-small cell lung cancer

(NSCLC) and other malignancies. Of these BRAF mutation cancer diagnoses, up to 90 percent contain an activating BRAF V600 mutation. BRAF V600 mutations are observed in up to 50 percent of patients with melanoma, nearly 10 percent of patients with CRC and approximately five percent of patients with NSCLC. Resistance to FDA-approved BRAF inhibitors results in median progression-free survival rates of less than 15 months across all indications.

About CFT1946
CFT1946 is an investigational, orally bioavailable small molecule degrader of BRAF V600 mutations in solid tumors currently being evaluated in a Phase 1/2 global clinical trial in patients refractory to BRAF inhibitors. CFT1946 is designed to be potent and selective against the BRAF V600 mutant form. Initial clinical data from the Phase 1 trial demonstrate that CFT1946 has a well-tolerated safety profile, demonstrates dose-dependent bioavailability and degradation of BRAF V600E protein, and demonstrates evidence of monotherapy anti-tumor activity. CFT1946 is the only degrader of BRAF V600 mutant solid tumors in clinical trials. More information about this trial may be accessed at www.clinicaltrials.gov (identifier: NCT05668585).

About C4 Therapeutics
C4 Therapeutics (C4T) (Nasdaq: CCCC) is a clinical-stage biopharmaceutical company dedicated to delivering on the promise of targeted protein degradation science to create a new generation of medicines that transforms patients' lives. C4T is progressing targeted oncology programs through clinical studies and leveraging its TORPEDO® platform to efficiently design and optimize small-molecule medicines to address difficult-to-treat diseases. C4T's degrader medicines are designed to harness the body's natural protein recycling system to rapidly degrade disease-causing proteins, offering the potential to overcome drug resistance, drug undruggable targets and improve patient outcomes. For more information, please visit www.c4therapeutics.com.

Forward-Looking Statements
This press release contains "forward-looking statements" of C4 Therapeutics, Inc. within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, express or implied statements regarding our ability to develop potential therapies for patients; the design and potential efficacy of our therapeutic approaches; the predictive capability of our TORPEDO® platform in the development of novel, selective, orally bioavailable BiDAC™ and MonoDAC™ degraders; the potential timing, design and advancement of our preclinical studies and clinical trials, including the potential timing for and receipt of regulatory authorization related to clinical trials and other clinical development activities including clinical trial commencement or cohort initiation; our ability and the potential to successfully manufacture and supply our product candidates for clinical trials; our ability to replicate results achieved in our preclinical studies or clinical trials in any future studies or trials; our ability to replicate interim or early-stage results from our clinical trials in the results obtained when those clinical trials are completed or when those therapies complete later stage clinical trials; regulatory developments in the United States and foreign countries; the potential timing for updates on our clinical and research programs; and our ability to fund our future operations. Any forward-looking statements in this press release are based on management's current expectations and beliefs of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: uncertainties related to the initiation, timing, advancement and conduct of preclinical and clinical studies and other development requirements for our product candidates; the risk that any one or more of our product candidates will cost more to develop or may not be successfully developed and commercialized; and the risk that the results of preclinical studies and/or clinical trials will or will not be predictive of results in connection with future studies or trials. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in C4 Therapeutics' most recent Annual Report on Form 10-K and/or Quarterly Report on Form 10-Q, as filed with the Securities and Exchange Commission. All information in this press release is as of the date of the release and C4 Therapeutics undertakes no duty to update this information unless required by law.

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