Candel Therapeutics Announces Nature Publication Showing Extended Survival Associated with Immune Activation in Patients with Recurrent High-Grade Glioma Treated with CAN-3110

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- *CAN-3110 is a first-in-class herpes simplex virus-1 oncolytic immunotherapy candidate with dual activity for oncolysis and immune activation in a single therapeutic*
- *In a first-in-human clinical trial of CAN-3110 in recurrent high-grade glioma, CAN-3110 was well tolerated and treatment was associate with improved survival*
- *Positive HSV-1 serology, before or after CAN-3110 injection, was a predictor of response and was associated with improved survival*
- *Increased infiltrating immune cells in the tumor microenvironment and expansion of the T cell repertoire after treatment were associated with improved survival*

NEEDHAM, Mass., Oct. 18, 2023 (GLOBE NEWSWIRE) -- Candel Therapeutics, Inc. (the Company or Candel) (Nasdaq: CADL), a clinical stage biopharmaceutical company focused on developing viral immunotherapies to help patients fight cancer, today announced that *Nature* published results from the ongoing first-in-human phase 1 investigator-sponsored clinical trial of CAN-3110, a first-in-class, replication-competent herpes simplex virus-1 (HSV-1) oncolytic viral immunotherapy candidate, in patients with recurrent high-grade glioma (HGG), of which 86.7% were glioblastoma, that had returned after standard of care (SoC) treatment.

The study is being conducted in a collaboration between Brigham and Women's Hospital and Candel. The publication titled "*Clinical trial links oncolytic immunoactivation to survival in glioblastoma*" can be accessed here.

Key findings of the manuscript: Tolerability of a single injection of CAN-3110 in recurrent HGG with no dose limiting toxicity reported, improved median overall survival in 41 patients treated in Arm A (11.6 months as of data cutoff in October 2022) and correlation between anti-HSV-1 serology and survival. Importantly, CAN-3110 treatment was associated with a significant increase in immune cells in the tumor microenvironment and in the peripheral blood. The activation of both local and systemic immune response, including the expansion of the T-cell repertoire diversity as well as HSV-1 immune status, correlate with survival suggesting that CAN-3110 can enhance anti-cancer immune responses even in immunosuppressive tumor microenvironments.

"There is an urgent need to develop novel therapies for recurrent HGG," said E. Antonio Chiocca, MD, PhD, Head of Department of Neurosurgery at Brigham and Women's Hospital, Professor at Harvard Medical School, and Principal Investigator of the clinical trial. "Failure of standard of care and conventional immunotherapy in recurrent HGG largely resides in the inability of available therapies to efficiently activate the immune system in the cold tumor microenvironment that is characteristic for this condition. In this manuscript we provide evidence that, after a single injection, the direct oncolytic activity combined with the ability of CAN-3110 to elicit a strong anti-tumoral response, resulted in conversion of the cold tumor microenvironment and induced a systemic immune response linked to improved patient survival."

Dr. Chiocca continued, "Prolonged survival was associated with HSV-1 seropositivity, either before or after CAN-3110 treatment. Importantly, approximately 30% of seronegative patients at baseline seroconverted after CAN-3110 treatment. Those patients also exhibited increased survival suggesting the possibility of leveraging this mechanism and further improving survival upon multiple injections."

"This high impact publication detailing results from 41 patients in the phase 1 clinical trial of CAN-3110 is an important validation of how Candel, in collaboration with academic leaders in the field, are working to address the critical challenges in recurrent HGG," said Paul Peter Tak, MD, PhD, FMedSci, President and Chief Executive Officer of Candel. "In the clinical study, we observed a nearly doubling of the expected median overall survival after a single CAN-3110 injection, compared to historical reports of less than 6 to 9 months. We reported transformative improvements after a single injection of CAN-3110 in patients affected by aggressive tumors who had failed multiple resections, chemotherapy and radiotherapy."

Dr. Tak continued, "As a next step, we are currently evaluating the effects of multiple CAN-3110 injections in recurrent HGG, supported by the Break Through Cancer foundation. The data reported in the manuscript reinforce our confidence in CAN-3110 and its potential to change disease outcomes in difficult-to-treat solid tumors that express Nestin. In the future, we could possibly expand the development of this agent into other indications characterized by Nestin expression, such as triple negative breast cancer or sarcoma."

"The publication of this manuscript in *Nature*, strongly underscores the relevance and novelty of our clinical and biological findings," said Francesca Barone, MD, PhD, Chief Scientific Officer of Candel. "The molecular construct of CAN-3110 makes this virus unique as a next generation viral immunotherapy candidate, combining in a single agent potent oncolysis and immune activation. Of importance, patients with recurrent HGG who had pre-existing antibodies to HSV-1 virus (66% of the patients) had a median overall survival of 14.2 months. In these patients, we observed clear evidence of immune activation in the tumor microenvironment. Those without antibodies (34%) had median overall survival of 7.8 months, which is in the same range as historical survival times. Different from conventional immunotherapy, CAN-3110 is designed to expand but also diversify the immune response. Accordingly, we observed increased diversity of the T-cell receptor repertoire after a single injection of CAN-3110 in recurrent HGG patients. We have started to evaluate the effects of repeated injection with CAN-3110, which has the potential to result in the HSV-1 seroconversion associated with improved survival."

About the phase 1 clinical trial of CAN-3110 in recurrent HGG

This investigator-sponsored study is led by E. Antonio Chiocca, MD, PhD, Head of the Department of Neurosurgery at Brigham & Women's Hospital and Professor at Harvard Medical School. The clinical trial comprises three arms. In arm A, 41 patients with recurrent HGG were treated by a single intratumoral injection of CAN-3110 (dose ranging from $1x10^6$ plaque forming units (pfu) to $1x10^{10}$ pfu), including nine patients with multifocal/multicentric, deep or bilateral tumors associated with poor survival. After observing this regimen was generally well tolerated without dose-limiting toxicity, patients in arm B (n=9) were treated with a single dose of cyclophosphamide (24 mg/kg), two days before CAN-3110 injection at doses of 1×10^8 pfu (n=3) and 1×10^9 pfu (n=6). The rationale is based on findings in mouse models, where cyclophosphamide improved viral persistence in injected tumors. In arm C, supported by the Break Through Cancer foundation, two cohorts of 12 patients with recurrent HGG will receive up to six injections of CAN-3110 over a four-month period.

Early results from the phase 1 clinical trial were presented in May 2023 at the American Society of Gene and Cell Therapy 26th Annual Meeting. The oral presentation highlighted that in arm A (n=41), treatment with a single dose of CAN-3110 was generally well tolerated and resulted in median overall survival (mOS) of 11.8 months as of the data cutoff date on April 20, 2023. In addition, at the same data cutoff date, median overall survival in arm B (n=9) was ongoing at 12.0 months, supporting the encouraging clinical activity of CAN-3110 observed in in arm A. Of note, responses were shown in both injected and uninjected lesions in patients with multifocal disease. Analysis of post treatment samples demonstrated evidence of persistent HSV antigen expression and replication in uninjected tumor tissue associated with CD8+ T cell infiltration, which may explain the clinical responses observed in uninjected tumors.

About Candel Therapeutics

Candel is a clinical stage biopharmaceutical company focused on developing off-the-shelf viral immunotherapies that elicit an individualized, systemic anti-tumor immune response to help patients fight cancer. Candel's engineered viruses are designed to induce immunogenic cell death through direct viral-mediated cytotoxicity in cancer cells, thus releasing tumor neo-antigens while creating a pro-inflammatory microenvironment at the site of injection. This leads to in situ vaccination against the injected tumor and uninjected distant metastases.

Candel has established two clinical stage viral immunotherapy platforms based on novel, genetically modified adenovirus and herpes simplex virus (HSV) gene constructs, respectively. CAN-2409 is the lead product candidate from the adenovirus platform and is currently in ongoing clinical trials in NSCLC (phase 2), pancreatic cancer (phase 2), and localized, non-metastatic prostate cancer (phase 2 and phase 3). CAN-3110 is the lead product candidate from the HSV platform and is currently in an ongoing investigator-sponsored phase 1 clinical trial in recurrent high-grade glioma. In addition, Candel's enLIGHTEN™ Discovery Platform is a systematic, iterative HSV-based discovery platform leveraging human biology and advanced analytics to create new viral immunotherapies for solid tumors.

For more information about Candel, visit: www.candeltx.com

Forward-Looking Statements

This press release includes certain disclosures that contain "forward-looking statements," within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, express or implied statements regarding the timing and advancement of current and future development programs, including the timing and availability of additional data, the possibility to use early biological readouts as predictor of clinical response and expectations regarding the therapeutic benefit of its programs, including the potential for CAN-3110 to extend patient survival. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, those risks and uncertainties related to the timing and advancement of current and future development programs; that final data from our pre-clinical studies and completed clinical trials may differ materially from reported interim data from ongoing studies and trials; expectations regarding the therapeutic benefit of the Company's programs; the Company's ability to efficiently discover and develop product candidates; the Company's ability to obtain and maintain regulatory approval of product candidates; the Company's ability to maintain its intellectual property; the implementation of the Company's business model, and strategic

plans for the Company's business and product candidates, and other risks identified in the Company's SEC filings, including the Company's most recent Quarterly Report on Form 10-Q filed with the SEC, and subsequent filings with the SEC. The Company cautions you not to place undue reliance on any forward-looking statements, which speak only as of the date they are made. The Company disclaims any obligation to publicly update or revise any such statements to reflect any change in expectations or in events, conditions, or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements. Any forward-looking statements contained in this press release represent the Company's views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date.

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