Carthera partners with Agenus and Northwestern University for phase 2a trial combining SonoCloud-9 with checkpoint inhibitors to treat glioblastoma

World-first trial at Northwestern University could change standard of care for unmethylated glioblastoma patients

Carthera's SonoCloud-9 device will be used to increase delivery of Agenus' checkpoint inhibitors balstilimab (anti-PD-1) and botensilimab (anti-CTLA-4) into brain

Paris, France, April 8, 2024 - Carthera, a spin-off from Sorbonne University founded by Pr. Alexandre Carpentier, and developer of SonoCloud®, an innovative ultrasound-based medical device to treat a wide range of brain disorders, today announces the launch of a phase 2a clinical trial (NCT05864534). This Northwestern University sponsored trial will use Carthera's SonoCloud-9 device with Agenus' checkpoint inhibitors balstilimab and botensilimab in patients with newly diagnosed glioblastoma (GBM) who have completed radiotherapy.

Patients with unmethylated GBM typically have a survival expectancy of less than 12-15 months. Standard of care includes surgical resection followed by radiochemotherapy and additional maintenance chemotherapy. However, tumors with an unmethylated MGMT gene promoter are commonly resistant to temozolomide chemotherapy and new approaches are urgently needed. So far, conventional immunotherapy treatments have been unsuccessful in improving outcomes in glioblastoma patients. In this novel trial, to be conducted in Chicago, Northwestern University will use Agenus' next generation multifunctional Fc-enhanced anti-CTLA-4, botensilimab, and anti-PD-1 bastilimab, in combination with Carthera's implantable ultrasound device SonoCloud-9, which opens the Blood-Brain Barrier (BBB), allowing for better penetration of drug molecules into the brain.

The phase 2a trial will assess the safety and efficacy of immune modulating checkpoint therapies for the treatment of GBM when combined with BBB opening. Patients who have completed radiochemotherapy will be enrolled within three to four weeks and will then receive treatment using Carthera's SonoCloud-9 device in combination with low-dose liposomal doxorubicin, to modulate the tumor microenvironment, along with Agenus' checkpoint inhibitors balstilimab and botensilimab. Botensilimab and Balstilimab have shown favorable responses in other difficult to treat cancers that are poorly immunogenic or previously failed immunotherapies. This pilot trial aims to recruit 25 patients to assess safety and preliminary efficacy.

The SonoCloud-9 device has been extensively tested in phase 1/2 trials in combination with different chemotherapy regimen for patients with recurrent glioblastoma. The innovative use of this ultrasound-based device to open the BBB markedly enhances the delivery of monoclonal antibodies to disease sites within the brain. Low-dose doxorubicin is also used to further enhance the immune response.

Dr. Adam Sonabend's lab at Northwestern University has carried out extensive preclinical work on the use of the SonoCloud-9 device in the treatment of GBM, which forms the basis of this new strategy.

"Our preclinical data has provided new insights into the mechanism of action and combined activity of immunotherapy and ultrasound. Our preclinical results are encouraging and we

are excited to move this approach forward to benefit our patients," said Dr. Adam Sonabend, associate professor of neurological surgery at Northwestern University Feinberg School of Medicine and the lead neurosurgeon and investigator on this trial.

"Combining our checkpoint inhibitors balstilimab and botensilimab with Carthera's SonoCloud-9 technology has the potential to revolutionize the treatment landscape for patients newly diagnosed with glioblastoma," said Dr. Steven O'Day, chief medical officer at Agenus. "By optimizing drug delivery and modulating the immune response within the brain, we could open up new possibilities for the treatment of glioblastoma."

"This approach has the potential to transform the standard of care for patients suffering from glioblastoma, in particular for patients with tumors harboring an unmethylated MGMT promoter, who have a particularly poor prognosis," said Roger Stupp, professor of medicine (hem/onc), neurology and neurological surgery and medical director of the Malnati Brain Tumor Institute of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University. Dr. Stupp was the lead investigator on the trials that led to the FDA approval of the current standard of care using temozolomide, and Tumor Treating Fields (TTF).

"Our SonoCloud-9 device, that temporarily opens the blood-brain barrier, provides opportunities for entirely novel treatments against glioblastoma. We are excited about this trial which will, for the first time, allow the delivery of immunotherapy into large parts of the brain tissue," added Dr. Michael Canney, chief scientific officer at Carthera.

"This collaboration with Agenus and Northwestern illustrates the combinational potential of the SonoCloud device with various innovative therapeutic agents and opens new perspectives for patients with glioblastoma. It further confirms Carthera's position as a leader in the development of therapeutic ultrasound for the treatment of brain diseases," said Frederic Sottilini, CEO of Carthera.

About SonoCloud-9
The SonoCloud-9 device is implanted in a skull window, below the skin. Once in place it is invisible. When activated for a few minutes, using a transdermal needle connected to an external control unit, the BBB is disrupted for several hours; a window during which drug therapies can be administered. When the BBB is disrupted, drugs can reach the brain in higher and more effective concentrations. This treatment can be repeated at each cycle of drug therapy.

The use of the SonoCloud-9 device is investigational, the device has not yet received EMA or FDA approval.

About Botensilimab
Botensilimab is an investigational multifunctional anti-CTLA-4 immune activator (antibody) designed to boost both innate and adaptive anti-tumor immune responses. Its novel design leverages mechanisms of action to extend immunotherapy benefits to 'cold' tumors which generally respond poorly to standard of care or are refractory to conventional PD-1/CTLA-4 therapies and investigational therapies. Botensilimab augments immune responses across a wide range of tumor types by priming and activating T-cells, downregulating intratumoral regulatory T-cells, activating myeloid cells and inducing long-term memory responses.
Approximately 900 patients have been treated with botensilimab in phase 1 and 2 clinical trials. Botensilimab alone, or in combination with Agenus' investigational PD-1 antibody, balstilimab, has shown clinical responses across nine metastatic, late-line cancers. For more information about botensilimab trials, visit www.clinicaltrials.gov with the identifiers NCT03860272, NCT05608044, NCT05630183 and NCT05529316.

About Agenus
Agenus is a leading immuno-oncology company targeting cancer and infectious diseases with a comprehensive pipeline of immunological agents. The company's mission is to expand patient populations benefiting from cancer immunotherapy through combination approaches, using a broad repertoire of antibody therapeutics, adoptive cell therapies (through MiNK Therapeutics) and adjuvants (through SaponiQx). Agenus is headquartered in Lexington, MA.
For more information, visit www.agenusbio.com or @agenus_bio. Information that may be important to investors will be routinely posted on our website and social media channels.

About Northwestern University Feinberg School of Medicine
Northwestern University (Chicago, Illinois, US) is a leading research university; home to more than 90 school-based centers and more than 50 University research centers. With an interdisciplinary culture, our research spans a spectrum of areas including neuroscience, nanotechnology, biotechnology and drug discovery.
Northwestern's Feinberg School of Medicine is a top 20 medical school, where nationally recognized researchers collaborate with skilled clinicians to improve human health. Feinberg provides 70% of all research funds across Northwestern University, with approximately 6,093 clinical trials and research studies taking place in 2021-2022.
The collaborative medical school faculty conducts basic science, clinical and translational research on campuses in Chicago and Evanston.
www.feinberg.northwestern.edu

About Carthera
Carthera is a clinical-stage medtech company focused on developing innovative ultrasound-based medical devices to treat a wide range of brain disorders.
The company is a spin-off from AP-HP Paris and Sorbonne University. Carthera leverages the inventions of Pr. Alexandre Carpentier, head neurosurgeon at AP-HP Sorbonne university, who has achieved worldwide recognition for his innovative developments in treating brain disorders. Carthera is developing SonoCloud®, an intracranial implant that temporarily opens the Blood-Brain Barrier (BBB). The device is currently in clinical trials in Europe and the United States. It received FDA Breakthrough Device Designation in 2022.
Founded in 2010 by Pr. Alexandre Carpentier, run by CEO Frederic Sottilini and chaired by Oern Stuge MD, Carthera has offices in France (Lyon and Paris) and a subsidiary in Boston, Massachusetts, USA. Since its inception, the technical and clinical development of SonoCloud has received support from the National Research Agency (ANR), the French public investment bank (Bpifrance), the National Institutes of Health (NIH) and the European Innovation Council (EIC).
www.carthera.eu

Media and analysts contact
Andrew Lloyd & Associates
Saffiyah Khalique– Juliette Schmitt
saffiyah@ala.associates – juliette@ala.associates
Tel: +44 1273 952 481
@ALA_Group