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After flicker, investor enthusiasm for Candel burns brighter

By Michael Fitzhugh, Managing Editor

Paul Peter Tak means business. In one very active year, the entrepreneurial president and CEO of Candel Therapeutics Inc., an oncolytic viral immunotherapy company he said was long run as cost-efficient "semi-academic lab," has hired on a new chief business officer and CFO, recruited a new research advisory board, and led the company to completion of a $79.1 million IPO. Now, ahead of a weekend presentation of data on one of the company's lead candidates for fast-growing brain tumors, shares (NASDAQ:CADL) that dipped post-IPO are again climbing as the company works to develop a slow-growing class of new medicines.

Tak, the former chief immunology officer and global development leader of Glaxosmithkline plc, oversaw there the creation of a portfolio of new therapies for cancer, immune-mediated inflammatory diseases, and infectious disease. He joined Candel in September 2020 after talking with Advantagene, a company that together with Periphagen Holdings Inc. were combined to create today's Candel. From those conversations, he concluded it would be "extremely unlikely" that all the company's data across multiple solid tumors would be explained by chance and that furthermore, his experience might help take the company to the next level, he said.

The Needham, Mass.-based company's core focus is the creation of viruses designed to kill cancer cells, with two in the lead: CAN-2409 (aglatimagene besadenovec), the lead from its adenovirus platform, and CAN-3110, the lead from its herpes simplex virus (HSV) platform.

CAN-2409, formerly known as gene mediated cytotoxic immunotherapy, is the company's most advanced candidate, currently under study in a phase III trial in newly diagnosed localized prostate cancer in intermediate and high-risk patients due to read out in 2024. It's based on a replication deficient adenovirus that has been genetically modified to encode the enzyme thymidine kinase. Injected into a tumor, the enzyme activates an orally co-administered prodrug of the antiviral valacyclovir. The combination generates a toxic metabolite that kills cancer cells, thereby releasing tumor neo-antigens and creating a pro-inflammatory microenvironment at the site of injection.

"We've shown extensively in in vivo models there were CD8-positive tumor-infiltrating lymphocyte response against the injected tumor, and distant un-injected metastases... in other words, an abscopal effect," Tak told *BioWorld*. So far, investigators have teste d the candidate in more than 700 patients, he said.

The company is also testing '2409 in early localized low- to intermediate-risk prostate cancer. It has been granted fast track for the use of the candidate for the treatment of localized, primary prostate cancer in combination with radiation therapy to improve the local control rate, as well as for CAN-2409 in combination with standard of care surgery and chemoradiation to improve survival in adults with newly diagnosed high grade glioma decrease recurrence and improve disease-free survival.

Other tests of '2409 have so far included trials in pancreatic cancer - slated to yield interim data in 2023 - and non-small-cell lung cancer not responding to a first line immune checkpoint inhibitor. Yet another trial is exploring the administration of '2409 for the treatment of glioblastoma during first treatment with neurosurgery.

"The difficult part here is for the neurosurgeon to remove the tumor. The easy part is to leave behind some of CAN-2409 in the wound bed, where we know that almost always there are tumor cells staying behind on the microscopic level, which explains the very poor prognosis of these patients," Tak said.

The company intends to start a potential registrational phase III trial in high grade glioma in the first half of 2022, as well as to test it in HGG with standard of care and Opdivo (nivolumab, Bristol Myers Squibb Co.)

A long-evolving field

Oncolytic viral therapies have been slow to gain traction. So far, just a handful have won global approvals, most notably Amgen Inc.'s Imlygic (talimogene laherparepvec) for melanoma, and Daiichi Sankyo Co. Ltd.'s Delytact (teserpaturev), which in June became the first oncolytic virus ever approved for the treatment of malignant glioma or any primary brain cancer. It received a conditional and time-limited approval from Japan's Ministry of Health, Labour and Welfare.

Like Imlygic, Candel's second major asset, CAN-3110, is a replication-competent HSV gene construct. But in contrast, Candel's team has re-inserted one allele of the ICP34.5 gene, a gene deleted in Imlygic to prevent viral growth in normal cells.

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That change "often results in weak viruses characterized by poor replication ability and an ability to generate limited immune response," the company said.

Candel's trick is to put the gene under transcriptional control of a tumor-specific promoter of nestin, a cytoskeletal protein that is overexpressed in glioma cells. That change of the viral genome enables viral replication selectively in tumor cells with the intention of providing tumor-specific cytolytic activity while sparing healthy cells.

So far, an ongoing phase I study of the approach indicates it has promise. Among 30 patients with biopsy-confirmed recurrent high-grade glioma treated in an open-label trial of '3110, median overall survival of the entire group was 11.7 months vs. expected survival of not more than six to nine months with current therapies. Since, an additional 12 patients have been enrolled into a dose expansion arm of the trial.

One patient enrolled in the study, a man with two brain tumors who refused further surgery, chemotherapy, radiotherapy and corticosteroid treatment, had '3110 injected into one of the tumors. "No other treatments were given in a completely therapy-resistant disease, and there was a very strong decrease in both tumors, allowing the patient to go back to work," Tak said. "I compare it to jumping out of a plane with a parachute or without a parachute."

The data, first presented at the American Society of Clinical Oncology in June, appeared to draw new attention from investors ahead of the European Association of Neuro-Oncology meeting, Sept. 25-26, sending company shares up 17.8%, from a close of $8.43 on Sept. 21 to $9.93 on Sept. 25.

"Now there's a real opportunity for Candel to expand into other indications, guarded by nestin expression," he said.

Further projects slated to gain support from the IPO proceeds will include development of new candidates from the company's Periphagen-sourced HSV discovery platform and the establishment of the construction of a company-owned manufacturing facility in Needham.

Candel has identified Oncorus Inc., Replimune Group Inc., Amgen Inc., Fergene Inc. and Iconovir Bio Inc., among others as developing viral immunotherapies that may have utility for the treatment of indications that it's targeting. But, from a high level, efforts in the field seem to be less of a race and more of a marathon.

"I think it is not unusual that it takes many, many years for a new modality to mature and to become acceptable as it generates enough data to show the community that we have transformational medicines here," said Tak.