Oncternal's Pipeline Candidates Featured in Presentations at American Society of Hematology Meeting

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- Initial data from ongoing Phase 1 trial in CLL patients show cirmtuzumab was well tolerated, with signs of biologic activity and prolonged progression free survival
- Cirmtuzumab shows evidence of synergistic activity with ibrutinib in preclinical models of CLL
- TK216 demonstrates *in vitro* anti-tumor activity in models of AML and DLBCL

SAN DIEGO, December 6, 2016 — Oncternal Therapeutics, Inc., a clinical-stage biotechnology company developing first-in-class therapies for rare and common malignancies, today announced that both of its clinical stage pipeline candidates were featured in poster presentations at the 58th Annual Meeting of the American Society of Hematology (ASH), held in San Diego, CA, December 3-6, 2016. Preclinical and clinical data were presented on cirmtuzumab, a first-in-class anti-ROR1 monoclonal antibody, including early signs of clinical activity in chronic lymphocytic leukemia (CLL) patients in the ongoing Phase 1 trial. In vitro data were also presented on TK216, a first-in-class small molecule that inhibits the biological activity of ets-family transcription factor oncoproteins, supporting development in acute myeloid leukemia (AML) and diffuse large B cell lymphoma (DLBCL). The cirmtuzumab and TK216 posters will be made available on the Oncternal website.

"The data reported in multiple presentations at ASH strongly support our clinical development strategy for both cirmtuzumab and TK2016 and highlight their therapeutic potential," said James Breitmeyer, M.D., Ph.D., Oncternal's President and CEO. "Our collaborators at UCSD reported early encouraging data from 20 CLL patients in the Phase 1 trial of cirmtuzumab, showing not only that the drug is well tolerated but that patients experienced prolonged PFS after just four doses. Furthermore, preclinical studies provided a rationale for the future combination of cirmtuzumab with ibrutinib in B-cell malignancies. In addition, in vitro data on TK216 support expanding development beyond the Phase 1 trial underway in Ewing sarcoma to hematologic malignancies."

Cirmtuzumab

The cirmtuzumab posters were presented by Oncternal collaborators from the University of California, San Diego, which is sponsoring the Phase 1 trial.

Immunotherapeutic Targeting of ROR1-Dependent, Non-Canonical Wnt5a-Signaling By Cirmtuzumab: A First-in-Human Phase I Trial for Patients with Intractable Chronic Lymphocytic Leukemia

The primary aims of this ongoing study are to evaluate the safety and tolerability of cirmtuzumab in approximately 56 patients with relapsed or refractory CLL who are ineligible for chemotherapy, and to determine the maximum tolerated dose or recommended dose for Phase 2. Secondary endpoints include antibody pharmacokinetics and pharmacodynamics. Four biweekly infusions of cirmtuzumab are administered at doses ranging from 15 mcg/kg to 16 mg/kg in the study and at the time of this analysis, 20 patients had received cirmtuzumab.

Cirmtuzumab was well tolerated, with no reported drug-related severe adverse events or dose-limiting toxicities. Anemia (7 patients), thrombocytopenia (4), and neutropenia (3) were the most common adverse events, were primarily grade 1, and were deemed likely to result from late-stage-disease-related cytopenias. Serum concentrations of cirmtuzumab were measured and half-life was determined to be >24 days, suggesting the feasibility of monthly dosing.

Biological activity was observed at multiple time points. Twenty-four hours following the first infusion, the leukemic cells of patients treated at cirmtuzumab doses >/= 2 mg/kg had inactivation of RhoA and Rac1, both of which were observed to be activated in all cases prior to therapy. Loss of GTPase activation also was observed for CLL cells sampled at later time points.

Of evaluable patients, 12 had stable disease and 2 had progressive disease, the latter having received <1 mg/kg per dose of cirmtuzumab. Some patients experienced reductions in lymph node size or in absolute lymphocyte count (max 58% reduction from baseline). The presenters noted a striking stabilization of disease after just 4 infusions of cirmtuzumab and with long progression-free survival (PFS): median PFS of 263 days with a range 112-414 days. A steep fall-off in the PFS survival curve was noted after a period equivalent to approximately 7x the half-life of cirmtuzumab, when the plasma antibody concentration is expected to be negligible. The presenters concluded that the results warrant Phase 2 testing of cirmtuzumab, either alone or in combination with other targeted therapies for leukemia.

Cirmtuzumab Targets ROR1 to Inhibit Ibrutinib-Resistant, Wnt5a-Induced Rac1 Activation in Chronic Lymphocytic Leukemia

BTK inhibitor, ibrutinib, blocks BCR-signaling and has demonstrated clinical effectiveness in CLL but has not shown the ability to induce complete responses or durable remissions without continued therapy, suggesting that ancillary pathways contribute to CLL growth and survival. ROR1 is a receptor for Wnt5a, which can promote activation of Rac1 to enhance CLL-cell proliferation and survival. Investigators hypothesized that the effects of ibrutinib on blocking BCR-signaling might be offset by non-canonical Wnt-signaling via ROR1, which would suggest that dual inhibition of ROR1- and BCR-signaling may have an enhanced anti-tumor effect.

Investigators observed that Wnt5a induced Rac1 activation and enhanced proliferation of CLL cells treated in vitro with ibrutinib, even at concentrations exceeding those required to fully inhibit BTK and BCR-signaling. However, cirmtuzumab was able to block Wnt5a-induced activation of Rac1 in the CLL cells. *In vivo*, cirmtuzumab and ibrutinib each demonstrated some leukemia-cell clearance, but together exhibited synergistic activity in clearing human CLL cells. Similarly, in an *in vivo* model of ROR1+ leukemia, treatment with the combination of cirmtuzumab and ibrutinib resulted in

smaller spleen size and synergistic clearance of leukemia cells. Investigators concluded that the results provide rationale for trials combining cirmtuzumab and ibrutinib in CLL or other B-cell malignancies.

Two additional posters were presented which provide preclinical evidence supporting the role of cirmtuzumab and blocking Wnt5a activation of ROR1 in the treatment of CLL:

- *Wnt5a Induces ROR1 to Complex with HS1, Which Undergoes Tyrosine Phosphorylation and Contributes to Planar-Cell-Polarity Migration in Chronic Lymphocytic Leukemia*
- *Wnt5a Induces Association of ROR1 with 14-3-3ζ to Enhance Chemotaxis and Proliferation in Chronic Lymphocytic Leukemia*

TK216

TK216, a Novel, Small Molecule Inhibitor of the ETS-Family of Transcription Factors, Displays Anti-Tumor Activity in AML and DLBCL

Oncternal and collaborators at Georgetown University and the IOR Institute of Oncology Research in Switzerland demonstrated that TK216 has anti-proliferative effects in *in vitro* models, causing cell cycle arrest and inducing apoptosis in AML and DLBCL cell lines. Treatment with TK216 showed a decrease in myeloid cellular viability and induced dose-dependentapoptosis of cells at 48 hours. Similarly, in a panel of DLBLC cell lines, TK216 treatment resulted in a decrease in cellular proliferation and an increase in apoptosis. The presenters conclude that these findings provide evidence of the utility and potential efficacy of TK216 in the treatment of AML and DLBCL by targeting the ETS-family of transcription factors.

About Cirmtuzumab

Cirmtuzumab is a first-in-class anti-ROR1 monoclonal antibody, currently in a Phase 1 clinical trial for patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Cirmtuzumab was developed at the Moores Cancer Center of UC San Diego following extensive research characterizing the function and expression of ROR1, which may identify cancer stem cells in a number of hematologic malignancies and solid tumors. Oncternal and UC San Diego are planning studies in CLL, breast cancer and mantle cell lymphoma.

About TK216

TK216 is a first-in-class small molecule that inhibits the biological activity of ets-family transcription factor oncoproteins in a variety of tumor types, stopping cancer cell growth and tumor formation. In Ewing sarcoma, it is designed to target a single and well-characterized genetic mutation that causes the disease. TK216 is being developed collaboratively by Georgetown University and Oncternal. Oncternal and Georgetown are also planning clinical studies of TK216 in glioblastoma, prostate cancer and leukemia.