# Oncternal Therapeutics Presents Updated Interim Data for Zilovertamab in Combination with Ibrutinib at ASH 2021

December 13, 2021

- *Updated mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) data from the CIRLL study are encouraging, and comparable to previous results presented at ASCO 2021*
- *Objective response rate (ORR) of 81% (21 of 26 evaluable patients) observed for heavily pre-treated patients with MCL treated with zilovertamab plus ibrutinib, which compares favorably to historical ORR of 66% for ibrutinib monotherapy*
- *Complete response (CR) rate of 35% for MCL patients treated with zilovertamab plus ibrutinib (9 of 26 evaluable patients), which compares favorably to historical ORR of 20% for ibrutinib monotherapy, with CRs remaining durable for up to 32 months*
- *Median progression-free survival (PFS) of 35.9 months for MCL patients with median follow-up of 14.4 months, which compares favorably to historical ibrutinib monotherapy PFS of 12.8 months*
- *Median PFS had not been reached for CLL patients with ≤ 2 prior lines of therapy, and median PFS was 36.1 months for patients receiving > 2 prior lines of therapy, with a median follow-up of 29.0 months*
- *Landmark PFS of ~ 85% and ~ 65% at 24 and 36 months, respectively, for CLL patients who had previously received > 2 prior lines of therapy, which compares favorably to historical ibrutinib monotherapy of ~ 65% and ~ 50%, respectively*
- *Landmark PFS of 100% at 36 months for CLL patients who had previously received ≤ 2 prior lines of therapy, which compares favorably to historical ibrutinib monotherapy PFS of ~ 75%*
- *The combination of zilovertamab and ibrutinib continued to be well tolerated, with a safety profile consistent or improved compared with historical data for ibrutinib monotherapy*

SAN DIEGO, Dec. 13, 2021 (GLOBE NEWSWIRE) -- Oncternal Therapeutics, Inc. (Nasdaq: ONCT), a clinical-stage biopharmaceutical company focused on the development of novel oncology therapies, today announced updated interim clinical data from the ongoing Phase 1/2 CIRLL (Cirmtuzumab and Ibrutinib targeting ROR1 for Leukemia and Lymphoma) clinical trial, that will be presented in a poster presentation at the American Society of Hematology (ASH) 2021 Annual Meeting. In the CIRLL study, zilovertamab, an investigational anti-ROR1 monoclonal antibody, is being evaluated in combination with ibrutinib in patients with MCL and CLL. The clinical trial is being conducted in collaboration with UC San Diego and is partially funded by the California Institute for Regenerative Medicine (CIRM).

The updated interim data will be presented as a poster presentation at the Mantle Cell, Follicular and Oher Indolent B Cell Lymphomas Clinical and Epidemiological session on December 13, 2021 as part of the ASH 2021 Annual Meeting:

- **Poster Title:** Phase 1/2 Study of Cirmtuzumab and Ibrutinib in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL)
- **Publication Number:** 3534
- **Session Name:** 623, Mantle Cell, Follicular and Oher Indolent B Cell Lymphomas Clinical and Epidemiological
- **Session Date and Time:** December 13, 2021 from 6:00-8:00 pm (Eastern Time)
- **Location:** Georgia World Congress Center, Hall B5

“Our confidence in the differentiation of zilovertamab enabled therapy continues to build as we strengthen our MCL and CLL data set. The median PFS of 35.9 months for heavily pre-treated MCL patients is approximately three times longer than the previously reported median PFS of 12.8 months for ibrutinib monotherapy. The landmark PFS of 85% at 24 months and 65% at 36 months for patients with CLL, regardless of the number of prior lines of therapy, are also encouraging. The combination continues to be generally well tolerated, and we are encouraged by the low grade 3/4 neutropenia rate of 10% for the combination therapy, compared to 29% for ibrutinib alone from its registration study in MCL,” said James Breitmeyer, M.D., Ph.D., Oncternal’s President and CEO. “We expect to provide an update regarding our dialogue with the U.S. FDA regarding Phase 3 study design later this month.”

The results that will be presented in poster form at ASH 2021 include 31 patients with relapsed/refractory MCL enrolled in the dose-finding and dose-expansion cohorts of the CIRLL clinical trial (Part 1 + Part 2), of whom 26 were evaluable for efficacy as of the October 1, 2021 data cut-off date.

- Patients had high-risk factors and were heavily pre-treated at study entry, with 52% having high Ki-67 proliferative index (≥30%) and 45% with intermediate/high sMIPI prognostic score.
- The ORR of 81% (21 of 26 evaluable patients), including recently enrolled patients with relatively short follow-up time, is comparable to the 83% ORR (15 of 18 evaluable patients) previously presented at the ASCO 2021 Annual Meeting.
- Twelve of 26 (46%) evaluable patients achieved a partial response (PR) and three patients (12%) had stable disease (SD), for a total clinical benefit rate (CR, PR and SD) of 92%.

- The complete response rate was 35% (9 of 26 evaluable patients). CRs have remained durable, for up to 32 months as of the data cutoff date.
- The ORR and median duration of response were favorable in patients with high-risk features associated with difficult to treat disease:
    - Ki-67 ≥30%: ORR of 85%; median duration of response of 14 months (95% CI: 13.7, NE), and
    - >1 prior systemic therapy: ORR of 82%; median duration of response not reached for patients receiving two prior lines of systemic therapy and 34 months (95% CI: 13.8, 34.1) for patients with ≥ 3 prior lines of systemic therapy
- Five patients had received prior treatment with ibrutinib, achieving two CRs and two PRs. One patient had SD.
- Median PFS was 35.9 months after a median follow-up of 14.4 months (95% CI: 11.4, 19.3), regardless of number of prior systemic therapies. Further, median PFS had not been reached for patients achieving a CR.
- Historical data published for single agent ibrutinib for 370 patients with relapsed/refractory MCL from three clinical trials showed an ORR of 66%, CR rate of 20% and median PFS of 12.8 months (*Rule et al.* 2017, British Journal of Haematology).

As of the October 1, 2021 data cut-off date, 34 patients with CLL have been enrolled in the dose-finding and dose-confirming cohorts of this clinical trial (Part 1 & Part 2), all of which were evaluable for efficacy. Patients had high-risk factors, and most were heavily pre-treated at study entry, with 71% having RAI staging ≥2 and a median of two systemic prior therapies (range 1-15).

- The ORR was 91% (31 of 34 evaluable patients), consistent with prior published results.
- The CR rate was 6% (2 of 34 evaluable patients), twenty-nine patients (85%) achieved a PR and three patients (9%) had SD, for a total clinical benefit rate (CR, PR and SD) of 100%.
- Median PFS in patients with ≤ 2 prior therapies had not been reached, and patients with > 2 prior therapies had a median PFS of ~36.1 months after a median follow up of 29.0 months (95% CI: 27.6, 31.6), in this high risk and mostly heavily pre-treated CLL population.
- Based on the Kaplan-Meier curve, landmark PFS of ~ 85% and ~ 65% at 24 and 36 months, respectively, for CLL patients receiving > 2 prior lines of therapy compared favorably to historical ibrutinib monotherapy of ~ 65% and ~ 50%, respectively (*Byrd* 2019). Landmark PFS was 100% at 36 months for CLL patients with ≤ 2 prior lines of therapy, which compares favorably to historical ibrutinib monotherapy of ~ 75% (*Byrd* 2019).

Thirty-one patients with CLL have also been enrolled in the randomized efficacy cohort of this clinical trial (Part 3), of which 22 were evaluable for efficacy. Data on this cohort is maturing, and median PFS had not been reached as of the October 1, 2021 cut-off date.

The combination of zilovertamab plus ibrutinib has been well tolerated, with treatment emergent adverse events consistent with those reported for ibrutinib alone. There have been no dose-limiting toxicities and no serious adverse events attributed to zilovertamab alone.

**About the CIRLL Clinical Trial**
The CIRLL clinical trial (CIRM-0001) is a Phase 1/2 trial evaluating zilovertamab in combination with ibrutinib in separate groups of patients with CLL or MCL. Enrollment of the dose-finding cohorts in CLL and MCL, dose-expansion cohort in CLL and randomized Phase 2 cohort in CLL has been completed. Enrollment of the dose-expansion cohort in MCL is ongoing. Additional information about the CIRM-0001 clinical trial and other clinical trials of zilovertamab may be accessed at ClinicalTrials.gov.

**About Zilovertamab (formerly Cirmtuzumab)**
Zilovertamab is an investigational, potentially first-in-class monoclonal antibody targeting ROR1, or Receptor tyrosine kinase-like Orphan Receptor 1. Zilovertamab is currently being evaluated in a Phase 1/2 clinical trial in combination with ibrutinib for the treatment of MCL or CLL, in a collaboration with the University of California San Diego (UC San Diego) School of Medicine and the California Institute for Regenerative Medicine (CIRM). In addition, Oncternal is supporting two investigator-sponsored studies being conducted at the UC San Diego School of Medicine: (i) a Phase 1b clinical trial of zilovertamab in combination with paclitaxel for the treatment of women with HER2-negative metastatic or locally advanced, unresectable breast cancer, and (ii) a Phase 2 clinical trial of zilovertamab in combination with venetoclax, a Bcl-2 inhibitor, in patients with relapsed/refractory CLL.

ROR1 is a potentially attractive target for cancer therapy because it is an onco-embryonic antigen – not usually expressed on adult cells, and its expression confers a survival and fitness advantage when reactivated and expressed by tumor cells. Researchers at the UC San Diego School of Medicine discovered that targeting a critical epitope on ROR1 was key to specifically targeting ROR1 expressing tumors. This led to the development of zilovertamab, that binds this critical epitope of ROR1, which is highly expressed on many different cancers but not on normal tissues. Preclinical data showed that when zilovertamab bound to ROR1, it blocked Wnt5a signaling, inhibited tumor cell proliferation, migration and survival, and induced differentiation of the tumor cells. The FDA has granted Orphan Drug Designations to zilovertamab for the treatment of MCL and CLL/small lymphocytic lymphoma. Zilovertamab is in clinical development and has not been approved by the FDA for any indication.

**About Oncternal Therapeutics**
Oncternal Therapeutics is a clinical-stage biopharmaceutical company focused on the development of novel oncology therapies for the treatment of cancers with critical unmet medical need. Oncternal focuses drug development on promising, yet untapped biological pathways implicated in cancer generation or progression. The clinical pipeline includes zilovertamab (formerly cirmtuzumab) an investigational monoclonal antibody designed to inhibit the ROR1 pathway, a type I tyrosine kinase-like orphan receptor, that is being evaluated in a Phase 1b/2 clinical trial in combination with ibrutinib for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) and in an investigator-sponsored, Phase 1b clinical trial in combination with paclitaxel for the treatment of women with HER2-negative metastatic or locally advanced, unresectable breast cancer, as well as a Phase 2 clinical trial of zilovertamab in combination with venetoclax, a Bcl-2 inhibitor, in patients with relapsed/refractory CLL. Oncternal is also developing ONCT-808, a chimeric antigen receptor T cell (CAR-T) therapy that targets ROR1, which is currently in preclinical

development as a potential treatment for hematologic cancers and solid tumors. The clinical pipeline also includes ONCT-216 (formerly TK216), an investigational targeted small-molecule inhibitor of the ETS family of oncoproteins, that is being evaluated in a Phase 1/2 clinical trial for patients with Ewing sarcoma alone and in combination with vincristine chemotherapy. The early-stage pipeline also includes ONCT-534 (formerly GTX-534), a dual-action androgen receptor inhibitor, that is in pre-clinical development as a potential treatment for castration resistant prostate cancer and other androgen-receptor dependent diseases. More information is available at https://oncternal.com/.

**Forward-Looking Information**

Oncternal cautions you that statements included in this press release that are not a description of historical facts are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negatives of these terms or other similar expressions. These statements are based on Oncternal’s current beliefs and expectations. Forward-looking statements include statements regarding the potential for zilovertamab in combination with ibrutinib to treat MCL or CLL; and timing of an update regarding our potential pivotal study designs. Forward-looking statements are subject to risks and uncertainties inherent in Oncternal’s business, including risks associated with the clinical development and process for obtaining regulatory approval of Oncternal’s product candidates, such as potential delays in the commencement, enrollment and completion of clinical trials; Oncternal has not conducted head-to-head studies of zilovertamab in combination with ibrutinib compared to ibrutinib monotherapy and data from separate studies may not be directly comparable due to the differences in study protocols, conditions and patient populations; the risk that interim results of a clinical trial do not predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, as follow-up on the outcome of any particular patient continues, and as more patient data become available; and other risks described in Oncternal’s filings with the U.S. Securities and Exchange Commission. All forward-looking statements in this press release are current only as of the date hereof and, except as required by applicable law, Oncternal undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise. All forward-looking statements are qualified in their entirety by this cautionary statement. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

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