# Oncternal Therapeutics Presents Updated Interim Data for Zilovertamab in Combination with Ibrutinib at ASH 2022

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- *Updated MCL and CLL data from the ongoing Phase 1/2 study of zilovertamab and ibrutinib are encouraging and continue to improve over prior reporting*
- *The ORR of 89% and CR rate of 43% for patients with MCL treated with zilovertamab plus ibrutinib compare favorably to the historical ORR of 66% and CR rate of 20% for ibrutinib monotherapy*
- *Median PFS and OS have not been reached after a median follow up of 19.5 months for patients with MCL treated with zilovertamab plus ibrutinib, which compares favorably to the historical median PFS and OS of 12.8 months and 25 months, respectively, for ibrutinib monotherapy*
- *Landmark PFS was 100% at 42 months for patients with CLL expressing p53 mutation/del(17p) treated with zilovertamab plus ibrutinib*

SAN DIEGO, Dec. 10, 2022 (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 ongoing Phase 1/2 Study CIRM-0001 in an oral presentation at the American Society of Hematology (ASH) 2022 Annual Meeting. In the study, zilovertamab, an investigational anti-ROR1 monoclonal antibody, is being evaluated in combination with ibrutinib in patients with mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) and in a recently opened cohort for patients with marginal zone lymphoma (MZL). The clinical trial is being conducted in collaboration with the University of California San Diego (UC San Diego) and has been partially funded by the California Institute for Regenerative Medicine (CIRM).

“The data presented in today’s oral session further strengthens our confidence in the significant clinical benefit the combination of zilovertamab and ibrutinib can provide to patients with MCL and CLL. The rapid onset of deep responses in patients with MCL supports our recently initiated randomized global registrational Phase 3 Study ZILO-301 of the combination of zilovertamab plus ibrutinib,” said James Breitmeyer, M.D., Ph.D., Oncternal’s President and CEO. “The robust response rates and prolonged PFS seen for MCL and CLL patients expressing the p53 mutation/del(17p), who are underserved by current standard of care treatments, is especially exciting. We continue to believe that the inhibition of ROR1 with zilovertamab can play a key role in addressing important unmet medical needs in difficult-to-treat patients across various hematological malignancies.”

The updated interim data presented during an oral presentation at the ASH 2022 meeting include 33 patients with relapsed/refractory (R/R) MCL enrolled in the dose-finding and dose-expansion cohorts of Study CIRM-0001 (Part 1 + Part 2), of whom 28 were evaluable for efficacy as of the October 11, 2022 data cut-off date.

- Patients had high-risk factors and were heavily pre-treated at study entry, with 52% having a high Ki-67 proliferative index (≥30%), 47% with p53 mutations or deletions in chromosome 17p (del(17p)), and 46% having an intermediate or high sMIPI prognostic score.
- The objective response rate (ORR) was 89% (25 of 28 evaluable patients) and includes recently enrolled patients.
- The complete response (CR) rate was 43% (12 of 28 evaluable patients) at 26 months and was already 18% (5 of 28 evaluable patients) at 3 months.
- Historical data published for single agent ibrutinib for 370 patients with R/R MCL from three clinical trials showed an ORR of 66%, CR rate of 20% and median PFS of 12.8 months (Rule 2017, British Journal of Haematology).
- The partial response (PR) rate was 46% (13 of 28 evaluable patients), and the stable disease (SD) rate was 4% (1 of 28 evaluable patients), for a total clinical benefit rate (CR, PR and SD) of 93%.
- The median PFS has not been reached after a median follow-up of 19.5 months (95% CI: 19.4, 28.5), regardless of the number of prior systemic therapies.
- Median PFS was also favorable in patients with high-risk features associated with disease difficult-to-treat with BTK inhibitors:
    - P53 mutation/del(17p): median PFS not reached (95% CI: 2.85, NE). Historical data for single agent ibrutinib in 20 patients with p53 mutation showed a median PFS of 4.0 months (Rule 2019, Haematologica).
    - Ki-67 ≥30%: median PFS 33.2 months (95% CI: 2.85, NE).
    - >1 prior systemic therapy: median PFS not reached (95% CI: 4.33, NE).

Thirty-four patients with CLL in the dose-finding and dose-confirming cohorts of this clinical trial (Part 1 & Part 2) as of the October 11, 2022 data cut-off date were all evaluable for efficacy. Patients had high-risk factors, and most were heavily pre-treated at study entry, with a median of two systemic prior therapies (range 1-9).

- Landmark PFS was 100% at 42 months in patients with R/R CLL expressing p53 mutation/del(17p) treated with the

combination of zilovertamab plus ibrutinib. The most recent data update from the ALPINE study in patients with R/R CLL expressing p53 mutation/del(17p) showed a landmark PFS of 77.6% at 24 months for zanubrutinib monotherapy and 55.7% at 24 months for ibrutinib monotherapy (Brown 2022, ASH).

- Landmark PFS was 95% at 24 months in all patients with R/R CLL treated with the combination of zilovertamab plus ibrutinib. The most recent data update from the ALPINE study in R/R CLL patients showed a landmark PFS at 24 months of 79.5% for zanubrutinib and 67.3% for ibrutinib monotherapy (Brown 2022, ASH).
- The median overall survival (OS) was not reached at 40 months for patients with CLL with p53 mutation/del(17p).

Thirty-one patients with CLL have also been enrolled in the randomized efficacy cohort of this clinical trial (Part 3), of which 23 were evaluable for efficacy. Data from this cohort are maturing. The median PFS had not been reached for either group as of the October 11, 2022 cut-off date after a median follow up of 29 months.

The combination of zilovertamab plus ibrutinib has been well tolerated as of the October 11, 2022 cut-off date, with treatment emergent adverse events consistent with or slightly improved compared to those reported for ibrutinib alone. There have been no dose-limiting toxicities and no serious adverse events attributed to zilovertamab alone. Atrial fibrillation was observed in only 9.4% of the patients and febrile neutropenia in 1.2% of patients.

**About the CIRM-0001 Study**
The CIRM-0001 Study is a Phase 1/2 trial evaluating zilovertamab in combination with ibrutinib in separate groups of patients with CLL, MCL or MZL. Enrollment of the dose-finding cohorts in CLL and MCL, dose-expansion cohort in CLL and MCL and randomized Phase 2 cohort in CLL has been completed. An additional dose-expansion cohort of up to 10 patients with MZL has started enrolling patients. Additional information about the CIRM-0001 clinical trial and other clinical trials of zilovertamab may be accessed at ClinicalTrials.gov.

**About Zilovertamab**
Zilovertamab is an investigational, humanized, potentially first-in-class monoclonal antibody targeting Receptor tyrosine kinase-like Orphan Receptor 1 (ROR1). A Phase 3 registrational trial evaluating zilovertamab plus ibrutinib versus ibrutinib plus placebo in relapsed or refractory Mantle Cell Lymphoma (MCL) has been initiated (NCT05431179). Zilovertamab is also being studied in a Phase 1/2 clinical trial in combination with ibrutinib for the treatment of patients with MCL, chronic lymphocytic leukemia (CLL) or marginal zone lymphoma (MZL), 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, a Phase 1b clinical trial for patients with metastatic castration-resistant prostate cancer (mCRPC), and a Phase 2 clinical trial of zilovertamab in combination with venetoclax, a Bcl-2 inhibitor, for patients with relapsed/refractory CLL. Both are open for enrollment.

ROR1 is a potentially attractive target for cancer therapy because it is an onco-embryonic antigen, not usually expressed on adult cells, but 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 inhibiting ROR1-expressing tumors. This led to the development of zilovertamab which binds this critical epitope of ROR1, 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 patients with 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 patients with cancers that have critical unmet medical need. Oncternal pursues drug development targeting promising, yet untapped biological pathways implicated in cancer generation or progression, focusing on hematological malignancies and prostate cancer. The lead clinical program is zilovertamab, an investigational monoclonal antibody designed to inhibit the function of Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1). ZILO-301, a global Phase 3 Study to evaluate zilovertamab in combination with ibrutinib for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL) has been initiated (NCT05431179). Zilovertamab continues to be evaluated in an ongoing Phase 1/2 study in combination with ibrutinib for the treatment of patients with MCL and chronic lymphocytic leukemia (CLL), and this trial was recently amended to include patients with marginal zone lymphoma (MZL) (NCT03088878). Zilovertamab is also being evaluated in two investigator-initiated studies, including a Phase 2 clinical trial of zilovertamab in combination with venetoclax, a Bcl-2 inhibitor, in patients with relapsed/refractory CLL, and in a Phase 1b study of zilovertamab in combination with docetaxel in patients with metastatic castration-resistant prostate cancer (mCRPC). Oncternal is also moving into the clinic with ONCT-808, an autologous chimeric antigen receptor T (CAR T) cell therapy that targets ROR1, with an active U.S. IND as of the end of September 2022 for the treatment of patients with relapsed or refractory aggressive B-cell lymphoma, including patients who have failed previous CD19 CAR T treatment. The preclinical pipeline also includes ONCT-534, a dual-action androgen receptor inhibitor (DAARI) that is undergoing final IND-enabling studies, as a potential treatment for castration resistant prostate cancer, including those with unmet medical need due to resistance to approved, standard of care androgen receptor inhibitors. 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, CLL or MZL; and the potential that Study ZILO-301 can serve as a registrational clinical trial. 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; we have 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; later developments with the FDA may be inconsistent with the minutes from the completed end of Phase 2 meeting, including that the proposed Study ZILO-301 that may not support registration of zilovertamab in combination

with ibrutinib which is a review issue with the FDA upon submission of a BLA; 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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