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

May 26, 2022

- *Updated MCL and CLL data from the CIRLL study are encouraging and continue to improve*
- *ORR of 85% (23 of 27 evaluable patients) and CR rate of 41% (11 of 27 evaluable patients) for patients with MCL treated with zilovertamab plus ibrutinib compare favorably to historical ORR of 66% and CR of 20% for ibrutinib monotherapy*
- *Data from p53-mutated MCL and CLL patients show encouraging response rates in sub-group analyses. Landmark PFS was over 80% at 15 months for MCL and 100% at 36 months for CLL in p53-mutated patients treated with zilovertamab plus ibrutinib*
- *The combination of zilovertamab and ibrutinib continued to be well tolerated, with an adverse event profile consistent or improved compared with historical data for ibrutinib monotherapy*

SAN DIEGO, May 26, 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 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 Clinical Oncology (ASCO) 2022 Annual Meeting. In the CIRLL study, zilovertamab, an investigational anti-ROR1 monoclonal antibody, is being evaluated in combination with ibrutinib in patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). 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 updated interim data will be presented as a poster discussion session at the Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia session on Saturday, June 4, 2022 as part of the ASCO 2022 Annual Meeting:

- **Poster Title:** Phase 1/2 study of zilovertamab and ibrutinib in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL)
- **Abstract Number:** 7520
- **Session Name:** Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
- **Session Date and Time:** June 4, 2022 from 8:00-11:30 am (Central Time)

“The interim data update presented today further strengthens our confidence in the significant clinical value the combination of zilovertamab and ibrutinib can deliver to MCL and CLL patients. Solid objective response rate (ORR) of 85% and median progression-free survival (PFS) of 36 months in heavily pre-treated MCL patients in our CIRLL study support our Phase 3 registrational study ZILO-301, which we plan to initiate in the third quarter,” said James Breitmeyer, M.D., Ph.D., Oncternal’s President and CEO. “We continue to be especially intrigued by the encouraging and robust response rate across multiple populations of high-risk MCL and CLL patients, most notably the prolonged PFS seen for those that express the p53 mutation, a particularly challenging population for BTK inhibitors. This is further proof that the combination is very active, and we believe it may address important unmet medical needs in difficult-to-treat patients with aggressive forms of hematological malignancies.”

The results that will be presented in poster form and reviewed in a poster discussion at the ASCO 2022 Annual Meeting include 33 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 27 were evaluable for efficacy as of the April 8, 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%), and 46% having an intermediate or high sMIPI prognostic score.
- The ORR of 85% (23 of 27 evaluable patients) includes recently enrolled patients with relatively short follow-up time.
- The complete response (CR) rate was 41% (11 of 27 evaluable patients). CRs have remained durable for up to 35 months.
- The partial response (PR) rate was 44% (12 of 27 evaluable patients), and the stable disease (SD) rate was 7% (2 of 27 evaluable patients), for a total clinical benefit rate (CR, PR and SD) of 93%.
- The ORR and median duration of response (DOR) were also favorable in patients with other high-risk features associated with disease difficult-to-treat with BTK inhibitors:
    - P53 mutation: ORR of 83%; median DOR of 13.8 months (95% CI: 11.9, NE), median PFS of 17.3 months (95% CI: 2.9, NE) and a landmark PFS over 80% at 15 months
    - Ki-67 ≥30%: ORR of 86%; median DOR not reached (95% CI: 13.7, NE)
    - >1 prior systemic therapy: ORR of 83%; median DOR 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
    - Prior treatment with ibrutinib: ORR of 80% (4/5), with two CRs, two PRs and one SD

- Median PFS was 35.9 months for all patients with MCL 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). Historical data in 20 patients with p53 mutation showed an ORR of 55% and median PFS of 4.0 months (Rule, 2019).

Thirty-four patients with CLL enrolled in the dose-finding and dose-confirming cohorts of this clinical trial (Part 1 & Part 2) as of the April 8, 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 71% having RAI staging ≥2 and a median of two systemic prior therapies (range 1-9).

- The ORR was 91% (31 of 34 evaluable patients).
- The CR rate was 9% (3 of 34 evaluable patients).
- The clinical benefit rate was 100%, with 28 of 34 (82%) evaluable patients achieving a PR, and three patients (9%) had SD.
- The median PFS had not been reached for all patients with CLL, whether treatment-naïve or those with relapsed refractory disease.
- Landmark PFS was 100% at 36 months for CLL patients with 1 or 2 prior lines of therapy, which compares favorably to historical ibrutinib monotherapy of ~ 73% (*Byrd.* 2019).
- For patients with CLL who had received > 2 prior lines of therapy, the landmark PFS was over 85% at 24 months and 70% at 36 months, which compares favorably to the historical ibrutinib monotherapy landmark PFS at 24 and 36 months of ~ 65% and ~ 50%, respectively (*Byrd.* 2019).

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 on this cohort are maturing. The median PFS had not been reached for either group as of the April 8, 2022 cut-off date after 24 months of follow up.

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. In patients with MCL, Grade 3-4 neutrophil decrease was documented in 9.1% of patients with zilovertamab plus ibrutinib, compared to 29% for ibrutinib alone from its registration study.

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 MCL and randomized Phase 2 cohort in CLL has been completed. An additional dose-expansion cohort of up to 10 patients with marginal zone lymphoma (MZL) has recently been added. Enrollment is expected to begin in Q2 2022. Additional information about the CIRM-0001 clinical trial and other clinical trials of zilovertamab may be accessed at ClinicalTrials.gov.

About Zilovertamab
Zilovertamab (formerly designated cirmtuzumab) is an investigational, humanized, potentially first-in-class monoclonal antibody targeting Receptor tyrosine kinase-like Orphan Receptor 1 (ROR1). Zilovertamab is currently being evaluated in a Phase 1/2 clinical trial in combination with ibrutinib for the treatment of patients with MCL, chronic lymphocytic leukemia (CLL) or 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 ROR1, a type I tyrosine kinase-like orphan receptor. Zilovertamab is being evaluated in a Phase 1/2 clinical trial in combination with ibrutinib for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL), in 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 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 early-stage pipeline also includes ONCT-534, a dual-action androgen receptor inhibitor (DAARI), that is in preclinical development as a potential treatment for

castration resistant prostate cancer, including those with clinically important resistance to approved 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 or CLL; the potential that Study ZILO-301 can serve as a registrational clinical trial; and the expected initiation or enrollment of clinical trials, including Study ZILO-301. 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; 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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