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Leap Therapeutics Reports Initial Clinical Data from Part B of the DeFianCe Study and Part C of the DisTinGuish Study

January 28, 2025

35% objective response rate (ORR) in second-line colorectal cancer (CRC) patients treated with sirexatamab (DKN-01) plus bevacizumab and chemotherapy, compared to 23% ORR in the control arm

DKK1 levels highly correlated with clinical activity in CRC population

ORR benefit with sirexatamab observed across multiple potential Phase 3 CRC populations

Preparations will begin for a registrational Phase 3 study in second-line CRC patients

DisTinGuish Part C study in gastric cancer demonstrates activity in biomarker populations, but not the signal necessary to advance into Phase 3

Leap to host a conference call to present clinical data today, January 28, 2025, at 8:00 a.m. ET

CAMBRIDGE, Mass., Jan. 28, 2025 /PRNewswire/ -- Leap Therapeutics, Inc. (Nasdaq:LPTX), a biotechnology company focused on developing targeted and immuno-oncology therapeutics, today announced positive initial data from Part B of the DeFianCe study evaluating sirexatamab (DKN-01) in combination with bevacizumab and chemotherapy as a second-line treatment for patients with advanced colorectal cancer (CRC), and initial data from Part C of the DisTinGuish study evaluating sirexatamab in combination with tislelizumab and chemotherapy in first-line patients with advanced gastroesophageal junction (GEJ) and gastric cancer.

Key Findings from Part B of the DeFianCe study:

"Data from Part B of the DeFianCe study closely mirror the findings from Part A, and together they demonstrate the potential of sirexatamab to provide a compelling treatment option for second-line CRC patients who do not benefit from current standard of care," said Cynthia Sirard, M.D., Chief Medical Officer of Leap. "Along with consistently achieving higher response rates than the control arm, the data also point to a favorable safety profile. While not yet fully mature, we are encouraged by the progression-free survival data thus far across key subgroups in the study. We look forward to reporting additional data from Part B as it matures over the coming months and beginning our planning for Phase 3 registrational studies."

"The patient population in second-line CRC is heterogeneous, and there is a true unmet need for new treatment options that are safe and effective. The latest findings from DeFianCe Part B are highly encouraging, as sirexatamab combination therapy is outperforming bevacizumab and chemotherapy alone in ORR in the intent-to-treat analysis and across key subgroups of interest," said Zev Wainberg, M.D., Professor of Medicine and Co-Director of the GI Oncology Program at UCLA. "Initial results also show increased response rates in patients with high DKK1 levels, directly correlating with sirexatamab's novel mechanism of action. These data support moving forward into Phase 3 registrational studies to further explore a unique treatment option for patients in need."

The DeFianCe study (NCT05480306) is a Phase 2, open-label, global study of sirexatamab in combination with bevacizumab and chemotherapy in patients with advanced microsatellite stable (MSS) CRC who have received one prior systemic therapy for advanced disease. Part B of the study is a 188 patient randomized controlled trial, with the primary objective being progression-free survival (PFS) in patients with left-sided cancers and in all patients. Key secondary and exploratory objectives include objective response rate (ORR), duration of response, and overall survival across tumor, treatment, and biomarker subgroups.

- Across the intent-to-treat (ITT) population with second-line MSS CRC (n=188):
  - Patients treated with sirexatamab plus bevacizumab and chemotherapy (Experimental Arm, n=94) had ORR of 35% and disease control rate (DCR) of 86%, compared to an ORR of 23% and DCR of 84% in patients treated with bevacizumab and chemotherapy alone (Control Arm, n=94)

- Across the population with left-sided primary tumors (n=144):
  - Patients treated in the Experimental Arm (n=71) had an ORR of 38%, compared to an ORR of 25% in the Control Arm (n=73)

- Plasma DKK1 highly correlated with clinical activity:
  - Patients in the Experimental Arm with DKK1 levels above the median (n=49) had an ORR of 39%, compared to 22% ORR in the Control Arm (n=36)
  - Patients in the upper-quartile of DKK1 levels in the Experimental Arm (n=25) had an ORR of 48%, compared to 11% ORR in the Control arm (n=18)

- Key patient subgroups demonstrated higher ORR in the Experimental Arm:
  - No prior anti-VEGF therapy: Patients in the Experimental Arm (n=49) had an ORR of 51%, compared to 29% ORR in the Control Arm (n=45)
  - Prior anti-EGFR therapy: Patients in the Experimental Arm (n=28) had an ORR of 54%, compared to 27% ORR in the Control Arm (n=22)

- RAS wildtype (RAS-wt) tumors: Patients in the Experimental Arm (n=35) had an ORR of 43%, compared to 32% ORR in the Control Arm (n=25)

- With only 3 months follow-up on the final patients enrolled and mean duration on study of approximately 6 months, PFS is not yet mature. Eighty-two patients are still on study, 46 in the Experimental Arm and 36 in the Control Arm. Early separation in the Kaplan-Meier PFS curves is being seen in many of the key patient subgroups, including DKK1 biomarker, anti-VEGF-naïve, anti-EGFR-experienced, and RAS-wt patients. Leap expects to report additional data as it matures in 2025.

- Sirexatamab plus bevacizumab and chemotherapy was well-tolerated, without additive toxicity to the standard of care.

The strong signal in CRC from the DeFianCe study supports Leap moving forward to plan a registrational Phase 3 clinical trial to evaluate sirexatamab plus bevacizumab and chemotherapy in second-line MSS CRC patients with high unmet need, subject to regulatory discussions. Potential Phase 3 patient populations include: DKK1 biomarker-selected, anti-VEGF naïve, anti-EGFR experienced, or RAS-wt patients. While the data matures, Leap intends to conduct global commercial and regulatory strategic analysis to select the optimal population.

Key Findings from Part C of the DisTinGuish study:

Leap also reported data from Part C of the DisTinGuish study evaluating sirexatamab in combination with tislelizumab, BeiGene's anti-PD-1 antibody, and chemotherapy in first-line patients with advanced GEJ and gastric cancer. While demonstrating activity in biomarker populations, the study did not generate a clear positive signal and will be negative on the primary PFS endpoints when the study completes, resulting in the decision not to move forward with Phase 3 studies in gastric cancer.

"Sirexatamab plus tislelizumab and chemotherapy demonstrated improved confirmed response rates compared to the control arm in the ITT, DKK1-high, and PD-L1 negative patients by Blinded Independent Central Review (BICR). However, gastric cancer is a difficult tumor to assess radiologically, and unfortunately, there was a high level of discordance between investigator assessment (IA) and BICR," said Dr. Sirard. "Therefore, we have decided to focus our internal effort and resources on advancing sirexatamab in CRC and will explore strategic partnership opportunities to advance sirexatamab plus anti-PD-1 antibodies in gastric cancer and other indications where there is high DKK1 expression."

Part C of the DisTinGuish study (NCT0436380) is a Phase 2, randomized, open-label, multicenter study of sirexatamab in combination with tislelizumab and chemotherapy in first-line patients with advanced GEJ and gastric cancer. Part C enrolled 170 first-line, HER2-negative patients. Patients were randomized 1:1 to evaluate sirexatamab in combination with tislelizumab and chemotherapy, compared to tislelizumab and chemotherapy alone. The primary objective is PFS by IA in all patients and in DKK1 TPS $\geq$ 20 (DKK1-high) patients. Secondary objectives include ORR, duration of response, and overall survival as measured by BICR and IA in all patients and in DKK1-high patients.

- Across the ITT population (n=170), patients treated with sirexatamab plus tislelizumab and chemotherapy (Experimental Arm, n=85) had a confirmed ORR of 52% by both IA and BICR, while patients treated with tislelizumab and chemotherapy alone (Control Arm, n=85) had a confirmed ORR of 56% by IA and 42% by BICR.

- Based on BICR:
  - Patients in the Experimental Arm with DKK1-high tumors (n=22) had a confirmed ORR of 59%, compared to 36% in the Control Arm (n=22)
  - Patients in the Experimental Arm with PD-L1-negative tumors (n=18) had a confirmed ORR of 44%, compared to 32% in the Control Arm (n=19)

- In the ITT population, preliminary median PFS in the Experimental Arm was 9.72 months by BICR and 7.66 months by IA compared to 11.99 months by BICR and 10.41 months by IA in the Control Arm. The median PFS for tislelizumab plus chemotherapy in the Phase 3 Rationale-305 study was 6.9 months (95% CI: 5.7, 7.2).

- In the DKK1-high population, preliminary median PFS in the Experimental Arm was 7.72 months by BICR and 7.43 months by IA compared to 7.79 months by BICR and 11.14 months by IA in the Control Arm. The hazard ratio for PFS by BICR was 0.68, representing a trend in favor of the Experimental Arm in the overall time to event analysis.

- Sirexatamab plus tislelizumab and chemotherapy was well tolerated, without additive toxicity to the standard of care.

Conference Call:
Leap's management team will host a conference call today, January 28, 2025 at 8:00 a.m. Eastern Time to further discuss the data. The conference call will be broadcast live in listen-only mode and can be accessed via the webcast URL: **https://edge.media-server.com/mmc/p/t93pn2ke**. A replay of the event will be available for a limited time on the Investors page of the Company's website at https://investors.leaptx.com/.

About Leap Therapeutics
Leap Therapeutics (Nasdaq: LPTX) is focused on developing targeted and immuno-oncology therapeutics. Leap's most advanced clinical candidate, sirexatamab (DKN-01), is a humanized monoclonal antibody targeting the Dickkopf-1 (DKK1) protein. Sirexatamab is being studied in patients with colorectal, esophagogastric, and gynecological cancers. Leap's pipeline also includes FL-501, a humanized monoclonal antibody targeting the growth and differentiation factor 15 (GDF-15) protein, in preclinical development. For more information about Leap Therapeutics, visit http://www.leaptx.com or view our public filings with the SEC that are available via EDGAR at http://www.sec.gov or via https://investors.leaptx.com/.

FORWARD-LOOKING STATEMENTS
This press release contains forward-looking statements within the meaning of the federal securities laws. Such statements are based upon current plans, estimates and expectations of the management of Leap that are subject to various risks and uncertainties that could cause actual results to differ materially from such statements. The inclusion of forward-looking statements should not be regarded as a representation that such plans, estimates and expectations will be achieved. Words such as "anticipate," "expect," "project," "intend," "believe," "may," "will," "should," "plan," "could," "continue," "target," "contemplate," "estimate," "forecast," "guidance," "predict," "possible," "potential," "pursue," "likely," and words and terms of similar substance used in connection with any discussion of future plans, actions or events identify forward-looking statements.

All statements, other than historical facts, including statements regarding the potential safety, efficacy, and regulatory and clinical progress of Leap's product candidates; the anticipated timing for initiation or completion of clinical trials and release of clinical trial data and the expectations surrounding the outcomes thereof; Leap's future clinical or preclinical product development plans for any of Leap's product candidates; Leap's estimations of projected cash runway; and any assumptions underlying any of the foregoing, are forward-looking statements. Important factors that could cause actual results to differ materially from Leap's plans, estimates or expectations could include, but are not limited to: (i) the results of Leap's clinical trials and pre-clinical studies, including whether the final data from Part B of the DeFianCe study or Part C of the DisTinGuish study are the same as the initial data reported, (ii) Leap's ability to successfully finance or enter into new strategic partnerships for sirexatamab or any of its other programs; (iii) any regulatory feedback that Leap may receive from U.S. Food and Drug Administration (FDA) or equivalent foreign regulatory agency with respect to the registrational Phase III clinical trials that Leap proposes to conduct using sirexatamab for the treatment of patients with second-line CRC or with respect to any other pre-clinical or clinical development activities that Leap will be required to conduct in order to obtain regulatory approval of sirexatamab for the treatment of second-line CRC; (iv) whether any Leap products will receive approval from the FDA or equivalent foreign regulatory agencies; and (v) exposure to inflation and interest rate fluctuations, as well as fluctuations in the market price of Leap's traded securities. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. Leap may not actually achieve the forecasts disclosed in such forward-looking statements, and you should not place undue reliance on such forward-looking statements. Such forward-looking statements are subject to a number of material risks and uncertainties including but not limited to those set forth under the caption "Risk Factors" in Leap's most recent Annual Report on Form 10-K filed with the SEC, as well as discussions of potential risks, uncertainties, and other important factors in its subsequent filings with the SEC. Any forward-looking statement speaks only as of the date on which it was made. Neither Leap, nor any of its affiliates, advisors or representatives, undertake any obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law. These forward-looking statements should not be relied upon as representing Leap's views as of any date subsequent to the date hereof.

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