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Leap Therapeutics Reports Positive Updated Data from Sirexatamab Colorectal Cancer Study

March 26, 2025

Updated data confirms statistically significant 32% higher ORR and 3.5 month longer PFS
in second-line CRC patients with high DKK1 levels treated with sirexatamab plus bevacizumab and chemotherapy

Statistically significant 22% higher ORR and 2.6 month longer PFS
in patients who had not had prior anti-VEGF therapy

Leap to host a conference call to present clinical data today, March 26, 2025, at 8:00 a.m. ET

CAMBRIDGE, Mass., March 26, 2025 /PRNewswire/ -- Leap Therapeutics, Inc. (Nasdaq:LPTX), a biotechnology company focused on developing targeted and immuno-oncology therapeutics, today presented updated preliminary data from Part B of the DeFianCe study (NCT05480306), a Phase 2, open-label, global study of sirexatamab (DKN-01), an anti-DKK1 monoclonal antibody, in combination with bevacizumab and chemotherapy (Experimental Arm) compared to bevacizumab and chemotherapy (Control Arm) in patients with advanced microsatellite stable (MSS) colorectal cancer (CRC) who have received one prior systemic therapy for advanced disease. The updated analysis includes overall response rate (ORR), by both investigator-assessment (IA) and blinded independent central review (BICR), an additional two months of patient follow-up for progression-free survival (PFS) that demonstrates a favorable maturation of the data, and initial overall survival (OS) data. As of March 12, 2025, 34 patients remain on study drug in the sirexatamab Experimental Arm compared to 24 patients in the Control Arm.

"The updated data from Part B of the DeFianCe study presented today confirms that sirexatamab can generate significantly higher ORR and longer PFS in CRC patients who have high levels of DKK1 or who have not had prior anti-VEGF therapy, two exploratory populations with strong scientific rationale. In the full intent-to-treat population, sirexatamab demonstrated a higher ORR and a tail population with longer PFS that continues to mature. With more sirexatamab-treated patients currently continuing on study drug than control arm patients, there is potential for the dataset to continue to strengthen over the coming months," said Cynthia Sirard, MD, Chief Medical Officer of Leap. "We believe that there is a compelling opportunity to move forward with a registrational study for sirexatamab to confirm these results and bring a new therapy to patients with CRC."

DeFianCe Study Update

- In patients with high DKK1 levels (upper quartile, n=44), the sirexatamab Experimental Arm has a statistically significant 32% higher ORR, 3.5 month longer PFS, and OS compared to the Control Arm:

	Sirexatamab Experimental Arm (n=25)	Control Arm (n=19)	
ORR by IA	48.0 %	15.8 %	p = 0.0067
ORR by BICR	40.0 %	5.3 %	p < 0.001
Median PFS	9.36 months	5.88 months	HR 0.46 95% CI: 0.21, 1.02 p = 0.0248
Median OS	Not Yet Reached	9.49 months	HR 0.09 95% CI: 0.01, 0.69 p = 0.0018
Patients on study drug	10	1	

- In patients who had not received prior anti-VEGF therapy (n=95), the sirexatamab Experimental Arm has a statisticially significant 22% higher ORR and 2.6 month longer PFS compared to the Control Arm, with OS not mature but favoring the sirexatamab Experimental Arm:

	Sirexatamab Experimental Arm (n=49)	Control Arm (n=46)	
ORR by IA	55.1 %	32.6 %	p = 0.0116
ORR by BICR	44.9 %	21.7 %	p = 0.0066
Median PFS	10.94 months	8.34 months	HR 0.59 95% CI: 0.32, 1.07 p = 0.0386
Median OS	Not Yet Reached	Not Yet Reached	HR 0.22 95% CI: 0.03, 2.01 p = 0.0719
Patients on study drug	23	8	

- Across the intent-to-treat population (n=188), the sirexatamab Experimental Arm has improved ORR compared to the

Control Arm, with the primary endpoint of PFS still to mature due to the higher number of patients remaining on sirexatamab driving separation after the median:

	Sirexatamab Experimental Arm (n=94)	Control Arm (n=94)	
ORR by IA	36.2 %	25.5 %	p = 0.0536
ORR by BICR	33.0 %	16.0 %	p = 0.0023
Median PFS	7.82 months	8.31 months	HR 0.83 95% CI: 0.56, 1.24 p = 0.1809
Patients on study drug	34	24	

- The combination of sirexatamab plus bevacizumab and chemotherapy is well tolerated with a safety profile that is consistent with previous studies.

- The strong signal from the DeFianCe study supports a registrational Phase 3 clinical trial to evaluate sirexatamab plus bevacizumab and chemotherapy in second-line MSS CRC patients with high DKK1 levels or in patients who have not received prior anti-VEGF therapy.

- With approximately 30,000 second-line treated CRC patients in the US and 160,000 in the next 7 largest markets, sirexatamab has a large market opportunity in the 25-50% of patients who have high DKK1 levels or in the approximately 50% of patients who did not receive prior anti-VEGF therapy. In addition, the outcomes in patients with no prior anti-VEGF therapy provides an opportunity to move into treating first-line CRC patients, where there are an estimated 45,000 patients in the US and 265,000 in the next 7 largest markets who receive therapy for their advanced disease.

- Leap has engaged a leading financial advisor to explore business development opportunities to further the development of sirexatamab.

Conference Call

- Leap's management team will host a conference call today, March 26, 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/t6576mgc. 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 cancer. 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 size of the potential addressable market for sirexatamab, including the number or percentage of patients with advanced CRC that have or are likely to have high levels of DKK1 or that have not had or are likely not to have prior anti-VEGF therapy; 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) the actual size of the potential addressable market for sirexatamab, including the number or percentage of patients with advanced CRC that have or are likely to have high levels of DKK1 or that have not had or are likely not to have prior anti-VEGF therapy, may be smaller than estimated, (iii) Leap's ability to successfully finance or enter into new strategic partnerships for sirexatamab or any of its other programs; (iv) 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; (v) whether any Leap products will receive approval from the FDA or equivalent foreign regulatory agencies; and (vi) 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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