Tango Therapeutics Reports Positive TNG462 Clinical Data and Provides Update on PRMT5 Development Program

November 6, 2024

– TNG462 demonstrated durable clinical activity across multiple tumor types, including non-small cell lung cancer (NSCLC) and pancreatic cancer, in ongoing phase 1/2 clinical trial, moving into full development –

– Multiple TNG462 combination studies planned in 1H 2025 –

– Clinical collaboration established with Revolution Medicines to evaluate TNG462 in combination with RAS(ON) multi- and G12D-selective inhibitors –

– TNG456, a next-generation brain penetrant MTA-cooperative PRMT5 inhibitor with enhanced potency and MTAP-deleted-selectivity, entering phase 1/2 clinical trial 1H 2025 to be evaluated both as a monotherapy and in combination with CDK4/6 inhibitor abemaciclib –

– TNG908 enrollment being stopped to fully resource TNG462 and TNG456 –

BOSTON--(BUSINESS WIRE)--Nov. 6, 2024-- Tango Therapeutics, Inc. (NASDAQ: TNGX), a clinical-stage biotechnology company committed to discovering and delivering the next generation of precision cancer medicines, announced an update on its PRMT5 program. Based on positive data from the dose escalation and early dose expansion cohorts of the TNG462 phase 1/2 clinical trial, the Company has selected TNG462 to move forward into full development. TNG908, an MTA-cooperative brain penetrant PRMT5 inhibitor, is clinically active and well-tolerated in non-CNS solid tumors including NSCLC and pancreatic cancer. However, TNG908 did not meet the pharmacokinetic exposure threshold for clinical efficacy in glioblastoma (GBM) in the phase 1/2 trial. Thus, the Company is introducing TNG456, a next-generation brain penetrant MTA-cooperative PRMT5 inhibitor with enhanced potency and selectivity for the treatment of GBM, NSCLC and selected other solid tumors. TNG908 enrollment is being stopped in order to fully resource TNG462 and TNG456.

“Early data from the TNG462 phase 1/2 clinical trial demonstrate activity, durability and tolerability, with the potential to be a best-in-class molecule. In this ongoing clinical trial, patients remain on treatment with a current median of 24 weeks and is still increasing,” said Adam Crystal, M.D., Ph.D., President, Research and Development of Tango Therapeutics. “In addition, we are introducing TNG456, our next-generation brain-penetrant molecule, which is anticipated to enter the clinic in the first half of next year. Given the increased potency, selectivity and predicted brain penetrance of TNG456, we expect CNS exposure to be in the range needed for meaningful efficacy in glioblastoma and brain metastases. While it’s disappointing that, unlike in other solid tumors, TNG908 is not active in GBM, we believe this is due to lower-than-predicted central nervous system exposure. We remain steadfastly committed to bringing an effective treatment to people with glioblastoma and we are strongly positioned to achieve our goal of reaching as many patients as possible with MTAP-deleted cancers.”

“Clinical data from the phase 1/2 trial demonstrate that TNG462 has potentially best-in-class characteristics including clinical activity across multiple tumor types included in the trial, substantive durability, and a good safety and tolerability profile, thus we are moving rapidly into the next phase of development. This includes clinical evaluation of TNG462 as a monotherapy and in multiple combinations of both targeted and standard of care agents to begin in 1H 2025, in preparation for registrational trials in NSCLC and pancreatic cancer. It also includes building key capabilities within Tango to bring TNG462 to a broad range of patients in the coming years. As part of this effort, we have entered into a clinical collaboration with Revolution Medicines under which we plan to conduct the first combination trials of an MTA-cooperative PRMT5 inhibitor with the exciting class of RAS(ON) tri-complex inhibitors. Given that nearly all MTAP-deleted pancreatic cancers have a co-occurring RAS mutation, we believe this could be a powerful approach to changing the treatment landscape for this challenging cancer,” said Barbara Weber, M.D., President and Chief Executive Officer of Tango Therapeutics.

TNG462, a potentially best-in-class MTA-cooperative PRMT5 inhibitor

- TNG462 dose escalation began in July 2023 and enrollment in the dose expansion cohorts began in June 2024. With a data cutoff of 20 October 2024, a total of 59 patients have been enrolled, 39 evaluable patients across 13 histologies at active doses (160-300 mg QD).
- TNG462 is active and well-tolerated across multiple tumor types, including NSCLC and pancreatic cancer, with a current median time on treatment of 24 weeks, and is still increasing.
- As has been reported with other MTA-cooperative PRMT5 inhibitors, tumors continue to shrink over time in multiple tumor types. Median time to response is 16 weeks (8-32 weeks) and ~60% of patients with partial responses were initially assessed with stable disease.
- While there is not yet a sufficient number of evaluable patients and follow-up to accurately estimate ORR for most cancer types, we have enrolled seven cholangiocarcinoma patients and observed confirmed partial responses in 3/7 of these patients (ORR 43%). 4/7 cholangiocarcinoma patients are ongoing with a median time on study of 24 weeks, and is still increasing.
- TNG462 has a good safety profile and is well-tolerated at active doses, with thrombocytopenia as the dose limiting toxicity. Other adverse events reported for the class, including nausea, vomiting, diarrhea, and fatigue, occurred in less than 20%

of patients and were predominantly grade 1. Dysgeusia has not been reported with the doses being evaluated in expansion.
- TNG462 efficacy and tolerability continue to be evaluated at 200 mg, 250 mg and 300 mg daily, predominantly in NSCLC and pancreatic cancer. The next clinical update is planned for 2025.
- Development plans for TNG462 being implemented include targeted combinations with two RAS(ON) inhibitors – RAS(ON) multi-selective inhibitor, RMC-6236, and RAS(ON) G12D-selective inhibitor, RMC-9805 (Revolution Medicines) – osimertinib (AstraZeneca) and pembrolizumab (Merck), with enrollment planned to start in 1H 2025.
- Combinations of TNG462 and standard of care chemotherapy for NSCLC and pancreatic cancer also are being planned as potential paths to approval in the first line setting and we are initiating conversations with the FDA in preparation for multiple registrational studies.

TNG908, a blood-brain barrier penetrant, MTA-cooperative PRMT5 inhibitor

- TNG908 dose escalation began in August 2022 and enrollment in the dose expansion cohorts began in April 2024. With a data cutoff of 20 October 2024, a total of 103 patients have been enrolled, 70 non-CNS patients across 24 histologies and 33 glioblastoma patients.
- TNG908 is active and well-tolerated across multiple non-CNS solid tumors, including NSCLC and pancreatic cancer, with a median time on study of 16 weeks.
- Of the 70 patients with non-CNS solid tumors, 31 were treated at active doses (400-600 mg BID) and had at least one tumor assessment. Four partial responses were observed. Responses occurred in pancreatic cancer (2/9), NSCLC (1/4) and urothelial cancer (1/1).
- Of note, there were a total of nine evaluable pancreatic cancer patients, two with partial responses (ORR 22%) and five with stable disease as best response to date. The five ongoing pancreatic cancer patients have been on study for an average of 24 weeks, the longest for 72 weeks.
- Of the 33 patients with glioblastoma, 23 were treated at active doses (400-600 mg BID) and had at least one tumor assessment. No partial responses by RANO criteria were observed and median time on study was less than 8 weeks.
- In preclinical primate studies of TNG908, cerebral spinal fluid (CSF) exposure was 50-70% of plasma exposure. In CSF samples from three glioblastoma patients on study, exposure was ~30% of plasma exposure and below the threshold required for efficacy.
- Dose-limiting toxicities were elevated creatine kinase and aspartate aminotransferase in one patient and altered mental status in a second patient, both at 900 mg BID. Nausea and fatigue were reported in ~40% of patients at 600 mg BID, the expansion dose.
- While TNG908 is an active and well-tolerated MTA-cooperative PRMT5 inhibitor in non-CNS solid tumors, enrollment is being stopped to allow full resourcing of TNG462 as a potential best-in-class molecule. In particular, the notably longer time on treatment observed – 24 weeks and still increasing for TNG462 versus 16 weeks for TNG908 – the superior target coverage and the safety and tolerability profile all support selection of TNG462 for further development.

TNG456, a next-generation, brain penetrant MTA-cooperative PRMT5 inhibitor

- TNG456 is a novel, brain-penetrant MTA-cooperative PRMT5 inhibitor that is 55X selective for MTAP deletion with 20 nM potency (GI50) in preclinical studies.
- Based on primate CSF exposure that is 50%-110% of plasma levels and the markedly increased potency and selectivity of TNG456 compared to TNG908 (GI50 120 nM, 15X MTAP-deleted selectivity), TNG456 CNS exposure is predicted to be in the range needed for efficacy in glioblastoma and brain metastases.
- TNG456 will be evaluated in glioblastoma, NSCLC and select other solid tumors as a monotherapy and in combination with the brain-penetrant CDK4/6 inhibitor abemaciclib (Lilly). The combination with abemaciclib is based on the co-deletion of CDKN2A and MTAP in essentially all MTAP-deleted cancers and on strong synergy observed in preclinical models.
- The Company plans to begin enrolling patients in the TNG456 phase 1/2 study in 1H 2025.

About Tango Therapeutics

Tango Therapeutics is a clinical-stage biotechnology company dedicated to discovering novel drug targets and delivering the next generation of precision medicine for the treatment of cancer. Using an approach that starts and ends with patients, Tango leverages the genetic principle of synthetic lethality to discover and develop therapies that take aim at critical targets in cancer. This includes expanding the universe of precision oncology targets into novel areas such as tumor suppressor gene loss and their contribution to the ability of cancer cells to evade immune cell killing. For more information, please visit www.tangotx.com.

Forward-Looking Statements

Certain statements in this press release may be considered forward-looking statements. Forward-looking statements generally relate to future events, Tango's future operating performance and goals, the anticipated benefits of therapies and combination therapies (that include a Tango pipeline product), as well as the expectations, beliefs and development objectives for Tango's product pipeline and clinical trials. In some cases, you can identify forward-looking statements by terminology such as "may", "should", "expect", "intend", "will", "goal", "estimate", "anticipate", "believe", "predict", "designed," "potential" or "continue", or the negatives of these terms or variations of them or similar terminology. For example, implicit or explicit

statements concerning the following include or constitute forward-looking statements: the Company is advancing TNG462 into clinical trials as a monotherapy and with multiple targeted and standard of care combinations, including two RAS(ON) tri-complex inhibitors from Revolution Medicines, Inc.; the Company believes the combination of TNG462 with RAS(ON) inhibitors could be a powerful approach to changing the treatment landscape for pancreatic cancer; potential combination strategies for PRMT5 inhibitors; the Company's view that TNG462 has the potential to be a best-in-class MTA-cooperative PRMT5 inhibitor in multiple tumor types, including pancreatic and non-small cell lung cancers; the Company is moving TNG462 into full development; the Company expects cash runway into the third quarter of 2026; the Company expects to share another clinical update on TNG462 in 2025; the Company continues to advance TNG260 for cancers with STK11 loss-of-function mutations, with the phase 1/2 clinical trial ongoing; Tango is committed to discovering and delivering the next generation of precision cancer medicines; Tango's commitment to bringing effective treatment to people with glioblastoma; the Company's planned and ongoing clinical trials, including the anticipated timing for enrollment and the timing to report results and updates of such trials; the Company's understanding of the central nervous system exposure required to provide meaningful efficacy in glioblastoma and brain metastases; the Company's belief that it is strongly positioned to achieve its goal of reaching as many patients as possible with MTAP-deleted cancers; the Company's ability to build key internal capabilities; the Company's plans to enter the clinic in a Phase 1/2 clinical trial for TNG456 in the first half of 2025; the Company's plans to evaluate TNG456 in certain solid tumors as a monotherapy and in combination with abemaciclib; Dr. Weber's and Dr. Crystal's statements in this press release; the Company's initiation of conversations with the FDA in preparation for multiple registrational studies; the potential paths to approval in a first line setting for combinations of TNG462 and standard of care chemotherapy for NSCLC and pancreatic cancer; and the expected timing of: (i) development candidate declaration for certain targets; (ii) initiating IND-enabling studies; (iii) filing INDs; (iv) clinical trial initiation, dose escalation and dose expansion (including for combination studies) and (v) disclosing initial, interim, additional and final clinical trial results; and the expected benefits of the Company's development candidates and other product candidates (including for combination studies). Such forward-looking statements are subject to risks, uncertainties, and other factors which could cause actual results to differ materially from those expressed or implied by such forward-looking statements. These forward-looking statements are based upon estimates and assumptions that, while considered reasonable by Tango and its management, are inherently uncertain. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Factors that may cause actual results to differ materially from current expectations include, but are not limited to: the benefits of product candidates seen in preclinical tests and analyses may not be evident when tested in later preclinical studies or in clinical trials or when used in broader patient populations (if approved for commercial sale); Tango has limited experience conducting clinical trials (and will rely on a third party to operate its clinical trials) and may not be able to commence its clinical trials (including opening clinical trial sites, dosing the first patient, and continued enrollment and dosing of an adequate number of clinical trial participants) when expected, may not be able to continue dosing, initiate dose escalation and/or dose expansion on anticipated timelines, and may not generate or report clinical trial results (including final, initial or additional safety, efficacy data and proof-of-mechanism and proof-of-concept) in the anticipated timeframe (or at all); future clinical trial data releases may differ materially from initial or interim data from our current and future clinical trials; Tango's pipeline products may not be safe and/or effective in humans; Tango has a limited operating history and has not generated any revenue to date from product sales, and may never become profitable; other companies may be able to identify and develop product candidates more quickly than the Company and commercially introduce the product prior to the Company; the Company's proprietary discovery platform is novel and may not identify any synthetic lethal targets for future development; the Company may not be able to identify development candidates on the schedule it anticipates due to technical, financial or other reasons; the Company may not be able to file INDs for development candidates on time, or at all, due to technical or financial reasons or otherwise; the Company may utilize cash resources more quickly than anticipated; Tango will need to raise capital in the future and if we are unable to raise capital when needed or on attractive terms, we would be forced to delay, scale back or discontinue some of our development programs or future commercialization efforts (which may delay filing of INDs, dosing patients, initiation of dose expansion, reporting clinical trial results and filing new drug applications); Tango's approach to the discovery and development of product candidates is novel and unproven, which makes it difficult to predict the time, cost of development, and likelihood of successfully developing any products; the Company may be unable to advance our preclinical development programs into and through the clinic for safety or efficacy reasons or commercialize our product candidates or we may experience significant delays in doing so as a result of factors beyond Tango's control; the Company may not be able to realize the benefits of orphan drug or Fast Track designation (and such designations may not advance any anticipated approval timelines); the expected benefits of our product candidates in patients as single agents and/or in combination may not be realized; the Company may experience delays or difficulties in the initiation, enrollment, or dosing of patients in clinical trials or the announcement of clinical trial results; Tango may not identify or discover additional product candidates or may expend limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success; the Company's product candidates may cause adverse or other undesirable side effects (or may not show requisite efficacy) that could, among other things, delay or prevent regulatory approval; our dependence on one or a limited number third parties for conducting clinical trials and producing drug substance and drug product (including drug substance, which is currently sole sourced); government regulation may negatively impact the Company's business, including the potential approval of the BIOSECURE Act; and our ability to obtain and maintain patent and other intellectual property protection for our technology and product candidates or the scope of intellectual property protection obtained is not sufficiently broad. Additional information concerning risks, uncertainties and assumptions can be found in Tango's filings with the Securities and Exchange Commission (SEC), including the risk factors referenced in Tango's Annual Report on Form 10-K for the fiscal year ended December 31, 2023, as supplemented and/or modified by its most recent Quarterly Report on Form 10-Q. You should not place undue reliance on forward-looking statements in this press release, which speak only as of the date they are made and are qualified in their entirety by reference to the cautionary statements herein. Tango specifically disclaims any duty to update these forward-looking statements.

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