Bicycle Therapeutics Announces Data Updates Across Zelenectide Pevedotin Program and Development Strategy Leveraging NECTIN4 Gene Amplification

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Topline combination data for zelenectide pevedotin plus pembrolizumab in first-line metastatic urothelial cancer demonstrated a 60% overall response rate, in line with existing therapies

Dose selection and topline data from Phase 2/3 Duravelo-2 trial planned for 2H 2025

Heavily pretreated breast cancer and non-small cell lung cancer patients with NECTIN4 gene amplification and/or polysomy demonstrated an enhanced response to zelenectide pevedotin

Company to advance development strategy leveraging NECTIN4 gene amplification, with Phase 1/2 trials in breast cancer, lung cancer and multi-tumor planned for 2025

Bicycle Therapeutics to host conference call and webcast with management and oncology experts on Friday, Dec. 13, at 8 a.m. ET

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Dec. 12, 2024-- Bicycle Therapeutics plc (NASDAQ: BCYC), a pharmaceutical company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle®) technology, today announced the presentation of data showing the enhanced anti-tumor activity of zelenectide pevedotin monotherapy in breast cancer patients with *NECTIN4* gene amplification at the 2024 San Antonio Breast Conference Symposium (SABCS) in San Antonio, Texas. The company also announced topline combination data for zelenectide pevedotin plus pembrolizumab in previously untreated (first-line) cisplatin-ineligible patients with metastatic urothelial cancer (mUC), provided an enrollment and timeline update for the company's Phase 2/3 Duravelo-2 trial and shared topline monotherapy data for zelenectide pevedotin in non-small cell lung cancer (NSCLC) patients with *NECTIN4* gene amplification. Bicycle Therapeutics will host a conference call and webcast tomorrow, Dec. 13, at 8 a.m. ET to review the data updates for zelenectide pevedotin and discuss its development strategy leveraging *NECTIN4* gene amplification. Management will be joined by oncology experts Sherene Loi, M.D., Ph.D., from the Peter MacCallum Cancer Centre in Melbourne, Australia, and Niklas Klümper, M.D., from the University Hospital Bonn in Germany.

"The totality of the data shared today builds on the breadth of previously reported data for zelenectide pevedotin that we believe, when combined with our ambitious development strategy leveraging *NECTIN4* gene amplification, position Bicycle as a leader in addressing Nectin-4 associated cancers," said Bicycle Therapeutics CEO Kevin Lee, Ph.D. "We are encouraged by the topline zelenectide pevedotin data in combination with pembrolizumab in first-line mUC patients, which demonstrate zelenectide pevedotin's response data are in line with other drug conjugates used to treat mUC while its safety and tolerability profile continues to be differentiated. Additionally, we are very pleased with our progress in enrolling our Duravelo-2 registrational trial for zelenectide pevedotin in mUC and look forward to providing dose selection and topline data in the second half of next year."

Dr. Lee continued: "While early, the zelenectide pevedotin monotherapy data in breast cancer and NSCLC patients with *NECTIN4* gene amplification underscore its promising anti-tumor activity and solidify our next steps for the therapy's development. By leveraging *NECTIN4* gene amplification, we expect to be able to identify the patients who may most benefit from zelenectide pevedotin and accelerate development for solid tumor indications beyond bladder cancer. Over the course of 2025, we plan to initiate Phase 1/2 trials evaluating zelenectide pevedotin in *NECTIN4* gene-amplified breast cancer, lung cancer and multiple other cancers."

Topline Zelenectide Pevedotin Plus Pembrolizumab Combination Data in First-line mUC Highlights

Zelenectide pevedotin is a Bicycle® Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen. Topline results from the ongoing Phase 1/2 Duravelo-1 trial evaluating zelenectide pevedotin 5 mg/m^2 weekly plus pembrolizumab 200 mg once every three weeks in 22 first-line cisplatin-ineligible patients with mUC showed:

- 60% overall response rate (ORR) (12/20) among efficacy-evaluable patients. Of the responses, 5 were confirmed and 7 were unconfirmed at the time of the data cut. Fifteen patients remained on treatment at the time of the data cut.
- Safety and tolerability profile was broadly consistent with late-line Duravelo-1 monotherapy and combination cohorts.
- Adverse events of clinical interest such as peripheral neuropathy, skin reactions and eye disorders were primarily low grade. There was one report of Grade 3 sensory peripheral neuropathy and one report of Grade 3 rash, both of which were transient and reverted to Grade 1 upon dose interruption.

More detailed data from this study will be presented at a future medical meeting.

Bicycle Therapeutics is currently conducting the Phase 2/3 Duravelo-2 trial evaluating zelenectide pevedotin plus pembrolizumab versus chemotherapy in first-line mUC (Cohort 1), and zelenectide pevedotin monotherapy and in combination with pembrolizumab in late-line mUC (Cohort 2). In each cohort, two doses of zelenectide pevedotin – 5 mg/m^2 weekly and 6 mg/m^2 two weeks on, one week off – are being initially assessed. Based on enrollment progress, the company plans to report dose selection and topline data for both cohorts in the second half of 2025.

Zelenectide Pevedotin Monotherapy Data in Breast Cancer Patients with *NECTIN4* Gene Amplification Highlights (Presented at 2024 SABCS)

Gene amplification is a common mechanism by which cancer cells gain function. Bicycle Therapeutics identified that the *NECTIN4* gene sits on a

commonly amplified chromosomal site in cancer, creating more copies of the gene and often translating to more protein expression. Since zelenectide pevedotin binds to Nectin-4, it was hypothesized that *NECTIN4* gene amplification may predict response and could serve as a biomarker for therapy stratification.

The company conducted a post-hoc analysis of 38 heavily pretreated breast cancer patients enrolled in Duravelo-1, of which 32 were confirmed to have triple-negative breast cancer (TNBC). The majority of patients were treated with zelenectide pevedotin 5 mg/m^2 weekly.

Of the 38 breast cancer patients enrolled, 35 patients were efficacy evaluable. Additionally, 23 breast cancer patient samples were available for *NECTIN4* testing, of which 8 demonstrated NECTIN4 gene amplification or harbored *NECTIN4* polysomy. Results showed:

- 62.5% ORR (5/8) among breast cancer patients with *NECTIN4* gene amplification or polysomy, compared to 14.3% ORR (5/35) among all efficacy-evaluable breast cancer patients.
- Of the 5 partial responses, 4 were confirmed and 1 was unconfirmed.
- No responses in non-amplified or non-polysomy patients.

Of the 32 TNBC patients enrolled, 30 patients were efficacy evaluable. Additionally, 19 TNBC patient samples were available for *NECTIN4* testing, of which 7 demonstrated *NECTIN4* gene amplification or harbored a *NECTIN4* polysomy. Results showed:

- 57.1% ORR (4/7) among TNBC patients with *NECTIN4* gene amplification or polysomy, compared to 13.3% ORR (4/30) among all efficacy-evaluable TNBC patients.
- Of the 4 partial responses, 3 were confirmed and 1 was unconfirmed.
- All 3 TNBC patients with *NECTIN4* gene amplification who responded to zelenectide pevedotin had prior treatment with sacituzumab govitecan.
- No responses in non-amplified or non-polysomy patients.

In this study of heavily pretreated breast cancer patients, zelenectide pevedotin was generally well tolerated, and its safety and tolerability profile was consistent with data from other Duravelo-1 cohorts. Low rates of Grade ≥3 treatment-related adverse events (TRAEs) (34.2%) and Grade ≥3 treatment-related serious adverse events (TRSAEs) (10.5%) occurred. The most common TRAEs were fever (pyrexia), nausea and diarrhea. TRAEs of clinical interest, including peripheral neuropathy (any kind) and skin reactions, were low grade.

“Although the sample size was limited, this post-hoc analysis highlights the encouraging anti-tumor activity of zelenectide pevedotin in breast cancer patients with *NECTIN4* gene amplification, particularly among those with TNBC who urgently need new treatment options,” said Professor Sherene Loi, M.D., Ph.D., consultant medical oncologist in the Breast Unit and group leader at the Peter MacCallum Cancer Centre in Melbourne, Australia. “As innovative and genomically targeted therapies for breast cancer continue to emerge, these findings position zelenectide pevedotin as a promising potential new therapy and *NECTIN4* gene amplification as a novel target for breast cancer drug development.”

The poster presentation, “Enhanced anti-tumor activity of zelenectide pevedotin in triple-negative breast cancer (TNBC) patients with *NECTIN4* gene amplification” is available in the Publications section of the Bicycle Therapeutics website.

Topline Zelenectide Pevedotin Monotherapy Data in NSCLC Patients with *NECTIN4* Gene Amplification Highlights
The company conducted a post-hoc analysis of 40 pretreated patients with NSCLC enrolled in Duravelo-1. The majority of patients received zelenectide pevedotin 5 mg/m^2 weekly.

Of the 40 patients enrolled, 34 patients were efficacy evaluable. Additionally, 19 patient samples were available for *NECTIN4* testing, of which 6 demonstrated *NECTIN4* gene amplification. Five out of 6 patients with *NECTIN4* gene amplification were efficacy evaluable. Results showed:

- 40.0% ORR (2/5) among patients with *NECTIN4* gene amplification, compared to 8.8% ORR (3/34) among all efficacy-evaluable patients.
- Of the 3 partial responses, 2 were confirmed and 1 was unconfirmed.
- Out of 19 patients tested for *NECTIN4* gene amplification, none of the non-amplified patients responded.

The safety and tolerability profile of zelenectide pevedotin was broadly consistent with data from other Duravelo-1 monotherapy cohorts.

More detailed data from this study will be presented at a future medical meeting.

Overview of Development Strategy Leveraging *NECTIN4* Gene Amplification
Bicycle Therapeutics plans to advance development of zelenectide pevedotin in broader indications outside of mUC utilizing a *NECTIN4* gene amplification strategy to target patients who have the potential for significantly deeper responses.

Over the course of 2025, Bicycle Therapeutics plans to initiate several additional Phase 1/2 trials to assess zelenectide pevedotin in *NECTIN4* gene-amplified breast cancer, lung cancer and multiple other cancers. Through this strategy, the company believes it has the opportunity to become the leader in addressing Nectin-4 associated cancers and potentially transform the treatment landscape for thousands of patients in the United States.

Conference Call Details
Bicycle Therapeutics will host a conference call and webcast on Friday, Dec. 13, at 8 a.m. ET to review the data updates for zelenectide pevedotin. The company’s management team will be joined by Sherene Loi, M.D., Ph.D., Peter MacCallum Cancer Centre, and Niklas Klümper, M.D., University Hospital Bonn.

To access the call, please dial +1-833-816-1408 (U.S.) or +1-412-317-0501 (international) and ask to join the Bicycle Therapeutics call. A live webcast and replay of the conference call will be accessible in the Investor section of the Company’s website at www.bicycletherapeutics.com.

About Bicycle Therapeutics

Bicycle Therapeutics is a clinical-stage pharmaceutical company developing a novel class of medicines, referred to as Bicycle® molecules, for diseases that are underserved by existing therapeutics. Bicycle molecules are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making Bicycle molecules attractive candidates for drug development. The company is evaluating zelenectide pevedotin (formerly BT8009), a Bicycle® Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen; BT5528, a BTC molecule targeting EphA2, a historically undruggable target; and BT7480, a Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®) targeting Nectin-4 and agonizing CD137, in company-sponsored clinical trials. Additionally, the company is developing Bicycle Radionuclide Conjugates (BRC®) for radiopharmaceutical use and, through various partnerships, is exploring the use of Bicycle® technology to develop therapies for diseases beyond oncology.

Bicycle Therapeutics is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Cambridge, Mass. For more information, visit www.bicycletherapeutics.com.

Forward Looking Statements
This press release may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “seeks,” “will” and variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding Bicycle’s development of zelenectide pevedotin, BT5528 and BT7480 as well as potential radiopharmaceutical product candidates; the company’s plans to utilize a NECTIN4 gene amplification strategy in the clinical development of zelenectide pevedotin; expectations with respect to Bicycle’s ability to identify the patients who may most benefit from zelenectide pevedotin, to advance or accelerate development of this product candidate for broader indications, including solid tumor cancers beyond bladder cancer, and to become a leader in addressing Nectin-4 associated cancers; the planned initiation of clinical trials of zelenectide pevedotin in breast cancer, lung cancer, and other cancers; the timing and manner of announcement of data and program updates from clinical trials for zelenectide pevedotin, including reporting of dose selection and topline data from the Duravelo-2 trial; and the use of Bicycle’s technology through various partnerships to develop potential therapies in diseases beyond oncology. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: uncertainties inherent in research and development and in the initiation, progress and completion of clinical trials and clinical development of Bicycle’s product candidates; the risk that Bicycle may not realize the intended benefits of its technology, partnerships or NECTIN4 gene amplification strategy; timing of results from clinical trials; whether the outcomes of preclinical studies and prior clinical trials will be predictive of future clinical trial results; the risk that trials may have unsatisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; and other important factors, any of which could cause Bicycle’s actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled “Risk Factors” in Bicycle’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on October 31, 2024, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether because of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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