Bicycle Therapeutics Presents Updated Clinical Results Across Oncology Pipeline at ESMO Congress 2024

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Updated monotherapy data for Nectin-4 targeting zelenectide pevedotin in metastatic urothelial cancer (mUC) showed a promising 45% overall response rate (ORR), 11.1 months median duration of response and a generally well-tolerated safety profile

EphA2-targeting BT5528 demonstrated an emerging differentiated safety profile and antitumor activity in patients with advanced solid tumors, including a 45% ORR in mUC 6.5 mg/m^2 every two weeks dose expansion cohort

Relatively low frequency and severity of treatment-related peripheral neuropathy following monotherapy with Bicycle Toxin Conjugates® zelenectide pevedotin and BT5528, with patients often able to continue therapy without modification

BT7480 demonstrated a favorable safety profile and preliminary antitumor activity in advanced Nectin-4-associated solid tumors

BARCELONA--(BUSINESS WIRE)--Sep. 14, 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 updated Phase 1/2 clinical results for Bicycle Toxin Conjugate (BTC®) zelenectide pevedotin (formerly BT8009) in metastatic urothelial cancer (mUC); BTC molecule BT5528 in advanced solid tumors, such as mUC and ovarian; and Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®) BT7480 in advanced solid tumors. The company also shared an analysis of peripheral neuropathy, a key adverse event of interest associated with monomethyl auristatin E (MMAE)-based drug conjugates, in patients treated with BTC molecules. These data will be presented during a poster session at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona today.

"We are pleased that the data presented at ESMO continue to support the promising response and differentiated safety profiles of our Bicycle molecules. Importantly, our lead investigational therapy zelenectide pevedotin continues to demonstrate an overall response rate that is in line with other drug conjugates used to treat metastatic urothelial cancer, but with a marked improvement in tolerability. Overall, we believe the data continue to demonstrate the potential of our Bicycle technology platform to create differentiated medicines designed to help patients not only to live longer but also to live well," said Kevin Lee, Ph.D., CEO of Bicycle Therapeutics. "These clinical data are just the first set of updates that we have guided to delivering this year. In the coming months, we look forward to sharing initial imaging data from our growing radiopharmaceutical pipeline and additional data for zelenectide pevedotin in bladder, breast and lung cancer."

ESMO 2024 Data Highlights

Zelenectide pevedotin is a BTC® molecule targeting Nectin-4, a well-validated tumor antigen, designed to overcome the significant toxicity associated with other drug conjugate approaches. Updated results from the ongoing Phase 1/2 Duravelo-1 trial evaluating 5 mg/m^2 weekly of zelenectide pevedotin monotherapy in 45 mUC patients who had not previously been treated with enfortumab vedotin showed:

- Among 38 efficacy-evaluable patients, a 45% overall response rate (ORR), including 1 confirmed complete response and 16 partial responses (13 confirmed). Stable disease was maintained in 9 patients, and 12 patients experienced progressive disease.
- A median duration of response of 11.1 months among the 14 patients with confirmed responses.
- An emerging differentiated safety profile, particularly around adverse events of interest such as peripheral neuropathy, skin reactions and eye disorders. Notably, there were no Grade ≥3 treatment-related adverse events (TRAEs) of peripheral neuropathy (any kind), skin reactions or eye disorders, and patients with pre-existing peripheral neuropathy were unlikely to develop worsening peripheral neuropathy during treatment with zelenectide pevedotin.

The global Phase 2/3 Duravelo-2 registrational trial of zelenectide pevedotin in patients with mUC is currently enrolling. Additional data updates for zelenectide pevedotin in combination with pembrolizumab in first line mUC and monotherapy in late line triple-negative breast cancer and non-small cell lung cancer (NSCLC) are planned for later this year.

BT5528 is a BTC molecule targeting EphA2, a tumor antigen that is widely expressed in many cancers and has historically been difficult to target using other drug conjugate approaches. Updated results from the ongoing Phase 1/2 trial evaluating 6.5 mg/m^2 every two weeks and 5 mg/m^2 weekly of BT5528 monotherapy in patients with advanced solid tumors showed:

- Among 113 efficacy-evaluable patients, a 12% ORR in patients with advanced solid tumors.
- The highest anti-tumor activity in mUC, with a 34% ORR in all efficacy-evaluable patients enrolled in the dose escalation and expansion cohorts. Among patients receiving 6.5 mg/m^2 every two weeks, a 31% ORR was observed in the dose escalation and expansion cohort and a 45% ORR was observed in the expansion cohort only. A lower but acceptable ORR of 27% was observed in patients receiving 5 mg/m^2 weekly.
- No objective responses in patients with ovarian cancer who received 5 mg/m^2 weekly. However, 5 patients maintained

stable disease.
- A suggested correlation between EphA2 expression and response. Among 14 patients with mUC who had available immunohistochemistry and response data, a 43% ORR was observed in EphA2-positive patients compared to a 20% ORR in EphA2-negative patients.
- A clearly differentiated emerging safety profile, with none of the hemorrhage events or hematological toxicities that have been associated with other EphA2-targeting drug conjugates.

The company has begun assessing BT5528 at 6.5 mg/m^2 every two weeks in combination with nivolumab. Results from this cohort are expected in 2025.

Low rates of treatment-related peripheral neuropathy (TRPN) following monotherapy treatment with BTC molecules zelenectide pevedotin or BT5528. In 149 patients treated with zelenectide pevedotin and 74 patients treated with BT5528 from ongoing Phase 1/2 studies, results showed:

- TRPN in 28% of patients treated with zelenectide pevedotin and 19% of patients treated with BT5528, nearly all of which were low grade (1-2). One Grade 3 event (neuralgia) was reported in a patient treated with zelenectide pevedotin following prior therapy with enfortumab vedotin. No Grade 3-4 events were observed for BT5528.
- Among zelenectide pevedotin-treated patients with peripheral neuropathy at baseline, 80% did not develop TRPN during treatment.
- TRPN resulted in few dose modifications across the overall patient populations for zelenectide pevedotin and BT5528, and no drug withdrawals were necessary for either BTC molecule.
- TRPN had completely resolved in 14% (zelenectide pevedotin) and 21% (BT5528) of patients, and 26% and 21%, respectively, had some resolution or improvement at time of reporting, though post-treatment follow-up was limited. Median time to resolution or improvement of TRPN was 2.2 weeks for zelenectide pevedotin and 1.7 weeks for BT5528.

The data support the hypothesis that the antibody-drug construct may be a primary driver of peripheral neuropathy rather than MMAE toxicity as was previously believed.

BT7480 is a Nectin-4 targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors. Initial data from the Phase 1/2 dose escalation trial evaluating BT7480 in patients with advanced solid tumors showed:

- Among 39 patients assigned to receive one of 10 different doses (0.002-3.5 mg/kg weekly) of BT7480, an emerging differentiated safety and tolerability profile with a low number of severe adverse events. Low rates of Grade ≥3 TRAEs (5%) and of treatment-related severe adverse events (TRSAEs) (8%) were reported, with no such events among those receiving the highest dose of 3.5 mg/kg.
- Best overall response of stable disease in 13 patients, 5 of whom had NSCLC. Stable disease was prolonged (>8 months) in 3 patients, 2 with NSCLC and 1 with anal cancer. There were 2 unconfirmed partial responses, both in patients with cervical cancer.
- Preliminary biomarker analyses that support BT7480 dual targeting of CD137 and Nectin-4 as demonstrated by enhanced immune cell activation, aligned with the proposed mechanism of action of BT7480.

As the maximum tolerated dose for BT7480 has not yet been reached, the company is continuing dose exploration in combination studies, starting with nivolumab.

The posters are available in the Publications section of the Bicycle Therapeutics website.

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® Radio 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 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 anticipated progress across its R&D pipeline and the advancement of its product candidates, including zelenectide pevedotin, BT5528 and BT7480; the anticipated progression of Bicycle’s clinical trials and the method and timing of announcement of data from clinical trials and program updates for clinical candidates; the potential of the Bicycle technology platform to create differentiated medicines; the development of potential radiopharmaceutical or other product candidates using Bicycle’s technology through various partnerships; and the

therapeutic potential for Bicycles in oncology and other applications. 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 or partnerships; timing of results from clinical trials; whether the outcomes of preclinical studies will be predictive of 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 August 6, 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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Investors and media:
Stephanie Yao
SVP, Investor Relations and Corporate Communications
ir@bicycletx.com
857-523-8544

Source: Bicycle Therapeutics plc