ImmunityBio Announces Over 24 Months Median Duration of Complete Remission, with 100% NMIBC CIS Patient Survival, Setting a New 'Magnitude of Benefit' in Patients with BCG Unresponsive Bladder Cancer

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- Results confirm prolonged sustained complete response, with 71% of patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) having a complete remission with a median duration of response of 24.1 months
- By contrast, historical complete response rates for FDA-approved therapies pembrolizumab and valrubicin are of 41% and 18%, respectively[1 & 2]
- In addition, for patients with papillary disease, a disease-free survival rate at 18 months of 53%, which more than doubles the 25% rate published by the International Bladder Cancer Group as clinically meaningful
- A cystectomy avoidance rate of over 90% (91% of CIS patients and 95% of papillary patients)
- A 96% avoidance rate of progression to muscle invasive bladder cancer for CIS patients who responded to therapy
- Zero treatment-related or immune-related adverse events or grade 4/5 adverse events

CULVER CITY, Calif.--(BUSINESS WIRE)--Feb. 14, 2022-- ImmunityBio, Inc. (NASDAQ: IBRX), a clinical-stage immunotherapy company, today announced positive data from the company's late-stage bladder cancer trial (QUILT-3.032). The data showed sustained complete response rates in patients with BCG-unresponsive non-muscle invasive carcinoma in situ (NMIBC CIS) bladder cancer (Cohort A) and with papillary disease (Cohort B). Of the 83 patients with BCG-unresponsive NMIBC CIS, 59 (71%) had a complete response with a median duration of response of 24.1 months —exceeding historical complete response rates of 41% and 18% for FDA-approved therapies pembrolizumab and valrubicin, respectively. In the papillary disease arm of the study (Cohort B), 57% of patients are disease free at 12 months and 53% at 18 months.

"We are excited with these promising results," said Sam Chang, M.D., Urologic Surgery Chief Surgical Officer, Vanderbilt Ingram Cancer Center and trial investigator. "This study suggests that BCG induces trained immunity as the prime, while N-803 serves as a vital boost for innate immune memory. These results of high efficacy activity and excellent safety profile set a new bar for NMIBC treatment, and together with the familiar and favorable mode of administration, will advance our current standards of care for patients with bladder cancer."

The latest data from this trial exceeds AUA-FDA workshop benchmarks for both the magnitude of complete remission and the duration of complete response for new therapies for BCG-unresponsive bladder cancer. Indeed, the benchmark of 30% durable response at 18 to 24 months for a clinically meaningful therapy "is likely too high and may not be realistically achievable,"[3] according to recommendations published in the *Journal of Clinical Oncology*. This "realistically unachievable" endpoint of 30% durable response at 18 months has in fact now been achieved and exceeded with the combination of Anktiva and BCG in this trial reported today. Taken together, the high rates of complete response, cystectomy avoidance, avoidance of progression to muscle invasive disease in the patients that responded, and the prolonged duration of complete response, as well as the favorable safety profile, places this novel immunotherapy combination at the forefront of both existing approved and potential treatments for bladder cancer patients.

"*Trained immunity* is a recently discovered immune system response triggered by BCG. Natural Killer (NK) and T cells are activated by BCG resulting in bladder cancer cell death. When an appropriate secondary stimulus is administered along with BCG, that trained immune response is enhanced to induce immune *memory* resulting in a prolonged duration of immunological response," said Patrick Soon-Shiong, M.D., Executive Chairman and Global Chief Scientific and Medical Officer of ImmunityBio. "N-803, our IL-15 superagonist which proliferates NK and T cells, serves as this enhancing *secondary boost* and augments the immunological response when given in combination with BCG. This mechanism of action of inducing trained innate immune *memory*, through the combination of N-803 and BCG, accounts for the prolonged 24-month durable complete response reported in this trial."

"These results support our hypothesis that immunogenic cell death can induce long-term memory and that N-803 increases the immunologic potential of BCG, even in patients who become unresponsive to BCG alone," Soon-Shiong said. "N-803 does this by stimulating proliferation and enhancing activity of tumor-killing Natural Killer (NK) cells and T cells, acting as a secondary stimulus or boost to the prime trained immunity induced by BCG."

The study results presented at ASCO GU are summarized below:

Cohort A (CIS)
Excellent safety and tolerability profile of N-803 + BCG for CIS

- **0%** treatment-related SAEs
- **0%** immune-related AE
- **0%** grade 4 and 5 AE

- **71%** Complete remission (CR) rate at anytime
- **24.1** Months median durable complete remission

- **96%** Avoidance of bladder cancer progression at 24 months in responders
- **91%** Avoidance of cystectomy at 24 months in responders
- **100%** Bladder cancer specific overall survival at 24 months
- Favorable & familiar dosing schedule with activity localized to the bladder

Cohort B (Papillary Disease)
Excellent safety and tolerability profile of N-803 + BCG for papillary disease

- **0%** treatment-related SAEs
- **0%** immune-related AE
- **0%** grade 4 and 5 AE

- **57%** Disease free survival rate at 12 months
- **99%** Overall bladder cancer specific survival
- **95%** Cystectomy avoidance rate
- Favorable & familiar dosing schedule with activity localized to the bladder

"When we began the QUILT trials across multiple tumor types, initiating our Cancer Moonshot program, the goal was to achieve a new paradigm in cancer care by activating the patient's own immune system to induce NK and T cell *memory* with long-term complete remission in patients who have failed all current therapies," Soon-Shiong said. "With these results in bladder cancer, as well as our recently reported results in pancreatic cancer, we are one step closer to proving our hypothesis that delivering therapies that harness the patient's own immune system is what will truly transform current standards of care."

The data will be announced on Friday, February 18 during an oral presentation at the 2022 ASCO Genitourinary Cancers Symposium titled *Phase II/III clinical results of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC)*

Incidence of Bladder Cancer

Bladder cancer has a high incidence worldwide; in 2020, an estimated 573,278 new cases were diagnosed and caused 212,536 deaths.[4] In the United States, bladder cancer is the fourth most commonly-diagnosed solid malignancy in men and the twelfth for women; the American Cancer Society estimates there will be 83,730 new cases and 17,200 deaths from bladder cancer in 2021.[5] Approximately 75–85% of bladder cancer patients present with a disease confined to the mucosa (stage Ta, carcinoma in situ) or submucosa (stage T1); these categories are grouped as non-muscle-invasive bladder cancer (NMIBC). Of these, approximately 70% present as stage Ta, 20% as T1, and 10% as CIS.[6]

For the last 30 years, BCG immunotherapy has been the standard for treating NMIBC. However, disease recurrence and progression rates remain unacceptably high. Standard-of-care recommendations include lifetime invasive surveillance and rapid treatment of recurrences, creating a substantial financial burden and drastic impact on quality of life. Of those patients who experience recurrence, approximately 30% will succumb to their disease over a 15-year period, and another 50% will undergo radical cystectomy of the bladder (surgical removal of the bladder that may require removing surrounding organs) in an attempt to control the disease.[7]

There is an urgent, unmet need to treat NMIBC and avoid cystectomy. Despite the advent of minimally-invasive procedures and robotic techniques, the 90-day mortality and morbidity rates in cystectomy patients remain unacceptably high at 3-6% and 28-64%, respectively.[8&9] Based on this urgent need, the FDA published guidance in February 2018 to address BCG unresponsive NMIBC, stating that the goal of therapy in patients with BCG-unresponsive NMIBC is to avoid cystectomy.

About the Study and Breakthrough Designation

QUILT 3.032 is an open-label, three cohort, multicenter Phase 2/3 study of intravesical BCG plus Anktiva (N-803) in patients with BCG-unresponsive high-grade NMIBC (NCT03022825) and was opened in 2017. The primary endpoint for Cohort A of this Phase 2/3 study is incidence of complete response (CR) of CIS at any time. The FDA had granted Fast Track Designation to the pivotal trial based on Phase I data. In December 2019, the FDA granted ImmunityBio Breakthrough Therapy Designation based on interim Phase 2 data indicating the primary endpoint of the trial was already met.

ImmunityBio's IL-15 superagonist Anktiva (N-803)

The cytokine interleukin-15 (IL-15) plays a crucial role in the immune system by affecting the development, maintenance, and function of the natural killer (NK) and T cells. N-803 is a novel IL-15 superagonist complex consisting of an IL-15 mutant (IL-15N72D) bound to an IL-15 receptor α/IgG1 Fc fusion protein. Its mechanism of action is direct specific stimulation of CD8+ T cells and NK cells through beta gamma T-cell receptor binding (not alpha) while avoiding T-reg stimulation. N-803 has improved pharmacokinetic properties, longer persistence in lymphoid tissues and enhanced anti-tumor activity compared to native, non-complexed IL-15 in vivo.

N-803 is currently being evaluated for adult patients in two clinical NMIBC trials. QUILT 2.005 is investigating use of N-803 in combination with BCG for patients with BCG-naïve NMIBC; QUILT 3.032 is studying N-803 in combination with BCG in patients with BCG-unresponsive NMIBC.

Mechanism of Action & Contribution of N-803 (Anktiva) and BCG for Bladder Cancer

Trained immunity[10] is a recently discovered immune system response triggered by BCG. Natural Killer (NK) and T cells[11] are activated by BCG resulting in bladder cancer cell death. When an appropriate secondary stimulus is administered along with BCG, that trained immune response is enhanced to induce immune *memory* resulting in a prolonged duration[12] of immunological response. N-803, an IL-15 superagonist which proliferates NK and T cells[13], serves as this enhancing *secondary boost* and augments the immunological response when given in combination with BCG. This mechanism of action of inducing *trained innate immune memory*, through the combination of N-803 and BCG, accounts for the prolonged 24-month durable complete response reported in this trial.

About ImmunityBio

ImmunityBio is a leading late-clinical-stage immunotherapy company developing next-generation therapies that drive immunogenic mechanisms for defeating cancers and infectious diseases. The company's broad immunotherapy and cell therapy platforms—including Antibody cytokine fusion proteins, synthetic immunomodulators, vaccine technologies (hAd5 viral vector, mRNA, recombinant protein, and adjuvant), and genetically-modified, off-the-shelf natural killer cells (autologous and allogenic cytokine-enhanced memory NK cells)—activate both the innate (natural killer cell and macrophage) and adaptive (T cell) immune systems to create long-term "immunological memory."

ImmunityBio's clinical pipeline consists of 21 clinical trials—13 of which are in Phase II or III development—across 12 indications in solid and liquid cancers (including bladder, pancreatic, and lung cancers) and infectious diseases (including SARS-CoV-2 and HIV). Anktiva™, ImmunityBio's lead cytokine infusion protein, is a novel interleukin-15 (IL-15) superagonist complex and has received Breakthrough Therapy and Fast Track Designations from the U.S. Food and Drug Administration (FDA) for BCG-unresponsive CIS non-muscle invasive bladder cancer (NMIBC).

The company has established GMP manufacturing capacity at scale with cutting-edge cell manufacturing expertise and ready-to-scale facilities, as well as extensive and seasoned R&D, clinical trial, and regulatory operations, and development teams. For more information, please visit: www.immunitybio.com

1. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00147-9/fulltext
2. https://www.sciencedirect.com/science/article/abs/pii/S1078143912001512
3. https://ascopubs.org/doi/10.1200/JCO.2015.64.4070
4. https://www.sciencedirect.com/science/article/abs/pii/S0302283808008397
5. Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries: https://gco.iarc.fr/
6. https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263923/
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12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8418256/
13. https://ashpublications.org/blood/article/131/23/2515/36958/First-in-human-phase-1-clinical-study-of-the-IL-15

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, such as statements regarding the development of therapeutics for cancer and infectious diseases, the advancement of our Phase II and III trials, the efficacy of ImmunityBio's product candidates as compared to existing treatment options, and regulatory approval, commercialization and commercial success of ImmunityBio's product candidates and related matters. Statements in this press release that are not statements of historical fact are considered forward-looking statements, which are usually identified by the use of words such as "anticipates," "believes," "continues," "could," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "projects," "seeks," "should," "will," and variations of such words or similar expressions. Statements of past performance, efforts, or results of our clinical trials, about which inferences or assumptions may be made, can also be forward-looking statements and are not indicative of future performance or results. Forward-looking statements are neither forecasts, promises nor guarantees, and are based on the current beliefs of ImmunityBio's management as well as assumptions made by and information currently available to ImmunityBio. Such statements reflect the current views of ImmunityBio with respect to future events and are subject to known and unknown risks, including business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about ImmunityBio, including, without limitation, (i) the ability of ImmunityBio to continue its planned preclinical and clinical development of its development programs, and the timing and success of any such continued preclinical and clinical development and planned regulatory submissions, (ii) ImmunityBio's ability to retain and hire key personnel, (iii) uncertainty of the expected financial performance and successful integration of the combined company following completion of the recent merger of ImmunityBio with NantCell (the "Merger"), including the possibility that the expected synergies and value creation from the Merger will not be realized or will not be realized within the expected time period, (iv) whether interim, initial, "top-line" and preliminary data from ImmunityBio's clinical trials that it announces or publishes from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data, (v) ImmunityBio's ability to obtain additional financing to fund its operations and complete the development and commercialization of its various product candidates, (vi) ImmunityBio's ability to obtain, maintain, protect and enforce patent protection and other proprietary rights for its product candidates and technologies, (vii) risks and uncertainties regarding the regulatory review and approval process, (viii) ImmunityBio's ability to successfully commercialize its product candidates and (ix) the unknown future impact of the COVID-19 pandemic delay on certain clinical trials or their milestones and/or ImmunityBio's operations or operating expenses. More details about these and other risks that may impact ImmunityBio's business are described under the heading "Risk Factors" in the Company's Form 8-K filed with the U.S. Securities and Exchange Commission ("SEC") on March 10, 2021, Form 10-Q filed with the SEC on August 12, 2021 and in subsequent filings made by ImmunityBio with the SEC, which are available on the SEC's website at www.sec.gov. ImmunityBio cautions you not to place undue reliance on any forward-looking statements, which speak only as of the date hereof. ImmunityBio does not undertake any duty to update any forward-looking statement or other information in this press release, except to the extent required by law.

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