Immuneering Presents Promising Preclinical Data on its Second Program IMM-6-415 at the 37th Annual Meeting of SITC

November 10, 2022

IMM-6-415 Shows Preclinical Activity as a Single Agent in RAF and RAS Mutant Tumors and Enhances PD1 and CTLA4 Checkpoint Blockade

IMM-6-415 is Designed to Provide Deep Cyclic Inhibition of the MAPK Pathway with an Accelerated Cadence Relative to the Once-Daily Dosing of IMM-1-104

CAMBRIDGE, Mass., Nov. 10, 2022 (GLOBE NEWSWIRE) -- Immuneering Corporation (Nasdaq: IMRX), a biopharmaceutical company that aims to create medicines for *all* patients with solid tumors driven by RAS mutations and other MAPK pathway activation events, today reported promising preclinical data in a poster presentation at the Society for Immunotherapy of Cancer (SITC) 37th Annual Meeting, highlighting the activity of IMM-6-415, the company's second program. IMM-6-415 is designed to target RAF and RAS mutant tumors as monotherapy and enhance therapeutic activity in select drug-drug combinations, including checkpoint inhibitors. The activity of IMM-6-415 is driven by an exceptionally short half-life that creates an accelerated cadence relative to the once-daily dosing of IMM-1-104.

"With IMM-1-104 we pioneered the mechanism of deep cyclic inhibition, which challenges the prevailing view that pathway inhibition must be sustained to be effective," stated Ben Zeskind, Ph.D., Chief Executive Officer of Immuneering Corporation. "Both IMM-1-104 and IMM-6-415 seek to deprive malignant cells of the continuous signaling they need to proliferate, while providing healthy cells with a cadenced, normalizing level of signaling designed to improve tolerability. IMM-6-415 is tuned to provide an accelerated cadence of deep cyclic inhibition, since different cadences may be optimal for different biology. The exciting data we are sharing today underscore the potential of IMM-6-415 to broadly target multiple RAF and RAS mutant tumors, and enhance the therapeutic activity of immune checkpoint inhibitors, especially in immunologically cold tumors with suboptimal T-cell responses. We look forward to completing ongoing IND-enabling studies and expect to submit an IND for IMM-6-415 in Q4 2023."

Highlights from the presentation are as follows:

Title: *Cyclic disruption of the mitogen-activated protein kinase (MAPK) pathway by the Dual MEK inhibitor, IMM-6-415, enhances PD1 and CTLA4 checkpoint blockade in RAS mutant tumors*
Abstract/Poster Number: 449
Authors: Brett Hall, Anna Travesa, Amy Yamamura, Amy Axel, Sarah Kolitz, Jason Funt, Kevin D Fowler, Matthew Nord, Praveen Nair, Scott Barrett, Benjamin J Zeskind, Peter J King
Primary Category: Checkpoint Blockade Therapy
DOI: 10.1136/jitc-2022-SITC2022.0449
Date: Thursday, November 10th, 9am-9pm
Location: Boston Convention & Exhibition Center – Hall C

In this preclinical study, Immuneering researchers tested IMM-6-415 alone and in combination with anti-PD1 or CTLA4 checkpoint inhibitors in a series of preclinical models to characterize single-agent activity as well as combination therapy with checkpoint inhibitors (CPIs) in RAS-mutant colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) models driven by diverse MAPK pathway mutations.

Cell-based 2D biochemical and 3D pharmacologic assays were performed showing that IMM-6-415 reduced pERK and pMEK across all RAF and RAS mutant models tested. Humanized 3D tumor models revealed a promising sensitivity profile for IMM-6-415 in RAF- and RAS-mutant models.

Multiple *in vivo* studies were performed in RAS mutant and wildtype models, including: (1.) Colon 26, a $KRAS^{G12D}$ CRC syngeneic model, (2.) A549, a $KRAS^{G12S}$ NSCLC xenograft model, (3.) CT-26, a $KRAS^{G12D}$ syngeneic model and (4.) MC38, a RAS wild-type syngeneic model. CT-26 (BALB/c) and MC38 (C57BL/6) *in vivo* studies evaluated single-agent IMM-6-415, PD-1 and CTLA-4 versus IMM-6-415 plus CPI combinations.

The maximum effective dose (MED) for BID dosing of IMM-6-415 was 175 to 180 mg/kg BID PO based on Colon 26 (96.4% TGI) and A549 (93.9% TGI) animal studies, yet enhanced MEKio + CPI combinations were identified at only 120 mg/kg BID PO IMM-6-415. At 28 days treatment, 33% (4/12) of CT-26 mice remained on study in the (10 mg/kg BIW IP) anti-PD-1 or anti-CTLA-4 alone treated groups, whereas 58% (7/12) mice remained in the IMM-6-415 treatment arm at 120 mg/kg BID PO.

However, 92% (11/12) and 83% (10/12) mice remained in the IMM-6-415 plus anti-PD-1 or anti-CTLA-4 combination at the same doses.

“These studies demonstrate monotherapy and combination activity of IMM-6-415 across multiple RAS-mutant models. IMM-6-415 also displays a differentiated short plasma half-life of approximately 0.3 hours and was observed to be well tolerated in mice.” stated Brett Hall, Ph.D., Chief Scientific Officer of Immuneering Corporation. “Our data suggest that deep cyclic inhibition of the MAPK pathway with an accelerated cadence is active in RAF and RAS mutant tumors and may enhance the therapeutic activity of immune checkpoint inhibitors when used as a MEKio combination in these hard-to-treat solid tumors.”

A copy of the abstract can be accessed at: https://www.sitcancer.org/2022/abstracts/abstract-titles-publications

About IMM-6-415
IMM-6-415 targets RAF and RAS mutant tumors through deep cyclic inhibition of the MAPK pathway with an accelerated cadence. IMM-6-415 was designed with unique drug-like properties that distinguish it from other programs in the Immuneering pipeline, including a substantially shorter half-life than IMM-1-104 which gives IMM-6-415 an accelerated cadence relative to the once-daily dosing of IMM-1-104. IMM-6-415 is being developed for monotherapy and combination applications in oncology, including the ability to enhance immune mediated therapy in certain settings.

About Immuneering Corporation
Immuneering aims to create medicines for *all* patients with solid tumors driven by RAS mutations and other MAPK pathway activation events. Immuneering has more than a decade of experience applying translational bioinformatics to generate insights into drug mechanism of action and patient treatment response. Building on this experience, Immuneering’s disease-agnostic discovery platform enables the company to create product candidates based on 1) biological insights that are both counterintuitive and deeply rooted in data, and 2) novel chemistry. Immuneering’s lead product candidate, IMM-1-104, aims to achieve pan-RAS activity that selectively impacts cancer cells to a greater extent than healthy cells. IMM-1-104 is designed to be a highly selective third generation dual MEK inhibitor that modulates the signaling dynamics of the MAPK pathway by driving deep cyclic inhibition that deprives tumor cells of the sustained proliferative signaling required for rapid growth, while providing a cadenced, normalized level of signaling designed to spare healthy cells. IMM-1-104 is being developed to treat advanced solid tumors in patients harboring RAS mutations, and is translationally guided by Immuneering's proprietary, human-aligned 3D tumor modeling platform combined with patient-aligned bioinformatics. In addition to IMM-1-104, Immuneering is currently evaluating IMM-6-415 in IND-enabling studies. The earlier Immuneering drug discovery pipeline includes five additional oncology programs as well as two neuroscience programs.

Forward-Looking Statements
This press release includes certain disclosures that contain "forward-looking statements," including, without limitation, statements regarding Immuneering’s expectations regarding the treatment potential of IMM-6-415, the timing of submission of the IND and commencement of clinical trials for IMM-6-415 and Immuneering’s ability to advance its pipeline and further diversify its portfolio and make progress towards its longstanding goal of creating better medicines for cancer patients. Forward-looking statements are based on Immuneering’s current expectations and are subject to inherent uncertainties, risks and assumptions that are difficult to predict. Factors that could cause actual results to differ include, but are not limited to, the risks inherent in oncology and neuroscience drug research and development, including target discovery, target validation, lead compound identification, lead compound optimization, preclinical studies and clinical trials. These and other risks and uncertainties are described more fully in the section titled "Risk Factors" in Immuneering’s most recent Form 10-Q filed with the U.S. Securities and Exchange Commission. Forward-looking statements contained in this announcement are made as of this date, and Immuneering undertakes no duty to update such information except as required under applicable law.

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