Zymeworks Showcases Preclinical Assets, Including New Therapeutic Platform, ProTECT™, and Zanidatamab Mechanisms of Action at AACR Annual Meeting

- *Zanidatamab preclinical data reveals additional differentiated mechanisms of action including unique ability to induce complement dependent cytotoxicity*
- *ProTECT™ (PROgrammed Tumor Engagement & Checkpoint/Co-stimulation Targeting), the first conditionally-active antibody technology that simultaneously addresses both ends of the therapeutic window*
- *Preclinical IL-12 and 4-1BB programs represent future therapeutic opportunities*

Vancouver, British Columbia (April 10, 2021) – Zymeworks Inc. (NYSE: ZYME), a clinical-stage biopharmaceutical company developing multifunctional biotherapeutics, today announced five presentations at the American Association for Cancer Research (AACR) Annual Meeting. The presentations highlight preclinical data that reveal new insights into the unique mechanisms of action of lead clinical candidate, zanidatamab, introduce Zymeworks' fourth therapeutic platform, ProTECT™, and describe two new preclinical assets focused on the cytokine, IL-12, and the immune-oncology target, 4-1BB.

Presentations are now available to registrants of the AACR Annual Meeting and will also be archived on the Zymeworks website.

Zanidatamab Presentations

Super-resolution imaging studies of zanidatamab: providing insights into its bispecific mode of action

Abstract: 1032
Session Category: Experimental and Molecular Therapeutics
Session Title: Cellular Responses to Anticancer Drugs

The bispecific antibody zanidatamab's (ZW25's) unique mechanisms of action and durable anti-tumor activity in HER2-expressing cancers

Abstract: 1005
Session Category: Experimental and Molecular Therapeutics
Session Title: Cellular Responses to Anticancer Drugs

Zanidatamab, Zymeworks' lead clinical candidate, is currently enrolling in a pivotal trial for refractory HER2-amplified biliary tract cancer (HERIZON-BTC-01) as well as several Phase 2 trials for HER2-expressing gastroesophageal and breast cancers. Zanidatamab is a bispecific antibody that simultaneously binds two distinct sites on HER2 resulting in multiple mechanisms of action. Research presented today at AACR continues to demonstrate that zanidatamab induces the formation of HER2 receptor clusters and receptor internalization resulting in their downregulation, inhibits growth factor-dependent and -independent tumor cell proliferation, and

potently activates the immune system via antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). New findings from this research have revealed that zanidatamab can form complexes with HER2 with distinct higher order geometry on the cell surface. The potential for zanidatamab-induced HER2 localization may promote C1q engagement and is consistent with the additional finding that zanidatamab has the unique ability to promote complement dependent cytotoxicity (CDC). This was not observed with either of the HER2-targeted monospecific antibodies, trastuzumab and pertuzumab, or their combination and may contribute to zanidatamab's promising clinical activity.

"In addition to the broad clinical validation of zanidatamab, we continue to value ongoing research designed to better understand its unique biparatopic mechanisms of action," said Ali Tehrani, Ph.D., Zymeworks' President & CEO. "These findings provide important insights for our clinical development strategy and support our goal of developing zanidatamab in earlier lines of therapy where the combination of trastuzumab and pertuzumab are the backbone of the current standard of care."

ProTECT™ Presentation

ProTECT™, a novel antibody platform for integrating tumor-specific immune modulation and enhancing the therapeutic window of targeted multispecific biologics

Abstract: 924
Session Category: Experimental and Molecular Therapeutics
Session Title: Antibody Technologies

The ProTECT™ platform is the first conditionally-active antibody technology that can simultaneously address both ends of the therapeutic window by potentially reducing toxicity and increasing efficacy. Functional, natural heterodimers (e.g. PD-1/PD-L1) are introduced to sterically block antigen binding outside the tumor. As a result, therapeutics utilizing ProTECT™ have limited activity in normal healthy tissue, avoiding on-target, off-tumor toxicities. Once in the tumor microenvironment, proteases cleave and release one half of the functional block activating both the targeting antibody and the immunomodulatory function. The resulting activated multifunctional therapeutic enables immune modulation in concert with antigen binding, leading to an overall increase in the therapeutic window through selective tumor activity and enhanced potency. This platform is also transferable with minimal engineering so it can be easily applied to different therapeutic targets. Data presented today at AACR showcase the utility of the ProTECT™ platform for the generation of a first-in-class CD3-redirecting multispecific that also comprises PD-L1 checkpoint blockade.

IL-12 and 4-1BB Presentations

Increasing the therapeutic index of IL-12 by engineering for tumor-specific protease activation

Abstract: 1788
Session Category: Immunology
Session Title: Modifiers of the Tumor Microenvironment

IL-12 is a cytokine produced by innate immune cells that potently stimulates anti-tumor cytotoxic T cell, T helper cell, and natural killer cell-mediated immunity. The use of IL-12 as a therapeutic approach has historically been limited by systemic toxicity observed in clinical trials, and current approaches to address this toxicity have focused on reducing the potency of IL-12, which may also limit its anti-tumor activity. To broaden the therapeutic window of this highly potent cytokine, systemic IL-12 activity was blocked with an anti-IL-12 antibody which was designed to be cleaved and released by proteases in the tumor microenvironment. Data presented at AACR show that the therapeutic window of IL-12 may be increased by the combination of antibody blockade and cytokine modifications that synergize to localize activity to the tumor.

Understanding the geometry and valency of bispecific antibodies in the optimization of tumor-dependent activation of 4-1BB

Abstract: 1737
Session Category: Immunology
Session Title: Immunomodulatory Agents and Interventions

4-1BB is a receptor expressed on the surface of tumor-infiltrating T cells that when activated, can enhance T cell function leading to tumor regression. Unfortunately, the clinical development of several 4-1BB targeting antibodies has been plagued by dose-limiting liver toxicity and subsequent lack of anti-tumor activity. To address this liability, multiple formats of 4-1BB x TAA (tumor associated antigen) bispecific candidates were developed to identify those that could selectively activate T cells within the tumor microenvironment. A promising bispecific format with bivalent 4-1BB targeting and monovalent TAA targeting demonstrated the highest potential for tumor selectivity across several different TAAs and was subsequently evaluated in an *in vivo* xenograft model where it showed robust anti-tumor activity.

"The presentations highlighted at the AACR Annual Meeting showcase Zymeworks' proprietary protein engineering capabilities and how they are being used to develop solutions for a broad set of therapeutic modalities," said Tony Polverino, Ph.D., Executive Vice President, Early Development and Chief Scientific Officer of Zymeworks. "Leveraging different approaches to achieve tumor selective activity, from the functional block of the ProTECT™ platform, to the antibody block used in our IL-12 cytokine candidates, to the use of format and valency in our 4-1BB program, we've demonstrated several versatile ways to increase the therapeutic window of our drug candidates. We continue to exploit these approaches along with our bispecific, antibody-drug conjugate, and immunomodulatory platforms to build a diverse therapeutic pipeline."

About Zanidatamab

Zanidatamab is a bispecific antibody, based on Zymeworks' Azymetric™ platform, that can simultaneously bind two non-overlapping epitopes of HER2, known as biparatopic binding. This unique design results in multiple mechanisms of action including dual HER2 signal blockade, increased binding, and removal of HER2 protein from the cell surface, and potent effector function leading to encouraging antitumor activity in patients. Zymeworks is developing zanidatamab in multiple Phase 1, Phase 2, and pivotal clinical trials globally as a targeted treatment option for patients with solid tumors that express HER2. The FDA has granted

Breakthrough Therapy designation for zanidatamab in patients with previously treated HER2 gene-amplified Biliary Tract Cancer (BTC), and two Fast Track designations to zanidatamab, one as a single agent for refractory BTC and one in combination with standard of care chemotherapy, for first-line gastroesophageal adenocarcinoma (GEA). These designations mean zanidatamab is eligible for Accelerated Approval, Priority Review and Rolling Review, as well as intensive FDA guidance on an efficient drug development program. Zanidatamab has also received Orphan Drug designations for the treatment of biliary tract, gastric and ovarian cancers, as well as Orphan Drug designation for the treatment of gastric cancer from the European Medicines Agency.

About Zymeworks Inc.

Zymeworks is a clinical-stage biopharmaceutical company dedicated to the development of next-generation multifunctional biotherapeutics. Zymeworks' suite of therapeutic platforms and its fully integrated drug development engine enable precise engineering of highly differentiated product candidates. Zymeworks' lead clinical candidate, zanidatamab (ZW25), is a novel Azymetric™ bispecific antibody which has been granted Breakthrough Therapy designation by the FDA and is currently enrolling in a pivotal clinical trial for refractory HER2-amplified biliary tract cancer (HERIZON-BTC-01) as well as several Phase 2 clinical trials for HER2-expressing gastroesophageal and breast cancers. Zymeworks' second clinical candidate, ZW49, is a novel bispecific HER2-targeting antibody-drug conjugate currently in Phase 1 clinical development and combines the unique design and antibody framework of zanidatamab with Zymeworks' proprietary ZymeLink™ linker and cytotoxin. Zymeworks is also advancing a deep preclinical pipeline in oncology (including immuno-oncology agents) and other therapeutic areas. In addition, its therapeutic platforms are being leveraged through strategic partnerships with nine biopharmaceutical companies. For additional information about Zymeworks, visit www.zymeworks.com and follow @ZymeworksInc on Twitter.

Cautionary Note Regarding Forward-Looking Statements

This press release includes "forward-looking statements" within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 and "forward-looking information" within the meaning of Canadian securities laws, or collectively, forward-looking statements. Forward-looking statements in this news release include, but are not limited to, statements that relate to Zymeworks' clinical and preclinical development of its product candidates, related clinical trials, and other information that is not historical information. When used herein, words such as "will", "continue", "can", "potential", "may", and similar expressions are intended to identify forward-looking statements. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon Zymeworks' current expectations and various assumptions. Zymeworks believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain. Zymeworks may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various factors, including, without limitation, market conditions and the factors described under "Risk Factors" in Zymeworks' Annual Report on Form 10-K for

its fiscal year ended December 31, 2020 (a copy of which may be obtained at www.sec.gov and www.sedar.com). Consequently, forward-looking statements should be regarded solely as Zymeworks' current plans, estimates and beliefs. Investors should not place undue reliance on forward-looking statements. Zymeworks cannot guarantee future results, events, levels of activity, performance or achievements. Zymeworks does not undertake and specifically declines any obligation to update, republish, or revise any forward-looking statements to reflect new information, future events or circumstances or to reflect the occurrences of unanticipated events, except as may be required by law.

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