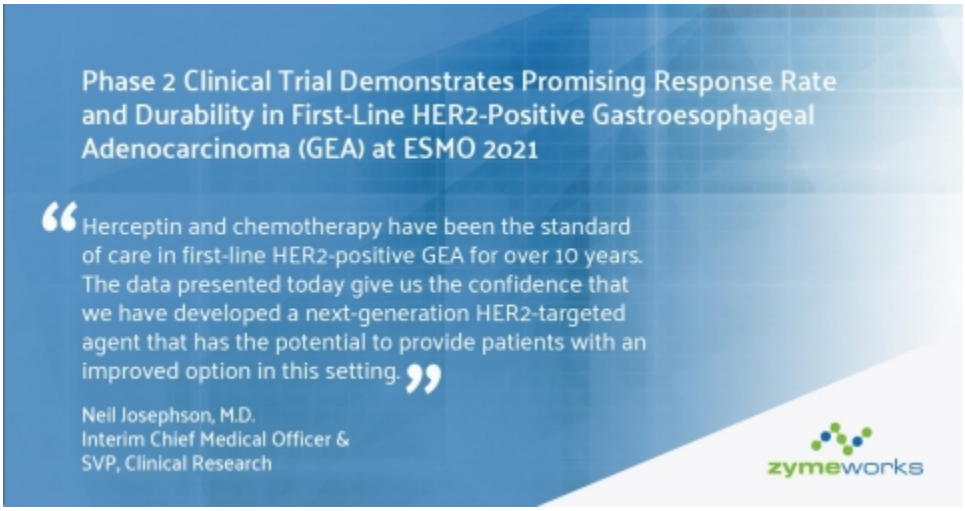
Zanidatamab Phase 2 Clinical Trial Demonstrates Promising Response Rate and Durability in First-Line HER2-Positive Gastroesophageal Adenocarcinoma (GEA) at the European Society for Medical Oncology (ESMO) Annual Congress

September 16, 2021

- *Confirmed objective response rate (cORR) of 75% overall and 93% for the proposed Phase 3 regimen (zanidatamab + CAPOX/FP)*
- *Median duration of response (mDOR) of 16.4 months and median progression free survival (mPFS) of 12 months*
- *Data support zanidatamab + chemotherapy as the foundation of a potential new standard of care in first-line HER2-positive GEA*
- *Global randomized Phase 3 trial scheduled to launch in fourth quarter (Q4) of 2021*

VANCOUVER, British Columbia--(BUSINESS WIRE)--Sep. 16, 2021-- Zymeworks Inc. (NYSE: ZYME), a clinical-stage biopharmaceutical company developing multifunctional biotherapeutics, today announced that new clinical data for zanidatamab, a HER2-targeted bispecific antibody, demonstrate promising response rates and durability in first-line HER2-positive GEA. These data were presented today by lead study investigator, Geoffrey Ku, M.D., Medical Oncologist at Memorial Sloan Kettering Cancer Center (MSK), at the ESMO Annual Congress.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20210916005389/en/



(Photo: Business Wire)

Phase 2 Study Results
The data presented at ESMO are from a clinical study of 36 patients with HER2-expressing GEA who received zanidatamab in combination with either CAPOX (capecitabine/oxaliplatin; n=14), FP (5FU/cisplatin; n=2), or mFOLFOX6 (5FU/leucovorin/oxaliplatin; n=20). None of the patients had received prior HER2-targeted therapies.

In 28 response-evaluable patients with metastatic HER2-positive GEA, zanidatamab plus chemotherapy resulted in a cORR of 75% and disease control rate (DCR) of 89% overall, with a cORR of 93% and DCR of 100% in the proposed Phase 3 regimen of zanidatamab + CAPOX/FP. All patients except one experienced a decrease in their tumor size. The mDOR is 16.4 months and the mPFS is 12.0 months across all treatment regimens with 61% of patients still on study at the time of data cutoff.

In addition, the data demonstrate that zanidatamab plus chemotherapy is generally well tolerated, with the majority of treatment-related adverse events (TRAEs) considered mild to moderate in severity (Grade 1 or 2). The most common grade ≥ 3 TRAE was diarrhea which was manageable in the outpatient setting; introduction of prophylactic loperamide reduced the incidence in cycle 1 from 44% to 18%. No severe (grade ≥ 3) infusion-related reactions or cardiac events were observed.

“Despite recent advances, metastatic HER2-expressing GEA has high morbidity and mortality, and new treatment options are desperately needed,” said the principal investigator on the trial, Geoffrey Ku, M.D., Medical Oncologist at MSK. “The data presented today at ESMO demonstrate the potential of zanidatamab in the first-line setting, highlighted by response rates and durability that compare favorably to the current standard of care as well as to emerging treatments. These data support further evaluation of zanidatamab plus chemotherapy in a randomized pivotal trial in first-line HER2-positive GEA.”

HER2 is overexpressed in approximately 20% of GEA patients. For these patients, Herceptin® (trastuzumab) is the only approved HER2-targeted therapy in 1L treatment, and therapeutic options are currently limited if disease progression occurs. Zanidatamab’s bispecific approach simultaneously binds two non-overlapping epitopes of HER2, ECD2 and ECD4, resulting in multiple mechanisms of action that provide potential therapeutic benefits beyond the combination of two monoclonal antibodies.

“Herceptin and chemotherapy have been the standard of care in first-line HER2-positive GEA for over 10 years. The data presented today give us the confidence that we have developed a next-generation HER2-targeted agent that has the potential to provide patients with an improved option in this setting,” said Neil Josephson, M.D., Zymeworks’ Interim Chief Medical Officer. “Based on these data, we will pursue a randomized, Phase 3 trial with

the aim of establishing zanidatamab as the foundational agent of a new standard of care in first-line HER2-positive GEA."

In addition to the Phase 2 study presented today, Zymeworks and its partner, BeiGene, Ltd., are conducting a parallel open-label Phase 2 clinical trial evaluating zanidatamab and chemotherapy in combination with the PD-1 inhibitor, tislelizumab, in first-line HER2-positive metastatic GEA. These results are expected to be presented at a future medical conference.

Zymeworks plans to launch, with BeiGene, a randomized, global Phase 3 study (HERIZON-GEA-01) in Q4 2021. The study will evaluate zanidatamab plus chemotherapy (CAPOX or FP) with or without tislelizumab, versus standard of care (trastuzumab plus chemotherapy), for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive GEA.

"Our long-standing vision for zanidatamab has been for it to become a best-in-class HER2 -targeted therapeutic that could address the needs of a broad spectrum of patients with HER2-expressing cancers," said Ali Tehrani, Ph.D., Zymeworks' President & CEO. "Over the years we have shared data that have showcased the promising anti-tumor activity and safety profile of zanidatamab; that said, the data shared today stand out as they represent the first clinical validation of zanidatamab in a front-line setting. As we embark on our second pivotal trial and prepare for commercialization, these data represent a landmark moment for zanidatamab and for Zymeworks."

Dr. Ku has provided advisory services for Zymeworks.

ESMO Presentation
The presentation will be available to conference registrants on the ESMO conference website as well as to the general public on the Zymeworks website at https://www.zymeworks.com/publications
The presentation will be available to conference registrants on the
Title: *Phase (Ph) 2 Study of Zanidatamab + Chemotherapy (chemo) in First Line (1L) HER2-expressing Gastroesophageal Adenocarcinoma (GEA)*
Lead Author: Geoffrey Ku, M.D., Memorial Sloan Kettering Cancer Center, New York, NY, US
Abstract: 3678
E-poster: 1380P

Conference Call and Webcast
The company will host a conference call and webcast to discuss the updated data. The event will be led by Ali Tehrani, Ph.D., Zymeworks' President and CEO and Neil Josephson, M.D., Zymeworks' Interim Chief Medical Officer, and will include a presentation by medical oncologist and principal investigator, Geoffrey Ku, M.D., Memorial Sloan Kettering Cancer Center. Dr. Ku and members of Zymeworks' executive team will be available to answer questions at the conclusion of the call.

Date: Thursday, September 16th
Time: 7:30 am ET

Interested parties can access the live webcast via the Zymeworks' website at https://ir.zymeworks.com/events-and-presentations. A recorded replay will be accessible after the event through the Zymeworks website.

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. Zanidatamab's unique binding properties result in multiple mechanisms of action including HER2-receptor clustering, internalization, and downregulation; inhibition of growth factor-dependent and -independent tumor cell proliferation; antibody-dependent cellular cytotoxicity and phagocytosis; and complement-dependent cytotoxicity. 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 monotherapy 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 designations from the European Medicines Agency for the treatments of biliary tract and gastric cancer.

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, colorectal, 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 development of its product candidates, related clinical trials, anticipated clinical data presentations, potential therapeutic effects of zanidatamab, Zymeworks' preclinical pipeline, and other information that is not historical information. When used herein, words such as "plan", "expect", "may", "potential", "will", "aim", 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' Quarterly Report on Form 10-Q for its quarter ended June 30, 2021 (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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