Zymeworks Presents New Data from Multiple Development Programs at 2025 AACR Annual Meeting

April 25, 2025

Six posters highlight continued progress across antibody-drug conjugate and T cell engager platforms

Novel T cell engager ZW209 demonstrates durable activity in small cell lung cancer; IND submission expected in 1H-2026

VANCOUVER, British Columbia, April 25, 2025 (GLOBE NEWSWIRE) -- Zymeworks Inc. (Nasdaq: ZYME), a clinical-stage biotechnology company developing a diverse pipeline of novel, multifunctional biotherapeutics to improve the standard of care for difficult-to-treat diseases, including cancer, inflammation, and autoimmune disease, today announced the presentation of six posters with new preclinical data from its preclinical, development-stage, and clinical programs at the American Association for Cancer Research (AACR) Annual Meeting being held April 25-30, 2025 in Chicago, IL.

"The breadth of data shared at AACR highlights the strength of our oncology portfolio across antibody-drug conjugates and T cell engagers, and demonstrates the novel approaches we employ using each modality," said Paul Moore, Ph.D., Chief Scientific Officer at Zymeworks. "We're particularly excited to share data on ZW209, the latest of our oncology nominated IND programs which has demonstrated promising anti-tumor activity in preclinical small cell lung cancer models by integrating CD28 co-stimulation into a trispecific T cell engager. We look forward to advancing ZW209 with an IND submission anticipated in the first half of 2026, while also progressing the differentiated programs in our wholly-owned pipeline."

Presentation Highlights

T cell Engagers (TCE):

ZW171, a differentiated 2+1 T cell-engaging bispecific antibody with antitumor activity in a range of mesothelin expressing cancers
Abstract: 3503
Session Category: Immunology
Session Title: T Cell Engagers

ZW171 is a mesothelin (MSLN)-targeting TCE currently in a global Phase 1 clinical study (NCT06523803) in a range of difficult-to-treat, MSLN-positive tumor models including ovarian, pancreatic, and non-small cell lung cancer (NSCLC).

Key findings include:

- ZW171 demonstrates cytolytic activity across a range of MSLN expressing tumor types including lung, ovarian and pancreatic cancers with anti-tumor activity correlating with MSLN cell surface expression and not related to soluble MSLN levels.
- ZW171 exhibits strong anti-tumor activity in patient derived xenograft (PDX) models of NSCLC and pancreatic cancer, and in ex-vivo patient-derived ovarian cancer organoids with endogenous tumor-infiltrating lymphocytes (TIL).
- Relative to other MSLN targeted T cell engagers in development, ZW171 exhibits reduced T cell binding but enhanced cytolytic activity.
- These data reinforce the differentiated profile of ZW171 and demonstrate its enhanced anti-tumor activity compared to other MSLN-targeting bispecifics.

ZW209, a DLL3 targeted trispecific T cell engager with integrated CD28 co-stimulation, demonstrates safety and potent preclinical efficacy in models of small cell lung cancer
Abstract: 7318
Session Category: Immunology
Session Title: T Cell Engagers and Novel Antibody-Based Therapies

Delta-like ligand 3 (DLL3) is a cell surface protein overexpressed in small cell lung cancer (SCLC) and other neuroendocrine carcinomas that has emerged as a promising therapeutic target for these aggressive and difficult-to-treat malignancies[1,2]. Clinical activity of bispecific TCEs may be limited by low T cell infiltration and poor T cell function, highlighting an opportunity to improve the rate and depth of response[3]. ZW209, a DLL3-targeting trispecific TCE, is designed to optimally co-engage CD3 and CD28 on T cells, and was engineered using the Company's TriTCE Co-Stim platform in

combination with its Azymetric™ and EFECT™ technologies.

Key findings include:

- ZW209 was designed for optimal T cell binding and enhanced target-dependent T cell activation that translates to increased antitumor activity compared to traditional bispecific T cell engagers.
- Relative to other DLL3 targeted T cell engagers in development, ZW209 exhibits enhanced and prolonged cytotoxicity over repeated tumor cell challenges and at low effector to target cell ratios. These data reinforce the potential of ZW209 to increase the depth and durability of responses in DLL3-expressing tumors by increasing T cell responses, which may translate to improved clinical outcomes.
- In a non-human primate (NHP) study, ZW209 demonstrated favorable pharmacokinetics (PK) and safety following repeat dosing.

Antibody-Drug Conjugates (ADCs):

ZW327, a novel Ly6E-targeting antibody-drug conjugate bearing a topoisomerase 1 inhibitor payload
Abstract: 2874
Session Category: Experimental and Molecular Therapeutics
Session Title: Antibody-Based Cancer Therapeutics 2

ZW327 is a potential first-in-class ADC targeting Ly6E, an antigen overexpressed in numerous tumor types including breast, lung, and digestive tract cancers. Utilization of a superior Ly6E binding and internalizing antibody with a proprietary topoisomerase 1 inhibitor payload[4], ZD06519, reinforces the highly differentiated profile of ZW327, with pronounced *in vitro* cytotoxicity against a panel of tumor cell line models.

Key findings include:

- ZW327 demonstrated robust anti-tumor activity in low, mid, and high Ly6E-expressing cell line-derived xenograft (CDX) and PDX models. ZW327 maintains potential in diverse indications including NSCLC, triple-negative breast cancer, head and neck squamous cell carcinoma, and gastrointestinal cancers, including pancreatic ductal adenocarcinoma.
- Across various tumor types, ZW327 exhibited favorable PK and tolerability in NHP at exposure levels above those projected to be efficacious.
- This promising preclinical activity highlights the potential to ZW327 as an innovative therapeutic option in Ly6E-expressing cancers.[5]

Design and development of biparatopic antibody-drug conjugates against protein tyrosine kinase 7
Abstract: 1565
Session Category: Experimental and Molecular Therapeutics
Session Title: Antibody-Based Cancer Therapeutics 1

Protein Tyrosine Kinase 7 (PTK7) over expression across multiple tumor types including breast, digestive tract, and lung cancers, makes it an attractive target for ADCs. To enable optimal targeting, and overcome limitations of prior PTK7 ADCs, Zymeworks identified a lead biparatopic antibody displaying improved binding and receptor-mediated internalization relative to that achieved with monospecific PTK7 antibodies. This lead PTK7 biparatopic antibody was evaluated as an ADC utilizing Zymeworks' proprietary topoisomerase 1 inhibitor (TOPO1i) payload, ZD06519.

Key findings include:

- Enhanced antibody internalization of a biparatopic ADC allows for increased delivery of cytotoxic payload.
- This first-in-class biparatopic TOPO1i PTK7 ADC demonstrated activity in breast and lung cancer models, reinforcing its potential improvement over cofetuzumab pelidotin, a prior clinical stage PTK7 ADC.
- This biparatopic TOPO1i PTK7 ADC was found to be well-tolerated in NHP at a dose of up to 60 mg/kg.

Additionally, Zymeworks scientists co-authored two poster presentations focused on leveraging technologies that support the design and characterizations of ADCs, including high-throughput functional screening in 3D tumor models and *in vitro* assays to assess potential hematologic toxicity:

High throughput quantitative molecular characterization of cytotoxic antibody-drug conjugates in spheroid models for improved functional characterization, screening and candidate selection
Abstract: 1230
Session Category: Tumor Biology
Session Title: 3D Models and Bioprinting

There is a need for improved *in vitro* models that better recapitulate *in vivo* tumor tissue complexity to aid in the screening and evaluation of novel ADCs during preclinical development. Zymeworks has developed *in vitro* 3D models from cancer cell lines yielding spheroids in a rapid, robust and uniform manner. Using these spheroid models, the Company has developed cell-based assays to functionally evaluate the cytotoxic activity of ADCs *in vitro*. Zymeworks utilized the nCounter® ADC Development Panel (nCounter), a specialized gene expression tool for molecular characterization of biological function with customizable gene content, to further characterize ADC activity in 3D cell line models.

Key findings include:

- nCounter is a robust and reliable platform to assess the gene expression of RNA samples especially using poor quality, fragmented FFPE derived samples, DV200 < 30% demonstrates its robustness and ease of use.
- nCounter demonstrated consistent genetic changes between cell culture methods (spheroids vs. monolayer), and the type

of ADC treatment.
- These results may allow for further improvement of ADC pipeline development with a focus on functional pathway evaluation.

In vitro assays for prediction of ADC hematological toxicity: contribution of antibody, linker, and payload
Abstract: 5482
Session Category: Experimental and Molecular Therapeutics
Session Title: Drug Discovery Assay Technologies

Hematological toxicities are commonly associated with many ADCs and may arise from the direct killing of hematopoietic cells by the ADC itself or indirectly from payload released elsewhere in the body. Development of *in vitro* assays capable of predicting clinical findings could improve ADC development and guide the selection of optimal linkers and payloads.

Key findings include:

- Clinical toxicity profile prediction largely depends on payload class and key ADC attributes. The poor translation of preclinical findings to predict ADC clinical toxicities has led to the empirical testing of ADC designs in patients.
- Colony forming cell (CFC) assays using primary bone marrow cells can be used to evaluate toxicities of both ADCs and their payloads on blood progenitor cell lineages.
- Comparison of ADC clinical toxicities and *in vitro* CFC assay results indicates that the CFC assay can effectively recapitulate specific clinical observations, making it a valuable screening tool for ADCs.
- The prediction of clinical toxicity profiles for ADCs remains a complex challenge due to the intricate ADC disposition in humans.

Posters are available on the Company's website located at https://www.zymeworks.com/publications/.

About Zymeworks Inc.
Zymeworks is a global clinical-stage biotechnology company committed to the discovery, development, and commercialization of novel, multifunctional biotherapeutics. Zymeworks' mission is to make a meaningful difference in the lives of people impacted by difficult-to-treat conditions such as cancer, inflammation, and autoimmune disease. The Company's complementary therapeutic platforms and fully integrated drug development engine provide the flexibility and compatibility to precisely engineer and develop highly differentiated antibody-based therapeutic candidates. Zymeworks engineered and developed zanidatamab, a HER2-targeted bispecific antibody using the Company's proprietary Azymetric™ technology.Zymeworks has entered into separate agreements with BeiGene, Ltd. (BeiGene) and Jazz Pharmaceuticals Ireland Limited (Jazz Pharmaceuticals), granting each exclusive rights to develop and commercialize zanidatamab in different territories. The U.S. FDA granted accelerated approval of Ziihera® (zanidatamab-hrii) 50mg/mL for injection for intravenous use for the treatment of adults with previously-treated, unresectable or metastatic HER2-positive (IHC 3+) second-line biliary tract cancer (BTC). Ziihera® is the first and only dual HER2-targeted bispecific antibody approved for HER2-positive BTC in the U.S. Zanidatamab is currently under regulatory review in the EU and China for second-line BTC and is being evaluated in multiple global clinical trials as a potential best-in-class treatment for patients with multiple HER2-expressing cancers. Zymeworks is rapidly advancing a robust pipeline of wholly-owned product candidates, leveraging its expertise in both antibody-drug conjugates and multispecific antibody therapeutics targeting novel pathways in areas of significant unmet medical need. Phase 1 studies for ZW171 and ZW191 are now actively recruiting with an investigational new drug application for ZW251 planned for mid-2025. In addition to Zymeworks' pipeline, its therapeutic platforms have been further leveraged through strategic partnerships with global biopharmaceutical companies. For information about Zymeworks, visit www.zymeworks.com and follow @ZymeworksInc on X.

Cautionary Note Regarding Forward-Looking Statements
This press release includes "forward-looking statements" or information within the meaning of the applicable securities legislation, including Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements in this press release include, but are not limited to, statements that relate to Zymeworks' preclinical pipeline; the potential therapeutic effects of and commercial potential of zanidatamab and Zymeworks' other product candidates; anticipated IND submissions and the timing thereof; Zymeworks' clinical development of its product candidates and enrollment in its clinical trials; anticipated preclinical and clinical data presentations and key findings; the ability to advance product candidates into later stages of development; and other information that is not historical information. When used herein, words such as "plan", "believe", "expect", "may", "anticipate", "potential", "will", "on track", "continues", 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: clinical trials may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; any of Zymeworks' or its partners' product candidates may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; the impact of new or changing laws and regulations; market conditions; inability to maintain or enter into new partnerships or strategic collaborations; and the factors described under "Risk Factors" in Zymeworks' quarterly and annual reports filed with the Securities and Exchange Commission, including its Annual Report on Form 10-K for its year ended December 31, 2024 (a copy of which may be obtained at www.sec.gov and www.sedarplus.ca).

Although Zymeworks believes that such forward-looking statements are reasonable, there can be no assurance they will prove to be correct. Investors should not place undue reliance on forward-looking statements. The above assumptions, risks and uncertainties are not exhaustive. Forward-looking statements are made as of the date hereof and, except as may be required by law, Zymeworks undertakes no 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.

Contacts:
Investor Inquiries:
Shrinal Inamdar
Senior Director, Investor Relations
(604) 678-1388
ir@zymeworks.com

Media Inquiries:
Diana Papove
Senior Director, Corporate Communications
(604) 678-1388
media@zymeworks.com

---

[1] Rojo, F. et al. 2020. International real-world study of DLL3 expression in patients with small cell lung cancer. Lung Cancer. Sep:147:237-2433.

[2] Yao, J. et al. 2022. DLL3 as an emerging target for the treatment of neuroendocrine neoplasms. Oncologist.

[3] Michael, L. et al. 2024. CD28 co-stimulation: novel insights and applications in cancer immunotherapy. Nat Rev Immunol. Dec;24(12):878-895.

[4] Petersen et al. Design and evaluation of ZD06519, a novel camptothecin payload for antibody drug conjugates. Mol Cancer Ther. 2024 May 2; 23(5):606-618.

[5] Tolaney et al. A Phase I Study of DLYE5953A, an anti-Ly6E antibody covalently linked to monomethyl auristatin E, in patients with refractory solid tumors. Clin Cancer Res. 2020 Nov 1; 26(21): 5588- 5597.

Source: Zymeworks Inc.