Zymeworks Presents New Data from Multiple Preclinical Development Programs at 2024 American Association for Cancer Research Annual Meeting

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VANCOUVER, British Columbia, April 08, 2024 (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, today announced five presentations including new data from its preclinical development-stage programs at the 2024 American Association for Cancer Research (AACR) Annual Meeting being held in San Diego, California April 5-10, 2024.

“Our team is looking forward to share new data from our strong portfolio of multispecific antibody therapeutics and antibody-drug conjugates including ZW191, an anticipated 2024 IND candidate,” said Paul Moore, Ph.D., Chief Scientific Officer at Zymeworks. “These data provide important new insights highlighting the potential of our candidates to represent major advances in the treatment of cancer while also demonstrating the potential to develop a new generation of novel antibody-drug conjugates and multispecific antibody therapeutics.”

Presentation Highlights

ZW191 - a FRα-targeting antibody-drug conjugate with strong preclinical activity across multiple FRα-expressing indications
Abstract: 1862
Session Category: Experimental and Molecular Therapeutics
Session Title: Antibody-Based Technologies and New Inhibitors

ZW191 is a FRα-targeting antibody-drug conjugate (ADC) differentiated by its novel antibody and novel topoisomerase I inhibitor payload. The compelling preclinical activity profile supports ZW191 development across multiple tumor types, including FRα-high/mid/low ovarian cancers and other FRα-expressing indications, including non-small cell lung cancer, endometrial cancer, and triple-negative breast cancer. An investigational new drug (IND) submission or foreign equivalent is planned for 2024.

Key Results:

- Superior internalization, payload delivery, and spheroid penetration to other FRα-targeted multi-specific antibodies.
- Bystander active payload drives activity in settings with heterogeneous FRα expression.
- Well-tolerated, with a highest non-severely toxic dose of 60 mg/kg in non-human primates.

Screening novel format antibodies to design bispecific ADCs that address target heterogeneity
Abstract: 2052
Session Category: Experimental and Molecular Therapeutics
Session Title: New Technologies

Inter-patient and intra-tumoral target expression heterogeneity is an obstacle in the design of ADCs that target a single tumor associated antigen (TAA). While bystander active payloads mitigate intra-tumoral target heterogeneity, bispecific ADCs that target two different TAAs independently provide an additional approach to overcome limitations associated with the expression profile of any single target antigen. Critical to this bispecific ADC approach however is identification of the optimal bispecific antibody format suited for payload delivery to two independent tumor antigens. To address this challenge a novel design and screening approach of bispecific ADCs was employed, using FRα and NaPi2b as an exemplary target pair, independently expressed across various cancer types.

Key Results:

- Leveraging Azymetric™, bioconjugation, analytical mass spectrometry, and high throughput functional screening, a workflow for the rapid generation and characterization of bispecific ADCs was established to identify optimal format, paratope, and valency.
- A library of 48 bispecific ADC molecules co-targeting FRα and NaPi2b was rapidly generated covering multiple paratopes, antibody formats, and valency bins (1+1, 2+1, 2+2). Functional screening of the library across multiple cancer cell lines expressing FRα and/or NaPi2b revealed ranges in binding, internalization, and cytotoxicity that were dependent on epitope, valency, and format geometry.

Development of three-dimensional cancer cell line spheroid models for the in vitro functional characterization of cytotoxic antibody-drug conjugates

Abstract: 3127
Session Category: Experimental and Molecular Therapeutics
Session Title: Antibody-Drug Conjugates

Antibody-drug conjugates are an effective class of cancer therapeutics comprised of a linker-payload conjugated to a monoclonal antibody targeting a TAA, to enable the delivery of the cytotoxic payload to cancer cells. Current standard in vitro monolayer models do not sufficiently reflect in vivo tumor tissue complexity, particularly in consideration of the interaction between protein-based therapeutics such as antibodies in a three-dimensional (3D) environment. To address this, methodology to yield in vitro 3D spheroid models from cancer cell lines in a rapid, robust, and uniform manner was developed. Subsequently methods were integrated to evaluate the tissue penetration capability and cytotoxic activity of structurally distinct antibodies or ADCs bearing various payload classes targeting multiple TAAs.

Key Results:

- A readily implementable method for the rapid generation of cancer cell line spheroids was established and applied to over 50 distinct immortalized cancer cell lines derived from more than 10 tissue types, demonstrating varying morphological features with a success rate of >95%.
- In vitro assays were developed to evaluate the spheroid penetration capability and 3D cytotoxic activity of multispecific antibodies and ADCs, enabling the interrogation of various antibody formats and payload classes.
- These 3D models and assays serve as valuable functional tools that provide improved translation between in vitro and in vivo activity, supporting the characterization of therapeutic ADC candidates and their pipeline advancement.

TriTCE Co-Stim: A next generation trispecific T cell engager platform with integrated CD28 costimulation, engineered to improve responses in the treatment of solid tumors
Abstract: 6719
Session Category: Immunology
Session Title: Targeted ICEs

Low T cell infiltration and T cell anergy are challenges associated with the treatment of solid tumors with conventional CD3-engaging bispecific T cell engagers (TCEs)[1]. By optimizing “Signal 1” (CD3) and “Signal 2” (CD28) within the context of a single molecule, co-stimulatory trispecific TCEs (TriTCE Co-Stim) have the potential to increase therapeutic responses beyond that achievable by conventional CD3-based TCEs by stimulating T cell proliferation in patients with poorly infiltrated tumors and providing more durable anti-tumor control by enhancing T cell activation.

Key Results:

- Relative to comparator bispecific TCEs, the lead CLDN18.2 TriTCE Co-Stim molecule mediates enhanced T cell-mediated killing of tumor cells at low E:T ratios, exhibits sustained T cell mediated activity in serial challenge assays and supports superior antitumor activity in humanized models of gastric cancer.
- TriTCE Co-stim design facilitates obligate cis T cell binding and activation of CD28 that requires co-engagement of CD3 with no detectable cytokine levels observed upon incubation with human peripheral blood mononuclear cells in the absence of tumor target engagement.
- CLDN18.2 TriTCE Co-stim was well tolerated in non-human primates upon repeat dosing, with minimal peripheral cytokine elevations and no on-target histopathological changes observed.

DLL3 TriTCE Co-Stim: A next generation trispecific T cell engager with integrated CD28 costimulation for the treatment of DLL3-expressing cancers
Abstract: 6716
Session Category: Immunology
Session Title: Targeted ICEs

Small cell lung cancer (SCLC) is an aggressive neuroendocrine cancer with a poor prognosis and high unmet medical need[2]. DLL3 is a therapeutic target that is selectively expressed in SCLC and other neuroendocrine tumors. Bispecific TCEs targeting DLL3 have entered the clinic and demonstrated encouraging anti-tumor activity in SCLC patients[3,4]; however, SCLC is frequently characterized by an immunosuppressive microenvironment and poor T cell infiltration, which may limit clinical activity of CD3 engagers[5]. DLL3 TriTCE Co-Stim is a TriTCE designed to optimally engage CD3 and CD28 to redirect and enhance cytotoxic T cell responses to DLL3-expressing tumor cells while maintaining a desired safety profile. This approach has the potential to improve outcomes for patients, especially those with poorly infiltrated tumors, by increasing the depth and durability of response.

Using Zymeworks’ TriTCE Co-stim platform in combination with our Azymetric™ and EFECT™ technologies, we generated a panel of DLL3 TriTCE Co-Stim antibody formats and evaluated multiple formats, geometries, and paratope affinities, which allowed for optimization of selectivity and activity to promote a widened therapeutic index with enhanced anti-tumor activity.

Key Results:

- Induces greater in vitro cytotoxicity and improves T cell proliferation and survival compared to bispecific TCEs.
- Displays no cross-linking of T cells and exhibits obligate cis T cell binding of CD28, requiring co-engagement of CD3.
- Mediates improved in vivo tumor regression in an established SCLC humanized xenograft model relative to a clinical benchmark TCE.

Posters will be available at the time of presentation at the conference on the Company's website located at www.zymeworks.com.

About Zymeworks Inc.

Zymeworks is a global 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 cancers and other diseases. 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), granting each exclusive rights to develop and commercialize zanidatamab in different territories. Zanidatamab is currently being evaluated in multiple global clinical trials as a potential best-in-class treatment for patients with HER2-expressing cancers. A Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) seeking accelerated approval for the HER2-targeted bispecific antibody zanidatamab as a treatment for previously treated, unresectable, locally advanced, or metastatic HER2-positive biliary tract cancer (BTC) has been submitted. If approved, zanidatamab would be the first HER2-targeted treatment specifically approved for BTC in the U.S. Zymeworks is rapidly advancing a deep pipeline of product candidates based on its experience and capabilities in both antibody-drug conjugates and multispecific antibody therapeutics across multiple novel targets in indications that represent areas of significant unmet medical need. In addition to Zymeworks' wholly owned 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 the anticipated data presentations; Zymeworks' preclinical pipeline; the potential therapeutic effects of zanidatamab and Zymeworks' other product candidates; anticipated regulatory submissions and the timing thereof; Zymeworks' clinical development of its product candidates and enrollment in its clinical trials; 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", "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: future clinical trials may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; 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 from time to time (copies of which may be obtained at www.sec.gov and www.sedar.com).

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.

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Source: Zymeworks Inc.