Zentalis Announces Preclinical Data Supporting Cyclin E1 As A Predictive Marker For Azenosertib Treatment At AACR Annual Meeting 2023

April 17, 2023 1:00 PM EDT

Data suggest Cyclin E1 plays a critical role in high proportion of multiple tumor types including platinum-resistant ovarian cancer

Company anticipates sharing clinical data from ovarian chemotherapy combination study, including data on CCNE1 amplification and / or Cyclin E1 expression, in the first half of 2023, in advance of original guidance

NEW YORK and SAN DIEGO, April 17, 2023 (GLOBE NEWSWIRE) -- Zentalis™ Pharmaceuticals, Inc. (Nasdaq: ZNTL), a clinical-stage biopharmaceutical company focused on discovering and developing clinically differentiated small molecule therapeutics targeting fundamental biological pathways of cancers, today announces preclinical data that supports CCNE1 amplification and / or Cyclin E1 expression as a potential marker for the enrichment of patient populations for treatment with azenosertib, the Company's potentially first-in-class Wee1 inhibitor product candidate. These new preclinical data demonstrate that azenosertib drives cancer cell death in Cyclin E1-high tumor cells *in vitro* and substantially inhibits the growth of Cyclin E1-high, patient-derived, *in vivo* tumor models.

The findings are being presented today at the 2023 American Association for Cancer Research (AACR) Annual Meeting, in a poster entitled "Cyclin E1 protein overexpression sensitizes ovarian cancer cells to azenosertib (ZN-c3), a novel, selective and orally bioavailable inhibitor of Wee1." The poster can be found on the Company's website at this link. The poster presentation details are below.

Session Category: Clinical Research Excluding Trials

Session Title: Biomarkers of Therapeutic Benefit 2

Session Date and Time: Monday, April 17, 2023, 9:00 AM ET - 12:30 PM ET

Location: Section 39

Poster Board Number: 27

Abstract Presentation Number: 2153

"We are excited to present new preclinical data demonstrating the utility of Cyclin E1 as a predictive marker to identify patients likely to respond to azenosertib," said Mark Lackner, Ph.D., Chief Translational Officer of Zentalis. "Our findings suggest that Cyclin E1 expression via gene amplification or independent mechanisms sensitizes ovarian cancer cells to azenosertib alone or in combination with chemotherapy. These data confirm and build upon our prior preclinical work, and the published research of others, and provide additional evidence that supports our ongoing clinical trial studying azenosertib as a monotherapy in patients with Cyclin E1-driven ovarian cancer. These data also support the potential development of companion diagnostics for azenosertib."

The study analyzed data from a panel of patient-derived ovarian cancer cell lines *in vitro* and *in vivo* models of ovarian cancer. The results show that high Cyclin E1 protein expression is significantly associated with sensitivity to azenosertib, and that artificial overexpression of Cyclin E1 in cell lines with low endogenous Cyclin E1 expression sensitizes those cells to azenosertib. In addition, the study provides foundational details on the mechanistic basis of Cyclin E1 sensitization to Wee1 inhibition, including that Cyclin E1 overexpression results in accumulation of replication stress biomarkers and that azenosertib sensitivity is mediated by CDK2 activity.

The study also provides supportive data for several relevant standard of care chemotherapy combinations based on *in vitro* synergy assays and suggests that Cyclin E1 expression is a relevant clinical predictive marker. The Company is conducting an analysis of CCNE1 copy number and Cyclin E1 protein expression in its Phase 1b study of azenosertib in combination with chemotherapy in patients with platinum-resistant ovarian cancer. The Company now anticipates sharing these clinical data in the first half of 2023, in advance of original guidance.

"These encouraging translational results support the use of CCNE1 copy number and / or Cyclin E1 protein expression as predictive markers that have the potential to significantly improve patient outcomes by enabling us to select the right patients for treatment with azenosertib," said Gordon Mills, M.D., Ph.D., Professor of Cell, Developmental and Cancer Biology, Oregon Health and Science University School of Medicine. The Company is collaborating with Dr. Mills on preclinical and clinical studies related to the effects of Wee1 inhibition on replicative stress, cell cycle modulation and DNA repair.

Another poster being presented at AACR by the Ivy Brain Tumor Center at Barrow Neurological Institute entitled "Tumor Pharmacokinetics, Pharmacodynamics and Efficacy Analysis of Wee1 inhibitor, Azenosertib in Patient-Derived Xenograft Models of Glioblastoma," demonstrates that azenosertib can achieve pharmacologically-relevant intracerebral free-drug concentrations, and that pharmacodynamic activity is observed in a preclinical glioblastoma model. This research underscores the potential of azenosertib as a therapy for a more extensive range of tumor types than those presently under clinical investigation. Once presented, the poster can be found on the Company's website using this link. The poster presentation details are below.

Session Category: Experimental and Molecular Therapeutics, Chemistry

Session Title: Pharmacokinetics, Pharmacodynamics, and Molecular Pharmacology

Session Date and Time: Monday, April 17, 2023, 1:30 PM ET – 5:00 PM ET

Location: Section 18

Poster Board Number: 19

Abstract Presentation Number: 2796

About Azenosertib

Zentalis' azenosertib (ZN-c3) has been designed to be a highly potent and selective Wee1 inhibitor. Azenosertib is currently being evaluated in the clinic for advanced solid tumors and hematological malignancies in the following three therapeutic settings of high unmet medical need: (1) as a monotherapy, (2) in combination with traditional chemotherapy and DNA damaging agents, and (3) in combination with molecularly targeted agents. As a monotherapy, azenosertib is currently being evaluated in a Phase 2 clinical trial in adult women with uterine serous carcinoma (USC), an aggressive form of endometrial cancer that accounts for approximately 10-15% of all endometrial cancers. We are also evaluating azenosertib as a monotherapy in a Phase 2 clinical trial in patients with Cyclin E1 driven high-grade serous ovarian cancer (HGSOC). The Company is evaluating azenosertib as a monotherapy in a Phase 1 dose optimization clinical trial in patients with advanced solid tumors, and plans to declare the recommended Phase 2 monotherapy dose and provide an update on dose optimization activities in the first half of 2023. In chemotherapy combinations, azenosertib is currently being evaluated in combination with each of paclitaxel, carboplatin, pegylated liposomal doxorubicin (PLD) and gemcitabine in four cohorts in a Phase 1b clinical trial in patients with advanced platinum-resistant ovarian, peritoneal or fallopian tube cancer. The Company plans to disclose results from this study in the first half of 2023, in advance of original guidance. Azenosertib is also currently being evaluated in combination with gemcitabine in a Phase 1/2 clinical trial in adult and pediatric patients with relapsed or refractory osteosarcoma. In combination with molecularly targeted agents, the Company is studying azenosertib in combination with GlaxoSmithKline plc's (GSK's) PARP inhibitor, niraparib (ZEJULA®), in a Phase 1/2 clinical trial in platinum-resistant ovarian cancer patients who have failed PARP inhibitor maintenance treatment as part of a clinical collaboration with GSK. The Company is also collaborating with Pfizer Inc. to evaluate azenosertib in combination with encorafenib and cetuximab, an FDA-approved standard of care known as the BEACON regimen, in patients with BRAF V600E mutant metastatic colorectal cancer in a Phase 1/2 clinical trial.

About Zentalis Pharmaceuticals

Zentalis™ Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company focused on discovering and developing small molecule therapeutics targeting fundamental biological pathways of cancers. Utilizing its Integrated Discovery Engine, the Company is developing a focused pipeline of potentially best-in-class oncology candidates, which include azenosertib (ZN-c3), a Wee1 inhibitor for advanced solid tumors, ZN-d5, a BCL-2 inhibitor for hematologic malignancies and related disorders, and a heterobifunctional degrader of BCL-xL for solid and hematological malignancies. The Company is also leveraging its extensive experience and capabilities across cancer biology and medicinal chemistry to advance its research on protein degraders. Zentalis has operations in both New York and San Diego.

For more information, please visit www.zentalis.com. Follow Zentalis on Twitter at @ZentalisP and on LinkedIn at www.linkedin.com/company/zentalis-pharmaceuticals.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including statements regarding the potential of Cyclin E1 as a predictive marker for azenosertib treatment, including its potential to significantly improve patient outcomes by enabling selection of the right patients for azenosertib treatment; the role Cyclin E1 may play in a high proportion of multiple tumor types; the timing of disclosure of preclinical and clinical data, the timing of declaration of the recommended Phase 2 monotherapy dose for azenosertib, and the timing of providing an update on the dose optimization activities for azenosertib; the potential for azenosertib to be first-in-class; the potential for our product candidates to be best-in-class; the potential for Cyclin E1 expression to sensitize ovarian cancer cells to azenosertib alone or in combination; the potential to develop companion diagnostics for azenosertib; the potential of azenosertib as a therapy for a more extensive range of tumor types than those presently under clinical investigation; the potential benefits of azenosertib, including the potential benefits of the design of azenosertib; and the market opportunity for azenosertib. The terms "anticipates," "can," "designed," "likely," "plan," "potential," "provide," "suggest," "support" and similar references are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: our limited operating history, which may make it difficult to evaluate our current business and predict our future success and viability; we have and expect to continue to incur significant losses; our need for additional funding, which may not be available; our plans, including the costs thereof, of development of any companion diagnostics; our substantial dependence on the success of our lead product candidates; the outcome of preclinical testing and early trials may not be predictive of the success of later clinical trials; failure to identify additional product candidates and develop or commercialize marketable products; potential unforeseen events during clinical trials could cause delays or other adverse consequences; risks relating to the regulatory approval process or ongoing regulatory obligations; failure to obtain U.S. or international marketing approval; our product candidates may cause serious adverse side effects; inability to maintain our collaborations, or the failure of these collaborations; our reliance on third parties; effects of significant competition; the possibility of system failures or security breaches; risks relating to intellectual property; our ability to attract, retain and motivate qualified personnel, and risks relating to management transitions; significant costs as a result of operating as a public company; and the other important factors discussed under the caption "Risk Factors" in our most recently filed periodic report on Form 10-K or 10-Q and subsequent filings with the U.S. Securities and Exchange Commission (SEC) and our other filings with the SEC. Any such forward-looking statements represent management's estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

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