Zentalis Pharmaceuticals to Highlight Preclinical Data Demonstrating that WEE1 Inhibitor Azenosertib Exerts Synergistic Anti-tumor Activity with KRAS(G12C) Inhibitors at AACR Annual Meeting 2024

April 2, 2024

Research supports azenosertib's potential to be highly synergistic in combination with KRAS targeted cancer therapeutics, creating an additional large opportunity to combine with other standard of care agents

NEW YORK and SAN DIEGO, April 02, 2024 (GLOBE NEWSWIRE) -- Zentalis® Pharmaceuticals, Inc. (Nasdaq: ZNTL), a clinical-stage biopharmaceutical company discovering and developing clinically differentiated small molecule therapeutics targeting fundamental biological pathways of cancers, will present a poster with new preclinical data at the 2024 Annual Meeting of the American Association for Cancer Research (AACR) taking place in San Diego April 5-10, 2024. Research demonstrated that the Company's WEE1 inhibitor, azenosertib, exerts synergistic anti-tumor activity when combined with $KRAS^{G12C}$ inhibitors.

"As we advance azenosertib in multiple ongoing clinical studies, our understanding of its potential utility as a monotherapy and in combination across diverse tumor types and treatment settings continues to deepen," said Mark Lackner, Ph.D., Chief Scientific Officer of Zentalis. "By exploiting azenosertib's mechanism, which targets common vulnerabilities related to cancer cell cycle dysregulation and high levels of replication stress and DNA damage, we sought to evaluate the anti-tumor activity of azenosertib in KRAS-driven cancers when combined with $KRAS^{G12C}$ inhibitors. Our preclinical data demonstrate that combining azenosertib with $KRAS^{G12C}$ inhibitors dramatically enhances anti-tumor activity. This compelling approach warrants further investigation as a potential treatment option for patients with $KRAS^{G12C}$ tumors."

Azenosertib is a potent and selective inhibitor of WEE1, a master cell cycle regulator that acts to slow cell cycle progression and enable DNA repair. Inhibition of WEE1 by azenosertib suppresses key cell cycle checkpoints, preventing DNA repair and increasing DNA damage, resulting in mitotic catastrophe and cell death. Previous research has determined that cancer cells, which are often characterized by cell cycle dysregulation and high levels of DNA damage, are highly sensitive to azenosertib. KRAS is a potent oncogenic driver that results in unchecked cell cycle progression while increasing replication stress and accumulation of DNA damage.

The research that will be presented at AACR Annual Meeting 2024 evaluated the anti-tumor activity of azenosertib when administered in combination with $KRAS^{G12C}$ inhibitors sotorasib or adagrasib. The data demonstrated synergistic cell growth inhibition across a panel of $KRAS^{G12C}$ cell lines in both 2D and 3D assays. Furthermore, administration of azenosertib in $KRAS^{G12C}$ inhibitor-sensitive and resistant xenograft models, including using non-small cell lung cancer, colorectal cancer, and pancreatic cancer cell lines, demonstrated monotherapy activity as well as synergistic tumor growth inhibition when combined with $KRAS^{G12C}$ inhibitors. In addition, extended administration of azenosertib combined with $KRAS^{G12C}$ inhibitors increased the duration of response versus single agent use. Together, these results support continued study of the potential for azenosertib to provide clinical benefit as a combination therapy.

Poster Presentation Details

- **Title**: The selective WEE1 inhibitor azenosertib shows synergistic anti-tumor activity with $KRAS^{G12C}$ inhibitors in multiple $KRAS^{G12C}$ models
- **Authors**: Jameson, N.M. et al.
- **Date/Time**: Tuesday, April 9, 2023 at 1:30 pm - 5:00 pm PT
- **Abstract Number**: 6487
- **Session**: Targeting Kinase and ERK Pathways

About Azenosertib
Azenosertib is a novel, selective, and orally bioavailable inhibitor of WEE1 currently being evaluated as a monotherapy and combination clinical studies in ovarian cancer and additional tumor types. WEE1 acts as a master regulator of the G1-S and G2-M cell cycle checkpoints, through negative regulation of both CDK1 and CDK2, to prevent replication of cells with damaged DNA. By inhibiting WEE1, azenosertib enables cell cycle progression, despite high levels of DNA damage, thereby resulting in the accumulation of DNA damage and leading to mitotic catastrophe and cancer cell death.

About Zentalis Pharmaceuticals
Zentalis® Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company discovering and developing clinically differentiated small molecule therapeutics targeting fundamental biological pathways of cancers. The Company's lead product candidate, azenosertib (ZN-c3), is a potentially first-in-class and best-in-class WEE1 inhibitor for advanced solid tumors and hematologic malignancies. Azenosertib is being evaluated as a monotherapy and in combination across multiple clinical trials and has broad franchise potential. In clinical trials, azenosertib has been well tolerated and has demonstrated anti-tumor activity as a single agent across multiple tumor types and in combination with several chemotherapy backbones. As part of its azenosertib clinical development program, the Company is exploring enrichment strategies targeting tumors of high genomic instability, such as Cyclin E1 positive tumors, homologous recombination deficient tumors and tumors with oncogenic driver mutations. 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 X/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 benefits of combining azenosertib with KRAS targeted therapies; the potential benefits of azenosertib as a monotherapy and in

combination; the potential for azenosertib to be best-in-class and first-in-class; the franchise potential of azenosertib. The terms “potential,” “will” 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 diagnostic tools; 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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