ORIC Pharmaceuticals Presents Preclinical Data on Two Programs at the 2024 American Association for Cancer Research (AACR) Annual Meeting

April 8, 2024 at 8:00 AM EDT

ORIC-944, a potent and selective allosteric PRC2 inhibitor, demonstrates superior preclinical drug properties and longer clinical half-life which supports a potential best-in-class profile versus competitor PRC2 inhibitors

Preclinical synergy data in prostate cancer models reinforces the promise of ORIC-944 as a potential best-in-class treatment for combinations with AR inhibitors

First data presentation on ORIC-613, a potential first- and best-in-class development candidate selectively inhibiting PLK4

SOUTH SAN FRANCISCO, Calif. and SAN DIEGO, April 08, 2024 (GLOBE NEWSWIRE) -- ORIC Pharmaceuticals, Inc. (Nasdaq: ORIC), a clinical stage oncology company focused on developing treatments that address mechanisms of therapeutic resistance, today announced two oral presentations on ORIC-944, a potent and selective allosteric inhibitor of PRC2, and presentation of a new discovery candidate, ORIC-613, an orally bioavailable, potent and selective PLK4 inhibitor, at the 2024 American Association for Cancer Research (AACR) Annual Meeting.

“ORIC-944 in combination with AR inhibitors demonstrates anti-tumor activity in multiple AR-positive prostate cancer models, supporting the planned expansion of our ORIC-944 clinical program in combination with AR inhibitors in metastatic prostate cancer,” said Lori Friedman, PhD, chief scientific officer. “These encouraging preclinical findings, coupled with potential best-in-class drug properties and deepened understanding of the mechanism driving synergy, fuel our optimism for advancing this program. Additionally, the unveiling of preclinical characterization of ORIC-613, a potential first- and best-in-class selective PLK4 inhibitor, marks a significant milestone in our discovery program, with preclinical data demonstrating synthetic lethality in TRIM37-high tumors.”

Presentation details:

ORIC-944: a potent and selective allosteric inhibitor of PRC2

Discovery of ORIC-944, a novel inhibitor of PRC2 with potential best-in-class properties for the treatment of prostate cancer

ORIC-944, a potent and selective allosteric PRC2 inhibitor with potential best-in-class properties, demonstrates combination synergy with AR pathway inhibitors in prostate cancer models (Presentation will be available on ORIC website on Tuesday, April 9, 2024 at 2:30 p.m. PT)

Key findings of the presentations:

- Discovery of ORIC-944 was enabled through structure-based drug design and leveraged a cryptic pocket in an allosteric site in EED, a subunit of PRC2
- Comprehensive profiling supports ORIC-944's best-in-class properties versus competitor PRC2 inhibitors, including PF-06821497, tazemetostat, and CPI-0209:
    - Strong potency with 106 picomolar EC50 in biochemical binding assay
    - Superior solubility, oral bioavailability, half-life, and CYP profile in preclinical studies
    - Clinical half-life estimated at approximately 20 hours, with no sign of CYP autoinduction that is observed with first-generation PRC2 inhibitors
    - Results from combinations with an AR inhibitor in an in vivo prostate model shows ORIC-944 provides better activity than PF-06821497
- Demonstrated that EED and EZH2 inhibitors act through the same mechanism of action, making prostate cancer cells more susceptible to AR inhibition:
    - Transcriptional changes induced by ORIC-944 were comparable to those of EZH2 inhibitors in prostate cancer models, indicating no mechanistic distinction between molecules targeting different core subunits of PRC2
    - RNA sequencing of prostate cancer models revealed that ORIC-944 increases AR signaling and luminal cell fate, thereby rendering these cells more susceptible to AR inhibition
    - Synergy was observed both in vitro and in vivo for ORIC-944 in combination with AR inhibitors in prostate cancer models
- These results position ORIC-944 as a potential best-in-class PRC2 inhibitor for combination with AR inhibitors in patients with prostate cancer

ORIC-613: a potent and selective PLK4 inhibitor

ORIC-613, a potential first- and best-in-class, orally bioavailable, potent and selective PLK4 inhibitor with synthetic lethality in TRIM37 high cancer models

Key findings of the presentation:

- ORIC-613 is an orally bioavailable, potent and exquisitely selective small molecule inhibitor of PLK4, which is synthetic lethal in tumor cells with high levels of TRIM37
- ORIC-613 has superior kinome selectivity versus comparator compounds CFI-400945 and RP-1664
- Preclinical assessment in cancer cell lines revealed synthetic lethality, with ORIC-613 inducing apoptotic tumor cell death specifically in TRIM37-high breast cancer and neuroblastoma cells versus TRIM37-wildtype cells
- Oral dosing of ORIC-613 at 150 mg/kg QD resulted in tumor regressions and tumor growth inhibition in TRIM37-high xenograft breast tumors
- ORIC-613 retained potency in breast cancer models resistant to CDK4/6 inhibitors
- These results position ORIC-613 as a potential first- and best-in-class development candidate, which has the potential to benefit patients with TRIM37-high tumors

About ORIC Pharmaceuticals, Inc.
ORIC Pharmaceuticals is a clinical stage biopharmaceutical company dedicated to improving patients' lives by *Overcoming Resistance In Cancer.* ORIC's clinical stage product candidates include (1) ORIC-114, a brain penetrant inhibitor designed to selectively target EGFR and HER2 with high potency against exon 20 insertion mutations, being developed across multiple genetically defined cancers, (2) ORIC-944, an allosteric inhibitor of the polycomb repressive complex 2 (PRC2) via the EED subunit, being developed for prostate cancer, and (3) ORIC-533, an orally bioavailable small molecule inhibitor of CD73, a key node in the adenosine pathway believed to play a central role in resistance to chemotherapy- and immunotherapy-based treatment regimens, being developed for multiple myeloma. Beyond these three product candidates, ORIC is also developing multiple precision medicines targeting other hallmark cancer resistance mechanisms. ORIC has offices in South San Francisco and San Diego, California. For more information, please go to www.oricpharma.com, and follow us on X or LinkedIn.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this press release that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the continued clinical development of ORIC-944; the development plans and timelines for ORIC-944 and ORIC's other product candidates; the potential advantages of ORIC-944, ORIC-613 and ORIC's other product candidates and programs; plans underlying ORIC's clinical trials and development; and statements by the company's chief scientific officer. Words such as "believes," "anticipates," "plans," "expects," "intends," "will," "goal," "potential" and similar expressions are intended to identify forward-looking statements. The forward-looking statements contained herein are based upon ORIC's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results could differ materially from those projected in any forward-looking statements due to numerous risks and uncertainties, including but not limited to: risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; ORIC's ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates; changes in ORIC's plans to develop and commercialize its product candidates; the potential for clinical trials of ORIC's product candidates to differ from preclinical, initial, interim, preliminary or expected results; negative impacts of health emergencies, economic instability or international conflicts on ORIC's operations, including clinical trials; the risk of the occurrence of any event, change or other circumstance that could give rise to the termination of ORIC's license and collaboration agreements; the potential market for ORIC's product candidates, and the progress and success of competing therapeutics currently available or in development; ORIC's ability to raise any additional funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; ORIC's reliance on third parties, including contract manufacturers and contract research organizations; ORIC's ability to obtain and maintain intellectual property protection for its product candidates; the loss of key scientific or management personnel; competition in the industry in which ORIC operates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in ORIC's Annual Report on Form 10-K filed with the Securities and Exchange Commission (the "SEC") on March 11, 2024, and ORIC's future reports to be filed with the SEC. These forward-looking statements are made as of the date of this press release, and ORIC assumes no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law.

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