ORIC Pharmaceuticals Presents Initial Clinical Data from Phase 1b Trial of ORIC-101 in Combination with Enzalutamide and Preclinical Data on ORIC-114 at AACR-NCI-EORTC

October 7, 2021 at 8:55 AM EDT

ORIC-101 and enzalutamide combination regimen at the recommended Phase 2 dose was well tolerated; adverse events generally consistent with single agent enzalutamide

ORIC-101 plasma concentrations provided excellent target coverage, consistent suppression of key glucocorticoid receptor (GR) biomarkers, and no evidence of drug-drug interaction impacting enzalutamide

The addition of ORIC-101 after progression on single agent enzalutamide enabled continued enzalutamide treatment, with preliminary evidence of longer time on treatment demonstrated in a key patient population with tumors having moderate to high GR versus low GR expression

ORIC-114 demonstrated compelling brain exposure and antitumor activity in preclinical studies of HER2-positive breast cancer

Conference call and webcast today at 9:00 a.m. ET

SOUTH SAN FRANCISCO, Calif. and SAN DIEGO, Oct. 07, 2021 (GLOBE NEWSWIRE) -- ORIC Pharmaceuticals, Inc. (Nasdaq: ORIC), a clinical stage oncology company focused on developing treatments that address mechanisms of therapeutic resistance, today announced multiple presentations, including initial clinical data from an ongoing Phase 1b study evaluating ORIC-101, a glucocorticoid receptor antagonist, in combination with enzalutamide, in patients with metastatic prostate cancer progressing on enzalutamide. The abstracts and presentations are available for on-demand viewing via the online platform for AACR-NCI-EORTC as of October 7, 2021, at 9 a.m. ET.

Presentations:

- Initial results from a Phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with enzalutamide in patients with metastatic prostate cancer
- Biomarker results supporting selection of RP2D from a Phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with enzalutamide in patients with metastatic prostate cancer progressing on enzalutamide
- ORIC-114, an orally bioavailable, irreversible kinase inhibitor, has superior brain penetrant properties and enhanced potency in preclinical studies of HER2-positive breast cancer

"We are pleased to share initial data from our ORIC-101 clinical program in patients with metastatic prostate cancer. The combination was well tolerated without evidence of drug-drug interaction affecting enzalutamide dosing and has demonstrated preliminary evidence of antitumor activity in the relevant patient population," said Pratik S. Multani, MD, chief medical officer. "Given the tumor heterogeneity in metastatic prostate cancer, we've made significant progress in identifying a key patient population that may benefit from ORIC-101 and, within these patients, seen preliminary evidence of more pronounced clinical benefit in patients whose tumors express higher GR levels. Patients are continuing to enroll in the expansion cohort and we look forward to reporting an update from the Phase 1b trial in 2022."

ORIC-101: Glucocorticoid Receptor (GR) Antagonist

The Phase 1b clinical trial of ORIC-101 in combination with enzalutamide is a single arm, multicenter, open-label study conducted in two parts, intended to establish the recommended Phase 2 dose (RP2D), safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity when administered in patients with metastatic prostate cancer progressing on enzalutamide.

In the Part I dose escalation portion of the trial, three cohorts of patients were enrolled to evaluate daily dosing of ORIC-101 with doses ranging from 80 to 240 mg, in combination with 160 mg of enzalutamide once daily dosing. Following the completion of the dose escalation portion of the study, the RP2D was determined to be 240 mg of ORIC-101 and 160 mg of enzalutamide once daily.

In the Part II dose expansion portion of the trial, up to 48 patients with metastatic prostate cancer progressing on enzalutamide are expected to be enrolled and treated with the combination at the RP2D. Patients are enrolled independent of GR status, with retrospective analysis of GR expression and other potentially predictive biomarkers. Enrollment continues in the Part II dose expansion cohorts at nine clinical sites across the United States.

As of the August 20, 2021, data cut-off date:

Preliminary Safety Analyses:

- 25 patients were enrolled across Parts I/II of the study, which included 7 patients treated at non-RP2D doses and 18 patients treated at the RP2D of 240 mg of ORIC-101 and 160 mg of enzalutamide once daily.
- RP2D was well tolerated; treatment-related adverse events were primarily Grade 1 or 2, with only four Grade 3 events, which all resolved with dose interruption.
- Tolerability profile for the combination was generally consistent with that of single agent enzalutamide.

Preliminary PK Analysis:

- Plasma concentrations exceeded the threshold for GR inhibition at all dose levels.
- ORIC-101 exposure increased with dose.
- No evidence observed of drug-drug interaction impacting enzalutamide levels.

Preliminary Biomarker Analyses:

- GR pathway suppression, evaluated using GR target gene expression, was observed after one dose of ORIC-101 in peripheral blood mononuclear cells from 22 of 23 patients.
- Moderate to high GR expression (IHC H-score ≥ 100) in prostate tumor cells was observed in 76% of pretreatment biopsies.
- Translational efforts identified a key patient population, in line with published literature, consisting of the ~60% of patients with tumors lacking biomarkers of AR resistance (e.g., ARv7 splice variant, AR L702H point mutation) and AR independence (e.g., lineage switching).

Preliminary Antitumor Activity:

- Within the key patient population (n=8), 75% (6 of 8) of patients' tumors expressed moderate to high GR and 25% (2 of 8) of patients' tumors expressed low GR.
- The two patients with low GR came off treatment at less than two months. In contrast, the six patients with moderate to high GR demonstrated prolonged time on treatment (with two patients on treatment for over seven months, and another four patients still ongoing at varying durations at the time of the data cut).

ORIC-101 is also being evaluated in a Phase 1b trial in combination with nab-paclitaxel in up to 132 patients across four cohorts, including pancreatic ductal adenocarcinoma, ovarian cancer, triple negative breast cancer, and other advanced solid tumors. Enrollment continues in this study at 12 clinical sites across the United States and an additional update is expected in 2022.

ORIC-114: EGFR/HER2 Inhibitor

ORIC-114 is a brain penetrant, orally bioavailable, irreversible inhibitor designed to selectively target EGFR and HER2 with high potency against exon 20 insertion mutations. These are the first publicly disclosed preclinical data with ORIC-114 demonstrating compelling activity in HER2-positive breast cancer models.

Key Findings of the Presentation:

- ORIC-114 demonstrated greater cell potency on HER2-positive breast cancer cell lines relative to non-amplified cell lines and was more potent than lapatinib and tucatinib, two approved tyrosine kinase inhibitors for the treatment of HER2-positive breast cancer.
- ORIC-114 demonstrated robust tumor regressions in a HER2-positive breast cancer in vivo model without significant body weight loss.
- ORIC-114 demonstrated superior brain exposure compared to other EGFR exon 20 and HER2 targeted agents.

Separately, today the company disclosed head to head in vivo preclinical data in an EGFR exon 20 NSCLC xenograft model demonstrating good tolerability and improved efficacy, including a 90% complete response rate, versus multiple clinical stage exon 20 inhibitors.

Webcast and Conference Call

ORIC will host a conference call and webcast today at 9:00 a.m. ET. To participate in the conference call, please dial (833) 651-0991 (domestic) or (918) 922-6080 (international) and refer to conference ID 3575856. A live webcast and audio archive of the conference call will be available through the investor section of the company's website at www.oricpharma.com. The webcast will be available for replay for 90 days following the presentation.

About ORIC-101

ORIC-101 is a potent and selective small molecule antagonist of the glucocorticoid receptor, which has been linked to resistance to multiple classes of cancer therapeutics across a variety of solid tumors. Preclinical in vitro and in vivo data suggest ORIC-101 is able to address key resistance mechanisms of multiple classes of cancer treatments, including taxanes and androgen receptor modulators. Based on preclinical and clinical studies, ORIC-101 is expected to have reduced drug-drug interaction liabilities than other glucocorticoid receptor antagonists. Currently, there are no glucocorticoid receptor antagonists approved by the FDA for the treatment of cancer. Following the successful completion of two Phase 1a trials in over 50 healthy volunteers, ORIC initiated two separate Phase 1b trials of ORIC-101 in combination with (1) Abraxane (nab-paclitaxel) in advanced or metastatic solid tumors and (2) Xtandi (enzalutamide) in metastatic prostate cancer.

About ORIC Pharmaceuticals, Inc.

ORIC Pharmaceuticals is a clinical stage biopharmaceutical company dedicated to improving patients' lives by *Overcoming Resistance In Cancer.* ORIC's lead product candidate, ORIC-101, is a potent and selective small molecule antagonist of the glucocorticoid receptor, which has been linked to resistance to multiple classes of cancer therapeutics across a variety of solid tumors. ORIC-101 is currently in two separate Phase 1b trials in combination with (1) Abraxane (nab-paclitaxel) in advanced or metastatic solid tumors and (2) Xtandi (enzalutamide) in metastatic prostate cancer. ORIC's other product candidates include (1) 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, (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-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. Beyond these four 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 Twitter 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-101 in combination with enzalutamide; clinical outcomes, which may materially change as patient enrollment continues or more patient data become available; the expected timing of reporting updated data from the ORIC-101 clinical trials in combination with nab-paclitaxel and enzalutamide; the potential benefits of ORIC-101, ORIC-114 or the company's other product candidates; and statements by the company's chief medical 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-101, ORIC-533, ORIC-944, ORIC-114 or any other product candidates to differ from preclinical, initial, interim, preliminary or expected results; negative impacts of the COVID-19 pandemic 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 agreements; 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 entitled "Risk Factors" in ORIC's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on August 10, 2021, 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.

This press release contains interim results based on initial data from the ORIC-101 clinical trial in combination with enzalutamide, including preliminary safety and antitumor activity analyses, as of the data cutoff date. These initial data, results and related findings and conclusions are subject to change materially based on patient data subsequent to the cutoff date or as patient enrollment continues.

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