Initial Phase 1 Dose Escalation Data of ORIC-114 in Patients with EGFR and HER2 Exon 20 Mutations Demonstrates Potential Best-In-Class Profile

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CNS activity observed at multiple dose levels, including the first reported confirmed CNS complete response by an EGFR exon 20 inhibitor in a patient with documented untreated brain metastases

Systemic responses observed at multiple dose levels in heavily pre-treated NSCLC patients, characterized by 81% having received prior EGFR exon 20 targeted agents and 86% having CNS metastases at baseline

At potential RP2D of 75 mg QD, responses observed in 2 of 3 EGFR exon 20 patients previously treated with amivantamab (67% ORR), including a confirmed complete response

Responses observed at multiple dose levels in HER2 exon 20 patients, including a partial response with 100% target lesion regression

Favorable safety profile with mainly Grade 1 and 2 treatment related adverse events; MTD not reached and dose escalation remains ongoing

Company to host conference call and webcast today at 9:00 am ET

SOUTH SAN FRANCISCO, Calif. and SAN DIEGO, Oct. 21, 2023 (GLOBE NEWSWIRE) -- ORIC Pharmaceuticals, Inc. (Nasdaq: ORIC), a clinical stage oncology company focused on developing treatments that address mechanisms of therapeutic resistance, today announced initial data from the ongoing ORIC-114 Phase 1 dose escalation trial for patients with EGFR or HER2 exon 20 mutated non-small cell lung cancer (NSCLC) at the European Society of Medical Oncology (ESMO) Congress 2023 (clinical poster here).

“We are excited to present the first look at ORIC-114 clinical data, which we believe supports the potential to address the key attributes of a potential best-in-class program for EGFR/HER2 exon 20 mutated NSCLC: minimal EGFR toxicity, minimal off-target toxicity, CNS activity, and systemic activity including post-amivantamab,” said Jacob M. Chacko, MD, chief executive officer. “Given the high rate of brain metastases in these patients and the high percentage of patients whose disease progresses in the brain, we believe that a well-tolerated CNS active agent has the potential to be transformative.”

“We are pleased with the emerging profile of ORIC-114 in these heavily pretreated patients, which includes clinical activity across multiple dose levels and the first reported intracranial complete response in a patient with EGFR exon 20 lung cancer and documented untreated brain metastases,” said Pratik Multani, MD, chief medical officer. “This is the first comprehensive data set for EGFR exon 20 patients with such an exceptionally high rate of CNS disease at baseline and prior exon 20 inhibitor therapy. Based on the encouraging clinical activity and favorable safety profile, we plan to advance this program into dose optimization to select RP2D and, ultimately, into one or more registrational cohorts for potential accelerated approval.”

ORIC-114 Phase 1 Study Design

ORIC-114 is being evaluated in a Phase 1 dose escalation clinical trial in patients with advanced solid tumors with EGFR and HER2 exon 20 alterations or HER2 amplifications. Patients previously treated with an exon 20 targeted agent are eligible, including patients with CNS metastases that are either treated or untreated but asymptomatic. Nearly all other clinical studies with EGFR exon 20 inhibitors severely restricted the eligible patient population and excluded patients with active or untreated brain metastases and patients previously treated with an EGFR exon 20 inhibitor, making this data set one of the first and most comprehensive in this population. The primary objectives are to determine the recommended Phase 2 dose (RP2D), and additional objectives include characterization of the safety, tolerability, pharmacokinetic, and preliminary antitumor activity.

ORIC-114 Phase 1 Dose Escalation Data

As of September 26, 2023, 50 patients (21 EGFR exon 20, 24 HER2 exon 20 and 5 HER2+ patients) received ORIC-114 and were heavily pre-treated, with exceptionally high rates of prior exon 20 targeted therapies and brain metastases at baseline.

- Of the 21 EGFR exon 20 insertion mutated NSCLC patients, in addition to chemotherapy
  - 81% were treated with ≥1 prior EGFR exon 20 targeted agent, nearly all of whom received prior amivantamab;
  - 19% were treated with multiple prior EGFR exon 20 targeted agents; and
  - 86% presented with CNS metastases at baseline
- Of the 24 HER2 exon 20 insertion mutated NSCLC patients
  - 30% were treated with a prior HER2 targeted agent; and
  - 38% presented with CNS metastases at baseline

Preliminary Pharmacokinetic Analysis and Safety

ORIC-114 demonstrated a favorable pharmacokinetic profile with dose proportional increase in exposure, low intra-cohort variability, and a half-life of ~10-15 hours, which supports QD dosing.

ORIC-114 was well-tolerated with mostly Grade 1 and 2 treatment-related adverse events (TRAEs) and little evidence of off-target toxicities. Rash was limited to Grade 1 and 2 events, and there was no Grade 3 or greater treatment related rash. Diarrhea was primarily Grade 1 and 2, with only 6% of patients experiencing Grade 3 diarrhea. There were only 4% discontinuations for TRAEs. The maximum tolerated dose has not been reached.

Preliminary Activity Analysis

Systemic and intracranial activity of ORIC-114 was demonstrated in this heavily pre-treated patient population across multiple dose levels. Preliminary activity data for patients treated at clinically active doses (total daily dose (TDD) ≥45 mg) as of the cut-off date were available for 15 response evaluable NSCLC patients with EGFR exon 20 insertion mutations and 13 response evaluable NSCLC patients with HER2 exon 20 insertion mutations.

EGFR exon 20 patients:

- Observed systemic and CNS activity at multiple dose levels, consisting of multiple partial responses and one ongoing confirmed complete response, including a confirmed complete response in the brain.
- Within the 45 mg dose level, a patient had an ongoing confirmed partial response and two of three brain lesions resolved on therapy.
- Within the 75 mg dose level, identified as a potential RP2D, of the three patients previously treated with amivantamab
    - All three patients experienced tumor shrinkage, and
    - There was an unconfirmed ORR of 67% and a confirmed ORR of 33%, including an ongoing systemic confirmed complete response and the first confirmed CNS complete response reported by an EGFR exon 20 inhibitor in a patient with documented untreated brain metastases at baseline.

HER2 exon 20 patients:

- Observed systemic and CNS activity at multiple dose levels, consisting of multiple partial responses, including an ongoing confirmed partial response with 100% regression of all target lesions, with only persistent non-target lesions preventing a complete response.
- Within the 30 mg BID dose level, a patient had an ongoing confirmed partial response and shrinkage of multiple brain lesions on therapy.

Next Steps

The Phase 1 trial of ORIC-114 is ongoing to determine the candidate recommended RP2Ds for dose optimization, and subsequently the selection of the final RP2D. Since the September 26, 2023 data cutoff, the 40 mg BID dose level has cleared the DLT evaluation period, and the study is now evaluating 50 mg BID and 120 mg QD dose levels. The Phase 1 trial will enroll patients with EGFR exon 20 insertion mutations that are EGFR exon 20 inhibitor-naïve, and additional patients who are post-amivantamab. Additionally, enrollment will be expanded to include patients with atypical EGFR mutations based on the promising preclinical activity presented at ESMO 2023 (preclinical poster here).

Conference Call and Webcast Details

To join the conference call via phone and participate in the live Q&A session, please pre-register online here to receive a telephone number and unique passcode required to enter the call. 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-114

ORIC-114 is a highly selective, brain penetrant, orally bioavailable, irreversible inhibitor designed to selectively target EGFR and HER2 with high potency against exon 20 insertion mutations, making it a promising therapeutic candidate to address the unmet medical need of having both meaningful systemic as well as CNS antitumor activity.

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-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, and (3) ORIC-944, an allosteric inhibitor of the polycomb repressive complex 2 (PRC2) via the EED subunit, being developed for prostate cancer. 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-114; ORIC-114 clinical outcomes, which may materially change as patient enrollment continues or more patient data become available; ORIC-114's development plans and timelines; the potential advantages of ORIC-114; plans underlying ORIC's clinical trials and development; and statements by the company's chief executive officer and 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-114 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 our 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 entitled "Risk Factors" in ORIC's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on August 10, 2023, 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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