ORIC-114

2022

https://aacrjournals.org/cancerres/article/82/12_Supplement/3335/701420

ORIC-114, an orally bioavailable, irreversible kinase inhibitor, has superior brain penetration and antitumor activity in subcutaneous and intracranial NSCLC models [abstract].

Citation

In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr 3335.

Authors

Long JE, Kim S, Kim HY, Shin DG, Park DH, Warne R, Das A, Hegde G, Narayanan P, Sambucetti L, Chan B, Chen X, Chang JH, Gibbons P, Sun J, Panuwat M, Friedman LS, Junttila MR.

Abstract

Exon 20 genomic insertions of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are oncogenic drivers and are most commonly found in non-small cell lung cancer (NSCLC). NSCLC patients with exon 20 insertions have a worse prognosis compared to those with other activating EGFR mutations. Moreover, approximately one-third of patients with exon 20 insertion mutations develop central nervous system (CNS) metastases over the course of their disease. Unfortunately, current therapeutics lack sufficient brain exposure for treating this patient population. ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecule inhibitor designed to target exon 20 insertions in EGFR and HER2. Notably, ORIC-114 is highly selective for the EGFR family of receptors, with excellent kinome selectivity compared to other reported exon 20 inhibitors, reducing the risk of off-target kinase liabilities. The superior brain penetration and free unbound exposure of ORIC-114 in preclinical studies also differentiates it from comparator EGFR and HER2 exon 20 targeted agents.

To further characterize ORIC-114, in vivo studies were undertaken to assess activity in both subcutaneous and intracranial NSCLC tumor patient-derived xenograft (PDX) models. Consistent with in vitro potency and selectivity, once daily oral administration of 3 mg/kg ORIC-114 induced robust tumor regressions with greater than 100% tumor growth inhibition in the absence of significant body weight loss in an EGFR exon 20 insertion H773_V774insNPH NSCLC PDX model. In this subcutaneous model, ORIC-114 was superior to CLN-081 in efficacy and tolerability, and superior to BDTX-189 in efficacy. To investigate whether the brain-penetrant attributes of ORIC-114 translated into antitumor activity in the CNS, we utilized an intracranial PC-9 luciferase-

labeled EGFR del 19 mutant cell line model. Once daily oral administration of ORIC-114 significantly regressed established intracranial NSCLC tumors and demonstrated greater efficacy than TAK-788, commensurate with the superior brain exposure of ORIC-114. We further explored dosing regimens in this intracranial model and found that ORIC-114 demonstrated equivalent regressions at 1.5 mg/kg twice daily and 3 mg/kg once daily, and strong efficacy with 1.5 mg/kg once daily dosing. Taken together, these data confirm ORIC-114 as a potent, selective, irreversible, brain penetrant exon 20 inhibitor, and a promising therapeutic candidate, including for patients with CNS metastases. Based upon these data, ORIC-114 is entering a Phase 1/1b clinical trial in genetically defined cancers.

2021

https://aacrjournals.org/mct/article/20/12_Supplement/P234/676103/Abstract-P234-ORIC-114-an-orally-bioavailable

ORIC-114, an orally bioavailable, irreversible kinase inhibitor, has superior brain penetrant properties and enhanced potency in preclinical studies of HER2-positive breast cancer [abstract].

Citation

In: Proceedings of the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics; 2021 Oct 7-10. Philadelphia (PA): AACR; Mol Cancer Ther 2021;20(12 Suppl):Abstract nr P234.

Authors

Junttila MR, Long JE, Warne R, Kim S, Lee Y, Kim H, Kang J, Seok J, Yoo J, Lee Y, Seo DH, Son JB, Kim D, Choi HG, Kim ND, Zavorotinskaya T, Chan C, Panuwat M, Sun J, Chang JH, Friedman LS.

Abstract

Amplification of human epidermal growth factor receptor 2 (HER2) is an oncogenic driver found in approximately 25% of breast cancer. Despite the arsenal of HER2-directed therapies available to patients, more than 50% of patients with HER2 amplification eventually develop central nervous system (CNS) metastases over the course of their disease indicating a clear medical need for brain penetrant therapies in this patient population. ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecule inhibitor that was designed to target exon20 insertions in epidermal growth factor receptor (EGFR) and HER2. ORIC-114 is highly selective for the EGFR/HER2 family of receptors, reducing the risk for off-target kinase liabilities. In biochemical assays, ORIC-114 displayed low nanomolar potency on HER2. To explore the application of ORIC-114 in the HER2-amplified tumor setting, a cell viability screen was performed against a panel of human breast cancer lines containing

both HER2-amplified and non HER2-amplified cell lines. ORIC-114 demonstrated greater than 100-fold enhanced cellular potency on HER2-amplified cancer cell lines relative to non-amplified cancer cell lines. Notably, ORIC-114 cellular EC50s in HER2-amplified breast cancer cell lines were below 30 nM and more potent than both lapatinib and tucatinib, two FDA-approved tyrosine kinase inhibitors for the treatment of HER2-positive breast cancer. ORIC-114 was designed to incorporate physicochemical properties suitable to cross the blood-brain barrier and has exhibited good brain penetration across multiple preclinical species. To further investigate the brain penetrant attributes of ORIC-114 in the context of HER2-positive breast cancer with brain metastases, key features were assessed relative to tucatinib, which has demonstrated clinical efficacy in this setting. In contrast to tucatinib, ORIC-114 displayed minimal impact on efflux transporters as it was only a weak substrate for P-glycoprotein (P-gp) and was not a substrate for breast cancer associated protein (BCRP) in vitro. In addition, ORIC-114 demonstrated superior in vivo brain penetration relative to tucatinib as measured by free brain-to-plasma ratio in mouse. Consequently, ORIC-114 free brain concentrations in rodents were greater than tucatinib, even when the active metabolites of tucatinib were considered. Taken together, these data further establish ORIC-114 as a selective, irreversible, and brain penetrant EGFR/HER2 inhibitor, making it a promising therapeutic candidate for development in patients with HER2-positive tumors including those with CNS metastases. A Clinical Trial Application for ORIC-114 is anticipated in the second half of 2021.

https://oricpharma.com/wp-content/uploads/2021/10/ORIC-114-an-orally-bioavailable-irreversible-kinase-inhibitor_FINAL.pdf

ORIC-114, an orally bioavailable, irreversible kinase inhibitor, has superior brain penetrant properties and enhanced potency in preclinical studies of HER2-positive breast cancer

Citation

Oricpharma.com. Accessed July 20, 2022.

Authors

Junttila MR, Long JE, Warne R, Kim S, Lee Y, Kim H, Kang J, Seok J, Yoo J, Lee Y, Seo DH, Son JB, Kim D, Choi HG, Kim ND, Zavorotinskaya T, Chen X, Panuwat M, Sun J, Chang JH, Friedman LS.

Abstract

Key Preclinical Highlights

ORIC-114 is a brain penetrant, orally bioavailable, irreversible inhibitor targeting EGFR and HER2 exon 20 insertion mutations

– Excellent kinome selectivity for EGFR family

– Enhanced potency for most EGFR exon 20 insertions

– Low to sub-nanomolar biochemical activity on exon 20 insertion mutations

– Robust single-agent regressions in EGFR exon 20 insertion PDX models in vivo at well-tolerated doses

– Superior brain penetrance with good brain to plasma exposure ratio in mice relative to other EGFR and HER2 exon 20 targeted agents

– Tumor regressions in intracranial EGFR mutant lung tumors

ORIC-114 is a clinical candidate with the potential for treatment of EGFR/HER2 driven cancer, including in patients with active brain metastases

Free Full Text of Entire Article

https://aacrjournals.org/cancerres/article/81/13_Supplement/1466/667339/Abstract-1466-ORIC-114-a-brain-penetrant-orally

ORIC-114, a brain penetrant, orally bioavailable, irreversible inhibitor selectively targets EGFR and HER2 exon20 insertion mutants and regresses intracranial NSCLC xenograft tumors [abstract].

Citation

In: Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10-15 and May 17-21. Philadelphia (PA): AACR; Cancer Res 2021;81(13_Suppl):Abstract nr 1466.

Authors

Junttila MR, Kim S, Lee Y, Kim H, Kang J, Seok J, Yoo J, Lee Y, Seo DH, Son JB, Kim D, Choi HG, Kim ND, Das A, Sutimantanapi D, Zavorotinskaya T, Chen C, Chang J, Panuwat M, Friedman L.

Abstract

Genomic insertions within exon20 of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are oncogenic drivers most commonly found in non-small cell lung cancer (NSCLC) but also occurring in multiple other tumor types. Exon20 insertions render the receptors resistant to currently approved inhibitors, giving patients with tumors harboring such insertions a worse prognosis than with other activating EGFR mutations. Moreover, approximately one-third of patients with exon20

insertion mutations may develop central nervous system (CNS) metastases over the course of their disease.

To address this unmet medical need, ORIC-114, a brain penetrant, orally bioavailable, irreversible small molecule inhibitor was designed to target exon20 insertions in EGFR and HER2. ORIC-114 is highly selective to the EGFR family of receptors, showing superior kinome selectivity compared with other reported exon20 inhibitors. In biochemical assays ORIC-114 displays low nanomolar potency, and importantly has enhanced potency on the EGFR exon20 NPG insertion relative to wildtype EGFR protein. ORIC-114 also demonstrates low nanomolar potency across exon20 insertion variants using cell-based assays measuring EGFR phosphorylation, downstream signaling and cell viability. ORIC-114 is readily brain available across multiple preclinical species hence studies were undertaken to investigate activity in both subcutaneous and intracranial tumor models.

Herein, we explored the in vivo activity of ORIC-114. Consistent with our in vitro findings, robust activity was observed in EGFR exon20 patient-derived xenograft models using once daily oral administration, with greater than 90% tumor growth inhibition in the absence of body weight loss. Moreover, these significant antitumor effects correlate with decreased pharmacodynamic response as measured by phosphorylated EGFR in terminal tumors. To investigate whether the brain-penetrant attributes of ORIC-114 translate into therapeutic CNS activity, we utilized an intracranial luciferase-labeled EGFR mutant cell line model. Once daily oral administration of ORIC-114 significantly regressed established intracranial NSCLC tumors, demonstrating greater efficacy than TAK-788, commensurate with the superior brain to plasma exposure of ORIC-114. Taken together, these data establish ORIC-114 as a selective, irreversible, and brain penetrant EGFR inhibitor, making it a promising therapeutic candidate for development in patients with tumors harboring EGFR and HER2 exon20 insertions, including those with CNS metastases. ORIC-114 is anticipated to enter a global Phase 1/2 tumor-agnostic trial in genetically defined cancers in the second half of 2021.

*ORIC-114 journal articles collated and curated by Exon 20 Group at ICAN Research Team Leader Maria Vasileiou, Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece.