ORIC-114, an Orally Bioavailable, Irreversible Kinase Inhibitor, Has Superior Brain Penetration and Antitumor Activity in Subcutaneous and Intracranial NSCLC Models

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Patients with EGFR/HER2 exon 20 insertion mutations represent a high unmet need

ORIC-114 is a potent, irreversible brain penetrant EGFR and HER2 exon 20 inhibitor with:
- low to sub-nanomolar biochemistry activity on EGFR exon 20 insertion mutations
- enhanced potency for most EGFR exon 20 insertions
- excellent kinase selectivity for EGFR family
- superior and robust single-agent efficacy in EGFR exon 20 wild-type tumors
- high brain penetration with good plasma unbound exposure ratio in mice
- tumor regressions in mouse intracranial EGFR mutant NSCLC tumors equivalent intracranial anti-VEGF activity for bid and qd dosing for 3 mg/kg daily delivery

ORIC-114 is a promising candidate for development in patients with tumors harboring EGFR/HER2 exon 20 insertion mutations, including those with brain metastases

1. ORIC-114 Has Excellent Potency in EGFR Exon 20 Assays

- In EGFR exon 20 biochemical assays, ORIC-114 has sub-nanomolar IC50 potency and greater average fold selectivity for exon 20 mutants over wild-type EGFR when compared to poziotinib, CLN-081 and BDTX-189

2. ORIC-114 Has Excellent Kinome Selectivity

- ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecule inhibitor was designed to target exon 20 insertions in EGFR and HER2

3. ORIC-114 Regresses NSCLC EGFR Exon 20 PDX Model Tumors

- In EGFR exon 20 cellular assays using Ba/F3 EGFR-expressing cells, ORIC-114 has nanomolar potency
- In EGFR exon 20 biochemical assays, ORIC-114 has sub-nanomolar IC50 potency and greater IC50 activity on EGFR exon 20 insertions
- Approximately one-third of patients develop central nervous system (CNS) metastases
- EGFR exon 20 mutations are most common in NSCLC, but also occur in other tumors

4. Transporters That Limit Brain Penetration Have Minimal Impact on ORIC-114

5. Superior Brain Penetration of ORIC-114 Differentiates From Comparator EGFR Agents

- ORIC-114 is a potent, irreversible brain penetrant EGFR and HER2 exon 20 inhibitor in targeted brain 28 injections in EGFR and HER2 mutant NSCLC xenograft models

- High brain penetration with good brain to plasma unbound exposure ratio in mice
- Superior and robust single-agent regressions in EGFR exon 20 insertion LU0387 PDX model tumors
- Enhanced potency for most EGFR exon 20 insertions
- Low to sub-nanomolar biochemical activity on EGFR exon 20 insertion mutations

6. ORIC-114 Demonstrates Superior Efficacy in EGFR del19 Tumors in Intracranial Setting

- ORIC-114 is a promising candidate for development in patients with tumors harboring EGFR/HER2 exon 20 insertion mutations, including those with brain metastases

7. Intracranial Regressions with No Significant Weight Loss in Alternative Dosing Regimen

- ORIC-114 is a promising candidate for development in patients with tumors harboring EGFR/HER2 exon 20 insertion mutations, including those with brain metastases

CONCLUSIONS

- ORIC-114 is a promising candidate for development in patients with tumors harboring EGFR/HER2 exon 20 insertion mutations, including those with brain metastases

ORIC-114 Phase 1 Trial Initiated in South Korea