ORIC-114, a Brain Penetrant, Orally Bioavailable, Irreversible Inhibitor Selectively Targets EGFR and HER2 Exon 20 Insertion Mutants and Regresses Intracranial NSCLC Xenograft Tumors


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AARC Virtual Annual Meeting, April 10-15, 2021

Abstract #1466

ORIC-114 Has Nanomolar Cell Potency in EGFR and HER2 Exon 20 Assays

1. ORIC-114 Has Nanomolar Cell Potency in EGFR and HER2 Exon 20 Mutants

- ORIC-114 Has Excellent Kinome Selectivity
- 5. Superior Brain Penetration of ORIC-114: ORIC-114 Regresses NSCLC EGFR Exon 20 PDX Model Tumors Without Significant Body Weight Loss

2. ORIC-114 Has Sub-nanomolar Potency Against EGFR Exon 20 Insertion Mutant Proteins

- Kinase inhibition profiles were performed across 60 kinase IC50 assays using SKM-1-based xenograft tumor lysates and are depicted with the results indicating low IC50 IC50 values.

3. ORIC-114 Has Excellent Kinome Selectivity

- Data is plotted as the mean % cell viability with 30 μM vehicle (DMSO) as the control (100% viability).

4. ORIC-114 Regresses NSCLC EGFR Exon 20 PDX Model Tumors Without Significant Body Weight Loss

- Data is plotted as the mean % cell viability with 30 μM vehicle (DMSO) as the control (100% viability).

5. Superior Brain Penetration of ORIC-114: ORIC-114 Regresses NSCLC EGFR Exon 20 PDX Model Tumors Without Significant Body Weight Loss

- Data is plotted as the mean % cell viability with 30 μM vehicle (DMSO) as the control (100% viability).

6. ORIC-114 Demonstrates Superior Efficacy in Intracranial NSCLC EGFR delt19 Mutant Tumors

- Data is plotted as the mean % cell viability with 30 μM vehicle (DMSO) as the control (100% viability).

Conclusions

- ORIC-114 is a potent, irreversible brain penetrant EGFR and HER2 exon 20 inhibitor with:
  - low sub-nanomolar biochemical activity on exon 20 mutation insertions
  - enhanced potency for most EGFR exon 20 insertions
  - excellent kinase selectivity for EGFR family
  - robust single-agent regression in EGFR exon 20 insertion PDX models in vivo
  - high brain penetration with good brain-to-plasma exposure ratios in mice
  - tumor regressions in intracranial EGFR mutant tumors
  - ORIC-114 is a promising candidate for development in patients with harboring EGFR/HER2 exon 20 insertion mutations, including those with brain metastases