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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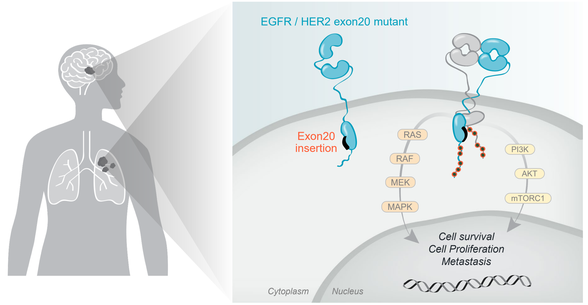
Patients with EGFR/HER2 Exon 20 Insertion Mutations Represent a High Unmet Need



- EGFR exon 20 mutations are most common in NSCLC, but also occur in other tumors
- Worse prognosis than other activating EGFR mutations
- Approximately one-third of patients develop central nervous system (CNS) metastases

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

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

- In EGFR exon 20 biochemical assays, ORIC-114 has sub-nanomolar IC_{50} potency and greater average fold selectivity for exon 20 mutants over wild-type EGFR when compared to poziotinib, CLN-081 and BDTX-189
- In EGFR exon 20 cellular assays using Ba/F3 EGFR-expressing cells, ORIC-114 has nanomolar GI_{50} potency across exon 20 mutants

2. ORIC-114 Has Excellent Kinome Selectivity

Kinome Profiles of EGFR Targeted Compounds

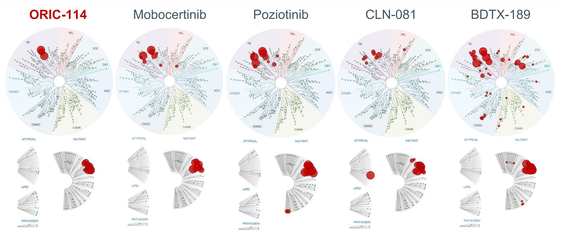


Figure 2: Kinase binding profiles across 489 kinases at 1uM assessed using KINOMEscan. Individual kinome trees are depicted with red circles indicating the kinases impacted within 10% of control. Mobocertinib, Doebele *et al.*, J Clin Oncol 2018; Poziotinib, Robichaux *et al.*, Nat Med 2018; CLN-081, Udagawa *et al.*, Mol Can Res 2019; BDTX-189, WO 2020/068867 A1

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

Subcutaneous LU0387 (EGFR Exon20 H773_V774insNPH) NSCLC Xenograft

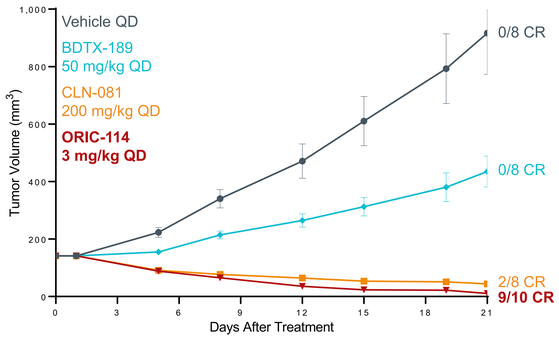


Figure 3: Subcutaneously implanted NSCLC patient-derived xenograft (PDX) model harboring an EGFR exon 20 insertion was treated with the following compounds once daily (QD) by oral gavage (PO) for 21 days: ORIC-114 at 3 mg/kg, BDTX-189 at 50 mg/kg or CLN-081 at 200 mg/kg (n=8-10 animals per cohort). Tumors were measured by caliper at the indicated days. Complete response (CR) defined as tumor measurements at the end of study being <30 mm^3. Unlike ORIC-114, CLN-081 had 25% of animals experience >20% body weight loss within the first 7 days of treatment.

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

Efflux Ratio in Cells Overexpressing Key Pumps Can Predict Brain Penetration

Compound	MDR1-MDCK Efflux Ratio	BCRP-MDCK Efflux Ratio
ORIC-114	**4**	**0.7**
Osimertinib[a]	13.4[b]	5.4[b]
Mobocertinib	3.4	1.4
Poziotinib	0.7[c]	3.5[c]

Figure 4: Endothelial cells at the blood brain barrier (BBB) contain efflux transporters that can actively bind small molecules and limit their brain penetration. A low efflux ratio of <3 can help predict brain penetration.
[a] Two active metabolites of osimertinib are MDR1 and BCRP substrates;
[b] Ballard *et al.*, Clin Cancer Res 2016;
[c] Colclough *et al.*, Clin Cancer Res 2020.

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

ORIC-114 Exhibits High Exposure in the Brain at Both 1 and 4 Hours

10 mg/kg PO in Mouse	Total Plasma (ng/mL)		Total Brain (ng/g tissue)	
	1 hr	4 hr	1 hr	4 hr
ORIC-114	**572**	**489**	**443**	**363**
Osimertinib	71	67	912	1330
Mobocertinib	304	45	30	22
Poziotinib	4830	3160	627	378
CLN-081[a]	367	29	*BQL*	*BQL*
BDTX-189[a]	617	74	*BQL*	*BQL*

ORIC-114 Also Exhibits High Free (Unbound) Brain/Plasma Ratio

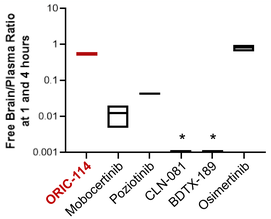


Figure 5: Mice dosed with 10 mg/kg PO with samples assessed 1 and 4 hours post dose. Junttila *et al.*, AACR Poster 2021;
Free unbound brain/plasma ratios at 1 and 4 hours are graphed as floating bars, with line at median.
BQL = below quantification limit (25 ng/mL in brain);
[a] = independent study
* = brain exposure is *BQL*

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

Subcutaneous PC9 NSCLC Xenograft

Intracranial PC9-luciferase NSCLC Xenograft

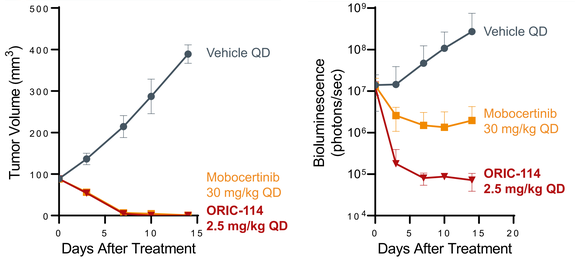


Figure 6. Left panel: Subcutaneously implanted EGFR del19 NSCLC PC9 xenografts were treated with either vehicle, ORIC-114 or mobocertinib PO once daily for 14 days (n=6 animals per cohort). All groups are significantly different compared to vehicle. Tumor volumes measured by caliper, mean +/- SEM. **Right panel:** Quantification of the bioluminescence photon flux in mice implanted with intracranial PC9-luciferase NSCLC cells and treated with either vehicle, ORIC-114 or mobocertinib once daily for 14 days (n=7 animals per cohort). Shown is mean +/- SEM.

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

Intracranial PC9-luciferase NSCLC Xenograft

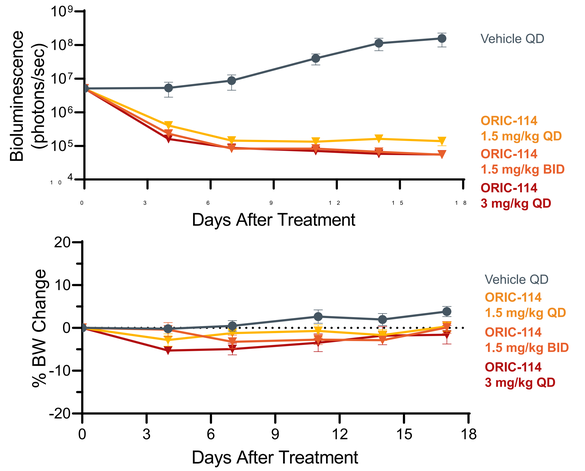


Figure 7. Top panel: Quantification of the bioluminescent photon flux in mice intracranially implanted with PC9-luc NSCLC cells and treated over 17 days with ORIC-114 at 1.5 mg/kg QD, 1.5 mg/kg BID or 3 mg/kg QD (n=7 animals per cohort). Shown is mean +/- SEM. **Bottom panel:** Body weights plotted as percent initial body weight change from day 0, plotted as mean +/- SEM.

CONCLUSIONS

ORIC-114 is a potent, irreversible brain penetrant EGFR and HER2 exon 20 inhibitor with:

- low to sub-nanomolar biochemical activity on EGFR exon 20 insertion mutations
- enhanced potency for most EGFR exon 20 insertions
- excellent kinome selectivity for EGFR family
- superior and robust single-agent regressions in EGFR exon 20 insertion LU0387 PDX model
- high brain penetrance with good brain to plasma unbound exposure ratio in mice
- tumor regressions in mouse intracranial EGFR mutant PC9 NSCLC tumors
- equivalent intracranial antitumor activity for BID and QD dosing for 3 mg/kg total 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

ORIC-114 Phase 1 trial initiated in South Korea