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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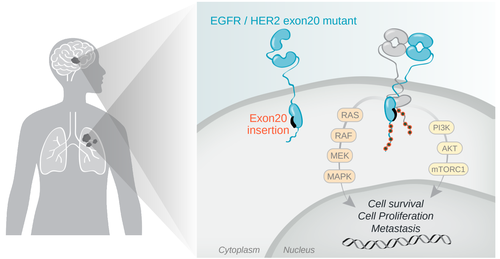
Background



EGFR/HER2 exon 20 insertion mutations are a high unmet need:

- 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 Nanomolar Cell Potency in EGFR and HER2 Exon 20 Assays

A. pEGFR in BaF3 EGFR-expressing Cell Lines

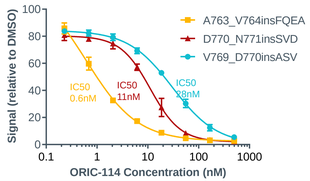


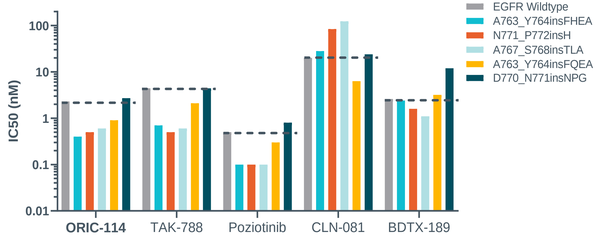
Figure 1. A. BaF3 cells expressing indicated EGFR exon 20 mutations were treated with ORIC-114 for 1hr. pEGFR in cell lysate was measured by MSD ELISA. Each dose treatment was performed in duplicate. **B.** Viability data as measured by CellTiter-Glo after 72hrs of ORIC-114 treatment. Each dose performed in triplicate.

B. ORIC-114 Potency and Selectivity in BaF3 EGFR-expressing Cell Lines

	Exon 20 Insertion	Cell TiterGlo Assay	
		GI50 (nM)	Ratio: EGFR WT / Mutant
EGFR	Wildtype	14	--
	A763_V764insFQEA	1.9	7
	D770_N771insNPG	2.4	6
	V769_D770insASV	4.4	3
	H773_V774insNPH	4.5	3
	D770_N771insSVD	10	1.4
	H773_V774insH	37	0.4
HER2	A775_G776insYVMA	12	1.2

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

Biochemical Potency in EGFR Exon 20 Insertions



ORIC-114 Selectivity in Biochemical Assays

	Exon 20 Insertion	Biochemical IC50 Ratio EGFR WT / Mutant				
		ORIC-114	TAK-788	Poziotinib	CLN-081	BDTX-189
EGFR	A763_Y764insFHEA	**6**	6	5	1	1
	N771_P772insH	**5**	9	5	0.2	2
	A767_S768insTLA	**4**	7	5	0.2	2
	A763_V764insFQEA	**3**	2	2	3	1
	D770_N771insNPG	**1**	1	1	1	0.2

Figure 2. Biochemical assays were performed with 16-point dose titration using AssayQuant Phosphosens detection technology with individual proteins. TAK-788, 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 Has Excellent Kinome Selectivity

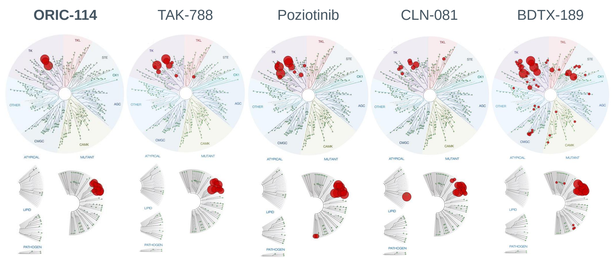
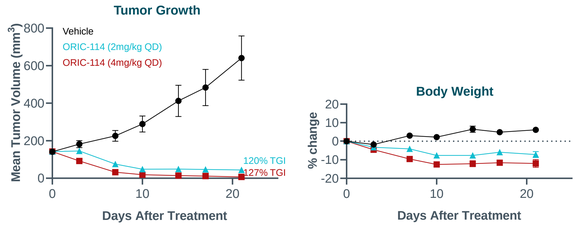


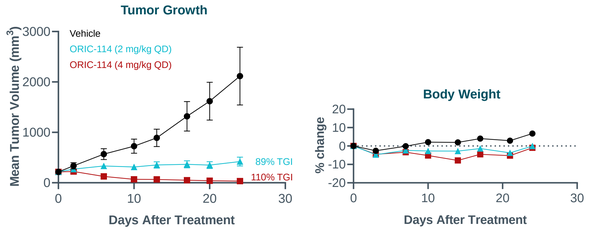
Figure 3. Kinase binding profiles were performed across 468 kinases at 1 µM for each compound using KINOMEscan. Individual kinome trees are depicted with red circles indicating top 10% kinases hit.

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

EGFR H773_V774insNPH PDX Model



EGFR V769_D770insASV PDX Model



EGFR D770_N771insG PDX Model

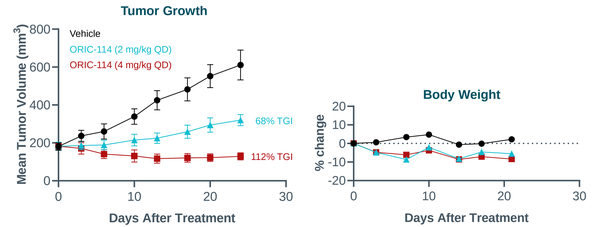


Figure 4. Subcutaneously implanted NSCLC patient-derived xenograft (PDX) models harboring EGFR exon 20 insertions were treated with ORIC-114 at 2 mg/kg and 4 mg/kg, PO once daily for 21 to 27 days (n>8 animals per cohort). Tumors were measured by caliper and mice weighed at the indicated days. Tumor volumes are average tumor size per treatment group +/- SEM. No significant body weight loss was observed.

5. Superior Brain Penetration of ORIC-114 Differentiates from Other EGFR and HER2 Exon 20 Targeted Agents

Brain Penetrance of EGFR/HER2 Exon 20 Targeted Agents

Compound	Microsomal stability in Mouse (%)	Mouse Dose	1 hour			4 hour		
			Plasma (ng/ml)	Brain (ng/ml)	Brain/Plasma Ratio	Plasma (ng/ml)	Brain (ng/ml)	Brain/Plasma Ratio
ORIC-114	**95**	10mg/kg PO	**572**	**443**	**0.8**	**489**	**363**	**0.7**
TAK-788	24.5		304	29.7	0.1	45.2	21.8	0.5
Poziotinib	68		4830	627	0.1	3160	378	0.1
CLN-081*	N.D.		367	BQL	BQL	29	BQL	BQL
BDTX-189*	N.D.		617	BQL	BQL	74	BQL	BQL

BQL = below quantification limit, 25 ng/mL in Brain; N.D.=not determined; *independent study

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

Subcutaneous PC9 NSCLC Xenograft | **Intracranial PC9-luciferase NSCLC Xenograft**

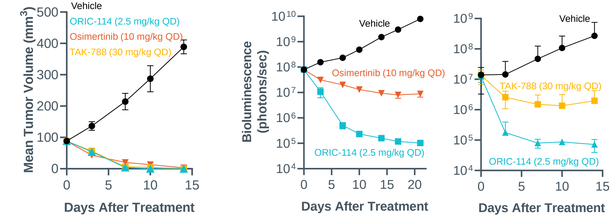


Figure 6. **Left panel:** Subcutaneously implanted EGFR del19 NSCLC PC9 xenografts were treated with either vehicle, ORIC-114, TAK-788 or osimertinib PO once daily for 10 days (n>8 animals per cohort). Tumor volumes measured by caliper, mean +/- SEM. All groups are significantly different compared to vehicle. **Middle and Right panels:** Quantification of the bioluminescence photon flux in mice implanted with intracranial PC9-Luciferase NSCLC cells and treated over 14 days with either vehicle, ORIC-114, osimertinib, or TAK-788 PO once daily. Shown is average +/- SEM

CONCLUSIONS

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

- low to sub-nanomolar biochemical activity on exon 20 insertion mutations
- enhanced potency for most EGFR exon 20 insertions
- excellent kinome selectivity for EGFR family
- robust single-agent regressions in EGFR exon 20 insertion PDX models in vivo
- high brain penetrance with good brain to plasma exposure ratio in mice
- tumor regressions in intracranial EGFR mutant lung tumors
- 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 CTA is anticipated to be filed in South Korea in the second half of 2021