Preclinical Activity of ORIC-114, a Highly Selective, Brain Penetrant, Irreversible Kinase Inhibitor, Against **Atypical Mutations in EGFR**

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INTRO: Atypical Mutations in EGFR Are an Unmet Medical Need



1. ORIC-114 Has Excellent Kinome Selectivity

- ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecule inhibitor designed to selectively target EGFR and HER2 with strong potency against exon 20 insertion mutations.
- Single agent in vivo regressions observed in EGFR exon 20 insertion models and EGFR mutant intracranial models (Junttila et al., AACR 2021; Long et al., AACR 2022).



						Atunical BACC Mutations	Biochemical IC50 Ratio EGFR WT / Mutant		
UPD						Atypical PACC mutations	ORIC-114	Afatinib	Furmonertinib
PATHOGEN	PATHOGEN	PATHODEN	PATHODEN	PATHOGEN	PATHODEN	G719C	5x	1x	0.08x
	Off-1	arget Wildtype (WT) Kina	ses Inhibited 80-100% at	1 иМ		G719S	3х	1x	0.04x
ORIC-114	Afatinib	Mobocertinib	Furmonertinib	CLN-081	BLU-451	L747S	1x	1x	0.3x
0	5	7	4	7	7*	L861Q	2x	1x	0.2x

Figure 1: Kinase binding profiles across 468 kinases at 1uM assessed using KINOMEscan. Individual kinome trees are depicted with red circles indicating the kinases impacted within 10% of control. Afatinib, mobocertinib, furmonertinib, CLN-081 assayed head-to-head; *BLU-451 inhibits 7 off-target kinases at 90% inhibition from Murray et al. AACR Poster (2022).

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2. ORIC-114 Is Brain Penetrant Across Species

Figure 2. Based on 10 mg/kg PO administration experiment in mouse assessing brain and plasma exposures, the free unbound brain/plasma ratios are graphed Junttila et al., AACR Poster 2021; ^a = independent study, BQL = below quantification limit of CLN-081 (25 ng/mL in brain); Dogs dosed with 1.5 mg/kg PO with samples assessed 1, 4, 8 hours post dose.

3. ORIC-114 Is Potent Against EGFR Atypical PACC Mutations in Biochemical Assays

ORIC-114 has low nanomolar biochemical potency on EGFR atypical PACC mutations

Figure 3. Biochemical assays were performed with 16-point dose titration using AssayQuant Phosphosens detection technology with individual proteins. IC50 ratios of EGFR WT/PACC mutant are indicated in the table.

4. ORIC-114 Is Potent on EGFR Atypical PACC Mutations in Cells

Туре	Atypical PACC Mutations	BaF3 Cell EC50 Ratio EGFR WT / Mutant					
Type		ORIC-114	Afatinib	Furmonertinib			
lary	G719C	8x	4x	2x			
	G719S	9x	4x	1x			
prim	L747S	1x	1x	1x			
	L747P	2x	1x	2x			
	L858R L718V	31x	13x	1x			
lired	L858R L718Q	7x	1x	0.1x			
acqu	del19 G796S	5x	5x	0.5x			
	del19 L792H	3x	1x	0.09x			

5. ORIC-114 Induces Complete Tumor Regressions In Vivo in EGFR G719S Atypical Mutant Xenograft Model



CONCLUSIONS

ORIC-114 is a potent, irreversible brain penetrant EGFR and HER2 inhibitor with best-in-class properties including:

- Exquisite selectivity across the kinome
- High free unbound exposure in brain across preclinical species
- Potent activity across atypical mutations in EGFR, including PACC mutations and exon 20 insertion mutations
- Tumor regressions in xenografts with atypical mutations in EGFR

Evidence of intracranial and systemic antitumor activity was observed in patients in Phase 1 dose escalation (NCT05315700). For further information see ESMO poster 1333P.

ORIC-114 is a promising therapy for NSCLC patients with EGFR exon 20 insertions or other atypical mutations in EGFR, including patients with active CNS metastases

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