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

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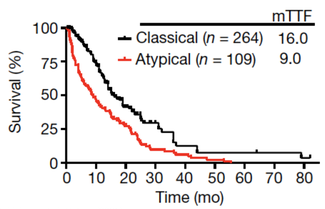
INTRO: Atypical Mutations in EGFR Are an Unmet Medical Need

Two main categories of atypical mutants

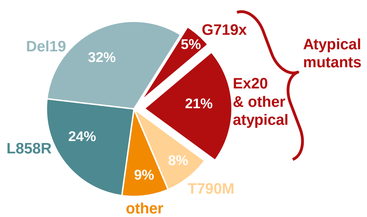
- Exon 20 insertion mutations
- P-loop and αC-helix compressing (PACC) mutations

Shorter time to treatment failure in NSCLC patients with atypical vs. classical EGFR mutations



Robichaux et al. Nature (2021)

Approximately 26% of EGFR mutant NSCLC tumors harbor atypical mutations (n=4,754 tumors)



AACR Project GENIE v14

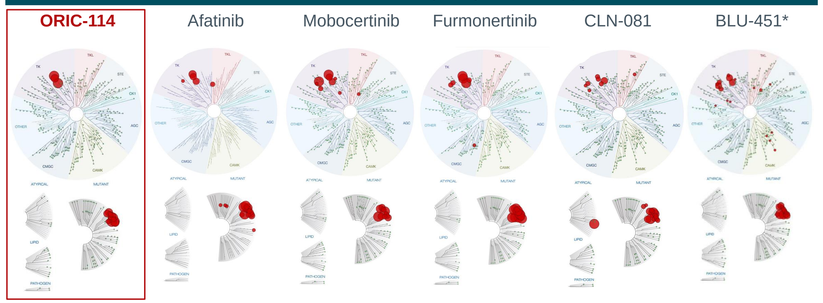
Molecule	Clinical Development For Atypical EGFR Mutants		Brain Penetrance
	Exon20	Other Atypical	
Afatinib	-	Approved (S768I, L861Q, G719x)	No
Mobocertinib	Failed Phase 3	-	No
Furmonertinib	Phase 3	Phase 1	Reported
CLN-081	Phase 2	Phase 2	No
BLU-451	Phase 1	Phase 1	Reported

Majority of EGFR atypical PACC mutations have no established FDA guidelines for treatment

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).

ORIC-114 has demonstrated an exquisitely clean kinome panel



Off-target Wildtype (WT) Kinases Inhibited 80-100% at 1 μM					
ORIC-114	Afatinib	Mobocertinib	Furmonertinib	CLN-081	BLU-451
0	5	7	4	7	7*

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).

2. ORIC-114 Is Brain Penetrant Across Species

ORIC-114 exhibits high exposure in brain across timepoints

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
Mobocertinib	304	45	30	22
CLN-081[a]	367	29	BQL	BQL
Osimertinib	71	67	912	1330

1.5 mg/kg PO in Dog	Total Plasma* (ng/mL)			Total Brain (ng/g tissue)		
	1 hr	4 hr	8 hr	1 hr	4 hr	8 hr
ORIC-114	23 ±5	39 ±8	19 ±5	136	197	109

*mean ± SD plasma concentrations based on three individual animals

ORIC-114 exhibits high free (unbound) exposure in brain

Brain and plasma free (unbound) concentration in mice dosed orally

Brain and plasma free (unbound) $AUC_{(0\text{-}8hr)}$ in dogs dosed orally

ng*hr/g (brain) / ng*hr/mL (plasma)

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

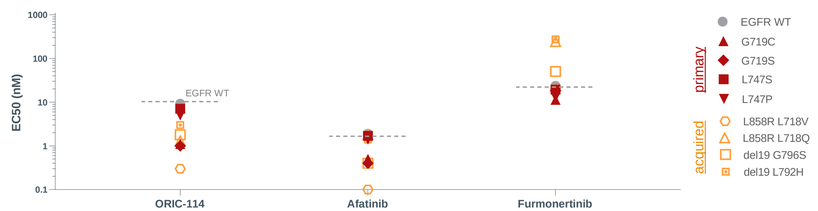
ORIC-114 has low nanomolar biochemical potency on EGFR atypical PACC mutations

Atypical PACC Mutations	Biochemical IC50 Ratio EGFR WT / Mutant		
	ORIC-114	Afatinib	Furmonertinib
G719C	**5x**	1x	0.08x
G719S	**3x**	1x	0.04x
L747S	**1x**	1x	0.3x
L861Q	**2x**	1x	0.2x

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

ORIC-114 has low nanomolar cellular potency on primary and acquired EGFR atypical PACC mutations

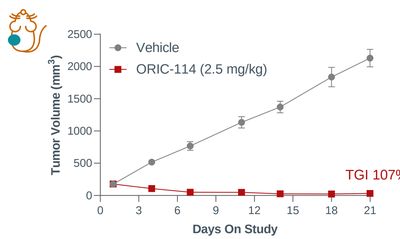


Type	Atypical PACC Mutations	BaF3 Cell EC50 Ratio EGFR WT / Mutant		
		ORIC-114	Afatinib	Furmonertinib
primary	G719C	**8x**	4x	2x
	G719S	**9x**	4x	1x
	L747S	**1x**	1x	1x
	L747P	**2x**	1x	2x
acquired	L858R L718V	**31x**	13x	1x
	L858R L718Q	**7x**	1x	0.1x
	del19 G796S	**5x**	5x	0.5x
	del19 L792H	**3x**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

Figure 4: BaF3 cells stably expressing EGFR wild-type or EGFR carrying atypical mutations were treated with vehicle or varying concentrations of ORIC-114, afatinib or furmonertinib for 72 hours as indicated. Viability was measured with CellTiter-Glo® (Promega), and absolute EC50s calculated for each EGFR protein-expressing cell line, as displayed above. BaF3 cell EC50 ratios of EGFR WT/PACC mutant are indicated in the table.

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

ORIC-114 regresses EGFR atypical PACC mutant tumors in vivo



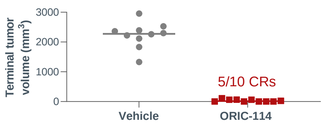


Figure 5. Left panel: Subcutaneously implanted EGFR G719S BaF3 cell lines were grown as xenografts and treated with either vehicle or ORIC-114 PO once daily for 21 days (n=10 animals per cohort). Tumor volumes measured by caliper, mean +/- SEM. Complete response, CR, defined as tumor of undetectable size. **Right panel:** Individual terminal tumor volumes at day 21. Mean is indicated by a line. No body weight loss observed.

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