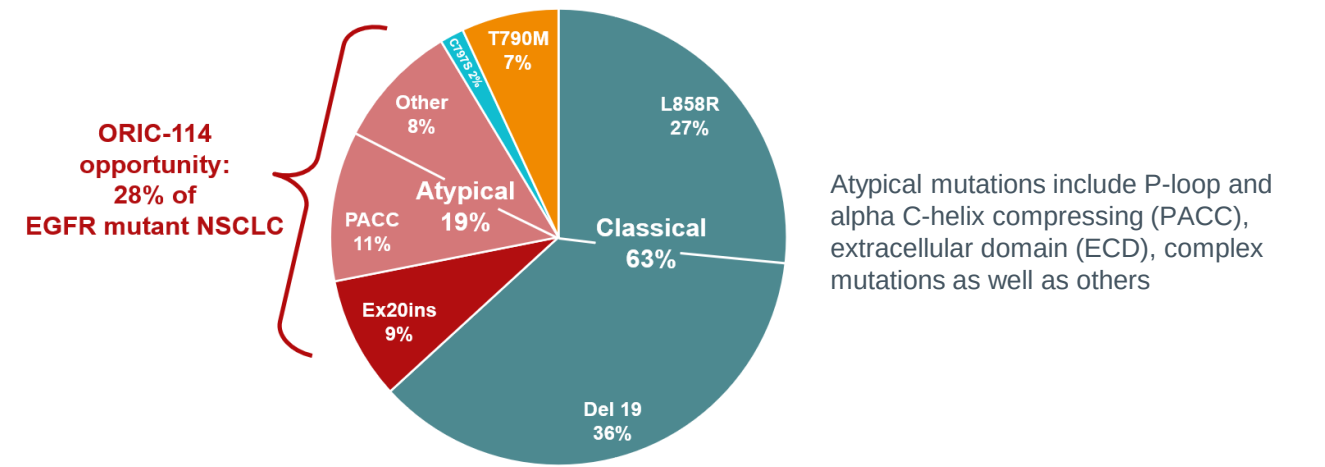


ORIC-114, a Highly Selective, Brain Penetrant EGFR and HER2 Inhibitor, Demonstrates Best-In-Class Properties Against Exon 20 Insertions and Other Atypical EGFR Mutations

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Background: EGFR Exon 20 Insertions and Atypical Mutations in EGFR Are an Unmet Medical Need in NSCLC

Approximately 28% of EGFR mutant NSCLC tumors harbor Exon 20 insertions or atypical mutations (n=3,115 patients)

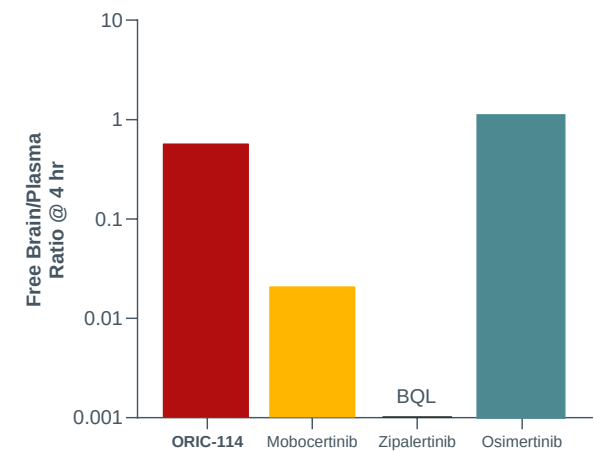


Molecule	Clinical Development For Lung Cancer Atypical EGFR Mutants	
	Exon 20 Insertions	Atypical
Afatinib	---	Approved (S768I, L861Q, G719x)
Firmonertinib	Phase 3	Phase 1
Zipalertinib	Phase 2	Phase 2
Lazertinib	---	Phase 1b combo with Amivantamab
BDTX-1535	---	Phase 2

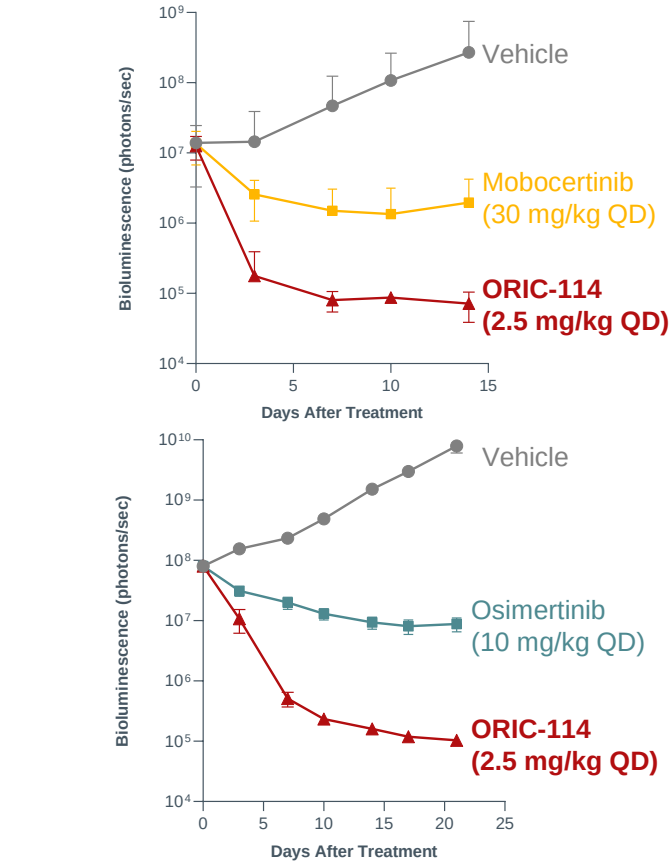
Note: PACC category includes classical + PACC and complex PACC mutants; Atypical Other category includes non-PACC, extracellular domain and classical-like mutants, alone or in complex with other EGFR mutations; T790M category includes any mutation that harbors T790M alone or in combination with other EGFR mutations; C797S category includes any mutation that harbors C797S alone or in combination with other EGFR mutations. Prevalence assessed in AACR Project GENIE v15.1 at the patient level (only one sequenced tumor considered per patient) with exclusion of sequencing panels without full coverage of EGFR.

1. ORIC-114 Exhibits Excellent Brain Penetrant Properties and Superior Intracranial Activity in Preclinical Studies

ORIC-114 Exhibits High Ratio of Free (Unbound) Brain/Plasma Exposure in Mice



Superior Efficacy of ORIC-114 In Intracranial PC9-luciferase NSCLC Xenograft



- Minimal P-gp and BCRP engagement
 - Key drug efflux pumps that limit brain penetration, PGP and BCRP transporters, have minimal impact in vitro on ORIC-114
- High free unbound exposure in brain tissue
 - Mouse Kp,uu 0.5
 - Dog Kp,uu 1.5

Figure 1. Left panel: Based on 10 mg/kg PO administration experiment in mouse assessing brain and plasma exposures, the free unbound brain/plasma ratios are graphed. Zipalertinib data from an independent study. BQL, below quantitation limit of zipalertinib detection (25 ng/mL in brain); Dogs dosed with 1.5 mg/kg PO with samples assessed 1, 4, 8 hours post dose. Junttila et al., AACR Poster 2021; Right panels: Quantification of the bioluminescence photon flux in mice implanted with intracranial PC9-luciferase NSCLC cells and treated with either vehicle, ORIC-114, mobocertinib, or osimertinib once daily for 14 or 21 days (n=6 or 7 animals per cohort). Shown is mean +/- SEM.

2. ORIC-114 Is the Most Potent Across EGFR Mutational Classes in Cell-Based Assays

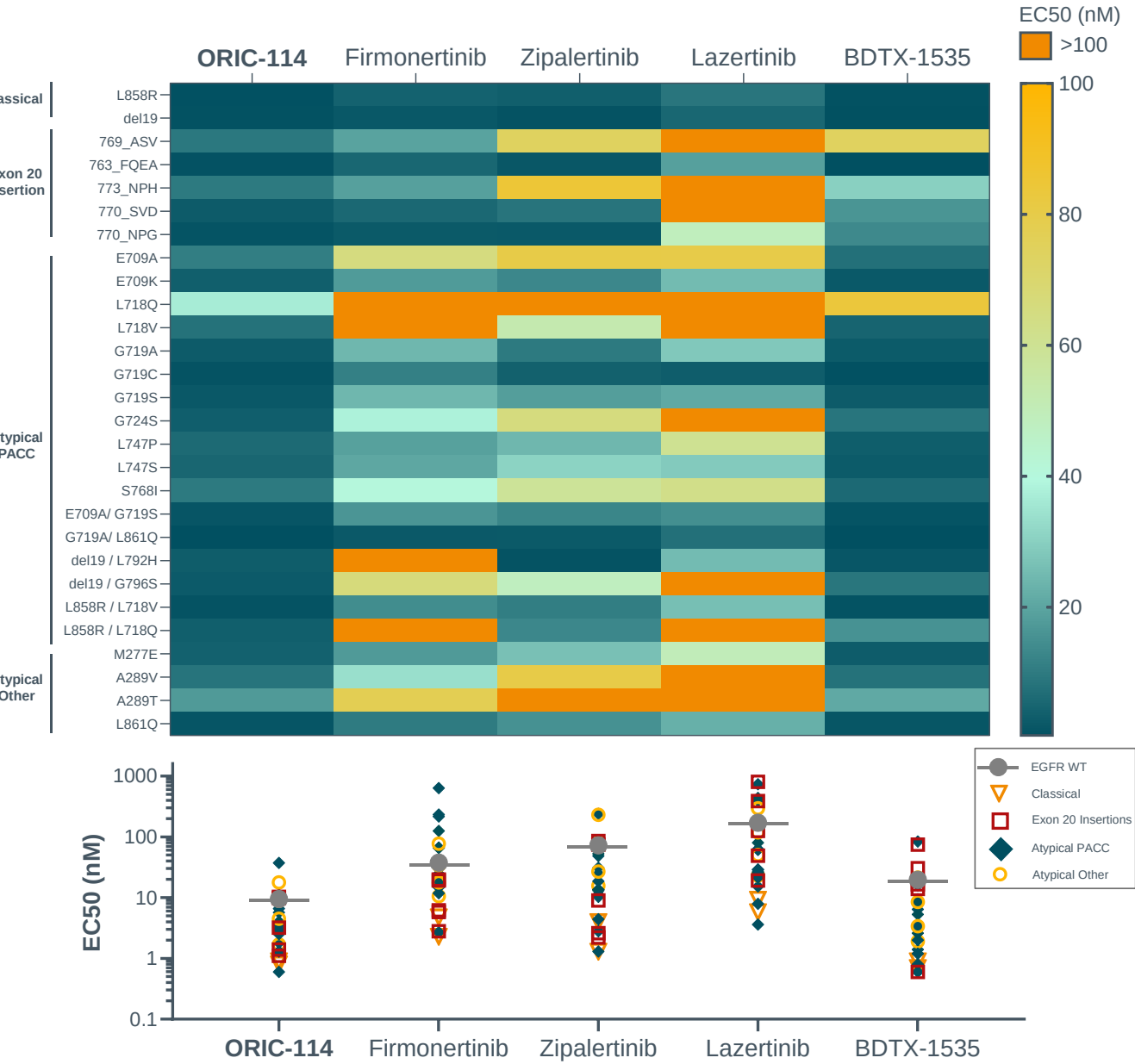


Figure 2. Upper panel: BaF3 cells stably expressing EGFR carrying classical mutations, Exon 20 insertions mutations or atypical mutations were treated with vehicle or varying concentrations of ORIC-114, firmonertinib, zipalertinib, lazertinib or BDTX-1535 for 72 hours as indicated. Viability was measured with CellTiter-Glo® (Promega), and absolute EC50s calculated for each EGFR protein-expressing cell line and displayed as a heatmap to illustrate relative potencies across individual mutations for each compound. Lower panel: Absolute EC50s displayed for BaF3 cells expressing EGFR wild-type (WT) or mutation by type. Shown are classical mutations, L858R and del19; EGFR Exon20 insertion mutations; Atypical PACC which includes PACC single mutants and complex PACC variants with classical + PACC or PACC + PACC; Atypical Other which includes extracellular domain (ECD) mutants and classical-like mutants. BDTX-1535, WO2021030711A1 and WO2023049168A1; Zipalertinib, Hasako et al., Mol Cancer Ther. 2018.

3. ORIC-114 Demonstrates Regressions in All EGFR Mutant Models Tested

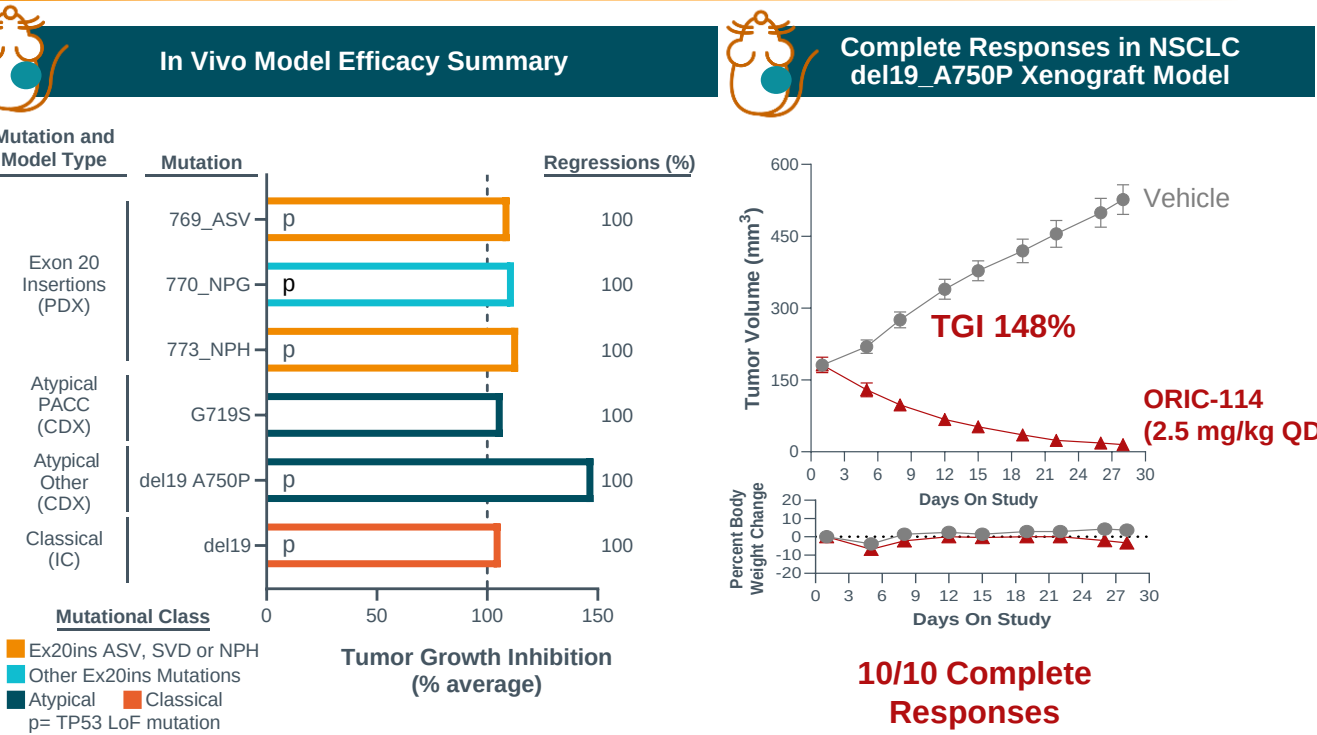


Figure 3. Left panel: Summary of in vivo efficacy studies. Doses in all studies above ranged from 2 to 4 mg/kg daily dosing by oral gavage. Tumor Growth Inhibition (TGI) was calculated using the formula $TGI = [1 - (TV_t - TV_0) / (TV_c - TV_0)] \times 100\%$ where TV_t was the mean tumor volume (TV) of treatment group at final or last treatment day, TV_0 was the mean TV of treatment group at treatment day 0, TV_c was the mean TV of control group at final or last treatment day and TV_0 was the mean TV of control group at treatment day 0. Regression was determined as the percentage of animals whose final tumor volume or bioluminescence reading was less than the tumor volume or bioluminescence reading upon study start. Right panel: Subcutaneously implanted HCC4006 was treated once daily (QD) by oral gavage (PO) for 28 days. Tumors were measured by caliper and mice weighed at the indicated days. Complete Response (CR) was calculated using the animal's final tumor volume and was considered a CR if it measured $<30mm^3$. LoF, loss-of-function; PDX, patient-derived xenografts; CDX, cell line-derived xenografts; IC, intracranial.

4. ORIC-114 Has Superior Kinome Selectivity With No Off-Target Kinase Liabilities

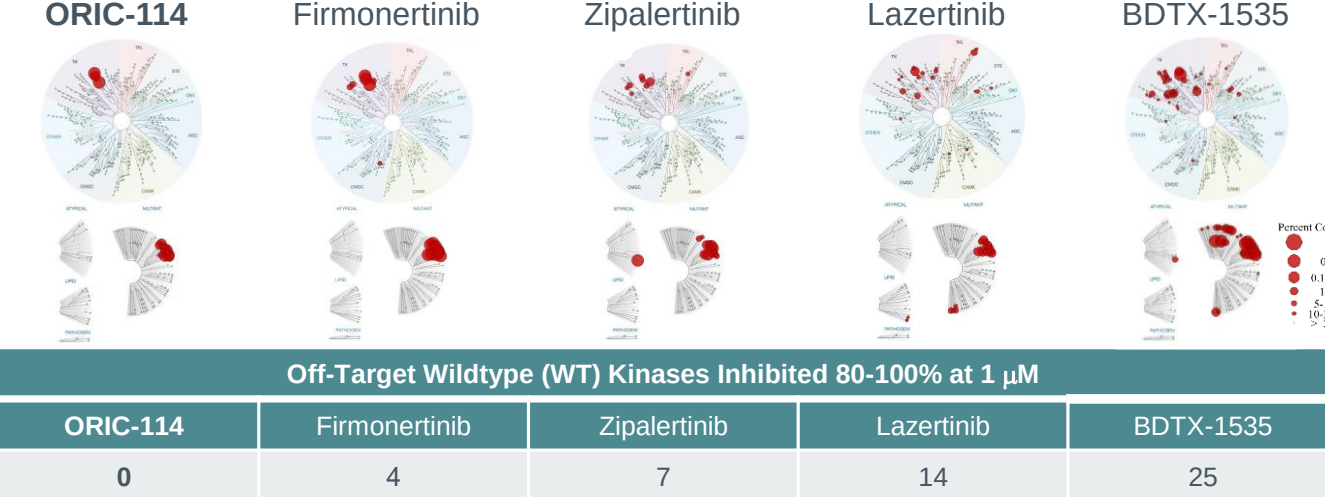


Figure 4. Kinase binding profiles across 468 kinases at 1µM assessed using KINOMEScan. Individual kinome trees are depicted with red circles indicating the kinases impacted within 10% of control. ORIC-114, firmonertinib, zipalertinib, lazertinib, and BDTX-1535 were tested.; Table reports the number of off-target wildtype kinases inhibited 80% or more.

5. ORIC-114 in a Phase 1b Study Showed Complete Molecular Responses in Patients With EGFR Exon 20 Insertion and PACC Mutations

Patient Characteristics	Key Takeaways From ctDNA Analysis
- A total of 27 EGFR-mutant NSCLC patients were treated with ORIC-114 at increasing doses QD and BID in the global Phase 1b dose escalation study (NCT05315700) - Of these patients with EGFR exon 20 insertion / atypical mutated NSCLC: 78% presented with CNS disease at baseline - median of 2 prior lines of therapies (range 0-6) 93% received prior chemotherapy 70% received EGFR targeted agents 59% treated with ≥1 prior EGFR exon 20 targeted agent 13% received multiple EGFR exon 20 targeted agents	- ORIC-114 achieved >75% molecular depletion in mutant EGFR by week 4 in 67% (18/27) of patients, including 100% in a patient with EGFR atypical PACC mutation - Molecular responses observed across dose escalation cohorts supports broad therapeutic window for ORIC-114 - Loss of TP53, observed in 67% of patients, did not significantly associate with molecular response (Fisher's test, p=0.25)

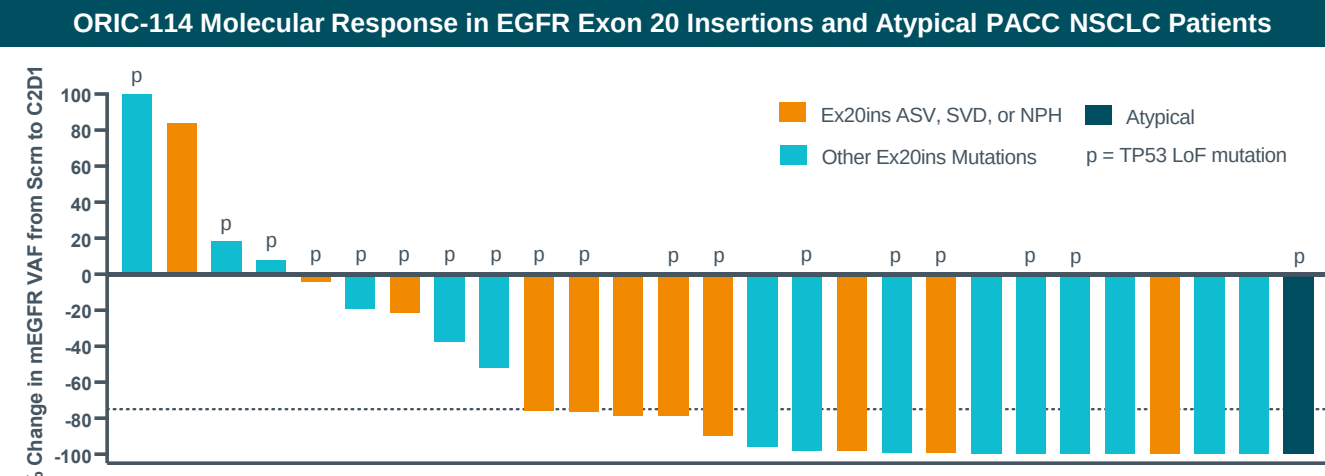


Figure 5. In the ORIC-114 Phase 1b dose escalation study, blood was collected at time of screening (Scrn) and at Cycle 2 Day 1 (C2D1) and analyzed for circulating tumor DNA (ctDNA) using Guardant360®. Twenty-seven EGFR-mutant NSCLC patients had matched blood samples with EGFR mutation detected at time of screening. Shown in the plot is the percentage change in the allele frequency of the EGFR mutation from screening to C2D1. VAF, variant allele frequency. LoF, loss-of-function mutation.

Conclusions

- ORIC-114 Potency Across EGFR Ex20ins and Atypical Mutant Classes
- Brain Penetrance
- Exquisite Selectivity With No Off-Target Liabilities
- Molecular Responses From Patients With EGFR Ex20ins and Atypical PACC
- Clinical Systemic Activity & CNS Activity Including Post-amivantamab

ORIC-114 is a promising therapeutic candidate with best-in-class potential for NSCLC patients with EGFR Exon 20 insertions and atypical mutations, including those with active CNS metastases, and is being evaluated in a global clinical trial (NCT05315700).

