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ORIC-114, an orally bioavailable, irreversible kinase inhibitor, has superior brain penetrant properties and enhanced potency in preclinical studies of HER2-positive breast cancer

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Virtual poster P234

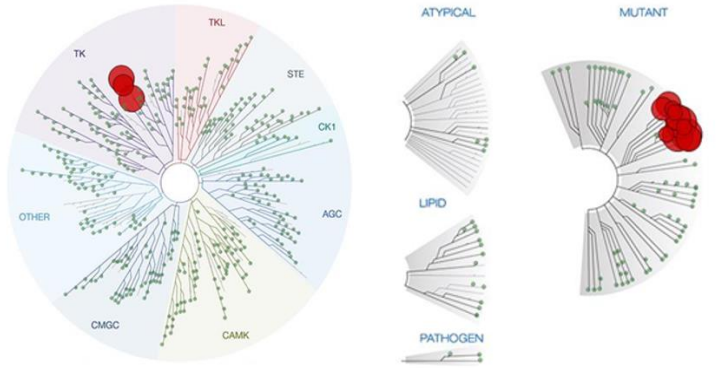
ORIC-114 Is Highly Selective for the EGFR/HER2 Receptor Family with High Brain Penetrance

Key Preclinical Highlights

ORIC-114 is a brain penetrant, orally bioavailable, irreversible inhibitor targeting EGFR and HER2 exon 20 insertion mutations

- Excellent kinome selectivity for EGFR family
- Enhanced potency for most EGFR exon 20 insertions
- Low to sub-nanomolar biochemical activity on exon 20 insertion mutations
- Robust single-agent regressions in EGFR exon 20 insertion PDX models in vivo at well-tolerated doses
- Superior brain penetrance with good brain to plasma exposure ratio in mice relative to other EGFR and HER2 exon 20 targeted agents
- Tumor regressions in intracranial EGFR mutant lung tumors

ORIC-114 kinome selectivity screen



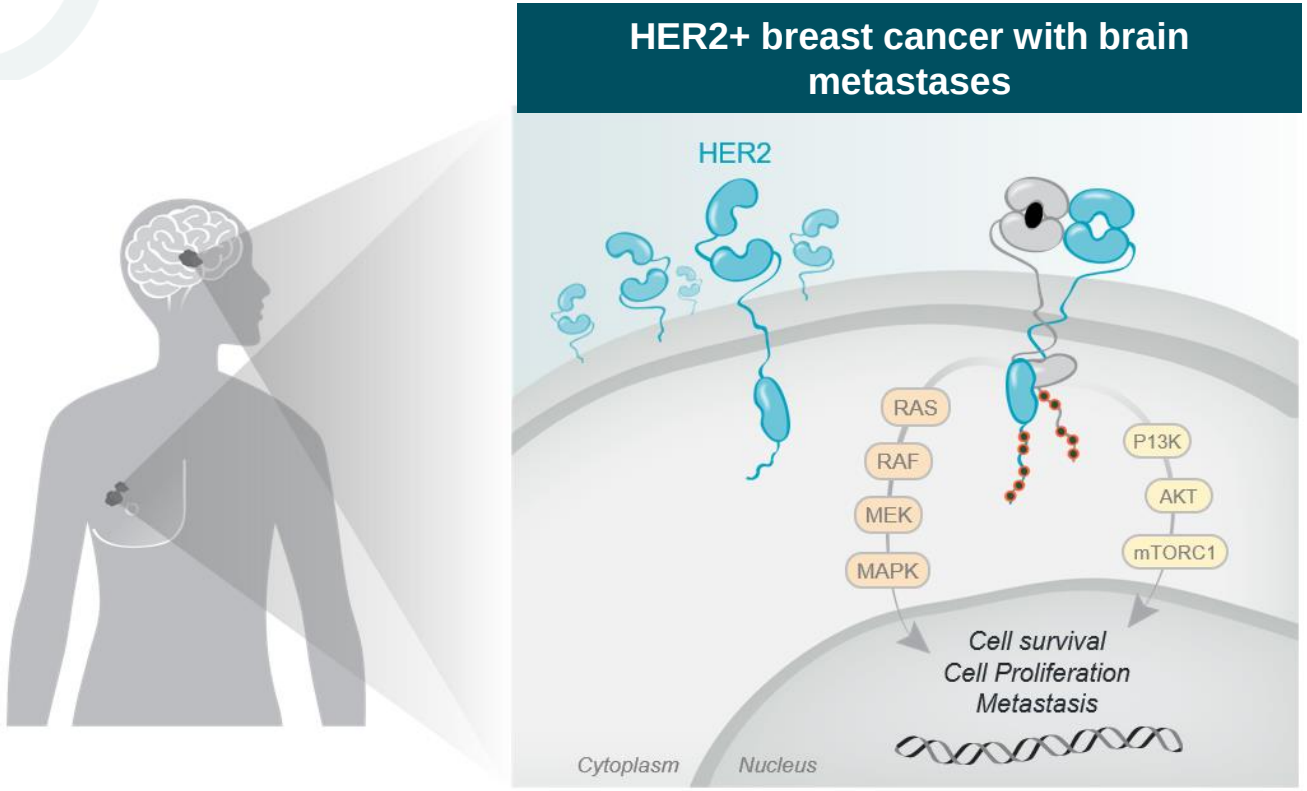
ORIC-114 biochemical potency

	protein	IC50 (nM)
WT	EGFR WT	2.3 ± 1.1
	HER2 WT	9.0 ± 4.5
Exon 20 insertion mutants	EGFR A763_V764insFQEA	0.9 ± 1.0
	EGFR A763_Y764insFHEA	0.6 ± 0.2
	EGFR D770_N771insNPG	2.7 ± 2.2
	EGFR N771_P772insH	0.5
	EGFR A767_S768insTLA	0.6

ORIC-114 is a clinical candidate with the potential for treatment of EGFR/HER2 driven cancer, including in patients with active brain metastases

Junttila et al. AACR Poster 2021. Kinome selectivity screen conducted in 468 kinases at 1 μM, Top 10% Shown

Patients with HER2+ Brain Metastases Represent a High Unmet Medical Need



https://www.cancer.net/cancer-types/breast-cancer/statistics

HER2 is an oncogenic driver amplified or overexpressed in ~25% of breast cancer

- HER2+ disease is associated with poor prognosis
- **~50% of HER2+ breast cancer patients develop brain metastases over the course of their disease**

Tucatinib was recently approved for HER2+ breast cancer patients with brain metastases (in combination with trastuzumab and capecitabine)

- Activity may be limited by modest brain exposure
- Brain exposure may be further limited by toxicity

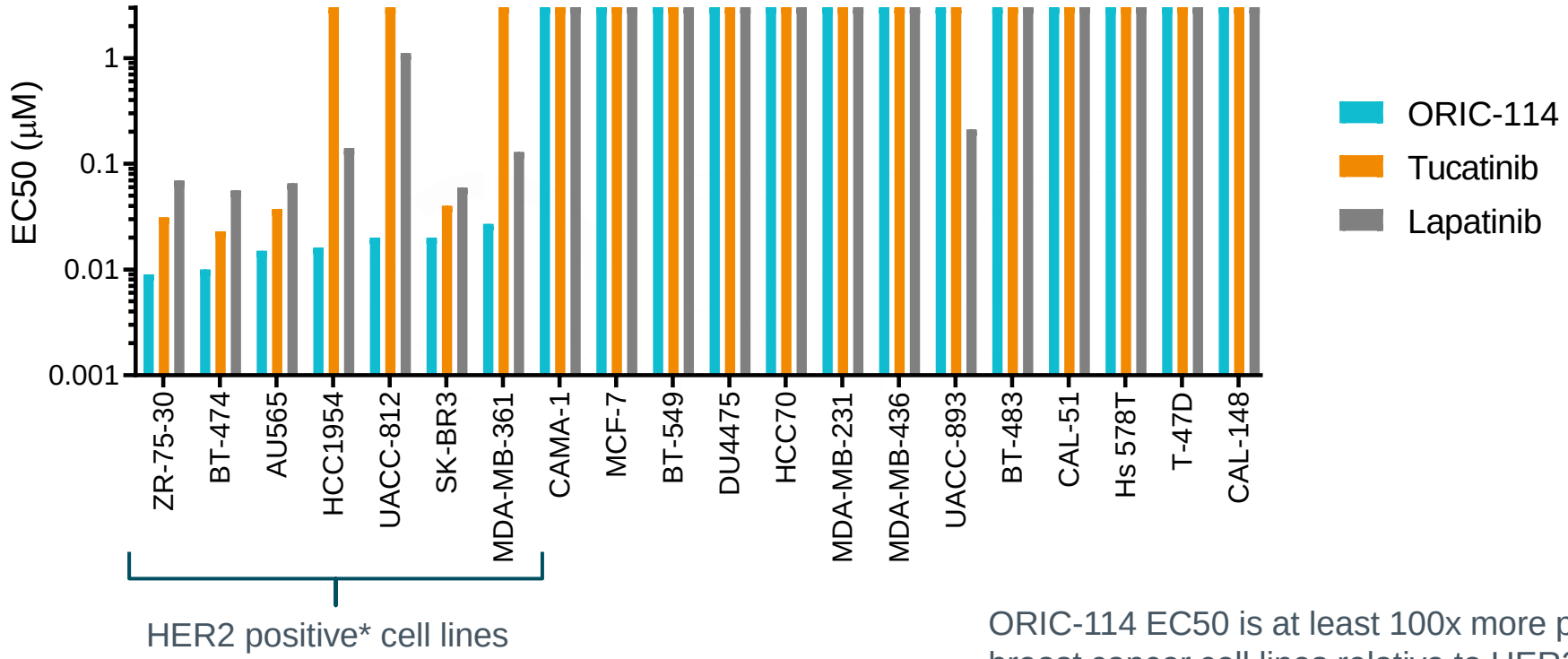
Patients with HER2+ brain metastases are a unique development opportunity for ORIC-114, given the limitations of current therapeutics

https://www.cancer.net/cancer-types/breast-cancer/statistics; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-patients-her2-positive-metastatic-breast-cancer;

HER2+ Breast Cancer Cell Lines are Sensitive to ORIC-114

Cell Viability Assay

ORIC-114 cell potency in breast cancer cell line panel indicates activity in HER2+ lines



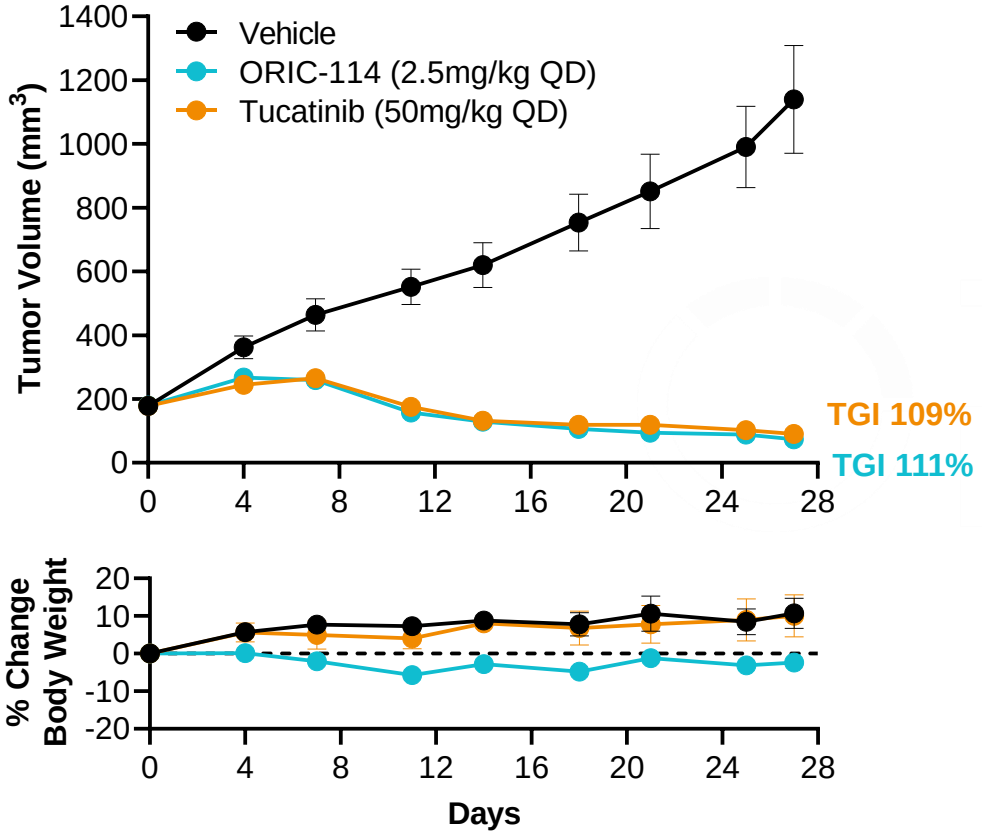
ORIC-114 EC50 is at least 100x more potent in HER2+ breast cancer cell lines relative to HER2-negative or low

ORIC-114 EC50s are below 0.1 μM and more potent than tucatinib and lapatinib in HER2+ breast cancer cell lines

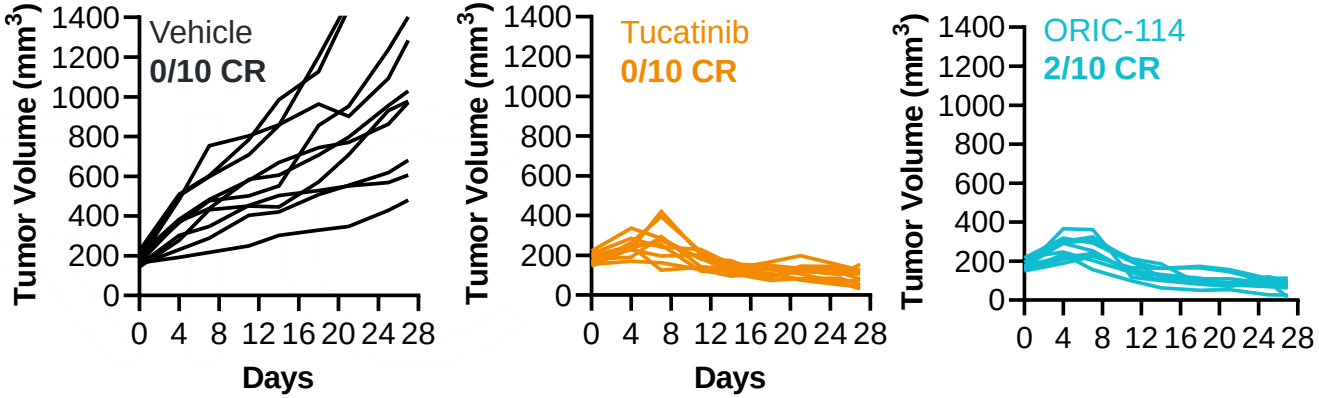
Note: 72 hour CellTiterGlo assay in 2 breast cancer cell lines, out of which are 7 HER2+cell lines. 10-point dose titration (maximum dose 3 μM). *HER2 expression >300,000 copied per cell

ORIC-114 Regresses HER2+ Breast Tumors in Vivo Without Significant Body Weight Loss

Subcutaneous BT474 Xenograft



Subcutaneous BT474 Xenograft Individual Tumor Growth



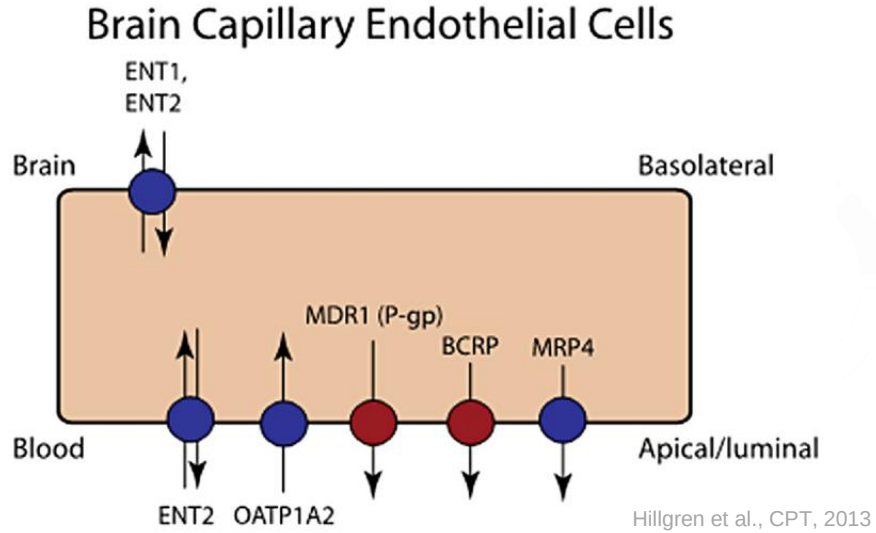
ORIC-114 treatment demonstrated 111% TGI & a complete response rate of 20% as a single agent

BT474 Model – Breast Ductal Carcinoma (60yo F); ER+, PR+, HER2+; Luminal B subtype; PO once daily for 21 (n=10 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. Complete Response (CR) defined as <30mm^3

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

Brain Transporter Cell Assays

High levels of efflux transporters at the BBB, in particular MDR1 (P-gp) and BCRP



Hillgren et al., CPT, 2013

- Small molecules can be substrates of efflux transporters that limit brain penetration
- Low efflux ratio (< 3) ideal for brain penetration

Efflux ratio in cells overexpressing key pumps can predict brain penetration

		MDR1-MDCK Efflux Ratio	BCRP-MDCK Efflux Ratio
	ORIC-114	**4.0**	**0.7**
HER2-positive targeted agent	Tucatinib	13	24.3
EGFR/HER2 targeted agents	Osimertinib[a]	13.4[b]	5.4[b]
	Mobocertinib (TAK-788)	3.4	1.4
	Poziotinib	0.7[c]	3.5[c]

[a]2 active metabolites of osimertinib are also P-gP and BCRP substrates
[b]Ballard et al., Clin Cancer Res 2016
[c]Colclough et al., Clin Cancer Res 2020;

Promising in vitro brain penetration profile of ORIC-114

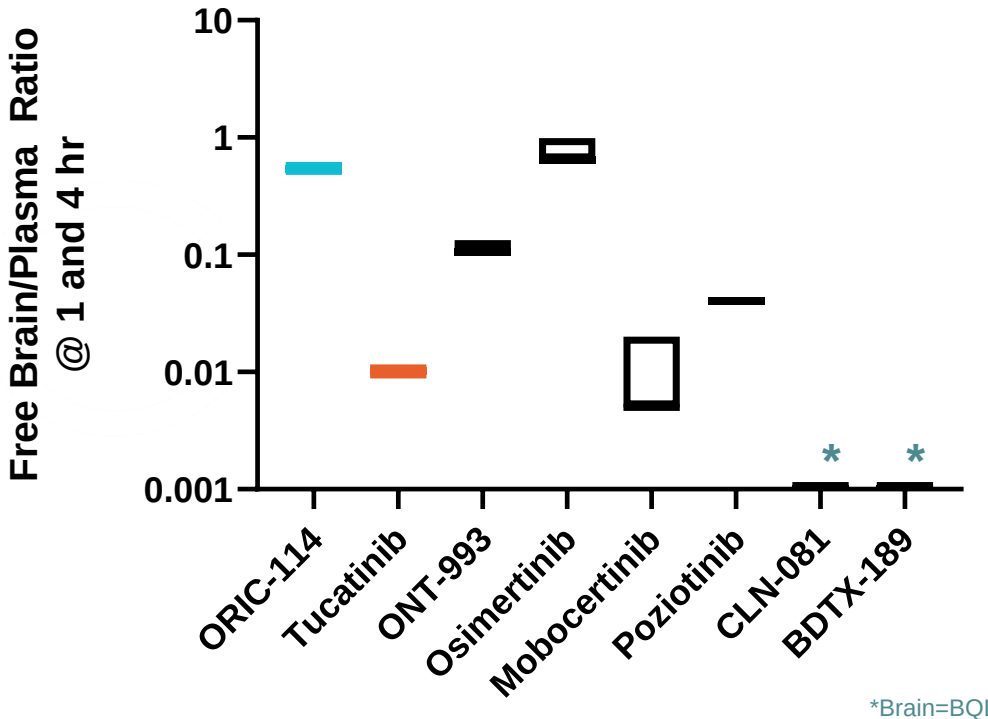
Superior Brain Penetration of ORIC-114 Differentiates from Comparator EGFR and HER2 Targeted Agents

Brain Penetrance of Targeted Agents in Mouse

ORIC-114 exhibits high exposure in 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**
HER2-positive targeted agent	Tucatinib [50 mg/kg][a]	3580	1360	62	24
	ONT-993 (Tucatinib metabolite)[a,b]	36	38	15	15
EGFR/HER2 targeted agents	Osimertinib	71	67	912	1330
	Mobocertinib (TAK-788)	304	45	30	22
	Poziotinib	4830	3160	627	378
	CLN-081[a]	367	29	BQL	BQL
	BDTX-189[a]	617	74	BQL	BQL

Brain/plasma ratio of free (unbound) exposures



*Brain=BQL

Brain exposure of free ORIC-114 and osimertinib in mice are superior to other compounds

Junttila et al. AACR Poster 2021; [a], independent study; [b], ONT-993 was measured in the same study where 50 mg/kg tucatinib was administered orally; BQL, below quantification limit

ORIC-114 Is a Brain Penetrant, Orally Bioavailable, Irreversible Inhibitor Targeting EGFR/HER2 Family of Receptors

ORIC-114 Key Takeaways from Preclinical Studies

- Excellent kinome selectivity for EGFR/HER2 family
- Strong potency in HER2+ breast cancer cell lines
- Robust single-agent activity in HER2+ breast cancer xenograft model in vivo
  - Intracranial HER2+ antitumor activity assessment ongoing
- High brain penetrance, notably with high free brain-to-plasma ratio in mice
  - Superior in vivo brain penetration relative to tucatinib and ONT-993 as measured by brain-to-plasma ratio in mice

This study reinforces the potential for ORIC-114 as a promising therapeutic candidate for development in patients with HER2+ tumors including those with brain metastases

A Clinical Trial Application for ORIC-114 is anticipated in the second half of 2021