ORIC-613, a Potential First- and Best-in-Class, Orally Bioavailable, Potent and Selective PLK4 Inhibitor with Synthetic Lethality in TRIM37 High Cancer Models

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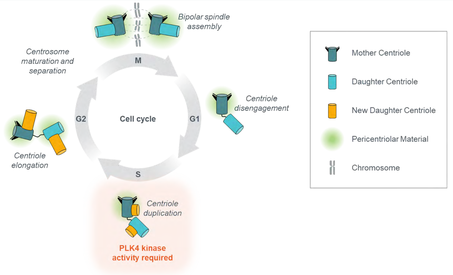
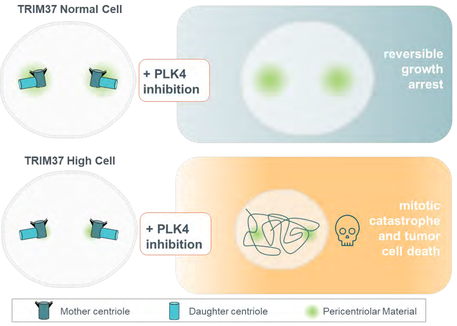
Abstract #6942

BACKGROUND

Polo-like Kinase 4 (PLK4) Is a Cell Cycle Kinase That Controls Centrosome Duplication

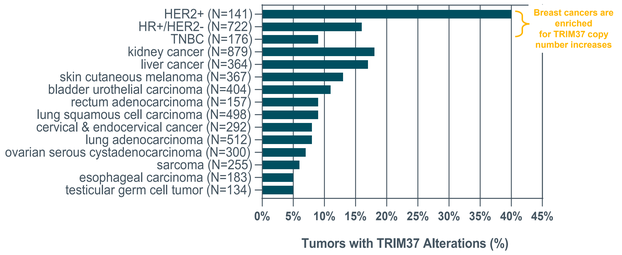


Synthetic Lethality of PLK4 Inhibition in TRIM37 High Tumor Cells



- PLK4 inhibition was recently identified as synthetic lethal in TRIM37 amplified tumors (Meitinger *et al.*, Nature 2020; Yeow *et al.*, Nature 2020)
- Amplifications of TRIM37 at 17q23 are common in breast cancer and neuroblastoma and have been associated with early relapse and poor prognosis

High Prevalence of TRIM37 Copy Number Aberrations (TCGA Dataset of >11,000 Primary Adult Tumors)



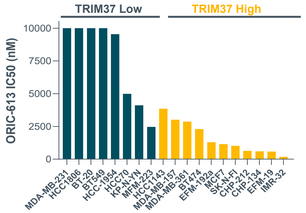
1. ORIC-613 Meets Best-in Class Target Candidate Profile

	ORIC-613	Centrinone	CFI-400945	RP-1664	EXEL-7871
Development Stage	**IND-ready**	NA	Phase 2	FPI 1Q'24	IND 2025
Dosing	**Oral**	Not Oral	Oral	Oral	Oral
PLK4 IC_{50} (nM)	**1.71**	0.55	0.50	1	8.3
Fold PLK1 / PLK4	**>30,000x**	>30,000x	>30,000x	Not reported	Not reported
Fold AurA / PLK4	**>7,000x**	92x	85x	>2,000x	Not reported
Fold AurB / PLK4	**>800x**	1,582x	12x	>2,000x	75x
Fold LRRK2/PLK4	**>5,500x**	1.19x	29x	1.48x**	Not reported
Kinome screen @100nM	**0/468**	12/468	11/290*	8/280	Not reported

Figure1. ORIC-613 and Centrinone assayed head-to-head; RP-1664, Repare Therapeutics Investor and Analyst Conference Call and Webcast Nov 15, 2023; EXEL-7871, Exelixis 2023 R&D Day: Science & Strategy Dec 12, 2023; *11 kinome hits confirmed to inhibit <100nM, CFI-400945 Mason *et al.*, 2014; **generated from REPARE patent #WO 2023/159307 Compounds 25,137,140,174.

2. ORIC-613 is Synthetic Lethal in TRIM37 High Cancer Models

ORIC-613 Shows Greater Potency in TRIM37 High vs. Low Cell Lines



ORIC-613 Shows Greater Tumor Growth Inhibition (TGI) in TRIM37 High vs. Low In Vivo Models

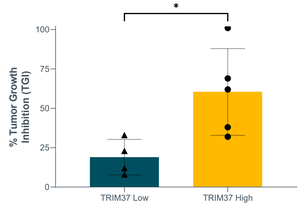
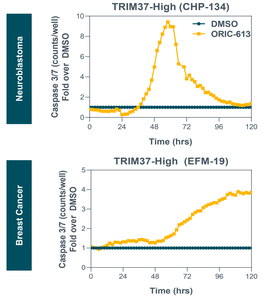


Figure 2. Neuroblastoma and breast cancer cell lines assessed after 3-4 cell doublings using a CellTiter-Glo assay (left). Tumor growth inhibition in xenograft models at day 28 dosed at 150 mpk QD.TRIM37 high/low as Copy Number >3 (right) .

3. ORIC-613 Confers Apoptotic Cell Death Solely in TRIM37 High Cancer Cells

ORIC-613 Induces Apoptotic Cell Death in TRIM37 High Cancer Cells



No Apoptotic Cell Death in TRIM37 Normal Cancer Cell Lines Treated with ORIC-613

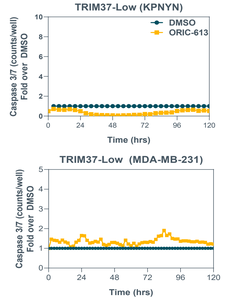


Figure 3. Cell lines were assessed using a caspase 3/7 assay; ORIC-613 dosed at 2x EC50; Doubling Times: CHP-134 =30 hrs; KPNYN=40 hr; EFM-19=80 hr; MDA-MB-231=24 hr

4. PLK4 Inhibition by ORIC-613 Leads to Protein Stabilization

PLK4 Activity Results in Trans-Autophosphorylation and PLK4 Degradation That is Specific to PLK4 Inhibition and Correlates with Cell Viability

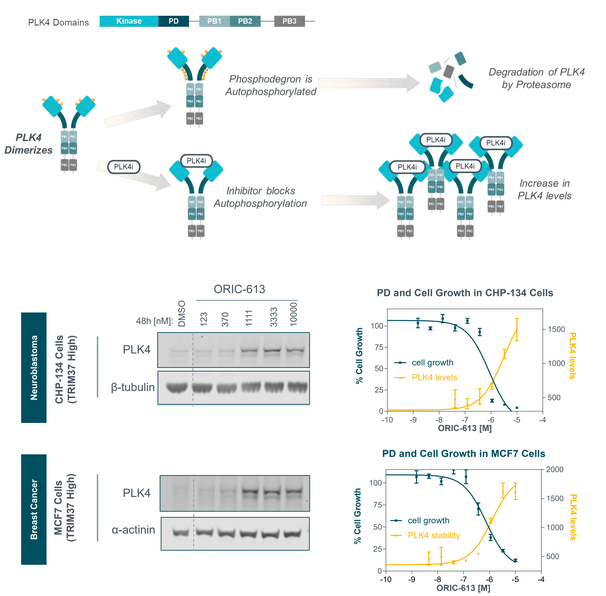


Figure 4. PLK4 stabilization occurs when autophosphorylation of the phosphodegron is inhibited, and PLK4 cannot be degraded by the proteosome. Protein extracts from CHP-134/MCF7 lysates treated for 48hrs with indicated compounds were run on 3-8% Tris-Acetate gels and transferred to nitrocellulose membranes. Blots were probed with antibodies to PLK4, α-actinin, β-tubulin.

5. ORIC-613 Requires PLK4 Binding for Activity Confirming Activity is On-Target

ORIC-613 Loses Activity Against PLK4 G95L Binding Mutant Protein

The G95L mutation sterically hinders compound binding, but PLK4 retains catalytic activity
- G95L is resistant to various type I ATP-competitive protein kinase inhibitors [1]
- G95L rescues effects of centrinone treatment [2]

Biochemical Activity	
	ORIC-613
PLK4 G95L IC_{50} (nM)	>50,000
PLK4 WT IC_{50} (nM)	137
Fold G95L/WT IC50	95x

On Target Activity Established for ORIC-613 in PLK4 WT vs. G95L Mutant Knock-in MCF7 Cells

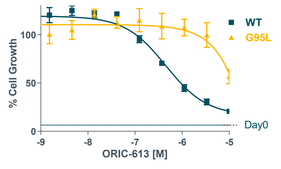
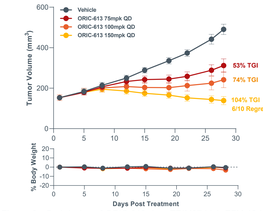


Figure 5. Biochemical IC50 obtained using Assay Quant in the presence of 1 mM ATP for the respective proteins (left). MCF7 cells with knock-in of PLK4 G95L were generated by CRISPR/Cas9 and validated by sequencing and thereafter tested for cell growth following 9 days of treatment (right). References: (1) Sloan et al. ACS Chem Biol (2010). (2) Wong et al. Science (2015).

6. ORIC-613 Is Well Tolerated and Efficacious as a Single Agent in TRIM37 High Xenografts

ORIC-613 Regresses EFM-19 TRIM37 High HR+/HER2- Breast Xenograft Model



ORIC-613 Significantly Reduces End-of-Study Tumor Volumes

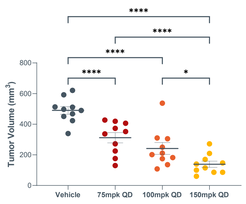
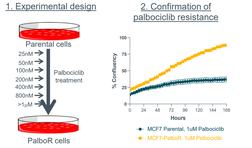


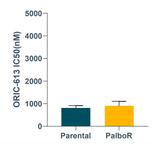
Figure 6. Oral dosing of ORIC-613 in a TRIM37 high EFM-19 breast cancer xenograft model leads to tumor regression (n=10 per cohort; mean +/- SEM) without significant body weight loss; Tumor growth inhibition (TGI) = [1 - (TVtf - TVt0) / (TVcf - TVc0)] × 100%; * p=0.0169; **** p<0.0001; Regression is defined by RECIST 1.1 criteria.

7. ORIC-613 Retains Potency in CDK4/6 Resistant Models Both In Vitro and In Vivo

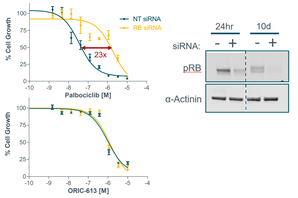
Generation of MCF7 Cells with Acquired Resistance to Palbociclib



ORIC-613 Maintains Potency in Palbo-Resistant Cells



ORIC-613 Is Equally Potent in RB Null Cells Resistant to Palbociclib



ORIC-613 Significantly Reduces End-of-Study Tumor Volumes in Palbociclib Resistant PDX Model

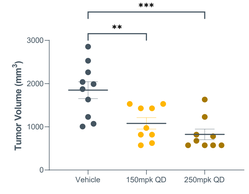


Figure 7: Palbociclib-resistant cell MCF7 cells were generated following in vitro dose-escalation until cells were capable of growing in 1 μM palbociclib. PalboR cell line demonstrated increased expression of cyclinE1. ORIC-613 remained equipotent in parental and PalboR cells (upper panel). Knockdown of RB by siRNA in MCF7 induced resistance to palbociclib by cell remained sensitive to ORIC-613 (lower panel, left). PDX model ST1799/PBR was generated in vivo through continuous palbociclib treatment (XenoSTART); ST1799 parental PDX model TGI of palbociclib ~100%; ST1799/PBR palbociclib-resistant model TGI of palbociclib ~18%; Oral dosing of ORIC-613 lead to decreased tumor volumes following 52 days of treatment. Animals were euthanized when tumor size exceeded 2500 mm³; Tumor growth inhibition (TGI) = [1 - (TVtf - TVt0) / (TVcf - TVc0)] × 100%; **p=0.005 , ***p=0.0003 (lower panel, right).

CONCLUSION

ORIC-613 is a potential first- and best-in-class, highly selective PLK4 inhibitor development candidate with:

- ✓ excellent kinome selectivity, superior to comparator compounds
- ✓ pharmacodynamic effects corresponding to cell activity
- ✓ apoptosis induction specifically in TRIM37 high cancer cells vs. TRIM37 WT cells
- ✓ oral bioavailability
- ✓ strong in vivo efficacy in TRIM37 high tumors with no body weight loss
- ✓ retained efficacy in palbociclib-resistant breast cancer xenografts
- ✓ the potential to benefit patients with TRIM37 high tumors

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