#5612

Taletrectinib, a next-generation selective ROS1 inhibitor, inhibits growth of ROS1 wild-type and ROS1-G2032R xenografts

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Background

- *ROS1* gene fusions occur in approximately 2% of patients with NSCLC[1]
  - *ROS1* gene fusions result in increased ROS1 autophosphorylation and constitutive activation[2]
- While 3 ROS1 TKIs are currently approved by the FDA for the treatment of *ROS1*+ NSCLC, there remains an unmet need for effective and tolerable treatment options[1]
  - Crizotinib and entrectinib are not active against many resistance mutations, including ROS1^{G2032R}, the most common mutation[1]
  - Repotrectinib, while active in the CNS, is associated with a high rate of neurologic AEs such as dizziness (65%), ataxia (28%), and cognitive impairment (25%), which are attributed to the drug's inhibition of TRKB[3]
- Taletrectinib is a next-generation, CNS-active, ROS1 TKI with selectivity over TRKB[4,5]
  - Taletrectinib demonstrated high and durable overall responses, robust intracranial responses, prolonged PFS, activity against G2032R, and had a favorable safety profile in the pivotal regional TRUST-I (NCT04395677)[4] and global TRUST-II (NCT04919811)[5] studies of *ROS1*+ NSCLC
  - NDA was accepted for priority review by the US FDA, with a PDUFA date of June 23, 2025

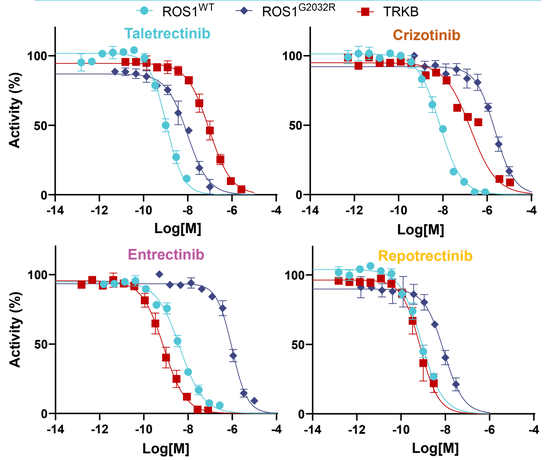
Methods

Study Design

- **Biochemical inhibition:** In vitro kinase activity was detected via Reaction Biology Hotspot Kinase Assay and measured using the P81 filter-binding method[6]
- **In vitro cell viability:** Ba/F3 cells harboring the respective *ROS1* wild type or mutant fusions were plated at a density of 500–2500 cells/well and treated the next day with respective treatments. Viability was assessed after 5 or 6 days of treatment, and data are represented in IC_{50} where 50% of growth inhibition relative to control was observed
- **Western blots:** Cells were harvested 2 hours post dosing, and protein expression was analyzed using the following antibodies: Phospho-ROS1 Tyr 2274 (CST-3028), ROS1 (CST-3287, OTI1A1-Invitrogen), and GAPDH (Proteintech_60004). Protein expression was quantified and normalized to GAPDH expression
- **In vivo CDX/PDX:** CDX or PDX studies were run as per standard practice. Briefly, cells or tumor fragments were implanted in mice, and mice were housed in pathogen-free housing with access to sterilized food and water ad libitum. Taletrectinib, crizotinib, entrectinib, or repotrectinib was administered orally. For subcutaneous models, tumors were measured twice/week and tumor volume was calculated using the formula: $(L*W^2)*0.52$. For intracranial models, survival of mice was evaluated

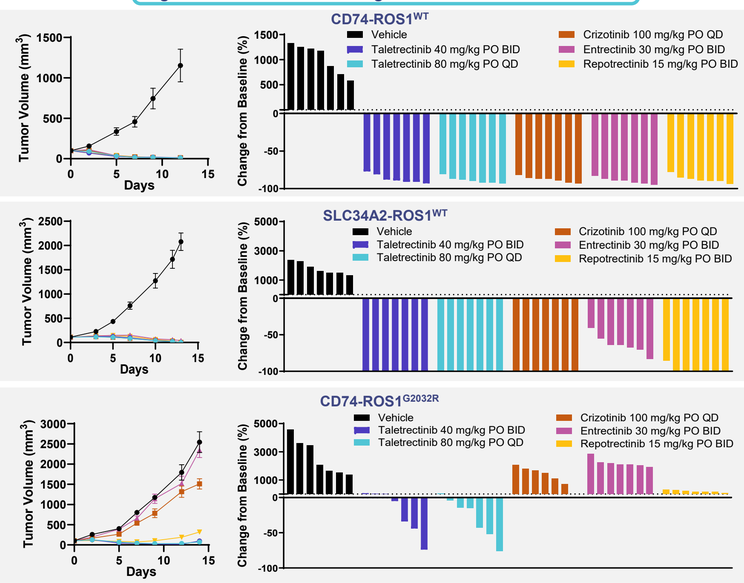
Results

Taletrectinib Demonstrates Selectivity for ROS1^{WT} and ROS1^{G2023R} Over TRKB at Physiologically Relevant ATP Concentrations

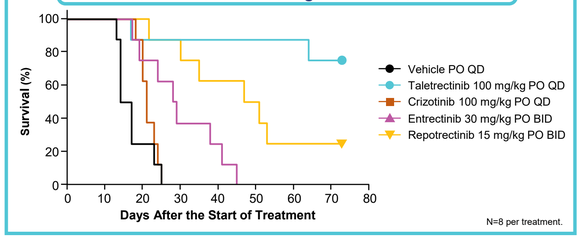


Kinase	IC_{50} (nM)			
	Taletrectinib	Crizotinib	Entrectinib	Repotrectinib
ROS1^{WT}	1	7	4	1
ROS1^{G2032R}	10	2259	981	9
TRKB	92	178	1	1
	Selectivity (fold)			
TRKB/ROS1^{WT}	92	25	0.25	1
TRKB/ROS1^{G2032R}	9	<0.1	<0.001	<0.1

Taletrectinib Demonstrates Growth Inhibition and Tumor Regression in Models Harboring ROS1^{WT} and ROS1^{G2032R} Fusions

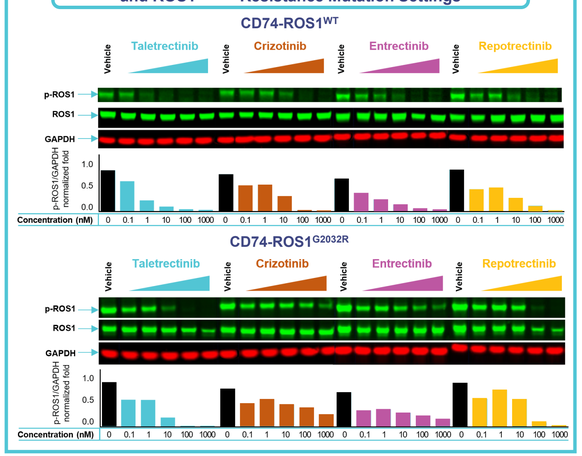


Taletrectinib Prolongs Survival in LU-01-0414 Intracranial Mouse PDX Model Harboring a SDC4-ROS1 Fusion

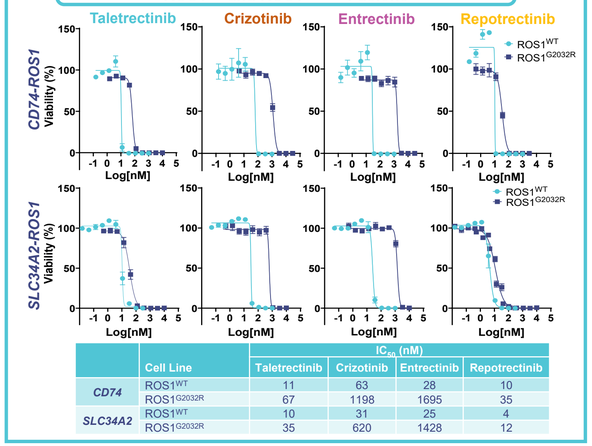


N=8 per treatment.

Taletrectinib Inhibits ROS1 Phosphorylation in Both ROS1^{WT} and ROS1^{G2032R} Resistance Mutation Settings

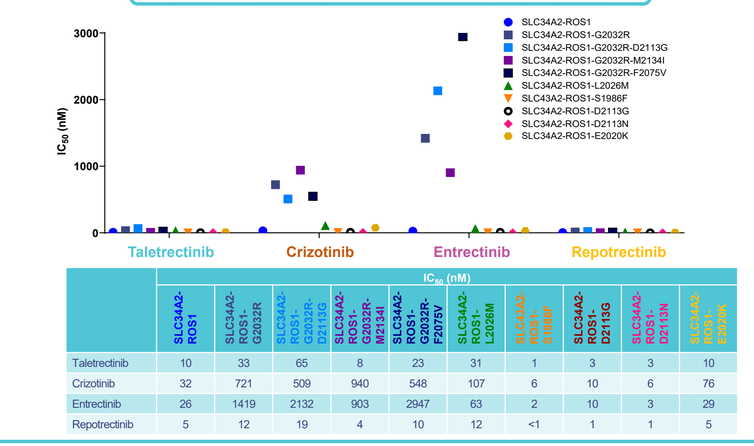


Taletrectinib Inhibits Cell Growth in Models Harboring ROS1^{WT} and ROS1^{G2032R} Fusions



	Cell Line	IC_{50} (nM)			
		Taletrectinib	Crizotinib	Entrectinib	Repotrectinib
CD74	ROS1^{WT}	11	63	28	10
	ROS1^{G2032R}	67	1198	1695	35
SLC34A2	ROS1^{WT}	10	31	25	4
	ROS1^{G2032R}	35	620	1428	12

Taletrectinib Demonstrates Activity Against Single and Double ROS1^{G2032R} Mutants Resistant to Crizotinib and Entrectinib



	IC_{50} (nM)									
	SLC34A2-ROS1	SLC34A2-ROS1-G2032R	SLC34A2-ROS1-G2032R-D2113G	SLC34A2-ROS1-G2032R-M2134I	SLC34A2-ROS1-G2032R-F2075V	SLC34A2-ROS1-L2026M	SLC43A2-ROS1-S1986F	SLC34A2-ROS1-D2113G	SLC34A2-ROS1-D2113N	SLC34A2-ROS1-E2020K
Taletrectinib	10	33	65	8	23	31	1	3	3	10
Crizotinib	32	721	509	940	548	107	6	10	6	76
Entrectinib	26	1419	2132	903	2947	63	2	10	3	29
Repotrectinib	5	12	19	4	10	12	<1	1	1	5

Conclusions

- **Taletrectinib demonstrates selectivity for ROS1^{WT} and ROS1^{G2032R} over TRKB at physiologically relevant ATP concentrations, whereas repotrectinib, crizotinib, and entrectinib did not demonstrate any selectivity over TRKB, a kinase whose inhibition is associated with CNS toxicity**
- **Taletrectinib demonstrated in vitro and in vivo activity against ROS1 regardless of fusion partner or resistance mutation, including the ROS1^{G2032R} mutation which is resistant to crizotinib and entrectinib**
- **Taletrectinib demonstrated tumor regression in models harboring ROS1^{WT} and ROS1^{G2032R} fusions**
- **Taletrectinib inhibits ROS1 phosphorylation in ROS1^{WT} and ROS1^{G2032R} models**
- **Taletrectinib treatment prolonged survival in mice implanted intracranially with a PDX model harboring a SDC4-ROS1 fusion**

Abbreviations

AE, adverse event; ATP, adenosine triphosphate; BID, twice daily; CDX, cell line-derived xenograft; CNS, central nervous system; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GI_{50}, growth inhibition 50%; IC_{50}, half-maximal inhibitory concentration; NDA, new drug application; NSCLC, non-small cell lung cancer; PDX, patient-derived xenograft; PFS, progression-free survival; p-ROS1, phosphorylated ROS1; PDUFA, Prescription Drug User Fee Act; PO, orally; QD, once daily; ROS1, proto-oncogene tyrosine-protein kinase 1; *ROS1*+, *ROS1* positive; *SDC4*, syndecan-4; *SLC34A2*, solute carrier family 34 member 2; TKI, tyrosine kinase inhibitor; TRKB, tropomyosin receptor kinase B; US FDA, US Food and Drug Administration; WT, wild type.

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