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LOXO-292, a Potent, Highly Selective RET Inhibitor, in Multi-Kinase Inhibitor-Resistant RET Fusion-Positive Lung Cancer Patients with and without Brain Metastases

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Disclosures

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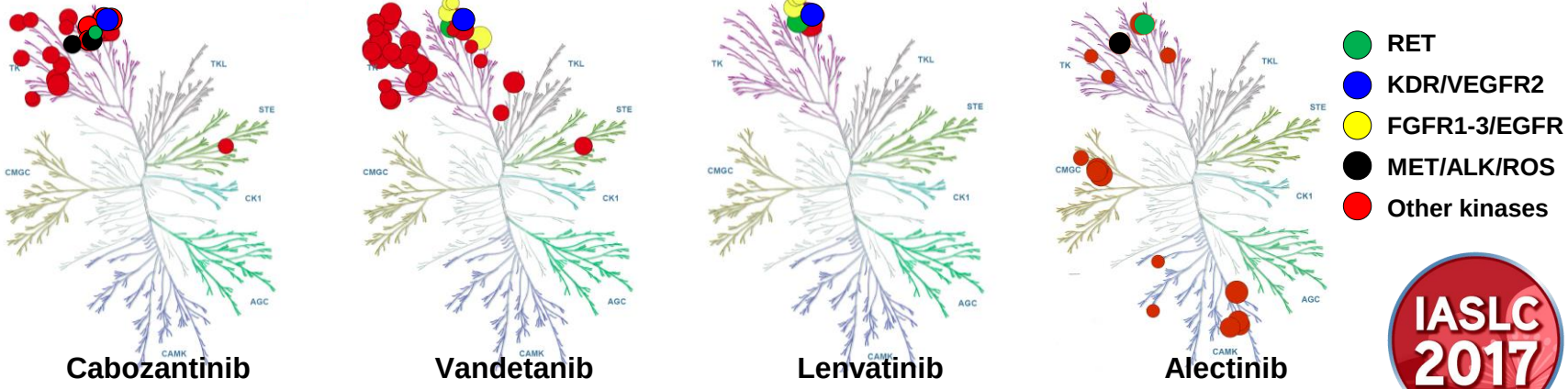
Repurposed "RET Inhibitors": poor RET coverage in humans

MKI	Approved Dose	Toxicities	RET Inhibition (Human C_{max})*
Cabozantinib	140 mg QD	Diarrhea, PPE, ↓weight/appetite, fatigue, hypertension	51%
Vandetanib	300 mg QD	Diarrhea, hypertension, QT prolonged, fatigue, rash	24%
Lenvatinib	24 mg QD	Diarrhea, hypertension, ↓weight/appetite, fatigue, proteinuria	47%
Alectinib	600 mg BID	↑ALT/AST/GGT/Bilirubin, anemia, nausea/vomiting, diarrhea	32%

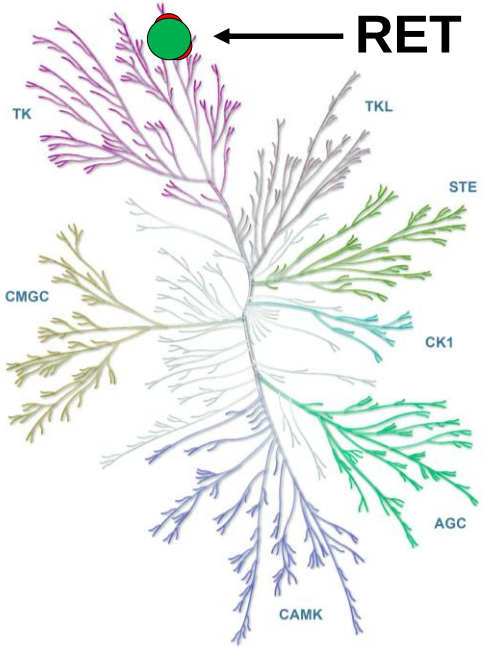


Cabozantinib Vandetanib Lenvatinib Alectinib

*cellular (phospho-RET) inhibitory concentration corrected for human plasma protein binding and published human PK

LOXO-292: potent and selective RET inhibition

- Rationally designed, informed by proprietary crystallography insights
- Highly selective
- Fusion- and mutation-independent RET inhibition
  - e.g. KIF5B-RET, CCDC6-RET
  - C634W, M918T, V804L/M (gatekeeper—acquired resistance)
- Favorable drug-like properties

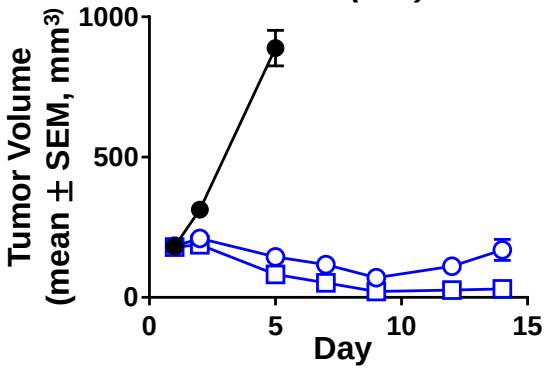


LOXO-292

LOXO-292's potential in lung cancer

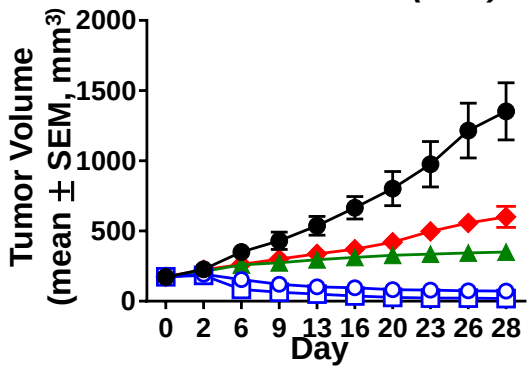
(1) Naïve RET Fusion

KIF5B-RET (3T3)



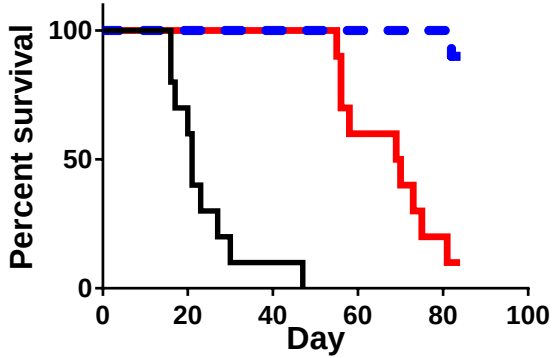
(2) Potential acquired resistance

CCDC6-RET V804M (PDX)



(3) Brain metastases

CCDC6-RET orthotopic brain (PDX)



Vehicle
3 mg/kg BID LOXO-292
10 mg/kg BID LOXO-292
30 mg/kg BID LOXO-292
40 mg/kg QD cabozantinib
20 mg/kg QD ponatinib

Vehicle
LOXO-292 30 → Day 52 → 3 mg/kg BID
Ponatinib 20 → Day 52 → 2 mg/kg QD

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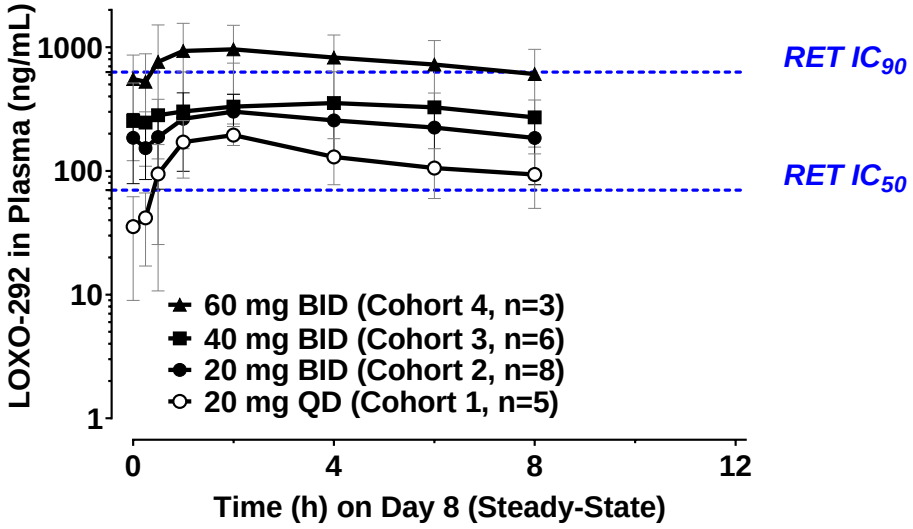
LOXO-292 Phase 1 study in progress

- 28 patients enrolled to 4 dose levels (first patient dosed May 2017)
- No DLTs
- PK dose proportional and consistent with significant RET target engagement



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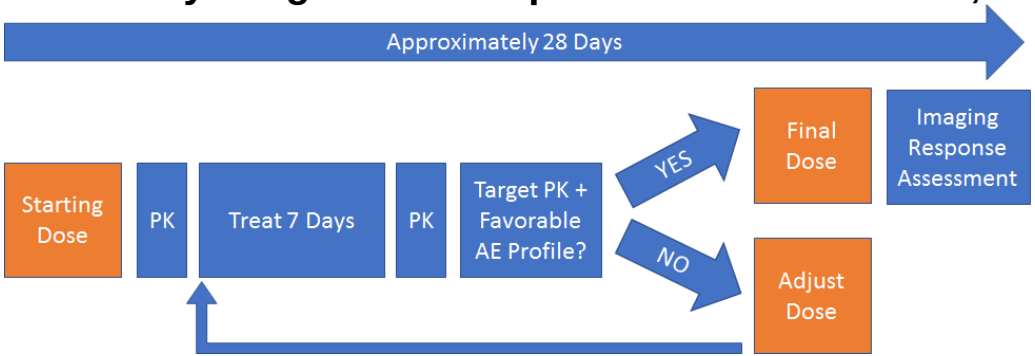
September 27, 2017 data cut-off date, cellular (phospho-RET) IC_{50}/IC_{90} corrected for human plasma protein binding

Patient 1: CCDC6-RET fusion

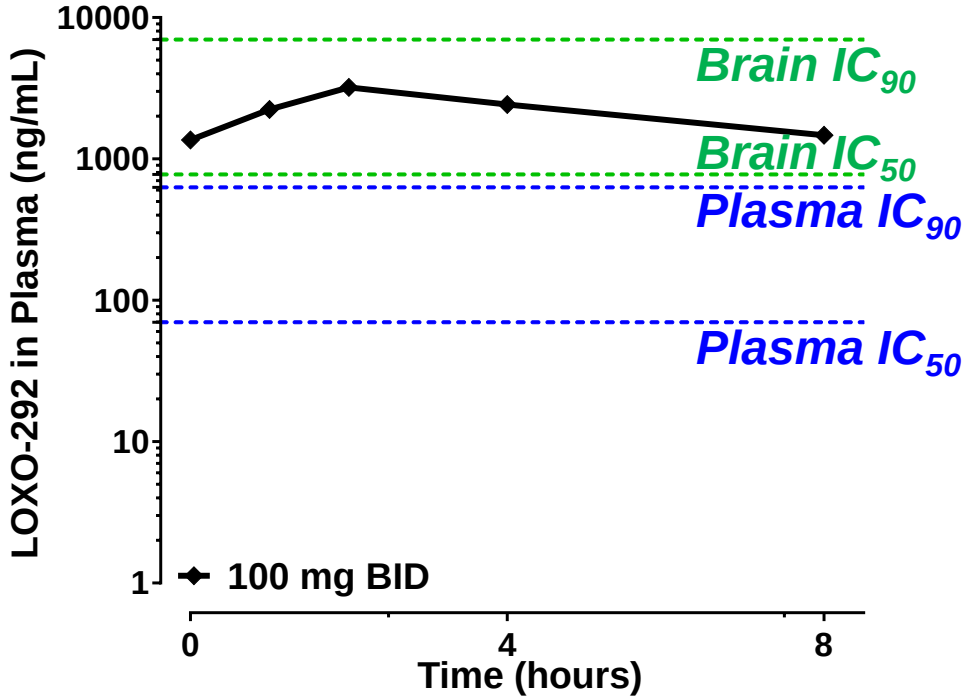
- 63-year old woman with advanced NSCLC: prior surgery, radiation, and chemotherapy
- After identification of CCDC6-RET fusion, received RXDX-105 for 7 months and then progressed
- First LOXO-292 patient treated with RET fusion lung cancer, on Phase 1 trial (20 mg QD)
- Confirmed PR by RECIST 1.1 (-44%) on 20 mg QD, dose escalated to 20 BID and currently 40 mg BID, remains on therapy in month 5

Patient 2: KIF5B-RET fusion

- 40-year old woman never-smoker with advanced NSCLC: 3 lines of chemotherapy, whole brain radiation, anti-PD1 antibody
- After identification of KIF5B-RET fusion, received 600 mg BID alectinib (PR, 7 months), increased to 900 mg BID for progressive brain metastases
- Treated with LOXO-292 under Single Patient Protocol due to symptomatic brain metastases (first LOXO-292 patient treated with RET fusion lung cancer with brain metastases)
- LOXO-292 administered by PK-guided intra-patient dose escalation, 20 mg/60 mg/100 mg BID



Patient 2 pharmacokinetics at current dose



- Patient experienced dramatic clinical improvement
- Neurologic symptoms (memory loss, gait unsteadiness) improved within 7 days
- Confirmed systemic PR (-64%, RECIST 1.1) and CNS response (-89%, RANO-BM)
- Patient remains on therapy in month 4

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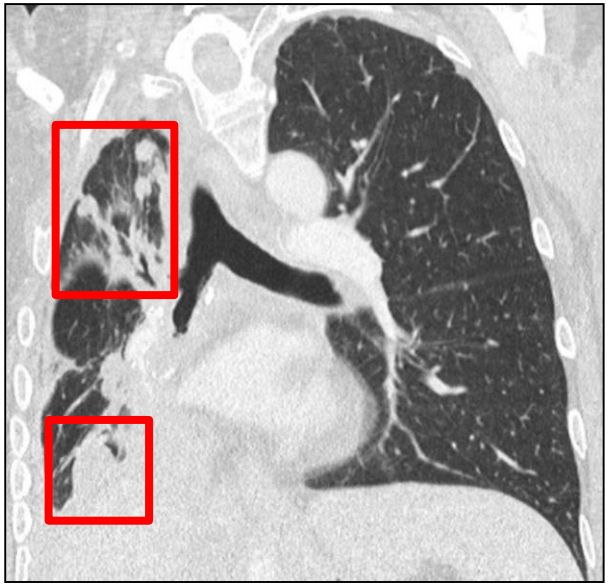
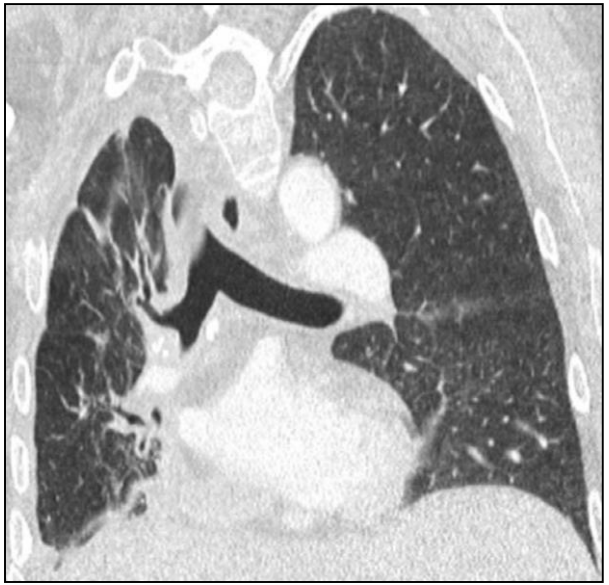
cellular (phospho-RET) IC_{50}/IC_{90} corrected for plasma/brain protein binding and estimated CNS penetration

Systemic tumor response

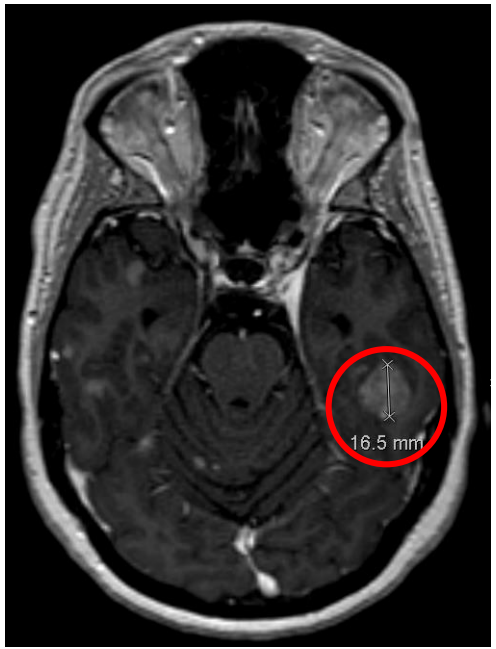


Pre-treatment

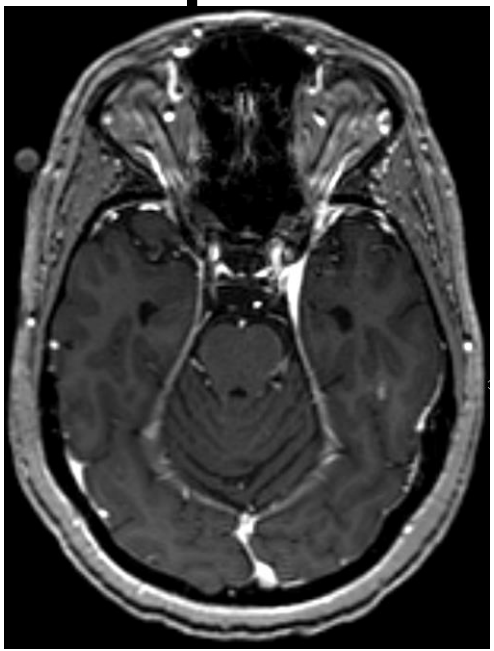


LOXO-292 at 2 mo.

Intracranial tumor response

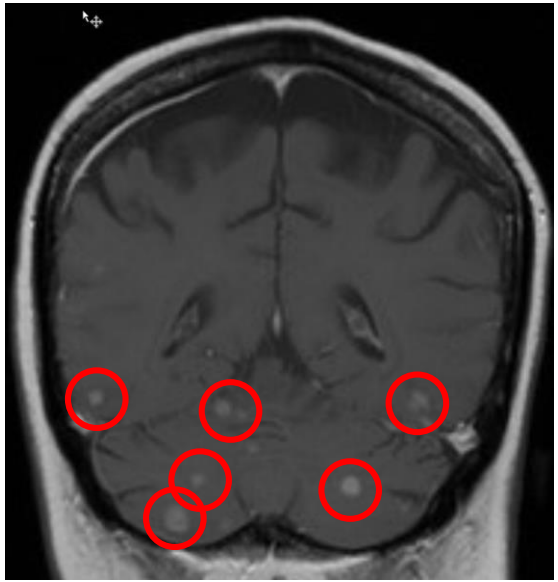


Pre-treatment

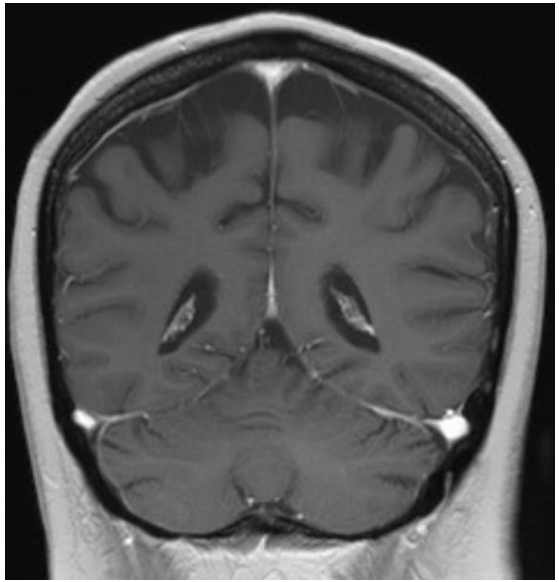


LOXO-292 at 3 mo.

Intracranial tumor response



Pre-treatment



LOXO-292 at 2 mo.

Conclusions

- **LOXO-292: RET inhibition in ongoing Phase 1 trial already greater than multikinase (MKI) inhibitors**
  - **Well-tolerated with no DLTs**
  - **Biologically relevant doses**

- **Proof concept anti-tumor efficacy in patients with RET-fusion NSCLC**
  - **Heavily pre-treated and MKI-experienced patients**
  - **With/without brain metastases**

- **Phase 1 study currently enrolling patients**
  - **855-RET-4-292 (855-738-4292)**
  - **clinicaltrials@loxooncology.com**

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