Clinical response to entrectinib in a patient with NTRK1-rearranged non-small cell lung cancer (NSCLC)

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NTRK gene rearrangements in human malignancies

Ligand-mediated signaling

Fusion oncogene signaling: ligand independent

TrkA/TrkB/TrkC

RAS/RAF/MEK
PLC-γ
PI3K/AKT

NSCLC
NSCLC, GBM
CRC, PTC, AML, DIPG, NBS-HGG, Sarcoma
CRC, Spitz melanoma, Sarcoma
Spitz melanoma
PTC
GBM
NSCLC
Sarcoma
Pilocytic astrocytoma
Pilocytic astrocytoma
DIPG, NBS-HGG
DIPG, NBS-HGG
Salivary gland tumor (incl. Acinic cell carcinoma), Secretory BC, AML, Sarcoma, Nephroma, DIPG, NBS-HGG
DIPG, NBS-HGG
Entrectinib: pan-Trk inhibitor with *in vitro* and *in vivo* activity

<table>
<thead>
<tr>
<th>Target</th>
<th>TrkA</th>
<th>TrkB</th>
<th>TrkC</th>
<th>ROS1</th>
<th>ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50* (nM)</td>
<td>1.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>1.6</td>
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* Biochemical kinase assay

- KM-12 is a human CRC line driven by a constitutively active TrkA fusion: *TPM3-NTRK1*

- Entrectinib potently inhibits TrkA phosphorylation and downstream signaling
- Entrectinib induces *in vivo* tumor regression and durable tumor stabilization

*In vitro*

- 0.5 µM, 2h
- P-trkA (Y490)
- Total TrkA
- P-PLCy (Y783)
- Total PLCy
- P-AKT (S473)
- Total AKT
- P-p42/44 (Thr202/Tyr204)
- Total p42/44

*In vivo xenograft*

- Vehicle
- Entrectinib (15 mg/kg)
MINI30.09 – Clinical response to entrectinib in a patient with NTRK1-rearranged non-small cell lung cancer (NSCLC) - Farago

NTRK1 gene rearrangement in NSCLC patient identified by anchored multiplex polymerase chain reaction

SQSTM1 (NM_001142298)
Chr5:179233388-179265077
Exon number: 6

NTRK1 (NM_001007792.1)
Chr1:156785542-156851642
Exon number: 10

AMP PCR technique described in Zheng et al., Nat Med 2014
Patient characteristics and clinical symptoms

- Male, 45 years old when diagnosed with stage IV (T1bN1M1a) NSCLC, adenocarcinoma histology, in November 2013
  - 30 pack-year cigarette history, quit in 2000
  - Developed progressive disease despite several lines of treatment, including chemotherapy and PD-1 inhibitor
- At the time of enrollment, the patient had ECOG PS 2 with baseline chest wall pain requiring PRN narcotics, dyspnea at rest, and an oxygen requirement of 3L/min by nasal cannula
- Staging head CT demonstrated 15-20 previously untreated brain metastases up to 1.7 cm in diameter
- Enrolled on phase I clinical trial with entrectinib at 400 mg/m² PO daily
- Entrectinib was well tolerated, with possibly related AEs:
  - Dysgeusia, grade 1
  - Paresthesias, grade 1
  - Fatigue, grade 2
- Within three weeks of starting treatment, the patient reported resolution of pain and dyspnea, and no longer required supplemental oxygen
Partial response by RECIST 1.1 at four weeks and ongoing

Baseline (Day -7)  Day 26: -47%  Day 155: -77.3%
Complete response of all brain metastases

Baseline (Day -7)  Day 26  Day 155
Conclusions:

• Entrectinib caused rapid and clinically significant improvement in a patient with NSCLC harboring an NTRK1 gene rearrangement.

• The patient experienced resolution of baseline symptoms related to disease, including pain, dyspnea, and hypoxia.

• Entrectinib was well tolerated with minimal side effects.

• The response is durable and ongoing, with current duration of response 4.1 months.

• Entrectinib caused complete response of previously untreated brain metastases in this patient, indicating potent CNS penetration and activity.

• Entrectinib may be an effective therapy for tumors harboring NTRK gene rearrangements, including those with CNS involvement.