Characterization of TRK fusions and therapeutic response to TRK inhibition in hematologic malignancies

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TRK fusions were among the first kinase fusions discovered

Neurotrophin family of receptors

TRKA (NTRK1) → Pain, thermoregulation

TRKB (NTRK2) → Movement, memory, mood, appetite, body weight

TRKC (NTRK3) → Proprioception

TRK fusions

• Ligand binding domain (LBD) replaced by 5′ fusion partner
• Drives overexpression and ligand-independent activation

TRK uncommonly expressed in normal tissues or cancer
Fusion drives abnormally high expression and activation of TRK kinase domain
TRK fusions now described across diverse cancer types

Occur exclusively to other activating kinase fusions

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Stransky et al. Nat Commun 2014
TRK fusions are targetable alterations

The frequency of TRK fusions in hematologic malignancies is unknown & there are no reports of TRK inhibition in patients with hematologic malignancies.
The frequency and characteristics of TRK fusions in hematologic malignancies are unknown

Case reports of TRK fusions in hematologic malignancies:

- *ETV6-NTRK3* described in AML in 1999 (Eguchi et al. *Blood* 1999)
- *ETV6-NTRK3* described in Ph-like ALL in 2014 (Roberts et al. *NEJM* 2014)

We performed targeted DNA and RNA sequencing across 7311 patients with hematologic malignancies:
1201 AML
744 MDS
659 ALL
23 Histiocytic neoplasms
1859 MM
3345 Other (NHL & HL)

Collaboration with Foundation Medicine Inc.

Identified N=8 patients with *NTRK1, 2, or 3* fusions (0.1%)
TRK fusions in hematologic malignancies

- TPR NTRK1
- LMNA NTRK1
- TFG NTRK1
- ETV6 NTRK2
- ETV6 NTRK3
- UBE2R2 NTRK3
- HNRNPA2B1 NTRK3

Diverse 5' Fusion Partners

Kinase Domain Retained in Each Case
TRK fusions in hematologic malignancies

- Not previously described
- Not previously functionally evaluated

**Interdigitating dendritic cell sarcoma**
- **TPR** NTRK1
- **LMNA** NTRK1
- **TFG** NTRK1

**Erdheim-Chester disease**
- **ETV6** NTRK2
- **ETV6** NTRK3

**AML**
- **UBE2R2** NTRK3

**B-ALL**
- **HNRNPA2B1** NTRK3

**Multiple myeloma**
TRK fusions transform hematopoietic cells

Myeloid (32D)

Lymphoid (Ba/F3)

TRK fusion transforming activity may be dependent on cell lineage/genetic background

Different TRK fusions have distinct potency on signaling
TRK fusion+ Ba/F3 cells are sensitive to TRK inhibition with larotrectinib

**Ba/F3 cells**

- **EV (+IL-3)**: ND
- **LMNA-NTRK1**: 10.7 nM
- **ETV6-NTRK2**: 13.2 nM
- **UBE2R2-NTRK3**: 15.9 nM

**32D cells**

- **EV (+IL-3)**: ND
- **LMNA-NTRK1**: 4.1 nM
- **ETV6-NTRK2**: 13.9 nM
- **UBE2R2-NTRK3**: 1.1 nM
- **HNRNPA2B1-NTRK3**: 22.6 nM

Cell Viability at 72hrs (%) vs. Log [Larotrectinib] (nM)
Generation of an *ETV6-NTRK2* AML patient-derived xenograft (PDX)

*ETV6-NTRK2* expressed in AML only; not CLL
Generation of an *ETV6-NTRK2* AML patient-derived xenograft (PDX)

77yo M with CLL & R/R AML with ETV6-MECOM & ETV6-NTRK2 fusions

Intrafemoral injection 0.2x10^6 cells

NSGS host

2cGy

FACS analysis of engrafted hCD45+ cells

Once hCD45+ reaches >10%

Randomize

LOXO-101

7 Days

Vehicle

7 Days

hCD45+ analysis

7 Days

PM aspirate

Sacrifice for analysis and FACS sorting of hCD45+ cells
ETV6-NTRK2 AML PDX sensitive to TRK inhibition with larotrectinib

% hCD45+ cells

* p<0.05

Days on treatment

% Reads supporting ETV6-NTRK2 Fusion

% Reads supporting ETV6-MECOM Fusion

hCD45 IHC

Vehicle

Larotrectinib

Vehicle

Larotrectinib
Clinical response to larotrectinib in ETV6-NTRK2 AML

- Rapidly rising WBC. Co-morbidities excluded induction chemotherapy, failed decitabine (20 mg/m² x 5d)
- Received larotrectinib 100 mg BID under FDA expanded access program
- Achieved partial remission
- Relapsed due to clone bearing ETV6-MECOM fusion
Clinical response to larotrectinib in *ETV6-NTRK2* AML

Clearance of TRK+ blasts but persistence of TRK fusion-negative blasts
Conclusions

• TRK fusions occur across a variety of hematologic malignancies at low frequencies
• As in solid tumors, TRK fusions are targetable drivers in hematologic malignancies
• There is a need for systematic evaluation for TRK fusions across patients with hematologic malignancies
• Further research is necessary to determine response rates to TRK inhibition in hematologic malignancies
• Further studies need to evaluate the clonality of TRK fusions across cancers and whether this is predictive of therapeutic response to TRK inhibition
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