PUBLICATION SNAPSHOT #5

Dr. Luca Toschi
Humanitas Research Hospital,
Milan, Italy
Please note: Views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author’s academic institution or the rest of NTRK CONNECT group.

This content is supported by an independent educational grant from Bayer.

Disclosures: Dr. Luca Toschi does not have any grant/funding support to disclose.
TRK xDFG MUTATIONS TRIGGER A SENSITIVITY SWITCH FROM TYPE I TO II KINASE INHIBITORS

BACKGROUND: ACQUISITION OF RESISTANCE MECHANISMS

• Acquired resistance to Tyrosine kinase inhibitor (TKI) therapy in patients with fusion-positive cancers can be mediated by on-target and off-target mechanisms
• The acquisition of resistance following tropomyosin receptor kinase (TRK) inhibition is mediated by kinase domain mutations in conserved regions such as solvent front, gatekeeper and xDFG

First-generation TRK Inhibitors
- Entrectinib
- Larotrectinib

Off-target resistance
Potential mechanisms identified
- KRAS mutation
- MET amplification
- BRAF mutation
- IGF1R activation

Acquisition of resistance

On-target resistance
Kinase domain Mutations
- Solvent front
- Gatekeeper
- xDFG
- Other

Second-generation TRK Inhibitors
- Repotrectinib
- Selitrectinib

B-Raf proto-oncogene; IGF1R, insulin-like growth factor 1 receptor
OBJECTIVE OF THE PAPER

Second-generation TRK inhibitors include:
- selitrectinib (selective TRK inhibitor)
- repotrectinib (TRK and ROS1 inhibitor)

Designed to target kinase domain mutations in TRK kinase

Shown clinical activity in NTRK fusion-positive tumours with kinase domain mutation-mediated resistance mechanisms to first-generation TRK inhibitors (larotrectinib and entrectinib)

Resistance mechanisms to second-generation TRK inhibitors have been documented

Understand the mechanism of resistance to second-generation TRK inhibitors

NTRK, neurotrophic receptor tyrosine kinase; TRK, tropomyosin receptor kinase
xDFG MUTATIONS CONFER RESISTANCE TO SECOND-GENERATION TRK INHIBITORS BY AFFECTING DRUG BINDING

ATP-binding site can be inhibited by first- and second-generation TRK inhibitors

ATP, adenosine triphosphate; TRK, tropomyosin receptor kinase; WT, wild-type
Type II inhibitors are required to address acquired-resistance mediated by xDFG mutations to second-generation agents.

First- and second-generation TRK inhibitors are Type I inhibitors.

- Larotrectinib
- Entrectinib
- Selirectinib
- Repotrectinib

Active conformation (DFG-in)

Type I inhibitors

Next-generation TRK inhibitor?

Inactive conformation (xDFG mutations, DFG-out)

Type II inhibitors

TRK, tropomyosin receptor kinase
Current second-generation TRK inhibitors cannot overcome all on-target acquired resistance mechanisms.

First- and second-generation TRK inhibitors are classified as Type I TKI inhibitors, which bind to the active DFG-in conformation of kinases.

xDFG substitutions lead to an inactive DFG-out conformation.
- This limits second-generation TRK inhibitor binding (e.g. selitrectinib and repotrectinib).

However, Type II TKI inhibitors such as cabozantinib, foretinib and ponatinib bind to the inactive DFG-out conformation.

This study provides the rationale for clinical development of Type II TRK inhibitors to overcome acquired-resistance mediated by xDFG mutations to second-generation TRK inhibitors.

Large studies are required to test for xDFG mutations, to validate and investigate additional mechanisms of resistance.

TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase
REACH NTRK CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP’S WEBSITE

http://www.ntrkconnect.info