TRK xDFG mutations trigger a sensitivity switch from type I to II kinase inhibitors


First-generation TRK inhibitors
- Larotrectinib
- Entrectinib

Active conformation DFG-in

Second-generation TRK inhibitors
- Selirectinib
- Repootrectinib

Active conformation DFG-in

Next-generation TRK inhibitors

Inactive conformation xDFG mutations, DFG-out

ATP Binding Pocket

Active conformation of the Trk kinase domain (xDFG WT, DFG-in)

Acquisition of resistance
- 1st

Active conformation (xDFG WT, DFG-in)
Solvent front mutation

Active conformation (xDFG WT, DFG-in)
Gatekeeper mutation

Inactive conformation xDFG mutations, DFG-out

Second-generation TRK inhibitors

1st

Active conformation (xDFG WT, DFG-in)
Solvent front mutation

Active conformation (xDFG WT, DFG-in)
Gatekeeper mutation

Inactive conformation xDFG mutations, DFG-out

Acquisition of resistance
- 1st

1st

1st

Type II TRK inhibitors are needed to address acquired resistance to xDFG mutations

Inactive conformation xDFG mutations, DFG-out

Type I kinase inhibitors

Type II kinase inhibitors

ATP, adenosine triphosphate; TRK, tropomyosin receptor kinase; WT, wild-type

For more information please visit: www.ntrkconnect.info

This content is supported by an Independent Educational Grant from Bayer

December 2020