Tracking TRK

The next generation TRKi are coming up quickly to challenge the initial positioning of Larotrectinib by targeting resistant TRK mutations. However, unlike historical precedence with other targeted therapies, the research is quickly evolving with next gen TRKi to circumvent resistance – upfront or in later lines. Of the several TRK related presentations at AACR, we selected four key presentations that focused on approaches to overcome resistance to first-gen TRKi such as Larotrectinib. Larotrectinib is the first TRKi that obtained a tumor agnostic approval in TRK fusion positive patients, with RR of 81% and mDOR not reached at 17.6 months.

Next Generation TRKi

Data was presented at AACR 2019 with three next gen TRKi that are currently in clinical development – LOXO-195, Repotrectinib and PBI-200 in resistant mutations and are positioning themselves subsequent to the first-gen TRKi (Larotrectinib and Entrectinib). Structural improvements for tighter binding of the next gen TRKi to the ATP pocket binding and avoiding steric clashes make them clinically active in resistant mutations.

LOXO-195 is a second-gene TRKi that is known to be active in all types of resistant mutations – solvent front (SFM), gatekeeper (GK) and xDFG mutations. SFM appear to be the most type of resistant mutation (~45%) acquired with a first-gen TRKi. Another 30% of patients harbor GK, XDFG and other bypass mutations.[1] Approximately 20% of patients had unknown mutations.

- 45% of patients with TRK resistant mutations had responded to LOXO-195, though data in specific subsets of TRK resistant mutations needs to be demonstrated; also, as expected, LOXO-195 was not effective in patients with TRK independent resistant mutations.

Repotrectinib is one such low molecular weight next gen TRKi that claimed activity in patients with diverse resistant mutations.[2]

- When compared to LOXO-195 (second-gen TRKi), it was 10 times more potent against solvent front (SFM, common form of resistance to first-gen TRKi), 100 times more potent against gatekeeper mutations and the only TRKi till date active in compound mutations.
- PR was observed in two Repotrectinib treated patients (metastatic salivary gland tumor and cholangiocarcinoma), who had previously received first-gen TRKi (Entrectinib or Larotrectinib).

PBI-200, as developed by Pyramid Biosciences is moving into the clinic, and is a second-gen TRKi.[3]

It demonstrated higher activity in G595R, G639R, G623R solvent front resistant mutations as compared to first-gen TRKi, Larotrectinib and Entrectinib, besides working in both WT and mutant TRK fusions. Permeability into the BBB has been an issue with Larotrectinib and less with Entrectinib. However, PBI-100 demonstrated several fold increase in brain penetration as compared to the first-gen TRKi and some of the second-gen TRKi such as LOXO-195 and Repotrectinib.

Off-Target Resistant Mutations

It has also been observed that TRK independent mechanisms maybe driving resistance to TRKi. Data from a study, supported by Loxo Oncology, presented some bypass resistant mechanisms that manifested in 6 TRK fusion + GI cancer patients treated with first or second-gen TRKi. These were primarily BRAFV600E mut, KRASG12a or D mutations, MET amp that notably converged on the ERK signaling pathway.[4]

- Preclinical study in the PDX models (derived from patients with BRAFV600E mutations) with LOXO-195 and Trametinib (MEKi) combination was effective in tumor growth inhibition and also the growth of resistant mutant cell lines.

Future Direction:

- The rapid evolution of the next gen TRKi shows potential to form a continuum of care for TRK fusion patients progressing on first-gen TRKi. Rational TRKi combination therapies in TRK dependent and independent resistant mutations should be explored further.

Sources:

1. Hyman David, Abstract CT127, AACR 2019
2. Drilon Alexander, Abstract 442, AACR 2019
3. Pal Kollol, Abstract 2198, AACR 2019
4. Cocco Emiliano, LB-118, AACR 2019

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