Medscape EDUCATION

NTRK Gene Fusions in Thyroid Cancer: From Molecular Diagnosis to Targeted Treatment

Introduction

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are rare in thyroid cancer. They typically exhibit a specific histology which is predominantly a follicular growth pattern or a mixed follicular-papillary growth pattern. Detecting tumors with these fusions with comprehensive genomic testing is crucial because they respond well to targeted therapy with tropomyosin receptor kinase (TRK) inhibitors, such as larotrectinib, entrectinib, and repotrectinib which are effective and well-tolerated.[1-4]

Molecular Testing for *NTRK* Gene Fusions

- *Detection Methods: NTRK* gene fusions can be identified using **immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), real-time PCR (RT-PCR), and next-generation sequencing (NGS).**[5]
- While **NGS** allows **comprehensive analysis, limited access and high costs** often necessitate combining IHC, FISH, and RT-PCR in practice.[5]
- **Accurate testing** is essential to guide treatment and ensure eligible patients receive effective targeted therapies.[6]

Efficacy and Safety of TRK Inhibitors in *NTRK* Fusion–Positive Thyroid Cancer

TRK Inhibitors/Mechanism	Clinical Trial Outcomes of Efficacy and Safety
Larotrectinib: First generation, highly selective TRK inhibitor with CNS activity[7]	• In phase 1/2 trials of TRK fusion–positive solid tumors, it showed an overall response rate (ORR) of 79%, including 79% in thyroid cancer.[7] • A matched real-world study showed longer overall survival compared to standard of care (hazard ratio 0.44).[8] • Grade ≥ 3 adverse events were reported in 13% of patients. (Most common: increased ALT, anemia, and decreased neutrophil count)[7]
Entrectinib: First generation, potent TRK, ROS1, and ALK inhibitor with CNS penetration[3]	• In phase 1/2 trials, it demonstrated an ORR of 61.2% overall and 53.8% in thyroid cancer. • Grade ≥ 3 adverse events occurred in 41.5% of patients. (Most common: weight gain, anemia, and fatigue)[3]
Repotrectinib: Next-generation pan-TRK, ROS1, and ALK inhibitor with efficacy against resistance mutations (solvent front and gatekeeper mutations)[4]	• In phase 1/2 trials, ORR was 59% in TKI-naïve and 48% in TKI-pretreated patients, with thyroid cancer response rates of 100% and 28.6%, respectively. • Grade ≥ 3 adverse events were reported in 43% of patients. (Most common: anemia, dyspnea, pneumonia, blood creatine phosphokinase increased, weight gain)[4]

ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; CNS, central nervous system; ROS1, c-ros oncogene 1; TRK, tropomyosin receptor kinase.

References

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