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TARGETED THERAPY

Larotrectinib effective against TRK-fusion-positive cancers

Gene fusions, owing to various genomic rearrangements, are attractive targets for highly selective anticancer drugs and are the targets of various FDA-approved agents. Now, the findings of a 'basket' trial involving a cohort of children or adults with one of 17 different types of cancer harbouring a tropomyosin kinase (TRK)-containing fusion reveal remarkable levels of responsiveness to the TRK1–3 inhibitor larotrectinib.

Explaining the histology-agnostic approach used, lead author David M. Hyman states, "unlike many oncogenic fusions, TRK fusions are typically rare events across a variety of cancers, with the exception of some very rare paediatric cancers," adding, "it was really only with the maturation of clinical-grade, highly multiplexed next-generation sequencing assays capable of identifying TRK fusions at the point of care that clinical programmes targeting this set of orphan oncogenes became possible."

Results from 55 prospectively identified and consecutively enrolled TRK-fusion positive patients were originally obtained in three separate trials; data on safety and efficacy from these three cohorts were incorporated into a single analysis. All patients had locally advanced or metastatic solid tumours, and had previously received the standard-of-care treatment. Secretory carcinoma of the salivary gland was the most common histological cancer type, in 12 patients, although patients with TRK-fusion-positive tumours of the colon, lung, and thyroid, among others, were also included in the cohort. Notably, 75% of patients had an objective response to larotrectinib monotherapy as confirmed by independent blinded review, including a complete response in 7 patients (13%) and a partial response in 34 (62%). In total, 86% of patients with an initial response either continued to receive treatment or had undergone surgery with a curative intent at the primary data cut-off.

No treatment-related grade 3 adverse events ocurred in >5% of patients. Ten patients developed acquired resistance to larotrectinib. Follow-up investigations revealed the presence of mutations in NTRK in all patients with samples available on progression, including *NTRK3*^{G623R} and its paralogue *NTRK1*^{G595R} in the kinase domain, *NTRK1*^{F589L} in the gatekeeper position, and *NTRK1*^{G667S} and *NTRK3*^{G696A} in the kinase-activation loop. The authors note that the next-generation TRK inhibitor LOXO-195, which is currently in clinical development, has the potential to overcome this mechanism of resistance.

Hyman summarizes: "These data demonstrate that larotrectinib is highly effective in TRK-fusion positive cancers, regardless of cancer type or the age of the patient," highlighting, "these data are expected to form the basis of global approval of larotrectinib for TRK-fusion-positive cancers across all cancer types and patient ages."

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ORIGINAL ARTICLE Drilon, A. *et al.* Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N. Engl. J. Med.* **378**, 731–739 (2018)