Pharmacologic targeting of specific genomic alterations has led to dramatic clinical successes in several molecularly defined cancer subtypes and has created the potential for a paradigm shift by which patients might be characterized and treated according to the molecular profile of their tumor, rather than their classic tumor type. Still, most successful targeted therapies to date have typically followed a traditional disease-specific drug development track, progressing through phase I, II, and III studies in a specific tumor type in which that alteration is predominant. Notable examples include EGFR inhibitors in EGFR-mutant lung cancer, BRAF inhibitors in BRAF-mutant melanoma, HER2 antibodies in HER2-amplified breast cancer, and ABL kinase inhibitors in BCR–ABL-rearranged chronic myeloid leukemia (1).

However, large-scale genome-discovery efforts, such as The Cancer Genome Atlas (TCGA), have identified a growing “long tail” of low-frequency targetable molecular alterations (2), and drug development for these important but rare molecular targets presents unique challenges, particularly when such targets are present across diverse cancer types. The traditional approach to drug development is not practical in this setting, as limited patient numbers preclude the ability to perform multiple randomized trials against disease-specific standards of care. Thus, several innovative approaches have been required to accelerate the development of drugs for rare molecular drivers across diverse tumor types, including “basker” trial designs, which incorporate disease-specific cohorts of patients with a common molecular target (3). More recently, a tissue-agnostic approach has gained momentum, particularly when the rarity of a molecular feature makes disease-specific groupings impractical. Recently, the FDA issued its first tissue-agnostic approval of the anti-PD-1 antibody pembrolizumab for microsatellite instability across all tumor types. Furthermore, identifying mechanisms of acquired resistance, which inevitably limit all targeted therapies, and eventually developing approaches to overcome them, creates an even more daunting challenge due to the rarity of these events in an already limited patient population. Thus, optimizing our approach to drug development for rare molecular targets may necessitate a dramatic change in the current paradigm.

Fusion events involving the neurotrophic tyrosine receptor kinases NTRK1, NTRK2, and NTRK3 represent one such class of rare molecular targets, which have been identified across many tumor types at low incidence (2). TRK inhibitors, such as larotrectinib, have been in development over the last several years and have demonstrated the ability to produce durable responses in patients with TRK fusion–positive cancers (4, 5). Given the rarity of TRK fusions and their presence at low frequency in multiple cancer types, a unique drug development strategy was undertaken for larotrectinib, which was tested in TRK fusion–positive cancers across all solid tumor types and was also simultaneously evaluated in adult and pediatric populations. Larotrectinib was recently reported to produce a confirmed response rate of 76% in 50 patients across 17 different tumor types and showed significant durability of response, with 75% of patients remaining on treatment or undergoing curative intent surgeries (5). This innovative strategy and the remarkable clinical efficacy observed could pave the way for a tissue-agnostic approval of this compound in TRK fusion–positive cancers.

However, as with most targeted therapies, clinical benefit is limited by the eventual emergence of acquired resistance to therapy. Prior studies have demonstrated that secondary resistance mutations in the TRK solvent front, such as the TRKA G595R and G667C mutations and the TRKC G623R mutation, can drive acquired resistance in patients and preclinical models by impairing the binding of larotrectinib and other TRK inhibitors (6, 7). Analogous secondary mutations in other kinase fusion paradigms, such as ALK fusion–positive lung cancer and FGFR2 fusion–positive cholangiocarcinoma, have been demonstrated to cause acquired resistance, but next-generation kinase inhibitors can be developed to overcome these alterations (8, 9). However, the development and clinical evaluation of next-generation inhibitors is typically undertaken sequentially, but this standard approach may not be feasible in such a rare patient population.
In this issue of Cancer Discovery, Drilon and colleagues report the development of and initial clinical experience with a next-generation TRK inhibitor, LOXO-195, specifically designed through structural modeling to overcome the secondary solvent front mutations that promote acquired resistance to larotrectinib and other TRK inhibitors (10). Importantly, utilizing an approach that is largely unprece-dented to date, LOXO-195 was developed in parallel with its first-generation predecessor, larotrectinib, and was available for evaluation in the same group of patients in which larotrectinib was being assessed upon disease progression in anticipation of acquired resistance. This innovative and dynamic approach provides a compelling and cutting-edge proof-of-concept design that can serve as a blueprint for drug development in rare molecular subtypes going forward.

Typically, standard initial drug development requires a conservative 3 + 3 dose escalation design to safely and slowly determine the MTD. Although it has a straightforward design, this process requires a large number of patients to establish dose and thus represents an inefficient and ineffective study design for rare molecular tumor subsets. Using this standard, sequential development approach for next-generation drugs to overcome resistance can take years and would eliminate the potential opportunity for the initial larotrectinib patient cohort to benefit from this next-generation therapy. Therefore, to circumvent these obstacles and to provide this rare patient population with access to LOXO-195 after larotrectinib failure, the investigators employed an innovative, FDA-allowed single-patient protocol with accelerated intrapatient dose escalation guided by real-time pharmacokinetic (PK) assessment. Under this schema, patients were treated with a starting dose of LOXO-195, with rapid PK assessment performed after 7 days of dosing, and the dose was increased if PK assessments were below the target threshold and no unacceptable toxicity was observed. This approach allowed patients to reach an effective drug exposure within weeks of initiating therapy and had the added benefit of providing each patient with a PK-optimized dose, whereas use of an MTD determined through standard 3 + 3 design is thought to leave many patients at subtherapeutic doses (11).

In this study, the investigators treated two patients with LOXO-195 using this accelerated intrapatient dose-escalation approach, in whom secondary TRK solvent front mutations were identified upon larotrectinib progression by tumor and/or liquid biopsy. The first patient was an adult patient with a colon cancer harboring a LMNA–NTRK1 fusion, who was found to have TRKA(G595R) mutations as a resistance mechanism to larotrectinib. After initial dosing with LOXO-195, the patient’s drug exposure upon initial PK assessment was below the target IC_{50}, and therefore the dose was escalated in real time. The patient achieved rapid clinical benefit and was found to have an initial 38% decrease in tumor burden that has remained durable for at least 6 months. Circulating tumor DNA was analyzed during therapy, and the mutant allele fraction of the G595R mutation resistance in the blood decreased to undetectable levels after 2 weeks of treatment, consistent with the clinical response. The second patient, a pediatric patient with an ETV6–NTRK3-positive infantile fibrosarcoma, was found to have a G623R mutation homologous to TRKA(G595R), and was also treated under a single-patient protocol, with two PK-driven dose escalations resulting in target drug exposure by 3 weeks. The patient experienced an initial clinical and radiographic tumor reduction for 3 months, but ultimately developed new sites of disease and passed away due to respiratory distress. Although evaluation of LOXO-195 in a larger number of patients with secondary TRK mutations will, of course, be needed to assess the efficacy of this agent, these initial clinical data are highly promising and provide an early and important proof of concept.

This study illustrates an innovative and dynamic clinical trial approach for the simultaneous development of a first-generation and next-generation kinase inhibitor in parallel for a rare molecular target. With rare patient populations, it is even more critical to learn as much as possible from each patient treated on a clinical trial to gain mechanistic insight into the determinants of response and resistance and to accelerate the development of next-generation strategies. In this way, robust correlative studies are key for such trials, and prior studies that incorporated tumor and liquid biopsies to identify initial mechanisms of acquired resistance in early patients treated with first-generation TRK inhibitors were indispensable for the design and development of LOXO-195 (6, 7). By developing a next-generation inhibitor in parallel within the same population of patients receiving the first-generation inhibitor, the investigators were able to accelerate proof of concept of a strategy to overcome acquired resistance and have provided patients receiving larotrectinib the important opportunity for potential benefit from a next-generation therapy through an innovative single-patient PK-guided protocol that is highly appropriate for this rare tumor agnostic molecular target. Had a standard clinical trial design and dose escalation strategy been used, it is unlikely that these patients would have had immediate access to LOXO-195.

Overall, this study provides a compelling example of how cutting-edge trial design can accelerate the pace of clinical development for rare molecular targets, and the strategies outlined herein can serve as a valuable precedent to guide the future development of agents for other rare molecular subtypes of cancer.

Disclosure of Potential Conflicts of Interest

R.B. Corcoran reports receiving commercial research support from Sanofi and AstraZeneca and is a consultant/advisory board member for Astex, Avidity Biosciences, Amgen, Genentech, Merrimack, Roche, BMS, Shire, and N-of-One. A.R. Parikh is a former employee of Genentech.

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