laxis with pneumatic compression, graduated stockings, or both. Thus, it is possible that even high-risk patients would have acceptably low rates of thromboembolism if mechanical prophylaxis were combined with the medical regimens used in the EPCAT II trial.

With respect to postoperative bleeding, the results suggest that starting on postoperative day 6, low-dose aspirin was as safe as (but not safer than) low-dose rivaroxaban. The bleeding rates in the two groups were at the low end of the previously reported range among patients receiving low-molecular-weight heparin,[5] perhaps partly because more than 50% of the patients received perioperative tranexamic acid, an antifibrinolytic agent that helps maintain hemostasis. The trend toward higher bleeding rates among the patients who continued long-term aspirin therapy in addition to trial-assigned aspirin serves as a reminder that, whenever possible, we should use daily aspirin doses of less than 100 mg. Going forward, the very low rates of bleeding and thrombosis seen with the relatively inexpensive and user-friendly aspirin-based strategy probably mean that the EPCAT II trial has established a prophylaxis regimen against which all strategies to prevent venous thromboembolism after joint replacement will be compared.

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Developing Anticancer Drugs in Orphan Molecular Entities — A Paradigm under Construction

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Genomic characterization of cancers has shown that some oncogenic alterations occur at very low frequency and are shared across tumor types. For example, *NTRK* translocations mediate malignant transformation and are observed in less than 1% of cancers and in more than 20 cancer types.[1] The genes *NTRK1*, *NTRK2*, and *NTRK3* encode for the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, respectively. In this issue of the *Journal*, Drilon et al.[2] report a pooled analysis of three prospective clinical trials testing larotrectinib, a TRK inhibitor, in 55 patients. The overall response rate was 80%, and 71% of the responses were still ongoing at 1 year. The authors used a noncomparative, genomic-driven, single-group trial across tumor types to change practice. This study is an illustration of what is likely to be the future of drug development in rare genomic entities (Fig. 1).

Although not specific to rare genomic segments, drug development that is based on single-group trials is particularly adapted to rare clinical scenarios with well-established natural histories. Indeed, because rare genomic segments are defined by a genomic alteration that drives cancer progression, they usually have high sensitivity to targeted therapies. In addition, the low incidence of these genomic segments makes randomized trials challenging. For example, a single-group trial led to the regulatory approval of combination therapy with dabrafenib and trametinib in patients with non–small-cell lung cancer expressing a *BRAF* V600E mutation, an alteration observed in 1% of lung adenocarcinomas.[5]

In line with this pathway for approval from regulatory agencies, the European Society of Medical Oncology has developed a Magnitude of Clinical Benefit Scale that is dedicated to single-group trials.[3] According to this scale, studies that show rates of objective response of more than 60% and a median progression-free survival of more than 6 months, as the study con-

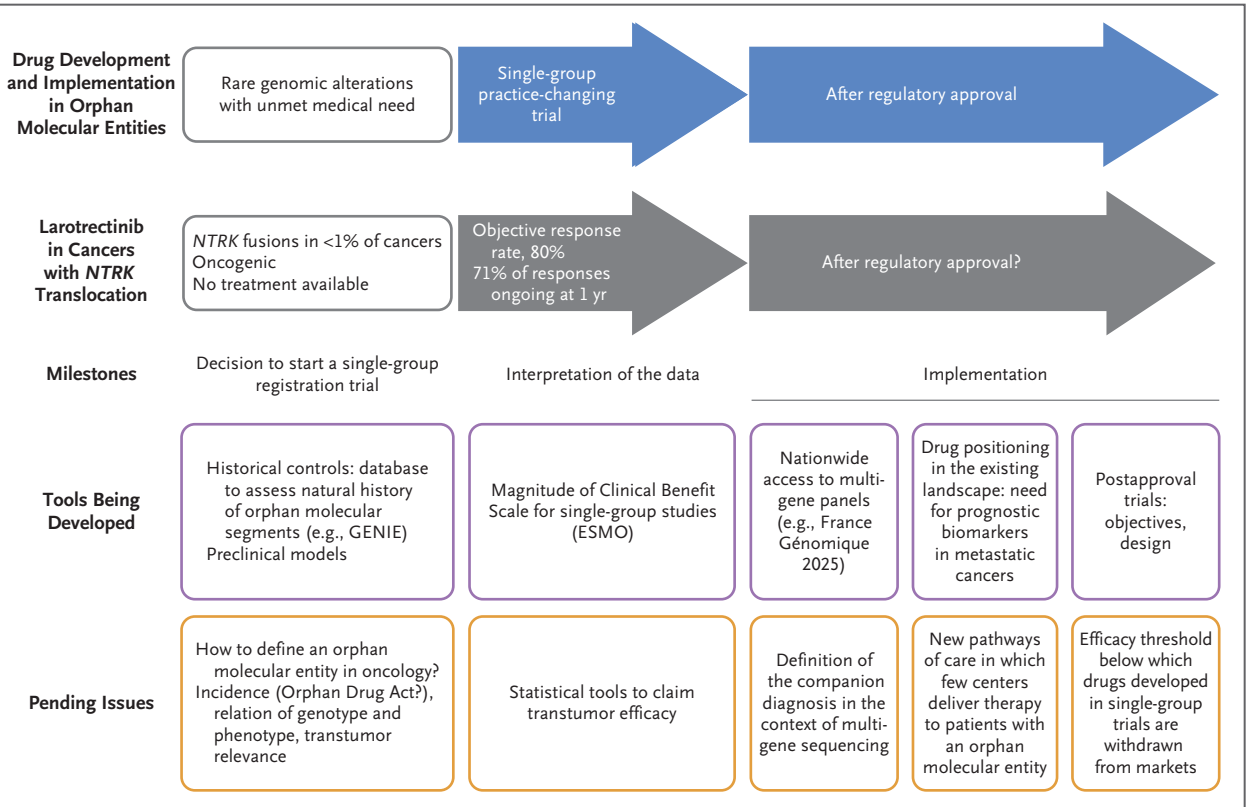

Figure 1. Future of Drug Development in Rare Genomic Entities.

The study by Drilon et al.[2] exemplifies the likely future of drug development in rare genomic entities. Shown is how the development of larotrectinib is integrated in the flow of drug development and the current challenges in the field of orphan molecular entities in oncology. The Genomics Evidence Neoplasia Information Exchange (GENIE) project has developed a clinical and genomic database that includes more than 50,000 patients. According to the Magnitude of Clinical Benefit Scale from the European Society of Medical Oncology (ESMO),[3] single-group studies that show rates of objective response of more than 60% and a median progression-free survival of more than 6 months are considered to have the highest magnitude of clinical benefit.[4] The incidence below which a genomic segment is considered to be rare is unclear. To address this issue, the definition of orphan disease according to the Orphan Drug Act could be adopted.

ducted by Drilon et al. does, are considered to have the highest magnitude of clinical benefit. From a professional perspective, a change in practice on the basis of single-group trials requires knowledge about the natural history of the disease. To address this question, the research community is currently developing large clinical and molecular data sets to provide baseline data that studies about new therapies need to improve on. For example, the Genomics Evidence Neoplasia Information Exchange (GENIE) project of the American Association for Cancer Research has developed a clinical and genomic database that now includes more than 50,000 patients.[4]

The second change led by the emergence of orphan molecular entities is the development of drugs across the tumor types that share the same alteration. For such development, investigators use "basket" trials (i.e., trials that include patients with various histotypes that have the same molecular alteration). In the study conducted by Drilon et al., 12 different tumor histotypes were included. The authors did not find any difference in efficacy among the histotypes that are commonly associated with *NTRK* fusions (e.g., salivary-gland tumor, sarcoma) and the other histotypes. Although this trans-tumor approach was successful in the case of *NTRK* fusions with larotrectinib, or in the case of mismatch repair–microsatellite instability with anti–programmed death 1 antibodies,[6] it is important to mention that some basket trials have not shown evidence of trans-tumor efficacy of targeted therapies, notably BRAF inhibitors.[7] Some challenges for the future of trans-tumor trials

include the development of statistical tools to support a claim that a drug works across tumor types and a more in-depth understanding of the failure of some targets in a trans-tumor approach. When the clinical development is successful, this leads to the creation of new diagnoses and subsets of diseases that are defined according to biomarkers and no longer according to histologic classification.

A key determinant for the success of genomic-driven drug development is the robustness of the companion diagnostic testing. Companion diagnostic testing used to involve a single test for each molecular alteration. This model is no longer useful, since each patient must be tested for a large number of rare genomic alterations. Instead of a large number of assays being used for each patient, it has been proposed that clinicians test a large number of genomic alterations in a single assay — a proposal made feasible by next-generation sequencing.[8] In the present trial, *NTRK* translocations were detected by multigene sequencing in 50 of 55 patients. The next challenge in the field of precision oncology will be to reconcile the concept of companion diagnostic testing with the use of multigene panels. A first step in this direction was the recent approval by the Food and Drug Administration of a multigene panel to detect multiple gene mutations for lung cancer in a single test of a single tissue specimen.[9] The long-term vision in this field could be to develop analytic guidelines for each genomic alteration, from the nucleotide to the variant call, that can be implemented in any sequencing platform. A second challenge in the field of diagnostic technologies will be to implement RNA sequencing as a screening tool to capture the expression of variants and to detect gene fusions better.

The effective implementation of treatment advances in orphan molecular entities will require the unlocking of several barriers. First, there is a need to provide broad access to genomic tests. Several countries, such as France and the United Kingdom, have launched nationwide programs.[10] Second, there is a need to consolidate efficacy data in postapproval studies with large sample sizes. Third, in diseases for which conventional treatments are available, the appropriate positioning of the precision medicine strategies in the treatment landscape will have to be defined. To this end, molecular assays must be developed to identify patients early in their disease course who have disease that will be refractory to conventional therapies. Finally, second-generation and third-generation inhibitors will need to be developed to overcome resistance. These four considerations could lead to a model of care in which molecular testing is done in a large number of centers and in which patients with orphan molecular entities are referred to a few expert centers that could run the relevant research protocols.

To address the challenge of orphan molecular segments such as *NTRK* fusions, the oncology community must pursue innovative trial designs, implement new biotechnologies for diagnosis, and radically change the current pathways of care. The major unknown factor in this field is how many other orphan molecular entities will meet the same therapeutic success as the one observed with larotrectinib. Finally, since these alterations are rare, there is a need for a global effort. This implies harmonization among regulatory agencies across the world and an expansion of global trials.

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