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Editorial

EDITORIAL

N of 2 Responders With LMNA-NTRK1

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With recent advances in molecular profiling, the ability to search for drivers of tumor promotion, propagation, and metastasis becomes almost pedestrian. In this setting, finding these molecular abnormalities allows opportunities to search for targeted treatment. One of the earliest success stories was using imatinib to target *BCR-ABL* translocation in CML (1). This story expanded to gastrointestinal stromal tumors using the same drug but a different target. On the other hand, some targets do cross histologies, as in the case of overexpression/amplification of *ERBB2* in breast and gastric or gastroesophageal cancers (2,3). For these interesting common targets, many agents with unique characteristics have been developed, for example, PARP inhibitors for tumors with *BRCA*1/2 mutations (4). Despite these successes, the field is still in infancy. The first step in the growth of precision medicine is the identification of a molecular abnormality.

This journal contains two reports of an *LMNA-NTRK1* rearrangement in different histologies, metastatic colorectal cancer and congenital infantile fibrosarcoma, which were treated successfully with different TRK inhibitors (5,6). The first step is the cognition of the abnormality. In both cases, exploratory molecular assays were used to identify novel gene fusions that resulted from chromosomal rearrangements in the *NTRK1* gene. Sartore-Bianchi and colleagues first observed elevated levels of *TRK1* protein by immunohistochemistry as well as an unexpected fluorescence in situ hybridization (FISH) pattern. They then employed RNA-based 5' rapid amplified cDNA end (RACE) to identify Lamin A as the 5'partner gene and the junction region. Wong and colleagues used DNA- and RNA-based probe captured NGS assays (Foundation Medicine) to sequence the coding regions of targeted cancer genes and intron regions known to be rearranged in different types of cancer. While both approaches were obviously successful in identifying the *LMNA-NTRK1* gene fusion, the RNA-based method takes advantage of overexpression and spliced partner genes' exons in transcripts and avoids complications resulting from numerous break points at the DNA level.

Recently, the rate at which gene fusion mutations in various types of cancers have been discovered has increased exponentially (7). Chromosomal rearrangement–causing gene fusions, especially to tyrosine kinase driver genes, have become important drug targets, for example, crizotinib for *ALK* and *ROS1* fusions (8,9) and trametinib for *BRAF* fusions (10). In addition, gene fusions resulted from exon skipping, ie, EGFRvIII and MET exon 14 skipping, have been shown to be good drug targets (11,12). As demonstrated in the two reports here, identification of those gene fusion variants and consequent application for clinical use depends heavily on molecular diagnostic assays. While 5' or 3' RACE work in a single drive gene model, an NGS-based approach that enables identification of novel 5' or 3' partner genes fused with driver genes is also available (FusionPlex NGS assay, Archer DX). This approach uses a multiplex platform to detect the fusion in a panel of common driver genes, accelerating the process of identifying unknown fusion partners. On the other hand, when high sensitivity and fast turnaround time are important for screening patients with known gene fusions, the amplicon-based sequencing approach targeted to a predefined gene fusion panel (ie, 271 unique fusions in the Oncomine Focus RNA fusion panel, ThermoFisher) would be more suitable. Using this amplicon sequencing approach, it is also possible to screen the gene fusion variants using circulating exosome RNA samples.

Although the identification methods of the *LMNA-NTRK1* gene fusion reported in this journal are slightly different, the responses to entrectinib, a pan TRK, ROS1, and ALK inhibitor and crizotinib, an ALK inhibitor with activity against NTRK1, implies that the proteins encoded by these gene fusion transcripts are a driving force in tumor progression. The willingness of Wong and colleagues to explore other possible genomic abnormalities outside of the expected *ETV6-NTRK3* or *DFSP-PDGFRB* fusions led to the discovery of the new *LMNA-NTRK1* fusion and consequently clinical benefit to their patient. Sartore-Bianchi and colleagues followed the observation that NTRK1 protein levels were increased to find the *LMNA-NTRK1* fusion. These "N of 1" cases are vital to the advancement of oncologic care—choice of treatment was determined after the driver mutation was identified. The National Cancer Institute's Exceptional Responder

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Initiative, in which patients who had unexpected responses to standard or investigational treatment consent to having their tumor tissue interrogated for the molecular changes that may explain the unexpected response (ClinicalTrials.gov Identifier NCT02496195), searches for "N of 1" incidence going from response to identification of driver mutation.

With the identification of driver mutations, the next step is to test the theory with agents that target those mutations. As screening for rare or new mutations one at a time is impractical, the ideal approach is to screen for multiple mutations at the same time. To adequately serve participating patients, a large number of agents with differing targets would have to be made available. Many basket trials have been initiated recently, the largest being NCI-MATCH, a multiple-arm phase II trial designed specifically to explore less prevalent mutations in patients with advanced cancers (ClinicalTrials.gov Identifier NCT02465060).

Recent advances in technology that allow identification of molecular changes and the analysis of large volumes of data as well as clinical trials designed to interrogate well-defined targeted agents are providing fertile ground for the development of precision medicine. One of the most vital elements is data sharing among investigators as evidenced in the reporting of the two *LMNA-NTRK1* rearrangements in this Journal.

Note

The authors have no conflicts of interest to declare.

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