The Oncologist®

Editorial

Understanding the Precision in "Precision Medicine"

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In this issue of ***The Oncologist***, we begin a series of articles that consider the often problematic challenge of understanding and applying genomic information to the practice of oncology. Bardia et al. [1] describe the genomic findings from a patient with estrogen receptor (ER)-positive breast cancer after progression on hormonal therapy. In this case, tumor profiling revealed an ESR1 mutation that conferred constitutive receptor activation. The authors discuss the significance of this mutation within the spectrum of hormonal resistance and its implications for further therapy.

The past decade has produced an explosion of such information about the mutations, translocations, and amplifications that drive tumor growth and promote drug resistance. Some of these changes can be exploited as targets for new therapies, and the list of "targeted agents" available to the practicing oncologist will soon surpass 100, as 15–20 new drugs are given marketing indications each year. Many cancer centers as well as industrial vendors offer tumor genomic platforms, and these results are increasingly available to oncologists in the community as well as those in academic practices. The use of such platforms is now routine for many metastatic epithelial tumors, such as lung, melanoma, colon, thyroid, prostate, and breast cancers.

The interpretation of these results in some cases is relatively straightforward. A V600E *BRAF* genetic mutation in a patient with metastatic melanoma calls for a *BRAF* kinase inhibitor backbone, nowadays in combination with a MEK inhibitor [2], whereas an EML-4 ALK translocation in lung cancer is best treated with one of several approved ALK tyrosine kinase inhibitors [3]. However, for many patients with the same mutations in tumors of other histology, or for tumors having unusual genomic findings, the implications of these tests may not be obvious [4–6]. To understand genomic reports and make appropriate clinical decisions, the oncologist must understand the language of genomics, the techniques used to discover genomic variants, and the importance of test results. The best way to achieve this understanding is to use the case method. In our new series, led by Dr. Aditya Bardia, we will recruit papers from leading genomic centers to present interesting, teachable cases and interpret the molecular findings regarding implications for prognosis and therapy selection for a general oncologist.

Underlying this new effort is this editor's conviction that genomic medicine is neither totally precise nor completely rational at this point in its development; collective sharing of findings and experiences among institutions will help improve the precision of precision medicine. We increasingly understand that the drugs are not "precisely" targeted. We have learned that targeted agents have multiple sites of action and unanticipated side effects. New generations of drugs, such as the new series of PI3K and EGFR inhibitors, reduce side effects and narrow their spectrum of action. In addition, the multiplicity of mutations in a single tumor and clonal evolution of tumors at different metastatic sites lead to further imprecision in treatment planning. Analysis of circulating tumor cells and cell-free, circulating DNA may provide a more complete picture than a single biopsy [7, 8]. At the heart of our dilemma is the need to understand and plan for the rational treatment of cancer based on new technology and a more complete genomic profile, to maximize therapeutic efficacy while minimizing toxicity, and thus achieving one day a truly precise practice of oncology. To facilitate communication between practicing oncologists and laboratories, we have initiated this series; at the same time, we solicit our readers' comments and contributions to the goal of integrating genomics into the practice of cancer medicine.

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References

1. Bardia A, Iafrate JA, Sundaresan T et al. Metastatic breast cancer with *ESR1* mutation: Clinical management considerations from the Molecular and Precision Medicine (MAP) Tumor Board at Massachusetts General Hospital. ***The Oncologist*** 2016;21:1035–1040.

2. Long GV, Weber JS, Infante JR et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol 2016;34:871–878.

3. Castellanos EH, Horn L. Re-evaluating progression in an era of progress: A review of first-and-second-line treatment options in anaplastic lymphoma kinase-positive non-small cell lung cancer. ***The Oncologist*** 2016;21:755–761.

4. Jänne PA, Yang JC, Kim DW et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689–1699.

5. Kwak EL, Ahronian LG, Siravegna G et al. Molecular heterogeneity and receptor co-amplification drive resistance to targeted therapy in MET-amplified esophagogastric cancer. Cancer Discov 2015;5:1271–1281.

6. Soucheray M, Capelletti M, Pulido I et al. Intratumoral heterogeneity in EGFR-mutant NSCLC results in divergent resistance mechanisms in response to EGFR Tyrosine kinase inhibition. Cancer Res 2015; 75:4372–4383.

7. Sarioglu AF, Aceto N, Kojic N et al. A microfluidic device for label-free, physical capture of circulating tumor cell clusters. Nat Methods 2015; 12:685–691.

8. Sacher AG, Paweletz C, Dahlberg SE et al. Prospective validation of rapid plasma genotyping for the detection of EGFR and KRAS mutations in advanced lung cancer. JAMA Oncol 2016 [Epub ahead of print].