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Issues in Combination Cancer Therapies With Immune Checkpoint Inhibitors

BY PEGGY EASTMAN

The development of immune checkpoint drugs such as PD-1/PD-L1 inhibitors has been explosive, and they now represent the majority of new or supplemental oncology drug applications to the FDA.

Recognizing there is strong interest in combining checkpoint inhibitors with other therapies, the National Cancer Policy Forum (NCPF) of the National Academies of Sciences, Engineering, and Medicine convened a workshop meeting with invited speakers in Washington, D.C., to discuss the clinical development of combination therapies with immune checkpoint inhibitors.

CME Article

Immunotherapies give cancer patients who have few treatment options new hope, which is why there is so much interest in

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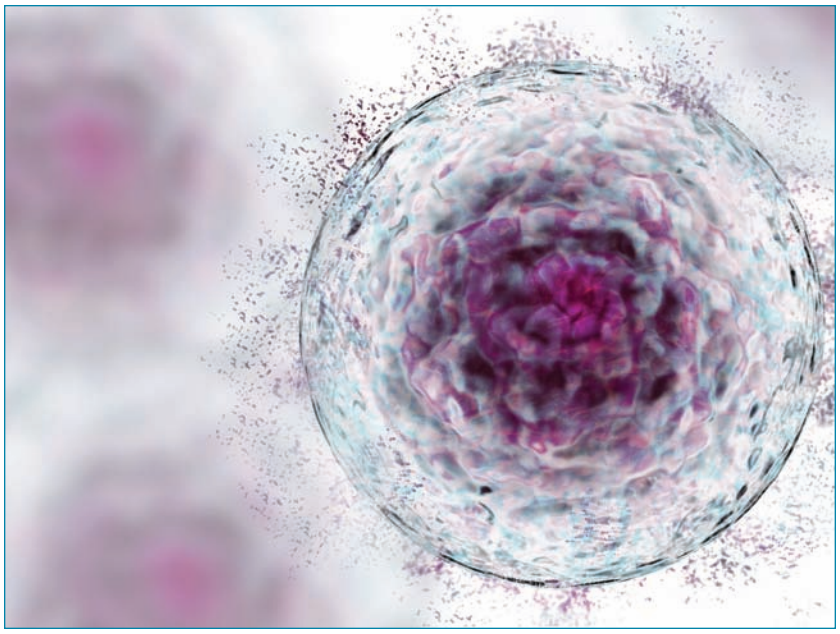

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Applying Genomics to Leukemias & Lymphomas

BY ANKUR R. PARIKH, DO

Utilization of next-generation sequencing (NGS) in clinical hematologic oncology practice is rapidly rising and may help further our knowledge in the diagnosis, treatment, and prognosis of these complex diseases.

An estimated combined total of 174,250 people in the U.S. are expected to be diagnosed with leukemia, lymphoma, or myeloma in 2018 (*Cancer Facts and Figures* [American Cancer Society; 2018]). These new cases are expected to represent 10 percent of all new U.S. cancer cases diagnosed in 2018.

In addition to advances in treatment, including chemotherapy, immunotherapy, and stem cell transplantation, genomics can be helpful in characterizing these diseases further, as well as potentially identifying other targeted treatment options. Though the role of NGS in hematologic malignancies can be expected to keep evolving, this overview will examine the current relevance of NGS in hematologic malignancies.

Genomics in Acute Myeloid Leukemia

NGS offers the ability to measure somatic allele frequencies from the complete coding sequences of many genes in the same assay, which is more comprehensive than traditional molecular assays that test only a relatively small panel of commonly mutated sites (*Clin Transl Sci* 2016;9(6):283-292).

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A Novel Biomarker Approach in MCL-1 Dependent Relapsed/ Refractory AML

BY JOSHUA ZEIDNER, MD

Although four new drugs (midostaurin, enasidenib, CPX-351, gemtuzumab ozogamicin) have been approved for the management of specific subpopulations of acute myeloid leukemia (AML) in the past year, overall outcomes remain poor. Alvocidib is a novel cyclin-dependent kinase-9 (CDK9) inhibitor that also possesses pan-CDK inhibitory activity. CDK9 is recruited to DNA regulatory elements, termed super enhancers, and thereby forms a complex with cyclin T1, known as PTEF-β, which activates transcriptional elongation by regulating the activity of RNA polymerase II (RNA Pol: Figure 1). RNA Pol regulates the transcription of genes critical for cell survival, including MCL-1 and MYC. Therefore, CDK9 inhibition leads to the suppression of genes associated with cell survival.

Serial phase I and II studies of alvocidib (formerly known as flavopiridol) followed by cytarabine and mitoxantrone (ACM, [formerly FLAM]) have shown activity in >400 newly diagnosed and relapsed/refractory AML patients over the last 15 years (*Leuk Res* 2015;39(12):1312-1318). The ACM regimen was designed as a timed-sequential therapy approach to exploit the CDK4/6 inhibition of alvocidib and thereby recruit the synchronization of leukemic blasts into cell cycle after administration (*Clin Cancer Res* 2003;9(1):307-315). Alvocidib has since shown antileukemic activity as a single agent, which appears to be predominantly due to CDK9 inhibition.

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their development. But speakers at the meeting addressed and discussed issues and challenges raised by immune checkpoint inhibitors used in combination regimens.

Currently there is no framework for the following items:

- prioritizing combinations for testing;
- determining what combinations are likely to work or not;
- identifying approaches to patients who are most likely to benefit from combinations, since they are costly;
- assessing endpoints for safety and clinical benefit;
- overcoming resistance to therapy;
- developing combinations in the context of cancer site-agnostic immune checkpoint inhibitor indications; and
- listening to the patient's voice in immunotherapy treatment.

Speakers also discussed concerns about management of potential increased toxicity with combination regimens. The National Academies will publish a written summary report from the meeting.

Noting that the NCPF usually focuses on "emerging areas of science" for its meeting topics, Samir N. Khlief, MD, a co-chair of the workshop, confirmed that "checkpoint inhibitors have been exploding," and are considered a hot topic in oncology. While the potential clinical benefit of combinations is great, a major challenge now is to make progress with the least amount of waste (both in terms of funding and patients who do not respond), said Khlief, Director of the Loop Immuno-Oncology Lab, Biomedical Scholar and Professor of Oncology at the Lombardi Comprehensive Cancer Center at Georgetown University.

In 2016, the NCPF held a workshop called Policy Issues in the Clinical Development and Use of Immunotherapy for Cancer Treatment. The report from that meeting noted that only a small subset of cancer patients will derive long-term benefit from immunotherapies, but those who have durable responses may live for decades.

What is needed today as the field of immunotherapy moves forward is to develop combinations using checkpoint inhibitors rationally, carefully, and thoughtfully, said workshop co-chair Roger Dansey, MD, Chief Medical Officer at Seattle Genetics, Inc. Dansey previously held senior positions at Merck and Gilead Sciences.

Investigating Combinations

Many combinations have been investigated in the setting of PD-1/PD-L1 proteins, and while meaningful clinical benefits have been observed, some results have been disappointing, noted Ramy Ibrahim, MD, Vice President of Clinical Development at the Parker Institute for Cancer Immunotherapy. He said it is important to build on evidence-based monotherapy successes in immunotherapy. "I think we need to spend more time focusing on existing data." He noted that PD-1/PD-L1 immunotherapy can be combined or sequenced with the standard of care, but cautioned that early trial data showing activity don't always translate to a definitive clinical benefit in a phase III trial.

The FDA requires evidence for the contribution of efficacy of each agent used in a combination, noted Amy McKee, MD, Acting Deputy Director of FDA's Oncology Center of Excellence and Supervisory Associate Director in the FDA's Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research (CDER). She said the FDA is committed to keeping its labeling updated, including cross-labeling information for drugs used in combination.

In lung cancer, "For the last 10 years, it has been all about targeted agents," said Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Professor of Pharmacology at Yale School of Medicine, Chief of Medical Oncology, Associate Director of Translational Research, and Director of the Thoracic Oncology Program at Yale Cancer Center. Now, he said, "I think we need to personalize immunotherapy." According to Herbst, the next treatment frontier will be using immune profiling to inform and guide treatment.

"We need predictive biomarkers; we need to know who to treat and who not to treat," he continued. For example, Herbst said patients with non-small cell lung cancer who have an inflamed phenotype ("hot" or immunologically active tumors) tend to respond better to immunotherapy than those who do not. He added that the scientific rationale for combination therapy with checkpoint inhibitors is that it can reduce tumor bulk and improve the T-cell tumor target ratio, factors which may be especially important for refractory patients. Herbst stressed that biomarkers will need to be validated, and that this validation "will require collaboration."

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to: 1. Assess challenges raised by immune checkpoint inhibitors used in combination regimens. 2. Critique developing new immunotherapy combinations and the requirements for the next treatment frontier.

Herbst said questions in the field that need answering include the following: Do immune therapies really work together? Are some immunotherapy agents incompatible with other therapies? Can the PD-1 response be enhanced with vaccines?

As reported in *Oncology Times,* the FDA recently approved an immunotherapy combination: nivolumab plus low-dose ipilimumab for the treatment of adult and pediatric (12 years and older) patients with high microsatellite instability (MSI-H) or mismatch repair (MMR)-deficient metastatic colon cancer. The indication, granted under an accelerated approval, was for colon cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Agreeing with Herbst on the need for validated biomarkers in immunotherapy in order to develop rational immune checkpoint inhibitor treatment combinations was David L. Rimm, MD, PhD, Professor in the Departments of Pathology and Medicine and Director of Yale Pathology Tissue Services at Yale University School of Medicine. He noted that trial data show that immune checkpoint inhibitors and tumor mutational burden (TMB) are complementary, and that TMB as a biomarker for immunotherapy is predictive for outcome. But, Rimm said TMB is not standardized and, in general, pathologists have difficulty reading immune cells.

Also discussing the correlation between TMB and response to immunotherapy was Naiyer A. Rizvi, MD, the Price Family Professor of Medicine at Columbia University Medical Center, Director of Thoracic Oncology and Co-Director of Cancer Immunotherapy. Rizvi noted that the Friends of Cancer Research has convened a working group to reach alignment on and publish standards for defining TMB. He noted TMB is an effective selection tool for accruing patients in phase III trials.

Histology-Agnostic Approvals

Workshop speakers discussed how much evidence is necessary for approval of cancer site-agnostic immune checkpoint inhibitors. In May 2017, the FDA granted accelerated approval to the checkpoint inhibitor pembrolizumab for patients with the MSI-H or MMR-deficient biomarkers, regardless of the tumor's location; it was the first such histology-agnostic approval.

This drug approval raises certain cautionary issues and questions for future histology-agnostic approvals, said Richard L. Schilsky, MD, FACP, FSCT, FASCO, Senior Vice President and Chief Medical Officer of ASCO. He said these issues include the following:

- There are small sample sizes for many tumor types.
- Not all tumor types respond to immunotherapy or respond equally well.
- The duration of response is variable across tumor types.

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IMMUNE CHECKPOINT INHIBITORS

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• Not all tumor types are represented in any dataset, yet approval is requested for all.

• Biomarker prevalence/predictive value may vary across tumor types.

• Molecular diagnostic tests are not uniform in their ability to detect biomarkers.

Schilsky, a member of the workshop planning committee, said it is important to know how effective pembrolizumab is in clinical practice and limit the drug's label if it becomes clear that patients with a particular tumor type or types do not benefit from it. Asked by *Oncology Times* if he has concerns about future histology-agnostic immunotherapy approvals given these issues, Schilsky said he does. He noted that since only one or two clinical trial participants may respond to the immunotherapy agent being studied and only a small percentage of patients will have the MSI-H biomarker, these are important considerations for clinical oncologists. "Are you going to test every patient for MSI status?" he asked. Such testing, to identify that small percentage, would be an added expense.

From the FDA's point of view, the key to approval of new tumor site-agnostic agents is whether they serve an unmet patient need, said Steven Lemery, MD, Associate Deputy Director in FDA's Division of Oncology Products 2, CDER. He said future questions for tissue-agnostic immunotherapy approvals include:

• How to define an indication with a quantitative biomarker? How many mutations constitute TMB?

• How should product labeling be handled for combinations?

• How many tumor types are necessary to support a new drug application?

• How many are necessary for fast track, breakthrough, and accelerated approval?

Given concerns and unanswered questions in immunotherapy, how can a framework be created for rational test results? asked Ron Kline, MD, Medical Officer for the Patient Care Models Group at the Center for Medicare & Medicaid Innovation and Clinical Lead for the Oncology Care Model.

Schilsky responded that there is a fundamental conundrum in clinical practice: "We derive evidence from study populations, but we have to make decisions for individual patients." Thus the oncologist has to decide how close his or her patient is to the study population. Schilsky noted that for each decision-maker, it comes down to whether he or she can say with confidence that there is enough evidence to approve a new product or use a new product for a specific patient in clinical practice. Schilsky also stressed the importance of obtaining post-marketing data once a new drug has been approved. "You need to get more data post-approval," he said.

Advancing Immunotherapy

To help immunotherapy and its use in combinations advance, it is important to have the right tissue specimens saved under standardized conditions, said Lisa H. Butterfield, PhD, Professor of Medicine, Surgery, Immunology and Clinical and Translational Science at the University of Pittsburgh, Director of the Immunologic Monitoring and Cellular Products Laboratory at the university's Hillman Cancer Center and President of the Society for Immunotherapy of Cancer (SITC).

In immunotherapy, including combinations, she said it is important to keep asking: Was the therapeutic intervention an improvement? Why or why not? And, she added, "What is an accurate measure of antigen-presenting T cells? I'm still not sure." Butterfield noted that SITC established an immunotherapy biomarker task force to strengthen the scientific rationale and evidence for use of drugs in the field.

"Science needs to drive the rationale for PD-1/PD-L1 combinations," stressed Elizabeth Jaffee, MD, the Dana and Albert "Cubby" Broccoli Professor of Oncology; Deputy Director of the Sidney Kimmel Comprehensive Cancer Center; and Co-Director of the Gastrointestinal Cancers Program at Johns Hopkins University School of Medicine. Jaffee, the 2018-19 President of the American Association for Cancer Research, added that studies aimed at uncovering signaling pathways within the tumor microenvironment, which has multiple dynamic signaling pathways, will help delineate such problems as cell resistance to immunotherapy.

Finally, a plea for always listening to the patient's voice when immunotherapies are used in combination was raised by Linda House, RN, BSN, MSM, President of the Cancer Support Community, a global information network. "The patient has been missing from this discussion; we've been talking about tumors, not patients," she said. She emphasized that information on the patient's experience with immunotherapy combinations needs to be incorporated into data on outcomes.

House told *Oncology Times* that the Cancer Support Community has created an online immunotherapy symptom tracker to identify what patients experience while taking these drugs. "Can we correlate these symptoms with major treatment-related events?" she asked. She also said her organization is running its own clinical trial, Immunotherapy and Me, to find out more about the patient's perspective. She said the goal is to accrue 300 patients for this trial. OT

Peggy Eastman is a contributing writer.

GENOMICS

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efficacy of using genomics-based therapy in hematologic malignancies remains limited; however, investigators recently published a meta-analysis comparing biomarker-based treatment strategies with other approaches. In trials of hematologic malignancies, they identified a higher relative response rate of 24.5 versus 13.5 percent ($p<0.001$) and a higher progression-free survival of 13.6 months versus 4 months in patients undergoing biomarker-based treatment, although the latter difference was not statistically significant (*JAMA Oncol* 2016;2(11):1452-1459).

One challenge to obtaining more robust data on hematologic malignancies may be lower clinical trial enrollment in biomarker-driven clinical trials. One report described the initial clinical trial accrual experience of three affiliated cancer programs, which did not bear NCI designation, after NGS and demonstrated only four of 200 (2%) patients had hematologic malignancies (*J Oncol Pract* 2016:12(4):e396-e404). Low accrual may be due to the lower incidence of hematologic malignancies in general, as well as the number of other clinical trial options available to those patients in particular.

Despite the paucity of data regarding treatment response based on genomics-based therapy, the application of genomics to hematologic malignancies, nevertheless, can help stratify diseases better and potentially identify specific patient populations more likely to benefit from genomics-based therapy.

As we start gathering more information and understanding the complexities in the genomic makeup of various hematologic malignancies, we will be able to design clinical trials better and gain more insight regarding mutations and biomarkers and their roles in the diagnosis, prognosis, treatment, and potential relapse of these diseases. Basket trials, which are based on molecular alterations or biomarkers rather than tumor histology, are currently enrolling patients with specific mutations, regardless of diagnosis; however, the lymphoma and leukemia patient population is small, and clinical trial accrual is low.

Nonetheless, in the future, through multi-institutional trials that include community hospitals, data sharing, and other collaborations—disease-specific advocacy groups, artificial intelligence platforms, and tumor registries—investigators are expected to be able to collect sufficient data on these cancers to make data interpretation valid, overcoming the low accrual that has undercut the feasibility of single-site or small multi-site clinical trials. OT