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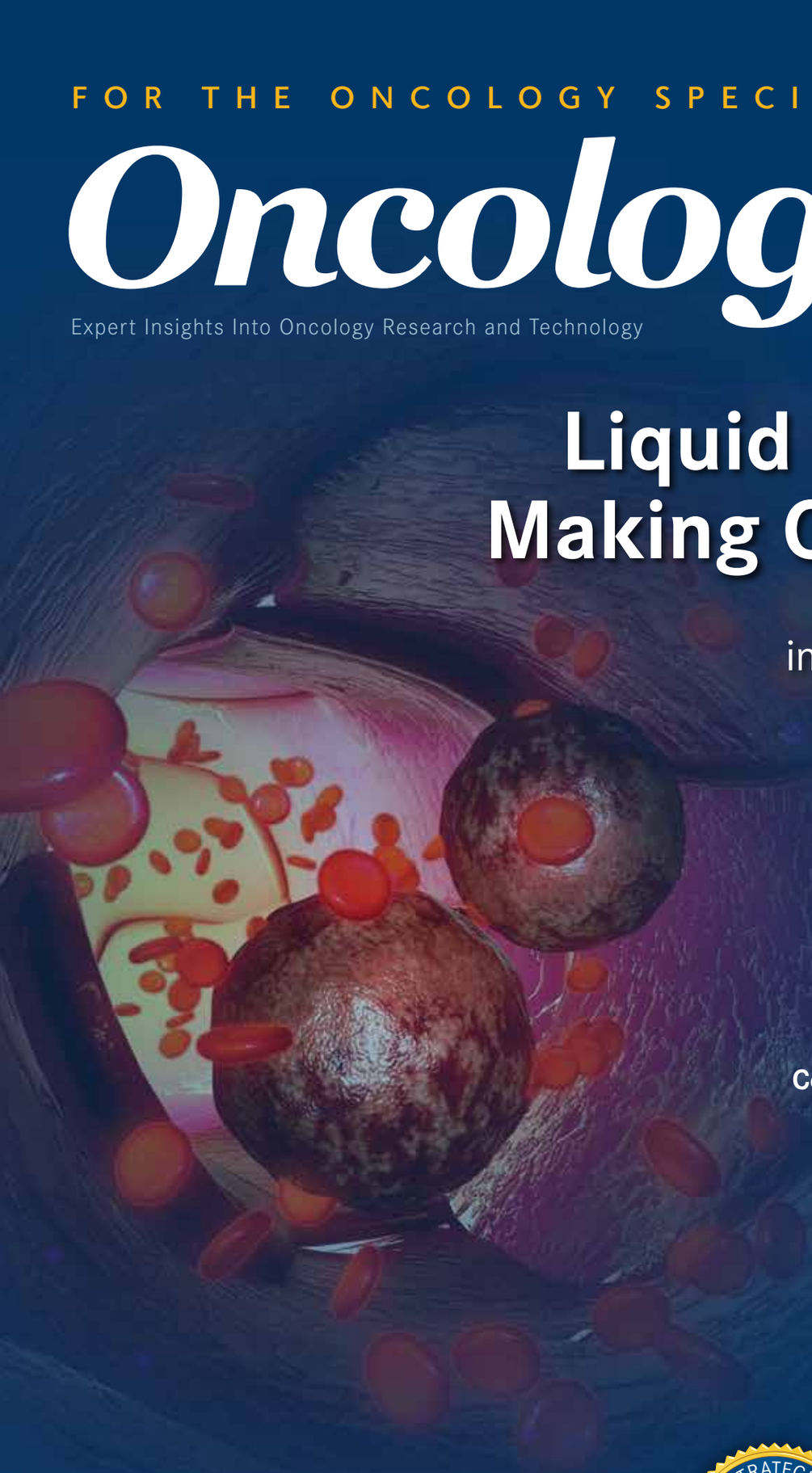

Liquid Biopsies Start Making Clinical Impact

Lung Cancer Leads the Way in a Rapidly Shifting Landscape

Practicing Oncology in the Gray Zone
By Maurie Markman, MD

*Onc*Pathways®

TIGIT Emerges as New Target for Immune Checkpoint Blockade Strategies

OncLive Peer Exchange®

Complex Scenarios in Advanced Melanoma: Examining Three Patient Cases

Clinical Insights

Metabolic Pathways Attract Fresh Interest in Gliomas
With Howard A. Fine, MD

Enhanced Recovery Program Improves Outcomes After Colorectal Cancer Surgery
By Traci L. Hedrick, MD, MS

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Strategic Alliance Partnership

Every month, our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month's Partner Perspectives, go to **page 26.**

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COVER STORY

14 Liquid Biopsies Start Making Clinical Impact

Lung Cancer Leads the Way in a Rapidly Shifting Landscape

By Anita T. Shaffer

The noninvasive testing that has long been the goal of solid tumor analysis is making its presence felt in lung cancer, and other malignancies likely will not be far behind, experts say. Although many potential uses for liquid biopsies are envisioned, much work remains to be done to establish the clinical utility of these tests.

DEPARTMENTS

ONCOLOGY & BIOTECH NEWS®

Conference Coverage | 2016 ESMO Asia

FEATURES

Rolling Out Technology

It is always a balancing act to describe the introduction of new technology in the medical field. We seek to juggle enthusiasm for the potential of an exciting new platform with the complexities of the long road ahead that adopting new technology usually bring.

The cover story in this issue, "Liquid Biopsies Start Making Clinical Impact," captures this dilemma. In some respects, the ability to perform liquid biopsies in solid tumors is having a notable impact in lung cancer and has thus entered clinical practice. In other ways, the clinical utility of conducting liquid biopsies, regardless of the type of technology employed, must still be established before it is truly useful in daily oncology practice.

There are so many potential uses for liquid biopsies across the spectrum of cancer care—and so many companies chasing these possibilities—that it's easy to get carried away. The possible uses include screening, diagnosing recurrence, identifying mutations, and directing therapy.

The reality underlying these exciting prospects is that there often is doubt about whether an identifiable mutation is driving the malignancy and whether there is an available targeted therapy to attack the aberrations that testing uncovers. Then there are questions about comparing tests and results.

These considerations point to the need for the oncology research establishment to organize a framework that sets standards for liquid biopsies and guides clinicians in evaluating testing options. The federal government is organizing collaborations that might help.

One example is the Blood Profiling Atlas, which is part of the Cancer Moonshot initiative. This project will bring together 20 leading industry and academic entities, with pharmaceutical and diagnostic companies partnering with cancer centers, to build a database for laboratory and clinical findings regarding liquid biopsies. The strategy will be similar to the approach used several years ago when the FDA tapped a next-generation sequencing database to approve a new screening test for cystic fibrosis.

The development of liquid biopsies is one of the major trends that we will be following this year. Please let us know what you would like to learn about this exciting new technology. As always, thank you for reading.

Mike Hennessy, Sr
Chairman and CEO

Conferences

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13th Annual **International Symposium on Melanoma and Other Cutaneous Malignancies®**

February 11, 2017
Sunny Isles Beach, FL

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New York, NY

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The Angeles Clinic and Research Institute
Los Angeles, CA

34th Annual **Miami Breast Cancer Conference®**

March 9-12, 2017
Fontainebleau Miami Beach Hotel
Miami Beach, FL

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The University of Texas
MD Anderson Cancer Center
Houston, TX

Elizabeth Mittendorf, MD, PhD
The University of Texas
MD Anderson Cancer Center
Houston, TX

21st Annual **International Congress on Hematologic Malignancies:® *Focus on Leukemias, Lymphomas, and Myeloma***

February 23-25, 2017
Trump International Miami
Sunny Isles Beach, FL

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University Medical Center
Hackensack, NJ

Sagar Lonial, MD
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4th Annual **Miami Lung Cancer Conference®**

April 8, 2017
Miami Beach, FL

Program Co-Chairs
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Massachusetts General Physicians Organization
Boston, MA

Heather A. Wakelee, MD
Stanford University Medical Center
Stanford, CA

2nd Annual **School of Gastrointestinal Oncology™**

April 22, 2017
Intercontinental
New York, NY

Program Co-Chairs
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Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, DC

Michael A Choti, MD, MBA, FACS
UT Southwestern Medical Center
Dallas, TX

New York GU™: 10th Annual **Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies**

March 18, 2017
New York, NY

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Kimmel Cancer Center
Philadelphia, PA

Daniel P. Petrylak, MD
Yale Cancer Center
New Haven, CT

16th Annual **International Congress on the Future of Breast Cancer®**

July 14-15, 2017
Marriott Marquis San Diego Marina
San Diego, CA

Program Director
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Baylor Charles A. Sammons Cancer Center
Texas Oncology
The US Oncology Network
Dallas, TX

18th Annual **International Lung Cancer Congress®**

July 27-29, 2017
Hyatt Regency Huntington Beach
Huntington Beach, CA

Program Directors
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UC Davis Comprehensive Cancer Center
Sacramento, CA

Roy S. Herbst, MD, PhD
Yale Cancer Center
Yale School of Medicine
New Haven, CT

15th Annual **School of Breast Oncology®**

November 2-4, 2017
Emory Conference Center Hotel
Atlanta, GA

Program Director
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Baylor Charles A. Sammons Cancer Center
Texas Oncology
The US Oncology Network
Dallas, TX

35th Annual CFS™: **Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow®**

November 8-10, 2017
New York Marriott Marquis
New York, NY

Program Co-Chairs
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New York, NY

Franco Muggia, MD
NYU Langone Medical Center
New York, NY

Benjamin P. Levy, MD
Mount Sinai Health System
Mount Sinai Hospital
New York, NY

12th Annual **New York Lung Cancer Symposium®**

November 11, 2017
Crowne Plaza Times Square—Manhattan
New York, NY

Program Chairs
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Memorial Sloan Kettering Cancer Center
New York, NY

Roman Perez-Soler, MD
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, NY

2nd Annual **International Congress on Immunotherapies in Cancer™: *Focus on Practice-Changing Application***

December 9, 2017
InterContinental New York Times Square
New York, NY

Program Chairs
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David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, CA

Naiyer A. Rizvi, MD
Columbia University Medical Center
New York, NY

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By Maurie Markman, MD
@DrMaurieMarkman

Practicing Oncology in the Gray Zone

Clinicians Struggle to Discuss Uncertain Prognoses With Patients

"Uncertainty" is a routine dilemma when discussing a prognosis with a patient with cancer and his or her family. The prognosis is, at best, a statistical probability—assuming the available objective data are somewhat representative of the individual patient.

"Uncertainty" is a difficult concept to address in clinical medicine in general and specifically in oncology. Consider the surgeon who meets the family of a patient after finishing the resection of what appears to be a large but localized high-grade non–small cell primary lung cancer. The surgeon might say, "I was able to remove the cancer." Alternatively, the surgeon might say, "I removed what I could see and, while it is reasonable to be hopeful the cancer has not spread, there is unfortunately a high statistical likelihood that in a relatively short period of time metastatic disease will be revealed in one or multiple locations. I am sorry, but we simply do not know with the desirable degree of certainty what exactly will happen or when it will occur, but the odds are not favorable."

Or consider the medical oncologist's dilemma when reporting the results of a CT scan to a patient with an advanced abdominal malignancy who has exhibited a most impressive response to cytotoxic chemotherapy. The oncologist might say that "there is no evidence of disease" or "the cancer is in remission." Alternatively, the oncologist could report that "the scan reveals no definite abnormalities, but the sensitivity of this test does not permit an examination for the presence of very small-volume macroscopic or persistent microscopic disease. Realistically, at this time we do not know if there is residual cancer, although statistically that is likely to be the case. Only with careful follow-up will we be able to determine if this cancer will exhibit a long-term remission."

Of course, there is no reason for the alternative words in these two scenarios to be spoken at this exact point in time in the patient's cancer journey, but they do express the reality of the situations.

Unfortunately, the myth of "certainty" permeates the entire realm of clinical medicine. Consider, for example, governmental regulatory or third-party payer coverage language where expressions such as "medical necessity" or "safe and effective" are used as the basis for defining clinical utility. Such terminology implies absolute determination that the drug, procedure, or approach "is medically necessary" or "is safe and effective." But it would be far more realistic to acknowledge that the benefits versus the risks of oncologic therapeutics are overwhelmingly relative to a specific clinical setting and recommendations should be based on both objective data and the subjective judgment of a thoughtful clinician.

Further, as noted in a most provocative and highly relevant commentary discussing what has been labeled "gray-zone medicine," the authors state[1]:

"One fundamental problem may be a misguided perspective that health care is a binary world in which interventions are either effective or ineffective, appropriate or inappropriate. In truth, there are large gray zones in which an intervention is neither clearly effective nor clearly ineffective–zones where benefits are unknown or uncertain and value may depend on patients' preferences and available alternatives."

Confronting the Data Gap

"Uncertainty" is a routine dilemma when discussing a prognosis with a patient with cancer and his or her family. The prognosis is, at best, a statistical probability–assuming the available objective data are somewhat representative of the individual patient. Unfortunately, this assumption can often be quite problematic.

Consider, for example, a newly diagnosed patient with stage IIIC high-grade ovarian cancer who inquires about the probability of whether she will survive at least 5 years. An examination of published survival statistics suggests an appropriate response would be less than 50%. But what happens to that statistically anticipated survival figure, as uncertain as these population-based figures are in defining individual outcomes, if that particular woman has already survived for several years without clinical evidence of progression? A recently reported analysis has suggested, not surprisingly, that the likelihood for her continuing to remain disease free substantially improves compared with the baseline assessment.[2] Yet it is uncertain if such data are routinely communicated to patients who may incorrectly continue to believe that the initial prognostic assessment remains accurate in their particular situation.

Uncertainty is also uncomfortable when addressing a patient with cancer regarding recommendations that must be made with data that are far less than perfect. One of the major attractions of the randomized trial may be that an outcome with $P < .05$ permits some clinicians to declare with an inappropriate or unreasonable degree of medical certainty that "Regimen A" is superior to "Regimen B" for a specific individual.

In fact, it is increasingly understood by clinicians and many academics that such logic is often fatally flawed, with the potential for most dangerous consequences. For example, the elderly and patients with very common and highly clinically relevant comorbidities, such as cardiac and hepatic problems or renal medication–controlled diabetes, are substantially underrepresented in the clinical trials that form the basis for standards of care. How can trial data so profoundly unrepresentative of real-world patients be employed to inform oncologists and their patients regarding the risks versus benefits of anticancer therapy?

It is here where Big Data, which includes the clinical courses of large real-world patient populations, may be helpful in reducing to a meaningful degree the uncertainty associated with cancer management decisions. The future development of robust clinical databases such as CancerLinQ that may be easily and routinely employed by cancer specialists are awaited with great interest. ■

Maurie Markman, MD, editor-in-chief, is president of Medicine & Science at Cancer Treatment Centers of America, and clinical professor of medicine, Drexel University College of Medicine. ***maurie.markman@ctca-hope.com.***

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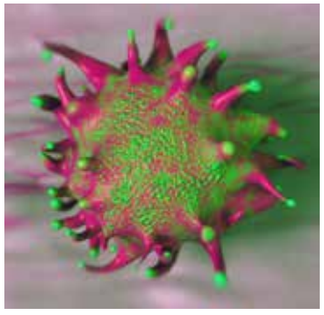
2. Kurta ML, Edwards RP, Moysich KB, et al. Prognosis and conditional disease-free survival among patients with ovarian cancer. *J Clin Oncol.* 2014;32(36):4102-4112. doi:10.1200/JCO.2014.55.1713.

FDA Digest

Ibrutinib Notches Fifth Indication



Lymphoma cancer cell

Ibrutinib (Imbruvica) gained FDA approval as a treatment for marginal zone lymphoma (MZL), bringing the number of indications to 5 for the Bruton tyrosine kinase inhibitor. The accelerated approval covers ibrutinib for patients with MZL who require systemic therapy following at least 1 prior anti–CD20-based therapy.

In the pivotal phase II study, the objective response rate with ibrutinib was 46% including a complete response rate of 3.2%, according to findings presented at the 2016 ASH Annual Meeting. The median progression-free survival was 14.2 months with ibrutinib (95% CI, 8.3-not reached) and the median overall survival was not yet reached at a median follow-up of 19.4 months.

The accelerated approval for MZL is contingent upon findings from a larger confirmatory study. Ibrutinib has previously been approved by the FDA for the treatment of patients with mantle cell lymphoma, 2 clinical settings for chronic lymphocytic leukemia and small lymphocytic lymphoma, and Waldenström's macroglobulinemia. **onclive.com/link/998**

Pembrolizumab May Shed PD-L1 Rule

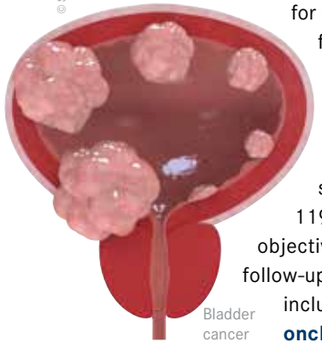
The FDA has granted a priority review to a supplemental biologics license application for pembrolizumab (Keytruda) in combination with pemetrexed plus carboplatin as a treatment for patients with metastatic or advanced nonsquamous non–small cell lung cancer (NSCLC) without *EGFR* or *ALK* mutations and regardless of PD-L1 expression. The target action date is May 10, 2017, according to Merck, the drug developer.

The PD-1 inhibitor currently has 2 indications in metastatic NSCLC: first-line treatment of patients whose tumors exhibit high PD-L1 expression measured as a tumor proportion score (TPS) ≥50%, and second-line treatment for those with TPS ≥1%.

The application for the new indication was based on part 2 of cohort G in the KEYNOTE-021 trial, in which the pembrolizumab triplet elicited an objective response rate of 55% compared with 29% with the chemotherapy agents alone (P = .0016). The median progression-free survival was 13.0 months with the addition of pembrolizumab versus 8.9 months for chemotherapy alone (HR, 0.53; 95% CI, 0.31-0.91; P = .010). **onclive.com/link/999**

Drugmaker Seeks Earlier Use of Atezolizumab

Atezolizumab (Tecentriq) could receive an expanded indication in locally advanced or metastatic urothelial carcinoma under a supplemental new drug application that the FDA has agreed to evaluate under its priority review program. The agency is scheduled to decide by April 30, 2017, according to Genentech, the manufacturer of the PD-L1 inhibitor.



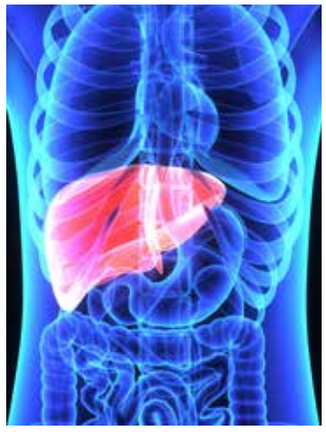
Bladder cancer

The application seeks approval for atezolizumab as a treatment for cisplatin-ineligible patients in a frontline setting or following progression occurring ≥12 months after neoadjuvant or adjuvant chemotherapy. The drug initially was approved for patients with previously treated advanced bladder cancer in May 2016.

The latest request is based on data from the single-arm phase II IMvigor210 trial. In a cohort of 119 cisplatin-ineligible, treatment-naïve patients, the objective response rate with atezolizumab at a median follow-up of 17.2 months was 23% (n = 27; 95% CI, 16-31), including a complete response rate of 9% (n = 11). **onclive.com/link/1000**

Guideline Updates

Priority Review for HCC Drug



Regorafenib (Stivarga) will be evaluated as a second-line treatment for patients with unresectable hepatocellular carcinoma (HCC) under the FDA's priority review program, according to Bayer, the manufacturer of the multikinase inhibitor.

The supplemental new drug application is based on the phase III RESORCE trial, in which the median overall survival was 10.6 months with regorafenib plus best supportive care compared with 7.8 months for placebo plus best supportive care, representing a 38% reduction in the risk of death (HR, 0.62; 95% CI, 0.50-0.78; P <.001).

Regorafenib is an oral kinase inhibitor that blocks VEGFR 1-3, TIE-2, RAF-1, BRAF, BRAFV600, KIT, RET, PDGFR, and FGFR. The agent is currently FDA approved for the treatment of patients with metastatic colorectal cancer and advanced gastrointestinal stromal tumors. **onclive.com/link/997**

Safety Alert Issued for Protein Drug

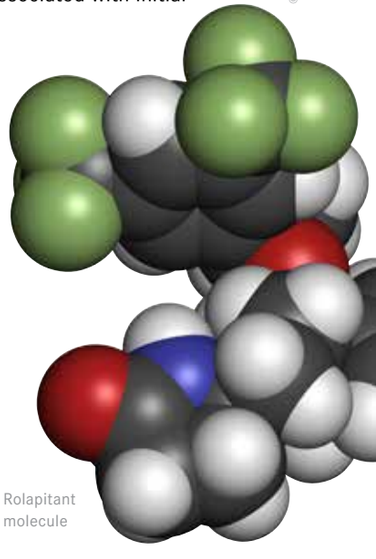
The FDA is warning consumers not to purchase or use PNC-27, which is being marketed through a website as a peptide designed with a supercomputer that can be used to treat any kind of cancer. The agency issued a safety alert about the product after the bacteria *Variovorax paradoxus* was found in an inhalation solution sample of the product.

Although no illnesses or serious adverse events related to PNC-27 have been reported to the FDA, contact with contaminated samples can lead to life-threatening infections, especially in vulnerable populations such as young children, elderly people, pregnant women, and people who have weakened immune systems, the agency said.

PNC-27, which the FDA has not evaluated, is being dosed in multiple ways, such as in a nebulized solution, intravenous solution, vaginal suppository, or rectal suppository. The FDA is advising patients to consult with doctors if they have already taken PNC-27. **onclive.com/link/996**

Agency Rejects IV Indication for CINV Agent

Tesaro must provide more data to the FDA before the agency will approve the company's application for an intravenous (IV) formulation of rolapitant for use in the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy.



Rolapitant molecule

Oral rolapitant (Varubi) was approved by the FDA in September 2015. Tesaro received a complete response letter from the FDA in January explaining the agency's decision on the IV formulation. The letter requested further information related to the in vitro method used to demonstrate comparability of drug product produced at the 2 proposed commercial manufacturers for rolapitant IV that were included in the application.

The letter did not identify concerns related to the safety or efficacy of rolapitant IV or request additional clinical studies, the company said. Tesaro said it would work with the FDA and that the company expects to gain approval for the new indication during the first half of 2017. **onclive.com/link/995**

FDA Labeling Changes

Darzalex (daratumumab)

- *Warnings and Precautions* added: new subsections on neutropenia and thrombocytopenia
  - Monitor complete blood cell counts periodically during treatment for signs of neutropenia; monitor for signs of infection in patients with neutropenia. Dose delay may be required to allow recovery of neutrophils. Dose reduction is not recommended. Consider supportive care with growth factors.
  - Daratumumab may increase thrombocytopenia induced by background therapy.
- *Patient Counseling Information* expanded: Advise patients taking daratumumab to seek medical attention if they have a fever or notice signs of bruising or bleeding.

Erivedge (vismodegib)

- *Warnings and Precautions* updated: embryo-fetal toxicity and blood donation
  - Advise females of reproductive potential to use effective contraception during therapy with vismodegib and for 24 months after the final dose.
  - Advise patients not to donate blood or blood products while receiving vismodegib and for 24 months after the final dose.
- *Adverse Reactions* added (postmarketing experience): premature fusion of the epiphyses; blood creatine phosphokinase increase

Kyprolis (carfilzomib)

- *Warnings and Precautions* added: hemorrhage
  - Fatal or serious cases of hemorrhage have been reported in patients treated with carfilzomib.
  - Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Bleeding can be spontaneous and intracranial events have occurred without trauma.
  - Hemorrhage has been reported in patients with low or normal platelet counts and in patients who were not receiving antiplatelet or anticoagulation therapy.
  - Promptly evaluate signs and symptoms of blood loss; reduce or withhold dose as appropriate.

Ninlaro (ixazomib)

- *Adverse Reactions* added: clinical trials experience with herpes zoster
  - Herpes zoster was reported in 4% of patients treated with ixazomib during a clinical study versus 2% in the placebo arm.
  - Patients in the ixazomib arm who received antiviral prophylaxis had a lower incidence (<1%) of herpes zoster infection compared with patients who did not receive prophylaxis (6%).
- *Use in Specific Populations* updated: lactation and contraception
  - Because the potential for serious adverse reaction from ixazomib in breastfed infants is unknown, advise nursing women not to breastfeed during treatment and for 90 days after the last dose.
  - Since ixazomib is administered with dexamethasone, the risk for reduced efficacy of contraceptives should be considered. Advise women using hormonal contraceptives to also use a barrier method of contraception.

For full details, visit the FDA's recently revised Drug Safety Labeling Changes database at **www.accessdata.fda.gov/scripts/cder/safetylabelingchanges.**

Journal Article

Large Study Confirms Impact of "Chemobrain"

The causes of cancer-related cognitive impairment in women who undergo chemotherapy for breast cancer, a condition often referred to as "chemobrain," are varied and complex, with medical, psychological, and demographic factors playing a role, according to a research report in the *Journal of Clinical Oncology* (doi:JCO2016685856).

Researchers from the University of Rochester Medical Center's Wilmot Center examined the cognitive difficulties of 581 patients with breast cancer recruited from community oncology clinics across the United States. Results were compared with those of a control group of 364 healthy individuals, some of whom were friends or family of patients in the study. The groups were balanced in age, ethnicity, and marital status.

Both groups were assessed using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) tool, which examines perceived cognitive impairment, cognitive abilities, the impact of cognitive impairment on quality of life, and cognitive impairment as perceived by others. Researchers conducted the FACT-Cog at 3 different points: 7 days before chemotherapy, within 4 weeks of chemotherapy completion, and 6 months after the second assessment.

In addition, investigators assessed participants' reading ability and depressive symptoms, the latter with an item from the Multidimensional Fatigue Symptom Inventory where participants responded to the statement "I feel depressed" using a scale ranging from "Not at all" to "Very much."

Before chemotherapy began, patients with breast cancer had lower FACT-Cog scores than their healthy counterparts. Investigators found that compared with participants who did not have cancer, the FACT-Cog scores of women with breast cancer indicated 45% more impairment. In fact, over the period of nearly 1 year from diagnosis and prechemotherapy to the postchemotherapy follow-up at 6 months, 36.5% of patients with breast cancer reported a decline in scores compared with 13.6% of the healthy women.

Overall, the study found that predictors of perceived cognitive impairment included increased baseline levels of anxiety and depressive symptoms, lower baseline cognitive reserve, perimenopausal or postmenopausal status, younger age, and black race. Additionally, women who underwent hormone therapy and/or radiation treatment following chemotherapy had similar cognitive problems as women who solely received chemotherapy. ■

Conference Report

Postmastectomy Radiation Increases Complications

Patients with breast cancer who received radiation therapy after undergoing a mastectomy reported increased complications and lower satisfaction, according to findings from a large multicenter study presented at the 2016 San Antonio Breast Cancer Symposium (Abstract S3-07).

Women diagnosed with early-stage breast cancer face several challenging decisions that will affect their long-term disease control and quality of life, said study author Reshma Jagsi, MD, DPhil. Jagsi, who is a professor and deputy chair in the Department of Radiation Oncology at the University of Michigan.

"Many patients must still decide whether they feel that the benefits, given their particular circumstances, outweigh the risks," said Jagsi. "One of the risks of radiation therapy is that it may affect the options and outcomes for breast reconstruction, which many women who receive mastectomy desire."

The Mastectomy Reconstruction Outcomes Consortium study collected medical and patient-reported outcomes data from women with breast cancer who were a median age of 49 and had elected different types of reconstruction between 2012 and 2015. Of these patients, 553 received radiotherapy and 1461 did not. Thirty-eight percent of women who received radiation and 25% who did not had autologous reconstruction, with remaining patients undergoing implant reconstruction.

From there, researchers determined whether radiotherapy was associated with complications postreconstruction, such as hematoma or wound infection. They also measured patient satisfaction using the BREAST-Q patient-reported outcome instrument 1 and 2 years after reconstruction.

After 1 year of follow-up, 28.8% of patients who had radiotherapy and 22.3% who did not had at least 1 complication. At 2 years' follow-up, 34.1% and 22.5% of those who did and did not receive radiotherapy, respectively, experienced a complication with their breast reconstruction.

After accounting for several variables, the researchers determined that radiotherapy was linked to more than double the odds of developing complications in patients who received implants but was not associated with complications in patients who received autologous reconstruction. Additionally, the BREAST-Q scores of patients who had received radiation showed significantly lower patient-reported satisfaction than those of the patients who did not receive radiation. Once more, these differences were not shown among the patients with autologous reconstruction. ■

Liquid Biopsies Start Making Clinical Impact

Lung Cancer Leads the Way in a Rapidly Shifting Landscape

By Anita T. Shaffer

At the Vidant Health System in North Carolina, patients with advanced lung cancer who are candidates for molecular analysis will receive plasma-based testing at the same time that they undergo a traditional biopsy. Reports from the "liquid biopsy" are available within 3 to 4 business days, and specialists are finding that the ability to obtain speedy results is making an impact on treatment decisions and possibly on outcomes.

Mark R. Bowling, MD

"If it's adenocarcinoma, knowing that there might be certain markers that can make a difference for that patient's treatment upfront and quickly is very helpful," says Mark R. Bowling, MD, the pulmonologist who performs many of the biopsies conducted at the center. "You can do the same thing on tissue, of course, but you usually have to wait 14 days.

"As much information as you can have on a patient to help you make decisions as soon as you can is very important," he added. "To the patient, it's an emergency. You're not going to fix it just by biopsying it—you have to start therapy."

The use of liquid biopsy testing at the center, which serves communities with a population of 1.2 million people, illustrates the rollout of a noninvasive approach that has long been the holy grail of solid tumor analysis. The era of the liquid biopsy has arrived in clinical practice in the United States—at least in lung cancer—with an expanding toolkit from commercial and academic providers and a growing body of clinical evidence.

The Cleveland Clinic has named the liquid biopsy, a term broadly used to describe blood-based testing for genetic mutations, as one of the top 10 medical innovations poised to make an impact on patient care in 2017.[1] As part of the Cancer Moonshot initiative, biopharmaceutical companies and academic institutions have agreed to collaborate on building a Blood Profiling Atlas that will aggregate raw datasets from liquid biopsy studies along with relevant clinical data.[2]

Many exciting uses for liquid biopsies that span the spectrum of cancer diagnosis and care that leverage existing and emerging platforms are under study, yet the clinical utility of such assays is an evolving question.

The liquid biopsy "is here today and it's already established, but the uses of it are much more limited than people understand," said Nathan A. Pennell, MD, PhD, director of the Lung Cancer Medical Oncology Program at the Cleveland Clinic's Taussig Cancer Center. "The validated uses are much more narrow. That may expand dependent on our identifying clinically proven uses for it as opposed to doing it because we can. There aren't that many cases where being able to detect something in the blood has been validated to impact patient outcomes and survival. That's what's missing from a lot of the liquid biopsies."

Nathan A. Pennell, MD, PhD

Pennell said 2 areas where the utility of liquid biopsies has been established thus far are in monitoring treatment for emerging resistance and in identifying targetable genetic mutations or fusions to guide therapy.

As a noninvasive diagnostic, the ability to learn such information from a blood sample is particularly helpful for patients who cannot undergo a biopsy or whose tumor sample is exhausted, noted Pasi A. Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute. Jänne co-chaired a workshop on liquid biopsies that the American Association for Cancer Research (AACR) and the FDA sponsored in July 2016.

"Today we have technology that can look at both single genetic alterations from cell-free DNA from the plasma or can sequence cell-free DNA from the plasma and look at multiple genetic alterations," said Jänne. "Both academic institutions and commercial vendors are providing that. The vast majority of what we need today are predictive markers. We need to be able to guide the care of patients who have advanced cancer."

Pasi A. Jänne, MD, PhD

Jänne said there is a pressing need for studies that compare the utility of liquid biopsies with tumor biopsies. "That is the body of evidence that we need for more drugs," he said. "There are some clinical trials that are allowing entry based on blood-based genotyping, not necessarily tumor-based genotyping. One of the questions is whether that is as good. That remains to be determined."

In the immediate future, Jänne expects liquid biopsies to be most beneficial in solid tumor types where targeted therapies already have been identified, starting with non–small cell lung cancer (NSCLC) and including colon cancer, breast cancer, and melanoma.

"As we find more and more actionable mutations, this is going to become more and more useful," said Pennell, noting the need to identify additional drugs that can target the growing body of mutations that researchers have characterized.

Testing Choices Grow

In June 2016, the FDA approved the first blood-based assay for use in clinical decision making, the cobas EGFR Mutation Test v2, for patients with NSCLC.[3] The test uses real-time polymerase chain reaction (PCR) technology on circulating-free tumor DNA derived from plasma.[4]

The assay is now approved as a companion diagnostic for the detection of *EGFR* exon 19 deletions and L858R substitutions as a means of selecting patients for frontline therapy with erlotinib (Tarceva) and for identifying the T790M resistance mutation as a screening tool for the use of osimertinib (Tagrisso) in individuals with progressive disease. The FDA said patients who test positive for the indicated mutations are eligible for the matching targeted therapy; however, those whose samples are negative on plasma-based testing should receive further testing with a tissue biopsy.

Although that test has gained the agency's stamp of approval as a companion diagnostic, the menu of commercially available assays is growing outside of that specific category. The assay that doctors at the Vidant center have chosen for liquid biopsies is GeneStrat, which uses droplet digital PCR technology to analyze circulating tumor DNA and RNA in plasma from a whole-blood sample.[5]

The test can detect *EGFR* sensitizing and resistance mutations, *EML4-ALK* fusions, and *KRAS* mutations, with sensitivities ranging from approximately 85% for the gene fusions to nearly 96% for *EGFR* alterations, according to Biodesix, the Colorado-based company that developed the test.[6]

For an analysis of turnaround times using the assay, Bowling and colleagues reviewed 179 samples from 5 oncology centers.[7] They found that the average time from receipt of test kit to biomarker results was about 33 hours compared with guideline recommendations of a maximum 10 business days for test reports.

Bowling said the information gleaned from GeneStrat not only helps direct the choice of therapy targeted to a specific alteration but also may affect whole brain radiotherapy recommendations, for example, for patients with *KRAS* mutations with brain lesions. The liquid biopsy is part of an aggressive treatment approach that may pay dividends throughout a patient's cancer journey, Bowling noted.

"What we're finding preliminarily is that by treating these patients very aggressively upfront, they're getting out of the hospital much faster," said Bowling, who also is an assistant professor of medicine and director of Interventional Pulmonology and Pulmonary Diagnostic Services at East Carolina University School of Medicine. "We believe what it's going to show is that they're not getting secondary pneumonia staying in the hospital, which means their performance status is better and they can tolerate their chemotherapy much better as outpatients.

"It's relatively new and there needs to be a lot more data gathered but I think the impact of liquid biopsies is going to be huge," added Bowling. "We're one center with a very organized multidisciplinary program that utilizes this technology and we think in a very effective way. That's going to be the future—getting as much information as you can quickly to direct you to therapies."

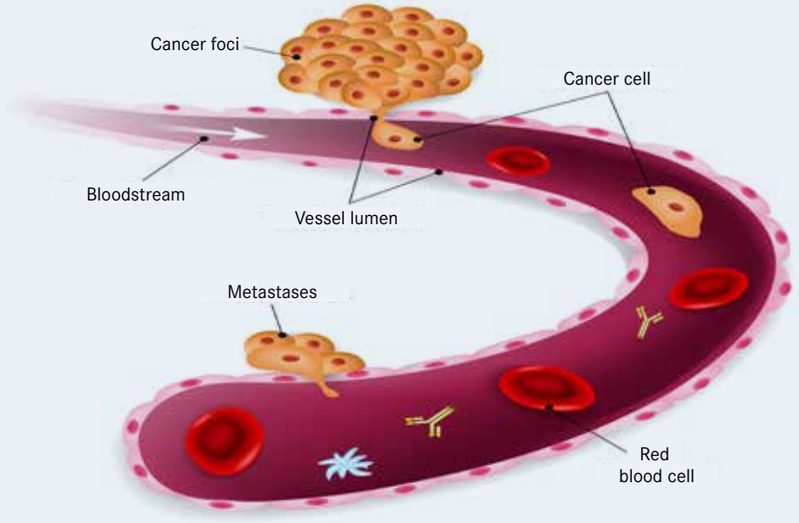
Assay Types and Challenges

In the current landscape, blood-based liquid biopsy tests fall into 1 of 2 categories: PCR-based tests that identify known mutations and next-generation sequencing (NGS) assays that detect a broader range of alterations including gene fusions. PCR testing is faster and less expensive but yields more limited information, Pennell noted.

He said the choice of test type depends upon the clinical situation. For example, if an oncologist has a patient with an *EGFR* mutation who is progressing, using a PCR-based assay to look for the T790M resistance mutation would be a valid initial step. "On the other hand, if you have a nonsmoker who you're highly suspicious may have some kind of targetable mutation and you've never been able to test them and you cannot get a biopsy safely or they don't have enough tissue to do it, then doing a more broad NGS-based plasma test in order to assay a wide range of defects including fusions would be a better choice than a PCR-based test," he said.

Regardless of the technology utilized, there are challenges with liquid biopsy testing. Geoffrey Oxnard, MD, a thoracic oncologist at the Dana-Farber Cancer Institute, said during the

Defining the Liquid Biopsy



Types of DNA

- Circulating cell-free DNA (ccfDNA or cfDNA)—Small DNA fragments shed by all cells into the circulation. Includes blood, lymph, urine, saliva, and cerebral spinal fluid
- Circulating tumor DNA (ctDNA)—DNA shed specifically by tumor cells into the circulation
- Plasma tumor DNA—Plasma component of ctDNA

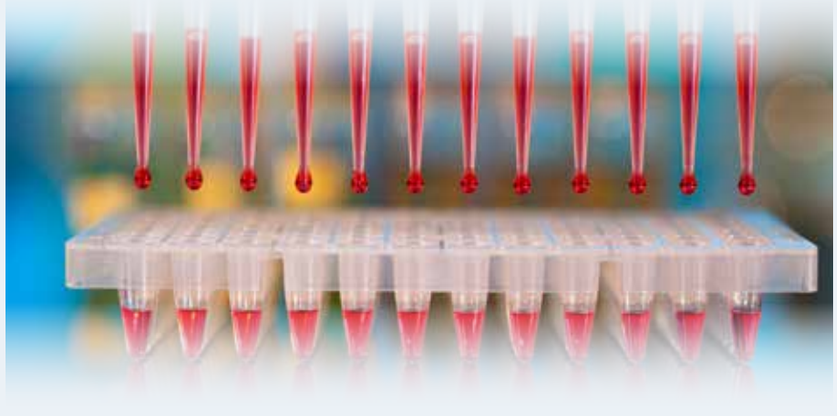
Methods for Analyzing Blood-Based DNA

- Digital polymerase chain reaction (PCR)
  - BEAMing (beads, emulsions, amplification, magnetics)
  - Droplet digital PCR
  - Microfluidics-based digital PCR
- Next-generation sequencing
  - Assays for single locus/amplicon
  - Cancer gene panels
  - Whole-exome sequencing
  - Whole-genome sequencing

Potential Categories of Clinical Utility for Blood-Based Biomarkers

- Predictive—Indicates whether individual patient will benefit from a particular therapy; for example, companion or complementary diagnostic
- Response—Assesses drug efficacy and monitors response to treatment
- Resistance—Measures emerging resistance to therapy
- Early detection—Identifies potential markers or signatures of disease; for example, adjunctive to lose-dose computed tomography scans in early lung cancer screening program
- Prognostic—Informs treatment selection

FDA-AACR Liquid Biopsies in Oncology Drug and Device Development Workshop; July 19, 2016; Washington, DC. http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/FDA-AACR-liquid-biopsies-in-oncology-drug-and-device-development.aspx#.WIYkrrYrJPU. Accessed January 22, 2017.



FDA-AACR workshop that assays are better able to detect mutations in patients with more advanced disease.[8]

Oxnard discussed the advantages and disadvantages of using plasma-based genotyping in 3 case study examples in patients with NSCLC: newly diagnosed NSCLC of an unknown genotype, acquired resistance to EGFR inhibitor therapy with an unknown mechanism of resistance, and suspected recurrence of NSCLC with surveillance.

Although testing was valuable for the newly diagnosed patient, the sensitivity of the assay was approximately 80%, creating the potential for false negatives. For the patient with acquired resistance, there is a "clear clinical need for plasma genotyping" but there is an unclear "reference standard" comparing these tests with tumor biopsies.

For the patient with prior treatment of NSCLC and suspicious signs of recurrence with a CT scan and bone scan, there are no "clear data" yet on the clinical utility of plasma genomics for making a diagnosis, Oxnard said. However, he said tumor NGS is proving increasingly useful in amplifying the standard pathological evaluation.

Overall, sensitivity and reference standards have emerged as 2 challenges for the plasma-based testing. "As you have more disease, your sensitivity goes up," said Oxnard. "If you have stage IV lung-only disease, your sensitivity was in the range of 50% or 60% because a lot of these patients just aren't shedding DNA into their blood for you to detect. If you start getting brain, bone, liver metastasis, if you start getting sick with a high-volume disease, your chance of shed DNA goes up and the chance of a liquid biopsy being successful goes up."

In the area of reference standards for resistance testing, Oxnard said "a single biopsy does not represent resistance. We need a better sense of what a reference standard should be and maybe that is, in fact, treatment outcome. Many of the available assays have not been optimized because of these complexities."

Oxnard also said mutation test results can be difficult to interpret.[8] "It's hard to know what a positive and negative is with these assays," he said. "There are low-level results you are seeing; you are not sure if it's in the noise range or not. Rigorously defining a positive for your assay is really important, and it's a place where a lot of these assays are struggling."


Geoffrey Oxnard, MD

Jänne agrees that additional steps must be taken to improve testing. "One of the things that deserves further work is making sure that there is a common set of standard principles by which these tests have been validated and that that's a transparent process," he said. "That's the only way you're going to be able to understand the performance characteristics of test A versus test B versus test C. It's both the analytical validation and ultimately you need some clinical validation. I don't think that [standard] exists at the moment."

Oxnard believes the standards set in lung cancer for reference testing will set the pace for other tumor types. "What we are establishing in lung cancer will be emulated across oncology," he said.

Beyond Lung Cancer

Although liquid biopsies are most advanced in lung cancer, researchers are actively delving into their potential in other solid tumor types. At the 2016 San Antonio Breast Cancer Symposium, Massimo Cristofanilli, MD, of the Robert H. Lurie Comprehensive Cancer Center, presented a retrospective study of 91 patients with locally and advanced and metastatic breast cancer. [9]


Massimo Cristofanilli, MD

Using Guardant360, an NGS panel that tests circulating tumor DNA (ctDNA) for more than 50 genes, Cristofanilli and colleagues found a statistically significant difference by log rank test in progression-free survival and overall survival associated with the percentage of ctDNA at baseline (<0.5 vs ≥0.5; P = .003 and P = .012, respectively) and number of mutations at baseline (<2 vs ≥2; P = .059 borderline and P = .0015). Targeted therapy was initiated for 16 patients (19%) based on the mutation analysis.

Investigators concluded that the biopsy provides real-time information useful for treatment planning, disease monitoring, and prognostic evaluation.

In prostate cancer, Howard I. Scher, MD, has been leading investigations into the use of liquid biopsies to translate growing knowledge about the biology of the tumor type to better direct therapies. In an interview with *OncLive*®, Scher noted the difficulty of conducting tissue biopsies in the malignancy, which most frequently metastasizes to the bone.

"The ability to do consistent molecular profiling is actually quite low. Our experience using directed biopsies, where we know exactly where the lesion is, is only about 50%. It's an invasive procedure and is costly," Scher said. "If a patient has 10 individual lesions, they are not all biologically the same. Inadvertently, we may biopsy a lesion, identify a specific gene or pathway, and that pathway is not the key driver of the resistant cell population."

Scher said there are several tumor biomarkers that can be extracted from a blood draw, including circulating tumor cells (CTCs), DNA, RNA, and exosomes. His team has been focusing on using technology developed by Epic Sciences to study an androgen receptor (AR) splice variant, AR-V7, that drives prostate cancer progression and its association with response to therapies.[10]


Howard I. Scher, MD

"We have seen that the frequency of this splice variant is relatively low in the first-line setting," Scher said. "It gets higher with each course. Each time we identify it, the patients treated with AR-signaling directed therapy do not respond. In contrast, there is no relationship between the presence of AR-V7 and response to chemotherapy–in this case, docetaxel or cabazitaxel (Jevtana). We have shown that the survival of patients is improved in those with AR-V7 present who receive a taxane, and it is inferior for those who receive AR-directed therapy."

Studies such as those that Scher is conducting are part of the future face of liquid biopsies, said Jänne. "This is a rapidly evolving area in terms of clinical use and the technology. It's giving us insights into cancer that we've never previously had and I think that's the exciting part from the cancer basic biology side and from the therapeutic side. This is an alternative that may help guide clinical care." ■

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Oncology& Biotech News

Conference Highlights

Singapore

ESMO Asia 2016

PD-1/PD-L1 Inhibitors Move Forward in Bladder Cancer

By Ariela Katz

Although bladder cancer was among the first tumor types where immunotherapy was routinely used, it wasn't until the FDA approved the PD-L1 inhibitor atezolizumab (Tecentriq) last May that new options employing the modality were introduced. Now, several agents that attack the PD-1/PD-L1 immune checkpoint pathway are in development for frontline settings.

Joaquim Bellmunt, MD, PhD, provided an overview of key clinical data for the emerging immunotheraoy options for patients with bladder cancer during a presentation at the 2016 ESMO Asia Congress, which was held December 16 to 19 in Singapore.

Joaquim Bellmunt, MD, PhD

"Bladder cancer has, in fact, been one of the first diseases for which immunotherapy was active, and we need to go back 15 years ago when BCG was shown to be effective," said Bellmunt, referring to the Bacillus Calmette-Guérin vaccine. "Since then, nothing has happened—until quite recently when the checkpoint inhibitors came.

"We are now in exciting times in terms of immunotherapy in bladder cancer," added Bellmunt, who is an associate professor of medicine at Harvard Medical School and director of the Bladder Cancer Center at the Dana-Farber Cancer Institute/Brigham and Women's Hospital. "We have seen that immunotherapies are well tolerated and active treatments for our patients."

Phase I Studies

Previous studies have strongly indicated the benefits of using immunotherapies in the treatment of bladder cancer, including a phase I study that demonstrated that tumors expressing PD-L1–positive immune cells (ICs) had particularly high response rates to atezolizumab.[1] Further, the study results suggested that, due to the lack of renal toxicity caused by the immunotherapy agent, patients with bladder cancer, who are often older and have a higher incidence of renal impairment, may be better able to tolerate atezolizumab versus chemotherapy.

In the phase I KEYNOTE-012 trial evaluating pembrolizumab (Keytruda) in patients with advanced urothelial cancer, results indicated that of the 28 patients with measureable disease at baseline, the objective response rate (ORR) was 25%, with 3 complete responses (CRs; 11%) and 4 partial responses (14%).[2] The study concluded that the PD-1 inhibitor demonstrated durable antitumor activity, with a higher response rate seen in patients with positive PD-L1 expression.

At the 2016 ASCO Annual Meeting, the safety and efficacy of durvalumab (MEDI4736) in patients with advanced urothelial bladder cancer were presented. The ORR was 31% (95% CI, 17.6-47.1) in the 42 evaluable patients, 46% (95% CI, 28-66) in the PD-L1–positive subgroup (≥25% in the tumor cells [TCs] or ICs), and 0% (95% CI, 0.0-23.2) in the PD-L1–negative subgroup.[3] It was determined that durvalumab had a manageable safety profile and showed evidence of significant clinical activity in heavily pretreated PD-L1–positive patients with advanced bladder cancer.

Bellmunt also pointed to the phase Ib JAVELIN Bladder 100 trial, which investigated the safety and efficacy of avelumab as a second-line therapy in patients with metastatic urothelial carcinoma (mUC).[4] Avelumab showed clinical activity, including 1 CR, an ORR of 15.9%, and a disease control rate (DCR) of 59.1%. The drug was also well tolerated, showing a low rate of grade 3/4 toxicities, no renal toxicity, and no deaths as a result of the treatment.

The fifth checkpoint inhibitor under investigation to treat bladder cancer, and another that Bellmunt discussed, was nivolumab (Opdivo). In an open-label, multicenter phase I/II study of previously treated patients with several tumor types, nivolumab showed an ORR of 24% and a median overall survival (OS) of 9.7 months.[5] The study concluded that nivolumab as a monotherapy for previously treated patients with mUC had encouraging safety and efficacy data.

Phase II Studies

The early-phase research laid excellent groundwork for future phase II studies, which, according to Bellmunt, generated additional promising information.

The FDA approved atezolizumab for the treatment of patients with urothelial carcinoma based on results of a phase II trial. The study showed durable activity and good tolerability in patients with locally advanced and mUC who have progressed following treatment with a platinum-based chemotherapy.[6]

Higher levels of PD-L1 expression (≥5%) on ICs were associated with an increased response, showing a 26% ORR compared with a 15% ORR in all patients. "Remember, in the *Nature* paper, it was initially a 45% ORR[1]; now here, despite using the same PD-L1 staining, the response rates go down to 26%, but there is still quite consistent data in terms of survival in the whole patient population, including 8 months of median survival in the second- and third-line setting," Bellmunt explained.

Results from the phase II CheckMate 275 study of nivolumab in previously treated patients with mUC showed that the confirmed ORR was 19.6% (95% CI 15.0–24.9) with PD-L1 expression (≥5%), and 16.1% (95% CI, 10.5-23.1) in patients with low to no PD-L1 expression.[7] The 8.74-month median OS was also longer than what is typically seen with chemotherapy.

These trials mostly explored checkpoint inhibitors in the second-line setting and beyond. "Because we know there are patients who are unable to receive platinum-based chemotherapy, we are presently using carboplatin, and we know that the results are not good enough," Bellmunt commented. "This is a setting where these agents have been tested in first-line therapy."

In a randomized phase II/III trial, patients with advanced urothelial cancer were treated with either a gemcitabine/carboplatin combination or atezolizumab as a first-line treatment. The study concluded that atezolizumab shows clinically meaningful activity in patients with mUC who are ineligible for cisplatin chemotherapy. The ORR was 24%, with a median OS of 14.8 months, compared with 9.3 months for gemcitabine and carboplatin, and 57% of patients were still alive after 1 year.[8] The durability and favorable toxicity profile shown in this study make atezolizumab an attractive alternative to chemotherapy.

In the IMvigor 210 trial, atezolizumab in the frontline setting demonstrated an ORR of 23% (95% CI, 16-31) and a CR rate of 9%. For the entire study population (n = 119), the median OS was 15.9 months, with 70% of responses ongoing.[9] "This is obviously beyond what we see in chemotherapy in the first line," Bellmunt commented, "and more data is needed in this setting."

Pembrolizumab was also assessed in the first-line setting for cisplatin-ineligible patients with advanced urothelial cancer in the KEYNOTE-052 trial. The ORR at a median follow-up of 8 months was 24% (95% CI, 16.0-33.6).[10] These results are similar to those seen in the atezolizumab trial in the first-line setting, showing a clear trend in using these agents as effective first-line therapies. However, Bellmunt cautioned, "this trial is still immature, and we don't know the median survival."

Among PD-L1–positive patients, pembrolizumab showed an ORR of 36.7% (95% CI, 19.9-56.1), as defined by a combined positive score between TCs and ICs of ≥10%. This was the highest expression level among the checkpoint inhibitors, but also showed the highest ORR (**Table 1**).

The challenge, in light of these positive results, is how to optimize the use of these checkpoint inhibitors. "As you can see from the response rates, which are quite consistently at 15%, 20%, or 25%, we are only benefiting a portion of our patients. The question is, how can we identify those patients who are going to respond [to immunotherapy]," Bellmunt noted.

Potential biomarkers include PD-L1 expression, mutational burden, The Cancer Genome Atlas (TCGA) subtype (luminal II), CD8 infiltration, immune-related gene expression signatures, and peripheral expansion of certain T-cell receptor clones.

Table 1. Clinical Efficacy Comparison of Checkpoint Inhibitors in Bladder Cancer

Agent	ORR, All Patients	ORR, PD-L1+ Patients	PD-L1+ Definition	Reference
Atezolizumab	15%	26%	≥5% on ICs	6
Nivolumab	19.6%	28.4%	≥5% on TCs	7
Pembrolizumab	24%	36.7%	≥10% on TCs + ICs	10

ICs indicates immune cells; ORR, objective reponse rate; TCs, tumor cells.

Table 2. Ongoing Phase III Immunotherapy Trials for Bladder Cancer

Trial Description	Study name/ ClinicalTrials.gov Identifier
Atezolizumab (Tecentriq)	
Atezolizumab plus gemcitabine/carboplatin versus the chemotherapy doublet with placebo in patients with untreated locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-based therapy	IMvigor 130 NCT02807636
Atezolizumab vs chemotherapy in locally advanced or metastatic urothelial bladder cancer that has progressed during or after platinum-based therapy	IMvigor211[a] NCT02302807
Avelumab	
Avelumab plus best supportive care (BSC) vs BSC as maintenance therapy for patients with locally advanced or metastatic urothelial cancer	JAVELIN Bladder 100 NCT02603432
Durvalumab	
Durvalumab as monotherapy and in combination with tremelimumab vs standard-of-care chemotherapy in first-line stage IV urothelial cancer	NCT02516241
Nivolumab (Opdivo)	
Nivolumab monotherapy vs placebo as adjuvant therapy in patients with high-risk, invasive urothelial carcinoma after radical surgical resection	CheckMate 274 NCT02632409
Pembrolizumab (Keytruda)	
Pembrolizumab with or without platinum-based chemotherapy vs chemotherapy alone in patients with unresectable, or metastatic urothelial carcinoma who have not received prior systemic chemotherapy for advanced disease	KEYNOTE-361 NCT02853305
Pembrolizumab vs paclitaxel, docetaxel, or vinflunine in participants with advanced urothelial cancer that has recurred after chemotherapy	KEYNOTE-045[a] NCT02256436

[a]Trial is ongoing but not recruiting participants.

A retrospective tissue analysis showed that the presence of PD-L1, which is widely expressed in tumor cell membranes and tumor-infiltrating mononuclear cells in urothelial carcinoma, was not predictive of OS, but instead was a prognostic biomarker.[11]

Tissue samples from patients in the IMvigor 210 trial were classified into luminal (n = 73) and basal (n = 122) TCGA subtypes. Although there were responses in all subgroups, patients in the luminal II group (n = 52) responded better to treatment with atezolizumab (ORR, 34%; $P = .0017$).[12] Outcomes were also better in patients with a higher mutational burden; however, Bellmunt noted the risk involved in retroactively analyzing patient tissue samples.

In a bladder cancer trial, the NanoString platform was used to assess and predict responses to pembrolizumab. The 13-gene T-cell receptor signaling signature predicted a higher clinical benefit ($P = .073$) and progression-free survival rate ($P = .024$) in patients receiving pembrolizumab.[2]

What the Future Holds

"There are a lot of trials now in different settings for bladder cancer," commented Bellmunt. For PD-1 inhibitors, there are several phase III studies in first- and second-line settings, and beyond (**Table 2**).

For example, based on the success of the phase

(Continued on page 22)

(Continued from page 19)

Ib JAVELIN study, the phase III JAVELIN Bladder 100 trial is planned to assess maintenance treatment with avelumab plus best supportive care (BSC) to determine if avelumab has an effect on survival in patients with locally advanced or mUC that did not worsen during or following completion of first-line chemotherapy (NCT02603432).

A phase III KEYNOTE-045 study of pembrolizumab versus paclitaxel, docetaxel, or vinflunine (at the discretion of the investigator) for patients with advanced urothelial carcinoma is currently ongoing, but is not recruiting participants (NCT02256436). The study's interim analysis results demonstrated a superior median OS in the pembrolizumab arm compared with chemotherapy (10.3 vs 7.4 months).

Bellmunt stressed that what is important about the KEYNOTE-045 trial is that the patients were carefully stratified based on ECOG performance status, hemoglobin level (<10 vs ≥10 g/dL), presence or absence of liver metastases, and time from the last dose of chemotherapy (<3 vs ≥3 months). Additionally, treatment-related adverse events (AEs) were generally mild, the most common including pruritus, fatigue, nausea, diarrhea, and decreased appetite. There were more and higher-grade AEs seen across the board with chemotherapy; however, the pembrolizumab arm saw more immune-related AEs, such as thyroid abnormalities and pneumonitis, compared with chemotherapy.

Bellmunt concluded that he believed that pembrolizumab was the most promising option, since it is the first agent to demonstrate an OS improvement compared with chemotherapy in patients with advanced urothelial carcinoma after failing treatment with platinum-based chemotherapy.

"Pembrolizumab has shown benefit in patients regardless of PD-L1 expression," Bellmunt said, "and probably should become the new standard-of-care second-line therapy for patients failing platinum-based chemotherapy." ■

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Mutational Link to Immunotherapy Response Unclear

By Lisa Miller

In the search for biomarkers that would help predict response to emerging immunotherapies, researchers are considering the impact of mutational load. Although some trials have shown a correlation between patients with a higher mutational burden and better responses to immunotherapy agents, particularly checkpoint inhibitors, this marker alone is not sufficient to affect treatment decision making, according to Caroline Robert, MD, PhD.

Caroline Robert, MD, PhD

Robert reviewed clinical evidence that argues against the importance of mutational load on patients' response to immunotherapy during a debate at the 2016 ESMO Asia Congress. Robert, head of the Dermatology Unit at the Institut Gustave-Roussy in France, contended that the formula for patient response to immunotherapy is much more complex.

A study by Van Allen et al showed a correlation between response to ipilimumab (Yervoy) in patients with metastatic melanoma and both mutational load (P = .0076) and neoantigen load (P = .027).[1] Patients with a higher mutational and/or neoantigen load were more likely to show a clinical benefit to ipilimumab therapy. However, among the 40 patients for whom transcriptome data were obtained and analyzed, no common neoantigen could be found that could be used in selecting patients for therapy with ipilimumab. In addition, a great deal of overlap was noted between the patients who did and did not respond in terms of both mutation and neoantigen load.

> *"We know that it's not sufficient to have a lot of mutation. We also have to prime correctly, we have to have T cells that are able to extravasate the vessels and go back to the tumors where they could still be facing resistance mechanisms."*
>
> —Caroline Robert, MD, PhD

In an analysis of patients with metastatic urothelial carcinoma, which has often been studied for its association with mutational load, Robert pointed out that in the IMvigor 210 trial, patients' mutational load was tested with the FoundationOne 315-cancer gene panel. Similarly, mutational loads were greater in the patients who responded to treatment with atezolizumab (Tecentriq) than in the nonresponders (P <.0001).[2] A correlation to both progression-free (P = .003) and overall survival (P = .014) was also noted. However, these associations were found to be statistically independent of other predictors of response.

"Clinically it doesn't seem to be helpful," Robert said. Instead, Robert suggested that perhaps mutational load may be a prognostic biomarker rather than a predictive biomarker.

A tumor genome analysis of more than 500 patients with cancers in 6 tumor sites showed that there was no difference in survival between patients with high mutation counts and low mutation counts (P = .55).[3] There was a statistical significance, though, between patients with at least 1 immunogenic mutation and higher survival rates (P = .0021). Concordance was also noted between immunogenic mutation count and CD8, PD-1, and CTLA-4 expression (P = .000001).

The mutational burden should not change the way oncologists treat their patients, Robert said, as it is not a complete picture of response to immunotherapies. "I see this as very important raw data that are necessary, but are not sufficient to mount an efficient immune response."

Instead, mutational load could be 1 piece of a more integrated and complex algorithm determining a patient's response to immunotherapy. This algorithm, Robert suggested, could also include considerations of the genetics of the host; tumor-specific parameters, including neoantigens, microsatellite instability status, and immune targets; tumor microenvironment; and the microbiome.

An association between mutational load and cytolytic activity has been suggested, especially as they yield neoepitopes and bind to the human leukocyte antigen (HLA). However, cytolytic activity inversely affects mutational load through immunoediting, as was seen in melanoma T-cell interactions.[4]

"We know that it's not sufficient to have a lot of mutation. We also have to prime correctly, we have to have T cells that are able to extravasate the vessels and go back to the tumors where they could still be facing resistance mechanisms," Robert said.

In an analysis of the association between PD-L1 expression, cytolytic activity, and mutational load studied across 9 tumor types, a wide difference was found between each of the tumor types with all 3 of the parameters, indicating the interdependent nature of each of the parameters.[5] The investigators noted that future biomarkers for anti–PD-1/PD-L1 therapy would benefit from tumor-specific, integrated, and genomic approaches.

Although the influence of mutational load should change the way oncologists view responses to immunotherapy, Robert said, it should not change the way that they treat patients. ■

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Nab-Paclitaxel Paired With Anti–PD-L1 Immunotherapies in TNBC Studies

By Anita T. Shaffer and Silas Inman

Combination regimens that pair nab-paclitaxel (Abraxane) with PD-L1 checkpoint blockade immunotherapy agents are emerging as a robust area of investigation in triple-negative breast cancer (TNBC), bolstered by clinical trial results that establish the chemotherapeutic agent as an effective partner for other therapies.

Although nab-paclitaxel has been combined in some studies with other chemotherapies, the focus is shifting to regimens that include immunotherapies as the efficacy of that approach continues to grow. Nab-paclitaxel, an albumin-bound form of paclitaxel, is indicated for patients with metastatic breast cancer after prior chemotherapy.

Several later-stage trials evaluating nab-paclitaxel in combination with anti–PD-L1 agents as neoadjuvant or first-line therapy for patients with TNBC are planned or underway (**Table**). The TNBC studies are part of a broader landscape in which nab-paclitaxel is partnered with PD-1 or PD-L1 inhibitors; a recent review counted approximately 20 ongoing trials in breast cancer, non–small cell lung cancer, and other malignancies.[1]

Early clinical trial findings indicate that nab-paclitaxel, which delivers faster and greater tissue penetration than paclitaxel, may amplify the antitumor activity of checkpoint blockade immunotherapy agents without overlapping or worsening immune-related toxicities.[1]

In a phase Ib trial, upfront treatment with the PD-L1 inhibitor atezolizumab (Tecentriq) plus nab-paclitaxel showed a confirmed objective response rate (ORR) of 46% in patients with metastatic TNBC (n = 13; 95% CI, 19-75).[2] The complete response in the frontline setting was 8%. The progression-free survival (PFS) and overall survival (OS) data were not yet mature.

The potential for nab-paclitaxel combinations in TNBC was discussed recently at the 2016 San Antonio Breast Cancer Symposium in the context of findings from the phase II tnAcity study.[3] "In the metastatic setting, where patients are going to get multiple lines of therapy, looking at the toxicity profile that Abraxane offers has been quite welcomed. It improves neuropathy issues and myelosuppression, leaving itself very open to be partnered with other agents," said Denise A. Yardley, MD, senior investigator at the Sarah Cannon Research Institute, who presented the tnAcity findings.

"It is very attractive in the triple-negative population because it partners very well with immunotherapy," Yardley said. "Because it does not require steroid premedication, which may mitigate some of the benefits of immune therapy, it is going in that direction, too."

The tnAcity study, which was initiated in 2013, was originally designed to advance the superior of the 2 nab-paclitaxel doublets into a 550-patient phase III study comparing the doublet with gemcitabine/carboplatin. However, the introduction of effective immunotherapies since the study was designed caused the investigators to reconsider a chemotherapeutic approach in favor of combination strategies with PD-1/PD-L1 inhibitors.

Table. Nab-Paclitaxel Plus PD-L1 Inhibitors in TNBC Trials

Description	Population	Target Enrollment	ClinicalTrials.gov Identifier
Phase III Trials			
Nab-paclitaxel + atezolizumab vs nab-paclitaxel + placebo (IMpassion130)	Previously untreated metastatic TNBC	900	NCT02425891
Nab-paclitaxel + carboplatin +/- atezolizumab followed by surgery + AC, EC, or FEC (NeoTRIPaPDL1)	Neoadjuvant therapy in locally advanced TNBC	272	NCT02620280
Phase II Trials			
Nab-paclitaxel + atezolizumab before surgery followed by atezolizumab monotherapy	First-Line, neoadjuvant TNBC	37	NCT02530489
Sequential nab-paclitaxel followed by EC +/- durvalumab vs chemotherapy alone (GeparNuevo)	Primary TNBC	174	NCT02685059[a]

[a]Study is not yet recruiting participants.

AC indicates adriamycin + cyclophosphamide; EC, epirubicin + cyclophosphamide; FEC, fluorouracil, epirubicin, + cyclophosphamide; TNBC, triple-negative breast cancer.

In the tnAcity trial, the combination of nab-paclitaxel and carboplatin reduced the risk of progression or death by 40% compared with 2 other chemotherapy doublets as a frontline therapy for patients with metastatic TNBC.[2]

The median PFS was 7.4 months with the nab-paclitaxel plus carboplatin regimen compared with 5.4 months for nab-paclitaxel plus gemcitabine (HR, 0.60; 95% CI, 0.39-0.93; P = .02) and 6.0 months for gemcitabine plus carboplatin (HR, 0.61; 95% CI, 0.39-0.94; P = .03). The 12-month PFS rate was 27% with nab-paclitaxel/carboplatin compared with 13% and 11% for nab-paclitaxel/gemcitabine and gemcitabine/carboplatin, respectively.

The study randomized 191 untreated patients with metastatic TNBC to receive the combination of carboplatin and gemcitabine (n = 66) or nab-paclitaxel with carboplatin (n = 64) or gemcitabine (n = 61). Nab-paclitaxel was administered at 125 mg/m^2, carboplatin at area under the curve 2, and gemcitabine was given at 1000 mg/m^2. In each arm, treatment was administered on day 1 and 8 every 3 weeks.

The ORR with nab-paclitaxel/carboplatin was 72%, which consisted of 7 complete responses (CR; 11%) and 39 partial responses (PR; 61%). The ORR was 39% with nab-paclitaxel/gemcitabine and 44% with gemcitabine/carboplatin. The CR rate in each of these arms was 8%.

Median OS was 16.4 months with nab-paclitaxel/carboplatin compared with 12.1 months with nab-paclitaxel/gemcitabine (HR, 0.66; 0.42-1.04; P = .07) and 12.6 months for gemcitabine/carboplatin (HR, 0.74; 0.48-1.16; P = .18). These findings were not statistically significant.

The most common grade ≥3 treatment-emergent AEs observed in the nab-paclitaxel/carboplatin, nab-paclitaxel/gemcitabine, and carboplatin/gemcitabine arms, respectively, were neutropenia (42%, 27%, 52%), anemia (13%, 12%, 27%), thrombocytopenia (9%, 7%, 28%), leukopenia (6%, 3%, 11%), febrile neutropenia (5%, 2%, 0%), fatigue (3%, 15%, 3%), and peripheral neuropathy (5%, 7%, 2%). Growth factors were needed for 45%, 26%, and 47% of patients in each arm, respectively. ■

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Metabolic Pathways Attract Fresh Interest in Gliomas

By Shannon Connelly

In neuro-oncology, interest in investigating metabolic pathways in tumors with the hope of identifying novel therapeutic targets is on the upswing, according to Howard A. Fine, MD.

"With new knowledge, all of a sudden there's a whole new level of science brought to it," said Fine, who is director of the Brain Tumor Center in the Sandra and Edward Meyer Cancer Center, and chief, of the Division of Neuro-Oncology at Weill Cornell Medicine. "I think that's where we are with tumor metabolism."


Howard A. Fine, MD

In an interview with *OncologyLive®*, Fine discussed the reasons behind this renewed interested, the impact the focus has had on the treament of patients with gliomas, and what he sees for the future of neuro-oncology in this area.

Q: Why has there been renewed interest in metabolic targets?

Metabolism in cancer is an interesting story in that some of the earliest approaches we used to try to fight cancer, starting 30 to 40 years ago, tried to target the metabolic pathways. Some of our earliest drugs to target cancer, like methotrexate (Trexall), interfered with folate metabolism, and that was our major way of fighting cancer.

With the advent of molecular biology and genetics, metabolism and the idea of targeting the aberrant metabolism kind of became passé, kind of like pharmacology did. We got into the genetic age and people began to forget about it, until we began to realize that many of the oncogenic pathways and many of the deregulated signal transduction pathways that we've been studying end up converging on pathways of metabolism.

There's been an increased interest in all [areas] of cancer, and certainly neuro-oncology, to not only begin to understand the aberrant metabolism in tumors to better understand tumor biology, but also to realize that there may be great opportunities for novel therapeutic targeting.

This particularly came to light with the discovery several years ago of the *IDH* mutation found in a large percentage of low-grade gliomas. The *IDH* mutation is in a gene that is central in the tricarboxylic acid (TCA) pathway and is a basic metabolic enzyme. That again brought to light how intrinsically important metabolism is in tumor biology, glioma biology, and the potential therapeutic options thereof.

Q: What was the significance of this finding?

It's the first mutation that has been shown in a TCA enzyme that produces a unique metabolite, now called an oncometabolite. It's kind of the paradigm for how metabolism is important for any cancer, so it has a special place in the heart of neuro-oncologists.

I think that increasingly so, in all of oncology, people are beginning to pay a lot more attention to the importance of cancer metabolism and how it may offer new therapeutic opportunities.

Q: What do you think is on the horizon, and what are you hoping to see?

I think *IDH1* is just the tip of the iceberg, although I don't know that we're going to find that many new mutations in oncometabolites. It is quite clear, and we've known this for many, many years, but now we're beginning to really understand the molecular details of it, that the metabolism in tumors is quite dramatically different than it is in normal tissue.

When you think about therapies, what are we trying to do? We're trying to find ways in which tumor tissue is different and behaves differently and has a different biology than normal tissue because that gives a therapeutic target. If you can find the therapeutic ratio that's different between normal tissue versus tumor tissue, that gives you something to aim at therapeutically without worrying about overlapping normal tissue toxicity.

Metabolism is just that: it's a very complex series of biochemical pathways that appear to be, in many respects, quite different in tumor tissue than in normal tissue, so it offers, theoretically, a very promising new area to therapeutically target.

I hope to see, and I think we will see, whole new strategies based on developing drugs against these novel metabolic targets and, in fact, possibly even diet modifications. There has been a lot over the last 10 or 20 years about special kind of diets, like ketogenic diets, that effectively target metabolism.

The studies haven't necessarily been done in the correct way—they haven't been done in conjunction with pharmacologic intervention. I think we're going to see those types of strategies. It's a great unexplored and an exciting old/new area.

Q: What are the effects of stress on the tumor metabolic environment?

We know that stress causes hormonal changes and hormonal changes are involved in metabolism. For instance, we know that stress induces glucocorticoids and causes adrenal hyperactivity. When you get high levels of adrenocorticotropic hormone (ACTH) and steroids, you increase insulin levels. We know that insulin drives tumor growth and tumor promotion.

Although there's no data, one could speculate that high levels of stress hormones over long periods of time may increase insulin, and may increase your chances of type 2 diabetes, which has been shown, and we think that high levels of insulin resistance, hypoglycemia, certainly can help fuel tumor metabolism.

Q: Does age play a factor in metabolic pathways?

The answer is we don't know, but I'm sure that it does. We know, for instance, that in a normal aging brain, metabolism is dramatically different than it is in developing in a middle-aged brain. That is well established and there's an increasing number of papers being published looking at the molecular mechanism of that.

If the normal surrounding brain metabolism is different, tumors don't live in isolation, they live within the host, so I'm sure the metabolic profile and the details of the metabolism of tumors in an older versus a younger brain is quite different, but I think we are just beginning to explore those aspects.

Q: Are there any ongoing trials that you are currently watching with interest?

There's a big focus on a whole new series of drugs that target this mutant *IDH* gene, so these IDH inhibitors are being explored now both in low-grade and high-grade gliomas with variable success. I think we're just beginning to learn to use those.

Centers like ours are looking at the old ketogenic diet in combination with very specific new pharmacologic interventions like PI3 kinase inhibitors and mTOR inhibitors as a way of trying to hit the metabolism in various fronts of tumors. We are just beginning to see those kinds of trials and therapeutic interventions. ■

Enhanced Recovery Program Improves Outcomes After Colorectal Cancer Surgery

By Traci L. Hedrick, MD, MS

Assistant Professor, Surgery
Co-Director, Enhanced Recovery Program
University of Virginia Health System

The adoption of enhanced recovery after surgery (ERAS) protocols can improve not only the outcomes of patients after a procedure but can also reduce hospital costs, as has been seen in an ERAS program in colorectal cancer at the University of Virginia (UVA) Health System.

Surgical resection offers a cure for thousands of patients with colorectal cancer each year. Yet for many, this experience can be accompanied by surgical complications and prolonged recovery times. Colorectal surgery has traditionally been associated with higher morbidity rates than many other types of surgery for a multitude of reasons. The surgeries are often complex, involving multiple quadrants, and are further complicated by the anatomical constraints of the pelvis. Even with the advent of minimally invasive surgery, it was not uncommon for patients to be incapacitated for several weeks.

The ERAS movement, first proposed by Danish surgeon Henrik Kehlet, MD, PhD, is based on many common-sense principles that had been overlooked with the advent of modern medicine.[1] The basic premise of enhanced recovery is to keep the patient in a normal physiologic state during the perioperative period. This is accomplished through the avoidance of many well-meaning, yet misguided, traditional surgical practices, including preoperative fasting, liberal intravenous administration of high-salt fluids, and opioid-centric pain management strategies.

To date, more than 10 case-control studies including over 3000 participants have demonstrated shortened recovery time and decreased complications in ERAS patients within a variety of surgical patient populations.[2-14]

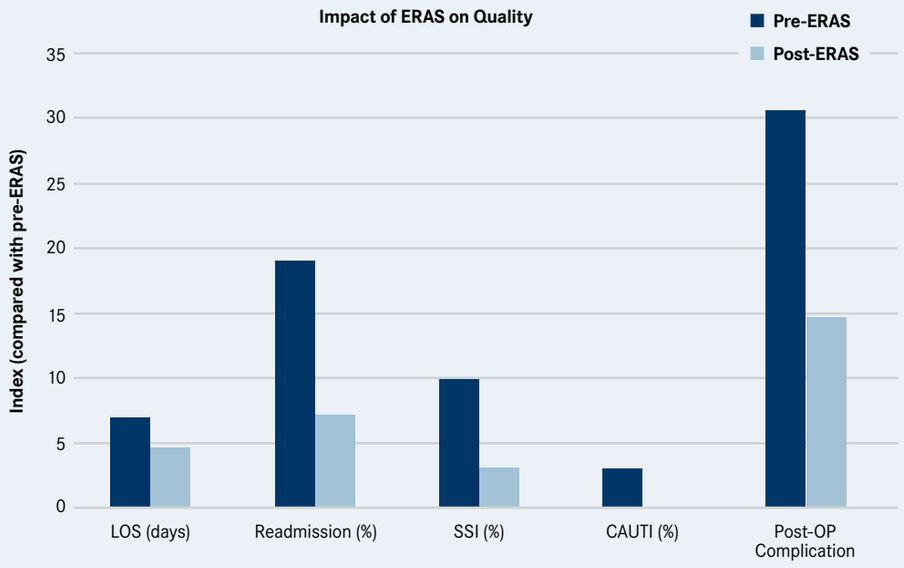
Instead of starving patients prior to surgery, patients are encouraged to consume clear liquids with carbohydrate loading up to 2 hours prior to surgery. This avoids the deleterious catabolic state at the onset of surgery, which has been shown to mediate insulin resistance, leading to loss of lean muscle.[15]

Given that patients are not dehydrated prior to surgery, they do not require resuscitation with salt-laden intravenous fluids that flow into the extracellular space. This helps to prevent peripheral edema, which can restrict movement postoperatively, and edema in the bowel wall, which contributes to ileus. To further reduce the reliance on intravenous fluids, patients are allowed oral intake immediately after surgery. Additionally, patients are mobilized early and frequently following surgery to further prevent muscle loss in the postoperative period.

Another one of the main tenets of ERAS protocols is the avoidance of opioids for pain control. For decades, opioid analgesia has provided the primary means of controlling pain in patients undergoing major surgery in the United States. However, opioid analgesia has deleterious effects on surgical recovery including respiratory depression, gut dysmotility, and delirium, in addition to the potential for abuse.

Prescription opioids are now among the leading causes of overdose deaths in the United States, and surgeons are one of the leading providers of opioid prescriptions nationwide.[16,17] ERAS aims to reduce opioid intake through the use of multimodal analgesia, such as anti-inflammatory agents, local anesthetics, and other nonopioid pain management strategies.

Figure 1. Differences in length of stay and complications before and after implementation of enhanced recovery



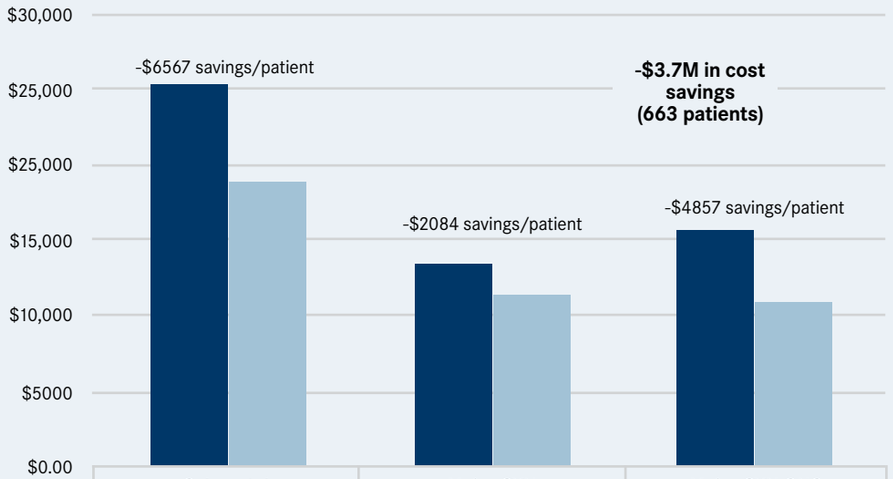
CAUTI indicates catheter-associated urinary tract infections; ERAS, enhanced recovery after surgery; LOS, length of stay; SSI, surgical site infection.

Impact of Enhanced Recovery at the University of Virginia

We implemented a multidisciplinary ERAS protocol in patients undergoing major colorectal surgery in 2013 at the UVA Medical Center.[18] We observed dramatic improvements in colorectal surgery quality outcomes including a 2-day reduction in length of stay, an 80% reduction in opioids, and a 50% reduction in overall complications (**Figure 1**). There was a $6567 per patient reduction in total hospital costs and significant improvements in patient satisfaction.

These quality improvements have been sustained for 3 years, as reflected in drastic improvements in UVA standings within the National Surgical Quality Improvement Program (NSQIP) as compared with our peer institutions. Our experience with enhanced recovery was subsequently featured in the *US News & World Report* as well as in the *Wall Street Journal*.[19,20]

Figure 2. Total hospital costs before and after enhanced recovery implemented in colorectal and gynecologic surgery at UVA.



	Colorectal (N = 503)	Major GYN (N = 120)	Major GYN ONC (N = 40)
Pre-ERAS	$25,344	$13,401	$15,655
Post-ERAS	$18,777	$11,317	$10,798

Based on our experience with colorectal surgery, we developed an institutional enhanced recovery program and hired a full-time dedicated nurse coordinator with a goal to implement enhanced recovery throughout UVA Health System. We implemented ERAS in obstetrics, thoracic surgery, and gynecology, which resulted in significant improvements similar to our experience with colorectal surgery,[21] and have plans to implement in orthopedics, hepatobiliary, and spine surgery.

To date, ERAS has accounted for $3.7 million in cost savings and more than 1100 bed-days saved at UVA. This has opened capacity for 204 new admissions over a 2-year period, which is critical given that our hospital runs chronically at near-full capacity (**Figure 2**).

Another key aspect of our success with the ERAS protocol has been patient engagement. We developed printed patient education materials, an educational video and website, and developed an app (UVA ERAS) to educate patients prior to colorectal surgery. This app was developed with stakeholder input from colorectal surgery patients and healthcare providers.

Each of these educational materials outlines exactly what is going to happen to the patient every step of the way and actively involves them as part of the treatment team. We have found that patients and their families take pride in managing their surgical care and derive great satisfaction from direct involvement.

Enhanced recovery is based on standardization of care and direct engagement of the patients and healthcare providers. Its impact reaches far beyond that of the perioperative period. Surgical complications are known to delay or prevent adjuvant chemotherapy in patients with colorectal cancer and are associated with an increased risk of recurrence. Through a reduction in surgical complications, it is our hope that oncologic outcomes will also improve as a direct result of the enhanced recovery protocol. ■

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BRCA Mutations Do Not Predict Breast Cancer Survival

By Beth Fand Incollingo @fandincollingo

Although mutations of the *BRCA* gene can increase a woman's chances of developing breast and ovarian cancers, the presence of an aberration made no difference in survival for women aged 40 years or younger who were diagnosed with early-stage breast cancer, according to a recent study that followed participants for approximately 8 years. These findings were presented at the 2016 San Antonio Breast Cancer Symposium in December.

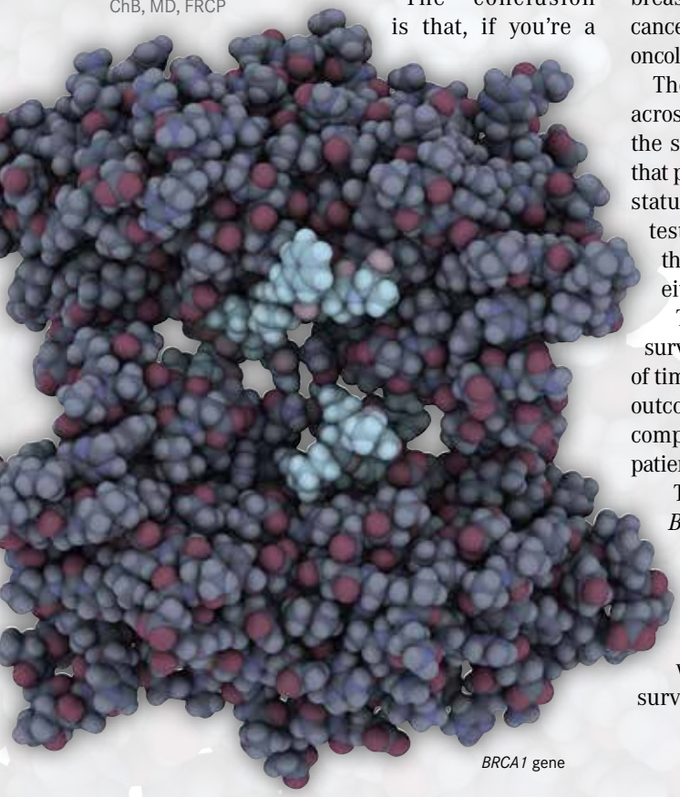
A multivariate analysis, which took into account *BRCA* status along with all other known factors that could influence prognosis, showed the maximum survival benefit for *BRCA* mutation carriers with triple-negative breast cancer (TNBC) emerging at 2 years, with survival becoming more similar between the carriers and noncarriers of the gene by 5 years.

According to the lead author of the study, Diana Eccles, MB, ChB, MD, FRCP, a professor of Cancer Genetics and head of the Cancer Sciences Academic Unit at the University of Southampton in England, these results are important because there is a commonly held misconception that carrying a *BRCA* mutation worsens the prognosis of a patient who develops breast cancer.

Diana Eccles, MB, ChB, MD, FRCP

"The conclusion is that, if you're a patient who's told you're a [*BRCA*] carrier and you don't [want to immediately undergo] a bilateral mastectomy, it's not an important part of your treatment," she said. "You can [wait and] make that decision separately from your treatment."

Moreover, for women in this population, having a prophylactic bilateral mastectomy did not improve the risk for cancer recurrence or death. Three percent of the study's non-*BRCA* carriers who had TNBC and 15% of *BRCA* carriers with TNBC underwent preventive bilateral mastectomy in their first year after diagnosis. When they were removed from researchers' calculations, the survival advantage of young *BRCA* carriers with TNBC jumped from 11% to 13%, Eccles said.



BRCA1 gene

POSH Study Results

The findings came out of a prospective study of nearly 2759 women aged 40 years or younger who had early-stage, invasive breast cancer. The study compared outcomes of treatment using breast-conserving surgery or unilateral mastectomy plus standard chemotherapy–an anthracycline, combined in some cases with a taxane–in women who had a *BRCA* mutation compared with women who did not, Eccles said.

The study, known as POSH, or the Prospective study of Outcomes for Sporadic versus Hereditary breast cancer, recruited participants with breast cancer who were in the target age group from 126 oncology clinics starting in 2000 and ending in 2008.

The patients represented a quarter of those across the United Kingdom who were eligible for the study, and so it was highly representative of that population. Few participants knew their *BRCA* status when diagnosed with cancer. They were tested for *BRCA* mutations this year as part of the study, and 14% were found to be positive for either a *BRCA1* or a *BRCA2* mutation.

The study's primary endpoint was overall survival, and a secondary endpoint was the length of time without a distant metastasis. In both areas, outcomes in *BRCA* mutation–positive women were compared with those in *BRCA* mutation–negative patients. They were followed for a median 8.2 years.

The study found no difference in survival for *BRCA* carriers versus noncarriers in the whole cohort overall. Within the study population, 19%, or 511 women, had TNBC. A univariate analysis of that group (excluding those who underwent prophylactic mastectomy), which analyzed the impact of *BRCA* status on survival, showed that, at 5 years, 85.64% of *BRCA* carriers were alive compared with 71.03% of non-*BRCA* mutation carriers.

At 10 years, 78.66% of *BRCA* carriers in this subgroup were alive, compared with 65.24% of non-*BRCA* carriers. A multivariate analysis, which took into account *BRCA* status along with all other known factors that could influence prognosis, showed the maximum survival benefit for *BRCA* carriers with TNBC peaking at 2 years, with survival advantage becoming more similar between the 2 groups by 5 years, Eccles said.

She cautioned, however, that the survival benefit for *BRCA* carriers is an idea suggested, but not proved, by the study. For the benefit to be considered statistically significant, she said, the study would have needed to include more than 1116 patients with TNBC.

Eccles went on to explain that the results of the study highlight the notion that younger, *BRCA*-positive patients diagnosed with breast cancer can at least temporarily put off decisions about preventive bilateral mastectomy and rely on regular screening for recurrence instead.

"Younger women will [tend to] take the most extreme treatment anybody will offer, because they think it will give them a better chance of surviving," she said. But, "there's evidence that, when patients have breast cancer and a *BRCA* gene mutation, if they wait for a year or 2, some opt for screening and not for major surgery." One argument for opting against immediate surgery, she said, is that there were "very few" instances in the study of second primary breast cancers occurring in *BRCA*-positive women in their first several years after treatment.

Eccles added that having nonessential surgery while being treated for cancer might compromise the body's immune system, jeopardizing the response to therapy.

"This is highly hypothetical, and we don't have big enough numbers to be sure," she said, "but it's thought provoking regarding how patients are managed in this setting."

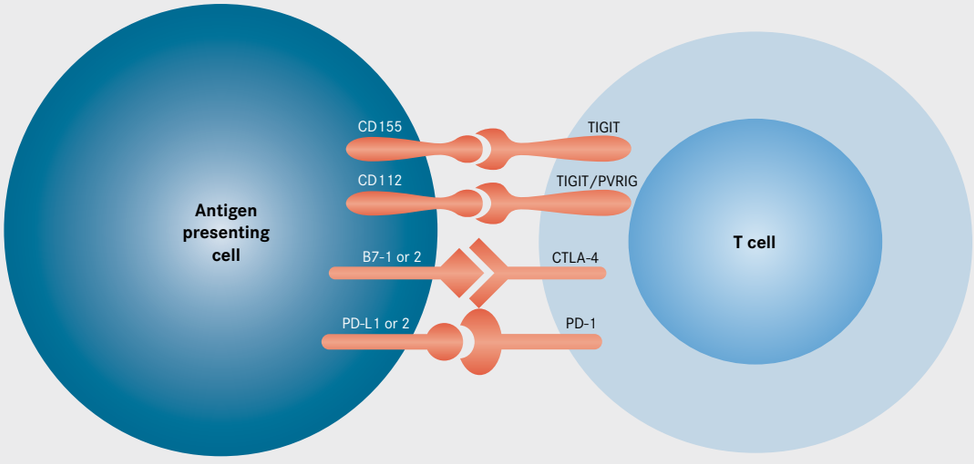
In fact, she said, it raises questions about "the reason patients tend to have *BRCA* testing" in the first place, which is that their surgeons want them to consider preventive bilateral mastectomy. The women in the POSH study didn't have the option of considering mastectomy to prevent a first breast cancer, since they were tested for *BRCA* status after they had been diagnosed with the disease. Among women such as these–aged 40 or younger and diagnosed with initial, early-stage breast cancers–non-*BRCA* carriers face a disease recurrence risk of about half a percent per year. For *BRCA* carriers, that risk is about 2% per year, Eccles said.

"They are very small numbers," she said. "If you know that, you can make an informed choice." ■

TIGIT Emerges as New Target for Immune Checkpoint Blockade Strategies

By Jane de Lartigue, PhD

Partners in Immune System Signaling



TIGIT is among the T-cell receptors that interact with proteins expressed by antigen presenting cells to send inhibitory signals to the immune system. Dysregulated interaction between TIGIT and its ligands serves to suppress immunity when under attack from cancer cells, similar to the activity of the PD-1 and CTLA-4 pathways.

As researchers continue to identify a growing number of immune checkpoints as targets for anticancer therapy, the recently discovered TIGIT pathway is emerging as a promising new avenue for exploration.

TIGIT is a poliovirus receptor (PVR)–like protein, an immunoreceptor expressed on T cells that contains immunoglobulin (Ig) and immunoreceptor tyrosine–based inhibitory motif (ITIM) domains. As such, TIGIT acts as an inhibitory immune checkpoint on both T cells and natural killer (NK) cells, providing an opportunity to target both the adaptive and innate arms of the immune system.

Although clinical development is in preliminary stages, TIGIT and related proteins show significant therapeutic promise, particularly in combination with other immune checkpoint inhibitors, with the potential to broaden the benefit of immunotherapy into previously unresponsive patient populations.

Genentech has launched a phase I trial evaluating MTIG7192A, a fully human monoclonal antibody that binds to TIGIT and prevents its interaction with PVR. The trial, which opened in June, will evaluate the safety and efficacy of MTIG7192A as monotherapy and in combination with the PD-L1 inhibitor atezolizumab (Tecentriq) in a 2-step study that aims to enroll 300 patients with locally advanced or metastatic tumors (NCT02794571).

In September 2016, Bristol-Myers Squibb initiated a phase I/II study of an anti-TIGIT monoclonal antibody, BMS-986207, as monotherapy and in combination with nivolumab (Opdivo) in advanced solid tumors (NCT02913313). The estimated enrollment for the trial is 170 participants.

Compugen Ltd is developing COM701, an antibody that targets PVRIG, another recently elucidated member of the PVR family. The company is planning to submit an Investigational New Drug application to the FDA during the fourth quarter of 2017.

Where TIGIT Fits In

The major effectors of the immune system are cytotoxic T cells, and these are activated in a 2-step process when they encounter antigen-presenting cells bearing foreign antigens. Antigens engage the T-cell receptor (TCR) on the surface of the T cell, but this signal is coupled with a second signal that determines whether the T cell is turned on or off. Together these costimulatory and coinhibitory signals are known as immune checkpoints.

CTLA-4 and PD-1, the most successful immune targets for anticancer therapies, generate coinhibitory signals. Since cancer cells and the cells of the surrounding microenvironment have been shown to upregulate the expression of components of their respective pathways as a means of suppressing the antitumor immune response, the development of antibodies that block their activity has been embraced by immuno-oncologists in the hopes of reversing these suppressive effects.

The anti–PD-1 antibodies nivolumab and pembrolizumab (Keytruda) and the PD-L1–targeting agent atezolizumab have been approved in multiple malignancies while ipilimumab (Yervoy) remains the only CTLA-4 inhibitor on the market.

TIGIT is among the novel coinhibitory immune checkpoints under study (**Table**). It was first identified about a decade ago in a genome-wide screening for potential immune inhibitory proteins. Researchers were searching for proteins that were expressed by immune cells and that contained an ITIM domain, which is known to mediate immune cell deactivating signals. TIGIT is a member of a recently discovered arm of the Ig superfamily, the PVR-like proteins, which contain PVR motifs in their Ig variable-like domain.

Further investigation revealed that TIGIT was reminiscent of the CTLA-4 protein, in that it shares ligands with an activating receptor. CTLA-4 is activated by binding to the B7-1 and B7-2 (also known as CD80 and CD86, respectively) proteins. These proteins also serve as ligands for the CD28 protein, a costimulatory molecule; thus the activating and deactivating receptors compete for the same ligand, with a delicate balance determining if the T cell is switched on or off.

The ligand for TIGIT is CD155 (alternatively known as PVR), but this protein also serves as a ligand for CD226, which, like CD28, is an activating receptor. When CD155 is bound to CD226, it conveys activating signals into the immune cell. Meanwhile, CD155 bound to TIGIT transmits an inhibitory signal by recruiting the SHP1 phosphatase to the membrane through its ITIM domain that subsequently deactivates numerous proteins involved in T-cell effector functions.

A third member of the PVR-like protein family, CD96 (sometimes referred to as T cell-activated increased late expression [TACTILE]), also binds to CD155. The function of this interaction is not yet understood, although mouse CD96 has been shown to be involved in inhibitory signaling like TIGIT.

Meanwhile, although TIGIT binds most strongly to the CD155 protein, it also partners with another ligand, CD112, with lower affinity, adding to the complexity of this pathway. Furthermore, PVRIG

Table. Inhibitory Immune Checkpoints

Target (APC or tumor cell)	Receptor (T cell or natural killer cell)
B7-1 (CD80)	PD-L1
B7-2 (CD86)	CTLA-4
PD-L1	PD-1
PD-L2	B7-1 and PD-1
CD48	CD244
CD155	TIGIT
CD112	TIGIT and PVRIG (CD112R)
KIR	MHC class I
NKGD2	RAE-1

(known as CD112R), another newly discovered member of the PVR-like family, also binds to CD112.

TIGIT is expressed by activated cytotoxic T cells and regulatory T cells and has also been shown to be upregulated on T cells in multiple cancer models. The ligands CD155 and CD112 are found on dendritic cells and macrophages and are also highly expressed in several types of cancer. Additionally, TIGIT expression is highly correlated with the expression of other coinhibitory molecules, including PD-1. Overall, this suggests that tumors upregulate the TIGIT pathway along with other inhibitory checkpoint networks to promote immunosuppressive mechanisms.

Ways to Attack TIGIT

Thus far, the development of drugs targeting TIGIT and other PVR-like proteins remains in the preliminary stages, but if they live up to the promise of preclinical studies they could prove to be an important addition to the immunotherapy arsenal.

TIGIT-targeting antibodies are the furthest along in development, although only a few agents have progressed to clinical trials thus far. Such antibodies disrupt binding of TIGIT to its ligands and block its inhibitory signals, shifting the balance in favor of CD226-mediated activating signals. Preclinical studies demonstrated that these drugs enhance the function of T cells and inhibit the growth of tumors, particularly when combined with blockade of other inhibitory checkpoints, such as PD-1.

In a preclinical study presented at the 2016 Annual Meeting of the Society for Immunotherapy of Cancer in November, the combination of TIGIT and PD-L1 blockade in humanized mouse models led to enhanced CD8-positive T-cell function, which subsequently significantly improved tumor clearance. The activity of TIGIT was dependent on the expression of its ligand, CD155, in the host tissue.

In data presented about the molecule COM701, PVRIG blockade resulted in enhanced activation of tumor-infiltrating lymphocytes, CD4-positive

(Continued on page 40)

Pharmaceutical Leaders Highlight Promise of TIGIT

John Hunter, PhD, is vice president and head of Antibody Research and Development for Compugen USA, Inc. He has more than 15 years of scientific research in monoclonal antibody research, genomics, and translational medicine.


John Hunter, PhD


Maya Kotturi, PhD

Hunter and Maya Kotturi, PhD, the project team leader for Compugen's TIGIT program, answered key questions about TIGIT as a target for anticancer therapy and the current development of TIGIT-targeting drugs.

Q: How does TIGIT act as an immune checkpoint?

TIGIT is a coinhibitory receptor that is highly expressed on effector and regulatory (Treg) CD4+ T cells, effector CD8+ T cells, and natural killer (NK) cells. TIGIT has been shown to attenuate the immune response by (1) direct signaling, (2) inducing ligand signaling, and (3) competition with and disruption of signaling by the costimulatory receptor CD226 (also known as DNAM-1).

TIGIT signaling has been best studied in NK cells, where it has been demonstrated that engagement with its cognate ligand, poliovirus receptor (PVR; also known as CD155) directly suppresses NK cell cytotoxicity through its cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) domain. Knockout of the *TIGIT* gene or antibody blockade of TIGIT/PVR interaction has shown to enhance NK cell killing in vitro, as well as to exacerbate autoimmune diseases in vivo.

In addition to its direct effects on T and NK cells, TIGIT can induce PVR-mediated signaling in dendritic or tumor cells, leading to the increase in production of anti-inflammatory cytokines such as IL-10. In T cells, TIGIT can also inhibit lymphocyte responses by disrupting homodimerization of the costimulatory receptor CD226, and by competing with it for binding to PVR.

More recently, Compugen and others have generated data suggesting that a new checkpoint inhibitor, PVRIG, is involved with TIGIT in modulating the CD226 pathway to downregulate T-cell response. As we recently demonstrated with our PVRIG-targeted antibody, COM701, combination blockade of TIGIT and PVRIG significantly increases T cell–mediated proinflammatory cytokine production in vitro.

Q: How does TIGIT compare with other immune checkpoints?

There are many parallels in regulation of T-cell–mediated immunity between the CD226/TIGIT-PVR pathway and the well-defined CD28/CTLA-4–CD80/CD86 pathway. Firstly, the expression kinetics of the costimulatory and coinhibitory receptors in these 2 pathways are very similar. The costimulatory receptors CD226 and CD28 are expressed on both naïve and resting T cells, while the expression of TIGIT and CTLA-4 is induced upon lymphocyte activation. Secondly, CD226 and CD28 have a lower affinity to their respective ligands, and are therefore outcompeted by TIGIT and CTLA-4 for ligand binding. Finally, ligand binding by TIGIT and CTLA-4 attenuates T-cell responses.

TIGIT is highly expressed on lymphocytes, including tumor-infiltrating lymphocytes (TILs) and regulatory T cells, that infiltrate different types of tumors. PVR is also broadly expressed in tumors, suggesting that the TIGIT-PVR signaling axis may be a dominant immune escape mechanism for cancer.

Notably, TIGIT expression is tightly correlated with the expression of another important coinhibitory receptor, PD-1. TIGIT and PD-1 are coexpressed on the TILs of numerous human and murine tumors. Unlike TIGIT and CTLA-4, PD-1 inhibition of T-cell response does not involve competition for ligand binding with a costimulatory receptor. Antibody blockade of both TIGIT and PD-1 in preclinical tumor models synergistically induces tumor rejection, thus providing a strong rationale for TIGIT/PD-1 antibody combinations in humans.

Q: How is TIGIT being targeted?

Different types of biological agents are being utilized to target immune checkpoint receptors and/or their ligands. Classically, coinhibitory receptors, such as CTLA-4, PD-1/PD-L1, and TIGIT are targeted with monoclonal antibodies that can block the interaction between the receptor and its ligand, releasing the inhibitory brake on T-cell activation.

In contrast, costimulatory receptors such as OX40, 41BB, and ICOS are targeted by monoclo-

(Continued on page 40)

(Pharmaceutical Leaders, continued from page 39)

nal antibodies that are agonistic, and that induce signaling by the target molecules. Fc-fusion proteins comprised of the extracellular domains of either coinhibitory or costimulatory molecules are also being tested clinically as cancer therapeutics.

A current focus in cancer immunotherapy, validated by recent clinical trials combining nivolumab and ipilimumab, is dual targeting of immune checkpoints with combination therapies. Trials are currently underway targeting TIGIT in combination with PD-1/PD-L1 blockade. Furthermore, Compugen's efforts to date suggest the potential for enhanced efficacy by combining a TIGIT antibody with a PVRIG-targeted antibody.

Q: What are the most significant unanswered questions or challenges relating to the targeting of TIGIT?

The biggest unanswered question, as is true with any first-in-class drug, is whether the antitumor activity seen with TIGIT blockade in preclinical tumor models will translate to tumor regression and improved overall survival in humans.

An additional question for clinical development of TIGIT antibodies relates to selection of the best patient population to target with an anti-TIGIT antibody. Preclinical data demonstrate that TIGIT inhibition can synergize with PD-1 pathway blockade, pointing to possible utility in treating patients refractory to therapies targeting PD-1 and PD-L1. Phase I clinical trials initiated with anti-TIGIT monoclonal antibodies, either administered alone or in combination with anti–PD-1/PD-L1 antibodies, will shed light on these questions.

Finally, there are still outstanding questions in terms of TIGIT biology. It is unclear whether TIGIT signals through its ITIM domain in T cells, and what signaling molecules may be involved. Could TIGIT have different signaling roles in NK cells, effector T cells and regulatory T cells? Understanding these aspects of TIGIT biology should lead to more effective targeting of TIGIT in patients. ■

(TIGIT Pathway, continued from page 39)

T cells, and CD8-positive T cells derived from the tumor. The use of a surrogate antibody, with similar characteristics to COM-701, showed synergy with anti-PD-L1 blockade in vivo in multiple cancer models. Compugen also reports on its website that in vitro studies have shown that dual blockade of PVRIG and TIGIT increases the activity of tumor-infiltrating T cells above the levels achieved by monotherapy against either target.

A Unique Checkpoint

Several studies have revealed TIGIT as a unique and potentially complementary target to other inhibitory immune checkpoints. First, in addition to directly inhibiting cytotoxic T-cell activity, TIGIT can foster an immunosuppressive microenvironment through its impact on other immune cells. For example, by binding to CD155 on the surface of dendritic cells, TIGIT increases the secretion of the immunosuppressive cytokine interleukin-10, and engagement of TIGIT on regulatory T cells enhances their immunosuppressive functions.

Second, TIGIT is also expressed on NK cells, the principal effector of the innate immune response that has been gaining traction as a target for anticancer therapy in recent years. Immune checkpoints have also been identified on NK cells, such as killer immunoglobulin-like receptor (KIR) that can be targeted to manipulate NK cell activity. In preclinical models, TIGIT blockade also boosts NK cell activation, suggesting that targeting TIGIT could offer a way of simultaneously boosting both arms of the immune response.

Most intriguingly, TIGIT has been shown to not simply outcompete CD226 for binding to CD155, but also to physically impede the dimerization of the activating receptor, blocking its costimulatory function. Thus, TIGIT inhibitors might not only release the brakes on the immune system, but at the same time may hit the gas by releasing TIGIT inhibition of CD226.

Certainly, the complexities of TIGIT and CD226 signaling are posing opportunities and challenges for clinical translation, and a fundamental understanding of these pathways will be essential going forward. ■

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Complex Scenarios in Advanced Melanoma:

Examining Three Patient Cases

By Christina Loguidice

The number of treatment options for advanced melanoma continues to increase steadily. Since March 2011, when ipilimumab (Yervoy) was the first new drug approved by the FDA for melanoma in 13 years, many agents and combination therapies have come to market or received expanded indications or other label changes (**Table**).[1-3] Many other treatments continue to show promise in clinical trials. Yet despite significant developments on the advanced melanoma treatment front, "many clinical scenarios remain where there is no clear-cut course of action," said **Robert H.I. Andtbacka, MD, CM**, during a recent *OncLive* Peer Exchange®.


Robert H.I. Andtbacka, MD, CM

During the Peer Exchange, Andtbacka used 3 case scenarios to lead a panel of melanoma experts in a discussion of some of the key challenges impacting clinical practice today. The cases consisted of an elderly adult with newly diagnosed *BRAF* wild-type stage IV melanoma, a patient with *BRAF*-mutant stage IV melanoma, and a patient with recurrent disease after resection.

CASE 1

BRAF Wild-type Stage IV Melanoma

- 75-year-old woman with *BRAF* wild-type metastatic melanoma
- Low tumor burden with lung and subcutaneous metastases
- Eastern Cooperative Oncology Group (ECOG) performance status of 0

A key area of discussion for this case scenario focused on molecular testing. In addition to testing for *BRAF*, the mutational status of 2 other genes were noted to be of potential interest: *NRAS* and the c-*Kit* oncogene. "*NRAS* is the second most common oncogenic mutation we see in cutaneous melanoma patients, and, in part, it's because the *NRAS* and *BRAF* V600 mutations are mutually exclusive. Seeing an *NRAS* mutation increases our confidence in the specificity and accuracy of a wild-type *BRAF* test," said **Michael A. Davies, MD, PhD**. Although these mutations are "quite rare," he explained that his interest in testing for these mutations stems from an availability of clinical trials for patients with *NRAS* mutations and clinical evidence that patients with *KIT* mutations, which occur more commonly with mucosal melanomas, can benefit from treatment with KIT inhibitors.


Michael A. Davies, MD, PhD

More evidence and standardization are needed, however, before *NRAS* and *KIT* mutations become routine testing targets in clinical practice. The panelists noted the same to be true for PD-L1 expression testing. "In melanoma, nivolumab and pembrolizumab do not require testing for PD-L1 expression," said **Antoni Ribas, MD, PhD**, whereas initiation of BRAF/MEK inhibitor therapy requires *BRAF* V600E or V600K testing, he explained. Furthermore, although PD-L1 expression has been associated with treatment response, it is not a definitive test.

"When you look at the receiver operating characteristic curve, there is no optimal cutoff; the test is not sensitive and it is not specific to predict response and progression-free survival [PFS]… so we [only] use it in research to look at the full tumor in the microenvironment," said **Georgina Long, MD, BSc, PhD, MBBS.** Nevertheless, as testing evolves and more data become available, mutation testing is expected to become more comprehensive. "In the future, we're going to be testing for as many mutations as possible. The techniques are already there, but their standardization and who pays for them is limiting our routine use of them," said Ribas.

In terms of treatment options, the panelists agreed that PD-1 inhibition would be an optimal approach for this patient, whether as single-agent therapy or as a combination therapy with ipilimumab. "For this patient with very low-volume metastatic disease involving the subcutaneous tissues and lung, I'd feel very comfortable starting her on a single-agent PD-1 inhibitor, such as nivolumab or pembrolizumab, as a first-line treatment approach," said **Michael A. Postow, MD**. "We've known that patients with small lung metastases can do very well with single-agent PD-1, and we don't yet have a perfect predictive set of clinical variables or any kind of correlative variables that tell us who exactly can benefit from PD-1 monotherapy versus who may need the combination," he said.

Although nivolumab/ipilimumab combination

"Practical Management of Advanced Melanoma: a Case-Based Discussion"

Moderator
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Co-Director, Melanoma Program
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therapy has shown a higher response rate than nivolumab monotherapy, it has a much higher toxicity rate, which can be a limiting factor, particularly in more vulnerable or frail patients. Thus, the panelists largely agreed that more aggressive combination immunotherapy might be better reserved for patients with signs of more aggressive disease, such as a rapid increase in tumor size or elevated serum lactate dehydrogenase (LDH) levels.

Regardless of treatment approach, "one of the keys in a 75-year-old patient that you would want to know is how hard would it be for this patient to be brought in for medical care if the patient were to get ill," said Davies. The panelists concurred that age alone should not be considered a contraindication to using a potentially more toxic regimen when it is needed, but that more careful planning is warranted in such cases to improve outcomes in the event adverse effects (AEs) occur.

CASE 2

BRAF-Mutant Stage IV Melanoma

- 50-year-old man with lung, liver, and bone metastases
- Slightly elevated LDH level (1.4 x ULN)
- ECOG performance status of 1
- *BRAF* V600E-mutant

A key area of focus this second case was on treatment and whether BRAF/MEK inhibitors are preferable to combination immunotherapy. "In Australia, we have funding rules, which means we must give a BRAF and MEK inhibitor for *BRAF*-mutant patients in the frontline setting no matter what their disease state is," said Long. "We actually don't agree with that, and things may be changing in some respects in the next few months, but I've tended to try and find immunotherapy clinical trials for my patients."

She said if she could choose a frontline immunotherapy in this setting, she'd select combination immunotherapy with nivolumab and ipilimumab, which has shown more robust response rates than other currently available treatments. However, this remains a data-free zone.

"At this point, we really don't have any head-to-head trials for patients with metastatic *BRAF*-mutant melanoma showing what is the right initial therapy," said Davies, noting that this is currently being evaluated in clinical trials. "Patients like [the case patient] are being randomized to start with a BRAF and MEK inhibitor combination therapy versus combination immunotherapy with ipilimumab and nivolumab, and if they progress, are crossed over to the other therapy," he explained. "This is really going to provide us with the definitive information about which of those therapeutic approaches is the right one to start with," he said, noting that trials are also currently underway assessing combining targeted therapy with immunotherapy.

Based on currently available evidence, patients who progress on immunotherapy can respond to subsequent targeted therapy and vice versa, said Ribas, although the response appears to be lower when immunotherapy is initiated after progression on targeted therapy. Nevertheless, it remains a viable option and he suggested that treatment decisions should continue to be personalized to patients' circumstances and preferences. "Even when we have randomized data, we can only tell what would happen to most patients, but it will never tell us what will happen to an individual patient, so we'll all continue to discuss and personalize therapy," he said.

When personalizing treatment, many key factors can impact decision making. One critical factor in

Table. Approvals and Label Changes for Melanoma Therapies From 2011-2016

2016	
Nivolumab (Opdivo)	Dosage regimen modified to 240 mg IV every 2 weeks
2015	
Pembrolizumab (Keytruda)	Label expanded to include patients initially being treated for unresectable or metastatic melanoma
Trametinib (Mekinist)/dabrafenib (Tafinlar) combination	Approved to treat unresectable or metastatic melanoma in patients with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test
Cobimetinib (Cotellic)	Approved in combination with vemurafenib to treat unresectable or metastatic melanoma in patients with *BRAF* V600E or V600K mutation; cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma
Ipilimumab (Yervoy)	Approval expanded to include adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of >1 mm who have undergone complete resection, including total lymphadenectomy
Talimogene laherparepvec (Imlygic; genetically modified oncolytic viral therapy)	Approved as local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
Nivolumab	Granted accelerated approval in combination with ipilimumab for unresectable or metastatic melanoma in patients with *BRAF* V600 wild-type disease
2014	
Nivolumab	Granted accelerated approval to treat unresectable or metastatic melanoma and disease progression in patients following ipilimumab therapy and, if *BRAF* V600 mutation–positive, a BRAF inhibitor
Pembrolizumab	Granted accelerated approval to treat unresectable or metastatic melanoma and disease progression in patients following ipilimumab therapy and, if *BRAF* V600 mutation positive, a BRAF inhibitor
Trametinib/dabrafenib	Granted accelerated approval for unresectable or metastatic melanoma in patients with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test
2013	
Trametinib	Approved to treat unresectable or metastatic melanoma in patients with *BRAF* V600E or V600K mutation, as detected by an FDA-approved test
Dabrafenib	Approved to treat unresectable or metastatic melanoma in patients with *BRAF* V600E or V600K mutation, as detected by an FDA-approved test
2012	
No new approvals	
2011	
Ipilimumab (Yervoy)	Treatment of unresectable or metastatic melanoma
Peginterferon alfa-2b (Sylatron)	Treatment of microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy
Vemurafenib tablets (Zelboraf)	Treatment of unresectable or metastatic melanoma in patients with the *BRAF* V600E mutation, as detected by an FDA-approved test

References
US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. 2016-2013. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Updated December 12, 2016. Accessed January 9, 2017.
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US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. 2011 Notifications. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm381453.htm. Updated September 4, 2015. Accessed January 9, 2017.

this case patient's scenario is his elevated LDH, which is a factor that has been associated with worse outcomes and a lower response to immunotherapy, though responses can be durable when they occur.

"For patients with a high LDH, we know the targeted therapies have very high response rates, probably higher than what we can achieve with immunotherapy, but the overwhelming majority of those responses have short duration," said Davies. However, because the case patient's LDH is only slightly elevated and he is not highly symptomatic, there is more flexibility in time to achieve response than in a highly symptomatic patient with markedly elevated LDH and high disease burden. This enables other key decision-making factors to bear more weight, such as the patient's ability and willingness to receive immunotherapy infusions every 2 to 3 weeks in the clinic versus orally taking a targeted agent at home.


Michael A. Postow, MD

Despite infusions being more burdensome upfront, Postow noted that they are not always a long-term burden. "At least with combination ipilimumab and nivolumab, a lot of patients discontinue treatment after just a few infusions upon achieving response, particularly in the setting of toxicity, and many of those patients are not on ongoing treatment longer term…so there is something to be said for the long-term PFS you can get from these short durations of treatment in some patients," he said.

At the same time, the panelists made clear that frontline BRAF inhibitor-based therapy does not preclude long-term survival, particularly in patients with normal LDH and 3 or fewer sites of metastasis. "The 3-year overall survival is well above 50% to 60% for these patients," said Long, with data also showing favorable PFS. More data will become available as clinical trials mature. "Once we start getting out to 3, 4, 5 years and see the pure activity of the drugs, we'll be able to have better conversations about upfront treatments," she said.

CASE 3

Recurrent Disease After Resection

- 60-year-old woman with history of 4.6-mm ulcerated nodular melanoma on her calf
- Underwent wide excision and was sentinel node negative
- Opted not to have adjuvant therapy
- Has disease recurrence at 18 months with large mass on her right superficial groin
- Metastatic disease found in her lymph node
- No evidence of disease at distant sites

This case scenario was the most controversial of the 3 because it covers an area where there are more limited data regarding the role of systemic treatments. The panelists agreed on resection being appropriate for the patient, but data on whether to use neoadjuvant or adjuvant therapy in such cases remains a murky area that still requires 2 key questions to be more definitively answered: (1) will systemic therapy reduce the risk of such high-risk patients developing distant metastatic disease; and (2) will using systemic therapy upfront in patients with large or impinging tumors sufficiently reduce tumor burden to improve postoperative morbidity.


Georgina Long, MD, BSc, PhD, MBBS

When neoadjuvant therapy is being pursued, it must be done in a clinical trial setting, the panelists noted. "Neoadjuvant would not be done outside of a clinical trial and surgery would be done upfront if we did not have a trial for this patient…and then discuss an adjuvant trial," said Long. In contrast, adjuvant systemic therapy could be done outside of a clinical trial. "[In the clinical setting], we would be discussing high-dose ipilimumab or high-dose interferon," said Ribas, who later said pegylated interferon could be another option for US patients, although it does not appear to offer an advantage over high-dose interferon in terms of toxicity or survival.

Compared with high-dose ipilimumab, high-dose interferon has significantly more toxicity, with most patients experiencing some AEs. "It's given intravenously for 5 days on, 2 days off for 1 month, and during that time, most patients have fevers, chills, and malaise, with treatment often needing to be stopped because of pancytopenia or elevated liver function tests," said Ribas. "Then patients continue with subcutaneous dosing 3 times a week for 1 year, where they would continue feeling tired most of the time, and they can also develop depression because of the drug," he said. Although most patients receiving high-dose ipilimumab will not develop AEs, when they occur, they can be severe and include complications like colitis, hypophysitis, and thyroiditis, he said.

In patients with metastatic disease, ipilimumab is dosed at 3 mg/kg, but in the adjuvant setting, a dose of 10 mg/kg has been approved. "In the community, we are still seeing patients being treated with 3 mg/kg with really no data to support that," said Andtbacka.

Current evidence suggests a dose-response effect with ipilimumab, with improved outcomes in patients receiving the 10 mg/kg dose versus the 3 mg/kg dose, which has led to a dosing conundrum because patients with more serious metastatic disease are being treated with lower doses of ipilimumab than patients in the adjuvant setting who may already be cured. The challenge with the higher dose, however, is significantly more toxicity, the extent of which still needs to be teased out in clinical trials.


Antoni Ribas, MD, PhD

"My standard is giving the 10 mg/kg dose and hoping that the patient will tolerate it," said Ribas. In the meantime, he said the 3 mg/kg is being tested prospectively in the ECOG1609 trial (NCT01274338), which is comparing high-dose interferon, ipilimumab 10 mg/kg, and ipilimumab 3 mg/kg in patients with high-risk stage III to IV melanoma that has been excised. Study results are anticipated this year.

The panelists agreed that biochemotherapy and radiation therapy would not be appropriate treatment options for the case patient. "At this point, the data have shown no impact on overall survival [in the adjuvant setting], so I would not recommend biochemotherapy," said Davies. He encouraged enrolling patients into clinical trials to improve the adjuvant therapy landscape for earlier stages of disease.

When considering radiation, the panelists agreed that large groin tumors are not ideally suited to this approach either. "Our experience with the groin is that the risk of having infections, lymphedema, and AEs most of the time outweighs the potential benefit, so we have really decreased the amount of radiation that we do to the groin," said Andtbacka. He said that vast improvements in systemic treatments have also helped move treatment away from radiating groin lesions.

In their concluding statements, the panelists concurred that treatment decisions always need to be personalized based on the best and most current data available and on the patient's preferences and tumor characteristics. "How we use our existing therapies most appropriately remains a challenge, but it's a challenge that's much more pleasant now that we have better therapies," said Davies. The panelists all agreed that the melanoma armamentarium is only going to continue to expand in the coming years. The hope is that this will help resolve some challenges and lead to a more acceptable melanoma landscape. ■

On the Move

Edelman Transfers to Fox Chase Cancer Center


Martin J. Edelman, MD

Lung cancer expert **Martin J. Edelman, MD**, has joined Fox Chase Cancer Center as chair of the Department of Hematology/Oncology. Edelman will also serve as the deputy cancer center director for clinical research, leading the effort to integrate discoveries from the Translational Research Initiative into clinical trials.

Edelman is currently head of solid tumor oncology and associate director of the Division of Hematology/Oncology at the University of Maryland Greenebaum Comprehensive Cancer Center. He will begin his new role effective February 6.

"Dr Edelman is a visionary in his field, and I am confident he will lead our Department of Hematology/Oncology to even greater heights," said Richard I. Fisher, MD, president and CEO of Fox Chase.

Known for developing one of the most commonly used regimens for treating advanced lung cancer, Edelman works to develop new agents and biomarkers to personalize the treatment of patients with lung cancer.

Dang Appointed New Scientific Director of Ludwig Institute


Chi Van Dang, MD, PhD

Chi Van Dang, MD, PhD, has been appointed scientific director of the Ludwig Institute for Cancer Research. In his new role, effective July 1, 2017, Dang will oversee the execution of Ludwig's scientific strategy to advance the prevention, diagnosis, and treatment of cancer and increase collaboration between Ludwig's global research community.

Dang, a hematological oncologist, is currently director of the University of Pennsylvania Perelman School of Medicine's Abramson Cancer Center and the John H. Glick Professor of Medicine. His research in the field of hematology has focused on molecular signaling pathways and mechanisms that govern the metabolism of cancer cells. His laboratory established the first mechanistic link between the *MYC* cancer gene and cellular energy metabolism.

"We are very pleased to have Dr Dang on board and have every confidence that his scientific insight and experience leading some of the best research institutions in the world will be of great benefit to Ludwig," said John L. Notter, chair of the board of the Ludwig Institute.

Maki Moves to Leadership Role at Northwell Health


Robert G. Maki, MD, PhD

Sarcoma physician and researcher **Robert G. Maki, MD, PhD**, has joined the leadership team at Northwell Health Cancer Institute. Maki will serve as director of experimental therapeutics of the Don Monti Division of Medical Oncology and Hematology at North Shore University Hospital and Long Island Jewish Medical Center and director of the Center for New Cancer Therapies at Northwell Health Cancer Institute.

He is currently a professor of hematology/oncology at the Hofstra Northwell School of Medicine and a professor and member of the National Cancer Institute-designated Cancer Center at Cold Spring Harbor Laboratory (CSHL).

Maki has extensive experience in the development of novel therapies that attack molecular targets for the treatment of soft tissue and bone sarcomas. In his move to Northwell, he will play a key role in the strategic affiliation between Northwell and CSHL. Additionally, he will oversee the expansion of the basic and translational sarcoma research program in collaboration with CSHL.

Simeone to Head New Pancreatic Center at NYU Langone


Diane M. Simeone, MD

Diane M. Simeone, MD, will be joining NYU Langone's Perlmutter Cancer Center as associate director for translational research, effective March 1, and will lead the newly established pancreatic cancer center. Simeone is currently the director of the Gastrointestinal Oncology program at University of Michigan's Comprehensive Cancer Center.

Simeone, a world-renowned surgeon and researcher, focuses on pancreatic cancer prevention, early detection, and therapeutics, including the investigation of molecular events in pancreatic cancer leading to new therapies to treat the disease. Her laboratory was the first to identify pancreatic cancer stem cells.

At the Perlmutter Cancer Center, she will continue to explore the management of pancreatic neoplasms while also bringing translational research into clinical practice.

Taking a Bow

Sondel to Receive SITC's Top Award

Paul M. Sondel, MD, PhD, will receive the Society for Immunotherapy of Cancer's (SITC) 2017 Richard V. Smalley, MD Memorial Lectureship Award. Sondel is the Reed and Carolee Walker Professor in Pediatric Oncology and research director at the University of Wisconsin, Madison, where he was also the head of the Division of Pediatric Hematology, Oncology, and Bone Marrow Transplant.

Sondel's research includes the biology of graft-versus-leukemia reactions, activations of antitumor immune destruction with interleukin-2, and the use of tumor reactive monoclonal antibodies and immunocytokines to facilitate tumor killing by leukocytes.


Paul M. Sondel, MD, PhD

He will be presented with the society's most prestigious award, honoring those who have been pioneers in their work and made a notable impact worthy of high regard, during the SITC 32nd Annual Meeting November 8 to 12, where he will also present a keynote address on his research.

"Dr Sondel has been a tireless champion of investigating immunotherapy approaches to combat pediatric cancers, particularly neuroblastoma," said Lisa H. Butterfield, PhD, president of SITC. "His collaborative work helped lead to the ultimate FDA approval of dinutuximab (Unituxin), which was a critical advance in this challenging childhood cancer."

Boxer, Nachman Honored With ASH Mentor Awards


Laurence Boxer, MD


Ralph Nachman, MD

The American Society of Hematology (ASH) honored **Laurence Boxer, MD**, and **Ralph Nachman, MD**, with 2016 Mentor Awards at the 58th ASH Annual Meeting and Exposition. Boxer was selected for the Clinical Investigator Award and Nachman, the Basic Science Award.

During his 40-year career in pediatrics, Boxer, professor emeritus of the Division of Pediatric Hematology/Oncology at the University of Michigan, has overseen the career development of more than 50 pediatric hematology/oncology fellows.

Nachman, professor emeritus of medicine at Weill Cornell Medicine, was recognized for his many years of guidance and support of students, residents, fellows, and faculty.

"The future of hematology depends on the selfless dedication of mentors like Drs Boxer and Nachman, whose commitment to grooming future generations of hematologists will lead to important research breakthroughs and advancements in patient care in the years to come," said Charles S. Abrams, MD, president of ASH. ■