### presented by Targeted SITC 2016 31<sup>st</sup> Annual Meeting & ASSOCIATED DAI NATIONAL HARBOR. MD **NOVEMBER 9 - 13. 2016** DAY Topalian Discusses the Evolution of Immunology 101: These Are Not Exploring Adoptive Cellular Therapy and 12 01 18 **Bispecific Antibodies** PD-1/PD-L1 Inhibitors in Cancer Care "Boutique Therapies" Anymore New Mechanisms in Tumor Rejection Oncology Nurses on the Frontlines of Emerging Technologies Session Places 01 14 Highlighted During Presidential Session Focus on Science Immunotherapy Care 03 **Exploring Combination Approaches to** 20 Your Guided Path to Our Today's Agenda Immunotherapy Treatment 04 Novel Immune Checkpoint Identified as Nation's Capital Promising Target for Blockade Strategies Learning to Manage Immune-Related Coming Together Over the Issue of 21

Adverse Events in a Clinical Setting

Response to Immunotherapies

Factors Affecting the Immune System

# **Exploring Adoptive** Cellular Therapy and Bispecific Antibodies

BY PETER J. SCIAVOLINO, PHD



RIDDELL

06

**Dual Biomarker Signature Correlates** 

With Outcomes in Anti-PD-L1 Therapy



MACKALL

lizing adoptive cellular therapy (ACT) or bispecific antibodies (BsAs) as cancer therapy will be compared in the "Adoptive Cellular Therapy vs Bispecific Antibodies" session this evening. Co-chairs for this session will be Stanley R. Riddell, MD, from Fred Hutchinson Cancer Research Center, and Crystal L. Mackall, MD, from Stanford University.

mmunotherapy approaches uti-

Although cytotoxic T lymphocytes are important in facilitating the immune response to cancer, it is now well known that tumor cells have evolved elaborate mechanisms to manipulate the tumor microenvironment, create local-

ized immunosuppression, and effectively evade immune detection.<sup>1,2</sup> One type of adoptive T-cell therapy exploits the sensitivity of T cells to be triggered upon recognition, via the T-cell receptor, of foreign antigens complexed on the cell surface with major histocompatibility complex proteins.3,4

ACT utilizes tumor-reactive T cells, which are identified and expanded ex vivo then reintroduced into the patient; the approach has been utilized, and refined, over 30 years to achieve durable responses in leukemias, melanoma, and other types of solid tumors.<sup>4,5</sup> This approach may, in part, help overcome local immunosuppressive effects in the tumor microenvironment by shifting cytokine secretion in favor of

TARGETED TREATMENTS CONTINUED ON PAGE 8

# New Mechanisms in Tumor Rejection Highlighted During Presidential Session

SATURDAY

BY TONY BERBERABE, MPH

he scientific abstracts chosen for presentation today during the Presidential Session represent some of the best abstracts submitted to the society, said Howard L. Kaufman, MD, FACS, associate director for clinical science, Rutgers Cancer Institute of New Jersey.

"The work collectively represents a sampling of the best science in the field right now," said Kaufman, president of SITC. "I think the presentations cover a range of different topics, reflecting the diverse interests across the field."

Five presentations will be highlighted during the session, which tend to be from individuals who are early in their career



Value of Cancer Immunotherapy

Experts Cut Loose

22

The CheckPoints Let Immunotherapy

path, said Kaufman. "It gives the presenters a chance to showcase their work in front of a large international audience." In addition, a new feature to the session is that 2 highly regarded experts in the field will provide commentary and offer their perspectives on why these abstracts are important.

KAUFMAN

The first presentation, by Peled et al, addresses the potential influence of gut microbiota on mortality outcomes in patients who have recently received an allogeneic hematopoietic-cell transplantation (allo-HCT).1 In cases of allo-HCT, common causes of mortality include relapse, graft-versus-host disease (GVHD), and infection. In previous studies, the researchers reported that the intestinal flora was associated with the development of GVHD, bacteremia, and reduced overall survival after allo-HCT. In the research that will be presented, the authors hypothesize that specific components of the intestinal flora are associated with relapse after transplantation.

Researchers profiled the intestinal flora of 541 patients who underwent allo-HCT, following them for 2 years posttransplantation. They determined the relationship between the abundance of microbiota species or groups of related species with relapse/progression of disease using the Cox proportional hazards model in this retrospective discovery-validation study. The

GENITOURINARY CANCERS CONTINUED ON PAGE 10



# NOW ENROLLING IN

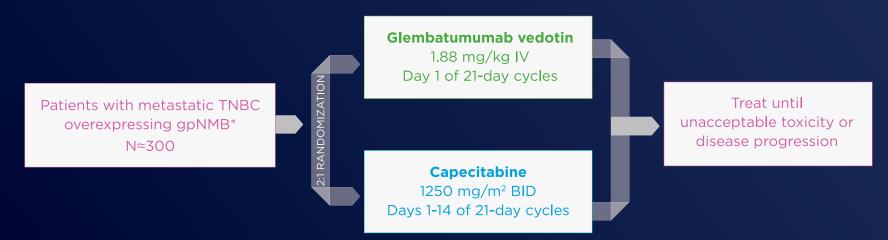
# Triple-Negative Breast Cancer



• gpNMB is a transmembrane protein<sup>1</sup> that is frequently overexpressed in the tumor in triple-negative breast cancer (TNBC).<sup>2</sup> Overexpression of gpNMB is associated with reduced recurrence-free survival in TNBC<sup>2</sup>

A Clinical Trial of CDX-011 in Metastati Triple-Negative Breast Cance

- Glembatumumab vedotin is an investigational antibody-drug conjugate (ADC) that targets gpNMB. It consists of a fully human monoclonal antibody against gpNMB conjugated to the potent microtubule inhibitor monomethyl auristatin E<sup>3</sup>
- METRIC is an open-label, prospectively controlled, randomized trial<sup>4,5</sup>



\*Patients will be stratified by 0-1 line or 2 lines of therapy for advanced disease, prior receipt of anthracyclines, and duration of progression-free interval after receipt of taxane therapy.

### **KEY INCLUSION CRITERIA**<sup>4,5</sup>

- Women and men age ≥18 years with metastatic, gpNMB-overexpressing<sup>+</sup> TNBC
- TNBC defined as: -ER/PR - less than 10% of cells positive for estrogen/progesterone receptor expression —HER2 - 0-1+ IHC, or ISH copy number <4.0/ratio <2
- 0 to 2 prior chemotherapy-containing regimens for advanced (locally advanced, recurrent, or metastatic) breast cancer
- Prior receipt of both anthracycline- (if clinically indicated) and taxane-containing chemotherapy in any setting
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1

### **KEY EXCLUSION CRITERIA**<sup>4,5</sup>

- Progression/recurrence of breast cancer during or within 3 months of completion of neoadjuvant or adjuvant chemotherapy
- Persistent neuropathy >NCI-CTCAE Grade1(at randomization)
- Known brain metastases unless previously treated, asymptomatic, and not progressive

### **KEY TRIAL ENDPOINTS<sup>4,5</sup>**

- **Primary:** Progression-free survival (PFS)
- **Secondary:** Overall survival (OS), overall response rate (ORR), and duration of response (DOR)

gpNMB=glycoprotein nonmetastatic melanoma B; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. \*gpNMB overexpression defined as ≥25% tumor epithelial cells expressing gpNMB by immunohistochemistry.

**References: 1.** Rose AA, Annis MG, Dong Z, et al. ADAM10 releases a soluble form of the GPNMB/osteoactivin extracellular domain with angiogenic properties. *PLoS One*. 2010;5(8):e12093. **2.** Rose AA, Grosset A-A, Dong Z, et al. Glycoprotein nonmetastatic B is an independent prognostic indicator of recurrence and a novel therapeutic target in breast cancer. Clin Cancer Res. 2010;16:2147-2156. 3. Tse KF, Jeffers M, Pollack VA, et al. CR011, a fully human monoclonal antibody-auristatin E conjugate, for the treatment of melanoma. Clin Cancer Res. 2006;12:1373-1382. 4. US National Institutes of Health. Available at www.clinicaltrials.gov/show/NCT01997333. Accessed July 20, 2016. 5. Data on file; Celldex Therapeutics.



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7/16





## **Targeted** Oncology

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Saturday at a Glance

Today's Agenda

7:55-8:40AM Richard Smalley, MD Memorial Lectureship 0.75 AMA PRA CATEGORY 1 CREDITS™

8:40–11:45AM Beyond Single Agents: The Future of Combination Immunotherapy 2 AMA PRA CATEGORY 1 CREDITS™

**11:15–1:00**PM Late-Breaking Abstract Session II and Poster Viewing

1:00-2:25PM Concurrent Session I: Presidential Session 1.25 AMA PRA CATEGORY 1 CREDITS™

1:00-2:25PM Concurrent Session II: *Tumor Immunology 101 (Nurse/ Pharmacist Track)* 1.5 AMA PRA CATEGORY 1 CREDITS™

**2:40–4:20**PM Concurrent Session I: *Microbiome and the Impact on Local Inflammation and Host Immunity* 

**1.75 AMA PRA** CATEGORY 1 CREDITS™ 2:40-4:20PM Concurrent Session II: *Clinical Management (Nurse/ Pharmacist Track)* 1.75 AMA PRA CATEGORY 1 CREDITS<sup>™</sup>

**4:50–6:15**PM Concurrent Session I: *Diet, Exercise, Stress and the Impact on the Immune System* **1.5 AMA PRA** CATEGORY 1 CREDITS<sup>™</sup>

**4:50–6:15PM** Concurrent Session II: Adoptive Cellular Therapy vs. Bispecific Antibodies **1.5 AMA PRA** CATEGORY 1 CREDITS™

**4:50–6:15**PM Concurrent Session III: *Emerging Technologies* 

**6:15–6:45**РМ Award Ceremony

**6:45–8:00**РМ Poster Reception

8:30–11:30рм The CheckPoints Party





This first edition of the Daily News is published by OncLive's **Targeted Oncology** division (TargetedOnc.com), publisher of *The Journal of Targeted Therapies* and *Targeted Therapies in Oncology*. TargetedOnc.com provides the latest news and insight focused on next-generation therapeutics and their molecular targets for practicing oncologists.

# Novel Immune Checkpoint Identified as Promising Target for Blockade Strategies

BY ANITA T. SHAFFER



HUNTER

new immune checkpoint called PVRIG has emerged as a ripe target for anticancer therapy in solid tumors and an antibody that blocks its ability to suppress an antitumor response is in development, according to original research presented in a latebreaking abstract on Friday.<sup>1</sup>

Researchers have demonstrated in preclinical experiments that inhibiting PVRIG results in enhanced activation of tumor-infiltrating lymphocytes (TILs), primary CD4-positive T cells, and tumor-derived CD8+ T cells.

In humanized mouse models, there was a reduction in tumor growth and increased survival when anti-PVRIG antibodies were used in combination with PD-L1 pathway blockade. Tumor growth also was reduced in PVRIG knockout mice.

The goal of the research is to find a way to boost the efficacy of checkpoint blockade immunotherapy strategies, said John Hunter, PhD, site head and vice president of antibody research at Compugen USA, Inc., who presented the findings on behalf of the company.

"Despite the outstanding advancements that were made in the last 6 years, we're still in the position where the majority of patients do not derive long-term benefit from these treatments, and this constitutes a very large unmet medical need," said Hunter.

The company plans to file an investigational new drug application with the FDA in 2017 for COM701, its lead antibody that targets PVRIG, said Hunter. The compound binds to PVRIG with high affinity ( $K_{\rm D}$  <1nM) and blocks the receptor from binding to its ligand, PVRL2.

Compugen identified PVRIG as a novel im-



mune system target through the use of computational biology tools. The company, based in Israel with a US headquarters in South San Francisco, works with researchers at Johns Hopkins University, Bar-Ilan University, and Tel Aviv University.

Hunter said PVRIG's functional gene structure matched that of known checkpoint receptors such as PD-1 and CTLA-4. Additionally, the tumor expression characteristics of PVRIG were similar to those of T-cell receptor checkpoints.

PVRIG is an immunoglobulin (Ig) domain protein that can be expressed on the surface of tumor cells or on myeloid cells in the tumor microenvironment, Hunter said in an interview. Although researchers are still developing an understanding of the functioning of PVRIG, Hunter said it exerts negative regulatory effects on T-cell activation.

"Likely, in a normal cell setting, it plays a role in keeping the immune response in check, similar to the other co-inhibitory checkpoints," said Hunter. "There's differences among the known checkpoints in terms of where they operate and the exact mechanism of action. But in a broader sense, we do think that [PVRIG] serves in the normal immune system to make sure that the immune system does not become hyperstimulated."

In human cancer, increased expression of PVRIG would inhibit an antitumor response. Specifically, investigators found that expression of PVRIG was highest in CD8+ effector memory RA T cells, Hunter said. its expression also was found to be upregulated in human and mouse tumors.

In further characterizing the activity of PVRIG, researchers focused on its binding partner, PVRL2, by designing COM701 to target the interaction of the receptor and its ligand. "The antibody binds to a site on PVRIG that is required for the interaction with PVRL2, and, because it binds at a higher affinity than PVRL2, it blocks that binding site so that you can't get that interaction," explained Hunter. "We think that that interaction is required for activating PVRIG and inducing the inhibition of T-cell response."

Moreover, this interaction is important because PVRL2 is known to be a binding counterpart to DNAM-1, a key element in the TIGIT immune checkpoint axis, Hunter said. Compugen found that combined blockade of PVRIG and TIGIT also enhanced TIL activation.

The company's experiments are in keeping with a current trend toward exploring com-

bination checkpoint blockade approaches, Hunter noted. "Obviously the existing immune checkpoints aren't effective in all patients and we think one of the underlying reasons is that there may be other checkpoints that have to be inhibited as well to reactivate the immune response," he said.

Hunter said Compugen's findings about PVRIG's mechanisms of action complement conclusions reached by University of Colorado researchers earlier this year.<sup>2</sup> Zhu et al described PVRIG (also called CD112R) as a poliovirus receptor (PVR)–like protein that is a member of the B7/CD28 family.

DNAM-1 (also known as CD226) competes with PVRIG to bind to PVRL2 (also called CD112).<sup>2</sup> Disrupting the ability of PVRIG to interact with its ligand enhances T-cell response, Zhu and colleagues said.

Meanwhile, TIGIT is becoming an increasing focus of immuno-oncology research. In another poster presented at the (*SITC*) 31<sup>st</sup> Annual Meeting & Associated Programs, researchers from Genentech described efforts to inhibit expression of TIGIT in conjunction with PD-L1 inhibition in mouse models as a means of enhancing CD8+ T-cell function.<sup>3</sup> The strategy resulted in significant tumor clearance, and Genentech has moved into phase I testing of an anti-TIGIT molecule.

MTIG7192A is 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 a 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.<sup>4</sup>

### REFERENCES

 Levy O, Chan C, Cojocaru G, et al. Computational identification, functional characterization, and antibody blockade of a new immune checkpoint in the TIGIT family of interacting molecules. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract O3.

2. Zhu Y, Paniccia A, Schulick AC, et al. Identification of CD112R as a novel checkpoint for human T cells. *J Exp Med*. 2016;213(2):167-176. doi: 10.1084/jem.20150785.

3. Grogan J, Manieri N, Chiang E, et al. The immunoreceptor TIGIT regulates anti-tumor immunity. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 214.

4. NIH Clinical Trials Registry. www.ClinicalTrials.gov. Identifier: NCT02794571. Accessed November 11, 2016.



# **NOW ENROLLING**



A Phase 3 Study of Epacadostat + Pembrolizumab Versus Placebo + Pembrolizumab in Subjects With Unresectable or Metastatic Melanoma

	<b>EPACADOSTAT:</b> an investigational, selective oral inhibitor of indoleamine-2,3-dioxygenase 1 (IDO1)
<u>600</u>	<b>PHASE 3 STUDY</b> of Epacadostat and Pembrolizumab (ECHO-301/Keynote-252)
	<b>ENROLLING</b> ~600 patients with unresectable or metastatic melanoma
	<b>STRATIFICATION</b> by PD-L1 expression status, <i>BRAF</i> mutation status
<i>℃</i> \$	<b>RANDOMIZATION:</b> Epacadostat + Pembrolizumab versus Placebo + Pembrolizumab
8	<b>DUAL PRIMARY END POINTS</b> of progression-free survival and overall survival

This study will enroll in the following regions: North America, Central/South America, Europe, Australia, and Other Regions

Contact us to learn if any of your patients might be eligible for participation in ECHO-301 at **1-855-4MEDINFO** (1-855-463-3463) / **MEDINFO@INCYTE.COM** 

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The efficacy and safety of the investigational compounds discussed have not been established. There is no guarantee that these compounds will become commercially available for the use(s) under investigation.



# Dual Biomarker Signature Correlates With Outcomes in Anti–PD-L1 Therapy

BY LISA MILLER

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ALTHAMMER

he presence of both PD-L1–positive and CD8+ cells may help to predict response in patients with non–small cell lung cancer (NSCLC) treated with durvalumab (MEDI4736), according to findings presented during yesterday's late-breaking abstract session.

Sonja Althammer, PhD, presented on the correlation between improved survival rates to durvalumab treatment and high CD8+ and PD-L1+ cell densities.<sup>1</sup>

It is already commonly known that expression of PD-L1 on tumor cells is associated with improved responses to anti–PD-L1 therapy, said Althammer, leader of the Bioinformatics team at Definiens in Munich, Germany. "Knowing that, we were wondering if we could improve the predictive character of PD-L1 by including inflammation from CD8."

The researchers explored 12 similar approaches in a hypothesis-driven analysis to see how CD8 and PD-L1 cells could best predict patient responses to durvalumab treatment. Their goal was to improve patient selection for treatment with this anti–PD-L1 monoclonal antibody.

In findings from a phase I/II trial of durvalumab presented at the 2015 ASCO Annual Meeting,<sup>2</sup> durvalumab showed a manageable safety profile in patients with NSCLC and durable responses, with 76% of patients (n = 149) still receiving treatment after 24 weeks. The objective response rate (ORR) for all evaluable patients was 14% and the ORR rate for patients with PD-L1+ expression was 23%.

To explore possible predictive biomarkers to the treatment, researchers examined biopsies from 163 patients with NSCLC to be treated with durvalumab. Each biopsy was tested for CD8 and PD-L1 cell densities through immunohistochemistry, and for combined expres-



TABLE. Clinical outcomes in NSCLC patients with CD8+ and/or PD-L1 cell densities.<sup>1</sup>

	CD8+ and PD-L1+	PD-L1+ alone	CD8+ alone	All patients
Number of patients	n = 59	n = 96	n = 74	n = 163
Median overall sur- vival, in months	24.3 (95% CI, 14.5-NE)	17.1 (95% Cl, 9.8-25.3)	17.8 (95% Cl, 14.0-NE)	11.1 (7.9-15.0)
Median progression- free survival, in months	7.3 (4.0-7.9)	3.6 (2.6-5.3)	5.3 (3.1-7.4)	2.8 (1.7-3.8)
NF not evaluable				

sion using automated image analysis. Patients were considered to have high PD-L1 expression if there was  $\geq 25\%$  expression in the tumor cells at any intensity level. The amount of CD8 expression necessary was not expressed during the presentation.

Patients were divided into a discovery set (n = 84) and a validation set (n = 79) to confirm the hypothesis. The datasets were well balanced in terms of objective response rates, prevalence of PD-L1 status, lines of prior therapy, ECOG performance status scores, and response.

The determined cellular signature was based on the density of CD8 and PD-L1 cells in the tested tumor area. That density was determined with a ratio comparing the number of cells to the total analyzed tissue area.

"The beauty of this signature is that it is actually quite simple to calculate and you do not need any co-registration or alignment of the sections," Althammer said.

Together, the CD8+ and PD-L1+ cell densities were associated with higher responses and improved survival rates. "For a response to durvalumab treatment, both cell populations actually need to be present," Althammer stated.

In the discovery set, the ORR of patients with positive densities for both cell populations, which Althammer referred to as double-positive patients, was 42% (n = 26; 95% CI, 23-63), and in the validation set, the ORR of the double-positive subgroup (n = 33) was 36% (95% CI, 20-55). In both datasets, the ORR rate was greater for the double-positive subgroup than for patients with high CD8+ or PD-L1+ expression alone, and was significantly greater than the rate for patients with negative expression of either cell **(TABLE)**.

For the combined datasets, the median overall survival (OS) for the 59 patients with CD8+ and PD-L1+ cell densities was 24.3 months (14.5-not evaluable) compared with 17.1 months (9.8-25.3) and 17.8 months (14.0-not evaluable) for patients with PD-L1+ expression alone and CD8+ expression alone, respectively. The median OS for all 163 patients in both sets was 11.1 months (7.9-15.0).

The OS for the double-positive subgroup was found to be clinically significant with a log-rank *P*-value of .0005.

Median progression-free survival (PFS) for the combined groups was 7.3 months (4.0-7.9) for the double-positive subgroup, compared with 3.6 months (2.6-5.3) and 5.3 months (3.1-7.4) for patients with PD-L1+ expression alone and CD8+ expression alone, respectively. Overall median PFS was 2.8 months (1.7-3.8).

While the results did show an increased correlation to improved outcomes for patients with high CD8+ and PD-L1+ expression, this biomarker approach is still far off from being used in clinical practice.

"These are very encouraging results for us, however, we need to keep in mind that this is preliminary data and that it is important to confirm this analysis on an independent dataset," Althammer said. In an interview, Althammer expressed that, with AstraZeneca, the manufacturer of the drug, researchers are looking to identify further trials for a confirmation study. •

### REFERENCES

 Althammer S, Steele K, Rebelatto M, et al. Combinational CD8+ and PD-L1+ cell densities correlate with response and improved survival in non-small cell lung cancer (NSCLC) patients treated with durvalumab. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract O1.

 Rizvi NA, Brahmer JR, Ou S-HI, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). *J Clin Oncol* 33, 2015 (suppl; abstr 8032).

# SITC 2017 November 8-12 NATIONAL HARBOR MARYLAND Gaylord National Hotel & Convention Center

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### Workshop on Single Cell Techniques in Immunology and Cancer Immunotherapy

Nir Hacohen, PhD – Massachusetts General Hospital

**Primer on Tumor Immunology and Cancer Immunotherapy**<sup>TM</sup> Nina Bhardwaj, MD, PhD – The Tisch Cancer Institute at The Mount Sinai Medical Center

Grant Writing Workshop on Cancer Immunotherapy Protocol Development

Organized by the Early Career Scientist Committee



# Exploring Adoptive Cellular Therapy and Bispecific Antibodies

BY PETER J. SCIAVOLINO, PHD



### CONTINUED FROM COVER

pro-inflammatory Th1-type mediators, such as interferon-gamma and tumor necrosis factor.<sup>5</sup> BsAs are another type of immunotherapy approach utilizing antibodies designed to redirect T cells into proximity with specific types of tumor cells, leading to T-cell activation and subsequent tumor cell lysis.<sup>1</sup> One example is the currently approved blinatumomab (Blincyto), which transiently links CD3-positive T cells to CD19+ B cells,<sup>6</sup> and has been approved for the treatment of Ph-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

The session will feature presentations on the biology and clinical application of bispecific T cell engagers (BiTEs), and on the design of chimeric antigen receptors (CARs) for safe and effective Tcell therapy.

Another highlight from this session will be a presentation from Lawrence G. Lum, MD, DSc, from the University of Virginia Cancer Center,<sup>7</sup> "Clinical Responses in Advanced Pancreatic Patients Treated with Bispecific Antibody Armed T Cells (BATS)." In Lum's approach, which essentially combines the 2 strategies, patient Tcells are isolated and expanded for 2 weeks and armed with a BsA. Lum will be describing results in patients with locally advanced and metastatic pancreatic cancer, which is typically associated with very poor survival and response rates.

Lum believes his strategy avoids some of the problems associated with infusions of BsAs, namely nonspecific T-cell activation, cytokine release, and/or "cytokine storm" effects. He emphasizes that, despite extensive development over the last 25 years, only blinatumomab is approved at present, and even then, there are many limitations to the drug, including cytokine storm risk. He also cited lingering unresolved issues with the ACT approach, such as toxicity (including patient deaths) that have been associated with CAR T-cell therapy.

Lum describes his strategy as taking the best of both the ACT and BsA worlds. "I use anti-CD3 to engage the T-cell receptor, and the other end of the bispecific antibody is whatever tumor-associated antigen you want to target," he says. In the present study, an antibody targeting the epidermal growth factor receptor (EGFR) was used.

"I know that [the re-introduced T cells] will kill and divide. And as they divide, they dilute out the amount of [bispecific] antibody that I coated them with," says Lum. This approach, Lum believes, allows the T cells to quench (thus limiting potential side effects), and facilitates multiple infusions. The approach also allows the procedure to be completed on an entirely outpatient basis.

Among some 140 patients treated thus far,

Lum reports that no one has died from a side effect of the cells, and only 2 have required hospitalization (1 of which was for suspicion of anticipated noncompliance with the therapy). Thus, as will be detailed further at the meeting, Lum notes that the procedure has been well tolerated, with no dose-limiting toxicities in the phase I trial for pancreatic cancer.

"The vast majority of pancreatic patients are dead between 6 and 12 months, even if you are a stable patient," Lum says. Considering this set of patients, he was especially struck by the median overall survival in the study, which was approximately 25 months. "In fact," he says, "2 of the patients are still alive, with 1 still in complete remission ... there is no tumor in her body."

He also noted the course of another patient that was taken off therapy, and restarted on a previous chemotherapy, with subsequent tumor reduction. Lum speculates that the latter phenomenon may be in part due to an alteration in the local tumor microenvironment.

Through the elaboration of local Th1 cytokines, such as gamma interferon, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor, Lum believes the BATS immunotherapy essentially "vaccinates" the patient against the tumor, and causes disruption of the cell matrix and the local tumor microenvironment, to allow for greater penetration of any subsequent therapy. As a result, Lum believes that repeated cycling of therapies (ie, BATS immunotherapy followed by chemotherapy) is feasible. "One of the patients, who lived 930-plus days, we treated him twice, and each time we gave him immunotherapy, he was again [subsequently] responsive to chemotherapy."

Next, Lum hopes to attain breakthrough status for the procedure from the FDA, with a randomized phase II study. "If we can show that we can go from 7-and-a-half months to 10-and-a-half, or 12 months, median overall survival in this population, that would be huge."

Lum also sees potential for the approach to be used as a platform to target other tumor cell markers, such as HER2, CD20, and CD2, for which antibodies are readily available "off the shelf" to use in coating the BATS. Lum's colleagues are already applying the strategy to other tumors, such as refractory neuroblastoma (using anti-CD2), with some very encouraging results. •

### REFERENCES

 Fan G, Wang Z, Hao M, Li J. Bispecific antibodies and their applications. J Hematol Oncol. 2015; 8: 130. doi: 10.1186/s13045-015-0227-0.

2. Almåsbak H, Aarvak T, Vemuri MC. CAR T cell therapy: a game



Emerging Leaders Igniting Innovation

The SITC Sparkathon – Emerging Leaders, Igniting Innovation is an exciting opportunity for early career professionals seeking to participate in new research that contributes to the cancer immunotherapy field and the society as a whole. Through an application process, a group of 30 emerging leaders will explore the critical hurdles that have been challenging the cancer immunotherapy field for years. Once projects have been determined, teams will embark on formulating plans to solve these major issues. Strategies will be presented to a panel of SITC leaders who will select the top proposals for implementation.

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changer in cancer treatment. J Immunol Res. 2016; 2016:5474602 doi: 10.1155/2016/5474602.

 Sharma P, Kranz DM. Recent advances in T-cell engineering for use in immunotherapy. *F1000Res.* 2016; 5. pii: F1000 Faculty Rev-2344.
 Suryadevara CM, Gedeon PC, Sanchez-Perez L, et al. Are BiTEs

the "missing link" in cancer therapy? *Oncoimmunology*. 2015; 4(6):e1008339.

5. Ishikawa T, Kokura S, Sakamoto N, et al. Adoptive cellular therapy enhances the helper T cell response and reduces the number of regulatory T cells. *Exp Ther Med.* 2011; 2(4):737-743.

6. Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood.* 2016; 127(11): 1410-1416. doi: 10.1182/blood-2015-06-651380.

7. Lum L, Choi M, Thakur A, et al. Clinical responses in advanced pancreatic patients treated with bispecific antibody armed T cells (BATS). Presented at: 2016 SITC Annual Meeting. November 9-13, 2016; National Harbor, MD. Abstract 129.

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# New Mechanisms in Tumor Rejection Highlighted During Presidential Session

BY TONY BERBERABE, MPH



10

KAUFMAN

### CONTINUED FROM COVER

researchers suggest that the association between the abundance of a group of bacteria in intestinal flora and relapse/progression of disease could serve as a potential biomarker to prevent relapse and improve survival, said Kaufman. The researchers noted that the presence of

*Eubacterium limosum* in the validation set was associated with less relapse/progression of disease (HR, 0.52; 95% CI, 0.31-0.87; P = .01). They noted that the 2-year cumulative incidence of relapse/progression among patients with and without this group of bacteria was 33.8% and 19.8%, respectively. Less relapse/progression was observed when the bacteria were abundant (HR, 0.82; 95% CI, 0.71-0.95; P = .009).

"Research that involves the microbiome and its role in influencing immune response is somewhat controversial, and theories are evolving," said Kaufman.

Another presentation focuses on mitochondrial dysfunction within tumor-infiltrating CD8+ T cells. Scharping et al. hypothesized that metabolic mechanisms may have a role in suppressing tumor-infiltrating lymphocyte activity within the tumor microenvironment. Existing evidence, including the robust metabolic demands of T-cell activation and poor metabolite availability within the tumor microenvironment, supports a potential role of mitochondrial dysfunction in this process.<sup>2</sup>

"Emerging research shows that tumors can release soluble factors that interact at the cell surface causing dysfunction in T cells," said Kaufman. "But one of the things that is less well known is how the basic metabolism inside the cells can influence the immune responses to cancer." The researchers note that by understanding these metabolic insufficiencies, metabolic modulation strategies might improve cancer immunotherapy.

Two of the papers in the Presidential Session focus on various biomarkers associated with changes in the function of regulatory T cells  $(T_{regs})$  in clinical trials—1 presentation focuses on the effect of a glucocorticoid-induced tumor necrosis factor-related gene (GITR) agonist, and the other examines the role of STAT3 signaling.

Zappasodi et al. will present results of a pharmacodynamics analysis of the first-in-human phase I trial studying the fully humanized agonist anti-GITR antibody TRX518 as a monotherapy in patients with advanced refractory solid tumors.<sup>3</sup> GITR stimulation abrogates  $T_{reg}$  suppression and enhances T-cell effector function. This suggests that GITR could be an attractive target for immunotherapy with agonist antibodies.

Patients included in the analysis had received a single dose of TRX518  $\geq$ 0.005 mg/kg, including 6 patients with melanoma, 7 patients with nonsmall cell lung cancer (NSCLC), 7 patients with colorectal cancer (CRC), and 17 patients with other solid tumors. Serum samples collected at different time points, up to 12 weeks after treatment, were analyzed for cytokine levels, and, using flow cytometry, for the frequency and phenotype of circulating T cells.

Researchers identified frequent reductions in circulating  $T_{regs}$  after treatment with TRX518 across all cohorts that were maintained throughout the 12-week period. In patients with melanoma and CRC who had received TRX518, researchers identified a dose-dependent reduction in levels of peripheral  $T_{regs}$ . Reductions in levels of peripheral T<sub>regs</sub> were not always observed in patients with NSCLC.

In 6 patients who had undergone tumor biopsies before and after treatment, researchers assessed the effect of TRX518 on levels of intratumoral  $T_{regs}$ . In 4 of these patients (2 with melanoma and 2 with CRC), reductions in intratumoral Foxp3<sup>+</sup>  $T_{regs}$  were observed, consistent with downregulation of peripheral  $T_{regs}$  observed in these patients. Although reductions in levels of peripheral  $T_{regs}$  were not always observed in patients with NSCLC, reductions in peripheral  $T_{regs}$  among lung cancer patients were consistently associated with stable or increased intratumoral infiltration of  $T_{regs}$  after administration of TRX518.

Researchers concluded that circulating  $T_{regs}$  reduction is a potential pharmacodynamics biomarker of TRX518 activity that may enable for the prediction of stable or increased intratumoral  $T_{reg}$  infiltration. Further investigation is warranted.

In Woods et al, the authors identified decreased suppressive function of  $T_{regs}$  and increased STAT3 signaling in  $T_{regs}$  as predictive biomarkers of improved response to PD-1 blockade with nivolumab in patients with metastatic melanoma who received adjuvant immunotherapy before surgical resection.<sup>4</sup> Using an allogeneic mixed lymphocyte reac-

tion assay, researchers evaluated the suppressive capacity of  $\rm T_{regs}$  that were isolated for each patient before and after treatment. Researchers also evaluated levels of phosphorylated STAT3 (pSTAT3) in  $\rm T_{regs}$  through flow cytometry, and assessed changes in gene expression through RNA sequencing.

 $\rm T_{regs}$  collected before and after nivolumab therapy from non-relapsing patients showed a significant decrease in suppressive capacity post-treatment (P < .05), as evaluated through the allogeneic mixed lymphocyte reaction. However, the suppressive capacity of  $\rm T_{regs}$  in relapsing patients did not decrease, and, relative to non-relapsers, the  $\rm T_{regs}$  of relapsing patients were significantly more suppressive after treatment (P < .01).

Consistent with these results, significant increases in levels of pSTAT3 were observed in nonrelapsers (P < .05) following treatment, but not in patients who relapsed (P < .40). These relationships between PD-1 blockade, increased STAT3 signaling, and  $T_{reg}$  proliferation were confirmed through in vitro studies. Relationships between relapse or non-relapse and genetic expression data were also identified.

The findings highlight pSTAT induction and reduced  $T_{regs}$  suppressive capacity as potential biomarkers of improved clinical outcomes in patients receiving nivolumab for metastatic melanoma. These results also demonstrate distinct differences in the impact of PD-1 blockade in  $T_{regs}$  versus conventional T cells.

"This should be a great session," concluded Kaufman. •

### REFERENCES

 Peled J, Devlin S, Staffas A, et al. Intestinal microbiota and relapse after hematopoietic-cell transplantation. Presented at: 2016 SITC Annual Meeting. November 9-13, 2016; National Harbor, MD. Abstract 300.

 Scharping N, Menk AV, Moreci R, et al. Mitochondrial biogenesis is repressed in tumor-infiltrating CD8+ T cells resulting in metabolic insufficiency and T cell dysfunction. Presented at: 2016 SITC Annual Meeting. November 9-13, 2016; National Harbor, MD. Abstract 280.

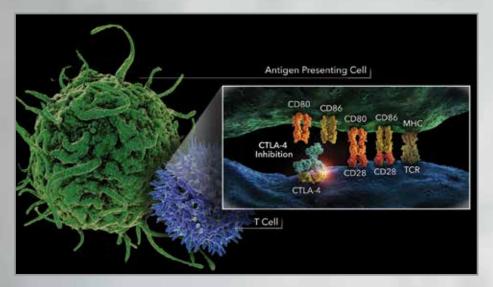
3. Zappasodi R, Li Y, Qi J, et al. Analysis of pharmacodynamic biomarkers in the first in-human trial of GITR co-stimulation with the agonist antibody TRX-518 in advanced solid cancer patients. Presented at: 2016 SITC Annual Meeting. November 9-13, 2016; National Harbor, MD. Abstract 125.

4. Woods D, Berglund A, Ramakrishnan R, et al. Increased STAT3 signaling and decreased suppressive function of regulatory T cells are biomarkers of positive patient outcome to nivolumab therapy. Presented at: 2016 SITC Annual Meeting. November 9-13, 2016; National Harbor, MD. Abstract 124.

# How does the combination of PD-L1 and CTLA-4 inhibition have the potential for synergistic effects?

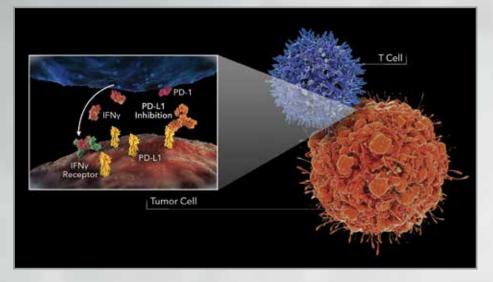
# Combination strategies that inhibit nonredundant pathways, such as PD-L1 and CTLA-4, may potentially have synergistic effects<sup>1,2</sup>

Targeting PD-L1 and CTLA-4 may release the brakes on adaptive (cellular) immune responses to potentially improve antitumor activity.<sup>3-5</sup>



**Inhibition of CTLA-4** leads to increased T-cell activation and proliferation by preventing interaction between the inhibitory receptor CTLA-4 and ligands CD80 and CD86<sup>1.6</sup>

Activated T cells migrate to the tumor microenvironment, with activity characterized by release of interferon gamma (IFN $\gamma$ ).<sup>4</sup> IFN $\gamma$  causes tumor and immune cells to upregulate PD-L1, which binds to PD-1 on T cells to help suppress the immune reaction.<sup>3,4,7</sup>



**Inhibition of PD-L1** helps prevent T-cell suppression, and may result in prolonged T-cell activation and antitumor immune response<sup>3,8</sup>

Combination approaches are a key area of clinical research and may unlock the potential of immuno-oncology (IO) therapies by overcoming multiple mechanisms of immune evasion.

Learn about the IO approaches AstraZeneca is taking at www.azimmuno-oncology.com. Watch mechanism of disease videos on the PD-L1, CTLA-4, and OX40 pathways. View the list of ongoing AstraZeneca IO clinical trials.

References: 1. Melero I, Berman DM, Anzar A, Korman AJ, Perez Garcia JL, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer*. 2015;8:457-472. 2. Drake CG. Combination immunotherapy approaches. *Ann Oncol*. 2012;23(suppl 8):viii41-viii46. 3. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. *Cancer Med*. 2013;2:662-673. 4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252-264. 5. Dizon DS, Krilov L, Cohen E, et al. Clinical cancer advances 2016: annual report on progress against cancer from the American Society of Clinical Oncology [published online ahead of print February 4, 2016]. *J Clin Oncol*. doi:pii:JCO658427. 6. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1-10. 7. Haile ST, Dalal SP, Clements V, et al. Soluble CD80 restores T cell activation and overcomes tumor cell programmed death ligand 1-mediated immune suppression. *J Immunol*. 2013;191:2829-2836. 8. Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer—response. *Clin Cancer Res*. 2013;19:5542.



SITC 2016 | 31<sup>st</sup> Annual Meeting & ASSOCIATED PROGRAMS DAILY

# Topalian Discusses the Evolution of PD-1/PD-L1 Inhibitors in Cancer Care

BY LAURA PANJWANI



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he identification of the PD-1/PD-L1 pathway and the development of therapies targeting it transformed the field of immunotherapy and brought decades of work to the forefront of cancer care, said Suzanne L. Topalian, MD.

"The development path for these drugs has been a long one, and has involved many investigators around the world," said Topalian, director, Melanoma Program, and professor of surgery and oncology, Johns Hopkins Medicine.

"This development really brought immunotherapy into the mainstream. We've moved information from bench to bedside, developing new treatments based on scientific knowledge, which has now proved to be effective in several different types of cancers."

With anti–PD-1 therapies rapidly gaining FDA approval across tumor types, the focus now needs to shift to identifying effective biomarkers to guide treatment decisions and determining which combination regimens will be the most effective with the least amount of toxicity, noted Topalian.

"There is a lot on the horizon," she said. "Clearly it will take a global team of researchers to address issues this broad and it will pull in people from all different areas of science and cancer biology."

Topalian, the Richard V. Smalley, MD Memorial Award and Lectureship Recipient, will give the Smalley keynote address this morning on PD-1 blockade in cancer treatment. The award is given each year to a recognizable clinician or scientist and luminary in the field who has significantly contributed to the advancement of cancer immunotherapy research.

In an interview, Topalian discussed key topics from her presentation, including the evolution of PD-1, emerging biomarkers, and why a precision medicine approach is necessary to identify effective immunotherapy combination regimens.

### Looking back, how has the role of PD-1 and other checkpoint molecules evolved to where we are today?

For a long time—and depending on whom you talk to, it could go back decades, a century, or even further than that—we've known that the immune system can recognize cancer and can sometimes play a role in combating cancer. But it was only more recently, through basic discovery in immunology laboratories, that people realized there are several different mechanisms by which tumors can escape immune attack. The overriding balance between the immune system and cancer is what we call tolerance, where the immune system tolerates the presence and growth of cancer cells, because cancer cells can masquerade as normal cells. All the signals that the immune system uses to detect cells that are not normal—for example, cells that are infected with viruses—those mechanisms are turned off by various other mechanisms that cancers have for immune evasion.

PD-1 is a so-called immune checkpoint molecule that is expressed on activated immune cells. But when it interacts with its major ligand PD-L1, [which is] expressed on cancer cells, then the immune attack is turned off. Once this pathway was identified, which was a result of many years of research in a variety of different laboratories, then this became a very attractive target to move into the clinic for cancer immunotherapy.

### The role of PD-L1 as a biomarker has been debated. How do you see it being utilized across the various tumor types?

The first evidence for PD-L1 as a potential biomarker was published from our group here at Johns Hopkins. Since then, many other groups and pharmaceutical companies have made their own versions of the PD-L1 immunohistochemistry test. This test has been used to look at tumor specimens from patients being treated on many different trials, such that thousands of patients' tumors have been tested for PD-L1 expression. Those results were correlated with clinical outcomes after treatment with anti–PD-1 or anti–PD-L1 drugs.

The story that emerged was that for several different kinds of cancers, if the tumor expresses PD-L1 those patients are more likely to respond to anti–PD-1 therapies, but it is not an absolute correlation. It is a greater likelihood of response, but it's not a guarantee.

Then, on the other side, there are a small number of patients whose tumors are PD-L1-negative on these tests who can still respond to anti-PD-1 therapy. It's not a perfect test, but it can be used to guide treatment decisions for patients who might be candidates to receive these drugs.

The FDA has now approved 3 different commercial PD-L1 immunohistochemistry tests to be used in patients with melanoma, non-small cell lung cancer, or bladder cancer to help physicians and patients discuss what the appropriate treatment options might be.

### Besides PD-L1, what other biomarkers are emerging for use with PD-1/PD-L1 agents?

There are many. This is ongoing work in our laboratory, as well as many cancer immunology laboratories around the world. There is a large family of immune checkpoint molecules that are related yet have distinct functions. These other checkpoints are being looked at as potential biomarkers for response to anti–PD-1 therapy. In addition, tumors may or may not be infiltrated by immune cells, and some researchers have proposed that tumors that do not contain immune cells are not likely to respond to anti-PD-1. There is evidence for this.

There is also evidence that a certain type of T cell or immune cell is needed to respond to anti–PD-1 therapies. It is generally thought that CD8-positive killer T cells are the most important T cells in the PD-1 pathway response. These are just some ideas, there are many others. Looking at immuno-logical markers is just the beginning of the story.

Another story that has emerged in the past year or 2 is the notion that tumors that contain higher mutational burdens might be more likely to respond to anti-PD-1 therapy. The idea is that these mutations lead to the expression of abnormal proteins that have never been seen before by the immune system, so they can create a strong immune stimulant.

There is a subtype of colon cancer that is very highly mutated, and it turns out that this subtype, which represents about 10% to 15% of all colon cancers, is highly responsive to anti–PD-1 therapy. The garden variety colon cancer, which only has a modest mutational burden, is not responsive to anti–PD-1 therapies. This is an example where 2 very different active fields of cancer research—cancer genetics and cancer immunology—have a direct point of intersection.

It is very possible that the microsatellite instability test, which identifies a genetic abnormality associated with a higher mutational burden in the tumor, could become a biomarker to select patients with cancer for anti–PD-1 therapy.

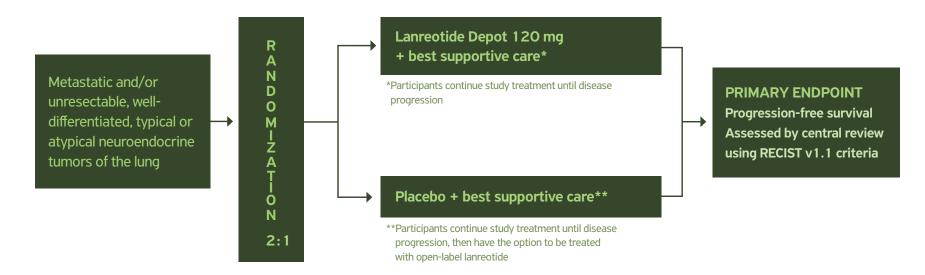
Biomarker research has the potential to reveal many of these markers or molecules that could be targeted. It could provide markers of patients more likely to respond to immunotherapy monotherapy, or the markers themselves could become targets for new drugs or combination therapies. Really, biomarkers are intimately associated with the developmment of combination therapies.

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Mitotic index < 2 mitoses/2 mm <sup>2</sup> for typical carcinoid and <10 mitoses/2 mm <sup>2</sup> and/or foci of necrosis for atypical carcinoid	Treatment with peptide receptor radionuclide therapy at any time prior to randomization
At least 1 measurable lesion of the disease on imaging (CT or MRI; RECIST 1.1 criteria)	Prior treatment with more than 1 course of cytotoxic chemotherapy or molecular targeted therapy, or interferon for lung NETs
Positive somatostatin receptor imaging	

### For more information, visit www.clinicaltrials.gov/ct2/show/NCT02683941



### CONTINUED FROM PAGE 12

### Are there particular combinations of anti–PD-1/PD-L1 agents for which you see great potential?

The first FDA-approved immunotherapy combination was the combination of drugs blocking 2 distinct immune checkpoints: anti–PD-1 plus anti–CTLA-4. That was approved in melanoma. The response rate in patients with advanced melanoma to the combination is higher than the response to either drug alone. The progressionfree survival with the combination is substantial, and that was the basis for approving this combination in melanoma.

But a lot of work still needs to be done because the combination has a high rate of serious side effects. Ongoing work is now looking at different doses of these drugs, either given at the same time or in sequence, the hope being that maybe a dosing regimen can be found that would still have the therapeutic impact with fewer serious side effects. I think research is well on its way in that area.

### Do you see potential for combining chemotherapy with anti–PD-1 therapies?

This is where the combinations need to be considered in terms of the different cancer types. For instance, in melanoma, chemotherapy is not really effective. The idea of combining anti– PD-1 with a standard melanoma chemotherapy is not really appealing. But in melanoma, a very big story is the BRAF inhibitors. Combinations of anti–PD-1 with BRAF and MEK inhibitors are looking very interesting.

In lung cancer, where platinum-based chemotherapy is a mainstay for treatment, that chemotherapy is being combined with anti–PD-1 therapies. We are looking to see if those effects might be additive or even synergistic. We've developed a common-denominator approach by applying anti–PD-1 as a single drug in various forms of cancer. The next step is going to be considering individual tumor types and how other treatments that are known to be effective in different cancer types might be combined with anti–PD-1 therapy. •

# Oncology Nurses on the Frontlines of Immunotherapy Care

early 3 decades have passed since the first immunotherapy for cancer was approved by the FDA (BCG for bladder cancer in 1990), yet treatments that engage the immune system to help it identify and reject cancer have only recently begun to achieve widespread recognition.

Broadly, immunotherapeutics can include tumor-targeting antibodies with the ability to eradicate tumor cells or boost anticancer activity by blocking immune cell "off switches," cancer vaccination strategies that help increase

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SITC's annual meeting and regional programs represent valuable opportunities for oncology nurses seeking to incorporate current immunotherapy treatment guidelines into clinical management of patients."

> —Laura Wood, RN, MSN, OCN, Cleveland Clinic Taussig Cancer Institute

immune recognition of cancer cells, or infusion of immune cells engineered to target and attack malignant cells. Alone and in combination with other treatments, cancer immunotherapies continue to show promising clinical outcomes, notably long-lasting remission, for an increasing number of malignancies. Indeed, hundreds of clinical trials of immunotherapies for cancer are currently underway, and even more effective approaches are anticipated as research and technological capabilities advance.

### A Multidisciplinary Team Effort

The emergence of immunotherapy from benchtop to bedside as a potent treatment strategy in the anticancer arsenal means that all members of the cancer care team require the knowledge and skills to incorporate immunotherapy treatment into their clinical practice.

Nurses, in particular, are often charged with managing patients on immunotherapy clinical trials and educating patients about the nature of their disease, available treatment options, and potential side effects.

The Society for Immunotherapy of Cancer (SITC) is a member-driven 501(c)(3) non-profit professional society dedicated to improving cancer patient outcomes by advancing the science and application of cancer immunotherapy. SITC is addressing the need to provide immunotherapy education for oncology advanced practitioners and nurses in several ways: (1) adding a new membership category; (2) special sessions at the *SITC 31st Annual Meeting & Associated Programs*, and (3) offering accredited regional education programs.

SITC's Nurse and Physician Extender membership category was added in an effort to provide resources to all stakeholders in the fight against cancer. Society membership benefits include free or discounted rates on all SITC live education programs, access to the SITC website's "members only" section, which includes slide decks from past live events, patient education resources on immunotherapy, and timely information about what is new and relevant to the field. Members can also take advantage of free article submissions to the *Journal for ImmunoTherapy of Cancer*, SITC's official open-access, peer-reviewed journal.

### **Spotlighting Nurse Education**

"SITC's Annual Meeting and regional programs represent valuable opportunities for oncology nurses seeking to incorporate current immunotherapy treatment guidelines into clinical management of patients." — Laura Wood, RN, MSN, OCN, Cleveland Clinic Taussig Cancer Institute

In line with SITC's commitment to providing oncology nurses and nurse practitioners with a robust framework for understanding the principles of tumor immunology and cancer immunotherapy, as well as opportunities to interact face-to-face with immunotherapy experts, at the 2016 SITC Annual Meeting & Associated Programs, are 2 CNE-certified sessions for nurses, presented by oncology physician scientists and nurse clinicians.

The recognized need for continuing education in basic immunology and cancer immunotherapy has driven the popularity of SITC's regional Cancer Immunotherapy 101 programs, part of the Advances in Cancer Immunotherapy<sup>™</sup> series, which have reached 3000 attendees in the past 3 years and are free of charge for SITC nurse members. Further highlighting how Cancer Immunotherapy 101 meets the needs of oncology nurses in this rapidly evolving field, a survey from the 2015 program series revealed that one-third of practicing nurse attendees had not received previous cancer immunotherapy education, and more than 99% of all responding attendees would recommend the program to others.

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# Exploring Combination Approaches to Immunotherapy Treatment

BY KATIE KOSKO AND LISA MILLER



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n recent years, immunotherapy has shown its potential for treating patients with cancer. Success has been especially notable with regards to checkpoint inhibitors, including PD-1/PD-L1 and CTLA-4 single agents. As researchers continue to explore new ways that immunotherapy can improve patient outcomes, the success of these checkpoint inhibitors and other proven agents are being extended to combination approaches to treat patients for an even greater response.

Seven physicians and clinical researchers will take the stage this morning to discuss what lies ahead for combination immunotherapy in cancer research during the "Beyond Single Agents" session, which will include 4 talks and 2 oral abstract presentations. Drew M. Pardoll, MD, PhD, and F. Stephen Hodi, MD will co-chair the session.

During the session, presenters will discuss future strategies in combination immunotherapy and the factors that will influence this approach, including biomarkers and selecting the patients that will respond best to combination therapies. Alan J. Korman, PhD, of Bristol-Myers Squibb, will discuss combining ipilimumab (Yervoy) with nivolumab (Opdivo) and how this combination can be advanced in the future, with a focus on methods to improve anti–CTLA-4 therapy. Korman said that the antibody could be made more potent by altering the Fc region or by activating the therapy at the tumor site through protease cleavage, which is currently being developed in collaboration with Cytomyx.

Erminia Massarelli, MD, PhD, MS, of City of Hope will discuss the clinical safety and efficacy of urelumab (BMS-663513), a novel anti-CD137 antibody with demonstrated antitumor potential through enhancement of T cell and natural killer cell activity. Urelumab was explored alone and in combination with the PD-1 inhibitor nivolumab (Opdivo), in patients with a variety of metastatic solid tumors and advanced non-Hodgkin lymphomas in 2 clinical trials.<sup>1</sup>

TABLE. Treatment-related adverse events across both studies of urelumab

	Urelumab Alone	Urelumab + Nivolumab
Total number of patients	123	104
Total treatment-related AEs	65 (53%)	65 (63%)
Fatigue	18 (15%)	27 (26%)
AST increase	16 (13%)	9 (9%)
ALT increase	12 (10%)	13 (13%)
Serious treatment-related AEs	9 (7%)	10 (10%)
Treatment-related AEs leading to discontinuation	6 (5%)	7 (7%)

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase

In the phase I monotherapy study, urelumab was given to patients with advanced solid tumors at a dose of 0.1 mg/kg or 0.3 mg/kg every 3 weeks, and to patients with advanced non-Hodgkin lymphoma at a dose of 8 mg every 3 or 6 weeks. Overall, 123 patients were given urelumab monotherapy, and 65 of these patients (53%) experienced a treatment-related adverse event (AE).

The phase I/II combination trial is still accruing patients, but as of this interim analysis, the study included a total of 104 patients, comprised of 40 patients with melanoma, 20 with non–small cell lung cancer, 22 with squamous cell carcinoma of the head and neck (SCCHN), and 22 with diffuse large B-cell lymphoma. Sixty-five of these patients (63%) experienced a treatment-related AE.

The most common treatment-related AEs experienced across both trials included fatigue (15% in the monotherapy study and 26% in the combination study), increased aspartate aminotransferase (AST; 13% and 9%, respectively), and increased alanine aminotransferase (ALT; 10% and 13%, respectively). Grade 3/4 AST and ALT increases were experienced by 3% and 2%, respectively, in the monotherapy trial, and 3% each in the combination trial **(TABLE)**.

Six patients discontinued treatment in the trial of urelumab alone, and 7 patients discontinued treatment in the combination study, both due to treatment-related AEs. No treatment-related deaths were reported in either study.

Partial remissions (PRs) were achieved by 3 patients with lymphoma in the monotherapy trial, and another 3 patients with lymphoma achieved a complete remission. In the combination study, a total of 9 out of 86 evaluable patients (10.5%) had a PR, including 8 patients with melanoma and one with SCCHN. Thirty-three out of 71 patients treated with combination therapy had a reduction in their tumor burden assessed by RECIST and iWG criteria.

The combination immunotherapy was found to increase T and natural killer cell numbers and expression of interferon-gamma (IFN-y) in the melanoma tumors evaluated. Additionally, the combination was associated with greater stimulation of peripheral IFN- $\gamma$ -induced cytokine production than with urelumab monotherapy. However, as of the interim analysis, the addition of nivolumab did not appear to add any significant clinical benefit at the doses that were investigated in this patient population.

The second study, to be presented by Jennifer Wu, PhD, Medical University of South Carolina, focused on a first-in-class antibody targeting soluble NKG2D ligand soluble MIC for cancer immunotherapy.<sup>2</sup>

"For a long time, my lab has been studying how tumor cells interact with the immune system and it happened to find a mechanism where tumor cells disable the immune system," Wu said in an interview.

Oncogene-induced transformation promotes the expression of MIC ligands, which bind and activate NKG2D immunoreceptors on T cells and natural killer cells, facilitating cancer cell clearance. However, advanced tumors produce a highly immunosuppressive soluble version of the MIC ligand (sMIC), which downregulates NKG2D expression on effector natural killer and T cells and immune response within the tumor microenvironment.

Wu led her research team in creating a humanized MIC-transgenic spontaneous prostate tumor mouse model in which to explore a potential antibody B10G5 therapy targeting sMIC, without blocking formation of the MIC/NKG2D complex. In preclinical proof-of-concept studies, CuraB-10 (B10G5) showed antitumor efficacy to eliminate metastasis, reduce tumor burden and increase survival when compared to placebo in these metastatic prostate cancer models. When combined with FDA-approved CTLA-4 and PD-1/PD-L1 checkpoint inhibitors, CuraB-10-mediated sMIC neutralization was found to synergize with checkpoint blockade with no observed toxicities, according to the abstract. CuraB-10 was also explored in combination with adoptive cellular therapy.

Wu said that her company CanCure, LLC, is working toward bringing this therapy into a first-in-human phase I/II trial, where it could be studied either as a monotherapy or in combination with checkpoint inhibitors, as in the proofof-concept studies. Wu sees CuraB-10 being especially useful in cancers that are not responsive to checkpoint inhibitors alone, such as prostate cancer, as well as certain types of kidney cancer and colon cancer, and maybe even lung cancer. She added that a full combination approach may also benefit patients with melanoma.

What excites her most about clinical trials and the future of combination immunotherapy? That there are new approaches to give hope to patients who have not responded to current therapies, such as vaccines, immune checkpoint inhibitors, or Tcell therapies. Wu said that there is hope for these patients as they continue to explore the emerging science behind immunology, patient responses, and novel therapeutics. •

### REFERENCES

 Massarelli E, Segal NH, Ribrag V, et al. Clinical safety and efficacy assessment of the CD137 agonist urelumab alone and in combination with nivolumab in patients with hematologic and solid tumor malignancies. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 239.

2. Wu J, Zhang J, Basher F, et al. Beyond immune checkpoint: first-inclass antibody targeting soluble NKG2D ligand sMIC for cancer immunotherapy. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 252.

# Learning to Manage Immune-Related Adverse Events in a Clinical Setting

BY KATIE KOSKO

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WOOD

**R** our oncology nurse practitioners and an oncologist will take the stage this afternoon to discuss the clinical management aspects of immunotherapy in oncology, specifically focusing on the immunerelated adverse events (irAEs) associated with immunotherapy agents.

Each speaker will address possible interventions to minimize the negative impact on efficacy and the patient's quality of life.

As immunotherapy continues to develop, there is a constant stream of new data and new approvals. With that growth, oncology professionals must continue to be educated on how to identify and manage irAEs.

"In order to provide patients with the opportunity to get the most benefit from treatment and maintain quality of life or improve quality of life, we really need to be on top of our game," said session co-chair Laura Wood, RN, MSN, OCN, Cleveland Clinic Taussig Cancer Institute in an interview. "We need to know what are these AEs and how can we effectively educate patients, because they need to call us when these changes are developing."

The irAEs that Wood sees most often among patients include gastrointestinal, skin toxicities, hepatitis and pneumonitis (inflammation of the lungs).

There will be 4 presentations during the session: immunotherapy agents currently approved for the treatment of cancer; assessment and management of irAEs; management of complex adverse events; and an abstract presentation.

The first will provide an overview of the immunotherapy agents currently approved for the treatment of malignancies. The second will focus



on the unique adverse events associated with immunotherapy, as well as assessments and interventions to minimize the toxicities experienced by individuals receiving these therapies.

The third presentation will use a case-based approach to provide participants with information regarding the complexity of irAEs, and how an understanding of these therapies will facilitate the identification, evaluation, and treatment of these toxicities.

The abstract presentation will show, for what Schvarstman and colleagues believe is the first time, that the incidence of central nervous system (CNS) metastasis has been seen as an initial site of disease progression in metastatic melanoma patients treated with therapy that blocks the programmed cell death-1 (PD-1) immune checkpoint. These patients were associated with worse overall survival (OS) rates despite receiving additional therapies upon progression. The type of anti–PD-1 therapy was not specified in the abstract.

Researchers from The University of Texas MD Anderson Cancer Center in Houston looked at 264 metastatic melanoma patients, who received an anti–PD-1 agent at the center between January 2012 and February 2016. They then assessed the association between development of CNS metastasis and OS. Time to CNS metastasis was treated as a time-varying covariate.

Patients were mostly male (62%), the majority were 62 years of age as of new CNS metastasis, and most patients had a cutaneous primary tumor (59%).

Of the 264 patients, 74 (28%) had CNS metastasis prior to the first dose of anti– PD-1 therapy. The melanoma patients were then followed for a median of 10.4 months (range, 0-51.6) from the start of therapy and 37 (19%) developed CNS metastasis after the start of anti–PD-1 therapy. Of that group, 27 patients were diagnosed with CNS metastasis during treatment or within 90 days of treatment discontinuation. Ten patients were diagnosed with CNS metastasis >90 days after the last dose of anti–PD-1 therapy.

Twenty-six patients were tested for mutations. Of those, *BRAF* was identified in 8 patients (22%)—including V600E in 6 and V600K in 2—*NRAS* in 5 (14%) and *KIT* in 6 (16%).

At least 1 CNS-directed treatment approach was used for 86% of the patients, 62% were treated with stereotactic radiosurgery, 11% received whole-brain radiation, and 30% underwent surgery.

Researchers noted that median OS from the



start of anti–PD-1 was 34 months (range, 0-51.6) for the whole anti-PD-1 treatment cohort. As a whole, development of CNS metastasis while on anti–PD-1 therapy was strongly significantly associated with risk of death (HR, 3.39; 95% CI, 2.06-5.59; P <.0001).

Wood wants attendees to walk away from the session with a better understanding of all these therapies, their impact on the immune system, and the differences between immunotherapy agents.

"The therapeutic landscape for all cancers is changing rapidly, and it's hard to keep up," she said. "Awareness of what irAEs are, what to expect, and what questions to ask based on what irAEs may occur will improve clinical outcomes and quality of life for those attending this session."

Wood adds that every institution learns differently, so by offering what she and fellow nurse practitioners know, others may be able to learn about immunotherapies and potential adverse events to empower themselves to achieve the best outcome possible while maximizing quality of life.

"The progress being made from the research laboratory to clinical practice is absolutely amazing. The more we can learn about which drug is appropriate for which individual, and in what setting—the better we can fight cancer," said Wood. •

### REFERENCE:

Schvartsman G, Bassett R, McQuade JL, et al. Incidence and outcomes of central nervous system metastases in metastatic melanoma patients treated with anti-PD-1 therapy. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 353.

# Society for Immunotherapy of Cancer

SITC is the world's leading member-driven society dedicated to professionals working in the field of cancer immunotherapy. SITC aims to make cancer immunotherapy a standard of care and the word "cure" a reality for cancer patients everywhere through...

- Dedication to education and outreach
- Commitment to collaboration with like-minded organizations and patient advocacy groups
- Focus on initiatives of major importance to the field
- Connection of all aspects of the cancer immunotherapy community



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# Factors Affecting the Immune System Response to Immunotherapies

BY BRIELLE URCIUOLI



ROGERS

hen it comes to immunotherapy, factors such as diet, exercise, and stress can have a considerable effect on the immune system, thus striking up the possibility of patients not receiving the full benefit from the immunotherapeutic agents prescribed. How to understand and combat these risks will be discussed during the "Diet, Exercise, Stress and the Impact on the Immune System" session, hosted in collaboration with the Society of Behavioral Medicine this evening.

"This symposium is relevant because the field of immunology has demonstrated that a whole host of responses are related to these kinds of lifestyle issues," Connie J. Rogers, PhD, MPH, associate professor of nutrition and physiology at Pennsylvania State University, said. "The world of immunotherapy is opening its eyes to these factors, and it's really exciting to have this inaugural interdisciplinary cross-talk."

Rogers is co-chairing the session along with Elizabeth A. Repasky, PhD, professor of on-

cology, Department of Immunology at the Roswell Park Cancer Institute.

In her talk, Rogers will discuss the effect that obesity prevention has had on animal models. "The combination of preventing weight gains and adding regular physical activity can really enhance the response to a cancer vaccine or novel immunotherapeutic agent for a mouse," she said.

Dana H. Bovbjerg, PhD, of the University of Pittsburgh Cancer Institute, will then explain how different stressors affect the immune response. Moving on to a more molecular level, Susan K. Lutgendorf, PhD, of the University of Iowa, will discuss the effects of biobehavioral stress on the tumor microenvironment.

Rogers commented on how this can directly relate to clinician-prescribed interventions as well as patient outcomes. "The response to therapy is mediated by the ability of the immunotherapy to get into these cells and work," Rogers said. "If something could affect this, we'd want to know."

As an example, temperature can alter the effi-

cacy of a therapy. Mark Bucsek, a PhD student at Roswell Park Cancer Institute will address this effect when he presents his abstract on beta-andrenegeric receptor ( $\beta$ -AR) signaling induced by cool temperatures. When given treatment at cooler housing temperatures, mice were found to have less of a response to anti–PD-1 therapy, as the elevated  $\beta$ -AR stress signaling caused by the lower temperatures impaired antitumor immunity.

"The immune system is complicated. There are metabolic, endocrine, and neuro factors affecting immune response," Rogers said. "These talks are really relevant to patients [because] they're living in a world where all of these things play a role in their health."

### REFERENCE

Bucsek M, Qiao G, MacDonald C, et al. β-adrenergic signaling induced by cool housing temperatures mediates immune suppression and impairs the efficacy of anti-PD-1 checkpoint blockade immunotherapy in laboratory mice. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 270.

# Immunology 101: These Are Not "Boutique Therapies" Anymore

BY LAUREN M. GREEN



OLIVEIRA

urses and pharmacists looking to expand their knowledge of how the ever-expanding class of cancer immunotherapy agents work will get a primer on the topic at today's concurrent session, "Tumor Immunology 101."

As session co-chair Satiro De Oliveira, MD, stressed, most of the advances in cancer immunotherapy have come from trials at restricted institutions, leading to the perception that they are "boutique" therapies; however, he added, "these drugs are not esoteric anymore."

"It's really important that the whole community of healthcare providers understand these therapeutic approaches, so that as more of these agents receive FDA approval, we can maximize their translation to the patients," explained De Oliveira, an assistant professor in the Department of Pediatrics, Division of Hematology/ Oncology, at the University of California, Los Angeles (UCLA). This is especially important, he continued, because the side effect profile and risks with these therapies that practitioners must become accustomed to, are different than what they are used to seeing when treating patients with cancer.

De Oliveira will be joined as co-chair this afternoon by Paul M. Sondel, MD, PhD, who is the Reed and Carolee Walker Professor in Pediatric Oncology at the University of Wisconsin (UW)–Madison. Sondel will introduce the session and speak on what nurses and pharmacists can look for on the horizon with regards to cancer immunotherapy.

Sondel's colleague at the UW School of Medicine and Public Health, Christian Capitini, MD, an assistant professor specializing in cancer biology and immunology, is also on the panel and will be presenting on, "Immunology 101 for the Non-Immunologist."

For his part, De Oliveira will be reviewing basic principles in immunology and how cancer has learned to avoid the protective functions of the immune system.

"Knowing this is a really important component in understanding the 'tricks' cancer uses to avoid the immune system. Our cancer immunotherapies are working because we understand these concepts," he said. De Oliveira will also be classifying the different immunotherapy drugs that are in the pipeline but not yet FDA approved, including cellular and gene therapies areas of research he is currently focusing on at UCLA in clinical trials.

It turns out that all 3 of the session's presenters work in the pediatric oncology setting, but that is just coincidental, noted De Oliveira. However, he does look forward to the expanded use of immunotherapy drugs in this setting because of their more favorable side effect profile. "These drugs can serve patients who are more susceptible to complications, such as pediatric patients and geriatric patients."

# Emerging Technologies Session Places Focus on Science

BY SHANNON CONNELLY



ZAHAROFF

onight's session on Emerging Technologies could have been heavily focused on technology, but co-chairs David A. Zaharoff, PhD, and Edward C. Stack, PhD, said they intentionally put science at the forefront of the session.

"What we have very intentionally tried to do is make these [presentations] less technology focused, but more application focused, and that has brought the science [forward]," said Stack, a pathology scientist at PerkinElmer. "I think that's going to make this a very good emerging technologies session."

The session will include 4 presentations, with 2 focused on enhancing an immunotherapy and 2 focused on measuring the effects of immunotherapy.

Zaharoff, of the University of North Carolina, Chapel Hill, and North Carolina State University, said that he believes this session is one of the broadest, if not the broadest, of all the presentations at the *SITC 31st Annual Meeting & Associated Programs*, in terms of the material it covers.

"Our session is to project 5 to 10 years into the future and see what might be coming down the [pipeline]," Zaharoff said.

In his presentation, Scott J. Rodig, MD, PhD, an associate professor of pathology at Harvard Medical School and an associate pathologist at Brigham and Women's Hospital, will be discussing how his ability to interrogate the tumor microenvironment in a more efficient manner has provided a deeper understanding of how the immune system is set up in the context of Hodgkin lymphoma.

Rodig will be sharing how having an indepth understanding of the immune system may provide a better understanding not only of the biological drivers of the disease, but also of ways that this can be leveraged for stratification purposes, Stack said.

Darrell J. Irvine, PhD, professor of materials science, engineering and biological engineering at the Massachusetts Institute of Technology, will be discussing

some of the more novel approaches to targeted delivery of therapeutics through the use of small biopolymers in his presentation, Stack said.

"One of the problems with targeted therapies is often, given the systemic nature of how the immune system works, you have a hard time driving immune responses in very specific and discrete locals," Stack said. Irvine, Stack said, is exploring way to



package drugs that can be more effectively delivered to the tumor-draining lymph node.

The oral abstracts selected for presentation in this session were chosen to develop the topics that Irvine and Rodig will raise.

Sean G. Smith, of the University of North Carolina, will give an overview of a study that looked at delivering CS/IL-12, a coformulation of the biopolymer chitosan linked to interleukin-12 (IL-12), intravesically in bladder cancer.<sup>1</sup> Stack said that this is a highly specific method of delivery and thus less likely to cause large-scale immune responses, which tend to be counterproductive.

The study was aimed at exploring the underlying mechanisms that eliminate existing bladder tumors and prevent new tumors from forming. Researchers analyzed the number of administrations, lymphocyte subtypes, and the immune cell infiltration throughout treatment to gain insights into how adaptive immunity can be manipulated.

Mice implanted with bladder cancer cells were administered CS/IL-12 twice weekly for 2 weeks starting 1 week after implantation of bladder cancer cells. Four of 10 mice treated with a single dose showed a higher rate of survival than mice treated with saline. Of the mice treated with 4 applications, 7 of 8 survived longer than mice treated with saline. Responses, in terms of changes in immune cell populations, were measured through flow cytometry. After the first application, treatment resulted in a 54% increase in macrophages in the bladder, and a 56% increase in the CD8:regulatory T cell ratio in bladder-draining lymph nodes. After the third treatment, researchers observed an increase in CD4+ and CD8+ T cells in the bladder, and a larger number of CD8+ T cells in bladder-draining lymph nodes.

In the next presentation, John-William Sidhom, of Johns Hopkins University, will be dis-

cussing a study that looked at a novel method utilizing phylogenetic and sequencing analysis to understand and quantify T-cell receptor (TCR) diversity, which has the potential to help scientists understand how the immune system responds to cancer and infectious diseases.<sup>2</sup>

The study is a very specific application of how spatial point patterning can be leveraged using point patterning mapping structures to get a greater understanding of the tumor microenvironment, Stack said.

TCR sequencing was applied to mouse models to investigate the CD8 T-cell response to antigens, including foreign antigens. The TCR sequencing technique was also used to characterize tumor-infiltrating lymphocytes from patients with metastatic melanoma being treated with nivolumab (Opdivo).

Sidhom will explain in his presentation the differences discovered between self and foreign antigens, and identify the utility of TCR sequencing data in predicting which patients will or will not respond to anti-PD-1 therapy.

"Overall, I hope [attendees] are excited to see what's being developed, the next great breakthrough," Zaharoff said. "We've all seen the benefits that checkpoint inhibitors have brought to patients. They're energizing the field, but it's not an approach that's going to solve all our problems; we need additional technologies, we need to be continuously pushing to find the next great breakthrough." •

### REFERENCES

 Smith S G, Nguyen K, Ravindranathan S, et al. Mechanisms of chitosan/IL-12 immunotherapy for the treatment of bladder cancer. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 349.

2. Sidhom J W, Bessell C A, Havel J, et al. ImmunoMap: a novel bioinformatics tool for analysis of T cell receptor repertoire data in model systems and clinical settings. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 112.

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-David A. Zaharoff. PhD

the next great

# Coming Together Over the Value of Cancer Immunotherapy

BY TONY HAGEN

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KAUFMAN

need for a conversation about how to accurately assess the value of cancer immunotherapy has been developing for some time, which is why a halfday program on the subject has been scheduled for the final day of the *Society of Immunotherapy of Cancer (SITC) 31st Annual Meeting & Associated Programs*, said Howard L. Kaufman, MD, FACS, co-chair of the event.

Value models have been created to better understand the financial implications of therapy choices, but these models have been largely based on chemotherapy regimens. Immunotherapy drugs are completely different and their value should be assessed through a different structure, said Kaufman, associate director for clinical science at Rutgers Cancer Institute of New Jersey.

"They're different in terms of their effectiveness, because there's often a durability associated with them, although admittedly it's often in a subset of patients; and the side effects are very different than what you see with chemotherapy. As for cost, they're expensive," he said.

Whereas value is often a concern among payors, the truth is that many others involved in oncology care are directly and indirectly affected. They need to be a part of the discussion, too, Kaufman said.

Today's slate of presentations on arriving at value determinations in cancer care includes perspectives from industry, which makes the decisions about manufacturing and pricing; patients and patient advocacy, which represents the end user; pharmacy, which makes decisions about what drugs to supply; and the academic– research community, which prescribes these drugs and studies them for efficacy.

"The agenda is really designed to get all of these key stakeholders together in the same room," Kaufman said, adding that issues will be articulated and, hopefully, participants will agree on what the next steps should be.

The first speakers are program co-chairs Peter P. Yu, MD, FACP, FASCO, of Hartford HealthCare Cancer Institute, and Michael B. Atkins, MD, of Georgetown-Lombardi Comprehensive Cancer Center. Kaufman said they will address some of the current value models available for use and how they could be modified to better accommodate cancer immunotherapy treatment decisions.

Cancer immunotherapy is not only very different from cytotoxic drugs, but also, over the long term, survival can be very durable—potentially even curative—which should influence the way this special class of drugs is valued, Kaufman



said. In addition, there's not enough information on how well these drugs work. The toxicity profiles of these drugs are different too, and as management techniques improve, the value proposition also changes, Kaufman said.

Lou Garrison, PhD, AB, president of the International Society for Pharmacoeconomics and Outcomes Research, will address the pharmacy perspective on these drugs. Pharmacy needs to be part of the discussion, because pharmacies often decide what drugs to make available to physicians. Also, because immunotherapy is often vastly more expensive than other forms of medicine, incorrect decisions that are made about which drugs to stock can be very costly, Kaufman said.

"When they come to me, they want to hear what's the right thing for the patient." They also may not have the clinical knowledge that would enable them to understand the doctor's decisionmaking process, Kaufman pointed out. "One of the common questions I get is, 'Why did you pick a monotherapy versus a combination? What's your thinking there?"

Payers, like pharmacists, need to hear more from clinicians about therapies and efficacy, particularly with regard to biomarkers, which remain nebulous in terms of value because there is not enough clear evidence that they are fully reliable for clinical use, Kaufman said. "Payers don't want to deny a potentially lifesaving treatment for a patient, but they need more information. They need to know what the right thing to do is, and I think that if we don't step up and answer them, they'll have to answer on their own, and then it's our fault for not talking to them." The payer perspective of this discussion will be handled by William McGivney, PhD, of McGivney Global Advisers. More discussion of the biomarker aspect of value will be offered by Roy S. Herbst, MD, PhD, of Yale Cancer Center.

The patient advocacy perspective will be represented by Steven Silverstein, MBA, of the Melanoma Research Foundation. "Steve is a good example of someone who went to 1 physician and was told to get his affairs in order, and he went to another and got a life-saving drug, so he is able to articulate the patient perspective," Kaufman said.

One thing that should be taken into account in determining the value of immunotherapy medications is how patients feel about the toxicity levels of their treatment. Patients often have widely different views from doctors of good versus bad. For example, hair loss during treatment is often the biggest fear among patients, whereas doctors rate it fairly low on the scale of side effects to be concerned about, Kaufman noted. This perspective will be handled by Adam P. Dicker, MD, PhD, of Thomas Jefferson University, and Heather S. Jim, PhD, of the H. Lee Moffitt Cancer Center & Research Institute.

Industry is key to any value discussion, Kaufman said. He said that in some respects drug makers may be more advanced in their thinking on how to improve the value equation than others, but competitive barriers may stand in the way of the type of collective action that is needed. "To a certain extent, they do follow industry norms, and those may need to change, but a lot of the companies are independently looking at the value proposition. I think that some are potentially open to renegotiating the pricing of these drugs, but they want everybody to do it." Certainly, the FDA is a proponent of greater industry harmonization in this regard, Kaufman added.

The value program will also include 2 panel discussions as well as open debate. •

# The CheckPoints Let Immunotherapy Experts Cut Loose

BY LAURA PANJWANI

usic is often considered to be therapeutic for those going through cancer treatment. But it is not just oncology patients that may find it beneficial, said Patrick Hwu, MD.

"There are a lot of people in medicine that love listening to and playing music," said Hwu, department chair, Department of Melanoma Medical Oncology, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center. "It is a really important thing to do because, as oncologists, when we take care of cancer patients, it can be very stressful. Music can help us exercise our right brain, our creative side, and relieve that stress."

Hwu, a keyboardist, has taken his "stressreliever" further than he ever imagined. For the past 10 years, he has been a member of The CheckPoints, a band made up entirely of oncologists and cancer researchers focused on immunotherapy. The group—considered the official house band of the Society for Immunotherapy of Cancer (SITC)—performs every year at the annual meeting, as well as at a SITC sponsored event at the ASCO annual meeting each year.

They will be performing tonight from 8:30 to 11:00 PM in the Maryland Ballroom.

The idea for the band came from Hwu and Thomas Gajewski, MD, PhD, a professor of medicine at the University of Chicago who plays the guitar. At an ASCO meeting, the 2 bonded over their joint love of music and discussed starting a band. When Hu found out that one of his residents at John Hopkins School of Medicine, Rachel Humphrey, MD—now the chief medical officer, CytomX Therapeutics—was a singer, the idea was settled. Hwu then recruited harmonica player and professor and chair of Immunology at MD Anderson Cancer Center, James Allison, PhD, and The CheckPoints band was formed.

Today the group consists of the original 4, plus guitarist John Timmerman, MD, an associate professor of medicine in the Division of Hematology and Oncology, David Geffen School of Medicine at University of California, Los Angeles, and drummer Dirk Spitzer, PhD, an assistant professor of surgery, Division of General Surgery, Washington University School of Medicine, Siteman Cancer Center.

Recently the band added brass players to the group, with Ferran Prat, PhD, vice president, Strategic Industry Ventures at MD Anderson, on saxophone, and Jason Luke, MD, assistant professor of medicine at University of Chicago Medicine, on trumpet. Tonight, Brad Reinfeld, an MD/

PhD student from Vanderbilt University, will make his debut with the group on bass guitar.

The group plays a wide range of music. "We literally cover everything from A to Z," said Spitzer. "We cover several decades of music, from the 60s to now and everything from Adele to ZZ Top."

"We've been extending our repertoire," added Allison. "Rock and roll, popular songs, blues. We have a lot of fun. We play everything."

The songs they play are mostly light and upbeat. The group focuses on covers the audience will recognize, even incorporating songs that pay tribute to their field of study.

"For many years, no one believed in immunotherapy," said Hwu. "So, we end every show with 'Don't Stop Believin' by Journey. It is



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kind of our anthem to show that we've persisted through all of these years and now everyone understands that immunotherapy is important."

This year, The CheckPoints will also debut new songs that feature their brass players, Luke and Prat.

With band members spread across the country, finding rehearsal time can be difficult for The CheckPoints. To overcome this, they rely heavily on technology, sharing song lyrics, set lists, and more using an online dropbox. The group typically meet a day or 2 before each performance to rehearse. Several of the band members, including Hu and Allison, also play together regularly in non-CheckPoint gigs.

The band encourages members of the audience to join them on stage, and they often have guest performers. Special guests have included Lisa H. Butterfield, PhD, the vice president of SITC.

"I think this breaks the ice at these meetings," said Spitzer. "We have guest singers, players. Many society members have gotten involved as guest musicians. It is just amazing."

The main goal is really to have fun, said Allison. "With the work that we do, we want to have fun;it's not just the grind," he said. "We try and have as much fun as possible and get everyone is the audience to have fun. Work hard, play harder." •



SITC 2016 NATIONAL HARBOR MD NOVEMBER 9 - 12 2016



# Your Guided Path to Our Nation's Capital

KATIE KOSKO

ur nation's capital is one of the most vibrant and historical places to visit in the United States. With dozens of museums, memorials in honor of past presidents, the White House, Capitol Hill, and must-try eateries-there are endless possibilities for things to see and do in Washington, DC.

### **Historical Highlights**

DC is home to the most famous address in the country. At the heart of the district sits the White House at 1600 Pennsylvania Avenue. While public tour requests have to be made in advance by a member of congress, you can peek through the fence to see where 44 presidents have resided.

Over on Capitol Hill, you can check out the US Capitol Building, Library of Congress, and the Supreme Court Building. Tours of the Capitol are offered Monday through Saturday at 8:50 AM and 3:20 PM, with limited ticket availability. The Library of Congress and Supreme Court do not require tickets.

The National Mall and Memorial Parks are open 24 hours a day, 7 days a week. Made to honor our first president, George Washington, the Washington Monument remains the tallest stone structure in the world. And just steps away are 8 memorials, including: Lincoln Memorial, Thomas Jefferson Memorial, Franklin Delano Roosevelt Memorial, Martin Luther King Jr. Memorial, World War II Memorial, Vietnam Veterans Memorial, Korean War Veterans Memorial, and the DC War Memorial.

### **Museum Must-Sees**

### Smithsonian Museums and Galleries

There are dozens of museums in Washington, DC, including 19 of the Smithsonian museums and galleries, its 9 research centers, and the Smithsonian National Zoo. These museums fulfill a variety of interests such as the National Museum of the American Indian, the National Museum of American History, and the National Air and Space Museum. Brand new this year to the group is the National Museum of African American History and Culture. Location: Various throughout the district Hours: Most museums are open daily from 10:00 AM to 5:30 PM. The American Art Museum and Portrait Gal-

lery are open from 11:30 AM to 7:00 PM. Admission: Most are free

### National Gallery of Art

If you're an art lover, the National Gallery of Art features

thousands of works from the Renaissance to present. Its sculpture garden includes 17 works from the Gallery's growing collection, as well as special exhibits on loan. The ice rink is now open for skating among the sculptures.

Location: 6th and Constitution Avenue NW Hours: Open Monday through Saturday from 10:00 ам to 5:00 рм, Sunday from 11:00 ам to 6:00 рм

### The U.S. Holocaust Memorial Museum

The U.S. Holocaust Memorial Museum takes visitors back in time to one of the most tragic times in history, where approximately 6 million Jews were murdered by the Nazi regime in Germany. The museum is a place to learn, reflect, and remember those whose lives were taken. Location: 100 Raoul Wallenberg Place SW Hours: Open from 10:00 AM to 5:20 PM

### Ford's Theatre

See the very place where President Abraham Lincoln was assassinated in 1865. Ford's Theatre takes you through his presidency until his death. Filled with artifacts, it is a museum and working theatre.

Location: 511 10th Street NW

Hours: Open daily from 9:00 AM to 4:00 PM Admission: Tickets are free on a first-come basis. There is a \$3 convenience fee for reserved tickets.

### The Newseum

Besides having one of the greatest views of the Capitol Building, the Newseum has 15 galleries and 15 theaters, including a memorable 9/11 Gallery. It is considered one of the most interactive museums in the world. The Newseum traces the evolution of electronic communication, from the birth of radio to the technologies of the present and future. Location: 555 Pennsylvania Avenue NW

Hours: Open daily from 9:00 AM to 5:00 PM Admission: Adults (19-64) \$22.95 plus tax, Seniors (65+) \$18.95 plus tax, Youths (7-18) \$13.95 plus tax, Children (up to 6) Free. Save 15% if you order online, or 10% at the door if you are Military, a college student, or an AAA member.

### International Spy Museum

Pretend as if you were never there! The International Spy Museum takes visitors on the journey of a spy. The stories of individual spies are told through film, interac-





tives, and state-of-the-art exhibits. This is the only espionage museum in the world to give a global perspective. Location: 800 F Street NW

Hours: Open daily from 10:00 AM to 6:00 PM

Admission: Adults (12-64) \$21.95; Seniors (65+), Military, Fire & Law Enforcement \$15.95; Youths (7-11) \$14.95; Children (up to 6) Free.

### Madame Tussauds

Get a selfie with Marilyn Monroe, George Clooney or even Grumpy Cat. Madame Tussauds wax museum brings presidents, first ladies, movie stars, and sports stars, past and present-to life. The first museum was opened more than 200 years ago by Marie Grosholtz (Madame Tussaud), who first sculpted the famous author and philosopher, Voltaire.

Location: 1001 F Street NW

Hours: Open Monday through Saturday from 10:00 AM to 6:00 PM, Sunday 10:00 AM to 5:00 PM

Admission: Online ticket packages are available starting at \$17.60 for adults (13+).

### **Local Restaurant Hotspots**

Ambar features international Balkan cuisine served in tapas "small plate" style. The goal of the restaurant is to bring Old World and New World together. For \$49 you can have a bottomless dinner.

Location: Capitol Hill - 523 8th Street SE, on Barracks Row

Cadillac Ranch offers a wide variety of foods-from steaks to seafood-or chili nachos. There is also a long list of cocktails-and maybe after a few drinks you'll take a spin on their mechanical bull! Location: National Harbor - 186 Fleet Street, Oxon Hill, MD

Ben's Chili Bowl is a Washington, DC landmark with Ben's Famous All Meat Chili Dog. Its 4 locations allow for easy access no matter where you are in the district. The best part is that it's open late.

Locations: U Street Metro; 1213 U Street NW; 1001 H Street NE; and 1725 Wilson Boulevard, Arlington, VA

We, The Pizza offers a slice of heaven in our nation's capital. It offers pizza, salads, tossed wings, and a flavorful list of homemade sodas.

Locations: Capitol Hill - 305 Pennsylvania Avenue SE; Crystal City – 2100 Crystal Drive Arlington, VA •

### **TECENTRIQ®** [atezolizumab]

Initial U.S. Approval: 2016 This is a bird summary of information about TECENTRIQ. Before prescribing, please see full Prescribing INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Urothelial Carcinoma TECENTRIQ (aterolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

Locaring (attecniculate) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

 Have disease progression during or following platinum-containing chemotherapy
 Have disease progression during or following platinum-containing chemotherapy
 Have disease progression during or following platinum-containing chemotherapy
 Have disease progression during cacelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see Clinical Studies (14.1)].

 **1.2 Metastatic Non-Small Cell Lung Cancer** 
 TeCENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALX genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ [see Clinical Studies (14.2)].
 **4 CONTRAINDICATIONS**

### WARNINGS AND PRECAUTIONS

None. 5 WANINGS AND PRECAUTIONS 5 WANINGS AND PRECAUTIONS 5.1 Immune-mediated pneumonitis Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate tetiology, occurred in patients receiving TECENTRIO. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer steroids at a dose of 1 to 2 mg/kg/day predisione equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Withhold TECENTRIQ until resolution for Grade 2 pneumonitis. Permanentlydiscontinue TECENTRIQ or Grade 3 or 4 pneumonitis (see Dosage and Administration (2.2)). Across clinical trials, 2.6% (51/1978) of patients developed pneumonitis. Fatal pneumonitis occurred in two patients. Urothelial Carcinoma In 523 patients with urothelial carcinoma who received TECENTRIQ, pneumonitis occurred in sk (1.1%) patients. Of these patients, there was one patient with fatal pneumonitis, no patient with Grade 3, three patients with Grade 2, and energies and the patient with Grade 1 pneumonitis. TECENTRIQ was held in all cases and five patients were treated with corticosteroids. Pneumonitis resolved in TeCENTRIQ was held in all cases at 0.3.1.+ months. NSCLC In 1027 patients with NSCLC who received TECENTRIQ, pneumonitis cocurred in 38 (3.7%) patients. Of these patients, there was one patient with Grade 2, and elven patients with Grade 1 pneumonitis. TECENTRIQ was held in 24 patients and 21 patients were treated with corticosteroids. Pneumonitis resolved in 26 of the 38 patients. The median tup to onset was 3.3 months (ange: 3 days to 1.8. months). The median duration was 1.4 months (range: 0 days to 1.2.6+ months). 5.2 Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, recurred in adients received TECENTRIQ interesting and with no clear alternate etiology.

The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median time of the patitis.
 S.2 Immune-Related Hepatitis
 Immune-Related Hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology. occurred in patients receiving TECENTRIO treatment. Liver test abnormalies occurred in a tainets who received TECENTRIO months). For Grade 2 or 4 immune-mediated hepatitis. Gee Dosage and Administration (2.2) and Adverse Reactions (6.1). Across clinical trais (n=1978), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%).
 Urothelial Carcinoma in patients with urothelial carcinoma (n=523), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (2.4%). Immune-mediated hepatitis for result and 3.3 months (range: 0.4 to 7.7 months). TECENTRIO was temporarily interrupted in low patients, one of these patients (adveloped recurrence of hepatitis after resuming TECENTRIO.
 NSCL in patients with NSCL (2.6%) and total bilirubin (2.4%). AST (1.3%), and total bilirubin (2.6%).
 NSCL in patients with NSCL (2.6W) in mune-mediate the patients. Of these nine patients, one patient head frade 3 are equiving use of corticosteroids and with no clear alternate etiology. occurred in a fart (1.4%). AST (1.3%), and total bilirubin (2.6%). MST (1.3%), and total bilirubin (2.6%). MST (1.3%), and total bilirubin (2.6%). Immune-mediated hepatitis after resuming TECENTRIO.
 NSCL in patients with NSCL (2.6%) and the patitis for signs and symptoms of diarhea or colits. Withold treatment with TECENTRIO or Grade

patients, one had Grade 3, two had Grade 2, and two had Grade 1 immune-mediated colitis or diarrhea. Immune-mediated colitis or diarrhea resolved with corticosteroid administration in four of these patients, while the fifth patient died due to disease progression prior to resolution of colitis. **5.4** Immune-Related Endocrinopathies Immune-related thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving TECENTRIO. Monitor patients for clinical signs and symptoms of endocrinopathies. **Hypophysitis** Hypophysitis accurred in 0.2% (1/523) of patients with urothelial cancer receiving TECENTRIO. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold TECENTRIO for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis *Bee Dosage and Administration (2.2) and Adverse Reactions (6.1)*. **Thyroid Disorders** Thyroid function was assessed routinely only at baseline and the end of the study. Monitor thyroid function tests can receive TECENTRIO. For symptomatic hypothyroidism, withindia TECENTRIQ and initiate thyroid hormone replacement as needed. Manage isolated hypothyroidism with replacement theraay and without corticostroids. For symptomatic hypothyroidism, withhoid TECENTRIQ and initiate a nanti-thyroid may a needed. Resume treatment with TECENTRIQ when symptoms of hypothyroidism or hypothyroidism and hyperthyroidism occurred in 3.9% (77/1978) and 1.0% (20/1978) of patients, respectively. **Urothelial Carcinoma** In 523 patients with urothelial carcinoma who received TECENTRIQ, hypothyroidism. The median time to first onset was 5.4 months (range: 21 days to 11.3 months). Thyroid simulating hormon (TSH) was elevated and above the patient's baseline in 16% (21/131) of patients with a follow-up measurement. Hyperthyroidism accurred in 0.6% (3/523) of patients with urothelial carcinoma. Of the three urothelial carcinoma and S1.4 to 5.8 months). TSH wa Reactions Diabetes

s (6.1)]. Mellitus New onset diabetes with ketoacidosis has occurred in patients receiving TECENTRIO. Diabetes mellitus without an alternative etiology occurred in one (0.2%) patient with urbitleil a carcinoma and three (0.3%) patients with NSCLC. Initiate treatment with insulin for type 1 diabetes mellitus. For 2 Grade 3 hyperglycemia (fasting glucose 250–500 mg/dL), withhold TECENTRIC. Resume treatment with TECENTRIC when metabolic control is achieved on insulin replacement therapy *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Administration (2.2) and Adverse Reactions (6.1)]. **5.5** Other Immune-Related Adverse Reactions Other immune-related adverse reactions including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, ocular inflammatory toxicity, and pancreativis, including increases in serum amylase and ipase levels, have occurred in s 1.0% of patients treated with TECENTRIO. Meningitis / Encephalitis Monitor patients for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue TECENTRIO for any grade of meningitis or encephalitis. Treat with IIV steroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once the patient has improved. When symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIO for any grade of menings of motor and sensory neuropathy. Permanently discontinue TECENTRIO for any grade of menings of motor and sensory neuropathy. Permanently discontinue TECENTRIO for any grade of meningsthenia gravis or Guillain-Barré syndrome. Institute medical intervention as appropriate. Consider initiation of systemic corticosteroids at a dose of 1-2 mg/kg/day predinsone [see Dosage and Administration (2.2) and Adverse Reactions (6.1)].

ons (6.1)]. eatitis Symptomatic pancreatitis without an alternative etiology occurred in 0.1% (2/1978) of patients clinical trials. Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ

for  $\geq$  Grade 3 serum amylase or lipase levels (> 2.0 ULN), or Grade 2 or 3 pancreatitis. Treat with 1–2 mg/kg IV methylprednisolone or equivalent per day. Once symptoms improve, follow with 1–2 mg/kg of oral prednisone or equivalent per day. Resume treatment with TECENTRIQ when serum amylase and lipase levels improve to  $\leq$  Grade 1 within 12 weeks or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to 1 0 mg oral prednisone or equivalent per day. The grade 1 mg oral prednet per day. The grade 1 mg or grade of the grade 1 mg or grade 1 mg of the grade 1 mg or grade 1 mg or grade 1 mg of the grade 1 mg or grade 1

or any grade of recurrent pancreatitis *[see Dosage and Administration (2.2) and Adverse Heactions (6:1)].*  **5.6 Infection** Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retropertoneal hemorrhage occurred in patients receiving TECENTRIQ. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for 5 Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6:1)].*  **Lorothelial Carcinoma** In 523 patients with urothelial carcinoma who received TECENTRIQ, infection occurred in 197 (37.7%) patients. Grade 3 or 4 infection occurred in sixty (11.5%) patients, while three patients died due to infections. Unany tract infections were the most common cause of Grade 3 or higher infection, occurring in 37 (7.1%) patients. **NSCLC** In Study 3, a randomized trial in patients with NSCLC, infections were more common in patients treated with TECENTRIQ (43%) compared with the common cause of Grade 3 or higher infection. Photomized trial in patients with MSCLC, infections were more common in patients treated with TECENTRIQ (43%) compared with TECENTRIQ compared with 2.2% in patients treated with docetaxel. Two patients treated with TECENTRIQ and three patients (2.2%) treated with docetaxel died due to infection. Pheumonia was the most common cause of Grade 3 or higher infection, occurring in 7.7% of patients treated with TECENTRIQ. **5.7 Infusion-Related Reactions** Severe influsion-related reactions Soccurred in 1.3%, (25/1978) of patients across clinical trials of TECENTRIQ. Infusion-related reactions soccurred in 1.3%, (25/1978) of patients across clinical trials of TECENTRIQ. Infusion-related reactions soccurred in 1.3%, (25/1978) of patients across clinical trials of TECENTRIQ. Infusion-related reactions soccurred in 1.3%, (25/1978) of patients across clinical trials of TECENTRIQ. Infusion-related reactions Soccurred in 1.3%, (25/1978) of patien

Severe initiation reactions rate occurred in 1,24% of the severe initiation reaction in the initiation related reactions occurred in 1,3% (25/1978) of patients across clinical triats, 1,7% (9/523) of patients with urothelial carcinoma, and 1,6% (16/1027) of patients with NSCLC. Interruptor show the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue TECNTRIG in patients with Grade 3 or 4 infusion reactions (see Dosage and Administration (2.2) and Adverse Reactions (6.1)].

infusion reactions [see Dosage and Administration (2.2) and Adverse Reactions (6.1)]. 5.8 Embryo-Fetal Toxicity Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)]. 6 ADVERS PERACTIONS

pregnatcy, of *n* the patient becomes pregnant while taking this drug, advise the patient of the polential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)].
6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:

immune-Related Pneumonitis (see Warnings and Precautions (5.1)]
immune-Related Colitis (see Warnings and Precautions (5.3)]
immune-Related Colitis (see Warnings and Precautions (5.4)]
immune-Related Colitis (see Warnings and Precautions (5.5)]
infection (see Warnings and Precautions (5.7)]

Clinical Trials Experience
Because clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Urothelial Carcinoma The data described in Table 1 reflects exposure to TECENTRIQ in Cohort 2 of Study 1.
This cohort enrolled 310 patients in a single arm trial with locally advanced or metastatic urothelial carcinoma who had disease progression wiring or following at least one platinum-containing chemotherapy regime or who had disease progression wiring or following at the sot common Grade -44 diverse reactions (20%) were unitary adverse (ration 4.4 were). Previous (20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), who were treated with TECENTRIQ oscurred in trading reactions (20%) were fatigue, dehydration, intestinal obstruction, wirinary bacturion, diverse reactions (20%) were reactions in the diverse reactions (a diverse reactions is 2.2%), were unitary tract infection, diverse, neactions (2.5%), Table 1: All Grade Adverse Reactions in  $\geq$  10% of Patients with Urothelial Carcinoma in Study 1

TECENTRIQ

	N =	N = 310		
Adverse Reaction	All Grades (%)	Grades 3-4 (%)		
All Adverse Reactions	96	50		
Gastrointestinal Disorders				
Nausea	25	2		
Constipation	21	0.3		
Diarrhea	18	1		
Abdominal pain	17	4		
Vomiting	17	1		
General Disorders and Administra	ation			
Fatigue	52	6		
Pyrexia	21	1		
Peripheral edema	18	1		
Infections and Infestations				
Urinary tract infection	22	9		
Metabolism and Nutrition Disorde	ers			
Decreased appetite	26	1		
Musculoskeletal and Connective	Tissue Disorders			
Back/Neck pain	15	2		
Arthralgia	14	1		
Renal and urinary disorders				
Hematuria	14	3		
Respiratory, Thoracic, and Media	stinal Disorders			
Dyspnea	16	4		
Cough	14	0.3		
Skin and Subcutaneous Tissue Di	sorders			
Rash	15	0.3		
Pruritus	13	0.3		

≥ 1% of Patients

Laboratory lest	Grades 3-4 (%)
Lymphopenia	10
Hyponatremia	10
Anemia	8
Hyperglycemia	5
Increased Alkaline phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2
Hypoalbuminemia	1

Hypoalburninemia 1 NSCLC The safety of TECENTRIQ was evaluated in Study 3, a multi-center, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [*See Clinical Studies* (14.2)]. Patients received 1200 mg of TECENTRIQ (n=142) administered intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel (n=153) administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 3, 7 months (range: 0–1 months) in TECENTRIQ the trade patients and 2.1 months (range: 0–17 months) in docetaxel tradiographic (b), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3-4 adverse reactions (>2%) were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, AST increase, AJT increase, dysphagia, and arthraigia. Nine patients (6.3%) who were treated with TECENTRIQ experienced either pulmonary embolism (2), pneumonia (2), pneumothorax, uicer hemorrhage, cachexia secondary to dysphagia, myocardial infarction, or large intestinal perforation which led to death. TECENTRIQ was discontinued due to adverse reactions in 4% (6/142) of patients. Adverse reactions leading to intervaption of TECENTRIQ occurred in 24% of patients; the most common (>1%) were pneumonia, liver function test abnormality, upper respiratory tract infection, pneumonitis, acute kidney injury, hypoxia, hypothyroidism, dyspnea, amenia, and fatigue. Serious adverse reactions cluerue in 37% of patients. The most frequent testous adverse reactions (> 2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism. Table 3 summarizes adverse reactions had cocurred in a 10% of TECENTRIQ. treated patients and at a higher incidence than in the docetaxel arm.

le 3: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients wit	h NSCLC and at a
her Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [A	I Grades] or ≥2%
ades 3–4]) (Study 3)	-

	TECENTRIQ (n=142)		Docetaxel (n=135)		
Adverse Reaction	All grades	Grade 3–4	All grades	Grade 3–4	
		Percentage (	%) of Patients		
General Disorders and Admin	nistration Site (	Conditions			
Pyrexia	18	0	13	0	
Infections and infestations					
Pneumonia	18	6	4	2	
Metabolism and nutrition disorders					
Decreased appetite	35	1	22	0	
Musculoskeletal and connective tissue disorders					
Arthralgia	16	2	9	2	
Back Pain	14	1	9	1	
Psychiatric Disorders					
Insomnia	14	0	8	2	
Respiratory, thoracic and mediastinal disorders					
Dyspnea	32	7	24	2	
Cough	30	1	25	0	

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\ge 10\%$  of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of  $\ge 5\%$  [All Grades] or  $\ge 2\%$  [Grades 3–4]) (Study 3)

	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ		Docetaxel	
Test	All grades (%) Grade 3-4 (%)		All grades (%)	Grade 3-4 (%)
Hyponatremia	48	13	28	8
Hypoalbuminemia	48	5	49	1
Alkaline Phosphatase increased	42	2	24	1
Aspartate aminotransferase increased	33	2	15	0
Alanine aminotransferase increased	31	2	9	1
Creatinine increased	19	1	14	2
Hypokalemia	18	2	11	4
Hypercalcemia	13	0	5	0
Total Bilirubin increased	11	0	5	1

6.2 Immunogenicity As with all therapeutic proteins, there is a potential for immunogenicity. Among 275 patients in Study 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. Among 135 patients in Study 3, 73 patients (54.19%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In Study 1 and Study 3, the presence of ATA of the cancer to heve a chically is confident primed on pharmacolinetics. safety or efficary. patients (34.17) tested positive to readment entropy the positive to readment entropy (1) the presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy, Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of ATAs to TECENTRIQ with the incidence of antibodies to other products may be misleading.

**USE IN SPECIFIC POPULATIONS** 

High (Gra

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1)). There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-11/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (see Data). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data Animal Data Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect

and miscaringe in clinically recognized pregnances to 2 in 04 v and 10 in 02 00, respectively. **Joint Data Animal Data** Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-11/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-11 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stilbirth. As reported in the literature, there were no malformations related to the blockade of PD-11/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-11 knockout mice. Based on its mechanism of action, fiteal exposure to ateazolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response. **8.2** Lactation

8.2 Lactation nary

There is no in infant, or the absorption an <u>Hisk summary</u> There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise a lactating woman not to breastfeed during treatment and for at the series of t

Best 5 months after the last cose.
 S.3 Females and Males of Reproductive Potential
 <u>Contraception</u>
 Females Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a
 pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use
 effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Effective Contracteption on mg a cannow mark the resonance of the contract of the contrac

The safety and effectiveness of LECENTING matches been determined by the second statement of the seco

8.6 Renal Impairment Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)].

Patients with renal impairment [see Clinical Pharmacology (12.3)]. 8.7 Hepatic Impairment Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with mild hepatic impairment. TECENTRIQ has not been studied in patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3)].

Batierts with mild hepatic impairment. TECENTRIO has not been studied in patients with moderate or severe hepatic impairment (see Clinical Pharmacology (12.3).
IO OVERDOSAGE
There is no information on overdose with TECENTRIO.
TATENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the risk of immune-related adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIO. Including: Pheumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Varings and Precautions (5.1)]. Hepatitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdomining pain on the right side of abdomen. leftnargy, or easy bruides or bleeding [see Warnings and Precautions (5.2)]. Meditis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.3)]. Hepotencipathenia gravis, and Guillain-Barré syndrome: (5.4)! Meningoencephalitis, myasthenia syndrome/myasthenia gravis, and Guillain-Barré syndrome (5.3). Coltis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdoming pain fee Warnings and Precautions (5.4)! Meningoencephalitis, myasthenia syndrome/myasthenia gravis, and Guillain-Barré syndrome/myasthenia gravis, and Guillain-Barré syndrome/myasthenia gravis, and Guillain-Barré syndrome (5.5). Interductions (5.5)! Nectorial their healthcare provider immediately for signs or symptoms of cuciar inflammatory toxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of ocular inflammatory toxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of ocular inflammatory toxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of ocucar infl

### Genentech

TECENTRIQ® (atezolizumab) Manufactured by: Genentech, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990 U.S. License No. 1048

PDL/080916/0193 PDL/080916/0193 Initial U.S. Approval: *May* 2016 Code Revision Date: *October* 2016 tered trademark of Genentech, Inc. © 2016 Genentech, Inc. TECENTRIQ is a register

# **TECENTRIO**<sup>®</sup> THE FIRST AND ONLY FDA-APPROVED **ANTI-PDL1 CANCER IMMUNOTHERAPY**

NOW APPROVED FOR 2 TUMOR TYPES

### FOR PREVIOUSLY TREATED LOCALLY ADVANCED **OR METASTATIC UROTHELIAL CARCINOMA**

TECENTRIQ is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

### Important Safety Information

### **Serious Adverse Reactions**

Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

- Immune-related pneumonitis. Immune-mediated pneumonitis or interstitial lung disease have occurred. Fatal cases have been observed in patients with urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC). Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis
- Immune-related hepatitis. Immune-mediated hepatitis and liver test abnormalities, including a fatal case of hepatitis in a patient with UC, have occurred. Permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated hepatitis
- Immune-related colitis. Immune-mediated colitis or diarrhea, including a fatal case of diarrhea-associated renal failure in a patient with UC, occurred. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis
- Immune-related endocrinopathies. Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred. Permanently discontinue TECENTRIQ for Grade 4 hypophysitis
- Other immune-related adverse reactions. Meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis, or any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Permanently discontinue TECENTRIQ for Grade 4 or any grade of recurrent pancreatitis



### FOR PREVIOUSLY TREATED METASTATIC NON-SMALL CELL LUNG CANCER

TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; PD-L1=programmed death-ligand 1.

### Learn more at TECENTRIQ.com/learn

- Infection. Severe infections, such as sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage, have occurred. Fatal cases have been observed in patients with UC and NSCLC
- Infusion-related reactions. Severe infusion reactions occurred. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions
- Embryo-fetal toxicity. TECENTRIQ can cause fetal harm in pregnant women. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose
- Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

### Most Common Adverse Reactions

The most common adverse reactions (rate  $\geq$ 20%) in UC included fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%).

The most common adverse reactions in NSCLC (rate  $\geq$ 20%) included fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/ medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages.



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