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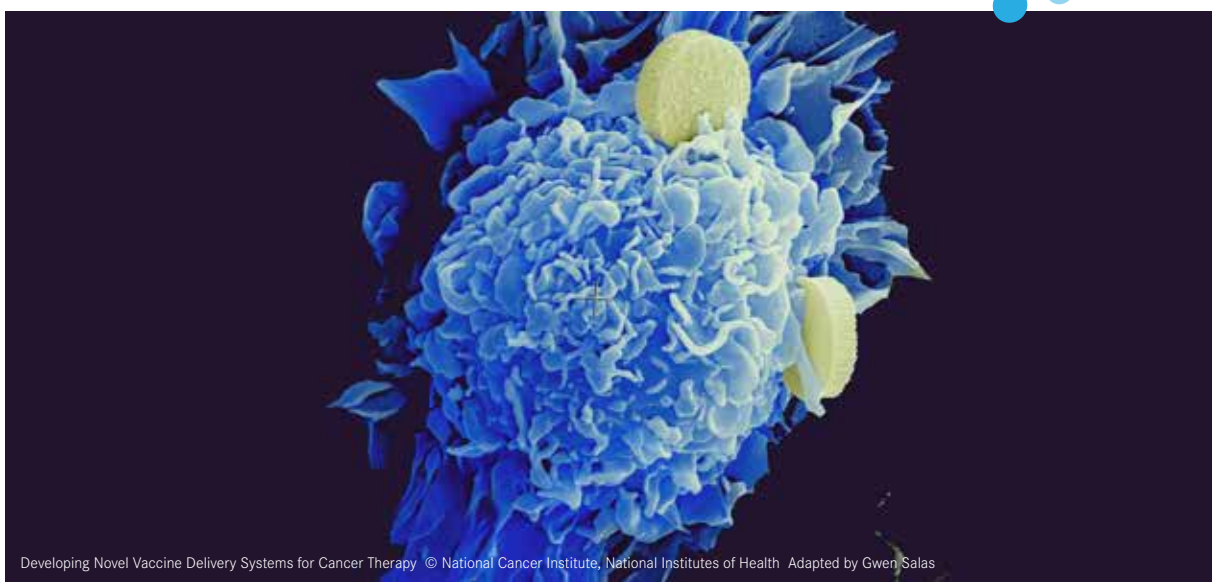
SITC 2016
NATIONAL HARBOR, MD
NOVEMBER 9 - 13, 2016

31st Annual Meeting & ASSOCIATED PROGRAMS DAILY

DAY 2
FRIDAY
NOVEMBER 11, 2016



Developing Novel Vaccine Delivery Systems for Cancer Therapy © National Cancer Institute, National Institutes of Health Adapted by Gwen Salas

Tumor Microenvironment Emerges as a Focus in Immuno-Oncology

BY TONY BERBERABE, MPH

DISIS

GAJEWSKI

The tumor microenvironment has emerged as the next focal point in the ongoing battle against cancer, especially with the success that checkpoint inhibitor agents have demonstrated in recent months. Efforts to modulate the tumor microenvironment by characterizing pathways that influence antitumor immune response is the major focus of ongoing research, said Mary L. Disis, MD, professor of medicine at the University of Washington. Disis, along with Thomas Gajewski, MD, PhD, professor of medicine at the University of Chicago, will co-moderate the "Tumor Microenvironment" session today. Disis was interviewed prior to the start of the meeting.

"We hope some of these strategies have either the same impact of immune checkpoint inhibitors or [could] be additive to immune checkpoint inhibitor therapy in the clinical setting," said Disis. "But clearly, modulating the tumor microenvironment is a major area of research, and we're going to be hearing about some of these new approaches during the session."

The tumor microenvironment is an elaborate web of diverse cell types that fosters ongoing malignant tumor cell interactions with tumor-associated vasculature, fibroblasts, and a variety of immune cells. It is within the microenvironment that tumor growth,

MICROENVIRONMENT CONTINUED ON PAGE 8

Methods to Predict Response to Immunotherapeutics

BY LISA MILLER

While a great deal of research has focused on tumor biopsies for biomarkers and predicting responses, there are other ways to assess which patients may benefit from receiving immunotherapy.

"There's an enormous amount of work looking at the tumor for a signal as to which patients will respond. That's very important, especially in diseases like melanoma or lymphoma where you can easily access tumor, but the majority of patients with metastatic cancer have lesions that are not easily accessible to biopsy," Jeffrey Schlom, PhD, co-chair of the session, explained in an interview.

SCHLOM

During the "Promoting and Measuring Antitumor Immunity" session this evening, presenters will turn their attention to newer methods of predicting immune responses. Schlom, chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute, National Institutes of Health, will kick off the session by discussing the role of the peripheral immunome in immunotherapies.

Schlom believes that by studying immune cells in the periphery, which is easier to access than most tumor tissue samples, much can be learned concerning which patients may benefit from immunotherapy regimens. Unlike assays that characterize standard immune cell types—such as CD8, CD4, regulatory T cells, natural killer cells, and more—the assay developed by Schlom and colleagues can define 123 immune cell subsets in the periphery.[1]

To accomplish this, researchers use advanced techniques, such as polychromatic flow cytometry and immune cell marker identification using monoclonal antibodies. By analyzing the results, researchers can characterize subtle differences between standard immune cells types, further classifying known cell types into 123 unique subsets of cells present in peripheral blood. Researchers noted that these 123 subsets could aid in predicting which patients may benefit from receiving immunotherapy.

IMMUNOTHERAPEUTICS CONTINUED ON PAGE 10

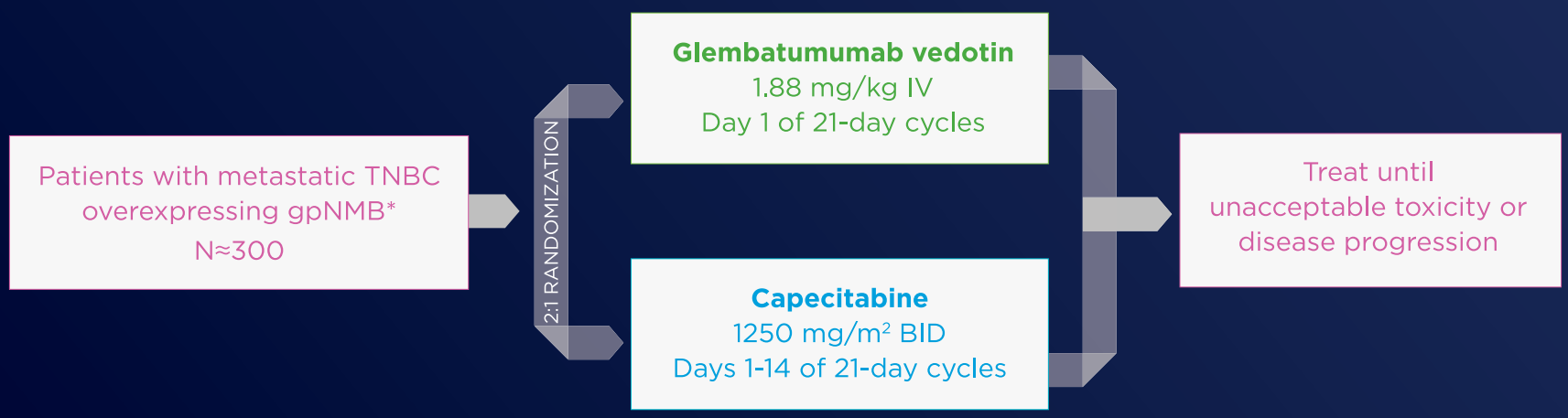
NOW ENROLLING IN

Triple-Negative Breast Cancer

metric
A Clinical Trial of CDX-011 in Metastatic Triple-Negative Breast Cancer

A RANDOMIZED PIVOTAL STUDY OF GLEMBATUMUMAB VEDOTIN (CDX-011) IN gpNMB-OVEREXPRESSING METASTATIC TNBC

- **gpNMB** is a transmembrane protein[1] that is frequently overexpressed in the tumor in triple-negative breast cancer (TNBC).[2] Overexpression of gpNMB is associated with reduced recurrence-free survival in TNBC[2]
- **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[3]
- **METRIC** is an open-label, prospectively controlled, randomized trial[4,5]



*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[4,5]

- Women and men age ≥18 years with metastatic, gpNMB-overexpressing† 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[4,5]

- Progression/recurrence of breast cancer during or within 3 months of completion of neoadjuvant or adjuvant chemotherapy
- Persistent neuropathy >NCI-CTCAE Grade 1 (at randomization)
- Known brain metastases unless previously treated, asymptomatic, and not progressive

KEY TRIAL ENDPOINTS[4,5]

- **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.

Celldex therapeutics

For more information, visit www.celldex.com or www.clinicaltrials.gov/ct2/show/NCT01997333, or e-mail medinfo@celldex.com.

Targeted Oncology

EDITORIAL & PRODUCTION

Director, Editorial & Multimedia
Silas Inman

Managing Editor
Lisa Miller
lmiller@TargetedOnc.com

Editors
Anthony Berberabe, Jason M. Broderick, Allie Casey, Gina Columbus, Shannon Connelly, Lauren M. Green, Tony Hagen, Beth Fand Incollingo, Katie Kosko, Laura Panjwani, Anita T. Shaffer, Brielle Urciuoli

Designer
Gwendolyn Salas

SALES & MARKETING

VICE PRESIDENT OF SALES, ONCOLOGY
Erik Lohrmann

VICE PRESIDENT, SALES & MARKETING
Lisa Greene; lgreene@TargetedHC.com

SENIOR NATIONAL ACCOUNTS MANAGER
Nicole Jussen; njussen@TargetedHC.com

NATIONAL ACCOUNTS ASSOCIATE
Abigail Fox; afox@TargetedHC.com

OPERATIONS & FINANCE

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Office Center at Princeton Meadows, Bldg. 300
Plainsboro, NJ 08536 • (609) 716-7777

DAY 2 FRIDAY NOVEMBER 11, 2016

Today's Agenda

Friday at a Glance

7:35–8:00AM
Holbrook Edwin Kidd Kohrt, MD, PhD Tribute

8:00–8:25AM
Cancer Immunotherapy Trials Network: *Ten Trials with High-Priority Agents in Twenty Five-Minutes*
0.25 AMA PRA
CATEGORY 1 CREDITS™

8:25–9:10AM
Keynote Address: *The Mechanistic Basis of Cancer Immunotherapy*

9:10–11:45AM
Tumor Microenvironment
2.25 AMA PRA
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11:45–1:30PM
Late-Breaking Abstract Session I and Poster Viewing

1:30–2:00PM
Update Session: *Government Agencies*
0.5 AMA PRA
CATEGORY 1 CREDITS™

2:00–4:15PM
State-of-the-Art Immunotherapies: *Challenges and Opportunities*
2.25 AMA PRA
CATEGORY 1 CREDITS™

4:45–6:10PM
Concurrent Session I: *Metabolic and Age-Associated Dysregulation of Anti-Cancer Immunity*
1.5 AMA PRA
CATEGORY 1 CREDITS™

4:45–6:10PM
Concurrent Session II: *Promoting and Measuring Antitumor Immunity*
1.25 AMA PRA
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6:15–7:30PM
Poster Reception

KOHRT

The *SITC 31st Annual Meeting & Associated Programs* is dedicated to the memory of **Holbrook Edwin Kidd Kohrt, MD, PhD**. Kohrt, one of the organizers and session co-chairs of the Annual Meeting, passed away earlier this year and will truly be missed by all.

Kohrt (1977-2016) was a widely respected clinician-researcher and assistant professor of oncology at Stanford Cancer Institute. He significantly impacted the field of tumor immunology and cancer immunotherapy and worked determinedly to make a difference in the treatment of patients with cancer despite his own illness.

In his research, Kohrt examined the immune system and the potential to influence it to recognize and kill cancer cells. He was involved in many clinical trials exploring immunotherapy agents in patients with various tumor types, including non-Hodgkin lymphoma, cervical cancer, ovarian cancer, and more.

A tribute will be held in his honor this morning at 7:35 AM, organized by Daniel S. Chen, MD, PhD; Amani Makkouk, PhD; Ignacio Melero, MD, PhD; and Russell Pachynski, MD. Please join us in a celebration of the life and the many contributions that Kohrt made to the field.

Targeted Oncology

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.

Atkins Describes Lessons of Immunotherapy Learned from Cytokines

BY ANITA T. SHAFFER

ATKINS

Cytokine-based immunotherapies developed over the past 30 years are playing a fading role in the new era of checkpoint blockade antibodies, but research into these agents has helped pave the way for current advances in the field, according to Michael B. Atkins, MD.

Interferon-alpha (IFNα) and interleukin-2 (IL-2) are early forms of biological therapies that "established proof of principle that immunotherapy can be curative," said Atkins, deputy director of Georgetown Lombardi Comprehensive Cancer Center, in a presentation during the "Primer on Tumor Immunology and Cancer Immunotherapy™" program. He has helped pioneer the development of these therapies.

Atkins described interferons and interleukins as part of a "diverse family of immune cell regulators" that interact with cell-surface receptors to affect varied functions, such as proliferation and cytotoxicity, and to "trigger a cascade of immunological events."

Atkins said IFNα has a place in anticancer therapy in 3 areas: as adjuvant therapy for high-risk melanoma, as treatment for renal cell carcinoma (RCC), and in the hematologic malignancies of hairy cell leukemia and chronic myeloid leukemia. The FDA first approved IFNα in 1986.

In melanoma, a meta-analysis of 14 randomized trials demonstrated that IFNα resulted in statistically significant improvements in disease-free survival and overall survival (OS) as adjuvant treatment in patients with high-risk cutaneous disease (Mocellin et al. *J Natl Cancer Inst*. 2010).

High-dose IFNα has shown a significant recurrence-free survival benefit and a likely OS impact, although it is accompanied by a flu-like syndrome of variable severity, Atkins said. "The benefit can be correlated with autoimmunity," said Atkins. "It's a harbinger of that effect with other immunotherapies."

In October 2015, the FDA approved the anti–CTLA-4 checkpoint blockade agent ipilimumab (Yervoy) as adjuvant therapy for patients with stage III melanoma, signaling a changing approach. "Because of the checkpoint inhibitors, interferon's days are numbered as adjuvant therapy in melanoma and primarily it's of historical significance with regard to cancer immunotherapy," said Atkins.

Going forward, he sees the role of IFNα as adjuvant treatment for patients with high-risk melanoma "limited mainly to patients with stage II disease."

High-dose IL-2 treatment has demonstrated durable responses in 6% to 10% of patients with advanced melanoma and RCC, and few relapses among patients whose responses have persisted for more than 2.5 years, Atkins said. (Atkins et al. *J Clin Oncol*. 1999; Fyfe et al. *J Clin Oncol*. 1992). The FDA approved its use for patients with RCC in 1992 and for melanoma in 1998.

However, the adverse effects associated with the therapy constitute a cytokine storm that affects every major organ system, Atkins said. Nevertheless, he said, these toxicities are caused by the treatment and can typically be resolved in 8 to 24 hours. In most centers, the death rate from the therapy was less than 1%, Atkins added.

In 1985, IL-2 was hailed as a breakthrough that represented the future of cancer therapy. "Looking at this 30 years later, I think many people would consider this a case study for what's wrong with cancer clinical development," Atkins remarked, noting that experiments were not conducted with controls, did not target specific populations, and were conducted on an in-patient basis.

"Nonetheless, it was proof of principle that, if the immune system was properly activated, you could eliminate the last cancer cell and produce cures in solid tumors," said Atkins. "It was that observation that has kept the immune therapy field alive until we can figure out better ways of activating the immune system."

Thus far, efforts to develop more tolerable high-dose IL-2 regimens have proved unsuccessful, and the use of therapy is limited to selected patients treated at experienced centers, Atkins said. Additionally, other interleukins such as IL-12, IL-15, IL-18, and IL-21 have not proven to be particularly active, he indicated.

The future of IL-2 likely will be in combination regimens with checkpoint agents or to boost the efficacy of T-cell therapy, he said. •

The Effects of Aging on Immunotherapy

BY LISA MILLER

PAWELEC

The age of a patient with cancer is a concern of clinicians when considering the efficacy of a drug for potential treatment. A common worry is that a treatment could be less effective in an older patient who is likely to have comorbidities. Yet, in a preclinical or clinical setting, younger animal models or patients often form the basis for ascertaining the greatest possible benefit of the agent.

Mouse models of cancer are most often completed in younger mice, Graham P. Pawelec, PhD pointed out in an interview prior to tonight's "Metabolic and Age-Associated Dysregulation of Anti-Cancer Immunity" session, for which he is a co-chair. Researchers have shown that what works in young animals doesn't necessarily work in the same strains in older animals (Myers et al. *Aging Dis*. 2011). However, solid tumor-type cancers are more prevalent in older patients due to immunosenescence. This may impact the efficacy of cancer immunotherapy because of the decreased capability of the patient's immune system due to his or her age.

Pawelec, a professor of experimental immunology in the Department of Hematology/Oncology at the University of Tübingen in Germany, is interested in the association between age, the immune system, and the efficacy of immunotherapy agents.

When selecting patients for clinical trials, older patients are often excluded from the trials in order to test the efficacy of the drug in participants whose immune systems function better and who have a higher performance status. Over time, this exclusion may be changing due to awareness and the requests of patients, Pawelec said.

Pawelec addressed the vast number of melanoma patients who have been treated with ipilimumab (Yervoy; anti–CTLA-4 therapy). Anecdotal reports show that older patients with melanoma have a clinical benefit equal to that of younger patients when receiving ipilimumab.

A retrospective study showed that that older patients with melanoma treated with ipilimumab have a comparable rate of immune-related adverse events to younger patients receiving ipilimumab (Mian et al. *J Clin Oncol*. 2016). The side effect profile of immunotherapy agents is a great concern when treating older patients, Pawelec noted, as it was suspected that older patients may have more numerous and severe adverse events than younger patients.

"At least in the case of melanoma and ipilimumab, I think we have enough data to say that side effects are no worse, clinical benefit is equally good, and this is reassuring," Pawelec said.

This topic of age association will be explored further in the session during a presentation by Dawn Bowdish, PhD, who has focused on the changes to myeloid-derived suppressor cells (MDSCs) with age. Pawelec is interested to learn from this presentation how these immune cells react in older cancer patients. •

ECHO 301

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DUAL PRIMARY END POINTS
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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.

Incyte

New Cytokine Approach is Synergistic With Checkpoint Inhibitors

BY LISA MILLER

DIAB

Among the new agents currently being explored in clinical trials, NKTR-214, one of the agents highlighted during Wednesday's "New Cancer Immunotherapy Agents in Development" session, stands out as a new cytokine therapy approach that could show additive benefit when combined with checkpoint inhibitors.

During the session, Adi Diab, MD, presented interim results from the phase I/II first-in-human study of NKTR-214 in patients with locally advanced or metastatic solid tumor malignancies (NCT02869295). The open-label, multicenter, dose escalation and expansion study showed that treatment with NKTR-214 has been well tolerated and is able to be administered on an outpatient basis.[1] Of 18 evaluable patients, only 1 patient experienced a dose-limiting toxicity of grade 3 syncope and hypotension at 0.012 mg/kg.

Patients showed an increase in CD8+ T cells and natural killer cells in the tumor microenvironment. Six patients showed a 10-fold increase of CD8+ T cells and natural killer cells with minimal changes in the amount of regulatory T cells.

Across all doses given, no immune-related adverse events (AEs), treatment-related AEs leading to discontinuation from treatment, or deaths have been noted so far in the trial.

Following his presentation, Diab discussed details of the current safety and efficacy data for NKTR-214, the potential to combine the agent with checkpoint inhibitors and other treatments, and what makes this agent stand apart from other cytokine therapies.

What is the mechanism of action and benefit of NKTR-214?

NKTR-214 is a cytokine resembling interleukin, except that it has a pegylation so it can be given as a pro-drug every 2 to 3 weeks. Its major mechanism of action is to lead to proliferation and lower the threshold of activation of T cells. Also, it's structured in a way to overcome some of the problems we see with interleukein-2 (IL-2). High-dose IL-2 is given to [patients with] melanoma and renal cell carcinoma. It's delivered in the intensive care Unit [and requires] very intensive monitoring of the patient because of the high degree of toxicities we receive with these drugs.

NKTR-214 is structured to minimize the toxicity, so the pegylation site really minimizes the activation of the drug with the alpha-subunit of the IL-2 receptor. Activation with that subunit has a lot of correlation with some of the major toxicities we see with high-dose IL-2. More importantly, the protract of NKTR-214 minimizes the activation of the alpha subunits, also known as CD25. It gives it bias to activate it through the other subunits of the IL-2 receptor, the beta and the gamma subunits. This bias activation allows for a preferential expansion of the effector CD8, CD4, and natural killer cells inside the tumor, without expansion of the deregulatory cells.

That gives an increased ratio of effector CD8 cells over deregulatory cells in the tumor, and that has a clinical impact. Traditionally it's correlated with higher responses with the checkpoint inhibitors; but overall, tumors and cancers that have naturally higher ratios of CD8 cells to deregulatory cells have had better overall and disease-free survival [rates].

What differentiates NKTR-214 from other cytokine therapies and why is this approach effective?

Cytokine therapies are usually administered on an inpatient basis, usually with Intensive Care Unit-like care, or very close monitoring. Also, usually you deliver more than 1 dose daily, or even 3 times daily. Here, you're talking about a drug that can be given every 2 to 3 weeks, which is very convenient for patients.

We think that this drug will lead to synergy not only with the checkpoint inhibitors, but also with other immunotherapy strategies. I think NKTR-214 will have activity and synergy, based on preclinical data, with vaccines, with adoptive T-cell therapy, and possibly with tyrosine kinase inhibitors or small molecules.

What has the clinical trial of NKTR-214 demonstrated so far?

We demonstrated that the drug has favorable safety and tolerability. It also has some encouraging clinical activity. [In] phase I you don't really evaluate clinical activity, but we certainly saw encouraging clinical activity, including 1 patient with a partial response.

The trial is designed to obtain a longitudinal biopsy, which means you have a tumor biopsy early in the treatment and later in the treatment. You get to really evaluate the immune response dynamics for a long time, and not only snapshot pictures of 1 biopsy 1 time.

The biopsy demonstrated that inside the tumor, after you treat patients with NKTR-214, you see expansion of CD8 cells and natural killer cells, but without the expansion of deregulatory cells.

What have you seen in terms of the clinical activity of the single agent so far?

We have enrolled close to 20 patients [so far] and have 18 evaluable patients to date. We've seen several patients who have stable disease who are on the trial for 3 or 4 months. They have some tumor reduction, a decrease of 6% to 10%. One patient has durable stable disease, he's been on the trial for 9 months and is still gaining a clinical benefit. We also have 1 patient who achieved a partial response, which we are very excited about.

One of the patients who has stable disease is a patient with *BRAF*-positive melanoma. He was treated with ipilimumab and developed severe grade 3 colitis with ipilimumab, so his primary doctor was hesitant to treat him with anti–PD-1 [therapy]. They treated him with NKTR-214 and he's been on it for 9 months.

Not only is there biological activity [with NKTR-214], there's no reactivation of the toxicity of ipilimumab. With NKTR-214, in this patient specifically, we did not activate the immune toxicities. That mechanism of action not only affects the biological effect of this drug on the tumor, but also has an independent toxicity profile that does not overlap with a checkpoint inhibitor. That has a lot of implication when combining those drugs together. You have different toxicity profiles that allow you to give NKTR-214 with a checkpoint inhibitor without worrying about increased toxicity.

Is NKTR-214 best treated as a single agent or as part of a combination?

Although we sometimes see [clinical activity with] single agents, I think for the current development of this drug, the major activity will be seen in combination with checkpoint blockers. But that does not mean that there's no development of a single-agent activity for this drug in the future as well.

We want to approach this drug with checkpoint blockers, initially with anti–PD-1 therapy. We want to approach it in multiple solid tumors, as a first-line therapy and also in the second-line for patients who failed on checkpoint inhibitors, to see if we can reactivate and resurrect the activity of checkpoint inhibitors when combined with this drug. This is one major way to see how much the drug really contributes to the checkpoint inhibitors.

Right now phase I is open for all solid tumors histologies. Clearly melanoma and renal cell carcinoma are attractive and we see those patients more than others. But we are looking into triple-negative breast cancer, bladder cancer, and lung cancer. These patients are going to be enriched in the second phase of this trial, and we're hoping to see some sort of activity [in these patients]. •

REFERENCE

1. Bernatchez C, Haymaker C, Tannir NM, et al. A CD122-biased agonist increases CD8+T Cells and natural killer cells in the tumor microenvironment; making cold tumors hot with NKTR-214. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 387.

SAVE THE DATES

SITC 2017

November 8-12

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Susan M. Kaech, PhD – *Yale University*
Marcela V. Maus, MD, PhD – *Massachusetts General Hospital Cancer Center*
Laura S. Wood, RN, MSN, OCN – *Cleveland Clinic Taussig Cancer Center*

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Grant Writing Workshop on Cancer Immunotherapy Protocol Development

Organized by the Early Career Scientist Committee

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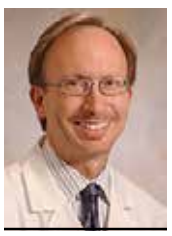
Society for Immunotherapy of Cancer

Tumor Microenvironment Emerges as a Focus in Immuno-Oncology

BY TONY BERBERABE, MPH

CONTINUED FROM **COVER**

DISIS



GAJEWSKI

invasion, and metastasis first starts. As researchers gain a greater understanding of this environment, the emergence of potential targets for therapeutic agents becomes apparent. Ongoing clinical research aims to characterize the tumor microenvironment and gain insight into cancer prognosis and treatment selection, as well as to further understand mechanisms that drive immune-based tumor rejection.

Disis noted that researchers have been able to enhance activation and proliferation of immune cells, such as T cells and B cells; however, when these cells migrate into the dysregulated tumor microenvironment, their activity is halted. "That's why immune checkpoint inhibitor drugs are so effective. They are preventing the tumor microenvironment from limiting the immune response."

With more research focused on modulating the tumor microenvironment, checkpoint inhibitor agents have now become standard-of-care. "Upregulation of proteins that block the immune response is only 1 mechanism by which tumors or innate immune cells impact immunity," said Disis.

Those other mechanisms will be addressed during the session, including in her own presentation, said Disis. "CD4 T Cells as Regulators of Tumor Growth" will focus on CD4 T cells, which can be stimulated to secrete cytokines that have a profound effect on tumor growth. One effect of Type I cytokines is to stimulate the proliferation of CD8 T cells. An additional effect is to block signaling through dominant growth factor receptors, which results in more sensitive chemotherapy-induced cancer cell death.

The important role of CD8 T cells will also be explored in the session, she said. "The CD8 T cell is responsible for direct tumor killing," said Disis. "Researchers are exploring ways to modulate the tumor microenvironment that encourages CD8 T-cell proliferation."

> **"...modulating the tumor microenvironment is a major area of research and we're going to be hearing about some of these new approaches during the session."**
>
> *—Mary L. Disis, MD*

CD8+ T cells (often called cytotoxic T lymphocytes, or CTLs) are very important for immune defense against intracellular pathogens, including viruses and bacteria, and for tumor surveillance. When a CD8+ T cell recognizes its antigen and becomes activated, it secretes cytokines, primarily tumor necrosis factor-alpha and interferon-gamma (IFN-γ), which have antitumor and anti-viral microbial effects.

A presentation by Justin Kline et al will also be given during the session. The authors will present a body of evidence that further defines the role of basic leucine zipper transcription factor ATF-like 3 (Batf3)-dependent dendritic cells (DCs) in regulating anticancer immune responses. In contrast, the antigen-presenting cells (APCs) that regulate immune responses against hematological malignancies have not been characterized. Syngeneic transplantable and genetically engineered acute myeloid leukemia (AML) models associated with a dense CD8+ T-cell-tolerant state were employed to identify the APCs responsible for inducing T-cell tolerance *in vivo*.

A packed house of attendees during yesterday's Primer session.

Following systemic introduction of viable, CellTrace violet-labeled AML cells, leukemia cell-derived fluorescence was observed exclusively within splenic CD8α+ DCs, whereas uptake of proteins from dead AML cells was mediated by CD11b+ macrophages. CD8α+ DCs were also uniquely capable of cross-presenting leukemia antigens to CD8+ T cells directly *ex vivo*.

Batf3-lineage DCs generate functional CD8+ T cell responses against solid tumors, but actively and exclusively induce CD8+ T-cell tolerance to systemic leukemia, indicating that the same DC lineage can imprint disparate T-cell fates in mice with solid versus hematologic tumors. It also suggests that environmental cues perceived by CD8α+ DCs may rule their ability to activate or tolerize cancer-specific CD8+ T cells.

Abigail Overacre and colleagues will discuss the role of neuropilin 1 (Nrp1)-deficient T cells. Regulatory T cells (T_{regs}) play an integral role in maintaining immune homeostasis; however, they are detrimental in cancer through suppression of the antitumor immune response. Therefore, identifying T_{reg} targets that are specifically required in the tumor microenvironment is warranted. The authors have previously shown that the Nrp1 pathway is required for functional stability of intratumoral T_{regs}, but remains disposable in maintaining peripheral immune homeostasis.

The authors found that intratumoral Nrp1-deficient T_{regs} produce IFN-γ, driving the functional destabilization of surrounding wild-type T_{regs}, which in turn boosts antitumor immunity and facilitates tumor clearance. Furthermore, they demonstrated that Nrp1 is expressed on a proportion of tumor-infiltrating lymphocytes (TIL) T_{regs} in head and neck cancer as well as metastatic melanoma, and that the IFN-γ pathway is likely conserved in human T_{regs}. In addition, human TIL T_{regs} pre-treated with IFN-γ show significantly reduced suppressive function compared with those without pre-treatment.

It has been suggested that Nrp1 is required for functional stability of intratumoral T_{regs}. Without Nrp1, the tumor microenvironment is altered and leads to an enhanced antitumor immune response. Disis said that the work by Overacre and others may help uncover a novel potential target for cancer immunotherapies that preserves peripheral immune health. This could be clinically relevant, since Nrp1 is expressed on select T_{regs} in human melanoma and head and neck cancer.

Disis said that she is intrigued by the basic mechanisms of immunity that will be presented at the meeting. "Many of these investigators are the top of their field. What I'm really fascinated about is hearing these scientists tell us the best way to take their findings and apply it to the clinic. We could very well be learning about mechanisms that will be used to manipulate the microenvironment in the clinic in the next 2 or 3 years." •

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Methods to Predict Response to Immunotherapeutics

BY LISA MILLER

CONTINUED FROM **COVER**

SCHLOM

To determine the predictive value of this approach to characterizing peripheral immune cells, researchers analyzed differences in peripheral immune cells drawn from younger versus older individuals (ie, those aged <40 years vs those ≥40 years), and healthy adults versus age-matched patients with metastatic cancer.

Compared with healthy individuals aged <40, individuals aged ≥40 showed lower levels of markers indicating activation of CD8+ T cells. A trend suggesting increased levels of markers associated with CD4+ T-cell activation in older individuals than in younger was also identified. Other analyses showed increased levels of markers associated with immune checkpoint pathway activation, increased PD-L1 expression on antigen-presenting cells, and other differences in patients with metastatic cancer versus age-matched healthy individuals.

Explaining the potential therapeutic relevance of these and newer findings,[2] Schlom stated, "The immune cells in the periphery can be very important in terms of analysis to potentially define which patients may respond best to immunotherapy, either prior to the initiation of immunotherapy or early on in the therapeutic regimen."

Next, Lisa H. Butterfield, PhD, the incoming president of the Society for Immunotherapy of Cancer (SITC), will discuss immune responses to vaccines and tumor antigens. According to Schlom, Butterfield has been researching cytokines, such as transforming growth factor-beta (TGF-β), interleukin-10, and interleukin-17, in the periphery in order to determine a patient's expected outcome. Butterfield has been examining these cytokines with regards to expected responses and potential adverse events to ipilimumab (Yervoy) treatment for melanoma patients.

> **"The immune cells in the periphery can be very important in terms of analysis to potentially define which patients may respond best to immunotherapy…"**
>
> *—Jeffrey Schlom, PhD*

In his talk, Lawrence Fong, MD, will be addressing T-cell receptors as an approach to predicting patient responses. Fong is currently researching the changes in T-cell receptors on clones bearing specific T-cell receptors immediately after the initiation of immunotherapy, and investigating how this correlates with clinical activity, says Schlom.

"This has mostly been done in melanoma and prostate cancer, where there are associations between enhancements of specific clones of T cells and how patients respond," Schlom stated.

Fabienne Hermitte, PhD, vice president of research and development, regulatory and medical affairs, HalioDx, will present on the analytical performance of the Immunoscore® in colon cancer.

In 2012, the Society for Immunotherapy of Cancer (SITC) led a 23-center study of more than 3800 patients to validate the Immunoscore as a standardized immune-based assay in colon cancer. A study presented in June 2016 showed the prognostic value of the Immunoscore® in predicting time to recurrence, disease-free survival, and overall survival in stage I-III colon cancer.[3,4] The Immunoscore has also been shown to predict response to chemotherapy in patients with stage II and III colon cancer.[5]

"There's been some extremely good work done looking at biopsies of primary tumors in colon cancer and being able to determine that patients are going to respond to chemotherapy if they have a large amount of immune cell infiltrate in their primary tumor," Schlom said.

The Immunoscore stratifies colon cancer patients into 5 categories from 0 to 4 for Immunoscore-Low to Immunoscore-High, based on the density of T lymphocytes present, whereby Immunoscore-High patients have a longer time to recurrence.[4] HalioDx created a standardized version and tested it to prove the accuracy and reproducibility of the Immunoscore assay.[6]

Researchers used a software program (Immunoscore® Analyzer, HalioDx) to analyze slides of formalin-fixed paraffin-embedded colon tumor blocks with immunohistochemistry staining to compare densities of CD3+ and CD8+ lymphocytes in the core and invasive margin of the tumor. Accuracy was assessed by comparing Immunoscore results with a reference assessment by experts at the European Hospital Georges Pompidou (HEGP).

The Immunoscore assay was proven accurate with only 1 change noted in the Immunoscore category out of 62 assessments. In cell density assessments, among the different instruments, lots, and operators/readers, the coefficient of variation was lower than 12%, 22%, and 18%, respectively, showing the ease of reproducibility. Additionally, comparing reference HEGP assessment with the Immunoscore revealed a Pearson correlation coefficient greater than 0.89, indicating high concordance.

Although the Immunoscore has previously been used to predict how well patients will respond to treatment, other methods may also have a role.[5] For instance, a patient's prior response to chemotherapy can also play a role in predicting how a patient will respond to immunotherapy agents. According to Schlom, "It is generally believed that standard of care chemotherapy and immunotherapy do not mix well, and this is really the case in patients who have had many different cycles of chemotherapy, because their immune system is weakened."

However, Schlom suggested that patients who were less heavily pretreated with chemotherapy, or treated concurrently with immunotherapy, may actually gain more of a benefit from immunotherapy. "What is not well understood yet is that, early on in the disease process when they're getting their first- or second-line chemotherapy, some of these chemotherapies can make the immune system more amenable to immunotherapy."

This sensitivity will continue to be explored, along with additional approaches to predicting a patient's response to immunotherapeutics.

Schlom believes that this session will have a broad appeal to a variety of attendees, as they will have the opportunity to learn about the biggest advancements within the area of antitumor immunity that can be used toward clinical practice. •

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How do PD-L1 inhibition and PD-1 inhibition differ?

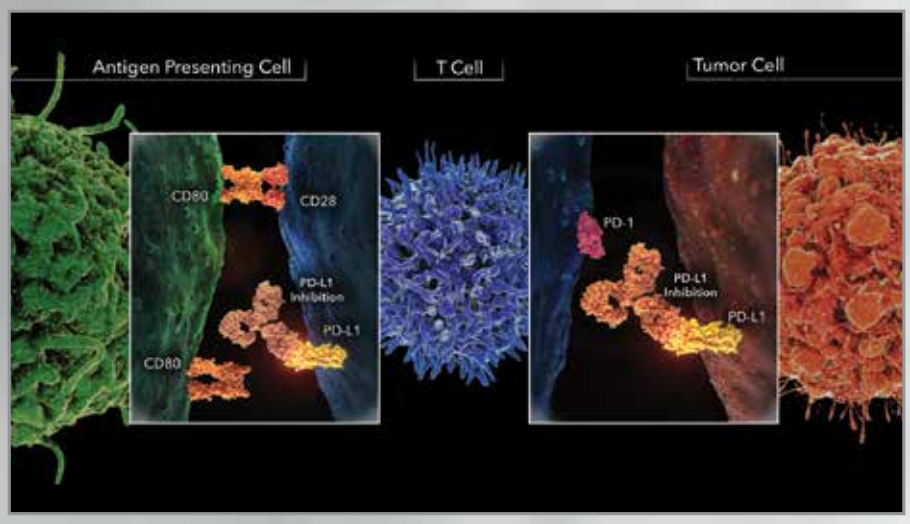
PD-L1 provides an important target to help reactivate the immune system

Immune checkpoint molecules ensure appropriate immune function by modulating T-cell activation[1,2]

- PD-L1 (programmed death ligand-1), expressed on a variety of normal cells, binds to PD-1 to inhibit T-cell activity[2,3]
- PD-L1 has also been shown to sequester the co-stimulatory ligand CD80 (also called B7.1), therefore limiting its ability to co-activate T cells[4,5]
- Tumor cells upregulate PD-L1 to evade the antitumor immune response[1-3]

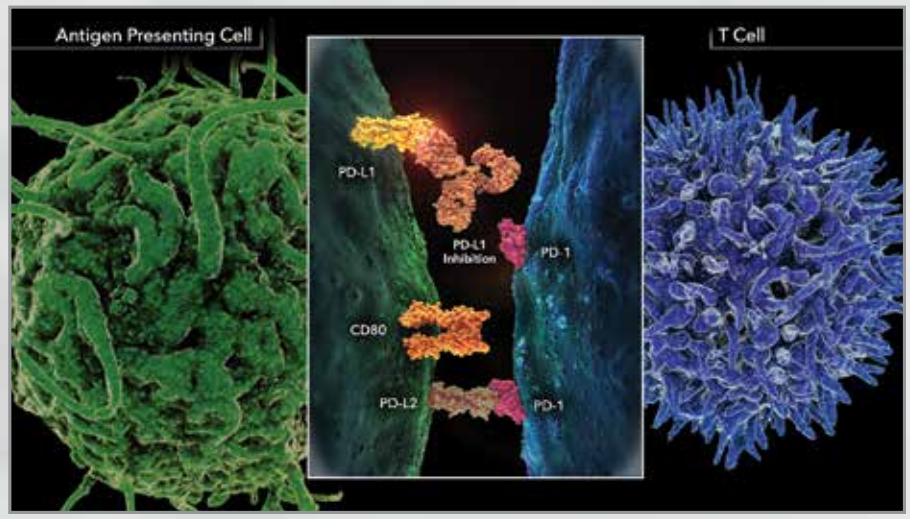
PD-L1 and PD-1 play different roles in immune regulation and T-cell activation

The role of interaction between PD-L1 and CD80



- PD-L1 and PD-1 inhibition block PD-L1 interaction with the inhibitory receptor PD-1, which helps restore T-cell activity[2,3]
- PD-L1 inhibition prevents PD-L1 interaction with the co-stimulatory ligand CD80, maximizing its availability to activate T cells[3,6]
- PD-1 inhibition does not prevent the interaction between PD-L1 and CD80[3,5]

The role of PD-1:PD-L2 interaction in immune regulation



- PD-L1 inhibition leaves the PD-L2 pathway intact so that PD-L2 can continue to play an important role in immune regulation[7,8]
- Leaving PD-L2 intact may prevent tissue damage[5,7,8]
- PD-1 inhibition prevents the interaction between PD-L2 and PD-1[9]

PD-L1 pathway inhibition offers a new foundation for immunotherapy combination research

- Combination with another immune pathway may combat multiple mechanisms of tumor immune escape, potentially allowing for greater antitumor activity than with either pathway alone[10,11]
- AstraZeneca is conducting numerous clinical trials evaluating PD-L1 inhibition in combination with other immune pathways (such as CTLA-4 inhibition), targeted agents, and chemotherapy[12]

Learn about the Immuno-Oncology (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.

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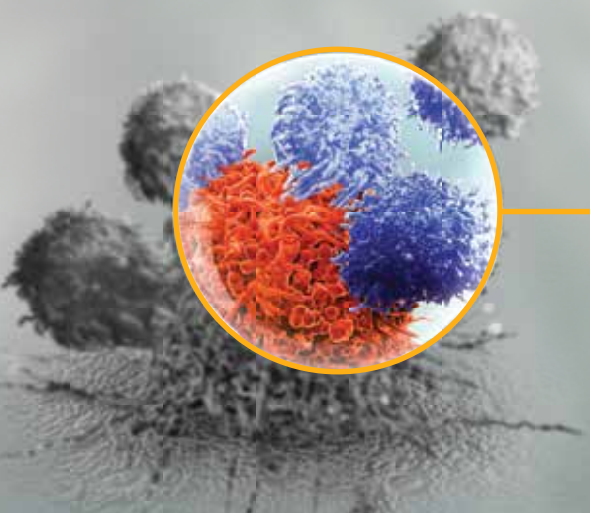

AstraZeneca

Exploring Metabolic Pathways and Aging to Make Immune Cells Stronger

BY LAUREN M. GREEN

MISTELI

An international group of experts will be on hand for this afternoon's concurrent session focused on the role of metabolism and aging in anticancer immunity, a panel which will spotlight the natural synergy between immunology and cell biology.

For the first time, the Society for Immunotherapy of Cancer (SITC) is collaborating with the American Society for Cell Biology (ASCB). The joint session entitled "Metabolic and Age-Associated Dysregulation of Anticancer Immunity," was a logical fit, explained Tom Misteli, PhD, who is co-chairing the session as ASCB's representative.

Joining him will be Graham P. Pawelec, PhD, an immunologist with the University of Tübingen in Germany, where he leads the Tübingen Aging and Tumor Immunology (TATI) Group. TATI conducts research in human immunosenescence, vaccination, tumor immunity, immunotherapy, Alzheimer's disease, longevity, immunity, and aging.

The session the 2 will be moderating underscores the importance of "bringing basic cell biology closer to clinical application," said Misteli, who currently directs the Center for Cancer Research at the National Cancer Institute.

"These are not 2 separate worlds. Whenever we think about clinical applications—clinical interventions of any kind—we're really dealing with cell biology," Misteli continued. "Any drug that we're interested in has to reach its target in the cell."

Misteli said that the SITC/ASCB collaborative session centers on the importance of making better immune cells for immune therapy. He noted that a lot of activity in the field is currently looking precisely at this question of how to improve immune cells, such as subsets of T cells.

"We're at the stage in this field where we have proof of principle that immunotherapy can work and is incredibly promising, but we have to make it more efficient and more targeted.... The question is: how do you do this?"

"...we have to make [immunotherapy] more efficient and more targeted.... The question is: how do you do this?"

—Tom Misteli, PhD

Although Misteli and his research colleagues do not work on the immune system in their laboratory, they are exploring the processes involved in premature aging. Their focus currently is on how the genome functions in an intact cell nucleus. "We hear a lot about sequencing genomes, but we're looking at how the genome is folded in three-dimensional space, and how that higher order organization affects the function of that genome and, ultimately, of an organism."

Overall, on the immunology front "there is a lot of activity in the field looking at the metabolic state of immune cells to try to, essentially, make them stronger."

To boost the cells, a better understanding of the metabolic pathways is needed, explained Misteli, adding that with age, the activity of the immune system declines. Together, he said, these concepts suggest a logical area of investigation: "Which are the important pathways in these immune cells that could be improved, because these are likely the pathways affected during aging; that's really the connection."

One pathway of interest is Wnt5a-beta-catenin, and Brent A. Hanks, MD, PhD, will be reporting on research he and colleagues at Duke University Medical Center and the Lineberger Comprehensive Cancer Center in North Carolina have been conducting to help illuminate why many cancers do not respond to available immunotherapies.[1]

Molecular characterization of the Wnt signaling pathway is of great interest to cancer researchers due to its aberrant regulation and cooperativity with other signaling networks from cells within the tumor microenvironment. Preclinical models throughout the last decade have established this pathway as an attractive drug target for anticancer therapeutics.

The research team used real-time metabolic flux analysis to study the role of the Wnt5a-beta-catenin-PPARg pathway in the metabolic reprogramming of dendritic cells from melanoma tumor samples, because dendritic cells are suspected to play an important role in immune evasion within the tumor microenvironment. Results indicated that the Wnt5a-beta-catenin-PPARg pathway shifts dendritic cells from glycolysis to fatty acid oxidation within the melanoma microenvironment. Accordingly, this CPT1A-dependent metabolic shift increases the tolerization of dendritic cells and the generation of regulatory T cells. Investigators showed that targeted inhibition of regulators within this pathway promotes greater effector T-cell responses and T-cell tumor infiltrates, and alters PD-L1 expression in melanoma-derived models.

In Hanks' presentation, he will discuss the potential for the Wnt5a-beta-catenin pathway as a pharmacologic target for increasing tumor responsiveness of "non-inflamed tumors" to anti–PD-1 immunotherapy.

Another intriguing area of research involves the role of Th17 cells, a subset of activated CD4+ T cells, also known as "helper cells." A presentation by Shilpak Chatterjee, PhD, a postdoctoral research scholar at the Medical University of South Carolina, will highlight work of his research team that is focused on combining the culture conditions of Th1 and Th17 cells to generate hybrid Th1/17 cells with enhanced antitumor properties.

Also presenting at the session will be Mads Hald Andersen, PhD, of Herlev University Hospital in Denmark, where he is a professor and co-founder of the Center for Cancer Immune Therapy (CCIT). The overall goal of CCIT is to bridge the gap between discovery and clinical implementation in the field of cancer immunotherapy.

Anderson's presentation will focus on how T cells recognize indoleamine 2,3-dioxygenase (IDO) or PD-L1. IDO has been identified as a checkpoint protein involved in generating the immunosuppressive tumor microenvironment that supports tumor growth. Anderson and colleagues have been exploring IDO vaccination and they reported their findings last year in *Oncoimmunology* suggesting that, "boosting specific T cells that recognize immune regulatory proteins, such as IDO or PD-L1, may directly modulate immune regulation, potentially altering tolerance to tumor antigens."[2]

Rounding out this concurrent session is Dawn Bowdish, PhD, who will be discussing the interplay of myeloid-derived suppressor cells, age, and cancer. Bowdish is head of the Bowdish Macrophage Biology Lab at McMaster University in Toronto, Canada. Her lab's research priorities include studying age-related changes in the immune response and developing immunomodulatory therapies. •

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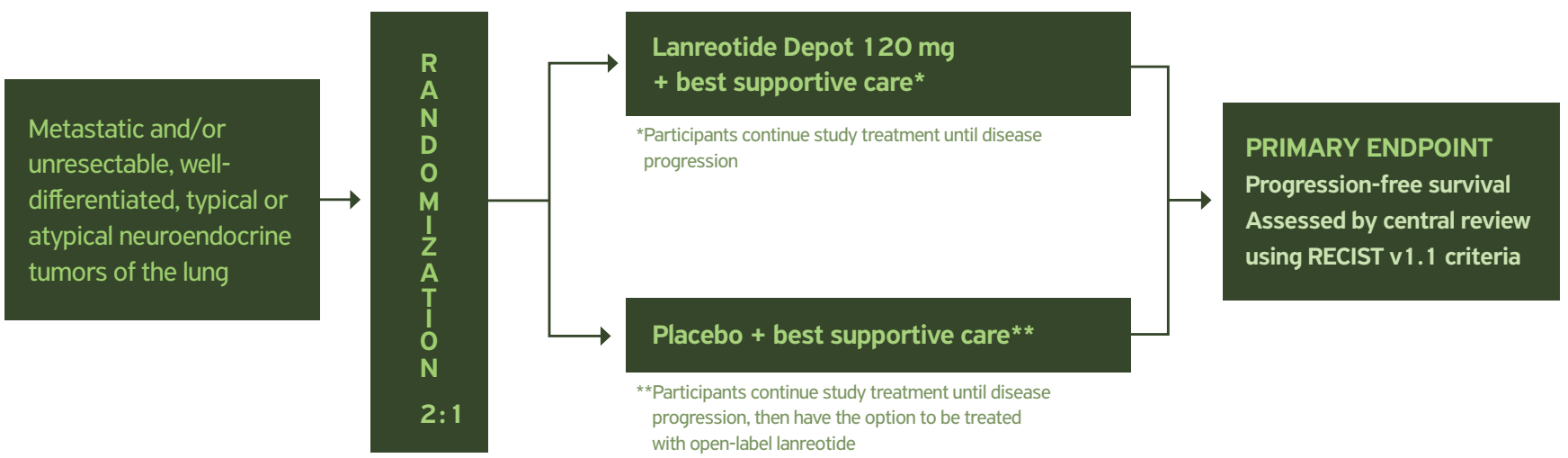

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Mitotic index < 2 mitoses/2 mm^2 for typical carcinoid and <10 mitoses/2 mm^2 and/or foci of necrosis for atypical carcinoid	Treatment with peptide receptor radionuclide therapy at any time prior to randomization
At least 1 measurable lesion of the 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
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Innovation for patient care

SITC's Consensus Statements Guide Immunotherapy Treatment into Practice

The rapidly growing field of cancer immunotherapy continues to generate enthusiasm due to positive and durable outcomes in responding patients for whom traditional therapeutic approaches have failed. As new drugs and combinations gain approvals for a broad range of malignancies, there is a growing need for disease-specific recommendations to help guide the integration of immunotherapy treatments into current practice. The evidence-based clinical practice guidelines provided by the National Comprehensive Cancer Network (NCCN) are a widely recognized resource and standard for the treatment of cancer, yet the NCCN guidelines do not cover the unique aspects of immunotherapy. In particular, guidance is needed to determine patient eligibility, assess responses due to the unique pharmacokinetics, and manage the immune-related toxicities associated with these agents.

To address the deficiency in physician resources regarding current best practices for the use of immunotherapeutics, the Society for Immunotherapy of Cancer (SITC) has established disease-specific panels of experts to attend to knowledge gaps associated with specific facets of the clinical management of immunotherapy, including patient selection criteria, the sequencing or combination of therapies, response assessment, management of toxicities, and clinical endpoints. Each panel is comprised of a multidisciplinary group of physicians as well as a combination of researchers, nurses, and patients or patient advocates invited from institutions across the United States, both SITC members and non-members, with the goal of publishing an evidence-based manuscript to be utilized as a set of guidelines for practicing oncologists.

SITC's first consensus statement was published in 2013 to guide the use of immunotherapy for the treatment of melanoma.[1] In response to the ever-growing demand for expert advice on the optimal use of immunotherapy treatments, SITC has since appointed Task Forces (TF) to develop guidelines for genitourinary malignancies (kidney, bladder, and prostate cancer), hematologic malignancies, and lung cancer. The rapid changes in available immunotherapy treatment options for melanoma have also triggered an update to the original melanoma statement. New guidelines for kidney cancer, prostate cancer, hematologic malignancies, and a melanoma update are expected to be published in 2016, with statements for bladder and lung cancer slated for publication in 2017.

To ensure fairness and transparency, the Institute of Medicine's (IOM) March 2011 Standards for Developing Trustworthy Clinical Practice Guidelines[2] were used as the infrastructure upon which the recommendations was established. For example, these standards provide guidance on the proper management of conflicts of interest, selection of Task Force participants to include all populations expected to be affected by the development of guidelines, a preferred model for systematic reviews, the establishment of a rating system for the strength of evidence identified, and the means by which recommendations should be updated in the future.

The cancer immunotherapy guidelines' Oversight Committee (OC) was established to serve as the mechanism for identifying new disease settings or recommending updates to an existing set of guidelines, and to help lead each new disease-specific panel. Once a TF is established, the scope of the project must be determined in order to develop questions that focus on critical aspects of FDA-approved immunotherapy treatments available for the malignancy of interest. These questions are intended to address key knowledge gaps in the clinical application of immunotherapy and are distributed as a survey to all TF members for the purposes of establishing an expert consensus opinion.

A comprehensive literature search is also conducted to identify and evaluate literature according to the predetermined rating system. A bibliography is then compiled based on search results and serves as the evidence base for the strength of the recommendations that arise from the consensus opinions.

Each TF holds live meetings structured around the key knowledge gaps identified at the outset. The survey results and bibliography are discussed and any meeting outcomes, such as important conversation points and votes on key issues, are recorded for use in drafting the consensus statements. Drafts of the cancer immunotherapy guidelines are then routed for an extensive review process. Members of the TF and OC begin with an initial review, after which all SITC members are invited to review and provide comments. Consensus statements are then peer reviewed upon submission to the society's *Journal for ImmunoTherapy of Cancer*, an open-access journal. Following publication, the guidelines will be reviewed annually by the OC and will be updated when evidence suggests the need for modification of clinically relevant information.

"There is a growing need for disease-specific recommendations to help guide the integration of immunotherapy treatments into current practice."

To learn more about how SITC's consensus statements are addressing the need for disease-specific resources on the appropriate use of cancer immunotherapy, please visit **www.sitcancer.org/targeted-therapies-oncology**. •

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Prognostic Tool for Immunotherapy Age Debuts

BY ANITA T. SHAFFER

GALON

FOX

An assay that analyzes key elements of the tumor microenvironment in patients with colon cancer marks the first standardized method for evaluating an individual's underlying immune system to be developed and sets the pace for tests in other malignancies that could be incorporated into conventional classification paradigms, according to a worldwide group of researchers who collaborated on the project.

The Immunoscore characterizes the number, density, and distribution of CD3-positive lymphocytes and CD8+ cytotoxic T cells in the tumor core and invasive margins using a combination of automated immunohistochemistry testing and digital pathology. A patient can then be categorized as having a low, intermediate, or high Immunoscore depending upon preset parameters.

The assay has been validated in a study of tumor samples from more than 2600 patients with stages I-III colon cancer, according to results presented at the 2016 ASCO Annual Meeting in June.[1] The time to recurrence (TTR) was significantly longer in patients with a high Immunoscore, and the test was able to predict disease-free and overall survival. Additionally, a subgroup of patients with high-risk stage II colon cancer was identified through a low Immunoscore.

The Immunoscore breaks new ground in classifying cancers, said lead investigator Jérôme Galon, PhD, research director of the Laboratory of Integrative Cancer Immunology at the Inserm public research institute in France, who presented the results at ASCO. He is also co-founder of HalioDX, a diagnostic company seeking to commercialize Immunoscore.

"Today, there is not a single host immune characteristic that is taken into account for cancer patients. We don't know anything about the immune system of a cancer patient because there is not a single standardized assay," Galon said during the presentation. "In the era of immunotherapy, it is becoming essential to start classifying cancer patients based on immune parameters."

As research on the new analytical tool moves forward, the Immunoscore could be used to enhance prognostic assessment and therapeutic management in a range of solid tumors, investigators have indicated.[2] An assessment of a patient's innate and adaptive immune responses could predict whether chemotherapy, radiotherapy, or checkpoint blockade immunotherapy agents would be effective.

"This is a particularly timely finding in the era of immunotherapy, as Immunoscore-based assays could be used to predict which patients would be more likely to benefit from treatment modalities such as checkpoint blockade or whether strategies, such as adjuvant therapy or cancer vaccines to prime immunity, might be more appropriate," said the Society for Immunotherapy of Cancer (SITC), which led the formation of the worldwide consortium that developed the Immunoscore.[3] "More broadly, the results of the Immunoscore study have potential implications for the field of immune monitoring as a rapid means of determining response to treatment."

The next step for the Immunoscore will be to incorporate the assay into randomized clinical trials "to stratify the patients based on what will be the first immune-based assay to measure the immune system of a cancer patient," Galon said in an interview.

Research is underway on Immunoscore tests for hepatocellular carcinoma and brain metastases.[2] In July, HalioDx announced that the Immunoscore Colon test would be available to pathologists in Europe as a laboratory service and to researchers throughout the world by the end of this year.[4]

Bernard A. Fox, PhD, past president of SITC, said the Immunoscore is not yet ready to be incorporated into clinical practice but that assays evaluating the immune system to predict therapeutic outcomes would probably be introduced within the next 2 years. Fox is chief of the Laboratory of Molecular and Tumor Immunology at the Earle A. Chiles Research Institute at Providence Portland Medical Center in Oregon.

"This is a great step, but it's still a first step and it's a small step," Fox said in an interview. "There's going to be additional information that we're going to get in the next generation."

How Immunoscore Was Developed

The Immunoscore findings presented at ASCO represent a milestone in an effort to develop a standardized assay that began more than a decade ago and required an unusual international partnership.

Galon noted that he and colleagues had demonstrated the prognostic value of a patient's preexisting immunity by quantifying immune cells, categorizing their location, and analyzing the impact on clinical outcomes in colorectal cancers in the mid-2000s.[5,6] Subsequent research built upon the concept of creating a method for evaluating immune system biomarkers.

Nevertheless, SITC faced considerable hurdles in forming partnerships that would help advance development of a classification system, Fox said. He said the organization approached nearly 20 companies, starting with those that had the advanced technology needed to conduct the analyses, about collaborating on the project.

"Nobody wanted to support it, even though we were pointing out that if you knew you could stratify patients in your clinical trials, you may have drugs that worked but you took them off the shelf," said Fox.

In 2012, SITC decided to help support the concept and began recruiting centers to participate. Ultimately, 23 pathology centers in 17 countries in North America, Europe, and Asia joined the study.

"I'm very proud that the society pushed this," said Fox. "I'm proud of the group of people who participated in this, for their generosity of their time and their treasure—all to benefit the patients."

Evidence Presented at ASCO

In conducting the Immunoscore study, the participating centers collected tissue samples, performed staining on their slides, and then sent multiple consecutive slides and raw data to a reference center for testing and harmonization. The Mayo Clinic in Rochester, Minnesota, served as the external statistician.

For analysis, the Immunoscore employs computer technology and digital imaging, Galon explained. "There is software that is automatically counting every single immune cell that is infiltrating a tumor separately in the 2 tumor regions—the center and the invasive margin," he said in an interview. "And then the software automatically calculates all the cells, all the cell density, and gives back the report of Immunoscore. It's a fully automated process."

Patients are stratified into 1 of 3 levels based on a score ranging from 10 to 14, depending upon the total number of high densities observed.[2] Both CD3 and CD8 are assessed in the tumor core and in the invasive margins.

The study criteria included patients with stages I/II/III colon cancer (T1-T4, N0-N2, M0) who had not received neoadjuvant treatment. In all, 3855 patients were evaluated for the Immunoscore but many did not meet the inclusion criteria for the study; the analysis »

Analyzing Colon Cancer

Current Classification Systems

Staging
TNM—Primary tumor, regional Lymph nodes, distant metastasis

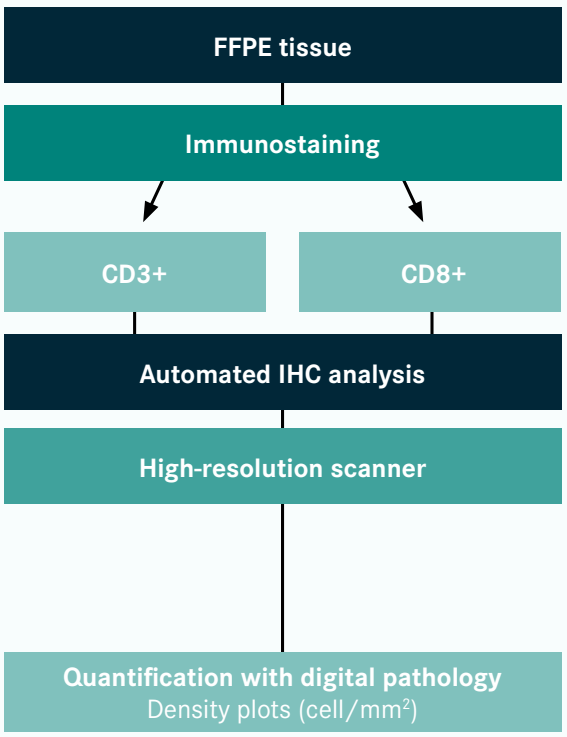
Histology
Adenocarcinoma, mucinous adenocarcinoma, other variants

Cell of origin
Enterocyte, goblet, stem-like

Mutation status
KRAS, *NRAS*, *BRAF*, MSI, MMR

Molecular features[a]
4 categories based on genomic data including MSI, CIN, metabolic deregulation, and activated pathway

Immunoscore



[a]Colorectal Cancer Subtyping Consortium categories

CIN indicates chromosomal instability; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; MSI, microsatellite instability, MMR, mismatch repair.

Adapted from Galon J, Validation of the Immunoscore as a prognostic marker in stage I/II/III colon cancer: results of a worldwide consortium: final analysis on 3855 patients. Presented at: 2016 ASCO Annual Meeting; June 3-7, 2016; Chicago, IL. Abstract 3500.

was therefore conducted on the tissue of 2667 patients who were deemed eligible.

The participants were divided into a training set and 2 independent cohorts, an internal validation set and an external validation set. Galon said the arms were generally well balanced for age, with a median of 68 years, and tumor status, with 64.6% to 67.1% in each group, at T3.

The proportion of patients with N0 nodal status was higher in the training and internal validation groups at 73.4% and 76.3%, respectively, than in the external validation group at 64.1%. The proportion of right-sided (proximal) and left-sided (distal) tumors was approximately even in the training and internal validation groups; right-sided tumors were more prevalent in the external validation cohort.

> **The Immunoscore assay, as we have demonstrated in this international study, has all the characteristics of a biomarker that can be done in routine practice."**
>
> *—Jérôme Galon, PhD*

The higher the Immunoscore, the better the prognosis. Twenty-six percent of participants had a high score, 49% had an intermediate score, and 25% had a low score. Patients were followed for recurrence for a median duration across centers of 5.9 years. Overall, participating centers counted more than 352 million CD3+ T cells in the samples during the study, Galon said. The Immunoscore proved to be highly reproducible, with rates of whole-slide correlation between analysis by pathologist and assay at 0.98 for the center tumor region and 0.96 for the invasive margin region.

The study met is primary endpoint correlating TTR with the Immunoscore. The TTR was significantly longer in patients classified as Immunoscore-high versus Immunoscore-low in all 3 cohorts: the training subset of patients (HR, 0.41; 95% CI, 0.28-0.61), the internal validation set (HR, 0.41; 95% CI, 0.27-0.65), and the external validation set (HR, 0.51; 95% CI, 0.38-0.68). Those results were statistically significant for each group (P <.0001).

Galon said similar results were found for the secondary objectives of predicting disease-free and overall survival but did not provide details during his ASCO presentation.

Additionally, the Immunoscore lined up with the TTR for all 3 levels in a subset of patients with stage II colon cancer (n = 1433). The hazard ratio for this group was 0.36 (95% CI, 0.23-0.56; P <.0001).

"The Immunoscore assay, as we have demonstrated in this international study, has all the characteristics of a biomarker that can be done in routine practice," Galon said. "It is pathology based, it is routinely feasible, it is reproducible, it is quantitative, it is standardized, and so, given the power of Immunoscore that we have demonstrated in this study, I believe it is now ready for clinical practice."

A Note of Caution

Amid the enthusiasm of the study team for the new assay, ASCO discussant Neil H. Segal, MD, PhD, wondered about the impact of microsatellite instability (MSI), which the Immunoscore does not specifically measure.

Microsatellites are short stretches of repetitive DNA that become unstable because of defects in the mismatch repair (MMR) system.

National Comprehensive Cancer Network guidelines recommend that MSI or MMR testing should be performed for all patients with metastatic colorectal cancer, patients with stage II disease because of the possibility that those with MSI-high scores would not benefit from adjuvant chemotherapy, and as part of Lynch syndrome screening.[7] Immunohistochemistry is used for MMR, while polymerase chain reaction is used for MSI assessment.

Segal, a medical oncologist at Memorial Sloan Kettering Cancer Center, said he does not think the Immunoscore is ready for clinical practice.

"This is still a work in progress," Segal said. "There is more information that we need in order to fully answer the question. The one caveat to interpreting this data is the contribution of MSI-high colon cancers, which accounts for 15% of localized colon cancer."

Targeting Immunity

The importance of the patient's immune system in responding to therapy is at the heart of SITC's efforts to develop the Immunoscore.

"The only thing that makes a difference in the life of a patient with metastatic cancer is their immune system," said Fox. "There's a lot of data in animal models that suggest that tumors that are not immunogenic—tumors that don't have immune infiltrates—are not going to respond to checkpoint blockade, are not going to respond to costimulatory molecules."

SITC researchers believe that the current reliance on the TNM staging system, with its tumor-focused methods of classifying all malignancies, has many shortcomings.[3] Additional information can be gleaned from other aspects of tumor analysis such as cellular morphology and molecular pathways.

"However, instances in which clinical outcomes are drastically different between patients within the same stage, patients who maintain stable late-stage disease for years, or the rapid decline of early-stage patients, underscore the limited ability of the current staging systems," SITC said.[3]

During the past 5 years, the focus on the tumor cell itself in malignancies has evolved into an expanded understanding of the role of the tumor microenvironment, which Immunoscore researchers describe as "a set of cellular com-

CONTINUED ON PAGE 18

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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CONTINUED FROM PAGE 16

This event, hosted by the SITC Early Career Scientist Committee, on ***Friday, November 11 at 8:00 PM in the National Pastime Sports Bar & Grill***, invites all early career scientist attendees to meet colleagues and make early connections that can be fostered throughout the rest of the conference. The scientists are asked to meet at The Node (***Booth #101***) at ***7:45 PM*** inside the Prince George's Exhibition Hall AB to head over to this networking event together.

partments comprising vascular, neuroendocrine, stromal, epithelial and immune cells."[2]

A growing body of evidence has demonstrated "a positive association between the density of intratumoral lymphocyte infiltrates in solid tumors and increased patient survival," the investigators said.[2]

Specifically, the level of T cells expressing CD3 with CD8 or CD4 and memory T cells expressing CD45RO have been associated with outcomes in ovarian, head and neck, bladder, breast, liver, prostate, lung, melanoma, esophageal, and colorectal cancers.

In designing the Immunoscore for colorectal cancer, researchers incorporated CD3 and CD8 testing because of prior research evidence about their significance but eliminated CD45RO because it is "highly overlapping" with T-cell density and is difficult to include in the staining and slide process.[2]

Fox believes much important information about the immune environment has been gained through the development of the Immunoscore that will be useful in designing future therapies, particularly combinations that include immunotherapies.

"What this points to is the fact that we need to have [agents] that are going to prime immunity," he said.

Fox said the research also shows that pathologists employing emerging digital imaging technology are going to be a vital part of the cancer care team going forward. "The pathologists are going to be at the heart of oncology in the future," Fox said. "They're the ones who are going to be able to tell us what kinds of combinations to give patients." •

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Advances in Cancer Immunotherapy™:
Regional SITC Meetings Explain the Basics of Immunotherapy

BY LISA MILLER

POWDERLY

In addition to the *SITC Annual Meeting & Associated Programs*, SITC hosts numerous educational events throughout the year across the country. The Advances in Cancer Immunotherapy™ (ACI) regional programs, represent another great way to pick up certification credits while learning more about the fascinating field of cancer immunotherapy.

These smaller, regional meetings offer an opportunity to learn about the field from local experts. Each of the presenters come from local hospitals and cancer centers so that the participants can hear about not only the basics of immunotherapy, but also the latest research in the field from local oncologists who are already incorporating these methods into their own clinical practices.

It's a dedicated day focused on modern immunotherapy, according to John Powderly II, MD, CPI, president of the Carolina BioOncology Institute, one of the members of the planning committee. "These regional immunotherapy meetings are dedicated to immunotherapy as a class and what's relevant to the practicing physician. As we would say in medical school, it's 'high yield' information."

Each ACI program explains the basics of immunotherapy to patient care providers who may be newer to the expanding field of immunotherapy. Starting with a history of immunotherapy, the principles of tumor immunology are broken down in general and then in terms of the treatment of genitourinary cancers, lung cancer, and melanoma, followed by future directions of immunotherapy for the treatment of cancer patients.

Presentations on the treatment of various cancers will focus on the effectiveness of immunotherapy agents, how to select which patients should receive immunotherapeutics, bringing current approved therapies into clinical practice, and current trials and emerging concepts within the field.

Designed for clinical oncologists, registered nurses, and pharmacists, anyone involved in the treatment of patients with cancer will benefit from attending a nearby ACI program. Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer, attendees of the ACI programs can receive A*MA PRA Category I Credits™* and are eligible to gain ACPE and ANCC credits. The meetings are also just the right size to do the best networking, Powderly said.

The final session of the year will take place in Tampa, Florida, on Saturday, December 10, but the program will be expanding in 2017. Powderly noted that nearly 25 meetings are expected for 2017 throughout the United States. For more information on this program and the dates for the Cancer Immunotherapy 101 meetings in 2017, visit **sitcancer.org/sitc-meetings/aci2016**. •

Two Microenvironment-Targeting Approaches Show Early Promise

BY SILAS INMAN

KLINE

A number of intriguing approaches for targeting the tumor microenvironment are being presented during the oral abstract portion of the Tumor Microenvironment session, which begins today at 9:10 AM. Chief among these approaches are those focused on dendritic cells (DCs) and regulatory T cells (T_{regs}).

In the first talk, Abigail Overacre, a graduate student at the University of Pittsburgh, will discuss the potential role of neuropilin-1 (Nrp1)-deficient T_{reg}-derived interferon-gamma (IFN-γ) for driving instability and tumor clearance in melanoma and head and neck cancer.[1] In a second talk, Justin Kline, MD, an assistant professor of hematology and oncology at the University of Chicago, will discuss how CD8α+ DCs regulate leukemia antigen-specific CD8+ T-cell tolerance.[2]

Nrp1-deficient T_{regs}

T_{regs} play an important role in the maintenance of the immune system's equilibrium. However, as cancer develops, T_{regs} suppress antitumor immune responses within the tumor microenvironment. This immune suppression makes T_{regs} a potential therapeutic target of high interest, with multiple strategies in development.

To this end, Overacre and colleagues explored NRP1 as a potential treatment strategy, since the Nrp1 pathway is required for intratumoral T_{reg} stability but does not impact the peripheral immune system.[1] For this study, the researchers injected the murine B16.F10 melanoma cells into mice that were heterozygous for $NRP1^{L/L}Foxp3^{Cre\text{-}YFP/DTR\text{-}GFP}$. Overall, 50% of the T_{regs} in these mice were Nrp1-deficient (Nrp1-/-) and the remainder were wild type.

Whole transcriptome sequencing was conducted to determine potential changes in these experimental mouse models. Once differentially regulated pathways were identified, they were explored with *ex vivo* functional assays and *in vivo* with T_{reg} transfers into Foxp3-deficient mice. The researchers also examined human melanoma and squamous cell carcinoma of the head and neck cells to determine the abundance of *NRP1* and its functionality on human T_{regs}.

The results indicate that not only are intratumoral T_{regs} dependent on Nrp1 for functional stability, but Nrp1 absence on T_{regs} induces changes within the tumor microenvironment that facilitate a greater antitumor immune response. Overacre et al found that mice with intratumoral Nrp1-/- T_{regs} produced IFN-γ, which led to the functional destabilization of neighboring wild-type T_{regs}. The suppressive activity of wild-type Nrp1 T_{regs} was altered with IFN-γ production from Nrp1-/- T_{regs}, facilitating greater antitumor immunity and tumor clearance in this mouse model.

"Overall, we have shown that Nrp1 is required for functional stability of intratumoral T_{regs}, and in its absence, there is an alteration in the tumor microenvironment, leading to an enhanced antitumor immune response," the authors noted in their abstract.

When exploring human head and neck cancer and metastatic melanoma cells, *NRP1* was expressed on some of the tumor infiltrating lymphocyte (TIL) T_{regs}. It was also determined that the IFN-γ pathway was intact in human T_{regs}. Moreover, when these TIL T_{regs} were pretreated with IFN-γ, they showed a reduced suppressive function compared with cells that were not pretreated.

"These studies uncover a novel potential target for cancer immunotherapies that preserves peripheral immune health. This is of clinical interest, given that NRP1 is expressed on select T_{regs} in human melanoma and head and neck cancer and that NRP1+ T_{regs} show a suppressive advantage over NRP1- T_{regs}," the authors noted.

CD8α+ Dendritic Cells

Research has indicated that basic leucine zipper transcription factor ATF-like 3 (Batf3)-lineage CD8α+ and CD103+ DCs are required to initiate CD8+ T cell priming against solid tumors. Although this immune response mechanism has been heavily explored in solid tumors, it remains largely unexamined for hematologic malignancies.

Kline and colleagues sought to explore CD8α+ in hematologic malignancies, by utilizing a syngeneic transplantable and genetically-engineered model for acute myeloid leukemia (AML) that was associated with a dense CD8+ T cell tolerant state.[2] The goal of utilizing this model was to find antigen-presenting cells that were responsible for inducing T-cell tolerance.

For the study, the researchers utilized the transplantable C1498 murine cell line, which is an aggressive, highly-lethal subtype of AML. Additionally, they tested their hypothesis on a genetically engineered AML model: *Mx1-Cre* x $LSL^{AML1\text{-}ETO/+}$ x $FLT3^{ITD/ITD}$ *x R26-LSL*$^{SIY/+}$ (MAFFS). These cell lines were violet-labeled using CellTrace.

Following systemic introduction and proliferation of AML cells, AML cell fluorescence was seen in CD8α+ DCs exclusively in the spleen. CD8α+ DCs exclusively cross-presented leukemia antigens to CD8+ T cells, in *ex vivo* experiments. As might be expected, since the final step of CD8α+ maturation is reliant upon *Batf3*, there were significantly fewer antigen encounters for leukemia-specific CD8+ T cells in *Batf3*-/- mice. These findings suggest that CD8α+ DCs are responsible for mediating the immune recognition of AML antigens.

However, *in vivo* experiments yielded intriguing results, which could be related to the microenvironment of hematologic malignancies, the authors noted. When explored in vivo, it appeared that CD8α+ DCs also played a role in inducing leukemia-specific immune tolerance.

In wild-type mice with an intact *Batf3* and functioning CD8α+ DC, a tolerizing antigen successfully stopped leukemia-specific CD8+ T-cell response. However, in *Batf3*-/- mice, the tolerizing antigen had no effect and the leukemia-specific CD8+ T cells continued to expand. These findings support the role of *Batf3*-dependent DCs in regulating anti-cancer immune responses, the authors noted.

"These results highlight stark differences in the regulation of anti-cancer immunity in hosts with solid versus hematological malignancies," the authors wrote.

In an attempt to exploit this regulatory mechanism for its therapeutic potential, the researchers sought to activate CD8α+ DCs using the TLR3 agonist polyinosinic-polycytidylic acid (poly[I:C]). This approach successfully restored the anti-leukemic T-cell response, which prevented disease progression in the mice.

A further RNA sequencing analysis was conducted to help determine the differences between the CD8α+ DCs that were leukemia-tolerant and those that were not. Overall, the tolerogenic DCs had approximately 200 differentially expressed genes compared with the non-tolerogenic cells. These findings suggested that induction of tolerance could be an active process.

"*Batf3*-lineage DCs generate functional CD8+ T cell responses against solid tumors, but actively and exclusively induce CD8+ T cell tolerance to systemic leukemia, indicating that the same DC lineage can imprint disparate T-cell fates in mice with solid verses hematopoietic malignancies, and suggesting that environmental cues perceived by CD8α+ DCs may dictate their ability to activate or tolerize cancer-specific CD8+ T cells," the authors wrote in their abstract. •

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What to Do in Nearby Arlington

BY ALLIE CASEY

While taking in the latest on advancements in immunotherapy, attendees will be surrounded on all sides by history.

A short trip up the Potomac River, Arlington, VA, hosts many departments and agencies of our federal government, including the Department of Defense, Drug Enforcement Administration, Transportation Security Administration, and the Defense Advanced Research Projects Agency.

Arlington also boasts many scenic escapes from the busy, urban life of the nearby DC area. If you're an outdoorsy person, this city is a dream for you. Nature isn't the only attraction here, though. There are plenty of memorials, museums, shopping, and dining to experience while in Arlington.

Getting around in Arlington is as easy as hopping on one of the Metro lines. There are also several regional public bus systems and a bike-sharing system, Capital Bikeshare.

Arlington National Cemetery's Landmarks

The Arlington National Cemetery serves as a final resting place for more than 400,000 active-duty service members, veterans, and their families. The sense of service and honor resounds over the cemetery's impressive landscape, grounds, and landmarks, including the Tomb of the Unknown Soldier, John F. Kennedy's grave and eternal flame, U.S. Marine Corps War Memorial (also called the Iwo Jima Memorial), the Arlington House, and countless other military memorials. There's also a mobile application, ANC Explorer, to help visitors explore the area.

Located atop a hill in the cemetery is the grave of an unknown soldier from World War I. The tomb is actually a large sarcophagus, adorned with Greek figures representing Peace, Victory, and Valor. Crypts of the unknown soldiers from World War II, Korea, and Vietnam, are also nearby. During the fall and winter, visitors to the Tomb can witness the Changing of the Guard every hour, on the hour.

Jacqueline Kennedy decided that John F. Kennedy should be buried in Arlington instead of his native Massachusetts. She said, "He belongs to the people." Over the head of the grave is the famous eternal flame lit by Mrs. Kennedy during the funeral service. A low memorial wall surrounds the terrace of the gravesite with inscriptions of quotations from JFK's inaugural address. Fifty feet away is the final resting place of Robert F. Kennedy. His gravesite is marked by a white cross, slate headstone, granite plaza, reflecting pool, and a wall inscribed with quotes from his speeches.

Mount Vernon Trail

This trail runs for 18 miles between George Washington's Mount Vernon Estate and Theodore Roosevelt Island. The paved path follows the Potomac River and offers views of the river as well as the monuments and skyline of Washington, DC. Along the way, you'll find George Washington's home at Mount Vernon, Old Town Alexandria, Arlington National Cemetery, and Gravelly Point. This is the perfect location for a walk, run, or bike ride.

West of the Potomac and just off the George Washington Memorial Parkway, Gravelly Point Park is one of the stops along the Mount Vernon Trail. You can fish, start a pick-up sports game, use the Mount Vernon Trail for a bike ride, or enjoy a quintessential fall picnic. The main draw, however, is the nearby Ronald Reagan National Airport. Locals and tourists, alike, rave that watching the aircrafts take off and land is an exhilarating experience.

Theodore Roosevelt Island

Set in the Potomac River, this island is the perfect memorial to our 26th president, known as the "Great Conservationist." There is an architectural memorial to Theodore Roosevelt, with an open plaza and larger than life-size statue. There are miles of trails that wind through amazing ecological diversity: an upland forest, swamp, and tidal marsh. You can even bring your own craft to canoe or kayak through the Potomac, or rent one across the way in Georgetown. If you'd like a more structured visit of the island, you can join in one of the ranger-led activities.

Arlington Arts Center

A non-profit, contemporary visual arts center, the Arlington Arts Center works to support and spread awareness of new artists in the Mid-Atlantic region. The Center holds 9 exhibition galleries, working studios, and educational classrooms. This month, the exhibit is Fall SOLOs, a semi-annual exhibit that brings 14 regional contemporary artists to Arlington.

The Village at Shirlington

Considered Arlington's "Arts and Entertainment District," The Village is an extensive retail, service, and residential complex. There are a variety of restaurants, enabling you to choose from Japanese, Thai, New American, and Mexican food. There's also a place or 2 to grab a drink—whether it's beer or coffee you're looking for. Shirlington is also the home of Arlington's Signature Theater, a non-profit, professional theatre (with a Tony award-winning company!).

Clarendon

Clarendon is a blend of suburban and city life—with small music venues, quality restaurants, and the Market Common Clarendon—there's something for everybody. The commercial area is a mainstay for Northern Virginia because of that blend—local, one-of-a-kind favorites and large chains sit side-by-side. Locals recommend the Liberty Tavern, Whitlow's on Wilson, Galaxy Hut, and Iota.

The Pentagon Tours

The headquarters of the Department of Defense, the Pentagon, is the world's largest, low-rise office building. Tours of the Pentagon highlight the mission of five Armed Services, the Office of the Secretary of Defense, and the Joint Staff. This isn't something to do on a whim, however! Tours of the Pentagon must be requested at least 2 weeks in advance, and are only scheduled Monday through Friday. There are also extensive security checks required—most recommend at least an hour to go through the process. The September 11th Pentagon Memorial can also be explored after your tour. The Memorial hosts 184 Memorial Units for each victim at the Pentagon that day. An audio tour of the Memorial can be accessed by calling (202) 741-1004 at the entrance. •

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- Nominations are open through March 20, 2017.
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- The 2017 *Giants of Cancer Care*® class of inductees will be announced in Chicago on June 1, 2017.

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Herbst on How to Advance Immunotherapy in Lung Cancer

BY LAURA PANJWANI

HERBST

In the age of immunotherapy, it is important that oncologists learn just as much from their patients as they do in the laboratory, said Roy S. Herbst, MD, PhD.

This is especially true in non–small cell lung cancer (NSCLC), where the PD-1 inhibitor pembrolizumab (Keytruda) was just approved as a frontline treatment for those with greater than 50% PD-L1 expression and the first PD-L1 inhibitor, atezolizumab (Tecentriq), was approved in the metastatic setting.

"Immunotherapy in lung cancer still only helps 1 in 4, maybe 1 in 5, patients," said Herbst, ensign professor of medicine (medical oncology), professor of pharmacology, chief of medical oncology, associate director for translational research, Disease Aligned Research Team Leader, Thoracic Oncology Program, Yale Cancer Center. "How are we going to benefit more patients? We need more science, good ideas, and more novel approaches. That is going to require taking science from the lab to the clinic and back to the lab again. That is what we need to stress."

> **PD-L1 is now a required biomarker that one should use to test patients with lung cancer to determine if they should get frontline immunotherapy. But we can't stop there."**
>
> *—Roy S. Herbst, MD, PhD*

Herbst will discuss the evolving field of immunotherapy in lung cancer and beyond in 2 talks, one held today on frontline therapy, predictive markers, and novel combinations, and a second, held Sunday on predictive and companion biomarkers.

In an interview, Herbst highlighted some of the topics he will focus on during his presentation today and Sunday, including the role of the PD-L1 biomarker in the frontline versus the refractory setting in lung cancer, other biomarkers on the horizon, and the impact of the first PD-L1 agent approved in lung cancer. He will also discuss potential novel combinations with atezolizumab and how biomarker analysis will play a role in determining which patients get the single agent versus the combination.

How has the role of the PD-L1 biomarker evolved in lung cancer?

A couple of years ago I was a discussant for the CheckMate-017 and -057 trials at ASCO and I made the case that the PD-L1 biomarker was not necessarily ready for primetime. At that point you would not do PD-L1 testing regularly, even though nivolumab (Opdivo) used the assay to decide who to treat in the refractory setting. However, with time, and as the PD-L1 biomarker has been developed in a better way, it is now important in the frontline setting.

In the refractory setting, with nivolumab approved based on PD-1 status, no one is performing the test because they are going to give the drug anyway. PD-L1 testing is something that is going to be used must more frequently, I think, in the frontline setting, where it is clear that only a subgroup of patients seem to be benefiting over chemotherapy.

We saw recently, with the publication of KEYNOTE-024, that the PD-L1 biomarker can determine which patients with lung cancer should get immunotherapy upfront with pembrolizumab. PD-L1 is now a required biomarker that one should use to test patients with lung cancer to determine if they should get frontline immunotherapy. But we can't stop there. We are still only treating 20% to 30% of patients and we know that other patients may benefit. We need to look for other biomarkers.

What other biomarkers are being investigated at this time?

Mutational burden, RNA expression profiles, immune microenvironment, and the presence or absence of TIL cells—all of that is going to be important [with regard to potential biomarkers].

People are currently looking into gene signatures, but with gene signatures you need to know what the genes are, and that is the million-dollar question. People are also looking at the quantitative measurement of T cells—that research is being done at Yale by some of my colleagues. That is very important.

I think, eventually, we are going to have multiple biomarkers for each patient. I think we are going to have a systems approach where we use PD-L1, gene signatures, mutational status, and maybe we will even identify a specific mutation. I think it will be more of a precision medicine approach.

Recently, the first PD-L1 inhibitor atezolizumab was approved for metastatic NSCLC. What impact will that approval have?

I am very excited about this, especially because we did the phase I work, which was published in *Nature* several years back. Now this agent can be used after patients have had chemotherapy for lung cancer, as many patients will still not be getting immunotherapy frontline. A biomarker is not required; it had activity even in the biomarker-negative group. Perhaps this agent is more active, even in the PD-L1–negative patients. We need to determine if it's because the assays are different or perhaps it's due to PD-L1 priming the immune system better and generating activity against tumor cells. Either way, I think this is a huge advance for patients with this disease.

We now have a PD-L1 inhibitor that we are going to see combined with other agents. I am very excited to use biomarker analysis to help us determine different combinations. This agent is also now in clinical trials in the frontline and other settings for lung cancer, so we will have to await those results, as well.

What potential combinations could be used with atezolizumab?

It could be combined with a CTLA-4 inhibitor, or anything that can effect the T cell either by stimulating it or blocking an inhibition. This could include LAG-3, TIM-3, or OX40, all of the agents we know that can have co-stimulatory effects on T cells. The sky is the limit. What we need now are smart trials based on biology to accelerate the field as quickly as possible. •

TECENTRIQ® [atezolizumab]

Initial U.S. Approval: 2016

This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Urothelial Carcinoma

TECENTRIQ (atezolizumab) 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 *[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 ALK 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

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Related Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer steroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Withhold TECENTRIQ until resolution for Grade 2 pneumonitis. Permanentlydiscontinue TECENTRIQ for 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 six (1.1%) patients. Of these patients, there was one patient with fatal pneumonitis, one patient with Grade 3, three patients with Grade 2, and one patient with Grade 1 pneumonitis. TECENTRIQ was held in all cases and five patients were treated with corticosteroids. Pneumonitis resolved in three patients. The median time to onset was 2.6 months (range: 15 days to 4.2 months). The median duration was 15 days (range: 6 days to 3.1+ months).

NSCLC In 1027 patients with NSCLC who received TECENTRIQ, pneumonitis occurred in 38 (3.7%) patients. Of these patients, there was one patient with fatal pneumonitis, two patients with Grade 4, thirteen patients with Grade 3, eleven patients with Grade 2, and eleven 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 time to onset was 3.3 months (range: 3 days to 18.7 months). The median duration was 1.4 months (range: 0 days to 12.6+ months).

5.2 Immune-Related Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ treatment. Liver test abnormalities occurred in patients who received TECENTRIQ. Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment with TECENTRIQ. Administer corticosteroids at a dose of 1–2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin, followed by corticosteroid taper. Withhold TECENTRIQ for Grade 2 and permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated hepatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*. Across clinical trials (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 (2.5%), and total bilirubin (2.1%). Immune-mediated hepatitis occurred in 1.3% of patients. Of these cases, one patient died from hepatitis, five patients had Grade 3, and one patient had Grade 2 hepatitis. The median time to onset was 1.1 months (range: 0.4 to 7.7 months). TECENTRIQ was temporarily interrupted in four patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.

NSCLC In patients with NSCLC, Grade 3 or 4 elevation occurred in ALT (1.4%), AST (1.3%), and total bilirubin (0.6%). Immune-mediated hepatitis occurred in 0.9% (9/1027) of patients. Of these nine patients, one patient had Grade 4, four patients had Grade 3, three patients had Grade 2, and one patient had Grade 1 immune-mediated hepatitis. The median time to onset was 28 days (range: 15 days to 4.2 months). TECENTRIQ was temporarily interrupted in seven patients; none of these patients developed recurrence of hepatitis after resuming TECENTRIQ.

5.3 Immune-Related Colitis

Immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer 1–2 mg/kg prednisone or equivalent per day. Withhold treatment with TECENTRIQ for Grade 3 diarrhea or colitis. Treat with IV methylprednisolone 1–2 mg/kg per day and convert to oral steroids once the patient has improved. For both Grade 2 and Grade 3 diarrhea or colitis, when symptoms improve to Grade 0 or Grade 1, taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*. Across clinical trials, colitis or diarrhea occurred in 19.7% (389/1978) of all patients.

Urothelial Carcinoma In 523 patients with urothelial carcinoma who received TECENTRIQ, colitis or diarrhea occurred in 98 (18.7%) patients. Ten patients (1.9%) developed Grade 3 or 4 diarrhea. Four patients (0.8%) had immune-mediated colitis or diarrhea with a median time to onset of 1.7 months (range: 1.1 to 3.1 months). Immune-mediated colitis resolved with corticosteroid administration in three of these patients, while the other patient died without resolution of colitis in the setting of diarrhea-associated renal failure.

NSCLC In 1027 patients with NSCLC who received TECENTRIQ, colitis or diarrhea occurred in 198 (19.3%) patients. Twelve patients (1.2%) developed Grade 3 colitis or diarrhea. Five patients (0.5%) had immune-mediated colitis or diarrhea with a median time to onset of 21 days (range: 12 days to 3.4 months). Of these 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 TECENTRIQ. Monitor patients for clinical signs and symptoms of endocrinopathies.

Hypophysitis Hypophysitis occurred in 0.2% (1/523) of patients with urothelial cancer receiving TECENTRIQ. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold TECENTRIQ for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis *[see 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 prior to and periodically during treatment with TECENTRIQ. Asymptomatic patients with abnormal thyroid function tests can receive TECENTRIQ. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate thyroid hormone replacement as needed. Manage isolated hypothyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed. Resume treatment with TECENTRIQ when symptoms of hypothyroidism or hyperthyroidism are controlled and thyroid function is improving *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Across clinical trials, 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 occurred in 2.5% (13/523). One patient had Grade 3 and twelve patients had Grade 1–2 hypothyroidism. The median time to first onset was 5.4 months (range: 21 days to 11.3 months). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 16% (21/131) of patients with a follow-up measurement. Hyperthyroidism occurred in 0.6% (3/523) of patients with urothelial carcinoma. Of the three urothelial carcinoma patients, one patient had Grade 2 and two patients had Grade 1 hyperthyroidism. The median time to onset was 3.2 months (range: 1.4 to 5.8 months). TSH was decreased and below the patient's baseline in 3.8% (5/131) of patients with a follow-up measurement.

NSCLC In 1027 patients with NSCLC who received TECENTRIQ, hypothyroidism occurred in 4.2% (43/1027). Three patients had Grade 3 and forty patients had Grade 1–2 hypothyroidism. The median time to onset was 4.8 months (range 15 days to 31 months.) TSH was elevated and above the patient's baseline in 17% (54/315) of patients with follow-up measurement. Hyperthyroidism occurred in 1.1% (11/1027) of patients with NSCLC. Eight patients had Grade 2 and three patients had Grade 1 hyperthyroidism. The median time to onset was 4.9 months (range: 21 days to 31 months). TSH was decreased and below the patient's baseline in 7.6% (24/315) of patients with a follow-up measurement.

Adrenal Insufficiency Adrenal insufficiency occurred in 0.4% (7/1978) of patients across clinical trials, including two patients with Grade 3, four patients with Grade 2, and one patient with Grade 1. Adrenal insufficiency resolved in two patients. For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer methylprednisolone 1–2 mg/kg per day IV followed by oral prednisone 1–2 mg/kg per day or equivalent once symptoms improve. Start steroid taper when symptoms improve to ≤ Grade 1 and taper steroids over ≥ 1 month. Resume treatment with TECENTRIQ if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient is stable on replacement therapy, if required *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Diabetes Mellitus New onset diabetes with ketoacidosis has occurred in patients receiving TECENTRIQ. Diabetes mellitus without an alternative etiology occurred in one (0.2%) patient with urothelial carcinoma and three (0.3%) patients with NSCLC. Initiate treatment with insulin for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250–500 mg/dL), withhold TECENTRIQ. Resume treatment with TECENTRIQ when metabolic control is achieved on insulin replacement therapy *[see Dosage and 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 pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤ 1.0% of patients treated with TECENTRIQ.

Meningitis / Encephalitis Monitor patients for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis. Treat with IV 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 improve to ≤ Grade 1, taper steroids over ≥ 1 month *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Motor and Sensory Neuropathy Monitor patients for symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIQ for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Institute medical intervention as appropriate. Consider initiation of systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Pancreatitis Symptomatic pancreatitis without an alternative etiology occurred in 0.1% (2/1978) of patients across clinical trials. Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ for ≥ 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 ≤ Grade 1 within 12 weeks or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Permanently discontinue TECENTRIQ for Grade 4 or any grade of recurrent pancreatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.6 Infection

Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal 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 ≥ Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*. Across clinical trials, infections occurred in 38.4% (759/1978) of patients.

Urothelial 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. Urinary 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 those treated with docetaxel (34%). Grade 3 or 4 infections occurred in 9.2% of patients treated with TECENTRIQ compared with 2.2% in patients treated with docetaxel. Two patients (1.4%) treated with TECENTRIQ and three patients (2.2%) treated with docetaxel died due to infection. Pneumonia 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 infusion reactions have occurred in patients in clinical trials of TECENTRIQ. Infusion-related reactions occurred in 1.3% (25/1978) of patients across clinical trials, 1.7% (9/523) of patients with urothelial carcinoma, and 1.6% (16/1027) of patients with NSCLC. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 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 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 Hepatitis *[see Warnings and Precautions (5.2)]*
- Immune-Related Colitis *[see Warnings and Precautions (5.3)]*
- Immune-Related Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Other Immune-Related Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Infection *[see Warnings and Precautions (5.6)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received 1200 mg of TECENTRIQ intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (range: 0.1, 46 weeks). The most common adverse reactions (≥ 20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common Grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (0.9%) who were treated with TECENTRIQ experienced either sepsis, pneumonitis, or intestinal obstruction which led to death. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of the 310 patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state. Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients while Table 2 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of Study 1.

Table 1: All Grade Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in Study 1

	TECENTRIQ 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 Administration		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
Infections and Infestations		
Urinary tract infection	22	9
Metabolism and Nutrition Disorders		
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 Mediastinal Disorders		
Dyspnea	16	4
Cough	14	0.3
Skin and Subcutaneous Tissue Disorders		
Rash	15	0.3
Pruritus	13	0.3

Table 2: Grade 3–4 Laboratory Abnormalities in Patients with Urothelial Carcinoma in Study 1 in ≥ 1% of Patients

Laboratory Test	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

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=135) administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 3.7 months (range: 0–19 months) in TECENTRIQ-treated patients and 2.1 months (range: 0–17 months) in docetaxel-treated patients. The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (46%), 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, ALT increase, dysphagia, and arthralgia. Nine patients (6.3%) who were treated with TECENTRIQ experienced either pulmonary embolism (2), pneumonia (2), pneumothorax, ulcer 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 interruption 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, anemia, and fatigue. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (> 2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism. Table 3 summarizes adverse reactions that occurred in at least 10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm. Table 4 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm.

Table 3: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 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 Administration 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 ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥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 (54.1%) 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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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-L1/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 on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 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 stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

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 least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

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.

Infertility

Females Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

8.5 Geriatric Use

Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. Of the 142 patients with NSCLC treated with TECENTRIQ in Study 3, 39% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

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)]*.

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)]*.

10 OVERDOSAGE

There is no information on overdose with TECENTRIQ.

17 PATIENT 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 TECENTRIQ, including: Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*. Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*. Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.3)]*. Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.4)]* Meningoencephalitis, myasthenic syndrome/myasthenia gravis, and Guillain-Barré syndrome: Advise patients to contact their healthcare provider immediately for signs or symptoms of meningitis, myasthenic syndrome/myasthenia gravis, or Guillain-Barré syndrome *[see Warnings and Precautions (5.5)]*. Ocular Inflammatory Toxicity: Advise patients to contact their healthcare provider immediately for signs or symptoms of ocular inflammatory toxicity *[see Warnings and Precautions (5.5)]*. Pancreatitis: Advise patients to contact their healthcare provider immediately for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*. Infection: Advise patients to contact their healthcare provider immediately for signs or symptoms of infection *[see Warnings and Precautions (5.6)]*. Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*. Rash: Advise patients to contact their healthcare provider immediately for signs or symptoms of rash *[see Dosage and Administration (2.2)]*.

Embryo-Fetal Toxicity Advise female patients that TECENTRIQ can cause fetal harm. Instruct females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Genentech
A Member of the Roche Group

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
Initial U.S. Approval: *May 2016*
Code Revision Date: *October 2016*

TECENTRIQ®

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.

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**

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
- **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 ≥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 ≥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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TECENTRIQ®
atezolizumab INJECTION FOR INTRAVENOUS USE 1200 mg