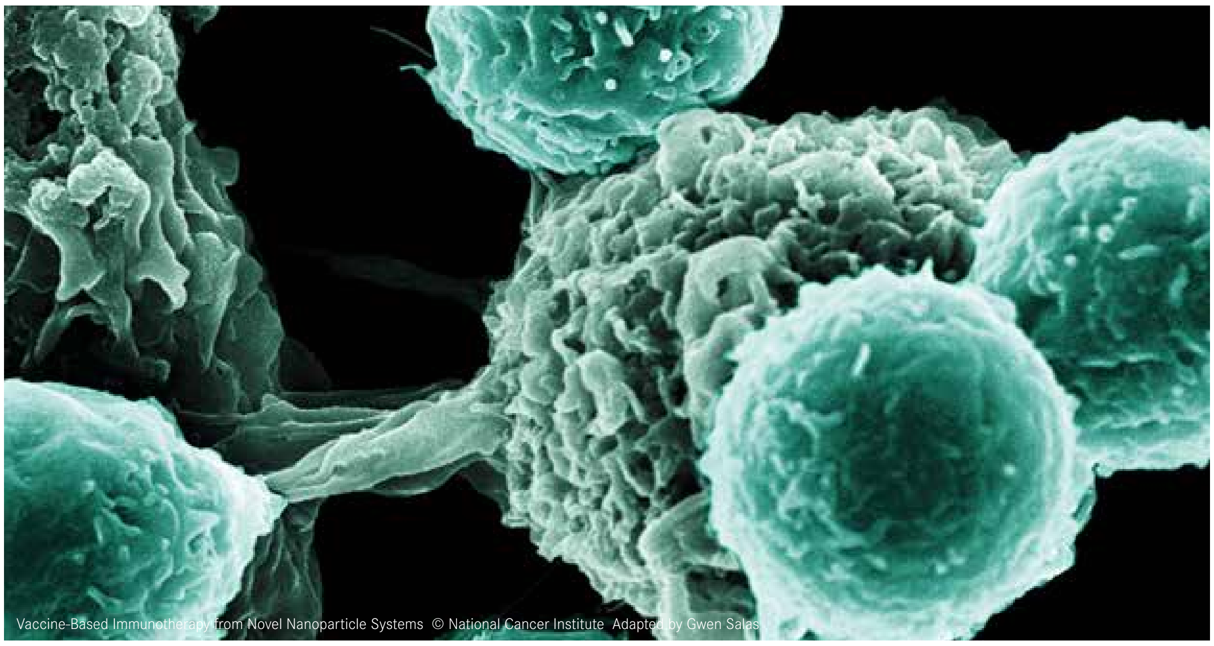
presented by Targeted Oncology

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

31st Annual Meeting & ASSOCIATED PROGRAMS DAILY

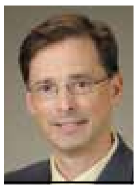
DAY 1
THURSDAY
NOVEMBER 10, 2016


Vaccine-Based Immunotherapy from Novel Nanoparticle Systems © National Cancer Institute Adapted by Gwen Salas

Embracing Immunology Across All Stakeholders

BY LISA MILLER


BUTTERFIELD


GULLEY

In its 31st year, the *Society for Immunotherapy of Cancer's (SITC) Annual Meeting & Associated Programs* has more in store for attendees than ever before. Over 5 days, the entire conference will enlighten all parties involved in the research and treatment of patients with cancer on novel agents and approaches within immunotherapy, divisive topics, and the fundamentals of immunology.

"The greatest benefit [of the Annual Meeting and Associated Programs] is the opportunity to interact across all of the stakeholders interested in cancer immunotherapy," said Lisa H. Butterfield, PhD. Butterfield, a professor of medicine, surgery, and immunology, as well as the director of the University of Pittsburgh Cancer Institute's Immunologic Monitoring and Cellular Products Laboratory, is the vice president of SITC.

SITC has provided a number of new sessions this year to accommodate each stakeholder within the research of and treatment with immunotherapeutics.

"This conference was designed to have not just the hardcore science," said James L. Gulley, MD, PhD, FACP. Sessions for pharmacists, research nurses, patient care, and more, are all included. Gulley is chief of the Genitourinary Malignancies Branch, head of the Immunotherapy department, and director, Medical Oncology Service, CCR Office of the Clinical Director for the National Cancer Institute.

EMBRACING IMMUNOLOGY CONTINUED ON PAGE 4

Expanding Immunotherapy's Reach

BY HOWARD L. KAUFMAN, MD, FACS

Welcome to the *Society for Immunotherapy of Cancer's (SITC) 31st Annual Meeting & Associated Programs*. Whether you are a first-time attendee, or a long-time supporter, there will be sessions to meet your educational needs. At its core, SITC has always been inclusive, bringing stakeholders from industry, academia, research, clinical care, policy, and government together. This year, we're including even more stakeholders with expansion into the nursing and pharmacist communities and allied healthcare professionals.


KAUFMAN

What will attendees gain from the annual meeting?

As you know, SITC's Annual Meeting is one of the few meetings that is dedicated to tumor immunology and cancer immunotherapy with a focus on the cancer patient. What the meeting will provide to attendees is both a comprehensive overview of developments in the field in a relatively condensed format, as well as access to the leaders who are involved in the basic science research and running the clinical trials.

What can first-time and long-time attendees expect from the conference?

The conference has been held for 31 years, and we have a number of tips to help novice and first-time attendees navigate the various sessions. Before the meeting starts, we have a "Primer on Tumor Immunology and Cancer Immunotherapy™" on November 10. The Primer is a half-day intensive course in which attendees can catch up on the latest terminology, hear the newest therapeutic concepts, and meet key leaders in the field. The course can help facilitate a better experience for the rest of the meeting, and I think this will prove a very positive and helpful experience for a first-time attendee or someone who doesn't have an advanced knowledge of immunology.

EXPANDING IMMUNOTHERAPY CONTINUED ON PAGE 5

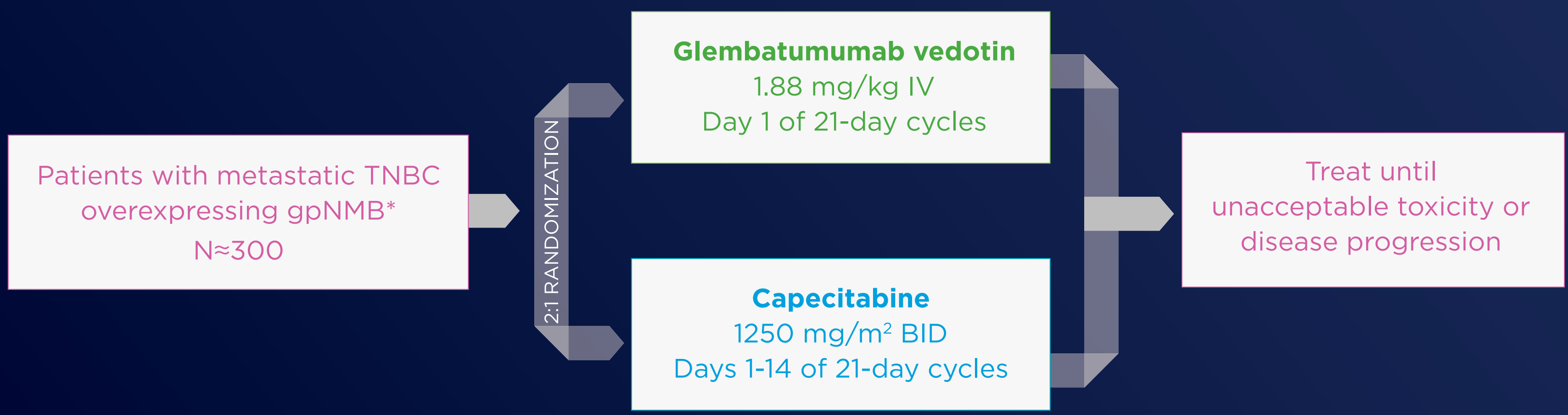
NOW ENROLLING IN

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.

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DAY 1 THURSDAY NOVEMBER 10, 2016

Today's Agenda

Thursday at a Glance

Primer on Tumor Immunology and Cancer Immunotherapy™

SESSION I

8:10–10:10AM
Basic Immunology

2 AMA PRA CATEGORY 1 CREDITS™

SESSION II

10:25–12:30PM
Treating Tumors with Passive Immunotherapy

2 AMA PRA CATEGORY 1 CREDITS™

SESSION III

1:30–3:00PM
Active Immunotherapy–Unleashing the Patient's Own Immune System

1.5 AMA PRA CATEGORY 1 CREDITS™

SESSION IV

3:15–5:00PM
Figuring out How it All Works and Future Directions

1.75 AMA PRA CATEGORY 1 CREDITS™

Workshop on Challenges, Insights, and Future Directions for Mouse and Humanized Models in Cancer Immunology and Immunotherapy

SESSION I

8:05–9:45AM
Introduction to Models of Immunotherapy

1.75 AMA PRA CATEGORY 1 CREDITS™

SESSION II

10:15–11:55PM
Modeling the Tumor Microenvironment

1.75 AMA PRA CATEGORY 1 CREDITS™

SESSION III

12:45–2:45PM
Modeling Evaluation of Immune Therapies

1.5 AMA PRA CATEGORY 1 CREDITS™

SESSION IV

3:15–4:45PM
Panel Discussion and Future Directions

5:30–6:30PM
Presidential Reception & State of SITC: *Membership Business Meeting*

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.

Embracing Immunology Across All Stakeholders

BY LISA MILLER

BUTTERFIELD

GULLEY

WOOD

CONTINUED FROM COVER

A new nurse/pharmacist track has been added to this year's annual meeting. Nurses and pharmacists can benefit from 2 sessions on Saturday, one on "Clinical Management" and a "Tumor Immunology 101" primer. Both of these sessions are CNE- and CPE-certified and will explain the principles attendees need to know in order to give immunotherapy agents and manage patients who are taking them.

"As a nurse, having the opportunity to attend SITC, to see what is going on and the science behind it, will help me better understand and complete the requirements that are asked of us to coordinate clinical trials. The more I understand the background of a drug or drug class, the more I can understand how to be aware of potential side effects, or how to better educate patients and their loved ones," said Laura S. Wood, RN, MSN, OCN, renal cancer research coordinator at the Cleveland Clinic Taussig Cancer Institute.

Wood, one of the organizers of the meeting, who will chair several of the sessions, said that immunotherapy is a big part of the future of cancer treatment and is grateful to SITC for welcoming nurses and pharmacists to participate.

Other new sessions during the Annual Meeting will integrate new collaborations. The "Metabolic and Age-Associated Dysregulation of Anti-Cancer Immunity" session taking place Friday evening is a product of a new collaboration with the American Society for Cell Biology. The "Diet, Exercise, Stress and the Impact on the Immune System" session has been organized in collaboration with the Society of Behavioral Medicine and will be taking place on Saturday evening.

"As a basic scientist, I'm particularly interested in our new collaborations," said Butterfield, who will be ushered in as the next president of the society—the society's first female president—during the Annual Meeting. "While I'm always interested in updates in the field—combinations, emerging technologies, adoptive transfer—to hear the most recent advancements, I'm personally most excited about bringing these new topics into discussion."

> **"The greatest benefit [of the Annual Meeting and Associated Programs] is the opportunity to interact across all of the stakeholders."**
>
> *—Lisa H. Butterfield, PhD*

During the Annual Meeting, taking place Friday through Sunday, attendees can hear keynote lectures from Suzanne L. Topalian, MD, and Ira Mellman, PhD, as well as late-breaking abstract sessions on the most recent advancements in the field. Friday morning will also include a brief update on exciting clinical trials with immunotherapy agents from the Cancer Immunotherapy Trials Network.

Attendees of a session during the SITC 30th Annual Meeting.

Taking place on the last day of the Annual Meeting, this year's Value of Cancer Immunotherapy Summit was created in collaboration with the American Society of Clinical Oncology. The summit will once again address a "hot topic" in the field: the value of cancer immunotherapy.

Gulley, one of the organizers of the SITC Annual Meeting and co-chair for the "State-of-the-Art Immunotherapies: Challenges and Opportunities" session on Friday, remarked that this will be a fun session to attend. After several days of exchanging information between stakeholders in the field, attendees will have a chance to be a part of discussion on a highly debated topic.

"We're opening up discussion around not just the price of these therapies, but also the value of these therapies. How much should we be paying for a cure? What is that really worth, and how do we measure that? These are all really big questions."

SITC will address matters of the cost of immunotherapy agents, the impact on insurance coverage, access to the agents, and the impact on patients among academic physicians, patient advocates, regulatory agencies, third-party payers, and more. This is such a critical issue being discussed at all levels, Butterfield said, and it is remarkable that SITC is identifying these issues and bringing all of the stakeholders together to discuss the next steps.

Before the Annual Meeting officially begins on Friday, there are a number of additional programs offered by SITC. Yesterday's program, the "New Cancer Immunotherapy Agents in Development" session explored a number of clinical and pre-clinical agents currently being developed for the treatment of cancer. Each agent selected for review in the session was given a brief overview in a concise presentation to whet the appetite for agents that may soon come into trials and, potentially, clinical practice.

Butterfield said that, by attending the New Agents session, everyone will have received a sneak peek into what will hit the clinic next via presentations of investigator-initiated translational research and basic research that will build the next generation of therapies.

Attendees to the session can connect with the presenters one-on-one to gain more information over the next few days. This, according to Gulley, is one of the great benefits of the meeting, the ability to communicate with other stakeholders that many may not normally interact with. "This is an incredible platform for the dissemination of information and for networking opportunities between people that are passionate about cancer immunotherapy."

Opportunities for networking are provided throughout the conference, including the Presidential Reception on Thursday night, during breaks and poster presentations, and on Saturday evening when The CheckPoints play. On Friday evening, scientists early on in their career can come together to connect with the next generation of immunologists, or they can attend a Meet-the-Expert session to interact with current leaders in the field.

Taking place concurrently today are a number of primer sessions and workshop sessions. The "Primer on Tumor Immunology and Cancer Immunotherapy™" will review the principles that are crucial to the discussion and study of immunology. The presenters will address the fundamentals of immunology as well as recent breakthroughs and advancements that are building upon our understanding of cancer immunotherapy.

The "Workshop on Challenges, Insights, and Future Directions for Mouse and Humanized Models in Cancer Immunology and Immunotherapy" will be taking place at the same time, and will dive into the approach to various pre-clinical models for immunotherapy. Presenters will speak to each model currently available in the research field and how these models mimic the tumor microenvironment to discover potential responses to new immunotherapy agents. New approaches within pre-clinical models will also be explored.

The meeting is once again being held close to our nation's capital at a momentous time for the country, as well as for the field of immunotherapy. The proximity to Washington, DC, Butterfield explained, allows for optimal interaction with FDA regulators and the National Cancer Institute (NCI), which play a large role in the approval of and access to immunotherapeutics. A "Government Agencies" session will also be provided on Friday in order to hear directly from members of the FDA and NCI.

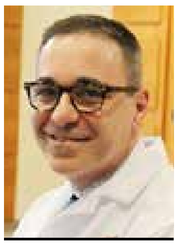
SITC's 31st Annual Meeting & Associated Programs truly will provide learning opportunities for everyone attending, whether they be immuno-oncologists, community oncologists, basic scientists, clinicians, translational researchers, industry members, regulators, nurses, pharmacists, patients, or patient advocates.

"I think the SITC meeting is all about bringing cutting-edge research and cutting-edge therapy strategies to the front stage, so that those of us that aren't deep in it can gain a better understanding of it. Ultimately, [immunotherapy is] going to involve all of us, and having the opportunity to participate and listen to some very elite individuals is a phenomenal opportunity," said Wood. •

Expanding Immunotherapy's Reach

BY HOWARD L. KAUFMAN, MD, FACS

CONTINUED FROM **COVER**



KAUFMAN

For the attendees who have participated in previous meetings, they will be impressed by the increased size and assembled content of this year's conference. There will be more data presented with a record breaking abstract submission of nearly 500 abstracts. It is also a unique meeting in that it is one of the few places where experts in all fields come together. The meeting will facilitate and encourage active networking.

How will the meeting expand the reach of SITC?

One of the other things that is unique this year is that our Board of Directors has approved 2 new categories for nurses and other allied healthcare providers. For the first time, we have a nurse committee and nurses are getting engaged in the society. They have been very helpful in terms of providing guidance on how to take care of the side effects of immunotherapy. And we have an increasing number of patients and patient advocates attending the meeting. We have been deepening our relationships with patient advocacy groups and welcome their input.

Another important topic that will be presented for the first time is SITC's national policy agenda. We have been working very closely with Vice President Biden's office on the Cancer Moonshot initiative. We have developed some firm policy road maps for the next several years.

SITC is a partnership organization and we take great pride in working with reputable organizations whose missions complement and align with that of ours. SITC is pleased to offer 2 Annual Meeting sessions that have been collaboratively developed with the American Society for Cell Biology and the Society of Behavioral Medicine. In addition, SITC has forged a fantastic partnership with the American Society of Clinical Oncology (ASCO). On Sunday, ASCO will join us as we continue to explore the value question related to cancer immunotherapy. Through these and other collaborative relationships, SITC is able to expand the reach and impact of cancer immunotherapy across many platforms.

Which sessions will you be looking forward to attending?

Personally, I'm looking forward to the Richard V. Smalley, MD, Memorial Lectureship Award. The Smalley Award serves as recognition of excellence in the field of therapeutic research with biological agents and is accompanied by an honorarium of $5000.

This year, Suzanne L. Topalian, MD, will be receiving the Smalley Award and presenting the Smalley Keynote Address. Topalian is one of the board members of SITC and has been pivotal to the implementation of PD-1 agents into clinical practice. Her lecture will provide an overview of where the whole field is, so there should be a lot of broad interest in her talk.

SITC will continue the value discussion at its summit on Sunday, November 13. A few important questions will address how we can afford the different immunotherapies and what value do they bring to the cancer patient that is distinct from other forms of cancer therapy.

Those are big picture questions that have not yet been answered. To begin chipping away at an answer, we have gathered experts from industry, academia, patient advocacy groups, and payers to try to understand how to develop a value framework for immuno-oncology drugs.

How far have we come in our understanding of, and the use of, immunotherapy in clinical practice?

There is no question that we are expanding the role of immunotherapy, and I think there are 2 big developments in the field. First, there are many more cancer types that seem amenable to immunotherapy, and this has been best confirmed by the increasing number of regulatory approvals that we're seeing. We have seen approvals of immunotherapy agents in bladder cancer, Hodgkin lymphoma, and head and neck cancer, and we widely anticipate [immunotherapy agents for] Merkel cell carcinoma to be approved shortly. These approvals firmly establish immunotherapy's role in the treatment of all cancers. That's more evident this year than last year.

Second, combination immunotherapy is a modality undergoing investigation. We now understand that it is possible to improve therapeutic responses by combining more than one drug with another. The objective is to understand what the optimal combinations are.

How is SITC contributing to the understanding of immunotherapy and the development of agents?

SITC is unique because I don't know of too many professional societies that, from its inception, included all of the key stakeholders. I think the philosophy of the society early on was that if we were ever going to make this a reality for patients we would have to include industry, basic scientists, regulatory experts, and biostatisticians. The society has always been inclusive from the start because we knew this was going to take a lot of work and effort.

It is also a unique meeting in that it is one of the few places where all these different experts come together. It's really getting all the experts talking so that we can accelerate the pace of development in the field. •

Howard L. Kaufman, MD, FACS
Chief Surgical Officer and
Associate Director of Clinical Science
Rutgers Cancer Institute of New Jersey

Introduction to the Society for Immunotherapy of Cancer

The Society for Immunotherapy of Cancer (SITC) is the world's leading member-driven organization dedicated to professionals working in the field of cancer immunotherapy. A 501(c)(3) non-profit organization, SITC was established in 1984 to advance the science, development, and application of tumor immunology and cancer immunotherapy. SITC aims to make cancer immunotherapy a standard of care and the word "cure" a reality.

We know it is critical to engage the oncology community in a broad-based campaign to support research and foster interest in immunotherapy as a viable—and preferred—treatment modality. That is why SITC has dedicated itself to:

- Creating society-driven resources and tools for professionals in the cancer immunotherapy field
- Providing increased opportunities for students and young investigators to draw more talented and innovative professionals to the medical profession
- Developing educational activities to reach community practitioners
- Providing additional funding sources for cancer immunotherapy-focused research
- Expanding networking opportunities for scientific interaction, career development, and information exchange
- Forming collaborative relationships with other membership-based associations, non-profit organizations, United States and global cancer immunotherapy research institutions, and patient advocacy groups

> **"We know it is critical to engage the oncology community...to support research and foster interest in immunotherapy as a viable...treatment modality."**

Member-Led Programs and Projects

The following represents a more in-depth introduction to how we translate the society's mission of improving cancer patient outcomes into actionable initiatives:

Critical Hurdles

Over a decade ago, SITC identified the interval between discoveries made in preclinical models and testing in patients with cancer as an opportunity for improvement. To approach this, SITC convened an Immunotherapy Summit including representatives from related organizations around the world (now the "World Immunotherapy Counsel"). These leaders identified the critical hurdles impeding timely clinical translation of promising advances in basic immunology, including the science-based limitations of animal models and lack of definitive biomarkers, along with other hurdles focused on aspects of governmental regulations and funding, such as the prolonged time to obtain approval to initiate clinical trials and limited funds available to translate science into patient care. In order to address these critical hurdles that are still relevant today, SITC initiated international working groups that continue to make recommendations to overcome these barriers to the field.

Cancer Immunotherapy Guidelines

The Cancer Immunotherapy Guidelines (CIG) were developed to provide guidance regarding the appropriate use of immunotherapy in various disease settings. Led by expert task forces, the aim of the CIG is to address knowledge gaps and provide evidence-based recommendations for each disease specialty. These guidelines focus on promoting enhanced clinical decision-making in terms of patient selection, toxicity management, clinical endpoints, and the sequencing or combination of therapies. SITC published the first consensus statement on the appropriate use of cancer immunotherapy for cutaneous melanoma in 2013. This initiative has now been expanded to include an update to the melanoma guidelines as well as consensus statements focused on genitourinary malignancies, hematologic malignancies, and lung cancer.

Immune Biomarkers Task Force

SITC remains active in investigating both predictive and prognostic biomarkers of response in cancer immunotherapy. In previous years, SITC has focused efforts in several dedicated workshops and has developed a series of recommendations, as well as resources, for researchers in the field. The SITC Immune Biomarkers Task Force was then reconvened in 2014 due to advances in cancer immunotherapy, including positive results from clinical trials, new technologies to monitor the immune response, and emerging candidate biomarkers from early phase trials. The resulting recommendations of this task force were presented at a meeting held in collaboration with the National Cancer Institute at the National Institutes of Health and will be made available via open access publication in the *Journal for ImmunoTherapy of Cancer* (*JITC*).

Immunoscore

Recent evidence has demonstrated that increased numbers of lymphocytic infiltrates both within the tumor as well as at the invasive margin correlate with survival. Termed the "Immunoscore," an international consortium led by SITC utilized digital pathology to quantify the immune presence within the tumor microenvironment of patients with colon cancer (stages I-III) in routine clinical settings. Although currently undergoing validation, previous studies have illustrated the proof of concept, as the time to recurrence was significantly longer in patients with a high Immunoscore. The results of this global validation may result in the implementation of Immunoscore as a novel component to help classify cancer and identify patients who are more likely to respond to immune-targeted therapies.

Adjuvant Settings

An upcoming topic of interest to SITC is the importance of cancer immunotherapy in an adjuvant setting. The recent approval of ipilimumab (anti–CTLA-4; Yervoy) as an adjuvant treatment for patients with stage III melanoma who have undergone complete resection and total lymphadenectomy has served to illustrate the potential of immunotherapeutics in extending recurrence-free survival. The groundwork laid by adjuvant ipilimumab is also significant in that it utilizes immunotherapy in earlier stages of disease, which could herald a number of exciting new treatment options for patients with cancer.

Conclusion

During this historic time in cancer immunotherapy, when scientific advancements are increasingly yielding tenable therapeutic options and the ideal of making the word "cure" a reality in our lifetime has become a unifying goal for researchers, physicians, and politicians alike, SITC continues to be an invaluable resource and community on the forefront of the field. •

ECHO 301

Epacadostat Clinical Development in Hematology and Oncology

NOW ENROLLING

NCT02752074

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

EPACADOSTAT:
an investigational, selective oral inhibitor of indoleamine-2,3-dioxygenase 1 (IDO1)

PHASE 3 STUDY
of Epacadostat and Pembrolizumab (ECHO-301/Keynote-252)

ENROLLING
~600 patients with unresectable or metastatic melanoma

STRATIFICATION
by PD-L1 expression status, *BRAF* mutation status

RANDOMIZATION:
Epacadostat + Pembrolizumab versus Placebo + Pembrolizumab

DUAL PRIMARY END POINTS
of progression-free survival and overall survival

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

---

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

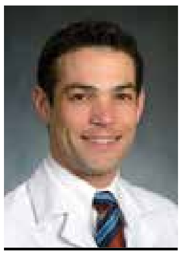
Visit ECHO301ClinicalTrial.com to learn more about the trial.

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

Macrophage CAR Therapies Show Early Signals of Activity Against Solid Tumors

BY ANITA T. SHAFFER



GILL

Although chimeric antigen receptor (CAR) T-cell therapies have been building a record of efficacy in advanced hematologic malignancies, the approach has not proved to be as successful in solid tumors, partly because of poor penetration of T cells into the tumor, prompting researchers to look for novel immunotherapy approaches.

To address this need, researchers at the University of Pennsylvania (UPenn) are currently developing cellular immunotherapy for solid tumors using genetically engineered CAR macrophages (CARMA), which have shown signs of antitumor activity during *in vivo* studies of an ovarian cancer mouse xenograft model.[1]

CARMA technology uses macrophages to penetrate solid tumors and clear cancer cells and other pathogenic accumulations via phagocytosis.[1] In the past, researchers believed that macrophages were tumoricidal, but it has been recently discovered that macrophages found in or around tumors are actually cancer promoting.[2] Using a patented technique, genetically engineered macrophages are no longer subject to tumor induced immunosuppression, but instead selectively track down and engulf cancer cells.[1]

CARMAs would promote antigen-specific, antitumor phagocytosis and the killing of cancer cells, potentially providing a novel immunotherapeutic platform for diverse solid tumors, according to an original research abstract from the laboratory of Saar I. Gill, MD, PhD, an assistant professor of Medicine at UPenn's Perelman School of Medicine. Lead author Michael Klichinsky, PharmD, will present the findings.[3]

> **"B-cell malignancies are particularly amenable to targeting using CAR T-cell therapy, due to the presence of the CD19 antigen..."**
>
> —*Saar I. Gill, MD, PhD*

"Our approach is to use the macrophages that we get from the blood and genetically engineer them to express a CAR—which means now we tell them what to eat—to set them loose on the tumor to destroy the malignant cells," Gill said in advance of the presentation.

Gill noted that some investigators are seeking to enhance the function of macrophages by attempting to block inhibitory ("don't eat me") signals of the cell-surface CD47 protein (overproduced on cancer cells) and its binding partner, signal regulatory protein alpha (SIRPα). At least 2 humanized anti-CD47 monoclonal antibodies and a fusion protein incorporating CD47 binding domains are in development.

By contrast, Gill and colleagues used a viral vector to express an anti-HER2 CAR that redirects the macrophages to perform a tumor-specific, cell-killing function. "Our work is more about increasing a positive signal rather than eliminating a negative signal," Gill said.

In the ovarian cancer xenograft model, mice that received CARMA demonstrated a decrease in tumor burden of 2 orders of magnitude and a statistically significant 30-day survival benefit compared with mice that had not received treatment ($P = .018$), investigators said in the abstract.

Investigators have not detected any toxicities as a result of the treatment, although next steps will include designing models to look at adverse effects, said Gill. He said researchers are several years away from proposing in-human studies.

Thus far, the development of CAR therapies designed with T cells has been most successful in patients with CD19-expressing B-cell malignancies.[1]

"B-cell malignancies are particularly amenable to targeting using CAR T-cell therapy, due to the presence of the CD19 antigen on all B-cell malignancies from the most immature B-ALL [B-cell acute lymphoid leukemia] to the most mature lymphomas and the fact that patients can tolerate prolonged periods of B-cell aplasia," Gill and colleagues wrote in a recent review.[4]

In one of the larger studies, the complete response (CR) rate reached 90% among 30 patients with relapsed/refractory ALL who were treated with anti-CD19 T-cell therapy at UPenn. In addition to ALL, CAR T-cell therapies have generated responses in non-Hodgkin lymphoma and chronic lymphocytic leukemia.[4]

In recent findings, KTE-C19, an anti-CD19 CAR T-cell therapy, demonstrated a 79% objective response rate, including 52% CR among 62 patients with chemorefractory lymphomas in the ZUMA-1 study.[5] In the ROCKET study, a similarly constructed agent, JCAR015, resulted in CR rates of 77% and 90%, respectively, among patients with morphologic-disease (n = 30) or minimal-disease (n = 20) ALL.[6]

Although such results have raised hopes for new therapeutic options for patients with refractory B-cell malignancies, progress has been slower in solid tumors. CAR-modified T cells have been associated with greater "on-target, off-tumor toxicity" than a naked antibody would generate. In 1 case report, an anti-HER2 CAR based on trastuzumab (Herceptin) resulted in fatal pulmonary toxicity in a patient with colon cancer.[4]

"Clearly, CAR T cells have not been successful in solid tumors," said Gill. "One issue involves the trafficking and penetration into the tumor. T cells are not particularly abundant within the majority of tumors. They seem to be excluded and somehow prevented from migrating into the tumor. It would stand to reason that, if the T cells are not able to get in, then they cannot locate their target and they're not able to exert their effector functions, so they will not work."

Other potential reasons include the impact of what Gill described as a "metabolic milieu" that makes the tumor microenvironment "unfavorable to T-cell entry and T-cell activity."

As a result, Gill and colleagues believe an approach that utilizes CARMA therapy may be able to leverage the benefits of the emerging CAR technologies while surmounting the difficulties in attacking solid tumors. •

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A Taste of What's Currently in Development

BY ANDREW SMITH

IBRAHIM

CHEN

The dramatic success of previous immunotherapy trials has spurred an exponential increase in new research. Investigators around the world are working on thousands of different projects.

Which are the most logical, most interesting, and most promising of those projects? A panel of experts considered more than 60 possibilities when putting together the "New Cancer Immunotherapy Agents in Development" session.

"What we're offering is essentially a speed-dating event for some of the novel combinations that we find most exciting. Presentations will only run 5 minutes, so audience members can get a taste of what's out there in this first session of the conference," said session co-chair Ramy Ibrahim, MD, vice president for Clinical Development at the Parker Institute for Cancer Immunotherapy in San Francisco.

Ibrahim and his co-chairs concentrated on what they believe to be the most exciting area of immunotherapy research: novel combinations. They were particularly keen on those that combined different immunotherapies with each other.

"Is it possible that some new agent will come along and prove itself powerful enough to cure all sorts of tumor types as monotherapy? Certainly. It seems a lot more likely, though, at least in the foreseeable future, that the key to maximizing the benefit from new medications will lie in combining those medications effectively with each other and with older medications," said another of the panel's co-chairs, Daniel S. Chen, MD, PhD, vice president and global head of Cancer Immunotherapy Product Development at Genentech and Roche.

The session will be divided evenly between presentations that discuss the results of very early clinical trials and those that discuss the results of pre-clinical investigations. Many of the experimental combinations employ the relatively small number of immunotherapies that have already been approved by the FDA, but many others use experimental immunotherapies, either in combination with those that are already approved or with other agents.

"Together, the presentations should illustrate how much diversity there is in immunotherapy research. Researchers are using different approaches to augment the immune response against cancer," Ibrahim said. "However, amid all the diversity, there is a unifying principle: synergy. We tried to steer clear of combinations that merely add immunotherapy to some existing regimen. We focused instead on combinations designed with the potential that each agent will strengthen the others and create a whole that's better than the sum of its parts."

Anti-Semaphorin4D VX15/2503 in Combination with Ipilimumab or Antibody to PD-1 or PD-L1

ELIZABETH EVANS, PHD, VACCINEX, INC.

The protein Semaphorin 4D (SEMA4D) is highly expressed at the growing invasive margins of tumors, where it restricts the infiltration and migration of anti-tumor immune cells, such as antigen presenting cells and T lymphocytes, into the tumor microenvironment, indicating its role in promoting tumor growth. Investigators evaluated anti-SEMA4D anti bodies alone and in combination with antibodies against immune checkpoints in pre-clinical and phase I trials, which found that anti-SEMA4D antibodies were well-tolerated in patients with advanced refractory solid tumors. In pre-clinical trials, antibody blockade of SEMA4D activity facilitated increase in the antitumor immune response through recruitment of activated antigen presenting cells and T lymphocytes, as well as a shift in proinflammatory cytokines within the tumor microenvironment. Results were even better when investigators added the second immunotherapy. The combination of anti-SEMA4D with anti–CTLA-4 (ipilimumab) acted synergistically, with a maximal increase in survival (P <0.01) and complete tumor regression in 100% of mice compared with 22% of mice treated with monotherapy (P <0.01). Phase Ib/IIa trials are planned to investigate the combination of anti-SEMA4D and immune checkpoint inhibitor therapies.

IMO-2125, an Investigational Intratumoral Toll-Like Receptor 9 Agonist, Modulates the Tumor Microenvironment to Enhance Antitumor Immunity

MARK CORNFELD, MD, MPH, IDERA PHARMACEUTICALS

Engagement of the Toll-like receptor 9 (TLR9) stimulates mature antigen presenting cells, namely dendritic cells, and improves T cell priming for antitumor immunity. Investigators reasoned that in patients with metastatic melanoma resistant to PD-1 blockade therapy, intratumoral injections of the combination treatment with an experimental TLR9 agonist, IMO-2125, given in conjunction with the immune checkpoint inhibitor, ipilimumab, therapy will induce tumor-specific effector T cells for generating an antitumor response and overcoming tumor immune-escape. According to the latest abstract, only 11 patients have been enrolled in the phase I trial, which has yet to observe any dose-limiting toxicities associated with the IMO-2125 injections. The only immune-related adverse event (AE) observed was grade 3 hypophysitis in 2 patients. Of the 5 patients enrolled long enough for a very early evaluation, 2 experienced partial remission, 2 experienced stable disease (SD), and 1 experienced progressive disease (PD). A phase II expansion will use IMO-2125 in combination with ipilimumab and an anti–PD-1 treatment. Updated data on safety, antitumor activity, and biomarkers will be presented during the session.

Cobimetinib in Combination With Atezolizumab

EDWARD CHA, GENENTECH

Dysfunctional regulation of the mitogen-activated protein kinase (MAPK) signaling network is associated with cancer cell survival and proliferation. In *BRAF*-mutated melanoma and *KRAS/BRAF*-mutated colorectal cancer, gain-of-function mutations to these oncogenes contributes to the over activity of downstream mitogen-activated protein kinase enzyme (MEK) within the signaling cascade leading to the transcription of genes mediating cancer cell survival. The MEK inhibitor cobimetinib (Cotellic), which is already approved against melanoma, was tested in conjunction with the PD-L1 inhibitor atezolizumab (Tecentriq) in a phase Ib trial on 23 patients with microsatellite stable colorectal cancer. Although study patients had received an average of 5 prior treatment regimens, investigators reported this summer that 4 of the patients achieved partial responses (PRs) and 5 more showed SD. It is the first study to show a response to either PD-1/PD-L1 blockade or an MEK inhibitor in patients with microsatellite stable colorectal cancer, which is far more common than the microsatellite instability-high colorectal cancer that responded to such immunotherapy in previous studies. The 4 patients who achieved PRs all saw their tumors shrink by at least 30%. Responses lasted for more than a year in some patients and were still going on when researchers first reported the data.

Combination Strategy for Varlilumab, an Agonist Anti-CD27 Monoclonal Antibody

THOMAS DAVIS, MD, CELLDEX

Varlilumab is a human monoclonal antibody targeted to the CD27 receptor expressed on lymphocytes, and is highly expressed on T and B lymphoma tumor types. Varlilumab binds and activates CD27 as the potent co-stimulatory signal for activation and proliferation of T cells when combined with T-cell receptor stimulation to enhance immune response and anti-tumor activity. Atezolizumab is a mAb which binds PD-L1 on tumor-infiltrating immune cells and tumor cells, inhibiting the PD-L1/PD-1 mediated escape of tumors from immune surveillance. The use of this immunotherapy combination in preclinical tumor models resulted in significant increases in survival (compared to atezolizumab alone) in a CT-26 colon model, an E.G7 thymoma model, and a BCL1 disseminated lymphoma model. The strength of those findings led, last December, to the initiation of a phase I/II study of varlilumab in combination with atezolizumab in patients with renal cell carcinoma. Results have already been reported on the phase I portion of a phase I/II study of varlilumab and nivolumab. Among the 36 patients in that part of the study, the combination showed acceptable tolerability and safety at all dosing levels and no evidence of an autoimmune reaction. Biomarker data from all varlilumab dose levels indicated increases in inflammatory chemokines and decreases in circulating T regulatory cells. Seven patients achieved stable or better disease during the trial. “Varlilumab is an attractive candidate for combination immunotherapy across a variety of cancers due to its target’s restricted expression and strong activity in a variety of tumor models,” Davis said.

Safety of the Natural Killer Cell-Targeted Anti-KIR Antibody, Lirilumab, in Combination with Nivolumab or Ipilimumab in 2 Phase I Studies in Advanced Refractory Solid Tumors

F. STEPHEN HODI, MD, DANA-FARBER CANCER INSTITUTE

Lirilumab is a checkpoint inhibitor designed to activate natural killer (NK) cells (and potentially some types of T cells) by blocking interaction between killer-cell immunoglobulin-like receptors (KIRs) and their ligands. Results from the phase I trial that combined lirilumab and nivolumab reported treatment-related AEs in 114 of 159 participating patients and grade 3/4 events in 24 of them. Results from the phase I trial that used lirilumab in combination with ipilimumab in patients with various solid tumors reported treatment-related AEs in 15 of the 22 patients who participated and grade 3/4 events in 2 of them. Although the rate of AEs (and serious AEs) was lower with the ipilimumab combination—indeed, it was about the same as that of ipilimumab monotherapy—Bristol-Myers Squibb has announced that it will stop investigating that combination while it continues investigating the nivolumab combination. This may be because of unreported data about antitumor activity from the 2 combinations. Bristol-Myers plans to report data on the lirilumab and nivolumab combination in a separate release.

A CD122-Biased Agonist Increases CD8+ T Cells and Natural Killer Cells in the Tumor Microenvironment; Making Cold Tumors Hot With NKTR-214

ADI DIAB, MD, THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

NKTR-214 binds and activates the CD122 cell surface receptor expressed on tumor-infiltrating lymphocytes. The breakdown of PEGylated NKTR-214 causes the release of active IL-2 conjugates to antagonize CD122. This provides sustained activation of the IL-2 pathway through controlled release of active CD122-biased (IL-2Rβγ) cytokines. Preclinical studies have found that NKTR-214, used alone or as combination immunotherapy with other checkpoint inhibitors, significantly suppressed tumor growth through increased proliferation and migration of effector CD8+ T cells and NK cells within the tumor microenvironment. The abstract showed very early results from a phase I trial. As of August, 18 patients with locally advanced or metastatic solid tumors were enrolled, 12 of whom have renal cell cancer. Among the 12 patients who had been participating long enough for evaluation, 7 patients had SD at their 6-week or 8-week scan. Only 1 patient had experienced dose-limiting toxicity from NKTR-214 (grade 3 syncope and hypotension). Tumor biopsies were conducted in 9 patients, and 6 of those patients’ tumors revealed an up to 10-fold increase from baseline in CD8+ T cells and NK cells in the tumor microenvironment. Most of the infiltrating CD8+ T cells were newly proliferative and cell-surface PD-1 expression was increased up to 2-fold. Analyses of blood samples showed concordant increases in Ki67+ immune cells, PD-1+ CD8+ T cells, and NK cells 8 days after a single dose of NKTR-214. Updated data will be presented during the session.

Activated Natural Killer Cell Therapy

PATRICK SOON-SHIONG, MD, FRCS, FACS, NANTBIOSCIENCE

A pair of experimental immunotherapies from Altor BioScience are undergoing a wide range of early-stage clinical trials—as both monotherapy and combination therapy—against metastatic melanoma, metastatic urothelial cancer, and other tumor types. ALT-801 is a fusion protein consisting of interleukin-2 (IL-2), and a single-chain T-cell receptor domain. Preclinical trials have shown that this combined molecule stimulates more immune response against both solid and hematological malignancies than IL-2. ALT-803 is a novel mutant of IL-15 that is both more stable than the normal strain and better at triggering the proliferation and activation of NK cells and CD8+ memory T cells. It is currently undergoing 7 phase I trials and 1 phase II trial in patients with a wide variety of cancers, as well as patients with HIV. A recently announced collaboration between Altor and NantKwest will likely see both of those treatments paired with NantKwest’s NK cell therapy.

CD3-EGFR Probody T Cell-Engaging Bispecific Induces Tumor Regressions and Substantially Increases Safety Window in Preclinical Studies

BRYAN A. IRVING, PHD, CYTOMX THERAPEUTICS

Many immunotherapies make the body attack tumors by binding to antigens that are abundantly expressed on tumors and preventing those antigens from blocking immune system attacks. Unfortunately, those same therapies can bind to those same antigens on healthy cells and lead the body to attack them, as well. CytomX Therapeutics hopes to change that with technology that can render immunotherapies (mostly) inactive, except when they’re in the presence of a tumor. Research in mice has shown that a “Probody” version of a PD-1 immunotherapy works about as well as the standard version but produces fewer side effects. Indeed, a CTLA-4/PD-1 antibody combination induced diabetes in 50% of non-obese young mice but the substitution of the Probody PD-1 formulation in another mouse cohort eliminated the incidence of diabetes. CytomX believes that its technology for making Probody versions of individual compounds will work on a wide range of immunotherapies with different targets and different biological pathways.

PRS-343, a CD137 (4-1BB)/HER2 Bispecific

SHANE A. OLWILL, PHD, PIERIS PHARMACEUTICALS, INC.

CD137 is a costimulatory immunoreceptor expressed on T cells, dendritic cells, and NK cells. Many studies have shown the ability of CD137-activating compounds to spur strong immune responses against tumors. Unfortunately, such compounds have also spurred » immune responses against healthy cells. PRS-343 was designed as a protein with CD137-targeting fused to a variant of a trastuzumab (Herceptin) HER2-targeting monoclonal antibody with an IgG4 protein backbone. *Ex vivo* experiments have previously shown that the compound can activate T cells in the presence of HER2+ cells. More recently, studies have shown that it can do the same in a humanized murine model. PRS-343 activity was investigated at 4 different weekly doses, ranging from 4µg to 200µg. Investigators found that PRS-343 dose dependently led to strong tumor growth inhibition compared with treatment with the isotype control. Tumor response was accompanied by a significantly higher frequency of hCD45(+) tumor infiltrating lymphocytes due to proliferation of CD3+ and CD8+ T cells.

pLADD: Personalized, Live, Attenuated Double-Deleted Listeria Monocytogenes

THOMAS W. DUBENSKY JR., PHD, ADURO BIOTECH

Today's immunotherapies target standard proteins that exist in both tumors and healthy cells, but what if it were possible to develop customized immunotherapies that were designed to attack the mutations in each patient's cancer? Such treatments, in theory, should lead the immune system to attack tumors without attacking healthy cells, as well. They're already being tested. Aduro used tumor-specific neoepitopes from murine MC38 tumor cells to formulate a personalized live, attenuated double-deleted Listeria monocytogene (pLADD). Administration of pLADD-MC38 in mice induced cellular immune responses against encoded neoepitopes but not against native sequences. Moreover, investigators found a synergistic antitumor efficacy with pLADD-MC38 and anti–PD-1. The FDA has given its approval for a phase I study and Dubensky will discuss its progress to date.

CA170: A Small Molecule Orally Available Checkpoint Inhibitor

DAVID TUCK, MD, CURIS

Checkpoint inhibitors have achieved impressive results in the battle against many tumors, but all currently available options have major drawbacks. They work in a relatively low percentage of patients because they target only a single pathway. Their long half-lives can trigger immune-related adverse events. They're all complex intravenously administered proteins that are difficult (and expensive) to manufacture. CA170 is an attempt to solve all of those problems at once: it's an oral small molecule with a short half-life that inhibits the PD-1/PD-L1/2 and VISTA/PD-1H immune checkpoint pathways. Tested in cell cultures, it shows as much immune activity as antibody treatments. In immune competent mice, moreover, orally administered CA-170 has been found to inhibit the growth of syngeneic tumors, enhance peripheral T-cell activation, and promote the immune activation of tumor infiltrating CD8+ T cells in a dose-dependent manner. The compound also shows no signs of toxicity in safety trials.

LAG-3Ig (IMP321) in Combination With Anti-PD-1 Therapy

FREDERIC TRIEBEL, MD, PHD, PRIMA BIOMED

Lymphocyte Activation Gene-3 (LAG-3 or CD223) is a cell surface protein that regulates signaling between antigen presenting cells and T cells in the immune response. In some conditions, it activates antigen presenting cells and increases the activity of CD8+ T cells, leading to enhanced immune response. However, LAG-3 can also act as a co-inhibitory receptor on the surface of activated T cells following antigen recognition and T-cell receptor stimulation, leading to a decrease in cytokine production and immune response. The experimental treatment IMP321 is a soluble dimer of LAG-3 that has been shown to induce immune responses in cancer patients through potent activation of antigen presenting cells. Investigators hope the treatment, which stimulates antigen presenting cells, will prove particularly effective when used with chemotherapy, which induces dying cancer cells to give off antigens. The compound has undergone several early trials to date and shown itself to be well tolerated. Prima Biomed says that repeated daily injections "have been able to demonstrate the induction of a sustained (eg, lasting over several months) APC activation and memory CD8 T-cell response in patients."

Agent A—PD-1 DNR-41BB: Converting Tumor-Mediated PD-L1 Inhibition Into CAR T-Cell Co-stimulation

PRASAD S. ADUSUMILLI, MD, FACS, FCCP, MEMORIAL SLOAN KETTERING CANCER CENTER

Following an immune attack, solid tumors upregulate co-inhibitory ligands that bind to inhibitory receptors on T cells. This adaptive resistance compromises the efficacy of chimeric antigen receptor (CAR) T-cell therapies, which redirect T cells to solid tumors. Investigators used an orthotopic mouse model of pleural mesothelioma to investigate various strategies for overcoming the inhibition of CAR T cells. They found that high doses of both CD28- and 4-1BB–based second-generation CAR T cells achieved tumor eradication. At lower doses, 4-1BB CAR T cells retained their cytotoxic and cytokine secretion functions longer than CD28 CAR T cells. The prolonged function of 4-1BB CAR T cells correlated with improved survival. Furthermore, PD-1/PD-L1 pathway interference restored the effector function of CD28 CAR T cells. These findings suggest that PD-1/PD-L1 blockade may be an effective strategy for improving the potency of CAR T-cell therapies.

The Immunoreceptor TIGIT Regulates Antitumor Immunity

JANE GROGAN, PHD, GENENTECH

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a dominant co-inhibitory receptor on tumor specific T cells and NK cells, and is co-expressed with other checkpoint immune receptors such as PD-1. TIGIT and CD226 on these tumor-specific T cells compete for binding to the PVR ligand on tumor cells. Upon binding to PVR, TIGIT receptor activation induces inhibitory signaling, which limits proliferation, effector cytokine production, and the killing of target tumor cells. Investigators used antibody blockade of TIGIT, CD226, and PD-L1 in syngeneic murine models of colorectal cancer and observed co-blockade of TIGIT and PD-L1 enhanced CD8+ T-cell effector function that produced significant tumor clearance. Specific ablation of TIGIT on CD8+ T cells resulted in tumor clearance, and was dependent on PVR in the host tissue. Models indicate that inhibition of TIGIT with a blocking monoclonal antibody may release CD226 to activate tumor-specific T cells. As TIGIT was found to be expressed on Treg cells, CD8+ T cells, and NK cells, another mechanism could involve regulation of T cell suppression by TIGIT on Tregs. Phase I clinical trials are underway.

The session will end with a 25-minute question-and-answer period, designed to give audience members a chance to dive deeper into whichever combinations interest them most. "We wanted to give people a quick taste of a lot of things in the first session so that they'd have several days to learn more about what they found most interesting," Ibrahim said. "Many of the presenters will stick around after the presentation, so they'll be around to talk during breaks."

"We hope the presentations will give the audience a sense of how many experimental immunotherapies are out there, how many pathways they operate on, and how investigators are choosing what treatments to use in combination with them," Chen said. •

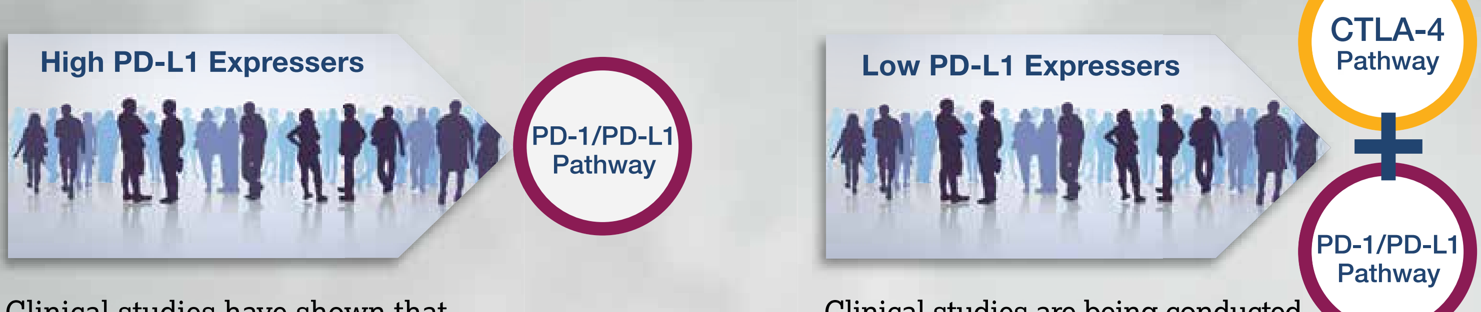
Does PD-L1 expression matter?

Not all patients have the same likelihood of responding to PD-1/PD-L1 pathway inhibition[1,2]

PD-L1 expression status may help identify patients most likely to:

1. Respond to PD-1/PD-L1 pathway inhibition *alone*[2,3]
2. Respond to PD-1/PD-L1 pathway inhibition *plus* inhibition of another immuno-oncology (IO) pathway[3-5]

PD-L1 expression is being studied as a way to identify patients who may be eligible for alternate approaches to targeting different pathways[3-9]



Clinical studies have shown that high PD-L1–expressing patients have demonstrated a higher likelihood of response through blockade of the PD-1/PD-L1 pathway[6-8]

Clinical studies are being conducted in bladder, SCCHN, and NSCLC to explore the role of PD-L1 expression in identifying patients who might respond to inhibition of the PD-1/PD-L1 pathway and the CTLA-4 pathway[5,10-12]

PD-L1 expression testing may be useful to help identify patients for which IO monotherapy or combination therapies, such as PD-L1 and CTLA-4 pathway inhibitors, may be an option[1,3]

- Inhibition of the PD-L1 pathway via monotherapy has demonstrated improvement in multiple tumor types in high PD-L1–expressing patients[6,8,12-16]
- Combination therapy targeting nonredundant pathways provides potential for synergistic effects[5,17,18]

The immunotherapy landscape is rapidly evolving; and PD-L1 expression status may become an important factor in clinical decisions[1,3]

- New therapies, indications, and data expected in the near future may change the treatment paradigm[1,17]
- PD-L1 is expressed on a variety of cancer cell types, including bladder, SCCHN, NSCLC, and melanoma[2,19,20]
- Knowing a patient's PD-L1 expression status may help determine future IO treatment options[3,5]

What science can do: AstraZeneca is leading IO combination research to explore customized treatment for your patients

- Numerous clinical trials in multiple tumor types, such as bladder cancer, SCCHN, and NSCLC, are under way evaluating PD-L1 inhibition as monotherapy and in combination with other IO pathways, targeted agents, and chemotherapy[17,21-23]

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

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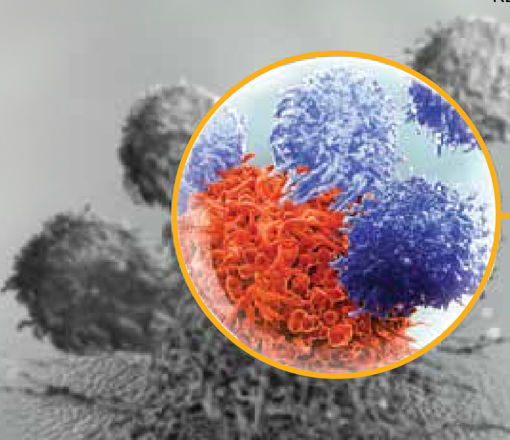
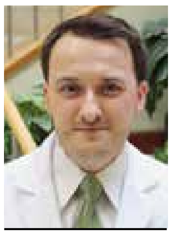


AstraZeneca

Workshop Examines Models for Preclinical Research

BY GINA COLUMBUS



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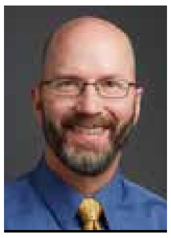

BOSENBERG

Immunotherapy researchers have long recognized the need to improve preclinical models for the innovative therapies they are testing. After convening an international summit of prominent immunologists, the Society for Immunotherapy of Cancer (SITC) in 2011 identified 9 "critical hurdles" impeding the development of anticancer strategies that leverage the immune system.[1]

At the top of the list was the limitations of animal models in use at that time, particularly in assessing the toxicity of monoclonal antibodies.[1] The possibility of setting standards for investigators using preclinical models was among the suggested improvements.

The topic of animal models will be very much in focus today when *SITC's 31st Annual Meeting & Associated Programs* features an in-depth discussion on preclinical models currently in use with a forward-looking assessment on future challenges.

Twelve presentations are scheduled for today's daylong "Workshop on Challenges, Insights, and Future Directions for Mouse and Humanized Models in Cancer Immunology and Immunotherapy."

Session I will examine the utility and impact of 3 types of preclinical models currently in use and in development: mouse–mouse models, humanized mouse models, and patient-derived xenograft (PDX) models.

Session II will focus more specifically on the tumor microenvironment and creating models to help predict the potential impact of novel therapies. In Session III, leading investigators will discuss strategies for modeling immune therapies, particularly agents that target checkpoints.

The day will conclude with a panel discussion among the presenting experts about future directions in creating and applying preclinical models in immunotherapy research.

The workshop offers a unique opportunity for attendees to obtain a broad understanding of preclinical models and listen to experts discuss the strengths and weaknesses of the options, according to Andrew Zloza, MD, PhD, section chief of Surgical Oncology Research at Rutgers Cancer Institute of New Jersey. He will provide introductions to Thursday's workshop sessions, and describe the latest advancements in PDX models in one of the presentations.

Attendees will also be educated on emerging theories and strategies. "This is a way of getting experts in the field who are using these mice to come together and tell us what insights they have gained," Zloza said. "What is the correlation between what they see in these models and what they see in patients?"

Zloza said the content and format of the workshop is unusual. "I don't think there has ever been a workshop like this, where experts have openly discussed the strengths and weaknesses of these models," he said (**Sidebar**).

He noted the diversity of models currently utilized throughout the immunotherapy field. "The question is, why are we using all of these? What does each of these tell us? Can we educate ourselves to other models that might be useful, to address the different strengths and weaknesses of this work?" he said.

"You're not going to find everything you want in any single model," Zloza added. "They are all going to have their strengths and weaknesses. The question is, can we learn how best to apply each one?"

Evolution of Preclinical Models

Although the first observations that the patient's immune system could be activated to promote antitumor effects were described in the late 1890s, progress in the field was not made until the development of inbred mice that could be used in experiments on tumors derived from mice with the same genetic background.[2]

Mouse cell lines have been developed for various cancer types from mice of different genetic backgrounds.[2] C57BL/6 mice have been used to generate cell lines for melanoma, colon cancer, prostate cancer, and lymohoma.[2] BALB/c mice have been used in breast and colon cancer cell lines.[2]

"Much of our development of immune therapies was based on mouse models initially," said Marcus W. Bosenberg, MD, PhD, an associate

Discussions continue long after the sessions are over. Photo from SITC's 30th Annual Meeting.

sitc
Society for Immunotherapy of Cancer

SITC Business Meeting

At ***5:30 PM on Thursday, November 10***, join your fellow colleagues and meeting attendees for the State of SITC: Membership Business Meeting, featuring updates on the current activities of the society, year in review and exciting initiatives moving forward. Immediately following, join other Annual Meeting attendees at the Presidential Reception, the official kickoff event of *SITC's 31st Annual Meeting*. This event, taking place in the Cherry Blossom Ballroom, is free of charge and open to anyone registered for the Annual Meeting, Workshop or Primer.

professor of Dermatology and Pathology at Yale School of Medicine, who will discuss these models during the workshop.

"The strengths of those phenotypes were what pushed the development of antibodies that can be used in humans for the purpose of treating patients," said Bosenberg, citing as examples the PD-1 and CTLA-4 inhibitors that have made such an impact in multiple tumor types. "Without the mouse phenotypes, it is hard to know if it ever would have happened."

The major criticism of mouse–mouse models is their lack of human material, noted Bosenberg. "The challenge is to find a preclinical model that predicts therapies that will work in people," he said.

Bosenberg and colleagues have developed the Yale University Mouse Melanoma (YUMM) lines with driver mutations relevant to human cancers. Recently, they used *BRAF* V600E-driven YUMM lines to study how PD-1 blockade therapy modulates the tumor-host interactions. The experiments demonstrated that CD4 and CD8 T cells along with costimulation mediated by dendritic cells and macrophages are necessary to generate a response to anti–PD-1 therapy.[3]

Similarly, the development of humanized, immunodeficient mouse models that permit the engraftment of human tumors was another significant advance in preclinical models for immunotherapy.[4] However, the ability to reproduce the functions of human immune cell types, such as monocytes, macrophages, and natural killer cells, remains lacking.[4]

At the Jackson Laboratory in Connecticut, researchers are seeking to build next-generation mice that will model the complete human monocyte and macrophage compartment.[4] A. Karolina Palucka, MD, PhD, a professor at the Jackson laboratory who is leading those efforts, will deliver the presentation on humanized mouse models at the workshop.

PDX models, in which patient tumor tissue is transplanted into mice, represent another step in developing more informative preclinical models. The tumor genetics and pathologic characteristics are maintained in PDX models, resulting in a more realistic model for evaluating therapies.[5]

At Rutgers, Zloza is working on personalized cancer care models including double-humanized PDX mice. In his presentation, Zloza will discuss PDX models in terms of their value in predicting how aggressively a tumor will grow and in evaluating their effectiveness in determining patient selection for therapies.

Many Moving Parts

The presentations in Session II of the workshop will delve into modeling the complex factors that create and influence the tumor microenvironment. Incorporating these elements into preclinical models is vital to the future development of immunotherapies, said Zloza.

"In trying to figure out how these immunotherapies work, we need to have the tumor microenvironment in these models be similar to what we see in patients," he said.

Bosenberg said there is broad agreement in the field on the need for improving the predictive value of preclinical models. He noted that many immunotherapies are currently in clinical trials after having "minimal input" from preclinical models. "There was basic biology, but it wasn't tested to see if a combination worked better or not," Bosenberg said.

In Session III of the workshop, speakers will discuss methodologies that can be used for evaluating checkpoint inhibitors and for developing new agents in preclinical models and in humans. One presentation will focus on IDO inhibitors in glioblastoma.

Zloza said melanoma is probably the most widely studied cancer type in terms of immunotherapy, but that the workshop would cast a wider net into other tumor types to consider where lessons learned in one malignancy can be applied more broadly.

Bosenberg, who will give the closing remarks for the workshop, said attendees will also learn about additional tools in the modeling process, such as testing biomarkers to predict response and improving methods of imaging and pathology.

Although pharmaceutical companies are expressing an immense amount of interest in developing next-generation immunotherapies through preclinical models, Bosenberg said the jury is still out on which approach will end up being the most informative.

Bosenberg said it would be desirable to develop mouse models that enable a 1:1 correlation between drugs tested in the model and their efficacy in humans. "I doubt it will ever really occur," he said. "But if we don't understand what we are doing, we are always going to have issues about predicting what the next step is." •

SIDEBAR. Advantages and Disadvantages of Preclinical Models

***Andrew Zloza, MD, PhD,** describes the strengths and weaknesses of the 3 major categories of preclinical animal models used in immunotherapy research.*

Mouse–Mouse Models

Strengths: "In that model, a cancer naturally occurred. We are able to harness that cancer now and learn from it. We put it into a fully competent mouse and, in terms of immunology and immunotherapy, that mouse is able to respond fully and immunologically to the cancer."

Weaknesses: "It's a mouse; it's just not human. While some reports say we are 97.5% genetically similar, it is still a mouse tumor, so it's not exactly what we're facing. We are not able to use the same drugs, most of the time, as we are using for humans. We can use similar drugs that target the same molecule or signaling pathway, but it's not the same drugs."

Humanized Mice

Strengths: "The strength here is we are now dealing with human cancer."

Weaknesses: "The mouse doesn't have an immune system. While we can learn a lot about the cancer itself, how it affects different things, and how it grows, we don't have an immune system response."

Patient-derived Xenografts

Strengths: "Now, we can look at human-immune interaction with human cancer."

Weaknesses: "These mice aren't fully immune-reconstituted; not every cell type of the immune system is reconstructed in this mouse. That's where a lot of the new technology and research is going. How do we make these immune-comprised models as immune-reconstituted as possible? Do we see the same things in patients as we see in these models?" •

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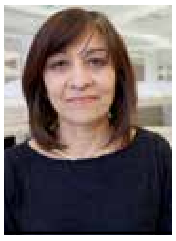
Presenters Break Down Tumor Immunology in Primer Sessions

BY ANDREW J. ROTH

CALLAHAN



BHARDWAJ

Twelve physicians and researchers will take the stage today to cover the gamut of immunology and immunotherapy—everything from how the immune system functions normally, to how it functions when a tumor is in the body, and how it can be engineered to fight cancer.

"The purpose of the primer is to really convey the fundamentals of immunology and immunotherapy to our target audience that we expect might not have a deep background [in these areas]," said Margaret K. Callahan, MD, PhD, who is introducing the day's sessions. Callahan is a medical oncologist at Memorial Sloan Kettering Cancer Center.

Innate and Adaptive Immunity

The first talk of the day will review the innate immune system, which includes antigen presenting cells, macrophages, monocytes, and neutrophils. The talk will be given by Miriam Merad, MD, PhD, a professor of oncological sciences and medicine, hematology and medical oncology, at the Icahn School of Medicine at Mount Sinai.

It's clear that immunotherapy is here to stay, according to Jonathan D. Powell, MD, PhD, who will deliver the second talk of the day on adaptive immunity.

Although most of the information may be a review for some, "...the idea is to review it in a way that everyone is up to speed, in terms of our latest knowledge, and therefore, it will engender a better understanding of how these novel agents work," said Powell, who is the associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy, and a professor of oncology at Johns Hopkins Medicine.

Powell says his talk should be attended by anyone working to develop immunotherapies—whether they're therapies that involve T-cell activation or deactivation, vaccines, or checkpoint inhibitors. It's that last group, checkpoint inhibitors, that he says is still underrated.

"The success of checkpoint blockade cannot be emphasized enough," Powell said, because it tells oncologists that the tools to destroy any tumor may already be in a patient's body in the form of their immune system.

> **"When we talk about an immune response, we usually first talk about what we do to activate an immune response."**
>
> *—Margaret K. Callahan, MD, PhD*

Networking in the exhibition hall. Photo from SITC's 30th Annual Meeting.

Obstacles to Driving an Immune Response

The immune system has 'intrinsic yin and yang' components that prevent it from getting out of control and destroying normal cells, according to Callahan. Nicholas Arpaia, PhD, a postdoctoral research fellow at Memorial Sloan Kettering Cancer Center, will address this 'yin and yang' dynamic in his talk.

"When we talk about an immune response, we usually first talk about what we do to activate an immune response," Callahan said. Regulatory T cells and myeloid-derived suppressor cells are both examples of elements that may subdue an immune response, Callahan noted.

Though this session has obvious applicability to checkpoint inhibitors, Callahan said, it's not the only one that will cover this class of agents.

Adoptive T-Cell Therapy

In the next session, Saar I. Gill, MD, PhD, will discuss adoptive T-cell therapies, one of the most talked about immunotherapies in hematologic malignancies (page 8). Gill is an assistant professor of medicine at the Hospital of the University of Pennsylvania, which is one of the leading cancer centers in the United States working to develop chimeric antigen receptor (CAR) T-cell therapies. This method is focused on infusing patients with genetically modified T cells primed to recognize tumor-associated antigens. "You transplant engineered T cells into the patient and the patient adopts those new cells. As opposed to, for example, checkpoint blockade, where you might be generating T cells in the patient by delivering these drugs," Callahan said.

Antitumor Antibody/Bispecifics

As the T-cell session will review how *cells* are transferred into patients, Callahan said, the next presentation on antitumor antibodies and bispecifics will review how *antibodies* are transferred into patients. This talk, delivered by Charles G. Drake, MD, PhD, will answer questions pertaining to what antibodies are, how they are used today as anticancer therapies, and the novel ways in which they are engineered. Drake is the director of genitourinary oncology and an associate director for clinical research at the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center.

Bispecifics, Callahan said, is a particularly interesting and novel approach in which a monoclonal antibody is artificially created from fragments of 2 different antigen-recognizing elements so that it can bind to 2 different types of antigens.

Cytokines: Interferons, Interleukins and Beyond

There is a long history—predating checkpoint blockade—of how cytokines can be used to modulate the immune system as a therapy for cancer. The most obvious and important example, Callahan said, is interleukin-2, which is approved to treat patients with melanoma and those with renal cell carcinoma.

CONTINUED ON PAGE 18

Now Enrolling

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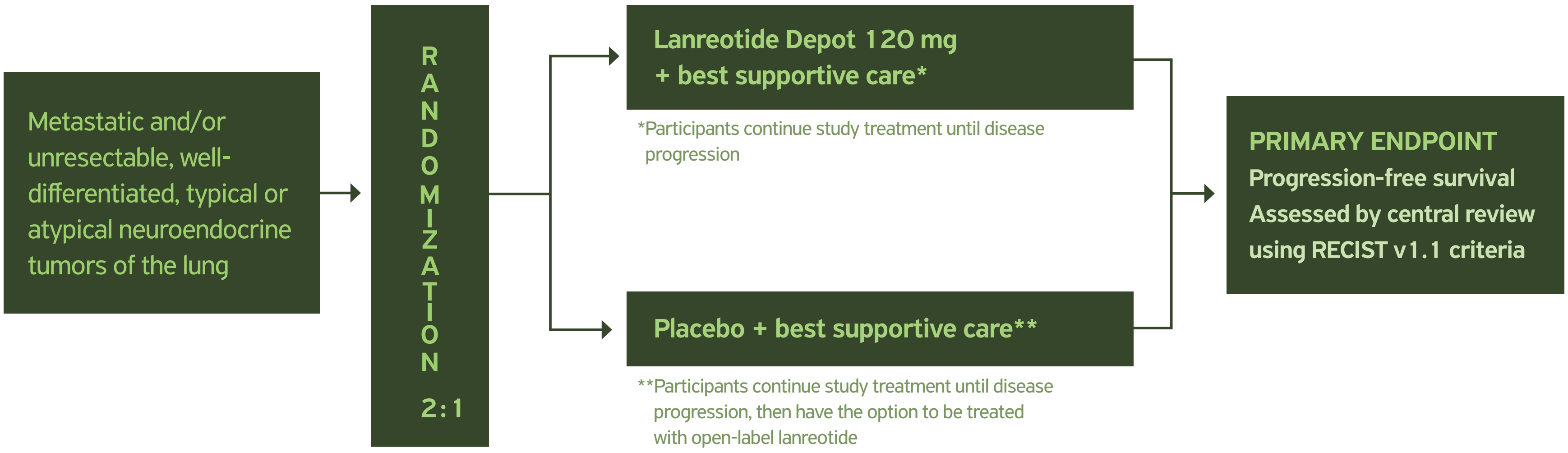
An Investigational Phase 3, Prospective, Randomized, Double-Blind, Multi-Center Study of the Efficacy and Safety of Lanreotide Depot 120 mg sc q 4 wks + Best Supportive Care (BSC) vs. Placebo Plus BSC for Tumor Control in Subjects with Well-Differentiated, Metastatic and/or Unresectable Typical or Atypical Lung Neuroendocrine Tumors



Lanreotide is an octapeptide analogue of somatostatin. The safety and efficacy of lanreotide has not been established in patients with neuroendocrine tumors of the lung. This is an investigational study evaluating an unapproved treatment regimen for Lung NETs. Ipsen does not recommend uses other than as described in the approved prescribing information for pharmaceutical products.

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Metastatic and/or unresectable, pathologically confirmed, well-differentiated typical or atypical neuroendocrine tumors (NETs) of the lung	Poorly differentiated or high-grade carcinoma, or patients with NETs not of lung origin
Histologic evidence of well-differentiated neuroendocrine tumors (NETs) of the lung (typical and atypical according to the World Health Organization criteria, evaluated locally)	Treatment with a somatostatin analog (SSA) at any time prior to randomization, except if that treatment was for less than 15 days (e.g. peri-operatively) with short-acting SSA or 1 dose of long-acting SSA and the treatment was received more than 6 weeks prior to randomization
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
Positive somatostatin receptor imaging	

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

IPSEN
Innovation for patient care

CONTINUED FROM PAGE 16

"It'll be a review of what we know about cytokines, how cytokines have been used as therapy, then some new cytokines that are being developed and understood, and how they might apply," Callahan said.

Cancer Vaccines

Patrick Ott, MD, PhD, the clinical director for the Melanoma Center and the Center for Immuno-Oncology at the Dana-Farber Cancer Institute, will provide an overview of new approaches to cancer vaccines in his presentation in the third session. In particular, he will cover neoantigens, which are identified through sequencing a patient's tumor to find mutations that encode novel antigenic epitopes for the purposes of vaccination.

This field is still in its infancy, according to Nina Bhardwaj, MD, PhD, who will introduce the afternoon's sessions. Bhardwaj is a professor of medicine, hematology, and medical oncology at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai.

"Much work still needs to be done regarding the vaccine adjuvant platforms themselves to make vaccines really immunogenic but with newer antigens and adjuvants," she said. "We are striving towards gaining better responses."

Targeting Regulatory Molecules in Cancer Therapy

In his talk, Michael A. Curran, PhD, will provide an update on the current and future statuses of the field of anti–CTLA-4 and anti–PD-1 therapies. Curran, who is an assistant professor in the department of immunology at The University of Texas MD Anderson Cancer Center, will summarize the efficacy of the agents—both alone and in combination—and will review the "ongoing efforts to reduce the associated toxicity and therefore, discontinuation rate, which can be quite high," he said.

Round table discussions. Photo from SITC's 30th Annual Meeting.

Curran will also discuss the landscape of clinical trials today with immunotherapies and the guiding principles that will help weave treatments together into combinations for appropriate patient subsets.

Immune Monitoring and the Next Generation

Sacha Gnjatic, PhD, will address immune monitoring—both current and future solutions—in his talk during the final session (page 20).

"We know that [these drugs] are supposed to be immunomodulators and act through changes and modulations of the immune response, but in the end, there's actually very little that we can show to understand who will respond better to a specific drug," Gnjatic said.

"Is it because they have a specific immune profile, for example? Why does another patient fail—is it because there's too much suppression going on at the tumor site?"

Gnjatic will mainly focus on reviewing the utility of high-dimensional tools to look, in broad ways, at the complexity of the immune system in order to answer these questions. Gnjatic is an associate professor of medicine, hematology, and medical oncology at Tisch Cancer Institute, and the Icahn School of Medicine at Mount Sinai.

Mass cytometry (CyTOF) is a novel approach for immune profiling that Gnjatic also plans to highlight in his talk. CyTOF is similar to flow cytometry, which is a standard immunological method, except that it uses more markers on a single cell. This method allows researchers to look at many labeled cells in one large panel and understand the diversity and changes that occur with respect to a specific treatment.

Researchers have also examined highly multiplexed imaging of the tissue itself. This involves looking at a variety of markers within the tissue as well as an immunohistochemical view within the tissue, which, Gnjatic notes, allows for the characterization of the complexity of the microenvironment. This characterization, Gnjatic said, is "not just by its composition and profile, but also its geographical location within the architecture of the tissue."

These methods are currently in use, Gnjatic pointed out, and are done at the single-cell level. Even though researchers are looking broadly at many markers and a variety of cells, they are still able to detect—at an individual cell level—what drives responses.

"The idea is to see, in the end, [if] you can correlate the presence of an immune-infiltrated tumor site or the presence of a specific immune subset in the blood with either an immune response that's generated to a treatment or with an eventual outcome of the patient," Gnjatic said.

Novel Avenues

In the next presentation, Bhardwaj says that new approaches and technologies for immunotherapy will be discussed. She noted that physicians are often only able to extract a small sampling of tumor tissue—sometimes just a few cells—from a patient, which makes it difficult to analyze.

"Being able to look at single cells and screen their specificities provides a window into the tissue that can provide key information about what is happening, and it provides insight into how to possibly assess these tumors," Bhardwaj said.

The day's sessions are important for researchers and oncologists looking to review the fundamentals of immunology and immunotherapy. Additionally, Callahan said, attendees will have the opportunity to interact with top experts in the field and get their feedback about the future of immunotherapy, the applicability of biomarkers, exciting new data with checkpoint inhibitors, and more.

The field of immunology and immunotherapy is exciting to Callahan—and should be to the entire cancer care community—because of its breadth of applicability.

"This seems to be a therapy that is not specific to a single tumor type or a single patient population, but is applicable to many tumor types, to many patient populations," she said. "I think we're really just scratching the surface of understanding how many different clinical settings these therapies are applicable for." •

Gnjatic Sheds Light on Emerging Immune Monitoring Techniques

BY GREG KENNELTY

GNJATIC

The development of anticancer checkpoint blockade agents and vaccines has generated a trove of information about the human immune system and the mechanisms through which cancer cells escape detection and destruction. Researchers are increasingly turning their attention to analyzing markers of response to immune therapies as a potential means of evaluating novel agents and combinations.

Sacha Gnjatic, PhD, will discuss this emerging field in his presentation, "Immune Monitoring and Next Generation," during the Primer session. Gnjatic is an associate professor of medicine at the Tisch Cancer Institute and Immunology Institute at the Icahn School of Medicine at Mount Sinai in New York City. In addition, he serves as associate director of the Human Immune Monitoring Center at Mount Sinai.

Gnjatic's research focus includes characterizing serological and cellular immune responses against tumor antigens such as MAGE-A3 and NY-ESO-1, and the impact of immunoregulation on tumor-specific responses to therapies, including co-inhibitory molecules expressed on T cells.

Notably, Gnjatic has conducted exploratory research into the cancer testis antigen NY-ESO-1. A novel T-cell therapy engineered to recognize an HLA-A2–restricted NY-ESO-1 peptide has received a breakthrough therapy designation in synovial sarcoma.

Gnjatic is helping to develop new technologies to investigate immune markers to novel therapies at Icahn's Human Immune Monitoring CoRE center, which offers analytical services to researchers in oncology and other medical fields. These include new platforms for characterizing T-cell and B-cell receptors and methods of flow cytometry.

He discussed key aspects of his presentation in advance of the Primer session today.

What do you hope oncologists take away from your presentation?

Based on all the clinical successes of the checkpoint-blockade drugs, it is becoming important for oncologists to educate themselves about topics in immunology.

I will be covering some of the approaches and methods to answer the question of how these drugs are acting. In the end, there is very little that we understand regarding who will respond to a specific drug or why a patient fails. Is it because there's too much suppression going on at the tumor site? Are there some molecules we should look at?

My session may particularly be for those who are already considering using immunotherapies as part of clinical trials, to sensitize them to what tools are available, and to enlighten their research. This will teach them that we do not have to aim just for overall or progression-free survival, but we can also try to generate some of the immune correlates to dig into the mechanisms of how the drugs are acting.

What role does immune monitoring play in understanding this?

With either biopsies or surgical specimens, we use these materials to help answer questions, with the hope of eventually finding any new biomarkers that may predict response or serve as a prognostic indicator.

One technique I will discuss is cytometry, which is a novel approach for immune profiling. It is similar to a more standard immunological method of flow cytometry, except it uses more markers on a single cell. You label the cells you put in suspension, either blood or tissue, with markers that can stain T cells, B cells, and other subsets of cells from the immune system. By putting all those together into one big panel, we can look at the diversity of the cells in the periphery and, potentially, see changes that happen in relation to specific treatments.

The other approach is the tissue itself. With cytometry, we don't know where those cells were originally in the tumor. Another way we have developed looks at multiple types of imaging in the tissue itself. I'll be discussing some of these approaches where we can look at a variety of markers within the tissue itself using standard immunohistochemistry methods that can be overlaid. We can then see all these markers within the tissue and characterize the complexity of the microenvironment.

Some of the newer approaches set out to answer more general questions, but many of these methods are still done at the single-cell level. Even though we look at many markers and a variety of different cells, we are still able to detect, at the individual cell levels, what drives these responses. We can distinguish each one of them separately.

The idea is to see if we can correlate the presence of an immune infiltrate at the tumor site, or of a specific immune subset in the blood, with either an immune response from a treatment or the overall outcome of the patients.

What do you see on the horizon in this space?

In the future, we should consider macrobiome data that we are not routinely asking for. There have been many recent articles about the gut flora that seems to affect every part of the disease and immunity itself. There are mice experiments that show, if you treat the mouse tumor with chemotherapy, it will not work at all, unless you first pretreat the mouse with antibiotics and remove some of the good bacteria. It is interesting to see how important the intestinal and tissue bacteria can be.

Some of the other next steps are looking at individual cells—not just for their markers, but to start sequencing their DNA and RNA—to begin looking at the heterogeneity of those cells within the tissue. If you conduct genomic studies, you do it on a bulk population of purified cells from the tumor, but now the progress of single-cell technology allows us to see each cell within that tumor and determine what is important, or not, for eventual response.

Are these methods going to work for all tumor types?

It should be applicable to the majority of the most common tumors, and even rarer ones. For solid tumors, we can do more of these tissue analyses because we can make nice sections of them. I think we can make the most of this for some of the hematological diseases, particularly ones in the bone marrow, where we can also access tissue and create slides. The architecture of these liquid tumors is much less strict. •

Take a Step Back in History in Alexandria

By Brielle Urciuoli

With this year's SITC Annual Meeting taking place across the river from Alexandria, VA, a town with a rich history, hopefully you'll be able to get out and explore a bit after sessions; you won't regret it. There's plenty to visit—from 18th century taverns to modern art galleries, all easily accessible thanks to the Potomac Riverboat Company and King Street Trolley.

Historic Attractions

One of the area's biggest claims to fame is being the hometown of our nation's first president, George Washington. By taking a short trip via car or the **Potomac Riverboat Company** (1 Cameron St.), visitors can travel centuries back in time and visit **George Washington's Mount Vernon Estate** (3200 Mount Vernon Memorial Highway, Mount Vernon, VA). The estate started off as a small farmhouse built by Washington's father, Augustine, in 1735. Once the general took over the property in 1754, he started the decades-long renovation project, turning the modest house into a 21-room residence that sits upon a beautiful estate. Every part of the post-Revolution renovation was meticulously planned out by George Washington himself.

At Mount Vernon, visitors can take one of many tours, including one that visits sights from the movie *National Treasure 2: Book of Secrets*, and another capturing what life was like for the people who were enslaved that built and maintained the premises. Foodies can take the 60-minute "Dinner for the Washingtons" tour, which walks through the various dining and cooking areas of the house.

Though Mount Vernon and Washington, DC, are not far away, if you are looking to stay in Alexandria, you still have plenty of historically significant sites to see. The **Alexandria Black History Museum** (902 Wythe St.) documents both the national and local history of African Americans, which was the inspiration for the PBS drama series, *Mercy Street*. The museum was originally built as a segregated library for the town's black residents, but now boasts multiple exhibits throughout the year, including their permanent exhibition, Securing the Blessings of Liberty, chronicling how local black people survived and helped abolish slavery, and molded the town that is Alexandria today.

After learning about the latest advancements in cancer drugs at the SITC Annual Meeting, attendees can step back in time and see what life was like as a doctor or pharmacist centuries ago at the **Stabler-Leadbeater Apothecary Museum** (105-107 S. Fairfax St.). There, rows of shelves are lined with thousands of authentic hand-blown bottles of herbal botanicals, early medical and surgical tools, as well as paint and farm equipment. The museum replicates the apothecary that operated in that location from 1792 to 1933, treating esteemed American icons such as Martha Washington and Robert E. Lee.

Once they were feeling better thanks to the treatments they received at the apothecary, many prominent 18th century Americans then went over to Gadsby's Tavern, now **Gadsby's Tavern Museum** (134 N. Royal St.), for food, drink, lodging, and entertainment. With patrons such as Thomas Jefferson and John Adams, the tavern was also a hot spot for business and political discussion, and even hosted Jefferson's 1801 inaugural banquet. Now, visitors can eat in their dining room and take tours of the museum, getting a glimpse into what life was like in the late 1700's.

Arts, Culture, and Shopping

Alexandria's culture did not end with our founding fathers and the closing of the 18th century. Visitors can take a stroll down **King Street**, a walkable, mile-long stretch that is abundant with more than 150 stores and 100 restaurants, perfect for getting ahead on your holiday shopping. You can start on Upper King Street (accessible via the free King Street Trolley), where there are plenty of home décor shops. Here you'll also find upscale and custom apparel, as well as children's stores, such as **Pink and Brown** (1129 King St.), which sells organic clothing and toys.

While Upper King Street is mainly independent boutiques, Middle King Street is where you'll find more recognizable retailers, such as Anthropologie, Gap, lululemon, and Banana Republic. This is also the spot to take home something for your four-legged family members from the **Dog Park** store (705 King St.).

If you're looking for a unique piece of art, décor, or jewelry to remember your trip, Lower King Street is the place to be. This area is not only home to the **Torpedo Factory Art Center** (105 N. Union St.), a World War II factory turned art studio in 1974, that now houses more than 80 working artist studios and 160 visual artists, but also other art galleries and accessory stores.

Food and Drink

There are many great places to eat in Alexandria, such as the high-end **Restaurant Eve** (110 South Pitt St.), which received the highest ZAGAT ratings in the whole town. The Irish-inspired "New American" restaurant gets their ingredients from local, organic, sustainable farms and crafts them into picturesque lunch and dinner plates. Restaurant Eve offers tasting menus ranging from $65 to $140 per person, a three-course dinner option for $50 per person, or a three-course lunch option for $28 per person.

For those who want more casual dining without sparing big taste, **Holy Cow Del Ray's Gourmet Burger Joint** (2312 Mt. Vernon Ave.) may be the place to go. The spot was recently listed on Thrillist's "20 Best Burgers in VA" list, and in 2014 appeared in *Washington Magazine* as one of the best burgers in Washington. Holy Cow is also partnered with ACT for Alexandria, which allows you to choose from a list of more than 70 local charities to donate 25 cents with each burger purchase.

To get a taste of Alexandria's beer scene, you can embark on the self-guided tour titled, "Alexandria's Historic Breweries: A Walking Tour & Pub Guide." Guides can be picked up at the **Alexandria Visitor Center** (221 King St.) and will lead you through 16 of the city's favorite watering holes, and a brewing history of the area. One notable stop includes the **Port City Brewing Company** (3950 Wheeler Ave.), previously known as the Robert Portner Brewing Company, which was the largest pre-Prohibition brewery in the south. The site closed with the passing of the 18th Amendment, but reopened 5 years ago as the Port City Brewing Company. Share your brew tour experiences on social media with the hashtag ***#ALXBrewTour***. •

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)]*.

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TECENTRIQ® (atezolizumab)

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PDL/080916/0193
Initial U.S. Approval: *May 2016*
Code Revision Date: *October 2016*