Tumor Microenvironment Emerges as a Focus in Immuno-Oncology

By Tony Berberabe, MPH

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

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

The tumor microenvironment is an elaborate web of diverse cell types that fosters ongoing malignant tumor cell interactions with tumor-associated vasculature, fibroblasts, and a variety of immune cells. It is within the microenvironment that tumor growth, progression and metastasis occur. It is within the tumor microenvironment that therapies can be successful or fail.

Disis said the tumor microenvironment is highly complex and multi-dimensional. “It’s not a smooth, flat surface,” she said. “It has things coming out of it.”

In the microenvironment, tumors interact with neighboring cells in a highly complex manner, creating an environment that is difficult to penetrate and treat. Disis said there are several different strategies that can be used to modulate the tumor microenvironment, including the use of checkpoint inhibitors, which have shown promise in recent years.

The tumor microenvironment is not just a site of cancer growth, but also a site of inflammation, with immune cells playing a critical role in the regulation of tumor growth. Disis said the tumor microenvironment is a site where immune cells can be trained to recognize and destroy cancer cells, but also a site where cancer cells can evade immune surveillance.

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NOW ENROLLING IN

Triple-Negative Breast Cancer

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

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

• 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.

• METRIC is an open-label, prospectively controlled, randomized trial.

Patients with metastatic TNBC overexpressing gpNMB
N=300

Glembatumumab vedotin
1.88 mg/kg IV
Day 1 of 21-day cycles

Capecitabine
1250 mg/m² BID
Days 1-14 of 21-day cycles

Treat until unacceptable toxicity or disease progression

KEY INCLUSION CRITERIA

• 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

• 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

• 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.

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

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

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

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

Kohrt, one of the organizers and session co-chairs of the Annual Meeting, passed away earlier this year and will truly be missed by all.
Atkins Describes Lessons of Immunotherapy Learned from Cytokines

**By Anita T. Shaffer**

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

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

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

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

In melanoma, a meta-analysis of 14 randomized trials demonstrated that IFNα resulted in statistically significant improvements in disease-free survival and overall survival (OS) as adjuvant treatment in patients with high-risk cutaneous disease (Mocellin et al. J Natl Cancer Inst. 2010). High-dose IFNα has shown a significant recurrence-free survival benefit and a likely OS impact, although it is accompanied by a flu-like syndrome of variable severity, Atkins said. “The benefit can be correlated with autoimmunity,” said Atkins. “It’s a bane or an effect of that effect with other immunotherapies.”

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

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

High-dose IL-2 treatment has demonstrated durable responses in 6% to 16% of patients with advanced melanoma and RCC, and few relapses among patients whose responses have persisted for more than 2.5 years, Atkins said. (Atkins et al. J Clin Oncol. 1995; Fyfe et al. J Clin Oncol. 1992). The FDA approved its use for patients with RCC in 1992 and for melanoma in 1998.

High-dose IFNα has shown a significant recurrence-free survival benefit and a likely OS impact, although it is accompanied by a flu-like syndrome of variable severity, Atkins said. “The benefit can be correlated with autoimmunity,” said Atkins. “It was that observation that has kept the immune therapy field alive until we can figure out better ways of activating the immune system.”

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

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

The Effects of Aging on Immunotherapy

**By Lisa Miller**

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

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

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

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

Pawelec addressed the vast number of melanoma patients who have been treated with ipilimumab (Yervoy; anti-CTLA-4 therapy). Anecdotal reports show that older patients with melanoma have a clinical benefit equal to that of younger patients when receiving ipilimumab. A retrospective study showed that that older patients with melanoma treated with ipilimumab have a comparable rate of immune-related adverse events to younger patients receiving ipilimumab (Mian et al. J Clin Oncol. 2016). The side effect profile of immunotherapy agents is a great concern when treating older patients, Pawelec noted, as it was suspected that older patients may have more numerous and severe adverse events than younger patients.

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

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

BY LISA MILLER

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Right now phase 1 is open for all solid tumors histologies. Clearly melanoma and renal cell carcinoma are attractive and we see those patients more than others. But we are looking into triple-negative breast cancer, bladder cancer, and lung cancer. These patients are going to be enriched in the second phase of this trial, and we’re hoping to see some sort of activity [in these patients].

REFERENCE

Thank You to Our Organizers!

SITC 32nd Annual Meeting
Charles G. Drake, MD, PhD – Columbia University Herbert Irving Comprehensive Cancer Center
Susan M. Kaech, PhD – Yale University
Marcela V. Maus, MD, PhD – Massachusetts General Hospital Cancer Center
Laura S. Wood, RN, MSN, OCN – Cleveland Clinic Taussig Cancer Center

Workshop on Single Cell Techniques in Immunology and Cancer Immunotherapy
Nir Hacohen, PhD – Massachusetts General Hospital

Primer on Tumor Immunology and Cancer Immunotherapy™
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...modulating the tumor microenvironment is a major area of research and we’re going to be hearing about some of these new approaches during the session.”
—Mary L. Disis, MD
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Methods to Predict Response to Immunotherapeutics

BY LISA MILLER

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

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

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

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

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

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

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

In 2012, the Society for Immunotherapy of Cancer (SITC) led a 23-center study of more than 3,800 patients to validate the Immunoscore as a standardized immune-based assay in colon cancer. A study presented in June 2016 showed the prognostic value of the Immunoscore® in predicting time to recurrence, disease-free survival, and overall survival in stage I-III colon cancer.4 The Immunoscore has also been shown to predict response to chemotherapy in patients with stage II and III colon cancer.5

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

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

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

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

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

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

This sensitivity will continue to be explored, along with additional approaches to predicting a patient’s response to immunotherapies. Schlom believes that this session will have a broad appeal to a variety of attendees, as they will have the opportunity to learn about the biggest advancements within the area of antitumor immunity that can be used to clinical practice.

REFERENCES
5) Galon J, Mlecnik B, Harbort F, et al. Validation of the Immunoscore category out of 62 assessments. In cell density assessments, among the different instruments, lots, and operators/readers, the coefficient of variation was lower than 12%, 22%, and 18%, respectively, showing the ease of reproducibility. Additionally, comparing reference HEGP assessment with the Immunoscore revealed a Pearson correlation coefficient greater than 0.89, indicating high concordance.
How do PD-L1 inhibition and PD-1 inhibition differ?

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

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

- PD-L1 (programmed death ligand-1), expressed on a variety of normal cells, binds to PD-1 to inhibit T-cell activity.3-5
- PD-L1 has also been shown to sequester the co-stimulatory ligand CD80 (also called B7.1), therefore limiting its ability to co-activate T cells.6,7
- Tumor cells upregulate PD-L1 to evade the antitumor immune response.1,2

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

The role of interaction between PD-L1 and CD80

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

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

- PD-L1 inhibition leaves the PD-L2 pathway intact so that PD-L2 can continue to play an important role in immune regulation.8,9
- Leaking PD-L2 intact may prevent tissue damage.10,11
- PD-1 inhibition prevents the interaction between PD-L2 and PD-1.9

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

- Combination with another immune pathway may combat multiple mechanisms of tumor immune escape, potentially allowing for greater antitumor activity than with either pathway alone.1,11
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Exploring Metabolic Pathways and Aging to Make Immune Cells Stronger

BY LAUREN M. GREEN

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

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

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

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

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

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

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

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

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

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

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

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

The research team used real-time metabolic flux analysis to study the role of the Wnt5a-beta-catenin-PPARg pathway in the metabolic reprogramming of dendritic cells from melanoma tumor samples, because dendritic cells are suspected to play an important role in immune evasion within the tumor microenvironment. Results indicated that the Wnt5a-beta-catenin-PPARg pathway shifts dendritic cells from glycolysis to fatty acid oxidation within the melanoma microenvironment. Accord-
inently, this CPT1A-dependent metabolic shift increases the tolerization of dendritic cells and the generation of regulatory T cells. Investigators showed that targeted inhibition of regulators within this pathway promotes greater effector T-cell responses and T-cell tumor infiltrates, and alters PD-1 expression in melanoma-derived models.

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

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

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

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

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

REFERENCES
Now Enrolling

**NCT02683941**
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**

- Metastatic and/or unresectable, well-differentiated, typical or atypical neuroendocrine tumors of the lung
- Histologic evidence of well-differentiated neuroendocrine tumors (NETs) of the lung (typical and atypical according to the World Health Organization criteria, evaluated locally)
- Mitotic index < 2 mitoses/2 mm² for typical carcinoid and <10 mitoses/2 mm² and/or foci of necrosis for atypical carcinoid
- At least 1 measurable lesion of the disease on imaging (CT or MRI; RECIST 1.1 criteria)
- Positive somatostatin receptor imaging

**KEY EXCLUSION CRITERIA**

- Poorly differentiated or high-grade carcinoma, or patients with NETs not of lung origin
- 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
- Treatment with peptide receptor radionuclide therapy at any time prior to randomization
- Prior treatment with more than 1 course of cytotoxic chemotherapy or molecular targeted therapy, or interferon for lung NETs

For more information, visit www.clinicaltrials.gov/ct2/show/NCT02683941
The rapidly growing field of cancer immunotherapy continues to generate enthusiasm due to positive and durable outcomes in responding patients for whom traditional therapeutic approaches have failed. As new drugs and combinations gain approvals for a broad range of malignancies, there is a growing need for disease-specific recommendations to help guide the integration of immunotherapy treatments into current practice. The evidence-based clinical practice guidelines provided by the National Comprehensive Cancer Network (NCCN) are a widely recognized resource and standard for the treatment of cancer, yet the NCCN guidelines do not cover the unique aspects of immunotherapy. In particular, guidance is needed to determine patient eligibility, assess responses due to the unique pharmacokinetics, and manage the immune-related toxicities associated with these agents.

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

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

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

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

A comprehensive literature search is also conducted to identify and evaluate literature according to the predetermined rating system. A bibliography is then compiled based on search results and serves as the evidence base for the strength of the recommendations that arise from the consensus opinions. Each TF holds live meetings structured around the key knowledge gaps identified at the outset. The survey results and bibliography are discussed and any meeting outcomes, such as important conversation points and votes on key issues, are recorded for use in drafting the consensus statements. Drafts of the cancer immunotherapy guidelines are then routed for an extensive review process. Members of the TF and OC begin with an initial review, after which all SITC members are invited to review and provide comments. Consensus statements are then peer reviewed upon submission to the society’s Journal for ImmunoTherapy of Cancer, an open-access journal. Following publication, the guidelines will be reviewed annually by the OC and will be updated when evidence suggests the need for modification of clinically relevant information.

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

**REFERENCES**


Prognostic Tool for Immunotherapy Age Debuts

BY ANITA T. SHAFFER

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

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

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

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

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

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

“This is a particularly timely finding in the era of immunotherapy, as Immunoscore-based assays could be used to predict which patients would be more likely to benefit from treatment modalities such as checkpoint blockade or whether strategies, such as adjuvant therapy or cancer vaccines to prime immunity, might be more appropriate,” said the Society for Immunotherapy of Cancer (SITC), which led the formation of the worldwide consortium that developed the Immunoscore.

“More broadly, the results of the Immunoscore study have potential implications for the field of immune monitoring as a rapid means of determining response to treatment.”

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

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

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

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

Evidence Presented at ASCO

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

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

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

The study criteria included patients with stages I/II/III colon cancer (T1-T4, N0-N2, Mo) who had not received neoadjuvant treatment. In all, 3855 patients were evaluated for the Immunoscore but many did not meet the inclusion criteria for the study; the analysis...
The Immunoscore assay, as we have demonstrated in this international study, has all the characteristics of a biomarker that can be done in routine practice.”

—Jérôme Galon, PhD

The importance of the patient’s immune system in responding to therapy is at the heart of SITC’s efforts to develop the Immunoscore. “The only thing that makes a difference in the life of a patient with metastatic cancer is their immune system,” said Fox. “There’s a lot of data in animal models that suggest that tumors that are not immunogenic—tumors that don’t have immune infiltrates—are not going to respond to costimulatory molecules.”

SITC researchers believe that the current reliance on the TNM staging system, with its tumor-focused methods of classifying all malignancies, has many shortcomings. Additional information can be gleaned from other aspects of tumor analysis such as cellular morphology and molecular pathways. “However, instances in which clinical outcomes are drastically different between patients within the same stage, patients who maintain stable late-stage disease for years, or maintain stable late-stage disease for years, or the rapid decline of early-stage patients, underscore the limited ability of the current staging systems,” SITC said.

During the past 5 years, the focus on the tumor cell itself in malignancies has evolved into an expanded understanding of the role of the tumor microenvironment, which Immunoscore researchers describe as “a set of cellular com-
SITC is the world’s leading member-driven society dedicated to professionals working in the field of cancer immunotherapy. SITC aims to make cancer immunotherapy a standard of care and the word “cure” a reality for cancer patients everywhere through...

- Dedication to education and outreach
- Commitment to collaboration with like-minded organizations and patient advocacy groups
- Focus on initiatives of major importance to the field
- Connection of all aspects of the cancer immunotherapy community
Advances in Cancer Immunotherapy™: Regional SITC Meetings Explain the Basics of Immunotherapy

By Lisa Miller

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

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

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

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

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

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

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

BY SILAS INMAN

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

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

**Nrp1-deficient Tregs**

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

To this end, Overacre and colleagues explored Nrp1 as a potential treatment strategy, since the Nrp1 pathway is required for intratumoral Treg stability but does not impact the peripheral immune system. For this study, the researchers injected the murine B16.F10 melanoma cells into mice that were heterozygous for NRP1Flox/Flox;Nrp1Cre-loxP;R26-LSL-YFP. Overall, 50% of the Tregs in these mice were Nrp1-deficient (Nrp1-/-) and the remainder were wild type.

Whole transcriptome sequencing was conducted to determine potential changes in these experimental mouse models. Once differentially regulated pathways were identified, they were explored with ex vivo functional assays and in vivo with Tregs transfers into Foxp3-deficient mice. The researchers also examined human melanoma and squamous cell carcinoma of the head and neck cells to determine the abundance of Nrp1 and its functionality on human Tregs.

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

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

When exploring human head and neck cancer and metastatic melanoma cells, Nrp1 was expressed on some of the tumor infiltrating lymphocyte (TIL) Tregs. It was also determined that the IFN-γ pathway was intact in human Tregs. Moreover, when these TIL Tregs were pretreated with IFN-γ, they showed a reduced suppressive function compared with cells that were not pretreated.

“This study uncovers a novel potential target for cancer immunotherapies that preserves peripheral immune health. This is of clinical interest, given that Nrp1 is expressed on select Tregs in human melanoma and head and neck cancer and that Nrp1-/- Tregs show a suppressive advantage over Nrp1+ Tregs,” the authors noted.

**CD8α+ Dendritic Cells**

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

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

For the study, the researchers utilized the transplantable C1498 murine cell line, which is an aggressive, highly-lethal subtype of AML. Additionally, they tested their hypothesis on a genetically engineered AML model: Mdx-Cre x LSL-AML-CUG mice with FLT3 mutant (FLT3ITD/ITD x FLT3ITD/ITD x R26-LSL-SIY) x FLTP(CDG)y x R26-LSL-GFP (MAFFS). These cell lines were violet-labeled using CellTrace.

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

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

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

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

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

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

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

**References**


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While taking in the latest on advancements in immunotherapy, attendees will be surrounded on all sides by history. A short trip up the Potomac River, Arlington, VA, hosts many departments and agencies of our federal government, including the Department of Defense, Drug Enforcement Administration, Transportation Security Administration, and the Defense Advanced Research Projects Agency.

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

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

**Arlington National Cemetery’s Landmarks**

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

Located atop a hill in the cemetery is the grave of an unknown soldier from World War I. The tomb is actually a large sarcophagus, adorned with Greek figures representing Peace, Victory, and Valor. Crypts of the unknown soldiers from World War II, Korea, and Vietnam, are also nearby. During the fall and winter, visitors to the Tomb can witness the Changing of the Guard every hour, on the hour. If you’d like a more structured visit of the island, you can join in one of the ranger-led activities. If you’re an outdoorsy person, this city is a dream for you. Nature isn’t the only attraction here, though. There are plenty of memorials, museums, shopping, and dining to experience while in Arlington.

**Mount Vernon Trail**

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

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

**Theodore Roosevelt Island**

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

**Arlington Arts Center**

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

**The Village at Shirlington**

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

**Clarendon**

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

**The Pentagon Tours**

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

Giants of Cancer Care®

The Giants of Cancer Care® Awards celebrate those individuals who have achieved landmark success within the field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

NOMINATIONS FOR THE CLASS OF 2017
GIANTS OF CANCER CARE®
are now being accepted online
giantsofcancercare.com/nominate

The Giants of Cancer Care® Awards celebrate those individuals who have achieved landmark success within the field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

PROGRAM OVERVIEW

- Nominations are open through March 20, 2017.
- Domestic and international nominations will be accepted. Self-nominations are permitted and encouraged.
- The Giants of Cancer Care® Advisory Board will vet all nominations to determine finalists in each category.
- A Selection Committee of 90+ oncologists will vote to determine the 2017 winners.
- The 2017 Giants of Cancer Care® class of inductees will be announced in Chicago on June 1, 2017.
In the age of immunotherapy, it is important that oncologists learn just as much from their patients as they do in the laboratory, said Roy S. Herbst, MD, PhD.

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

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

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

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

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

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

We saw recently, with the publication of KEYNOTE-024, that the PD-L1 biomarker can determine which patients with lung cancer should get immunotherapy upfront with pembrolizumab. PD-L1 is now a required biomarker that one should use to test patients with lung cancer to determine if they should get frontline immunotherapy. But we can’t stop there.

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

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

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

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who are progression-free after Concurrent platinum-based chemoradiation followed by platinum-based chemotherapy.

1 INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Urothelial Carcinoma

TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC), with progression after platinum-based chemotherapy, in combination with pemetrexed and pembrolizumab.

2 CONTRAINDICATIONS

2.1 Hypersensitivity to a components of TECENTRIQ

Precautions

3.1 Adrenal Insufficiency

Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Asymptomatic patients may develop symptomatic hypophysitis. Any patient with clinical signs or symptoms of hypophysitis should be managed as indicated in the management of hypophysitis. For patients with hypophysitis, if the signs and symptoms of hypophysitis improve or resolve, TECENTRIQ can be resumed at the equivalent of 10 mg/m² oral prednisone per day.

3.2 Immune-mediated Pneumonitis

Adrenal insufficiency occurred in 0.4% (7/1978) of patients across clinical trials. For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer reconstitution with adrenal insufficiency replacement therapy, if indicated. In patients with Grade 3 or 4 adrenal insufficiency, resume TECENTRIQ at the equivalent of ≤ 10 mg/m² oral prednisone per day.

3.3 Adverse Reactions That May Cause Permanent Discontinuation of TECENTRIQ

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

5.2 Infusion-Related Reactions

Infusion-related reactions have been reported with TECENTRIQ during administration. Monitor patients for signs and symptoms of infusion-related reactions, and immediately discontinue TECENTRIQ for Grade 3 or 4 reactions. Treatment-related serious infusion-related reactions occurred in 19% (344/1805) of patients treated with TECENTRIQ in Study 1. The most common adverse reactions associated with Grade 3 or 4 infusion-related reactions were hypotension (5% of patients), flushing (4%), chills (3%), nausea (3%), vomiting (3%), and dyspnea (2%).

5.3 Immune-Related Colitis

5.4 Immune-Related Endocrinopathies

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

7.2 Urothelial Carcinoma

8.2 Lactation

The safety of TECENTRIQ was evaluated in Study 1, a multi-center, international, randomized, Phase 3 study that compared TECENTRIQ (n=142) to docetaxel (n=135) in patients with previously treated advanced urothelial carcinoma.

9.1 Pregnancy

9.2 Lactation

9.3 Females of Reproductive Potential

9.4 Males of Reproductive Potential

10 RENAL IMPAIRMENT

11 OVERDOSAGE

11.1 General Overdose Information

11.2 Management of a Single Dose Overdose

11.3 Management of Chronic Exposure

12 PATIENT COUNSELING INFORMATION

12.1 General Instructions

12.2 Administration of TECENTRIQ

12.3 Special Populations

12.4 Use in Specific Populations

12.5 Breastfeeding

13 HOW SUPPLIED/_STORAGE AND HANDLING

13.1 TECENTRIQ® (atezolizumab)

14 PATIENT INFORMATION

14.1 TECENTRIQ

14.2 Administering TECENTRIQ

14.3 TECENTRIQ Side Effects

14.4 TECENTRIQ Safety Information

15 VIRAL INFECTION

16 IMMUNE-MEDIATED REACTIONS

18 IMMUNE-MEDIATED REACTIONS

18.1 Immune-Mediated Adverse Reactions

18.2 Immune-Mediated Pneumonitis

18.3 Immune-Mediated Pneumonitis

18.4 Immune-Mediated Thyroid Dysfunction

18.5 Immune-Mediated Hypophysitis

18.6 Immune-Mediated Hypophysitis

18.7 Immune-Mediated Adrenal Insufficiency

18.8 Immune-Mediated Adrenal Insufficiency

18.9 Immune-Mediated Diabetes Mellitus

18.10 Immune-Mediated Diabetes Mellitus

19 NURSING CONSIDERATIONS

19.1 Nursing Considerations

19.2 Nursing Considerations

20 PATIENT EDUCATION

20.1 Patient Education

20.2 Patient Education

Table 3: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence Than in the Docetaxel Group during Study 1

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of TECENTRIQ-Treated Patients with Metastatic NSCLC and at a Higher Incidence Than in the Docetaxel Group (Between Mean Difference of ≥10% at ≥2 Grades [≥ Grade 3] and ≥ Grade 4)
Serious Adverse Reactions

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

• Immune-related pneumonitis. Immune-mediated pneumonitis or interstitial lung disease have occurred. Fatal cases have been observed in patients with urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC). Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis.

• Immune-related hepatitis. Immune-mediated hepatitis and liver test abnormalities, including a fatal case of hepatitis in a patient with UC, have occurred. Permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated hepatitis.

• Immune-related colitis. Immune-mediated colitis or diarrhea, including a fatal case of diarrhea-associated renal failure in a patient with UC, occurred. Permanently discontinue TECENTRIQ for Grade 3 or 4 immune-mediated colitis.

• Immune-related endocrinopathies. Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred. Permanently discontinue TECENTRIQ for Grade 4 hypophysitis.

• Other immune-related adverse reactions. Meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred. Permanently discontinue TECENTRIQ for any grade of meningoencephalitis or myasthenia gravis, or any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Permanently discontinue TECENTRIQ for Grade 4 or any grade of recurrent pancreatitis.

• Infection. Severe infections, such as sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage, have occurred. Fatal cases have been observed in patients with UC and NSCLC.

• Infusion-related reactions. Severe infusion reactions occurred. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions.

• Embryo-fetal toxicity. TECENTRIQ can cause fetal harm in pregnant women. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose.

• Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose.

Important Safety Information

FOR PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

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

• Have disease progression during or following platinum-containing chemotherapy.

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

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

FOR PREVIOUSLY TREATED METASTATIC NON-SMALL CELL LUNG CANCER

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

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