IMMUNO-ONCOLOGY

Transforming the Delivery of Cancer Care in the Community

IMMUNO-ONCOLOGY

ACCC
Association of Community Cancer Centers

2017-2018

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Immuno-Oncology: Transforming the Delivery of Cancer Care in the Community

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Executive Summary

THE IMMUNO-ONCOLOGY LANDSCAPE IN 2017

2017 marked another transformative year in immuno-oncology (I-O), with significant responses and accounts of durable remissions seen with monotherapy and combination treatment across several tumor types—melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and urothelial cancer. Although I-O therapy is diverse, encompassing cancer vaccines, monoclonal antibodies (notably, checkpoint inhibitors), adoptive cell therapies, oncolytic virus therapies, and non-specific immunotherapies (e.g., cytokines), approvals for immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy dominated the I-O field in 2017. In addition to indications for nivolumab, pembrolizumab, and ipilimumab in urothelial carcinoma, gastric or gastroesophageal junction cancer, and hepatocellular carcinoma, new anti-programmed death-ligand (PD-L1) agents were approved in metastatic Merkel cell carcinoma (avelumab) and urothelial carcinoma (durvalumab). Pembrolizumab also received pan-tumor approval for treating patients with microsatellite instability-high or mismatch repair deficient tumors (MSI-H/dMMR), while both nivolumab and pembrolizumab were approved for patients with MSI-H/dMMR metastatic colorectal cancer. In one of the most anticipated approvals for 2017, the United States Food and Drug Administration (FDA) approved a chimeric antigen receptor (CAR) T-cell therapy—tisagenlecleucel—in August, for the treatment of patients up to age 25 years old with refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL). This event marked the first approval for gene therapy in the U.S. and represents a major innovation for patients with hematologic malignancies. In October, the FDA approved a second CAR T-cell therapy, axicabtagene ciloleucel, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.

These approvals are undoubtedly transforming how community oncology clinicians manage patients across numerous tumors, but the rapid pace of advancement and the volume of information in the I-O arena remains challenging for clinicians to absorb. Adding to this challenge, patients continue to show interest in and ask to be treated with therapies for which they may not be eligible. Indeed, the question of patient selection and eligibility continued to be a strong focus of debate in 2017. Anti-PD-1/PD-L1 therapies are not effective against all types of cancer, nor do they have benefit for all patients with classically 'immunogenic' cancer types. What has become evident in 2017 is that given the complexity of tumor biology and immune response, it is likely that use of multiple biomarkers, including tumor mutational burden or T-cell markers, will be needed to predict individual clinical response to I-O therapy and to monitor immune response. To this end, two notable research initiatives were recently launched to explore a range of issues in biomarker-based therapy selection. The National Institutes of Health joined 11 biopharmaceutical companies to create a Partnership for Accelerating Cancer Therapies (PACT), and in October, Stand up to Cancer's Catalyst® announced 10 clinical trial projects—all with an immunotherapy component—combining cancer treatment from nine different pharmaceutical companies.

ACCC Meeting Educational Needs of Community Cancer Teams

Just as the clinical landscape of immuno-oncology is evolving, so too is the information on clinical optimization, coverage and reimbursement, operational effective practices, and patient access. Accordingly, 2017 needs assessment data gathered from surveys of the Association of Community Cancer Centers (ACCC) membership showed that as I-O is increasingly delivered in community cancer programs, familiarity with expanding indications for I-O and patient education are persistent challenges for community oncology providers. Moreover, the recognition and management of immune-related adverse events (irAEs) has emerged as a topic in urgent need of education, support, and resources for not only members of the oncology multidisciplinary team (MDT) but also for non-oncology specialists. It is becoming increasingly clear that irAE management relies heavily on building robust relationships with, and establishing effective lines of commmunication between, oncology providers and non-oncology specialists.

Thus, to meet the education needs of its members, ACCC provided several programs in 2017 designed to empower the multidisciplinary cancer care team to optimize I-O care:

- Visiting Experts Program
- Case Studies in I-O
- Non-Oncology Specialists Alliance
- Tumor-Specific Subcommittees
- Immune-Related Adverse Events Environmental Scan
- Policy, Access, and Value of I-O Survey and Policy Summit

The I-O wave continues to gather strength. ACCC is meeting evolving needs with programs and resources that connect oncology providers with non-oncology specialists; that collate from and convey effective practices to community cancer centers; and that create opportunities for real-time, clinician-to-clinician conversations about optimizing care for patients being treated with I-O agents for cancer.

ACCC CORE DOMAINS FOR IMMUNO-ONCOLOGY

1. Clinical Optimization
2. Coverage & Reimbursement
3. Operational Effective Practices
4. Patient Access & Advocacy
5. Training & Professional Development

Highlights from ACCC Educational Programs

1. Both the Visiting Experts Program and the Case Studies in I-O were structured around a **bi-directional, or peer-to-peer, learning format** that enabled cancer program participants and expert faculty to share experiences in real-time and identify effective practices for planning treatment and managing irAEs.

2. Data gathered via the Non-Oncology Specialists Alliance enabled ACCC to **establish a baseline of educational needs** for non-oncology specialists that will drive the development of immunotherapy education programs and resources in 2018. These programs will support oncology clinicians and non-oncology specialists in building relationships and strategies that optimize the management of patients treated with I-O therapies.

3. Expert faculty in Tumor-Specific Subcommittees identified a **range of real-world, relevant resources** that ACCC has bundled into online Tumor Toolkits.

4. An environmental scan of immune-related adverse events (irAEs) management materials enabled ACCC to **catalogue existing provider and patient irAE resources and effective practices** pertaining to monotherapy I-O agents and combination regimens. These resources will be indispensable in providing direction for the oncology multidisciplinary team as it expands to include non-oncology specialists with expertise in managing organ-specific toxicities.

5. Appraisal of policy, access, and value concerns in I-O via a policy survey and environmental scan revealed that as value-based programs gain traction in community cancer programs, community providers will need **education to help them prepare for the workflow, technical, and clinical changes necessary for success** in value-based payment models such as the Oncology Care Model (OCM).

6. The diversity of organizations represented by participants was a major strength of the Policy Summit. Stakeholders identified the following as **priority areas** for education in 2018:
    - Variation in coverage under different health plans
    - Meaningful quality measures in value-based programs
    - The role of biomarkers in cost mitigation
    - Strategies for ensuring practice sustainability in risk-sharing payment models

2017 Cancer Immunotherapy Clinical Highlights

2017 IMMUNO-ONCOLOGY APPROVALS: A BRIEF LOOK

FDA approvals for new cancer immunotherapy indications accelerated in 2017. By October, there were 13 approvals involving checkpoint inhibitors and two approvals for CAR-T cell therapies (refer to Figure 1, page 6).

- **Urothelial carcinoma.** Three additional checkpoint inhibitors (nivolumab, avelumab, durvalumab) joined atezolizumab as approved agents for the treatment of patients with locally advanced or metastatic urothelial cancer following disease progression during or after platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. In single-arm clinical trials, overall objective response rates (ORR) with atezolizumab, nivolumab, durvalumab, and avelumab, were 15%, 20%, 31%, and 18%, respectively.[1-4] Atezolizumab and pembrolizumab were also approved for the initial treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin chemotherapy, with ORRs in phase 2 trials of 23% and 27%, respectively.[5-6]
- **Merkel cell carcinoma.** Avelumab was approved for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma, based on data from the single-arm JAVELIN trial (n=88). ORR was 33% and the 6-month durable response rate was 30.6% (95% CI, 20.9-40.3). The estimated 1-year progression free survival (PFS) rate was 30%, and the 1-year overall survival (OS) rate was 52% with a median OS of 12.9 months.[7]
- **Classical Hodgkin lymphoma (CHL).** In March 2017, the FDA approved pembrolizumab for the treatment of CHL. A single-arm phase 2 KEYNOTE-087 trial of pembrolizumab in patients with relapsed or refractory CHL (n=210) included patients with disease progression after autologous stem cell transplant (ASCT) and subsequent brentuximab vedotin (BV); patients who were ineligible for ASCT due to chemoresistant disease following salvage chemotherapy and BV; and patients who underwent ASCT only. ORR was 69.0% (95% CI, 62.3%-75.2%) and complete response rate was 22.4%. A response ≥6 months was reported in 31 patients.[8]
- **MSI-H/dMMR solid tumors.** Pembrolizumab was the first agent to receive a tissue or disease site-agnostic approval for the treatment of patients with unresectable or metastatic MSI-H/dMMR solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options; or patients with colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Approval was based on data from five uncontrolled, single-arm clinical trials (KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158) that enrolled a total of 149 patients across trials with a total of 15 cancer types including colorectal, endometrial, and other gastrointestinal cancers. ORR was 39.6% (95% CI, 31.7-47.9) with a complete response rate of 7.4%.[9] The FDA also approved nivolumab for MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The CheckMate-142 phase 2, multicenter, single-arm study evaluated 74 patients and reported a 31.1% objective response at the median follow-up of 12.0 months.[10]
- **B-cell precursor acute lymphoblastic leukemia (ALL).** The first CAR-T cell therapy, tisagenlecleucel, was approved for the treatment of patients up to 25 years of age with refractory or second or later relapsed B-cell precursor ALL. Phase 2 data reported complete remission or complete remission with incomplete blood count recovery in 83% (n=52) of patients at three months post-treatment.[11]
- **Non-Hodgkin lymphoma (NHL).** A second CAR-T cell, axicabtagene ciloleucel, has been approved for the treatment of adults with refractory aggressive NHL based on results from the ZUMA-1 trial.[12] The Phase 2, ZUMA-1 trial met its primary endpoint of objective response rate with 82% of patients showing response. The median follow-up was 8.7 months in a population that has a historically poor prognosis. Among the responding patients, 44% had ongoing response, including 39% complete response.[12]
- **Metastatic NSCLC irrespective of PD-L1 expression.** Pembrolizumab combined with pemetrexed and carboplatin was approved for first-line therapy in patients with metastatic NSCLC irrespective of PD-L1 expression. Approval was based on the phase 2 KEYNOTE-021 trial involving 123 patients previously untreated with metastatic non-squamous NSCLC without EGFR or ALK genomic tumor aberrations. ORR for the pembrolizumab plus chemotherapy group was 55% (n=33) versus 29% (n=18) in the chemotherapy alone group.[13]

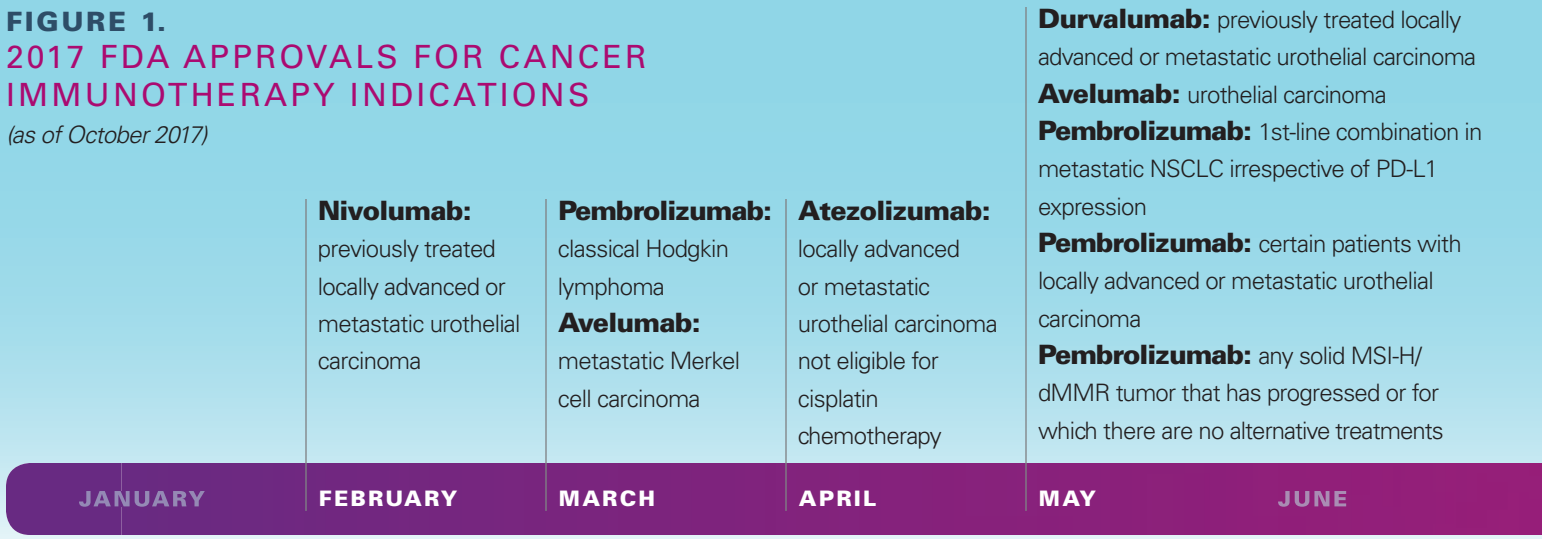
ONGOING STUDIES: I-O COMBINATION THERAPIES & NEW INDICATIONS

Cemiplimab, a PD-1 inhibitor, received breakthrough therapy designation for adults with metastatic or locally advanced and unresectable cutaneous squamous cell carcinoma. Preliminary results from a phase I study (n=26) showed an ORR of 52% and a disease control rate of 70%.[14]

Clinical benefits seen with checkpoint inhibitors are even more evident with combination regimens. Data highlights in 2017 include three-year OS outcomes from the CheckMate-067 trial, which evaluated nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone in 945 patients with unresectable stage III or IV melanoma. Significantly longer OS was seen in patients treated with combination therapy compared to monotherapy (58% for combination therapy vs 52% for nivolumab alone, and 34% for ipilimumab alone).[15] Similarly, positive results have been seen with other I-O agents in combination with checkpoint inhibitors. For instance, studies presented at the 2017 annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have shown efficacy and safety data for epacadostat—an indoleamine 2,3-dioxygenase (IDO) inhibitor—plus pembrolizumab in patients with NSCLC, urothelial cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma, triple-negative breast cancer, ovarian cancer, and advanced melanoma.[16-21]

Results like these have fortified a surge in next generation studies that are investigating the efficacy and safety of I-O combinations. The number of studies listed in clinicaltrials.gov that are investigating checkpoint inhibitor combinations (e.g., anti-PD-1/PD-L1 plus anti-CTLA-4 agents, plus other agents) has risen from 215 studies in 2015, to more than 760 studies in 2017.[22] In CAR-T cell therapy, other target antigens are being investigated in addition to CD19-directed autologous therapies, such as CD20, CD22, CD30, CD38, CD138, BCMA, and GD2, as well as allogeneic and haploidentical CAR-T cells. Evaluating checkpoint inhibitor therapy in yet-to-be-approved indications also emerged as an urgent area of focus in 2017. For instance, the multicenter, integrated, international, phase 1, 2, and 3 I-SPY trials are investigating novel therapies in women with high-risk breast cancer. Results from I-SPY2 presented at the 2017 ASCO Annual Meeting showed that the addition of pembrolizumab to standard neoadjuvant therapy improved the estimated pathological complete response rates compared with standard therapy alone in patients with metastatic HR+/HER2- and triple negative breast cancer (34% vs 14% and 62% vs 22%, respectively).[23]

FIGURE 1.
2017 FDA APPROVALS FOR CANCER IMMUNOTHERAPY INDICATIONS
(as of October 2017)



PREDICTIVE BIOMARKERS FOR CHECKPOINT INHIBITORS

While checkpoint inhibitors have shown remarkable success across numerous tumor types, an estimated 40% to 60% of patients do not respond to mono- or combination checkpoint inhibitor therapy.[24-25] Currently, there is one FDA approved companion diagnostic for checkpoint inhibition, which assesses for PD-L1 expression prior to the initiation of pembrolizumab monotherapy. Although other checkpoint inhibitors may include complementary diagnostics to determine PD-L1 expression, a companion diagnostic is not required. Moreover, treatment benefits with PD-1/PD-L1 agents are not restricted to PD-L1-positive patients, suggesting that other biomarkers may predict response to checkpoint inhibitors, such as high mutation load and tumors with mismatch repair genes.

- **Microsatellite instability.** Following the pan-tumor approval of pembrolizumab for MSI-H/dMMR tumors and nivolumab and pembrolizumab for MSI-H/dMMR metastatic colorectal cancer, testing for MSI is now recommended to identify patients with different cancer types, including pancreatic cancer and prostate cancer, who may be considered candidates for these checkpoint inhibitors.[26] These tests are commercially available and correspond with the anti-PD-1 agents.
- **Tumor mutation burden.** Tumor mutation burden (TMB) refers to the quantity of nonsynonymous mutations in a particular tissue type, and has been investigated as an emerging biomarker that predicts better clinical outcomes in bladder cancer, [27] melanoma (ipilimumab), [28-29] and NSCLC (pembrolizumab).[30] It is hypothesized that tumors with high TMB may express more neoantigens on the surface of the tumor that may induce a more robust anti-tumor immune response. TMB may also be used as a predictive biomarker for other immunotherapies, including T-cell therapies or cancer vaccines.
- **T-cell markers.** Emerging data suggest that the tumor microenvironment and T-cell repertoire and functional state may be germane to treatment response.[31] For instance, studies have reported a lack of upregulation of PD-L1 or activated T cells in patients with disease that did not respond or that progressed during checkpoint inhibitor therapy. T-cell markers that are emerging as potential biomarkers include circulating lymphocytes, neutrophils, eosinophils, and monocytes. CD8 infiltrate density, CD4+ICOShi T-cell counts, and T regulatory cell levels are also potential T-cell markers.
- **Other biomarkers.** Researchers are also looking beyond tumor tissue for potential predictive biomarkers. For instance, in melanoma, studies have used immune profiling of peripheral blood to correlate changes in circulating exhausted CD8+ T cells with tumor size; for instance, in melanoma immune profiling of peripheral blood has shown a correlation in circulating CD8+ T cells with tumor size; changes in immune profiles pre-treatment versus post-treatment with pembolizumab; and increases in absolute lymphocyte count following treatment with CTLA-4 inhibitors.[32-33] Interest in studying tumor-infiltrating lymphocyte (TIL) levels as a potential biomarker of treatment response for immunotherapy in breast cancer continues to build. Toxicity biomarkers are also an area of investigation.

JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER
Ipilimumab: pediatric patient ≥12 years with unresectable or metastatic melanoma	**Nivolumab:** MSI-H/dMMR metastatic colorectal cancer that has progressed after treatment **Tisagenlecleucel (CAR-T):** some children/young adults with advanced acute lymphoblastic leukemia	**Pembrolizumab:** previously treated recurrent locally advanced or metastatic gastric/GEJ cancer expressing PD-L1 **Nivolumab:** hepatocellular carcinoma previously treated with sorafenib	**Axicabtagene ciloleucel (CAR-T):** large B-cell lymphomas that have progressed after at least 2 prior therapies		

ACCELERATING BIOMARKER RESEARCH

Given the complexity of tumor biology and immune response, it is likely that multiple biomarkers will be needed to predict individual clinical response to I-O therapy, such as CD8 infiltrating T cells, PD-L1 expression, mutational load, IFN-gamma signature genes, and other markers. Reflecting this shift toward a more holistic approach, two notable research initiatives were recently launched to investigate robust predictive and prognostic biomarkers. The National Institutes of Health has joined with 11 biopharmaceutical companies to create a Partnership for Accelerating Cancer Therapies (PACT)—part of the Cancer Moonshot Initiative. This endeavor will focus its efforts on identifying, developing, validating, and standardizing biomarkers that can be reliably used to predict patient response to immunotherapies, ensure that the most effective therapy or combination is selected for patients to achieve the best possible response, and monitor immune response. A similar collaboration between Stand up to Cancer and Genentech is supporting research to identify biomarkers as predictors of response to immune therapies.

ROLE OF THE MICROBIOME IN IMMUNO-ONCOLOGY

Mounting evidence suggests that the gut microbiome (or microbiota), plays a fundamental role in the activation, regulation, and function of the immune system. A study presented at ASCO 2017 suggested that differential bacterial "signatures" in the gut may determine which patients will have a better response to immune checkpoint blockade.[34] Cultures from 105 fecal samples involving patients treated with checkpoint inhibitors showed distinct profiles for immune response at baseline, with higher immune infiltrates that correlated with CD8, CD3, PD1, and FoxP3 T-cell density. An abundance of Faecalibacterium prausnitzii was enriched in responders, and there was a higher diversity of gut microbiomes in responders versus non-responders (P = .03), even though there were no significant differences in oral microbiomes. These and other preclinical and clinical studies suggest that specific gut microbiomes could potentially act as biomarkers for identifying responders to checkpoint inhibitor therapy, or patients at risk of developing immune-related adverse events.

As immunotherapies continue to move into the community setting, the unremitting pace of approvals for new I-O treatments and indications for existing therapies has only intensified the imperative for targeted I-O education and resources for clinicians, patients, and caregivers.

Identifying Barriers & Sharing Solutions

I-O EDUCATION NEEDS IN THE COMMUNITY

In 2017 ACCC solicited the views of its members on a range of I-O topics via surveys, focus groups, and interviews with experts in the I-O field. For instance, a national I-O survey of oncology providers in a range of cancer program settings (n=64) found that 50% of the programs surveyed treat more than 100 patients per year with I-O agents. Despite this treatment volume, only a minority of respondents reported deep familiarity with checkpoint inhibitors (24%), monoclonal antibody therapy (32%), or combination treatment regimens (17%). Patient education, managing patient demand, familiarity with expanding indications for I-O, managing I-O toxicity, and communicating with non-oncology specialists represent unrelenting challenges for community oncology providers. Other areas of educational need that a majority of respondents identified as extremely important include patient access to and the financial implications of I-O, coverage and reimbursement issues, the clinical applications and optimization of I-O, and the practical and operational management of I-O, including having access to I-O experts. The unique toxicities and immune-related adverse events (irAEs) associated with checkpoint inhibitors emerged as an area in critical need of educational resources and pragmatic, evidence-based guidance from experts in the I-O field.

VISITING EXPERTS PROGRAM

The ACCC Visiting Experts program was established in December 2016 for ACCC Cancer Program Members. A series of seven workshops was designed to prepare the multidisciplinary cancer care team for the complex implementation of I-O with a focus on advancements, operations, and effective practices. Each tailored, one-day workshop convened a multidisciplinary oncology team experienced in the delivery of cancer immunotherapy, and was held onsite at select ACCC member cancer centers. Baseline data collected from each cancer program's workshop application, combined with information gleaned from a kick-off call with program staff, enabled faculty to tailor each workshop curriculum to meet the self-identified learning needs of cancer program staff. Table 1 summarizes the range of challenges identified at baseline.

PARTICIPATING PROGRAMS:

- Columbus Regional Health, Columbus, IN
- Lehigh Valley Health Network Cancer Institute, Allentown, PA
- Morristown Medical Center, Morristown, NJ
- Riverside Health System, Newport News, VA
- Saint Agnes Cancer Institute, Baltimore, MD
- St. Joseph Hospital, Orange, CA
- Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

TABLE 1.

VISITING EXPERTS PROGRAM PARTICIPANT-REPORTED I-O CHALLENGES

- Developing irAE protocols
- Building a comprehensive nurse triage knowledge-base
- Pharmacy inventory management
- Recognition and management of irAEs 'after hours'
- Lack of specialist familiarity with irAEs
- Differentiating between pseudoprogression and real progression
- Educating patients about symptom self-reporting
- Coordinating care following I-O treatment
- Communication and logistics in irAE management

WHAT ARE PARTICIPANTS SAYING?

"It was encouraging to see overlap in the workshop with what we see in our clinic. Our cancer center has a very interdisciplinary practice and patients tell different parts of their story to different clinicians, particularly about the side effects they are experiencing, so clinicians need to be able to communicate with each other in order to get the full story."

7 WORKSHOPS

264 PARTICIPANTS

28 FACULTY

"Programs like those put together by ACCC are good because they represent everyone's perspective, not just the oncologist. There was a medical oncologist, a pharmacist, an administrator, as well as a nurse—all of whom have extensive immuno-oncology experience and each with unique ways that their particular institutions have dealt with some of the challenges of delivering these therapies."

Each ACCC visiting expert team—comprised of a clinician, administrator, nurse, and pharmacist—fostered direct, actionable dialogue on critical I-O issues, and, where appropriate, drew on case-based material to address I-O challenges. The workshops were structured around a bi-directional learning format that fostered collaborative exchange between participants and faculty.

ACCC evaluated the impact of these workshops via participant questionnaires and follow-up debriefing telephone interviews with workshop participants and faculty members. Participants identified a range of key takeaways from the Visiting Experts workshops (Table 2, below), and evaluations affirm that the direct, clinician-to-clinician relationships fostered by bi-directional learning are key to validating program staff experiences and building I-O clinical capacity within community cancer centers. Notably, the exposure of participants to I-O experts—especially from those involved in early immunotherapy trials—shored up their clinical confidence. Participants valued the opportunity to connect with experts beyond their own programs who shared "on the ground" I-O expertise, such as effective practices and algorithms for managing irAEs in real-world settings.

TABLE 2.
VISITING EXPERTS PROGRAM GENERATED EFFECTIVE PRACTICES

- **Quick Clinics**
  Develop specialized clinics to treat patients with emergent irAEs, staffed by specialists with expertise in I-O side effects.
- **Virtual Tumor Boards**
  Educate staff via a broad range of specialist experts (e.g., dermatologists, endocrinologists, gastroenterologists, neurologists, ophthalmologists) who present a patient with emergent irAEs and discuss how to manage them.
- **I-O Patient Identification Card**
  Provide patients with an I-O patient identification card that has drug/biologic-related information and a 24/7 oncologist contact phone number so that non-oncology providers can reach the oncologist should the patient require emergency care.
- **Management Resources**
  Staff the I-O infusion clinic with a core group of nurses.
- **In-Service Education**
  Educate non-oncology staff (i.e., emergency room physicians and nurses, hospitalists, and intensivists) by providing an overview of what immunotherapy is, what adverse event signs and symptoms to look for, and how to start working patients up for non-oncology staff.
- **Patient Education**
  Ensure patients and caregivers understand how I-O differs from traditional cytotoxic cancer agents and provide reinforcement tools to help them communicate with other healthcare professionals in non-oncology settings.
- **irAE Working Groups/Toxicity Teams**
  Develop a list of knowledgeable, "go-to" specialists for questions regarding irAEs and as a mechanism to expedite referral and consultation when needed.

Evaluation results will also guide curriculum development for future Visiting Experts workshops in 2018. If you are interested in this education opportunity for your program, contact us at **resources@accc-cancer.org**.

CASE STUDIES IN IMMUNO-ONCOLOGY PROGRAM

Launched in April 2017, the Case Studies in Immuno-Oncology program is a personalized learning initiative for the multidisciplinary cancer care team designed to deliver evidence-based information on the latest developments in the use of cancer immunotherapy and effective management of associated irAEs. I-O expert faculty traveled to host ACCC member sites for these case-based programs. Multidisciplinary cancer care teams at these host sites were encouraged to present challenging, real-world patient cases for in-depth discussion. Participants gained the perspective of I-O expert faculty, who, in turn, benefited from learning about the I-O successes and challenges that multidisciplinary care team members shared based on their experiences of delivering immunotherapy in the community setting.

This unique experience is designed to enhance the current knowledge base and clinical reasoning skills of clinicians and to enable ACCC members to deliver their I-O programs across the care continuum. To date, eight of a series of ten programs have been conducted at community hospital sites throughout the nation, focused on cases involving head and neck cancer, melanoma, and NSCLC, among others. Participants (156) have included medical oncologists and hematologists, internists, physician assistants, nurses, nurse navigators, advanced practice providers, pharmacists, fellows, residents, and other members of the multidisciplinary cancer care team involved in treating or monitoring patients undergoing cancer immunotherapy.

CASE STUDIES IN IMMUNO-ONCOLOGY PROGRAM: PARTICIPATING SITES

- Christus St. Michael Cancer Center, Texarkana, TX
- Englewood Hospital and Medical Center, Englewood, NJ
- Florida Hospital Memorial Medical Center, Daytona Beach, FL
- Peninsula Regional Medical Center, Salisbury, MD
- Riverside Cancer Institute, Kankakee, IL
- Saint Agnes Cancer Institute, Baltimore, MD
- St. Joseph Hospital, Orange, CA
- Valley Health Hospital, Ridgewood, NJ

NON-ONCOLOGY SPECIALISTS ALLIANCE INITIATIVE

Patients who receive I-O agents often see clinicians and specialists outside of their main oncology care team, such as primary care providers, emergency room (ER) physicians, or specialists. Patients visit these clinicians for many reasons, including medical concerns that may or may not be related to treatment with cancer immunotherapy; however, non-oncology clinicians may be unaware that the patient is receiving or has received immunotherapy. In addition, patients may be referred by their primary oncologist to specialists (e.g., an endocrinologist, pulmonologist, dermatologist, gastroenterologist, or rheumatologist), to specifically address an emergent irAE. However, non-oncology specialists may be unfamiliar with the concept of immunotherapy. These knowledge gaps can result in suboptimal patient care, including unnecessary ER visits and hospital admissions.

To coordinate care for patients with emergent irAEs and ensure that patients receive optimal treatment in a timely fashion, it is imperative that non-oncology providers are familiar with I-O; appreciate how these new therapies and their side effects differ from traditional chemotherapy; and recognize the importance of cross-specialty communication regarding these patients. Therefore, to gain insight on the educational, operational, and communication needs of non-oncology clinicians, in 2017 ACCC conducted three virtual Non-Oncology Specialists Alliance focus groups with non-oncology specialists in radiology, emergency medicine, primary care, pulmonology, palliative care, and neurology. In addition, ACCC interviewed Jarushka Naidoo, MBBCh, Assistant Professor of Oncology at Johns Hopkins Medicine, Baltimore, Maryland, to gain a better understanding of communication and care coordination issues from the perspective of the medical oncologist. Dr. Naidoo specializes in lung cancer and has formed a toxicity team at her institution to address communication with non-oncology specialists and improve care coordination.

Discussions focused on the following key areas:

- Clinical assessment
- Educational assessment
- Interaction and communication with the multidisciplinary team
- Needs assessment

Analysis of these data points enabled ACCC to establish a baseline of educational needs for non-oncology specialists (Table 3, page 14).

TABLE 3.
FOCUS GROUP HIGHLIGHTS—KEY AREAS OF EDUCATIONAL AND OPERATIONAL NEEDS

1. Clinical Assessment

- The **frequency of interactions** between non-oncology specialists and patients who are taking an I-O agent varies depending on the specialty of the treating clinician. For instance, pulmonologists, radiologists, and palliative care clinicians see more I-O patients compared to hospitalists/PCPs (primary care physicians) or specialists who treat rare irAEs (e.g. neurologist).
- **Fragmented EHR/EMR systems** in some community hospitals remain a challenge. Specialists may be unaware of their patients' current medications and whether they are being or have been treated with an I-O agent.
- ER physicians are **not always able to easily identify** patients who are taking an I-O agent; sometimes patients may not be able to communicate that they are or have taken an I-O agent upon arrival to the ER.

2. Non-Oncologist Educational Assessment

- **Not all oncologists have experience with I-O** or with supportive care therapies prescribed by non-oncology specialists.
- Hospitalists/PCPs and ER staff have the **greatest need** for I-O education. I-O knowledge for specialists that interact less frequently with the primary oncology care team may be limited to select irAEs (e.g., neurologists may be limited to irAEs related to neurology).
- Formal courses can act as a resource for I-O education; however, many non-oncology specialists are **unaware of** specific I-O learning resources. **Patient education** is key.

3. Education to Support Interaction and Communication with the Multidisciplinary Cancer Care Team

- I-O education for non-oncology specialists needs to be **easily accessible**, available in real time, and constantly updated.
- Support **structured interactions** between non-oncology clinicians and oncology specialists.
- **Access to clinicians with I-O expertise** is key.
- Communication could **include one-on-one meetings or communication via weekly clinics**. Interactions with advanced practice practitioners were also recommended.
- **Dissemination of I-O education** through organizations such as the American College of Physicians, as well as through regional and national conferences.
- **Medical oncologists** should be responsible for educating clinical staff, while nurse navigators and pharmacists should support educating the team.

In late 2017, following these focus groups, ACCC designed and fielded surveys to members of the cancer care team and non-oncology specialists to gain a better understanding of the educational and operational needs of both oncology and non-oncology providers concerning communication and care coordination. Of 64 respondents comprising the multidisiplinary team, 83% reported that care coordination and communication with non-oncology specialists is a compelling challenge, and affirmed the need for ongoing educational support. ACCC will use these results to guide the development of immunotherapy education programs and resources to enable oncology clinicians and non-oncology specialists to partner effectively, establish effective practices regarding the sharing of I-O knowledge, and optimize the management of patients treated with I-O therapy.

IMMUNE-RELATED ADVERSE EVENTS INITIATIVE

The immunologic enhancement stimulated by checkpoint inhibitors can produce autoimmune-like and inflammatory toxicities that can cause damage to several organs and tissues, including the skin, gastrointestinal, hepatic, pulmonary, mucocutaneous, and endocrine systems. There are also toxicity concerns in CAR T-cell therapy related to cytokine release syndrome (CRS), which can occur after infusion (1-14 days post-infusion for patients with ALL and 14-21 days for patients with CLL).[35] Although irAEs can be addressed with prompt identification and treatment, challenges inherent in recognizing and managing irAEs were a strong and persistent theme across all 2017 programs. Provider education in this area clearly remains key.

As a critical step toward building the capacity of community cancer programs to develop irAE management programs, ACCC conducted an environmental scan of existing provider and patient irAE resources for monotherapy I-O agents and combination regimens. This scan also catalogued the communication processes involved in developing effective real-world irAE management solutions and in determining plans of action to rapidly disseminate irAE protocols among oncology providers and non-oncology specialists who treat I-O patients (see Appendix).

Current irAE Algorithms: A Snapshot

In addition to clinical management algorithms for common irAEs associated with ipilimumab in metastatic melanoma,[36] and Risk Evaluation and Mitigation Strategies (REMS) to assist clinicians in monitoring, recognizing, and managing irAEs associated with checkpoint inhibitors, the European Society of Medical Oncology (ESMO) published toxicity management guidelines in June 2017 that provide recommendations for both monotherapy and checkpoint blockade combination therapies.[36] The Oncology Nursing Society (ONS) has published a specific consensus statement on managing irAEs with ipilimumab monotherapy and combined with nivolumab in advanced melanoma, as well as for PD-1 inhibitor therapy more generally,[37] and in February 2017, the National Comprehensive Cancer Network (NCCN) and ASCO announced plans to collaboratively develop clinical practice guidelines on the management of irAEs, and their release is anticipated in 2018.

Many community cancer centers have also pioneered strategies to manage immune-related toxicity and care coordination across the oncology care team. Such strategies include:

- Identifying patients who have received or are receiving immunotherapy
- Triaging patients based on symptoms
- Developing same-day care models (e.g., via "quick clinics" or a symptom management workspace)
- Establishing standard of practice guidelines for irAE management
- Continuously educating providers, patients/caregivers, and non-clinical staff.

Effective Practices in irAE Management

In conjunction with the environmental scan, ACCC interviewed staff at three community cancer programs that have developed I-O programs who shared some of their strategies for managing irAEs. Figure 2 (page 16) provides a snapshot of these effective practices.

FIGURE 2.
EFFECTIVE PRACTICES IN irAE MANAGEMENT

PATIENT EDUCATION
University of Colorado Cancer Center, CO

- Use patient-friendly language to explain the mechanism of action, and help patients understand the differences between disease- and treatment-related side effects.
- An immunotherapy wallet card offers a clear mechanism for patients to communicate with their non-oncology providers.

COMMUNICATION
St. Joseph Cancer Center, Anaheim, CA

- Identify champions and front-line staff that will help you build an I-O program and manage patients being treated with immunotherapy.
- Promote awareness of irAEs across your organization through in-service training.
- Consider whether you need a molecular tumor board, an I-O nurse navigator, or I-O triage nurses.

EMPOWERMENT
White Plains Cancer Center, New York, NY

- Use education to prepare the whole team on how to recognize emergent irAEs—patients, oncology clinicians, specialties, and front desk staff.
- Establish the medical oncologist as the primary person for first-line patient communication and care coordination.
- Integrate non-oncology specialists to the I-O multidisciplinary team.

Ongoing Areas for irAE Education in 2018

Environmental scan and interview findings underscore a discernible need for highly pragmatic and detailed resources on irAE management strategies, especially in the combination regimen setting. There is a particular deficit in targeted information on and accessible algorithms for managing irAEs for an audience of nurses, emergency and primary care clinicians, and non-oncology specialists. Similarly, there are few resources that provide guidance on communication effective practices among members of the oncology multidisciplinary team or provide guidance on the roles and responsibilities of its members to ensure care coordination with non-oncology specialists. The absence of patient-directed materials for cancer programs represents an additional information gap. ACCC will draw on these environmental scan insights to guide the development of future educational resources and tools that support irAE management in community cancer programs.

TUMOR-SPECIFIC SUBCOMMITTEES

In 2016, ACCC established three Tumor-Specific Subcommittees to address key, real-world issues in clinical practice; institutional and operational issues; and reimbursement/coverage issues. Each subcommittee in Lung, Melanoma, and Emerging Tumors—which covers indications outside of Lung Cancer and Melanoma—is comprised of clinical experts representing different members of the primary oncology care team, including physicians, nurses, pharmacists, and administrators and other non-clinical experts with experience in areas such as operations management, social services, and research design. These subcommittee members contribute real world I-O expertise within their respective disciplines, and are tasked with identifying the issues, concerns, and needs of the multidisciplinary cancer care team related to I-O and specific tumor types, and providing suggestions for the development of resources to address those needs.

Although these subcommittees are tumor specific, there is some overlap in the issues that faculty have identified as challenging for clinicians involved in managing patients being treated with cancer immunotherapy. For instance, across the board, prior authorization for I-O therapy is becoming even more demanding for some cancer centers. Similarly, tumor-specific experts highlighted the common challenges associated with how to apply biomarkers in clinical practice, or how to recognize and manage emergent irAEs in concert with appropriate non-oncology specialists. Nonetheless, as Table 4 (below) summarizes, both lung cancer and melanoma are also characterized by unique, tumor-specific challenges.

TABLE 4.
TUMOR-SPECIFIC CHALLENGES IN 2017

1. Melanoma

- Selecting monotherapy vs combination therapy
- Managing increased toxicities due to combination therapies
- Being able to accurately assess response to immunotherapy in melanoma and identify pseudoprogression
- Managing patients with autoimmune disease and those taking immunosuppression agents

2. Lung

- Obtaining adequate tissue samples for biomarker testing
- Identifying candidates for combination therapies
- Appropriately tapering steroids in the context of irAE management
- Maintaining adherence when patient achieves durable response
- Addressing the financial strain of managing irAEs with supportive care
- EMR/EHR interoperability remains a national problem and does not always effectively support communication between academic/community centers

TUMOR-SPECIFIC TOOLKITS

Drawing on these expert insights, ACCC launched a series of tumor-specific toolkits in January 2017. These toolkits are shared electronically and feature real-world, relevant resources to keep community providers up-to-date on the rapidly expanding immunotherapy landscape, such as webinars, interviews, and case-based discussions.

In 2018, ACCC will also explore new resources to complement the toolkits such as:

- Accessible, laminated information cards to educate the multidisciplinary team and patients on toxicities and protocols associated with immunotherapies
- Smartphone applications for education and resource links
- Patient immunotherapy hotline regarding any potential or occurring issues as they relate to immunotherapy

eNEWSLETTERS AND WEBINARS

ACCC published a series of monthly e-newsletters and webinars in 2017 that addressed real-world practice considerations across five core areas: Clinical Optimization, Coverage & Reimbursement, Operational Effective Practices, Patient Access and Advocacy, and Training & Development. Educational content addressed topics such as:

- Defining value in I-O
- Managing patient expectations in I-O treatment
- Effective practices in I-O operations
- Recognizing and managing irAEs
- Emerging immunotherapies and biomarkers
- Tumor-specific I-O topics
- Financial advocacy and resources for I-O patients
- Role of the multidisciplinary team in cancer care
- Profiles of community-based cancer care team members
- CAR-T therapy approval and ongoing research
- The microbiome in cancer immunotherapy

ACCC will continue to provide a range of educational content on the practical application of immunotherapies, including role-specific webinars designed to assist multidisciplinary cancer care team members in the optimization of patient care, overcome reimbursement challenges, and inform on operational approaches for payment, among others. In an effort to further engage oncology stakeholders in the I-O dialogue, as well as help ACCC identify emerging I-O challenges for community cancer programs and develop effective practices to optimize I-O integration, ACCC will also post I-O topics/questions on ACCCExchange. ACCC members can access this online community forum at **mynetwork.accc-cancer.org/home**.

Policy, Access, & Value of Immuno-Oncology

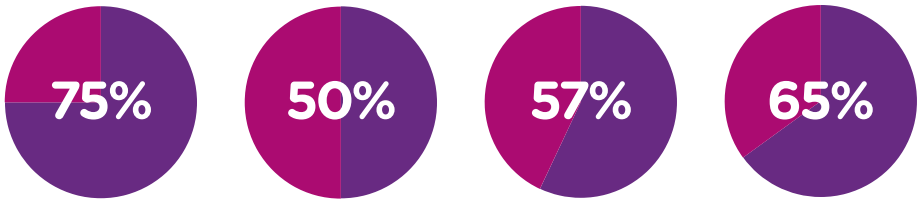
UNDERSTANDING VALUE: I-O POLICY SURVEY

While momentum around immunotherapies for cancer continues to build, the high cost of these therapies has placed them at the center of debate about how best to define and measure value in cancer care. To identify and overcome policy and financial barriers to accessing innovative therapies, ACCC reviewed the current I-O policy, reimbursement, and access landscape via an environmental scan and fielded a Policy, Access, and Value survey to the multidisciplinary cancer care team to better understand I-O access barriers and concerns.

A majority of survey respondents (n=107) were pharmacists or pharmacy technicians, with 45% of respondents based in hospital-based outpatient cancer centers. Results underscored the need for additional education on value-based programs that are impacting the delivery of care, including Medicare's Merit-based Incentive Payment System (MIPS), the Oncology Care Model (OCM)—in which at least 14 commercial payers are currently participating—and other alternative payment models (APMs).[37] For instance, fewer than 20% of respondents professed a working knowledge of Centers for Medicare & Medicaid Services (CMS) initiatives such as the Quality Payment Program (QPP), MIPS, or the OCM.

A majority of respondents (57%) reported that their cancer programs experience coverage reimbursement barriers related to I-O agents and view these barriers as a consequence of the struggle of payers to keep up with rapid FDA approvals and NCCN recommendations for I-O agents (65%).

There is also a clear need for additional educational efforts to ensure that oncology providers in the community are prepared for the workflow, technical, and clinical changes necessary for success in value-based payment models. Finally, the OCM pilot links payment to enhanced services, quality metric performance, and cost control; therefore, the ability to manage irAEs and better understand appropriate I-O combinations and sequencing from a safety perspective is more critical than ever. However, only 23% of respondents reported that their cancer program had a specific I-O strategy in place to diagnose and manage irAEs.



75%
Unfamiliar with value-based payment models

50%
Difficult to implement 24/7 clinician access as part of OCM

57%
Coverage and reimbursement barriers

65%
Respondents view payers as struggling to keep up

HIGHLIGHTS FROM THE ACCC I-O POLICY SUMMIT— A 360-DEGREE PERSPECTIVE

Survey and environmental scan results served as pre-reading to foster discussion among participants in an I-O Policy Summit hosted by ACCC on August 18, 2017. The I-O Policy Summit brought together a robust group of representatives from a diverse range of stakeholder organizations to share their perspectives on current real-world I-O challenges. Participants included patient advocacy groups, pharmacy, research, regulatory agencies, industry, oncology clinician leadership, oncology nursing leadership, pharmacy leadership, and payers (Table 5). Discussion focused on the following areas:

- Clinical and Policy Issues
- Alternative Payment Models
- Application and Impact of Quality Measures
- Payer Management of I-O
- Future Challenges and Opportunities

The conversation among stakeholders yielded a 360-degree perspective on the current landscape for the translation of immunotherapy from bench to bedside, and included discussion of the following top-level issues, which served to further reinforce key directions for future educational efforts.

Biomarkers. As the number of approvals for I-O agents and combinations continue to expand, biomarker-driven therapy will become an increasingly important strategy for identifying those patients most likely to benefit from being treated with an I-O agent and to help mitigate cost. The development of biomarkers could also be used to validate and expedite pre-authorizations and contribute to a "totality of evidence" if the FDA begins to incorporate expedited clinical review in the I-O field.

Education. Understanding of the side effects, late effects, and long-term effects, and the nuances of immunotherapy delivery for patients in the community continues to evolve. On-going education is imperative not only for the multidisciplinary oncology team, but also for other providers who care for I-O patients (e.g., primary care, endocrinologists, pulmonologists, radiologists, ER staff) as well as the patients and their caregivers. Education is necessary around combination therapy and I-O sequencing and irAE management.

Pharmacy Perspective. The arrival of I-O agents has fundamentally changed the landscape of clinical practice over the past three years. P&T Committees in the community setting must have the capacity to address issues around appropriate use, inventory management, and cost of expensive new and emerging I-O agents to avoid financial toxicity for patients, providers, and institutions.

Access to I-O Therapies. Prior authorizations continue to be a barrier to access. Although pharmacy and pharmacy benefit manager participants typically follow the lead of the NCCN Drugs & Biologics Compendium, the high cost of these agents leads to critical pharmacy questions about how to afford I-O therapies and how physicians will use them.

Clinical Trial Enrollment. It remains challenging to accrue patients to open I-O trials. Greater access to I-O clinical trials in the community setting may not only reduce patient access barriers, but also expand the potential for investigating combination therapy and I-O agent sequencing.

Alternative Payment Models. Discussion of APMs focused primarily on the Oncology Care Model (OCM). Summit attendees participating in the OCM agreed that during the first year of the model, efforts centered largely on establishing practice infrastructure for OCM requirements. With that accomplished, priorities for OCM practices include reducing inpatient admissions and ER visits and avoiding adverse events. Going forward, OCM participants will need to address issues around high-cost anticancer agents, as well as methods for ensuring practice sustainability in risk-sharing payment models.

Quality Measures. Coming to consensus on quality measures in oncology remains a challenge. From the patient advocate perspective, quality measure concerns are multifold, including:

- Tension between the driving trend in oncology toward standardized measure sets (e.g., pathways) and precision medicine, which is premised on using appropriate variations to individualize patient care.
- Current patient satisfaction measurement tools that do not assess what really matters to patients such as quality of life and outcomes.
- Quality measures that assess process rather than tangible patient outcomes (e.g., staying out of the hospital).

Many patient advocacy groups are developing their own quality measures based on what patients say is important to them, including not just clinical measures but also quality-of-life measures such as disruption to work, childcare, and transportation to treatment. Additionally, recent data presented at ASCO 2017 showed that using a web-based patient-reported outcomes (PROs) tool to monitor symptoms in patients being treated with chemotherapy was associated with a significantly better overall survival compared with usual care monitoring (31.2 months vs 26 months).[39] These data illustrate the potential benefit of integrating patient-centric quality measures and patient-reported outcomes into value-based programs like OCM and MIPS to improve patient experience and outcomes.

TABLE 5.
ACCC I-O POLICY SUMMIT PARTICIPANT GROUPS

PROVIDER	POLICY AND INNOVATORS	PATIENT ADVOCACY	PAYER
West Clinic, P.C.; The University of Tennessee	National Cancer Policy Forum, National Academies of Sciences, Engineering and Medicine (NASEM)	Patient Advocate Foundation (PAF)	CVS Caremark
Monocacy Health Partners; Frederick Regional Health System	The Pharmaceutical Research and Manufacturers of America (PhRMA)	Cancer Support Community (CSC)	
Johns Hopkins University School of Medicine	National Institutes of Health, National Cancer Institute (NCI)	National Coalition for Cancer Survivorship (NCCS)	
McKesson Specialty Health	Center for Drug Evaluation and Research (CDER), FDA		
Oncology Nursing Society (ONS)	Parker Institute for Cancer Immunotherapy		
Mission Health System	Society for Immunotherapy of Cancer (SITC)		
Hematology/Oncology Pharmacy Association (HOPA)			

Payer Management of I-O. As the oncology reimbursement landscape continues to evolve, key concerns include:

- The need for biomarkers for patient selection to ensure those most likely to benefit from the I-O therapy will receive it.
- The need for the healthcare system to be more adaptable in "looking at good data."
- Variation in coverage under different health plans.
- Prior authorizations creating barriers to access and uncertainty for patients, providers, and practices.
- Managed care organizations and others looking at how to bundle oncology products into trend management pools.

REAL-WORLD ISSUES FACING I-O IN 2018

- Quality measures that include a patient's functional status.
- Future treatment decisions informed by biomarkers and life circumstances.
- Patient navigation of the increasingly complex cancer care system.
- An adaptable healthcare delivery system that more nimbly accommodates major therapeutic advances.
- Comparative effectiveness based on real-world evidence.
- Develop and implement patient-reported outcomes.
- Strategies to bring clinical trials to community hospitals.
- Greater investment in analytics to support nimble feedback.
- Establish and maintain a national registry to capture and analyze data from real-world care.
- Prepare the oncology workforce to move from a disease-state-specific care model to a biomarker-driven model.

View ACCC videos for highlights from the policy summit by visiting **accc-iclio.org/policy**.

2017 & Beyond—Transforming the Delivery of Cancer Care in the Community

Immuno-oncology continues to advance with the approval of novel agents and supplemental indications for already approved immunotherapies for treating patients with cancer. With the plethora of clinical trials ongoing, combination immunotherapies and novel I-O agents with differing mechanisms of action will continue to improve overall outcomes for patients with cancer. Newer agents include approval of CAR T-cell therapies, tisagenlecleucel and axicabtagene ciloleucel, for hematologic malignancies, and IDO inhibitors in development in combination with a number of agents, including checkpoint inhibitors

The arrival of these newer agents brings about new issues and concerns, including operational challenges and the handling of toxicities with combination therapies and novel mechanisms of action. In addition, many of the issues and challenges of the past are still relevant today, including affordability and patient access to these agents.

As cancer immunotherapies continue to transform the delivery of cancer care, ACCC will continue to lead the exchange of information and solutions for care delivery with community cancer team members—with a focus on the key areas of coordination and communication, optimization, research, and clinical education. By centering on these critical operational areas, ACCC aims to support community cancer care teams to better identify appropriate patients for cancer immunotherapies, improve care coordination for irAE management, support patient access and mitigate reimbursement issues, identify and expand access to appropriate clinical trials for patients, and modify survivorship care plans as needed for patients who have been on an I-O therapy.

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Appendix

EFFECTIVE PRACTICES IN IMMUNE-RELATED ADVERSE EVENT MANAGEMENT

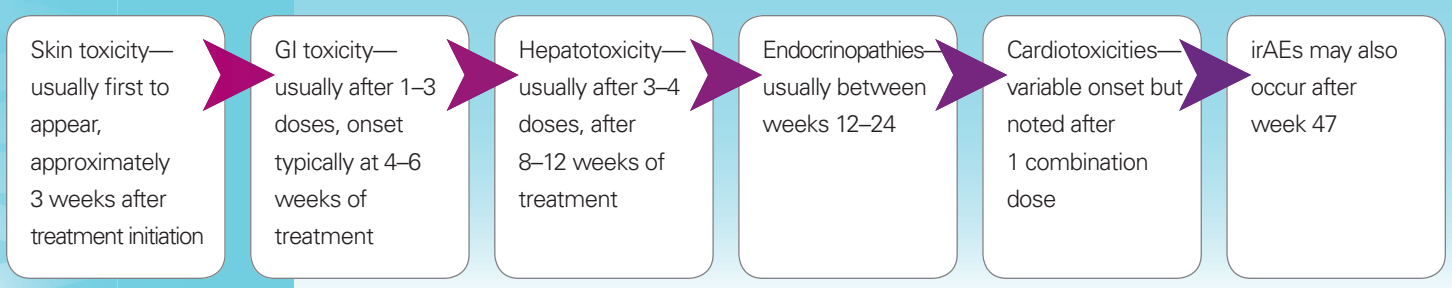
By Alexandra Howson, PhD

Since 2011, the U. S. Food and Drug Administration (FDA) has approved six immuno-oncology (I-O) checkpoint inhibitors that are adding months to the lives of patients with advanced cancers such as metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, Hodgkin lymphoma, head and neck cancer, bladder cancer, and microsatellite instability-high (MSI-H) or mismatch repair deficient tumors. These agents include CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitors (ipilimumab), cell death protein (PD-1) inhibitors (nivolumab, pembrolizumab), and programmed death ligand-1 (PD-L1) inhibitors (atezolizumab, avelumab, and durvalumab).[1] On August 30, 2017, the FDA also approved chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel (Kymriah), for the treatment of patients up to 25 years of age with refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL). This was followed on October 18, 2017, by FDA approval of a second CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment and certain patients with non-Hodgkin lymphoma. Emerging I-O agents (e.g., pidiluzumab) have also demonstrated anti-tumor activity in various tumor types, and several clinical trials are investigating immunotherapy agents in combination with other immunotherapy agents, radiation, or chemotherapy.

IMMUNE-RELATED ADVERSE EVENTS

Immunologic enhancement stimulated by checkpoint inhibitors can produce autoimmune-like and inflammatory toxicities. These immune-related adverse events (irAEs) have the ability to impact several organs and tissues, including the skin, gastrointestinal, hepatic, pulmonary, mucocutaneous, and endocrine systems.[2] The types and intensity of irAEs observed with checkpoint inhibitors are diverse. For instance, pneumonitis appears to be less common with CTLA-4 inhibitor treatment than with PD-1 blockade, while diarrhea/colitis is a more common toxicity in patients receiving therapy with a CTLA-4 inhibitor than with anti-PD-1 agents.[3-5] Timing of irAE onset also varies. In monotherapy checkpoint blockade, irAEs typically develop during the first 3 months of therapy, broadly following a predictable pattern of onset (Figure 1, below). Skin toxicities appear first; colitis after 1-3 doses; then hepatitis and endocrinopathies between weeks 12 and 24.[6] However, irAE onset can be rapid for ipilumumab, for which toxicities appear to be dose related,[6,7] and some irAEs may even occur after the final dose, beyond week 47.[6,8,9]

FIGURE 1.
CHECKPOINT INHIBITOR TOXICITY ONSET PATTERNS[6,7,10,11]



Several studies of anti-PD-1/PD-L1 agents in combination with other immunotherapeutic agents, as well as with chemotherapy, targeted therapy, and radiation therapy are also underway. Although these combinations show impressive response rates, they are also associated with increased toxicity and new irAEs;[2] time-to-onset may also be shorter for combination therapy irAEs.[6,8,9]

Currently, no prospective clinical trials have been conducted to guide the management of irAEs; therefore, many community cancer centers have pioneered algorithms and protocols to manage immune-related toxicity and care coordination across the oncology care team. In this article, we provide a snapshot of three community cancer programs that have developed I-O programs and strategies for managing irAEs.

UNIVERSITY OF COLORADO CANCER CENTER

The I-O program at the University of Colorado Cancer Center (UCCC) has grown rapidly, in part due to the development of its robust Targeted Therapy Trials (T3) program. This program accommodates umbrella or basket trials that are not within UCCC's Phase 1 clinical trial program, including immunotherapy trials in melanoma, lung cancer, and other tumor types. In addition to approximately 16 physicians with expertise across a range of solid and hematological cancers, the T3 program employs a team of 16 advanced practice providers (APPs).

Differentiating irAEs

Brianna Hoffner, MSN, NP, RN, the lead APP for medical oncology, is passionate about the benefits of I-O for patients with advanced cancer. She draws on several years of experience working in cancer immunotherapy trials, including the Keynote 001 initial melanoma expansion trial that led to the approval of pembrolizumab for patients with unresectable or metastatic melanoma with disease progression following ipilumumab and, if BRAFv600 mutated, a BRAF inhibitor.[12] Through clinical trial participation at UCCC, her team has garnered considerable experience in recognizing some of the most common irAEs, like dermatitis, hepatitis, pneumonitis, and thyroiditis. Even so, Hoffner says, it can be challenging to differentiate between a treatment- or disease-related side effect. For example, xerostomia (dry mouth resulting from reduced or absent saliva flow) can be a side effect of immunotherapy. When people with head and neck cancer who are treated with a checkpoint inhibitor have a dry mouth, it can be hard to determine whether the symptom is related to their prior therapies—such as radiation therapy—their underlying disease, or the checkpoint inhibitor. Similarly, most patients with lung cancer have a cough or shortness of breath, but this can also be a symptom of pneumonitis, which is a side effect of checkpoint inhibitor treatment.

Distinguishing between side effects of the underlying disease and side effects of I-O treatment is only going to become more complex with the approval of checkpoint inhibitors in combination with other modalities (e.g., chemotherapy, targeted therapy, other I-O agents). So Hoffner's team is developing strategies on how to recognize and manage irAEs that have more nuanced clinical presentations, and how to ensure that specialists are involved in determining the appropriate work-up for a patient who might have an irAE.

irAE Management Protocols: Observe, Listen, Grade

One of these strategies includes the development and implementation of irAE clinical management protocols. For instance, Hoffner has been instrumental in creating a non-branded, consensus Care Step Pathway (CSP) for 11 of the most common irAEs in ipilimumab-based melanoma treatment.[13] Developed in concert with the Melanoma Nursing Initiative, of which Hoffner is a member, the Care Step Pathway emphasizes the importance of observing and listening to patients and grading toxicity as the foundation for nursing interventions to manage irAEs. Hoffner explained the importance of having a protocol in place that supports appropriate and timely management to ensure that irAEs are swiftly resolved:

> *We had a patient recently who was on a clinical trial with a PD-L1 drug, (and) who came in with really bad headaches. The person who saw this patient was not an I-O provider and gave them Imitrex (sumatriptan, an anti-migraine agent) and other things. But at the next visit the patient saw a provider who's more familiar with I-O and who did the appropriate workup. The patient had some hypophysitis causing headaches, and with a little hydrocortisone, their symptoms resolved.*

A second strategy involves developing laboratory testing protocols for irAEs. For instance, if a lung cancer patient who is being treated with combination chemotherapy and I-O presents with anemia, it is not yet clear which tests to order to determine whether the anemia is related to the chemotherapy or the immunotherapy. To develop testing protocols that are specific to irAEs, Hoffner and the oncology team are collaborating with rheumatology, head and neck, and pulmonary services to identify the laboratory tests these specialists use to evaluate disease- and treatment-related side effects. Similarly, such collaboration in the case of dry mouth/xerostomia, as discussed above, has shown that clinicians can identify Sjögren's syndrome in an immune setting by evaluating patients via a serum solid phase immunoassay test for Ro/SSA and La/SSB antibodies.

Education, Education, Education

Education for all members of the multidisciplinary oncology care team is also key to establishing expertise on recognizing and managing irAEs. To this end, Hoffner is currently chairing a project to create a monthly immunotherapy tumor board in conjunction with UCCC leadership. This tumor board also serves as a means to initiate conversations with specialists and help them envision their role in the process of managing patients with irAEs. At UCCC, each disease type has a weekly tumor board, to which consulting specialists are invited to discuss more difficult irAEs as they emerge. Most recently, the onco-cardiology service was invited to review the case of a patient being treated with a checkpoint inhibitor who developed pericarditis.

Another area of targeted irAE education at UCCC concerns the spectrum of toxicity across I-O agents and differences in toxicity that are based on how each agent is manufactured. The widespread use of BRAF/MEK inhibitors in melanoma provides an example of these differences. Even though the targets are similar for currently approved BRAF agents (i.e., vemurafenib, dabrafenib) and MEK agents (trametinib), their side effect profile and monitoring parameters differ. To address those differences, Hoffner says UCCC has "done a ton of education on how to think about those drugs differently and what you should be watching for on one versus the other." She anticipates that UCCC will build on this established education strategy as new I-O combinations are approved to enable clinicians to consider what is distinct about each combination.

Hoffner personally compiles information on I-O agents that she presents to APPs who manage patients with melanoma, and she is passionate about doing so. This is because she's seen providers take patients off therapy too early because they fear symptom escalation, or take patients off therapy when their irAEs are beyond a point where they could have been safely treated. She says, "Immunotherapy has such incredible promise in so many different tumor types that if we, as providers, can understand it really well and have all of the best possible tools—which are changing on a daily basis—that's the best that we can do."

Other irAE education strategies at UCCC include encouraging membership of and attendance at I-O specific professional meetings (such as those organized by ACCC, or the Society for Immunotherapy of Cancer) circulating relevant publications to team members, and a monthly meeting on I-O for advanced practice providers.

EFFECTIVE PRACTICES IN PATIENT EDUCATION

1. Education on I-O mechanisms of action could involve a high-level conversation about tumor cells, T cells, and different receptor sites, or it could involve telling patients, "*Your tumor has the equivalent of a Halloween costume on, and this drug is going to take the Halloween costume off so that your immune system knows what it is.*" Whatever level your patient is at, meeting them where they are and making sure that they understand the mechanism of action is so important, because that leads to understanding of irAEs.
2. An immunotherapy wallet card offers a clear method for patients to communicate with their providers.
3. Immune-related side effects are generally manageable. Emphasize to patients that they need to tell their oncology care team about any symptomatic changes as soon as they occur so that clinicians can manage the toxicity and keep patients on treatment.

UCCC Patient Case Study: Sarcoma

Undifferentiated pleomorphic sarcoma is one of the tumor types where the oncology team at UCCC has seen some activity with PD-1 inhibitors. A patient with a good size abdominal tumor in his abdomen was transitioned to a PD-1 inhibitor (pembrolizumab) following failure of standard therapy. The patient received the first four cycles and was doing well, as measured by response criteria based on imaging. After the fifth cycle, the patient called the oncology team and said that he had been having some stomachaches and diarrhea. The team brought the patient in and at that point, he was having one episode of diarrhea a day and had no contact with other sick people. Following work-up, the team decided to very closely monitor the patient. A few days later, the patient called following seven episodes of diarrhea. Again, the team brought him in, acquired a stool sample to rule out any ova, parasites, or clostridium difficile, all of which were negative. Abdominal imaging revealed some dilatation of his colon that was consistent with a colitis, rather than tumor changes. Therefore, the team initiated steroid-dosing. The patient lives close to the cancer center and was able to visit daily. The first two days of steroids were intravenous (IV) because it is more challenging for patients with colitis to absorb oral doses. He was then transitioned to oral and tapered over three weeks, which he tolerated very well. He had well-formed stools and no other problems.

A UCCC oncology team member commented on this strategy: *In the original pembrolizumab trials, one thing that we used for management of symptoms that did not come out in the PI was that if patients had a grade 2 or higher irAE you would hold treatment until it was grade 1 or resolved. When you restarted pembrolizumab, you started at a widened dosing interval—every four weeks versus every three weeks. And so, that is something that I do continue to do for patients. For this patient, when we restarted him, we restarted him on pembrolizumab every four weeks, and he's done really well ever since. He's not had a recurrence of his colitis. He's pretty far into it now, and he's tolerating it really well.*

ST. JOSEPH HOSPITAL—THE CENTER FOR CANCER PREVENTION AND TREATMENT

St. Joseph Hospital in Orange County, Calif., has been using immuno-oncology (I-O) therapies to treat cancer patients as part of the cancer center's thoracic-oncology clinical trial program since 2014. Currently, the I-O program at St. Joseph's treats patients across various tumor types, with immunotherapies delivered at the cancer center's main infusion suite, as well as at two private offices within the St. Joseph campus.

Promote Awareness of irAEs

John Maurice, MD, is a thoracic surgeon and director of the Thoracic Oncology Program who oversees the day-to-day comings and goings of thoracic oncology patients at the cancer center. Although he is not involved directly in treating patients with I-O agents, he is a key point of contact after surgery. Patients turn up in Dr. Maurice's clinic with immunotherapy-related side effects, so he has to be aware of how medical oncologists are using immunotherapy to treat patients and be familiar with the clinical presentation of irAEs. For instance, Dr. Maurice has become increasingly attuned to the differences between a post-surgical infection and an immune-related colitis. In the past, he might have considered clostridium difficile as the most likely differential diagnosis for a patient with diarrhea after surgery, whereas now he immediately includes irAEs in his differential diagnosis.

This new awareness of, and growing expertise in, recognizing irAEs for Dr. Maurice has been engendered mostly by exposure to the growing volume of patients participating in I-O clinical trials. The oncology team has also used journal clubs to build an understanding about immunotherapy as they began using these agents, and has promoted the immunotherapy tumor board as a critical resource through which to educate oncology staff and non-oncology specialists involved in managing I-O patients.

Choose Your Champion

Early in the process of treating patients with immunotherapy, oncologists at St. Joseph's recognized that patients being treated with immunotherapy who showed up in the emergency room (ER) with irAE symptoms were being admitted to the hospital for a chemotherapy-related work-up (e.g., for infectious colitis). Failure to recognize irAEs contributed to delays in steroid treatment and to prolonged hospitalization.

Enza Nguyen, MSN, RN, ANP-BC, a nurse navigator, and Lavinia Dobrea, MS, BSN, RN, OCN, cancer research manager at St. Joseph Cancer Center, realized that ER staff needed education about how to recognize irAEs, but they needed a physician champion who understood both emergency medicine and immunotherapy to help them broker an entrée into the ER. Nguyen enlisted the support of the hospital's former chief medical officer, Ray Casciari, MD, a pulmonologist who was well known, liked, and familiar with immunotherapy and its side effects. She explained the need for education to Dr. Casciari, and shared their idea about developing an in-house wallet card that would prompt ER staff to contact the treating oncologist. She also explained that she needed access to ER staff. "'We have this idea. Can you help us?' And he said, 'Yes. What do you need?' I said, 'Well, we need access to the ER.' 'No problem.' I got it." Nguyen says that choosing an appropriate champion was key to creating a dialogue with ER staff. She says, "We right away got an appointment on the agenda for a meeting with the ER physicians. We were able to quickly reach the manager of the emergency room and meet with the different shifts of nurses."

An open flow of communication and professional respect are important ingredients in the St. Joseph oncology multidisciplinary team culture, and they provided a robust framework for developing dialogue with ER staff and beyond. But, as Dobrea notes, the I-O program team continues to work on building bridges with the non-oncology multidisciplinary team to address their evolving needs.

Provide In-Service Training

To ensure that ER staff were aware of immunotherapy and how irAEs differed from chemotherapy side effects, Nguyen, Dr. Maurice, and Dobrea developed an in-service session on immunotherapy for 14 ER physicians and nurses focused on immune-related "itises" and differential diagnoses in the context of ER patient work-up. Pre- and post-assessment of I-O knowledge among in-service participants showed that attendees learned key differences between work-up for infectious colitis and immune-related colitis, appreciated the need for speed in contacting the treating oncologist, and learned of the immunotherapy wallet card. Nguyen and Dobrea are hopeful that if ER physicians feel more comfortable recognizing irAEs and treating them promptly, this might also lower hospital admission rates.

In addition to educating front-line ER staff, Dobrea and Nguyen have educated nurses in the three private oncology groups that are part of St. Joseph's. They anticipate rolling the same education program out to the intensivists and hospitalists, who manage patients with irAEs following admission. But Dobrea and Nguyen also recognize the need to push education out even further to other specialties such as gastroenterology. Here, in person communication is key, as they explained:

> *We recently met with one of our nephrologists to review an algorithm for management of immune-related nephritis. After a quick discussion he understood the need for high-dose steroids. Interestingly, previous communication by email had not conveyed this message clearly.*

Streamline Communication

The immunotherapy wallet card is a critical tool for ensuring that all staff are aware that a patient is being treated with immunotherapy, know how to contact the treating oncologist, and are not hesitant to do so. Every I-O patient receives a St. Joseph-branded immunotherapy wallet card with their oncologist's name and 24-hour phone number. Patients and family members are taught to keep the card with their insurance card. ER staff now knows to ask for this card when patients present to the ER, and who to contact should they need to do so. The I-O program team developed its own in-house immunotherapy card to differentiate it from drug-branded cards. Nguyen and Dobrea also emphasize that by developing the card as a team, the oncology staff had buy-in and approval of its function. The immunotherapy wallet card, which represents the whole I-O program and not just one provider, has helped to clarify and consolidate messaging about the difference of irAEs from other cancer treatment side effects, streamline the irAE triage process, and reduce management fragmentation.

Crucially, the hospital's executive team supported implementation of the wallet card, in part because it has delivered a wider organizational payoff by helping St. Joseph's to meet the Commission on Cancer's Standards for accreditation.

Further, as members of the Nursing & Allied Health Professionals Committee of the International Association for the Study of Lung Cancer (IASLC), Nguyen and Dobrea have worked with this group of international specialists to develop an irAEs' resource guide. The first edition was released in October 2017 at the IASLC's 18th World Conference on Lung Cancer in Japan. Dobrea notes, "Ideally these irAE management pathways could be built into an EHR for comprehensive triaging and management for all patients on I-O." Dobrea notes that the I-O Program team is actively working with IT to ensure I-O treatment and irAEs are a drop-down option in their EHR.

Educate Patients

When patients attend the infusion center for their immunotherapy treatment, nurses provide both pharmaceutical-based and non-branded education materials describing what immunotherapy is, as well as signs and symptoms to look out for and what to report. Staff aim to include family members in this education. Patients can be reticent about calling attention to side effects because they do not want to be taken off I-O therapy. Nurses reassure patients that side effects can be managed as soon as they are recognized and encourage patients to be as direct as possible about anything that might be an irAE. This way, patients are likely to stay on therapy as long as is appropriate. If a patient does experience something that could be a side effect, St. Joseph's triage process kicks in. Patients can phone the cancer center, talk to somebody who has knowledge about irAEs, and receive information about appropriate action that they can take. Nguyen and Dobrea feel this strategy is effective. Although patients are occasionally afraid to report symptoms for fear of being taken off an I-O, with ongoing education, most patients realize how serious irAEs can be and are more reliable about reporting side effects.

Effective Practices in Communication

1. Communicate with and get agreement from the core oncology team, including surgical, medical, and radiation oncologists. They are an essential foundation for implementing an I-O program and standardized procedures around immunotherapy.
2. Identify champions and front-line staff that will help you build an I-O program and manage patients being treated with immunotherapy.
3. Outline the potential parameters of an I-O program with the oncology team and plan for progress by reviewing questions such as:
    - What is your biggest challenge with immunotherapy?
    - Do you need to create a molecular tumor board to integrate immunotherapy into your current tumor board?
    - What is your plan for managing the increasing volume of I-O clinical trials?
    - Should you consider an immunotherapy nurse navigator?
    - Should you consider specially trained triage nurses who know how to access and update algorithms?

St. Joseph Hospital Patient Case Study

We had a patient with a gynecology primary cancer on immunotherapy clinical trial. The patient's family was speaking with her research nurse over the phone and noted the patient had a rash. Although the patient didn't think it was 'a big deal,' the research nurse alerted the gynecology navigator and the gynecology clinic nurse practitioner (NP). The navigator and NP called the patient and asked her to come into the clinic, assessed the rash, and were able to dose reduce and evaluate. That ongoing dialogue between the entire team was key. Knowing how serious these toxicities can be, communication among the care team happened rapidly. In a matter of 15 minutes, three people were alerted, and the patient was seen promptly.

WHITE PLAINS CANCER CENTER

White Plains Cancer Center (WPCC) has been offering cutting-edge cancer treatment to patients for 20 years. Clinical trial participation has been a big part of that development, especially, in recent years, in immunotherapy across tumor types. Between 10 and 20 percent of the patients at WPCC are receiving immunotherapy. Una Hopkins, DNP, administrative director for the WPCC, believes changes in the approval landscape and National Comprehensive Cancer Network (NCCN) guideline recommendations have also driven WPCC to offer immunotherapies to patients.

While most WPCC patients are receiving checkpoint inhibitors according to FDA-approved indications, a number of ongoing clinical studies are addressing different roles and combinations of checkpoint inhibitors that have potential to revolutionize how WPCC is treating its patients. Currently, open clinical trials are addressing questions such as:

- When should we be using checkpoint inhibitors concurrently with chemotherapy?
- When is it appropriate to use a checkpoint inhibitor in upfront therapy as opposed to second line therapy or salvage therapy?
- When should we be using doublet checkpoint inhibitors?
- Should we be using flat dosing versus dosing based on weight?

As a result of this I-O treatment breadth, oncology staff at WPCC see an extensive range of irAEs that, if not diagnosed speedily, can be catastrophic for patients. Medical Director Dan Costin, MD, notes two different categories of irAEs. Systemic effects such as fatigue or infusion-related reactions have relatively clear symptoms that are relatively easy for both patients and clinicians to identify. In this category, education focuses on how to identify those symptoms and which interventions to implement. However, as the volume of patients being treated with immunotherapy increases, so too do system-specific irAEs (e.g., dermatologic or mucosal effects like rash or mucositis) and rare irAEs, like encephalitis, myasthenia-like illnesses, and myocarditis. As this second category of irAEs is trickier to identify and manage, ongoing patient and clinician education is a priority for WPCC.

Comprehensive Patient Education

Patient education starts before treatment initiation. For patients receiving standard, FDA-approved I-O treatment, infusion center nurse practitioners (NPs) or nurses educate patients before the first infusion on the general approach to treatment, as well as on which irAEs to anticipate with the specific immunotherapeutic agent being infused. This "dress rehearsal" gives patients a chance to ask questions and reinforces the message that patients should assume that anything that happens while on treatment may be connected to immunotherapy. For patients being treated in a clinical trial setting, education also includes a review of the unique trial focus, which might involve a combination regimen or dosing strategies.

Dr. Costin points out that side-effect symptoms can occur during the gap between receiving an infusion and the follow-up visit in two, three, or four weeks, depending on the administration schedule. To cover this gap, as well as to monitor patients who may need more concerted support, nurses call patients two to three days following infusion to ask, "How are you doing? What's going on? Have you had any of these symptoms? How many bowel movements are you having? Are you coughing? Are you short of breath? Do you feel any different?" As with both UCCC and St. Joseph, patients are central to keeping the symptom recognition process moving forward. With that in mind, patient education emphasizes that the oncology team should be the first point of contact for patients if they do experience symptoms.

However, not all patients are ready to learn at the first infusion session—many may still be processing their cancer diagnosis, and patient health literacy levels vary. With these variations in mind, nurses assess patients initially and individualize their teaching plans to account for the level of patient understanding and the support they have at home. Dr. Hopkins says, "You might teach an 87-year-old female very differently with her daughter or her son involved in her care, compared with how you might treat a 67-year-old who is still in the workforce. There are also language barriers. We all have diverse communities—we have a Spanish community—so we utilize whatever tools we can to make sure that patients have appropriate education from a health literacy standpoint, as well as culturally appropriate for their language." Such tools include text-based materials to explain medications, teaching sessions with physicians, NPs, and RNs using the "teach-back method,"[14] and using an interpreter if necessary.

Preparing the Whole Team

WPCC has also implemented three levels of specific clinician-facing education. First, through "Lunch and Learn" events, Dr. Hopkins and Dr. Costin have partnered with pharmaceutical companies to bring physician and nurse experts onsite. Education for general staff might focus on the scheduling requirements that support I-O therapies, whereas education for nurses who are assessing patients prior to treatment might focus on the unique language of immunotherapy and how to differentiate immunotherapy from other cancer therapies. Such education also teaches triage nurses and office staff to be aware that they are often the first staff to talk to patients who call to report symptoms. Such awareness-raising is important, because, as Dr. Costin cautions, "If the front desk says go to your PCP, and the PCP is one of 800 in the community, that could end up being trouble. That person may have pneumonitis, and we may lose three or four days. So, teaching our front desk, our triage nurses, the importance of understanding these concepts is crucial."

Second, WPCC has educated ER physicians and other specialists in cardiology, endocrinology, and nephrology on the types of I-Os that are approved and the kinds of irAEs with which they are associated. This approach helps to increase specialists' comfort level with immunotherapy. Having specialists who are primed with a raised suspicion level about symptoms in patients being treated with checkpoint inhibitors smooths the way for the oncology team to immediately discuss with specialists the best diagnostic and therapeutic approaches to evaluating and managing irAEs. Dr. Costin emphasizes:

> *It's not just education, but also being ready with your consultants. If you have somebody whose heart doesn't seem to be right, you're thinking myocarditis—you're going to need a cardiologist. If it's some kind of complex, unusual neurologic event that's happening, you're going to need a good neurologist. And neurologists or cardiologists or specialists that understand immunotherapy, that they're thinking about it, that they're well versed in it is crucial in terms of good patient care. In two to three years pretty much every specialist will be comfortable with this, but now we're still in that growing pains period where some of our specialists are beginning to see these things maybe for the first time, particularly the things that are less common.*

The third way that WPCC has delivered education is through its inpatient hospitalist group. Although few patients treated on I-O therapies are seen as inpatients, hospitalists also need to have a high level of suspicion when they assess patients who may be admitted for other reasons. For instance, some toxicities, such as endocrinopathies, can occur two years after therapy is finished; therefore, hospitalists need to be aware of subtle changes in signs and symptoms that could be related to immune-mediated effects on their radars.

Challenges Lie Ahead

WPCC staff acknowledge that as I-O therapies expand, they will need to further educate themselves on differences in irAEs. Dr. Costin says they have already noticed that infusion-related reactions may be a little more common in PD-L1 antibodies (atezolimumab, avelumab, durvalumab) than in treatments with PD-1 antibodies (pembrolizumab, nivolumab). Combinations of different forms of PD-1 antibodies (e.g., ipilimumab and nivolumab in metastatic melanoma) create more complex toxicities and make it more challenging to identify which agent is the adverse event culprit, and so determine dose adjustments and other interventions such as steroids. For each immunotherapy option, there are nuances in terms of:

- When is the appropriate time to start steroids?
- How long should the patient be on steroids?
- What should be the taper time?
- In what situation, after the patient has had an immune-mediated adverse event can we feel comfortable going back and reinitiating therapy?
- What are the situations where we should really never consider that?
- What happens when you give the patients steroids? Are you potentially compromising the benefit?

At the same time, although irAEs can occur in any part of the body, they are not necessarily all accompanied by symptoms, or symptoms may occur late in the toxicity development process. Hepatotoxicity is a case in point, in which sudden changes in liver function tests are often the first signal of immune-related toxicity. Similarly, kidney dysfunction can also be subtle, suggested in small increases in serum creatinine. Dr. Costin emphasizes that if clinicians are not checking routine labs, they are likely to miss these changes. As a result, having protocols in place to guide routine laboratory monitoring is key, as are algorithms and pathways that enable clinicians to diagnose and evaluate patients with symptoms of immune-related toxicity, identify the appropriate specialists, and implement appropriate interventions for each irAE.

EFFECTIVE PRACTICES IN EMPOWERMENT

1. Education across the board is paramount—patients, oncology clinicians, specialties, and front desk staff.
2. Maintain the medical oncologist as the primary person for first-line patient communication and care coordination. The medical oncologist is the most up-to-date on immunotherapy, its associated irAEs, and the timing of irAEs.
3. Develop and use clear evidence-based protocols that follow a pathway from diagnosis, to specialist and oncology team communication, to intervention. Following an established clinical pathway can make a huge difference to the outcome of irAE management.
4. Empower the whole community. Remember that you are not alone in treating patients with immunotherapy. Your specialists are very valuable. Even if you treat a high volume of patients with immunotherapy, don't hesitate to involve the neurologist, cardiologist, pulmonologist or nephrologist. Get them involved in the team.

WPCC PATIENT CASE STUDY: MELANOMA

A few years ago, a patient with recurrent metastatic malignant melanoma presented with the sudden onset of very bulky lymphadenopathy in the left side of his neck, growing into his chest. Surgical intervention was not an option because of the extent of disease. The patient was treated with ipilimumab and nivolumab, and in two to three weeks, all of his bulky, grapefruit-size masses had disappeared. The plan was to give him a certain duration of therapy, and then consider a surgical procedure to evaluate lymph nodes in more detail. After only two treatment cycles, he developed fever without clear explanation. Immediately the patient was aware that this was something different. He called the oncology team and had a complete evaluation. Chest x-ray was normal, and labs were unremarkable. The patient asked to come back in 24 hours, which he did with persistent unexplained fever. At this time, his urine showed a little bit of protein, but his kidney function was still intact. The patient was still treated conservatively and came back in another 24 hours, still with fever but without any other clear explanation. His creatinine had increased a little to 1.4 mg/dL, so he was given IV steroids and admitted for additional observation. Creatinine peaked at about 2.2 mg/dL, but within 24 hours of starting the steroids, immediately his kidney function began to return to normal and the fevers had resolved. He was discharged after 24 hours to his medical oncologist and nephrology to follow and to continue with appropriate slow taper on his steroids. The patient resumed therapy and responded rapidly after two cycles with a complete radiographic remission. He went on to have surgery to dissect the diseased lymph nodes and is now two-and-a-half years out, free of any cancer related to melanoma.

Dr. Costin comments: *This patient did not have pneumonia, an infection, or colitis. He had proteinuria and rising creatinine levels. At the time, immune-mediated renal toxicity had not been fully reported in the literature. In retrospect, two to three years later, it kind of all makes sense. It's a little easier now because we have seen every part of the body affected, so our level of suspicion is higher. But back then, as we looked through the literature—and there were only one or two reports of kidney toxicity—we were anxious that we were missing something else that was going on. This case is a reminder about how unusual toxicities can occur in these patients and that you've got to keep your antennae up. Ultimately, you need your partners, you need to have that low threshold of suspicion, you need to be ready to act, and you need to be questioning all of it.*

We don't recommend throwing steroids at every patient if it's not appropriate, and we recommend following evidence-based guidelines of when steroids should be considered. You have to grade toxicity appropriately and use them in the appropriate setting. But you should also remember that if a patient clearly has immune-mediated pneumonitis, they need steroids. You see situations where clinicians may be reluctant to give steroids because they don't want to compromise the patient's ability to respond to therapy or the long-term outlook. Rapid evidence-based decision-making is essential. In this particular patient, his creatinine went from 0.7 to 2.2 in less than 48 hours. If he stayed home for the weekend and hadn't come in for another 48 hours, he may have been on dialysis or he may have had really severe repercussions. Things happen on the turn of a dime very, very quickly. If things aren't adding up and it's not quite something that you can wrap yourself around, then have a low threshold to have the patient in the hospital to be observed and get other disciplines involved.

EMERGING IMMUNE-RELATED ADVERSE EVENT MANAGEMENT ALGORITHMS

In addition to the Risk Evaluation and Mitigation Strategies (REMS) that the FDA requires checkpoint inhibitor manufacturers to develop to assist clinicians in monitoring, recognizing, and managing irAEs, several cancer centers and researchers have proposed algorithms to support the management of common toxicities based on institutional and collaborative expertise in Europe and the U.S. These irAE management algorithms typically use the Common Terminology Criteria for Adverse Events, which is the mainstay of grading adverse events related to oncologic agents. Management algorithms provide a structured approach to effective identification and management of irAEs and are especially valuable for clinicians and care teams unaccustomed to immune-related toxicity.[15] Clinical algorithms have also been published based on clinical trial information and experience in metastatic melanoma with ipilimumab.[16] Building on this expertise, the Oncology Nursing Society has also published a specific consensus statement on managing irAEs with ipilumumab monotherapy and combined with nivolumab in advanced melanoma, as well as for PD-1 inhibitor therapy more generally.[13,17] In 2017, the European Society of Medical Oncology also published toxicity management guidelines that provide recommendations for both monotherapy and checkpoint blockade combination therapy.[18] Then, in February 2017, the NCCN and the American Society of Clinical Oncology announced plans to collaboratively develop clinical practice guidelines on the management of irAEs. Most recently, in November 2017, consensus recommendations on managing toxicities associated with immune checkpoint inhibitors from the Society for Immunotherapy of Cancer Toxicity Management Working Group were published in the *Journal for ImmunoTherapy of Cancer*.[19]

As immunotherapies for the treatment of cancer continue to expand and evolve, so too does our understanding of immune-related toxicities that may accompany these treatments. Along with emerging recommendations for managing irAEs, the experiences of those delivering immuno-oncologic agents at the front lines of care and real-world strategies for early recognition and treatment of immune-related adverse events are important to effective integration of these new therapies into practice.

Practical steps for raising awareness and effective management of irAEs shared by the three cancer programs highlighted in this article include:

- Identifying a I-O champion.
- Differentiating immune-related side effects.
- Ongoing education on irAEs for the I-O care team, non-oncology providers, patients, and caregivers.
- Developing and implementing evidence-based protocols that follow a pathway from diagnosis, to specialist and oncology team communication, to intervention.
- Streamlining communication among the I-O care team, as well as between this team and other providers such as hospitalists, ER staff, and non-oncology specialists.
- Utilizing a patient "wallet card" that includes oncologist name and contact information.

Additional resources for the multidisciplinary care team on understanding and managing irAEs are available at **accc-cancer.org**.

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THE ASSOCIATION OF COMMUNITY CANCER CENTERS (ACCC)

The Association of Community Cancer Centers (ACCC) is the leading advocacy and education organization for the multidisciplinary cancer care team. Approximately 23,000 cancer care professionals from 2,000 hospitals and practices nationwide are affiliated with ACCC. Providing a national forum for addressing issues that affect community cancer programs, ACCC is recognized as the premier provider of resources for the entire oncology care team. Our members include medical and radiation oncologists, surgeons, cancer program administrators and medical directors, senior hospital executives, practice managers, pharmacists, oncology nurses, radiation therapists, social workers, and cancer program data managers. Not a member? Join today at accc-cancer.org/membership or email: **membership@accc-cancer.org**.

The Association of Community Cancer Centers is the leading source of immuno-oncology resources focused on improving operations and processes so that the cancer care team can provide their patients access to cancer immunotherapies. ACCC empowers the multidisciplinary care team to:

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- Build and engage a community of thought leaders on innovations in program operations for integrating immunotherapies into practice
- Provide practical, data-driven resources on immunotherapy adoption
- Support cancer patient access to immunotherapy treatments

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