Immuno-Oncology: There's More to Discover

A WHITE PAPER FOR THE MULTIDISCIPLINARY CANCER CARE TEAM

ICLIO
INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

AN INSTITUTE OF ACCC
Association of Community Cancer Centers

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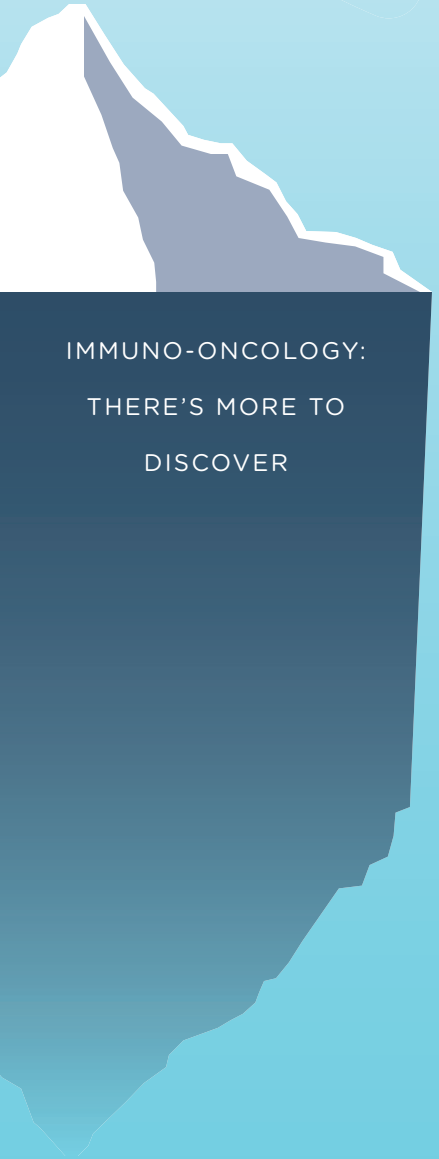


Introduction

Today, the potential of immunotherapy is being realized as a chief pillar of oncology treatment. From the first cytokine therapy approval by the U.S. Food and Drug and Administration (FDA) in 1986, followed by approval for a prostate cancer cell therapy/vaccine, and increasingly rapid approval for several checkpoint inhibitors (e.g., ipilimumab, nivolumab, pembrolizumab), to approvals in 2016 for new agents and new indications for existing agents, momentum in immunotherapy for cancer continues to build.

Cancer immunotherapy comprises many different approaches that can alter the host response to tumor, among which six are discussed here:

1. Vaccines
2. Immune modulatory antibodies
3. Adoptive T cell therapies
4. Cytokines
5. Oncolytic viruses
6. Reversal of immunosuppression

In addition, immunotherapies are currently being studied in combination with other agents (e.g., with other immunotherapies or chemotherapies). The adaptable nature of immunotherapy allows for highly specific therapies capable of recognizing and targeting only tumor cells that can achieve durable responses, and each therapeutic approach and immuno-oncology agent is accompanied by potential discrete toxicities that can affect patients differently. This landscape provides the backdrop to a coming tsunami of immuno-oncology therapies, since not only are new therapies being investigated, but several existing immunotherapy drugs are likely to be approved for different indications and tumors, as well as in a range of combination regimens. In the near future, checkpoint inhibitors are anticipated to move increasingly into first-line treatment, and combinations may likely expand across tumor types with increased response rates. Moreover, biomarker development will be increasingly important as a strategy to predict response.

In this rapidly evolving environment, clinicians need access to education and resources to help them make informed, evidence-based treatment decisions and manage patients in collaboration with all members of a growing multidisciplinary oncology team.

THIS LANDSCAPE PROVIDES THE BACKDROP TO A COMING TSUNAMI OF IMMUNO-ONCOLOGY THERAPIES.

The Institute for Clinical Immuno-Oncology: Meeting Evolving Needs

The Association of Community Cancer Centers (ACCC) established the Institute for Clinical Immuno-Oncology (ICLIO) in 2014 to help translate cancer-related immunotherapy advancements into practical applications in the community. ICLIO continues to evolve educational offerings and resources to empower the multidisciplinary cancer care team with essential knowledge about the ever-changing immunotherapy landscape and the support required to provide transformative care in the community setting.

ICLIO's Five Core Domains

In 2014 ACCC partnered with the National Comprehensive Cancer Network (NCCN) to conduct a needs assessment survey that identified five strategic areas of need for immunotherapy resources and education; these form the five core domains of ICLIO's educational programs:

1. Clinical Optimization
2. Coverage & Reimbursement
3. Management Best Practices
4. Patient Access & Advocacy
5. Training & Development

Building on year one accomplishments, in 2016 ICLIO provided education and resources for oncology clinicians, administrators, and supportive care providers through eCourses, eLearning modules, and monthly ICLIO e-newsletters. Since it launched, the ICLIO website attracted 41,743 visitors to full-access content covering key topics, including:

- Emerging alternative payment models
- Drug-drug interactions with checkpoint inhibitors
- Management of co-morbidities in patients being treated with immunotherapy agents
- Technologies that support patient engagement in oncology
- Resources to support the patient's voice.

In keeping with the expansion of immunotherapies for cancer, in 2016 ICLIO launched three subcommittees to consider tumor-specific challenges relating to immunotherapy and the healthcare community at large. To date, these subcommittees have provided expert insight into several critical issues including the role of biomarkers in clinical practice, the need for education on affordability of and the toxicities associated with combination immunotherapy, and strategies to address coverage and reimbursement challenges. Looking ahead, in 2017 ICLIO will support an ICLIO Visiting Experts program to foster sustainable and replicable immunotherapy care delivery models.

2016 Immunotherapy Clinical Highlights

Immuno-oncology is growing at an exponential pace, as demonstrated by the number of abstracts presented at key oncology meetings, the number of journal articles published on a monthly basis, and the rapidly increasing number of FDA-approved indications. For instance, at the American Society of Clinical Oncology (ASCO) Annual Meeting, presentations on checkpoint inhibition alone increased from 80 in 2015 to 215 in 2016, and, by November 2016, there were 6 new immunotherapy approvals for new indications, as well as an approval for a dose modification (see Figure 1, page 4 & 5).[1]

2016 Checkpoint Inhibitor Approvals & Label Modification

Approvals for Immuno-Oncology Monotherapies in 2016

- ***Nivolumab (anti-PD-L1 antibody).*** On May 17, the FDA approved nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL) that have relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin. On November 10, the FDA further expanded nivolumab's label to include patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) who progressed on or after platinum-based therapy. However, disappointing results were presented at the European Society for Medical Oncology annual meeting for nivolumab in its Phase III randomized study (CheckMate 026) in the first-line non-small cell lung cancer (NSCLC) setting.[2] Nivolumab did not meet the primary endpoint of progression-free survival (PFS) compared with chemotherapy in patients with 5% of greater programmed death ligand 1 (PD-L1) expression, and no difference was observed in objective response rate (ORR) or overall survival (OS). On the other hand, improvement in survival has recently been reported in a randomized Phase III trial for nivolumab in recurrent/refractory gastric cancer.[3]

Figure 1. Checkpoint Inhibitor Approvals & Label Modification

MAY 17, 2016
Accelerated approval for nivolumab for patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin.

MAY 18, 2016
Accelerated approval for atezolizumab for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

AUGUST 5, 2016
Accelerated approval to pembrolizumab for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy.

2016 Immunotherapy Clinical Highlights *continued*

- ***Pembrolizumab (anti-PD-L1 antibody).*** Pembrolizumab received FDA approvals for multiple new indications in 2016. On August 5, the FDA granted accelerated approval of pembrolizumab for the treatment of patients with recurrent or metastatic HNSCC that have continued to progress despite standard-of-care treatment with platinum-containing chemotherapy. Pembrolizumab was also approved for its fourth indication on October 24, for first-line treatment of metastatic NSCLC in patients whose tumors express ≥50% PD-L1 as determined by an FDA-approved test. This approval was based on the high-profile pivotal randomized Phase III study (KEYNOTE-024) that showed a 50% reduction in risk of disease progression or death and 40% reduction in risk of death with pembrolizumab in patients with 50% or greater PD-L1 expression, compared with standard chemotherapy.[4]

- ***Atezolizumab (anti-PD-L1 antibody).*** The FDA first approved atezolizumab as the first anti-PD-L1 antibody for the treatment of patients with locally advanced or metastatic urothelial carcinoma that progressed on platinum-based chemotherapy on May 18. A multi-center, single-arm, two-cohort Phase II trial showed that in patients with inoperable locally advanced or metastatic urothelial carcinoma that progressed after previous treatment, treatment with atezolizumab resulted in significantly improved ORR of 26%, 18%, and 15% among patients with PD-L1 expression of ≥5%, ≥1%, and in all patients, respectively.[5] Atezolizumab received a second approval on October 18 for use in patients with metastatic NSCLC whose disease has progressed during or following platinum-containing chemotherapy. This approval was based on results from a randomized Phase III clinical trial that showed median OS of 13.8 months for patients treated with atezolizumab versus 9.6 months for patients treated with docetaxel chemotherapy.[6]

IMMUNO-ONCOLOGY: THERE'S MORE TO DISCOVER

SEPTEMBER 13, 2016
Modified the dosage regimen for nivolumab for the currently approved indications for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer.

OCTOBER 18, 2016
Approved atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy.

OCTOBER 24, 2016
Approved pembrolizumab for patients with metastatic non-small cell lung cancer whose tumors express PD-L1 as determined by an FDA-approved test.

NOVEMBER 10, 2016
Approved nivolumab for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy.

2016 Immunotherapy Clinical Highlights *continued*

Immuno-Oncology Combination Therapies

- ***Combining Checkpoint Inhibitors.*** Many clinical studies are also currently testing checkpoint inhibitors in different combinations, either with other checkpoint inhibitors, targeted anti-tumor therapy, or chemotherapy. Updated results from the randomized Phase III CheckMate 067 study involving patients with previously untreated melanoma demonstrated a significant benefit on PFS with the combination of nivolumab and ipilimumab compared with either alone; the median PFS for the combination was 11.5 months compared to 6.9 months for nivolumab alone and 2.9 months for ipilumumab alone.[7] With the failure of nivolumab monotherapy in first-line NSCLC, there has been intense interest in the combination of nivolumab and ipilimumab in advanced NSCLC. Results from CheckMate-012, a Phase Ib study of 148 patients with advanced NSCLC without prior chemotherapy, were presented at ASCO in 2016. ORR was higher with the combination (57%) than with nivolumab alone (28%) in patients with PD-L1 ≥1%.[8] The combination achieved an impressive 92% ORR for patients with high PD-L1 expression (≥50%). Survival benefits were also observed. Toxicity remained a concern as the combination was associated with serious adverse events (Grade 3 or 4) in over a third of patients taking the combination; however, under 10% of patients discontinued treatment with no treatment-related deaths. The Phase I/II CheckMate 032 study demonstrated similar survival benefits with the combination in small cell lung cancer (SCLC) that progressed after platinum-based chemotherapy.[9]

- ***Checkpoint Inhibition with Chemotherapy.*** There was also significant attention focused on the combination of checkpoint inhibition with chemotherapy in the first-line NSCLC setting. Nivolumab combined with different chemotherapeutic regimens resulted in ORR ranging from 33% to 47% independent of PD-L1 expression.[10] Pembrolizumab plus chemotherapy also resulted in encouraging ORR from 48% to 71%, with overall survival not yet reached.[11] As with dual checkpoint inhibition, serious adverse events (Grade 3 or 4) were significant with the combination of anti-PD-1 and chemotherapy (36% to 45%).

  Atezolizumab is in a Phase III study in combination with chemotherapy agent oxaliplatin to increase dendritic cell maturation, cancer cell antigen presentation, and anti-cancer T cell activity in patients with solid tumors. Atezolizumab is also being studied in combination with nab-paclitaxel for the treatment of patients with metastatic triple-negative breast cancer. Preliminary results from a Phase Ib trial demonstrated promising activity in patients that had ≤ 2 prior cytotoxic regimens.[12] Atezolizumab + nab-paclitaxel is now in a Phase III study in patients with untreated metastatic triple-negative breast cancer (clinical trial NCT02425891).

- ***Checkpoint Inhibitors with Targeted Therapy.*** Atezolizumab is being studied in combination with cobimetinib, an inhibitor in the mitogen-activated protein kinase kinase pathway, to improve survival of anti-cancer T cells. In a Phase I study of atezolizumab plus cobimetinib, the ORR in patients with CRC was 17%, and with patients that had KRAS-mutant tumors, the ORR was 20%.[13]

  Clinical trials are investigating the efficacy of the anti-PD-L1 durvalumab in combination with the anti-VEGF bevacizumab in patients with glioblastoma. This trial is currently in Phase II development with an estimated completion date sometime in July 2017.[14]

COST HAS BECOME A NOTABLE CONCERN AS THESE EXPENSIVE AGENTS CAN INDUCE A HIGHLY VALUABLE DURABLE RESPONSE IN ONLY A FRACTION OF PATIENTS.

2016 Immunotherapy Clinical Highlights *continued*

Immuno-Oncology Therapies (Non-Checkpoint Inhibition) in Development

Chimeric antigen receptor T (CAR-T) cell therapy continues to be an intense research area. In July, Juno Therapeutics' Phase II trial on CAR-T cell therapy (JCAR015) came to an abrupt halt after three patients died; however, one week later, the FDA gave Juno permission to resume the trial after being convinced that the exclusion of fludarabine, a chemotherapy drug, would eliminate the risk of death to trial participants.[15]

Additionally, prophylactic and therapeutic vaccines are in development. ProscaVax (PSA[Prostate Specific Antigens]/IL-2 [Interleukin-2]/GM-CSF [granulocyte-macrophage colony-stimulating factor]) is one such vaccine that is currently being investigated for treatment of patients with recurrent prostate cancer in a Phase Ia/Ib trial. Interim data of PSA/IL-2/GM-CSF has shown that three-quarters of the patients taking the vaccine are experiencing a decrease of PSA levels, with no dose-limiting adverse events.[16]

CRS-207 is another immunotherapy vaccine in development. CRS-207 expresses a tumor-associated antigen protein, mesothelin, which is found across multiple tumor types. Interim results of a Phase Ib trial of CRS-207 in combination with pemetrexed/cisplatin as front-line therapy also demonstrated efficacy in patients with unresectable malignant pleural mesothelioma.[17] However, in May 2016, a Phase IIb trial combining CRS-207 and GVAX Pancreas in previously treated patients with metastatic pancreatic adenocarcinoma did not meet its primary endpoint of improvement in OS.[18]

Biomarkers

The importance of biomarkers is increasingly evident as efficacy and safety results for immunotherapies accumulate. Notably, high PD-L1 expression is associated with higher response rates in certain patient populations. PD-L1 expression by immunohistochemistry is currently the most commonly used biomarker for anti-PD-1 and anti-PD-L1 agents, although, as yet, only one PD-L1 biomarker is FDA-approved as a predictive companion diagnostic (for pembrolizumab in patients with advanced NSCLC).[19] Cost has become a notable concern as these expensive agents can induce a highly valuable durable response in only a fraction of patients, although some patients with low or even negative PD-L1 levels may also benefit from checkpoint inhibition. Other biomarkers being considered in anti-PD-1 therapies include total mutation burden and microsatellite instability-high (MSI-high) and mismatch-repair deficiency (MMR-D).[20]

Further biomarker research is needed to validate immune monitoring assays,[19] and improve immuno-oncology treatment precision through patient selection. The fruits of such research will enable clinicians and researchers to more effectively identify patients who might benefit from treatment, select more effective clinical trial endpoints, and reduce costs by optimizing dose selection.

ICLIO — Keeping Pace with Education & Resources

ICLIO eLearning Modules

In 2016 ICLIO launched an e-Learning portal providing user-friendly, on-demand learning modules for cancer care clinicians, administrators, and supportive care providers. The educational content of these modules is tailored to learner needs and supported by activity assessment materials designed to measure and facilitate participant understanding of integral concepts. The modules are accessible on the ICLIO website at accc-iclio.org/elearning. On completion of all online modules, participants' diligence and commitment are acknowledged with ICLIO Scholar recognition. In addition, ICLIO has developed three role-specific modules (e.g., cancer program providers, pharmacists, and patient navigators) to cultivate an understanding of these roles within the multidisciplinary team delivering immunotherapy to patients with cancer.

ICLIO e-Newsletters & e-Courses

ICLIO continues to disseminate monthly e-newsletters and a webinar series covering immunotherapy topics across the initiative's five strategic domains (see page 3). Topics addressed in 2016 include:

- Alternative payment models
- Drug-drug interactions with checkpoint inhibitors
- How to manage co-morbidities in patients treated with immuno-oncology agents
- Technologies to bolster patient engagement in oncology
- Resources to support the patient's voice

Throughout 2016, ICLIO e-newsletters also profiled clinicians, administrators, and non-clinical staff who are making a difference in the evolution of immuno-oncology in community settings.

Immunotherapy Tumor Subcommittees

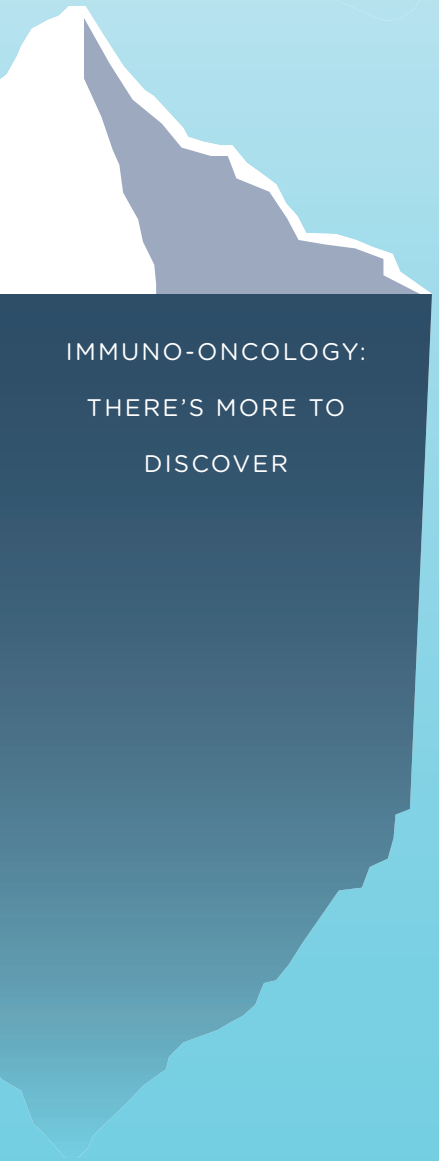
To address tumor-specific challenges relating to immunotherapy and the broader healthcare community, in 2016 ICLIO established subcommittees on lung, melanoma, and emerging tumors (e.g., bladder, kidney, hematologic malignancies, etc.). These three subcommittees are comprised of clinicians, pharmacists, nurses, and administrators who were chosen because of their real-world experience and expertise within their respective areas. The committees elicit unique expert perspectives on patient and provider issues with the goal of creating a holistic approach to everyday practice and management/operations. To date, the subcommittees have provided expert insight into the following key issues:

- ***Biomarkers.*** These are used to predict response rates and can be the primary influencer behind the choice of given immuno-oncology agents. There is consensus across the tumor subcommittees that more research is needed before biomarkers can be used consistently and with confidence.
- ***Monotherapy versus Combination Therapy.*** Experts believe that additional education—for both patients and healthcare providers—on therapeutic toxicities would benefit application of immunotherapy in the community. Affordability of combination therapies is a persistent concern among the healthcare community.

ICLIO — Keeping Pace with Education & Resources *continued*

- ***Expanded Indications.*** Barriers to receiving coverage for expanded usage of an immunotherapy remain a critical issue for providers in all care settings. Providers often see patients who are directly seeking immunotherapy over traditional chemotherapy; however, unless the immuno-oncology agents are under investigation via clinical trial, it is difficult for providers to obtain coverage.
- ***Coverage & Reimbursement.*** Obtaining preauthorization for immunotherapy use remains challenging. Due to the high-cost of these agents, the financial strain that accompanies immuno-oncology therapy increases the complexity of payer/provider relationships and can negatively impact patients and often significantly lengthens the pre-certification process, putting additional strain on already sparse support services in the community setting.

Subcommittee experts agree that the success of immunotherapy treatment regimens requires access to a multidisciplinary team. Accordingly, future ICLIO education and resource development should continue to focus on the multidisciplinary team, and address a range of tumor-specific issues to supplement the broader ICLIO portfolio. Such issues include toxicity management; raising awareness of tumor-specific immunotherapy issues among providers unfamiliar with immuno-oncology or providers in non-oncology specialties; and technology innovations to enhance and support immuno-oncology education. The educational content generated by these subcommittees will be used to develop toolkits for the cancer community and further support ICLIO's information platforms.



ICLIO Visiting Experts Program

The ICLIO Visiting Experts program, slated to launch in January 2017, will propel immuno-oncology education directly into the community setting. From a pool of applicants, ICLIO will select one ACCC Cancer Program Member to participate as a pilot host site. The selected site will receive a one-day, personalized learning workshop that connects members of their multidisciplinary staff with a team of four ICLIO Visiting Experts. This team of experts will include a clinician, administrator, nurse, and pharmacist who will foster direct, actionable dialogue on the critical issues affecting delivery of immunotherapies for cancer. Through a multidisciplinary curriculum tailored specifically for the immuno-oncology site, ICLIO Visiting Experts will engage with participants on the nuances and complexities of immuno-oncology effective practices, including strategies to optimize patient care, overcome reimbursement challenges, effectively operationalize approaches for payment, and more. Site-specific data will be collected to develop tailored educational content.

Policy Issues & Pressing Questions for the Future of Immuno-Oncology in Practice

In the fall of 2016 ICLIO hosted two in-person meetings—the ICLIO Stakeholder Summit and the 2nd ICLIO National Conference—designed to increase communication among the immuno-oncology community throughout the continuum of care and to identify and discuss solutions that address topics and issues associated with immunotherapies for cancer. The ICLIO Stakeholder Summit held September 29, 2016, in Philadelphia, Pennsylvania, gathered major stakeholders in oncology care (payers, providers, patients/patient advocates, and industry) for a robust discussion on access to immuno-oncology therapies; alternative payment models; value frameworks and metrics; and patient-centered care and shared decision-making tools. The 2nd ICLIO National Conference, held the following day, provided vital education for members of the multidisciplinary oncology team focused on operational and clinical issues associated with delivering cancer immunotherapies and managing their corresponding toxicities in the community setting. Topics covered included: real-world understanding and optimization of clinical immuno-oncology; reimbursement strategies of new treatments; tactics for operationalizing immuno-oncology in a cancer program; patient access and advocacy; and educational training opportunities. Key policy issues and pressing questions for the immuno-oncology community that emerged from these meetings are summarized below.

PATIENTS ARE INCREASINGLY EXPOSED TO, AND ARE BECOMING BETTER INFORMED ABOUT, IMMUNOTHERAPIES.

Perspectives on Access to Immuno-Oncology Therapies

Growing numbers of patients with NSCLC, melanoma, kidney, SCHNC, and bladder cancer are being treated with immuno-oncology agents. Yet, despite the benefits of these therapies, many obstacles continue to impede patient access to immunotherapy treatment, including payer and coverage policies, suboptimal patient access to clinical trials, and variable management operations in community settings.

Payer & Coverage Policies

Summit attendees broadly concurred that payers do not consistently provide coverage according to a drug's specific indication. This under-coverage may be due, in part, to payer policies that lag behind FDA label changes and new medication approvals. However, coverage is also limited because some payer-driven clinical pathways define the indications for drugs more narrowly than FDA indications. At the same time, access to therapy is further constrained by onerous reimbursement requirements. Indeed, Summit attendees believe it is increasingly evident that some payers request extensive prior authorization information from providers, which imposes an undue burden on both providers and patients.

Stakeholders agreed that prior authorization should not be a barrier to care for patients seeking access to immunotherapy therapies. Notably, the basis for authorization should be reconsidered so that physicians attempting to follow designated guidelines need not seek pre-authorization to administer the recommended regimen. Presentations during the ICLIO National Conference emphasized the continued important role that pharmacy services and reimbursement specialists will play in the process of reviewing the indications for immuno-oncology therapies and payer policies, establishing prior authorization strategies, handling denials, streamlining inventory management, and monitoring operations for underpayment or retrospective denials from payers.

Policy Issues & Pressing Questions for the Future of Immuno-Oncology in Practice *continued*

Concomitantly, it is difficult for providers to obtain coverage for expanded use of immuno-oncology therapies. As a result, clinicians are seldom able to prescribe or administer therapies that could be potentially effective for particular patients. While clinical trials potentially offer an alternative route to treatment for many patients, payers appear reluctant to cover immunotherapy agents in the clinical trial setting, especially when an arm of the trial includes standard of care (SOC) therapy or combination immuno-oncology therapies. Such payer reluctance further prevents patient access to therapies that may offer substantial benefit over SOC, and places a tremendous financial burden on all those involved in the immuno-oncology continuum of care. Therefore, strategies are needed to support expanded access to clinical trials and enable patients to more easily research and find viable clinical trial options.

Implementing Immuno-Oncology in Real-Time

Both Summit and National Conference attendees observed that patients themselves are driving discussion about expanded access to immuno-oncology therapies. Patients are increasingly exposed to, and are becoming better informed about, immunotherapies. Accordingly, many patients are becoming more assertive about demanding access to these therapies. However, some information sources are problematic and open to misinterpretation. For instance, patients may incorrectly interpret direct-to-consumer (DTC) advertising content to mean that a particular immunotherapy has benefit for all patients. This misinterpretation can lead to complex discussions with providers about patient eligibility for a particular therapy.

Additional education is needed to ensure that providers and patients are equipped to discuss the benefits and risks of a particular immunotherapy. In addition to educating patients about whether immuno-oncology treatment is right for their particular circumstances, the real-time implementation of immunotherapy in community settings requires strategies to support the recognition and management of responses to treatment, pseudoprogression, and the unique characteristics of immune-related adverse events (irAEs). However, as ICLIO National Conference presenters and attendees extensively discussed, community cancer programs differ in the resources available to them to address operational, financial, and clinical issues associated with immunotherapies. For instance, community practices—especially in rural areas—are challenged to address emergent operational complexities, such as inventory management. Immuno-oncology drugs are not only expensive to purchase, but their administration requires specialist personnel and highly educated staff (such as immuno-oncology dedicated pharmacists), thereby generating additional costs.

Similarly, recognition and management of irAEs generates additional expense and resource requirements across the care continuum, such as 24/7 access to providers with immuno-oncology expertise, since patients may report side effects during hours when community clinicians are not available. As ICLIO Summit participants emphasized, the approval of combination immunotherapies is likely to grow the significance of immunologic toxicities in community cancer programs. Thus, community providers will continue to need support to leverage their operational assets and marshal resources to adequately manage irAEs.

Policy Issues & Pressing Questions for the Future of Immuno-Oncology in Practice *continued*

ICLIO National Conference presentations described approaches to implementing immuno-oncology in community settings that have potential to streamline operational resources and minimize investment in infrastructure. For instance, although the geographic dispersal of specialist expertise poses a barrier to immuno-oncology access for rural populations, increased funding for advanced practice providers and the expansion of telehealth and clinical trial management are critical strategies to support real-time immuno-oncology implementation in community settings. Similarly, the strategy of creating a distinct space devoted to immuno-oncology within infusion centers, with dedicated immuno-oncology resources and nursing staff offers the advantage of building localized clinical expertise among nurses. Implementation of immuno-oncology in real-time, as therapies are approved, will require ongoing nursing education on immunotherapies, especially in relation to the prevention, recognition, mitigation, and management of immuno-oncology-related toxicities and irAEs. Indeed, a key ICLIO National Conference theme was the importance of ongoing immuno-therapy education for all members of the multidisciplinary oncology team, including primary care providers, emergency room and intensive care unit providers, surgeons, radiologists, and house staff.

Alternative Payment Models

As the U.S. healthcare system transitions away from volume-based, fee-for-service reimbursement to value-based payment, government agencies and commercial payers are developing and testing a number of alternative payment models (APMs) with the aim of better managing the cost of care while maintaining or improving care quality. Medicare's first oncology-specific pilot, the Oncology Care Model (OCM) was the focus of discussion in both the ICLIO Stakeholder Summit and the National Conference. Developed by the Center for Medicare and Medicaid Innovation (CMMI), the OCM aims to achieve higher quality care and enhanced services for beneficiaries undergoing treatment through a realigned financial incentive system.[21] As Summit participants observed, the current "buy and bill" model for drug acquistion brings reimbursement challenges for immunotherapy, given the high cost of these agents. For instance, many physicians pay out-of-pocket to stock and store expensive immunotherapies, without being reimbursed until after administration of the immuno-oncology agent. Presenters at both meetings acknowledged the importance of the OCM pilot, noting that if CMS deems the model successful and supports it, commercial payers are likely to adopt this approach as well.

A concern raised during both meetings: immuno-oncology involves not only drugs but considerable wrap-around care that will expand in the context of emerging combinations. This will make it more difficult to assign a dollar amount to the concept of value (see discussion on Oncology Value, Valuation & Metrics page 13).

Key Policy Issues & Future Concerns Emerging from the 2016 ICLIO Meetings

- Payer and coverage policies continue to pose barriers to access to immuno-therapies for cancer. Oncology providers in the community have an ongoing need for education on strategies to address prior authorization requirements and claims denials, and to support expanded access to clinical trials.
- Patients are driving discussion about expanded access to immuno-oncology therapies in response to information on immunotherapy drugs presented via direct-to-consumer and other advertising media, which may be problematic and open to misinterpretation. To support appropriate immuno-oncology implementation, education is needed to ensure that providers and patients are equipped to discuss the benefits and risks of a particular immunotherapy.
- Recognition and management of immune-related adverse events continue to generate additional expense and resource requirements across the care continuum. The significance of immunologic toxicities in community cancer programs is likely to grow as more combination immunotherapies are approved by the FDA. Community providers will continue to need support to leverage their operational assets and marshal resources to adequately recognize and manage irAEs.

Policy Issues & Pressing Questions for the Future of Immuno-Oncology in Practice *continued*

- Government agencies and commercial payers are currently developing alternative payment models as the U.S. healthcare system transitions from volume-based to value-based reimbursement. Defining value in oncology is an ongoing dilemma. The high cost of immuno-oncology therapies is fueling the debate over the meaning of value in cancer care and how best to measure it. It is imperative that the oncology community ensures that new and emerging models include input and buy-in from its members.

- As the range of tools and technologies to capture patient-reported outcomes, genetic profiles, and mutational status evolves, community cancer providers will need ongoing education on how to integrate and use such resources to engage patients in discussions about their care, and on how to build a foundation for immunotherapy research.

Implications for Expenditures, Innovation & Immuno-Oncology

Overall, Stakeholder Summit participants were concerned that APMs will favor cost-efficient therapies over evidence-based treatment in ways that are detrimental to quality care and safety for patients, especially as there is, as yet, little evidence of physician buy-in to APMs. Importantly for immuno-oncology, APMs could be developed without oncologist input, peer review, or evidence concerning immunotherapies for cancer. A further question remains about the affordability of APMs for smaller programs, for whom much overhead is already inadequately reimbursed. Many programs are concerned about how new reimbursement models might affect existing challenges (e.g., practice consolidation and wrap-around care issues, such as transport). The success of APMs will, in part, be based on the collection and analysis of data that compares the current costs of immunotherapies with their associated outcomes. However, concern is mounting that immuno-oncology providers lack the necessary infrastructure to collect such data, especially smaller practices that are attempting to provide access to immunotherapies. In response to this concern, as well as to challenging experiences with the implementation of electronic health records (EHR), the immunotherapy community is discussing the potential benefits of an oncologic-specific EHR system that could function as an aggregation of data for ongoing research.

Ultimately, APMs will also need to create and utilize quality measures that promote innovation rather than simply drive costs down, because it is often challenging to identify what a therapy's value is until providers use it in a real-world clinical context. However, the high cost of immunotherapies has implications for how innovation is funded, and raises questions about who will pay for it. ICLIO Stakeholder Summit participants noted that until an adequate value-based modified payment methodology is created, established payment models will continue to inhibit the use of innovative immunotherapies. Moreover, although it remains unclear whether payers, providers, or patients should ultimately be responsible for treatment decision-making, it is likely that decision-making power will accrue to the party accepting more of the downside risk. These issues will be even more significant as providers prepare to implement Medicare's Quality Payment Program under MACRA.[22]

Oncology Value, Valuation & Metrics

The immense cost of immuno-oncology therapies poses the backdrop for discussion of value in immuno-oncology, and has stimulated the creation of unique value frameworks intended to open discussion about the meaning of value in oncologic care and how best to measure it. As discussed at the ICLIO Stakeholder Summit, a number of value frameworks have been developed that broadly share the same explicit goal of establishing value for distinct therapeutic options. Existing value frameworks include assessments made by the Institute for Clinical and Economic Review (ICER), ASCO's Conceptual Framework to Assess the Value of Cancer Treatment Options, NCCN's Evidence Blocks, and Memorial Sloan Kettering Cancer Center's DrugAbacus.[23-26] These first generation value frameworks each have their own strengths and weaknesses, a discussion of which is beyond the scope of this white paper; however, in their attempt to define "value," each exposes, in some way, the inherent conflict between payer notions of value and physician and patient ideas about value. Broadly, where payers highlight the cost of drugs, providers highlight their effectiveness. Summit stakeholders conceded that the complexity inherent in the process of determining value will likely exacerbate existing tensions in the payer-provider relationship.

Policy Issues & Pressing Questions for the Future of Immuno-Oncology in Practice *continued*

While there is, as yet, little consensus on how to best define and measure the specific value of immuno-oncology therapeutics—including combinations—ICLIO Stakeholder Summit participants broadly agreed that any adequate assessment of value needs to move beyond the cost of a particular drug and its biologic effectiveness and incorporate patient perspectives on value. For instance, although patients often identify quality of life and length of life as the most important aspects of value, these categories are generally absent from value frameworks—with the exception of ASCO's value scores. While conversations about cost, resource stratification, and value metrics can be frustrating for patients, patient advocacy stakeholders emphasized that value for patients is likely to inhere in the quality care that immuno-oncology provides, as well as in the opportunities for goal-oriented decision-making that immunotherapy offers.

The oncology community continues to wrestle with the parameters of value as represented by these different value frameworks, which, both Stakeholder Summit participants and ICLIO National Conference attendees acknowledged, could be valuable if they are based on an effective methodology that acknowledges the durable responses associated with immunotherapy and are not used to limit access to immuno-oncology therapy. To incorporate patient perspectives on value, proposed value frameworks will need to be informed by meaningful data that captures how patients within disparate disease groups assess value beyond overall survival and overall response rate, and that helps providers consider "what matters to patients" as well as "what is the matter with the patient." To this end, patient education will be increasingly important as a strategy to expand the incorporation of patient voice in the development of value constructs and frameworks.

Measurement & Analysis of Patient-Centered Care & Shared Decision-Making Tools

A range of tools and technologies is emerging to support the goals of collaborative decision-making in oncologic care, and to enhance patient voice in ways that enable patients to achieve the outcomes that matter most to them. Such tools include iPads or other devices to both deliver accessible learning material to patients about treatment-related issues (e.g., treatment options, efficacy, toxicities, cost) at the point of care, and to capture patient-reported outcomes (PRO). ICLIO Stakeholder Summit participants and ICLIO National Conference presenters shared their experiences of using education and PRO tools (e.g., web-based platforms such as Patient Care Monitor) to engage patients in discussions about their oncology care, to capture information about patient performance status, and to help determine treatment options. An oncology-specific EHR system, as discussed above, that includes genetic profiles and mutational status could also improve the reliability of treatment decisions and serve as a powerful foundation for oncologic research.

A Look Ahead

Successful I-O therapy requires a well-educated multidisciplinary team that can effectively communicate to its constituent parts. As immunotherapy for cancer continues to evolve, clinical, administrative, and infrastructural operations education will become increasingly important. In the coming year, immuno-oncology professionals will have to sustain their efforts towards optimizing response rates, creating a team-based approach to immuno-oncology care, crafting value determination methodologies, and increasing overall access to available and emerging agents and combinations. It is, therefore, the goal of ICLIO to support this effort by providing education, tools, and resources to support access to immunotherapies in the community.

IMMUNO-ONCOLOGY:

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The Association of Community Cancer Centers

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 2,500 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.

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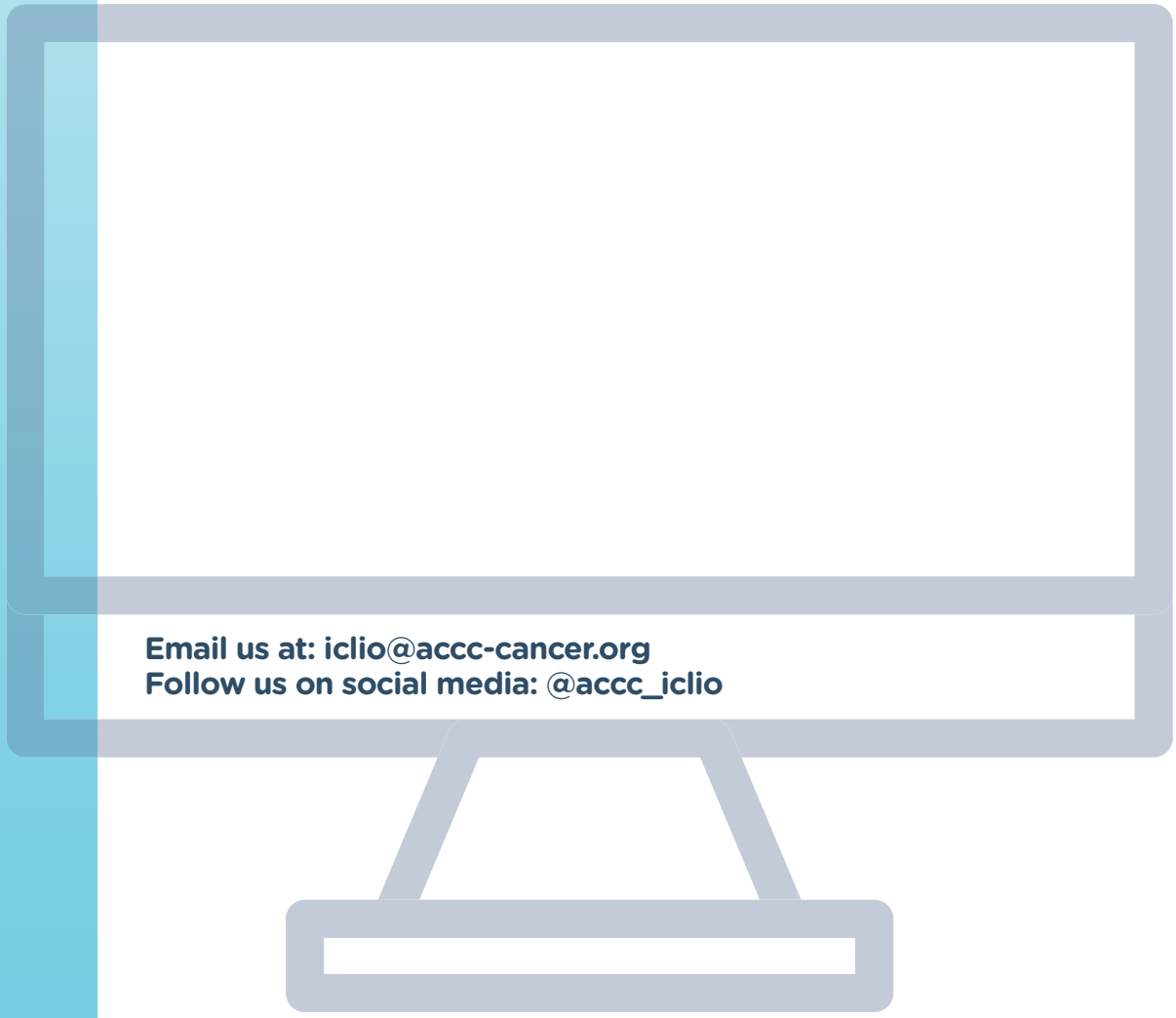

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