Managed Care Considerations in the Evolving Immuno-Oncology Treatment Landscape

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Managed Care Considerations in the Evolving Immuno-oncology Treatment Landscape

Instructions for CME/CNE: Activity is valid from February 20, 2018 to February 29, 2020.
A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send completed post test and evaluation to:

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Learning Objectives:
1. Analyze immuno-oncology and the different types of immuno-oncology treatments.
2. Identify immuno-oncology treatments that have been approved in the past 12 months and those likely to be approved in the next 12 months.
3. Discuss the impact of new immuno-oncology treatments on the managed care market.
4. Discuss the mechanism of action and indications of new and emerging immunotherapies.

Faculty Disclosure:
Dr. Owens has disclosed no relevant financial relationships.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN and Jeremy Williams have no relevant financial relationships to disclose.

Accreditation & Designation
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Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit.

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Post-Test Questions

1. Which of the following is NOT an accurate statement about how cancer cells evade detection by the immune system?
   a. Tumor cells may reduce the expression of tumor antigens on their surface.
   b. Tumor cells express proteins on their surfaces that induce immune cell inactivation.
   c. Tumor cells induce cells in the microenvironment to release substances that suppress immune responses.
   d. Tumor cells secrete tumor necrosis factor and other immune system stimulants.

2. Blocking the activity of immune checkpoint proteins releases the brakes on the immune system, increasing its ability to destroy cancer cells.
   a. True. b. False.

3. Which of the following is an accurate statement about the cytotoxic T-lymphocyte-associated antigen four (CTLA-4) pathway?
   a. It is a positive checkpoint.
   b. Blockade of the CTLA-4 receptor with a monoclonal antibody allows for activation of T-cells and anti-tumor effects.
   c. Activation enhances T-cell activation and proliferation in order to prevent autoimmune reactions against healthy tissue.
   d. When CTLA-4 on a T-cell is bound to B7 on antigen-presenting cells, T-cells are not able to recognize a tumor cell as foreign.

4. Programmed death one (PD-1) is a cell surface receptor that plays an important role in down-regulating the immune system by _____.
   a. Upregulating regulatory T-cells.
   b. Increasing the number of anergic T-cells.
   c. Suppressing T-cell inflammatory activity.
   d. Interfering with the inhibitory effect of regulatory T-cells.

5. Which of the following agents is FDA approved for any unresectable or metastatic solid tumor with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) without regard to the tissue type or site of the tumor?
   a. Ipilimumab b. Pembrolizumab
   c. Atezolizumab d. Avelumab

6. What percentage of patients treated with a checkpoint inhibitor will develop an immune mediated toxicity?
   a. 3 - 7% b. 10 - 15% c. 20 - 40% d. 50 - 70%

7. Which of the following is an anti-programmed death one (PD-1) agent?
   a. Durvalumab b. Nivolumab
   c. Pembrolizumab d. Ipilimumab

8. Why was the FDA approval of avelumab important?
   a. It is the most effective immuno-oncology agent developed so far.
   b. It causes the lowest rate of immune adverse reactions.
   c. The approval covers all types of solid tumors.
   d. It is the first FDA approved agent for metastatic Merkel cell carcinoma.

9. Which of the following is an accurate statement about tisagenlecleucel.
   a. A patient's B cells are bioengineered to recognize and kill their cancer cells.
   b. Cytokine release syndrome or neurological toxicities are the major adverse effects.
   c. It is FDA approved for various solid tumors expressing C19.
   d. Approval was based on the results of several large Phase III trials.

10. As discussed in the article, which of the following is NOT a typical part of a managed care's approach to managing cancer costs?
    a. Risk shifting or sharing
    b. Aggressive prior authorization programs
    c. PBM based counter detailing
    d. Contracting strategies

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented, I am better able to:

   Analyze immuno-oncology and the different types of immuno-oncology treatments.

   4 3 2 1

   Identify immuno-oncology treatments that have been approved in the past 12 months and those likely to be approved in the next 12 months.

   4 3 2 1

   Discuss the impact of new immuno-oncology treatments on the managed care market.

   4 3 2 1

   Discuss the mechanism of action and indications of new and emerging immunotherapies.

   4 3 2 1

2. The activity met my expectations. 4 3 2 1

3. The activity and presenters were free of bias. 4 3 2 1

4. The activity was applicable to my position. 4 3 2 1

5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4 3 2 1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

7. What other topics interest you? _____

8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills.
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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Gary M. Owens, MD

Introduction

Immuno-oncology, sometimes also referred to as IO or I/O, is the use of immunotherapies to stimulate the immune system to treat cancer. Immunotherapies either stimulate the activities of specific components of the immune system to attack tumor cells or counteract signals produced by cancer cells that suppress immune responses.

The immune system has a natural capacity to detect and destroy abnormal cells which likely prevents the development of many cancers. However, cancer cells can develop different ways to hide from the immune system. Cancer cells may reduce the expression of tumor antigens on their surface, express proteins on their surface that induce immune cell inactivation, or induce cells in the surrounding environment (micro-environment) to release substances that suppress immune responses and promote tumor cell proliferation and survival.[1] Cancer cells change cell surface antigens through genetic mutations to evade immune destruction. Cancer cells have been found to secrete immunosuppressive cytokines such as transforming growth factor β (TGF-β) and interleukin-10 (IL-10).[2]

History of Immunotherapy

In the 1890s, the antitumor effects of live bacteria (Streptococcus pyogenes) directly injected into tumors and a vaccine with two dead bacteria (S. pyogenes and Serratia marcescens, Colley's Toxin) provided the first evidence that the immune system could be harnessed to combat cancer.[3] During the mid to late 20th century, several key aspects of immune regulation through cytokines were discovered, leading to the approval of the first modern immunotherapies. In 1986, interferon (IFN) alpha 2A and 2B were approved for the treatment of hairy cell leukemia.[4] The use of IFN was expanded to metastatic melanoma and chronic myelogenous leukemia. Recombinant interleukin (IL-2, aldesleukin) was approved for the treatment of metastatic renal cell carcinoma in 1992 and is now also approved for metastatic melanoma.[5] IFN and IL-2 do not directly kill cancer cells but do interfere with cancer cell growth and multiplication, stimulate the immune system, and signal cancer cells to produce cytokines that attract immune system cells to them. Both these classes of immunotherapy cause significant adverse effects which can limit their use.

In 2010, the FDA approved sipuleucel T (Provenge®), an autologous cellular immuno-oncology treatment that takes a patient's dendritic cells and exposes them to antigen-targeting prostate cancer cells. The activated dendritic cells are then injected back into the patient. This therapy is indicated for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.[6]

The next stage of immuno-oncology development was the improved understanding of immune checkpoints. Immune checkpoints are mechanisms that exist in our immune system mainly in the interrelationship between dendritic cells, T-cells, and antigen-presenting cells that allow for the immune system to be both up and down regulated. Immune checkpoint proteins normally keep immune responses in check by preventing overly intense responses that might damage normal cells; thus, they can be thought of as the brakes on the immune system. Dysfunction of the immune checkpoint pathways contributes to development of autoimmune diseases.[7] Blocking the activity of immune checkpoint proteins releases the brakes on the immune system, increasing its ability to destroy cancer cells.[1]

The cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathway was first identified as a potential target for anticancer therapy in 2001.[8] CTLA-4, a transmembrane protein found on the surface of T-cells, is a negative checkpoint in that it prevents subsequent costimulatory signals and dampens T-cell activation and proliferation in order to prevent autoimmune reactions against healthy tissue while the immune system is activated against a pathogen.[9] When CTLA-4 on a T-cell is bound to B7 on antigen-presenting cells, dendritic cells

Exhibit 1: CTLA-4 Inhibition

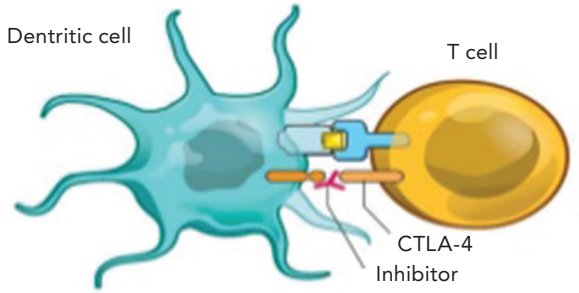
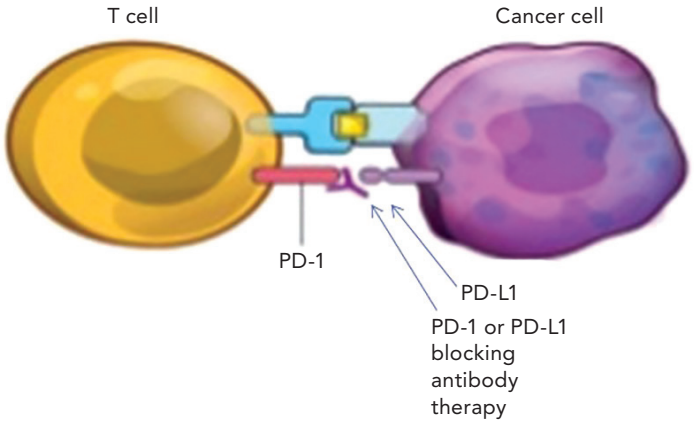


Exhibit 2: Anti-PD-1 Therapy



are prevented from priming or activating T-cells to recognize a tumor cell as foreign. Blockade of the CTLA-4 receptor with a monoclonal antibody allows for activation of T-cells and antitumor effects (Exhibit 1). The first anti-CTLA-4 agent, ipilimumab (Yervoy®) was FDA approved for the treatment of metastatic melanoma in 2011.

In metastatic melanoma, the overall response rate to this agent is 11 to 19 percent, and the median progression-free survival is 2.9 to 4.4 months.[10-12] The two-year overall survival in those with metastatic disease treated with ipilimumab is 25 percent.[13] Although a small percentage of patients respond to this immunotherapy, those who do respond have a dramatic and durable response.

A second checkpoint inhibitor, programmed death-1 (PD-1) has been known since 1992.[9] This is a transmembrane inhibitory protein not detected on resting T-cells but highly expressed on activated T-cells.[14] It plays an important role in down-regulating the immune system by promoting self-tolerance through suppressing T-cell inflammatory activity through a dual mechanism; it promotes apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes and simultaneously reduces apoptosis in regulatory T-cells.[15,16] Overall, PD-1 inhibits the immune system which prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells. Expression of PD-1 ligand (PD-L1) can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. Tumor cells that express PD-L1 bind to PD-1 receptors on T-cells to deactivate them. Blocking PD-1 by binding to either the PD-1 receptor on the T-cell or the PD-1 ligand (PD-L1) on tumor cells allows T-cell activation and antitumor effects (Exhibit 2).

Exhibit 3: Immuno-Oncology Pipeline

Agent	Phase	MOA
JCAR017	III	CAR-T (B-Cell Non Non-Hodgkins Lymphoma)
tremilimumab	III	CTLA-4 (multiple cancer types)
vesigenurtucel-L	II	CAR-T (Bladder cancer)
utomilumab	II	Anti-4-1BB (CD137, member of TNF family)
LN-144/145	II	Tumor infiltrating lymphocytes
MPDL3280A	II	PDL-1 Inhibitor

CAR-T = chimeric antigen receptor T cell
CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4
PDL-1 = programmed death one ligand
TNF = tumor necrosis factor

Approved Checkpoint Inhibitors

Approvals of immuno-oncology therapies in the past three years have been at a rapid pace. In addition to anti-CTLA-4 ipilimumab, there are now three anti-PD-L1 monoclonal antibodies and two anti PD-1 monoclonal antibodies. Additional indications have been rapidly added as well to the initial approvals for each of the anti-PD agents.

Pembrolizumab (Keytruda®) is a humanized monoclonal antibody that targets PD-1. It was first approved in 2014 under the FDA Fast Track Program for metastatic melanoma. Additional uses approved subsequently include non-small cell lung cancer (NSCLC), bladder cancer, squamous cell head and neck cancer, Hodgkin's lymphoma, and gastric cancer. In May 2017, it was approved for any unresectable or metastatic solid tumor with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) without regard to the tissue type or site of the tumor; this broad approval was a first for the FDA.

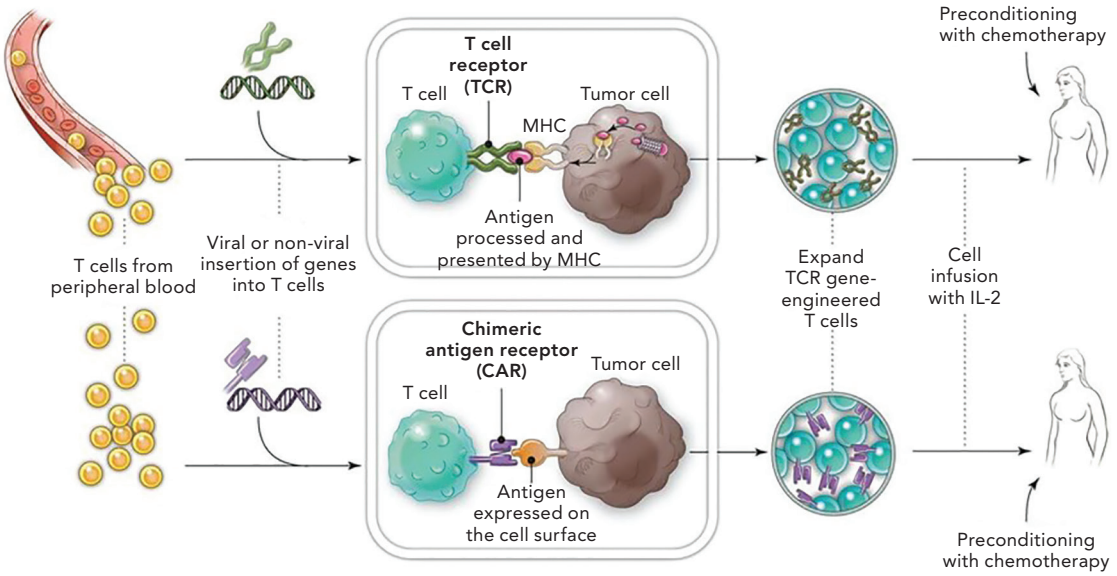
MSI-H or dMMR correlates with response to anti PD-1 immunotherapy. Many solid tumors have a significant number of mutations because of impaired mismatch repair pathway functions. This pathway is supposed to fix nucleotide mistakes in DNA replication. The dMMR results in MSI and increased duplication of tandem dinucleotide repeats (microsatellites), which results in an increased mutation rate and higher risk of certain cancers. MMR-deficient cells have large numbers of mutations;1,700 on average compared with just 70 in a typical cancer cell.[17] It appears that the large number of neoantigens, the fragments of altered proteins produced from mutated DNA, present in MMR-deficient tumors makes them responsive to anti PD-1 immunotherapy.[17]

Nivolumab (Opdivo®), a human IgG4 anti-PD-1 monoclonal antibody, was first approved for use in metastatic melanoma in 2014. Additional FDA approved indications include NSCLC, bladder cancer, Hodgkin's lymphoma, renal cell cancer, squamous cell head and neck cancer, and hepatocellular cancer. Like pembrolizumab, nivolumab is now approved for any un-resectable or metastatic solid tumor with MSI-H or dMMR.

Checkpoint inhibitor-based immunotherapy is generally well tolerated, but 20 to 40 percent of patients can develop an immune-mediated toxicity which can be very serious or even fatal.[18] Without the dampening effects of the checkpoint proteins, the body begins attacking itself. Immune toxicities occur most commonly in the lungs, skin, liver, kidneys, gastrointestinal tract, pancreas, and thyroid.

Combining the two checkpoint inhibitor classes is an option and is being studied in various different cancers. Nivolumab is approved for use in combination with ipilimumab in unresectable metastatic melanoma without the BRAF V600 mutation. When combined, nivolumab and ipilimumab were associated with a 12 percent reduction in the risk of death versus nivolumab monotherapy for patients with treatment-naïve advanced melanoma, according to results from the Phase III CheckMate-067 trial.[19] The median overall survival was not reached with nivolumab/ipilimumab compared with 20 months with ipilimumab alone. Importantly, the benefits of combination immuno-oncology therapies come at the cost of increased adverse events. In the aforementioned trial, 58.5 percent of patients experienced treatment-related Grade 3/4 adverse effects with the combination compared with 20.8 and 27.7 percent for nivolumab and ipilimumab alone, respectively. The majority of these adverse effects were immune-related adverse effects from taking the brakes off the immune system in two different ways.

Exhibit 4: TCR and CAR-T Therapy[21]



Atezolizumab (Tecentriq®), a monoclonal antibody of IgG1 isotype, was the first agent approved that targets the PD-L1. It was granted accelerated FDA approval in May 2016 for locally advanced or metastatic urothelial carcinoma treatment after failure of cisplatin-based chemotherapy. In October 2016, it gained approval for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or ALK genomic tumor mutations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab. As a condition of this and any other accelerated approval by the FDA, the manufacturer is required to complete ongoing clinical trials to confirm clinical benefit.

On May 1, 2017, the FDA granted accelerated approval to durvalumab (Imfinzi®), a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody against PD-L1. It is indicated for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or for those who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. A complementary diagnostic assay (VENTANA PD-L1) for the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded urothelial carcinoma tissue is approved for identifying urothelial carcinoma patients most likely to benefit from durvalumab. This assay provides robust PD-L1 staining in both tumor cells and tumor-infiltrating immune cells.

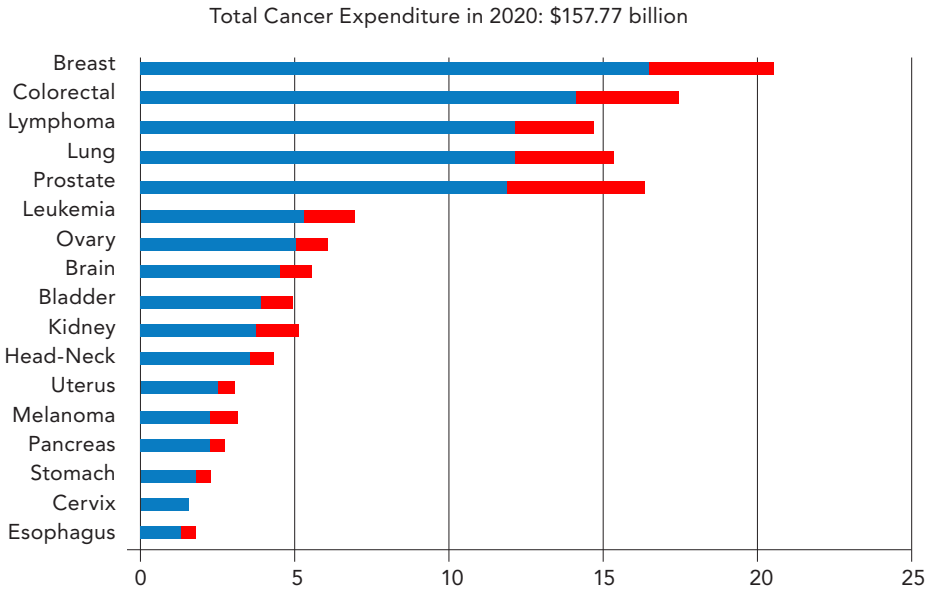
On March 23, 2017, avelumab (Bavencio®) was granted accelerated approval for treatment of patients 12 years and older with metastatic Merkel cell carcinoma. Avelumab is a PD-L1 blocking human IgG1 lambda monoclonal antibody and is the first FDA approved product to treat this type of cancer. It has also gained approval for locally advanced or metastatic urothelial carcinoma that has progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Adoptive Cell Transfer Therapies

Another form of immunotherapy that is being actively studied and showing tremendous promise is called adoptive cell transfer (ACT). ACT uses a patient's own immune cells—collected from their blood or directly from their tumors—to treat their cancer. Provenge, discussed earlier, was the first approved adoptive immunotherapy. The three additional forms are chimeric antigen receptor T-cells (CAR-T), T-cell receptor (TCR), and tumor-infiltrating lymphocytes (TILs).[20]

CAR-T cells are bioengineered to graft antigen receptors onto a T-cell (Exhibit 4).[21] T-cells are removed from a patient and modified in the laboratory so that they express receptors specific to the patient's particular cancer. Large numbers of the CAR-T

Exhibit 5: Estimated Cancer Expenditure by Site in 2020[1]



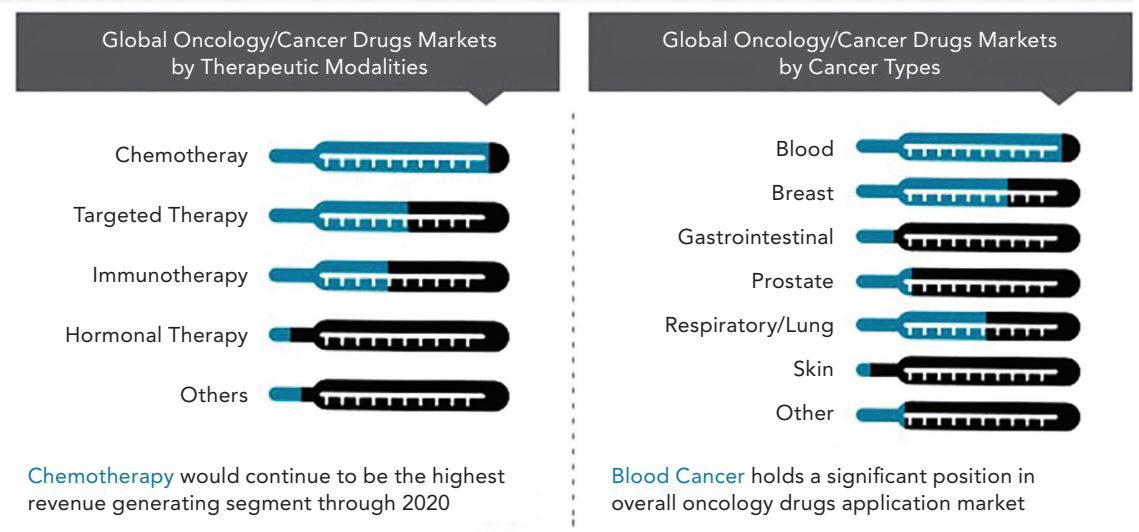
cells are grown in the laboratory and given to the patient by infusion. The T-cells can then recognize and kill the cancer cells. Modification of T-cells sourced from donors other than the patient is also under investigation, but this has serious immunologic adverse effect potential.

The first CAR-T gene therapy for cancer, tisagenlecleucel (Kymriah®), was recently approved (August 2017) by the FDA for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. This agent specifically binds the C19 protein on leukemia cells. Approval was based on Phase II results from a single-arm, international trial of 63 patients who received a single dose of tisagenlecleucel.[22] The overall remission rate was 82.5 percent in treated subjects. Forty patients (63%) had a complete remission (CR) and 12 (19%) had a CR with incomplete hematologic recovery. Because of potentially fatal or life-threatening adverse effects, such as cytokine release syndrome or neurological toxicities this therapy was approved with a risk evaluation and mitigation strategy (REMS) program. Cytokine release syndrome is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms. Other severe adverse effects include serious infections, hypotension, acute kidney injury, fever, and hypoxia. Most symptoms appear within one to 22 days following infusion. Since the CD19 antigen is also present on normal B-cells, this treatment will also destroy normal B cells that produce antibodies; there may be an increased risk of infections for a prolonged period of time after treatment.

The FDA has approved another CD19-directed CAR-T cell therapy, axicabtagene ciloleucel (Yescarta®), as a treatment for adults with relapsed or refractory non-Hodgkin's lymphoma (NHL), based on CR rates in a Phase II trial (October 2017). The approval was specifically for those with large B-cell lymphoma following two prior therapies, including those with diffuse large B-cell lymphoma (DLBCL). Additionally, the CAR-T cell therapy is now indicated for primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL transformed from follicular lymphoma (TFL). This therapy also was approved with a companion REMS and causes the same significant adverse effects.

In the single-arm study, which was presented at the 2017 AACR Annual Meeting, axicabtagene ciloleucel demonstrated an objective response rate (ORR) of 82 percent and a CR rate of 54 percent.[23] After 8.7 months of follow-up, 39 percent of patients remained in CR. The median duration of response in those with a CR was not reached at the time of the assessment (95% CI, 8.1-not estimable). In this trial, all patients had chemorefractory disease and had received a median of three prior lines of therapy, with 54 percent refractory to two consecutive lines of therapy. Overall, 79 percent of patients were refractory to their last line of chemotherapy without

Exhibit 6: Drivers of Cancer Markets



having received prior autologous stem cell transplant (ASCT) while the remainder had relapsed within 12 months of ASCT. Of note, there were four fatal events in the study, three of which were deemed related to the therapy. The causes of death were hemophagocytic lymphohistiocytosis and cardiac arrest in the setting of CRS (2), cerebral edema in the setting of Grade 3 CRS with multiorgan failure (1) and pulmonary embolism (1, unrelated).

Another form of ACT, called TCR therapy, is similar to CAR-T cell therapy. This form of ACT also involves engineering T-cells collected from patients to express a receptor on their surface. Unlike CAR-T, TCRs are naturally occurring. These receptors allow T-cells to recognize antigens from inside tumor cells that have been processed into small bits and transported to and displayed on the cell surface. The process for producing TCR cell therapies and administering them to patients is similar to the process for producing CAR-T cells.

The first form of ACT to be tested in humans used immune cells collected from a patient's tumor, called tumor-infiltrating lymphocytes (TILs). TILs are immune cells that have naturally entered a tumor, and their presence is thought to indicate that the immune system is trying to attack the cancer. However, the antitumor effect of the TILs is usually short-lived because there may not have been enough of these immune cells in the tumor microenvironment to eradicate it or overcome the immunosuppressant signals being released by the tumor.

Therapeutic TILs are autologous lymphocytes isolated from patients' tumors and cultured to large numbers of cells in the laboratory.[24] TILs are collected from a patient's tumor and tested in the laboratory to identify those with the greatest ability to recognize the patient's tumor cells. Unlike CARs or TCRs, they do not undergo any further modifications or engineering. Like CARs and TCRs, large populations of these cells are grown in the laboratory. Prior to TIL treatment, patients are given non-myeloablative chemotherapy to deplete native lymphocytes that can inhibit the response. Once lymphodepletion is completed, patients are infused with TILs in combination with interleukin-2. Introducing massive amounts of activated TILs can help to overcome the tumor microenvironment barriers, leading to tumor destruction. Therapeutic TILs are being studied alone, in combination with interleukin-2 infusions, and in combination with various other immuno-oncology therapies.

Immuno-Oncology Therapy Pipeline

There are more than 100 agents in the pipeline. A few of the contenders are listed in Exhibit 4. Additionally, the approved immuno-oncology therapies are likely to have continuing expansion of their FDA-approved indications. Another financially worrisome issue is the use of immuno-oncology therapy combinations. Several dual and triple combinations are currently under investigation.

Payer Strategies for Optimal Cost Management of Evolving Therapies

New cancer case numbers are increasing, mainly due to the aging demographic. Cancer deaths are

decreasing mainly due to the impact of early detection and new treatments. Therefore, cancer has become a chronic disease for many patients. Oncology is poised to be one of the largest growth areas in medicine today; thus, a perfect storm.

National expenditures for cancer care are predicted to be $157.77 billion in 2020 because of an aging and growing population (Exhibit 5).[25] This predicted total does not include the cost of all the newly approved immuno-oncology therapies.

Immunotherapy is a major cost driver in cancer care today. In a plenary session presentation at the American Society of Clinical Oncology annual meeting in 2015, Dr. Leonard Saltz estimated that the widespread use of immunotherapy agents could cost the United States $174 billion annually, which should be noted is more than the total estimated cost of cancer care for 2020.[26] The currently approved checkpoint inhibitors cost approximately $150,000 per year. Annual costs also depend on tumor type and dosing. The combination of ipilimumab and nivolumab costs an estimated $256,000 annually.[27] Payers view immunotherapy cost as representative of cancer care cost overall and often use the term "unsustainable." Historically, payers had limited tools to manage oncology costs and often those tools were relatively blunt instruments. Payers are not the only ones involved now; employers, who are paying for the care, are demanding cost control actions as well.

Traditionally, payer management of cancer care has been limited to a few management activities, including limited prior authorizations, case management of catastrophic cases, site of care shifts to outpatient treatment, and management of the cost of infusion therapies through average sales price-based reimbursement. Cancer management today includes aggressive prior authorization programs, risk shifting or sharing, and contracting strategies. Aggressive prior authorization programs only allow approval for FDA labeled indications and may restrict medication access to cases identical to populations studied in the clinical trials or to selected genetic subtypes using genetic markers. Some treatments are being limited to only payer-approved centers or groups. Risk shifting or sharing includes increased contracting with accountable care organizations (ACOs) and other risk-bearing entities, increased use of pathways, risk or value-based contracting with oncology groups, and contracting with centers of excellence. Aggressive contracting for preferred agent positioning, closed formularies even on the medical side, and outcomes-based contracting are some of the contracting strategies being used by various managed care organizations.

Many large payers have adopted new programs to try to manage oncology costs. Anthem has introduced its Cancer Care Quality Program, which is a pathway-based program with embedded quality measures. Based on a three-year pilot study in five practices that demonstrated a 34 percent reduction in cost, United has started offering bundled oncology payments. Cigna is focusing on improved access and care coordination.

The Centers for Medicare and Medicaid Services (CMS) Oncology Care Model (OCM) is impacting cancer care in the wider community. The program aims to provide higher quality, more highly coordinated oncology care at the same or lower cost. Under the OCM, physician practices have entered into payment arrangements with financial and performance accountability for episodes of care surrounding chemotherapy administration to cancer patients. The practices participating in OCM have committed to providing enhanced services to Medicare beneficiaries such as care coordination, navigation, and national treatment guidelines for care. This program pays practices a monthly fee for care coordination and pays additional moneys for outcomes and following guidelines. One hundred and ninety-two practices and 14 payers are participating in the OCM.[28]

There has been much discussion in the payer community about the role of value or outcomes-based contracting and whether it can be applied to cancer care, specifically immuno-oncology. There have been 16 risk-sharing pharmacy contracts announced publicly between 2015 and 2017. Most of these contracts focus on hepatitis C, diabetes, and lipid management with the PCSK9 inhibitors.[29] To date, there are no risk-sharing contracts publicly announced for use of immuno-oncology across multiple cancer types, but this may occur in the future.

Risk or value- based contracting will require a team-based approach with at least medical and pharmacy directors. There are numerous operational and legal issues that must be considered for this type of contracting. Legal considerations include pricing regulations, FDA regulations on economic claims, and anti-kickback statues. Operational considerations include choosing relevant outcomes that can be actually measured (e.g., overall survival, progression-free survival, overall response rate, or duration of response), availability of data of sufficient detail, and time frame (e.g., one year or longer). Patient factors also need to be considered. Quality of life should be a consideration in many cancers where survival is typically not long and the adverse effects of treatment can be significant. Once it arrives, value-based contracting for immunotherapy agents will likely cross the spectrum of multiple types of cancer.

Conclusion

Immuno-oncology agents have the potential to transform the management of many cancer types. The last two years have seen an explosion of approvals for immunotherapies for cancer.

Multiple cancers, both hematologic and solid organ cancers, are now being treated with these agents. Gene therapy for selected cancers has also been recently approved. However, there is a cost to these agents that payers are now struggling to manage. Old methods of management of cancer costs are being replaced with newer reimbursement models and value-based contracting. Because of the growing interest in new agents and the success of the treatment of cancer with immune checkpoint inhibitors, payers will need to better understand this disease and the emerging treatments to better manage cost and access to appropriate care. As immunotherapies move to the forefront of cancer treatment, health care professionals will need to understand the immune system, know how cancer circumvents it, and be aware of the mechanisms of action, efficacy, and safety of current and emerging immunotherapies.

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