SPECIAL ISSUE: IMMUNO-ONCOLOGY

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Evidence-Based ONCOLOGY™

FEBRUARY 2017
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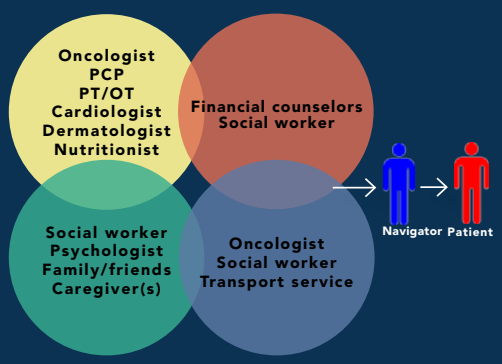
ALSO IN THIS ISSUE



PATIENT NAVIGATION

Patient navigation is immensely helpful in relieving some of the burden placed on cancer patients, and there are some particularly unique aspects of navigation as it pertains to immuno-oncology (SP46).


FEINBERG


FILLMAN

CAR-T REVIEW


NABHAN


SIMONCINI

CAR-T treatments are being evaluated in both liquid and solid tumors, in adults as well as the pediatric population. However, challenges pertaining to their manufacture and management of post infusion adverse effects remain (SP48).


CHANDRA

COMMUNITY CLINICS

As immune-oncology agents make their way from the bench to the clinic, community oncologists will have to develop models that incorporate these costly agents into treatment plans (SP57).


PORTER

AJMCTV® INTERVIEWS

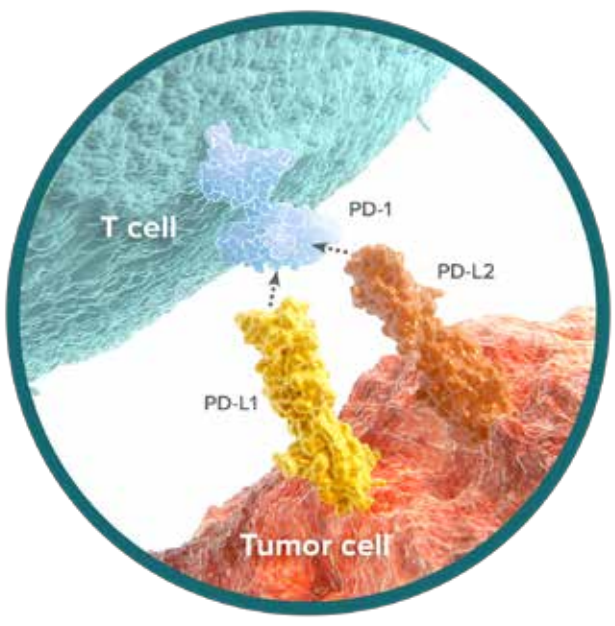
David L. Porter, MD, of the University of Pennsylvania Health System, explains why treating tumors with a combination of CAR-T cells and other immune-stimulating agents is a logical next step for investigators (SP67).

PAYMENT MODELS

Advanced APMs and the Emerging Role of Immuno-Oncology Agents: Balancing Innovation and Value

Michael V. Seiden, MD, PhD; Marcus Neubauer, MD; and Diana Verrilli

AS THE COST OF HEALTHCARE IN the United States surpasses $3 trillion and cancer care approaches $150 billion annually, there is a growing public discourse on strategies to mitigate healthcare expenditures.[1] Commercial payers, government agencies, and, in particular, HHS have begun piloting value-based reimbursement strategies to see how these perturbations might encourage the evolution of clinical practice and care delivery towards a value-based, alternative payment model (APM). The Center for Medicare & Medicaid Innovation (CMMI) Oncology Care Model (OCM)—proposed, and now active, in 196 predominantly community-based oncology practices across the country—will be particularly important, both due to the large number



PRECLINICAL STUDIES SUGGEST THAT COMPLETE INHIBITION OF PD-1 SIGNALING THROUGH BOTH PD-L1 AND PD-L2 MAY BE MORE EFFECTIVE AT REVERSING T-CELL EXHAUSTION THAN INHIBITING PD-L1 ALONE. IMAGE COURTESY OF BRISTOL-MYERS SQUIBB COMPANY.

of eligible participants, the complexity of the program design,[2] and the wealth of data that will be generated and shared between the payer (CMS) and the participating practices. If this program is successful at reducing Medicare program expenditures while preserving or improving the quality of cancer care for beneficiaries, it likely will have a profound impact on how cancer care is paid for in the future by both government and commercial payers.

APMs that incentivize reductions in the total cost of cancer care (like the OCM) will encourage providers to focus on 2 of the largest

CONTINUED ON SP69

PATIENT EDUCATION

Helping Cancer Patients and Caregivers Navigate Immunotherapy Treatment

Claire Saxton, MBA; Joanne Buzaglo, PhD; Sue Rochman, MA; and Alexandra Zaleta, PhD

IMMUNOTHERAPY IS ONE OF THE fastest growing areas of cancer research. The Cancer Moonshot 2020 Program calls for the creation of a Cancer Immunotherapy Translational Science Network to develop and implement immune-based approaches for preventing and treating adult and pediatric cancers.[1] There are more than 500 open immunotherapy trials listed on ClinicalTrials.gov,[2] and the list of immunotherapy drugs, as well as the cancers that are approved to treat, keeps growing.[3]

Currently, not all patients with cancer are aware that immunotherapy, either through a clinical trial or as a prescribed treatment, might be one of their options. Those who do, may not be fully aware of how immunotherapy works or of the short- and long-term side effects they may experience. Additionally, as with other oncology treatments, patients may not be aware of the total cost of these new treatments or the patient-assistance programs that can help to offset those costs.

CONTINUED ON SP78

PROVIDER INTERVIEW

Q&A With Dr Jae Park on the Promise of CAR-T Cells in Cancer Care

Surabhi Dangi-Garimella, PhD

JAE PARK, MD, IS A hematologist-oncologist, at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, who is leading a clinical trial using chimeric antigen receptor (CAR)-T cells in the treatment of patients diagnosed with chronic lymphocytic leukemia (CLL). Park is also a part of trials investigating CAR T-cell treatment in patients with acute lymphoblastic leukemia (ALL).

In an interview with *Evidence-Based Oncology*™ (*EBO*™), Park described how the treatment manipulates the body's immune system, reviewed some of

CONTINUED ON SP80

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SPECIAL ISSUE / IMMUNO-ONCOLOGY

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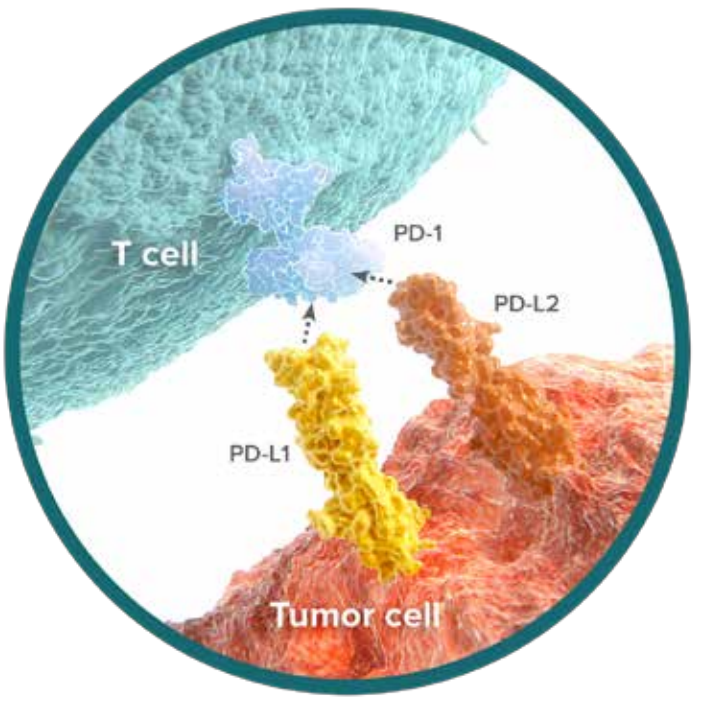
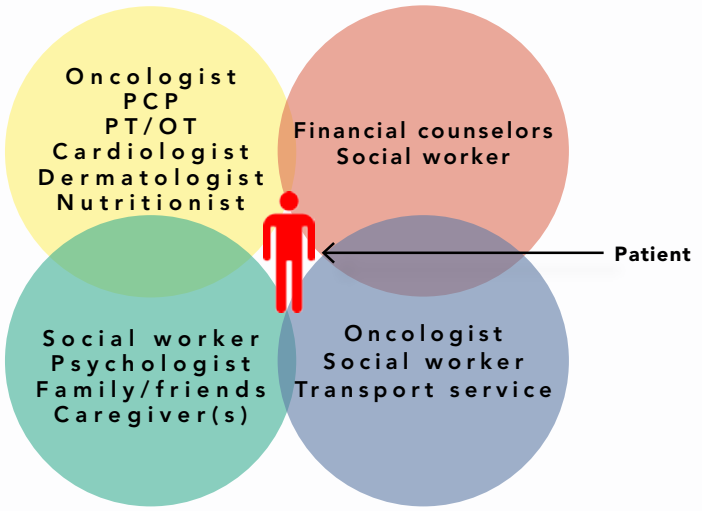
SP69



SP46. Coordination of I-O Care in the Absence of Patient Navigation



Without patient navigation the full burden of care coordination falls on the patient, which can make it seem like the walls are closing in.

I-O indicates immuno-oncology; PCP, primary care physician; PT, physical therapist; OT, occupational therapist.

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Medical World News®

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FROM THE CHAIRMAN

Immunotherapy Works—Now How Do We Pay for It?

MIKE HENNESSY, SR

FOR THE THIRD CONSECUTIVE YEAR, *Evidence-Based Oncology*™ has dedicated its first regular issue of the year to immuno-oncology (I-O). While the field is rapidly expanding—with several checkpoint inhibitors approved for multiple indications and the emergence of leukapheresis–based T-cell infusions—stakeholders are now faced with new challenges that range from raising awareness about these treatments among patients to ensuring adequate reimbursement for physicians.

Contributors to this issue share some of the progress and barriers with using this novel therapy. Experts from Cardinal Health Specialty Solutions provide an update on advancements with chimeric antigen receptor T-cell therapy and how this can be a stand-alone treatment or used in combination with I-O agents in the clinic. The article also provides a synopsis of ongoing clinical trials, toxicity management, and a prediction on the commercial success of these treatments.

The clinical developments, however, would be futile in the face of lack of awareness. Patients, caregivers, and providers need education on immunotherapy treatment, help with patient-provider communications, and support in mitigating the financial impact of immunotherapy treatment—which the Cancer Support Community (CSC) is ready to provide in the form of webinars, print and digital education materials, and workshops. CSC, the authors write, is also engaged with policy makers and other patient advocacy groups on discussions around the cost of I-O treatments.

Another invaluable resource for patients and their families is a patient navigator at the cancer clinic. Patients who receive care at the Lahey Hospital and Medical Center in Burlington, Massachusetts, can seek support from a patient-care coordinator throughout their care continuum—including survivorship and hospice care. The services also help patients navigate financial aspects of their care, including providing information on patient assistance programs.

A struggle for our healthcare system of late has been the cost of care, which includes the cost of innovative treatments such as I-O. Community oncologists face the brunt of this cost burden as well. The questions become how important are cost-effectiveness discussions, and can value frameworks, such as those developed by the Institute for Clinical and Economic Review, be brought into the mainstream? Sharing his thoughts on this, Sumeet Chandra, MD, Medical Associates of Brevard, Brevard County, Florida, writes that community oncologists should be strong advocates for greater information and affordability of these new and potentially groundbreaking therapies.

Experts from McKesson Specialty Solutions propose raising questions such as "Are all PD-1 and PD-L1 agents equivalent?" or "How can we identify patients who will benefit from I-O therapy?" to help moderate the costs of I-O agents. The authors also ask the pharmaceutical industry to share the burden of value-based pricing, especially with growing competition.

We hope you can draw benefit from the discussions presented in this issue and as always, thank you to our readers for their continued support. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

FROM THE EDITOR-IN-CHIEF

Keeping Pace With the Immunotherapy Revolution


JOSEPH ALVARNAS, MD

IN THE LATE 1970S, a member of my family underwent treatment for breast cancer. As she navigated the rigors of her treatment with a modified radical mastectomy and adjuvant chemotherapy (administered then without the effective antiemetic regimens of today), I recall the toll exacted upon her. Two decades later, as a fellow in bone marrow/hematopoietic cell transplantation, I recalled her experience as we attempted to push the boundaries of dose intensity in an attempt to more effectively care for patients with advanced, relapsed, and persisting malignancies. The side effects of these ever more intensive regimens proved challenging to many patients, and the experience showed us that increasing therapeutic intensity was ultimately limited in its potential effectiveness and applicability.

The quest for more effective cancer treatments has inspired generations of basic science researchers, medical oncologists, surgeons, and radiation oncologists to seek more effective and less morbid ways of treating patients. The extraordinary iterative efforts of basic scientists, physician investigators, and the pharmaceutical industry have led us to identify novel approaches outside the traditional triad of surgery/chemotherapy/radiation therapy for more effective treatment of patients with cancer. It is in this spirit of discovery and innovation that immuno-oncology has arisen as an essential avenue toward the more effective treatment of patients affected by a broad array of cancers.

THE EXPERIENCE WITH SIDE EFFECTS OF THE EVER MORE INTENSIVE AGENTS SHOWED US THAT INCREASING THERAPEUTIC INTENSITY IS LIMITED IN ITS POTENTIAL EFFECTIVENESS AND APPLICABILITY.

Investigators, in the early 1970s, had identified immune mediators as a potentially important set of tools for treating patients with cancers. During this period, *Time* magazine heralded the availability of these "magic bullets" as potential game-changing medications for patients affected by chemotherapy-refractory tumors, such as melanoma and renal cell cancer. The actual effectiveness of interleukin-2 and lymphokine-activated killer cells never quite fulfilled the promise of the *Time* cover story, but they did showcase the potential importance of the immune system in cancer treatment.[1,2]

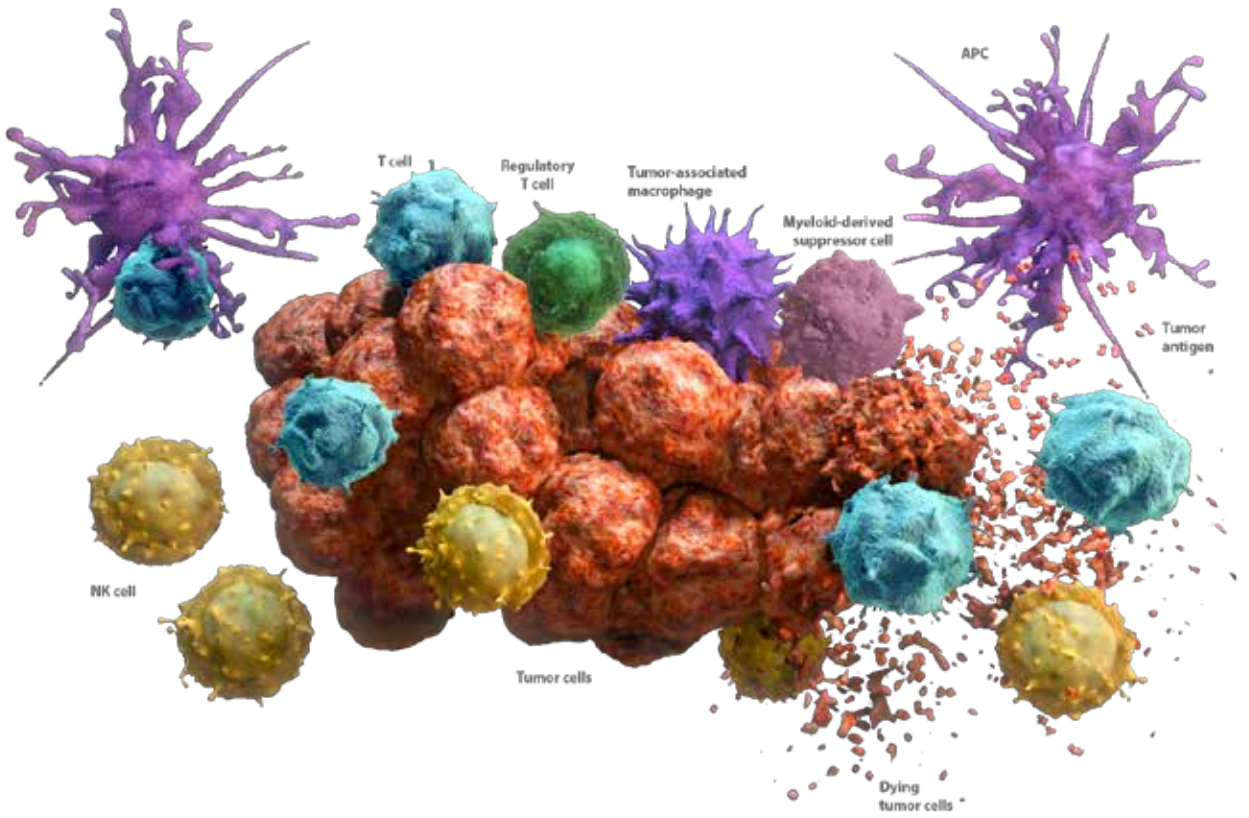
Flash forward 40 years, and a Google search of the term "immuno-oncology" yields more than 531,000 hits. The glimmer of promise demonstrated by early trials of immunomodulating drugs in the 1970s presaged the current era in which immuno-oncologic agents have been licensed by the FDA at an astonishing rate. The pace of innovation and the increasing breadth of immuno-therapeutic agents over the past 3 decades has accelerated beyond what any of us thought might be possible—the armamentarium has grown to include agents from an astonishingly wide variety of drug classes. These "magic bullets" now include the original set of therapeutic monoclonal antibodies, monoclonal antibody/drug conjugates, bispecific molecules, oncolytic viruses, cancer vaccines, chimeric antigen-receptor (CAR) T-cells, and the growing numbers of checkpoint inhibitors.

It would be difficult to overstate the impact of these new agents in the treatment of a wide variety of cancers. Therapeutic monoclonal antibodies like rituximab and trastuzumab play an indispensable role in the initial treatment of patients with CD20–expressing non-Hodgkin lymphomas and *her-2-neu*–expressing breast cancers, respectively, resulting in significant improvements in overall survival (OS).[3,4] Monoclonal antibody/drug conjugates, such as brentuximab, have demonstrated the ability to produce remissions »

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

FROM THE EDITOR-IN-CHIEF



THE ABILITY OF THE IMMUNE SYSTEM TO DETECT AND DESTROY CANCER IS THE FOUNDATION OF IMMUNO-ONCOLOGY RESEARCH. INNATE AND ADAPTIVE IMMUNITY ACT AS A COMPLEMENTARY NETWORK OF SELF-DEFENSE AGAINST FOREIGN THREATS. IMAGE COURTESY OF BRISTOL-MYERS SQUIBB COMPANY.

in previously refractory patients with Hodgkin lymphoma and improve OS for high-risk patients following transplantation. Emerging agents in this drug class have demonstrated significant promise in the treatment of patients with relapsed acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia.[5] The bispecific molecule blinatumomab has been approved for the treatment of patients with refractory and persistent ALL and can serve as an effective "bridge to transplant" for previously untreatable patients.[6]

Beyond the emerging wealth of antibody-based therapeutics, immuno-oncologic innovation now includes treatments based upon the use of oncolytic viruses (T VEC hsv-1 for treatment of melanoma),[7] cancer vaccines (Sipuleucel-T for treatment of prostate cancer),[8] and CAR T cell- based therapeutics.[9] The increasing promise of these agents for treating patients with diagnoses that are typically refractory to standard chemotherapeutic approaches demonstrates the extraordinary promise of these novel therapeutics.

THE MORE PROSAIC CHALLENGE IS TO ENSURE THAT IMMUNO-ONCOLOGY AGENTS ARE USED IN AN ECONOMICALLY SUSTAINABLE, EFFECTIVE, AND PATIENT-CENTERED WAY.

A recent case report in the *New England Journal of Medicine* published by a research group at the City of Hope, in Duarte, California, demonstrates the potential role for innovative immuno-oncological agents in the treatment of patients for whom therapeutic choices remain limited and largely unsatisfactory.[10] In this case report, a patient with recurrent multifocal glioblastoma received intraventricular and tumor cavity–directed injections of CAR T-cells targeted at the interleukin-13 receptor alpha 2—more commonly known as IL13Rα2—as a tumor-associated antigen. The patient achieved a complete response and the response has persisted through the time of publication of the report, 7.5 months after the initiation of CAR T-cell therapy.

These agents are merely the beginning of an immuno-oncological revolution. The emergence of the checkpoint inhibitor class of agents with activity directed at programmed death-1 and programmed death-ligand 1, promise an even more robust armamentarium of immuno-oncological agents in the near term.

It is in this context that we are pleased to bring you this issue of *Evidence-Based Oncology*™ in which the authors address many important aspects of this brave new field. Experts from the Cardinal Health Specialty Care Solutions provide an overview of CAR T-cell technologies and review how these therapeutics can be successfully integrated into patient care. Jae Park, MD, a CAR T-cell researcher and innovator from Memorial Sloan Kettering Cancer Center, provides his perspective on the value of these therapeutics in answering unmet patient needs. Shawn M. Regis, PhD, a patient navigator with the Lung Cancer Screening Program at Lahey Hospital & Medical Center, describes the various options offered by the hospital via its navigation program and addresses some unique aspects of navigation as it pertains to immuno-oncology. An article from authors at McKesson Specialty Solutions provides insight on how alternative payment models can absorb the impact of innovation in oncology care.

Over the past decade we have seen extraordinary advances in cancer therapeutics that have moved us far beyond what was imaginable early in my career. The idea of harnessing the power of the immune system as a means of bringing more effective, better tolerated treatment solutions to patients in need is deeply inspiring. As we have heard the heightened rhetoric associated with the Cancer Moonshot initiative, the increasing availability of immuno-oncological agents provides concrete evidence that understanding and conquering cancer is achievable. The more prosaic challenge is that of ensuring that as the wealth of new immuno-oncological agents come to market, they are used in an economically sustainable, effective, and patient-centered way. ◆

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DARZALEX® + Rd or Vd after first relapse in multiple myeloma

DISCOVER MORE

with the first and only CD38-directed monoclonal antibody (mAb)[1]

Indication

DARZALEX® (daratumumab) is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Rd=lenalidomide and dexamethasone; Vd=bortezomib and dexamethasone.

Important Safety Information

Warnings and precautions include: infusion reactions, interference with serological testing, neutropenia, thrombocytopenia, and interference with determination of complete response.

In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. **Serious adverse reactions were:** pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).

In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. **Serious adverse reactions were:** upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

Please see Important Safety Information and brief summary of full Prescribing Information on following pages.

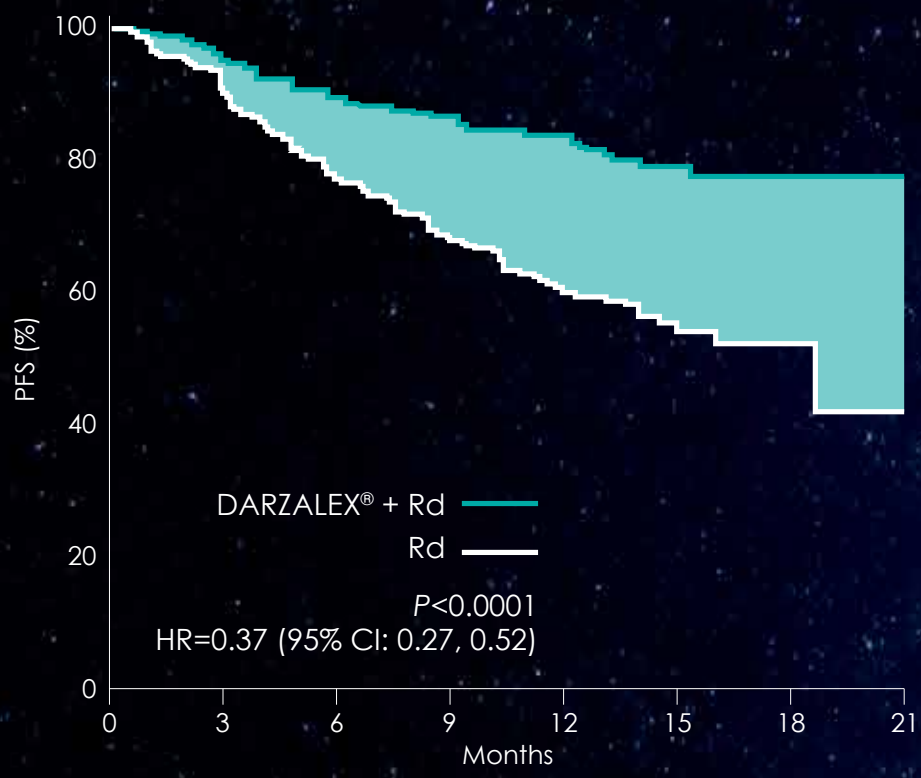
DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARE TO DREAM

Superior efficacy in combination

POLLUX

DARZALEX® (daratumumab) + Rd significantly improved PFS vs Rd alone[1]



63%
reduction in the risk of disease progression or death with DARZALEX® + Rd

POLLUX was an open-label, randomized, active-controlled phase 3 trial comparing treatment with DARZALEX® 16 mg/kg + Rd (n=286) to Rd alone (n=283) in multiple myeloma patients who received a minimum of 1 prior therapy. Patients were treated until unacceptable toxicity or disease progression. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria.[1]

91.3% **ORR** with DARZALEX® + Rd vs **74.6%** with Rd alone (*P*<0.0001). CR or better was 42.3% with DARZALEX® + Rd vs 18.8% with Rd alone. VGPR was 32.2% vs 24.4%, and PR was 16.8% vs 31.4% with DARZALEX® + Rd vs Rd alone, respectively.[1]

Rd=lenalidomide and dexamethasone; PFS=progression-free survival; HR=hazard ratio; ORR=overall response rate; CR=complete response; VGPR=very good partial response; PR=partial response.

Indication

DARZALEX® (daratumumab) is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Important Safety Information

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX® can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia

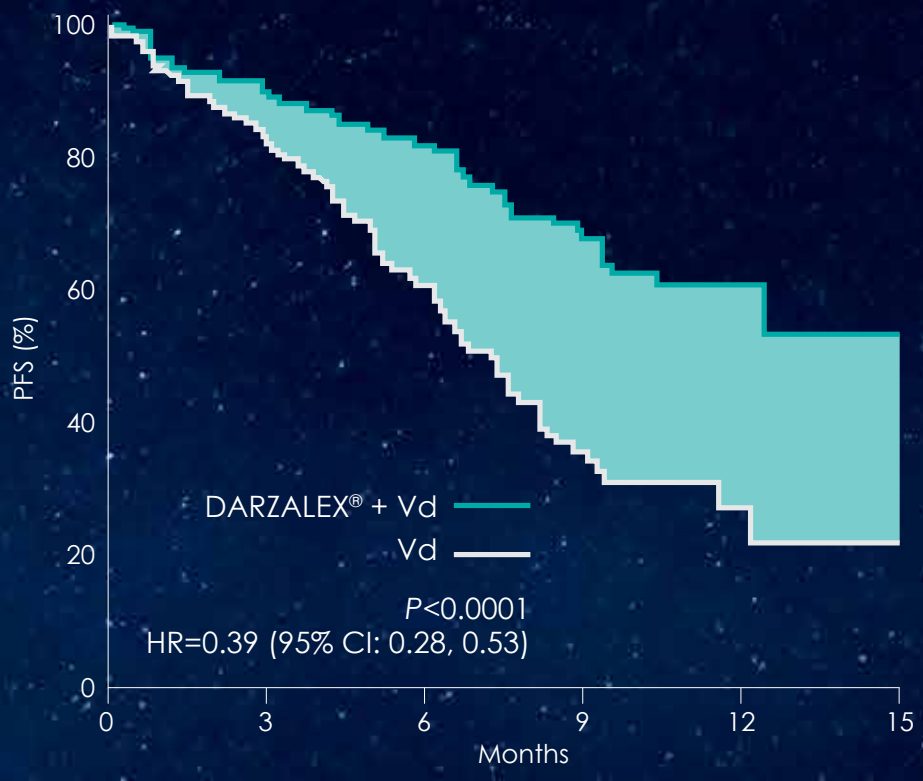
DARZALEX® may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors.

Thrombocytopenia

DARZALEX® may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX® dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with transfusions.

CASTOR

DARZALEX® + Vd significantly improved PFS vs Vd alone[1]



61%
reduction in the risk of disease progression or death with DARZALEX® + Vd

CASTOR was an open-label, randomized, active-controlled phase 3 trial comparing treatment with DARZALEX® 16 mg/kg + Vd (n=251) to Vd alone (n=247) in multiple myeloma patients who received a minimum of 1 prior therapy. DARZALEX® was given until disease progression. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria.[1,2]

79.3% **ORR** with DARZALEX® + Vd vs **59.9%** with Vd alone (*P*<0.0001). CR or better was 18.3% with DARZALEX® + Vd vs 8.5% with Vd alone. VGPR was 38.2% vs 19.0%, and PR was 22.7% vs 32.4% with DARZALEX® + Vd vs Vd alone, respectively.[1]

Vd=bortezomib and dexamethasone.

Important Safety Information (cont'd)

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Adverse Reactions

In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).

In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

DRUG INTERACTIONS

Effect of Other Drugs on Daratumumab: The coadministration of lenalidomide or bortezomib with DARZALEX® did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs: The coadministration of DARZALEX® with bortezomib did not affect the pharmacokinetics of bortezomib.

063483-161117

Please see brief summary of full Prescribing Information on adjacent pages.

For more information, visit **www.darzalexhcp.com**

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Palumbo A, Chanan-Khan A, Weisel K, et al; the CASTOR Investigators. *N Engl J Med.* 2016;375(8):754-766.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

 01/17 064370-161209

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARE TO DREAM

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Adverse Reactions]*.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum[1] *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions]*.
- Neutropenia *[see Warning and Precautions]*.
- Thrombocytopenia *[see Warning and Precautions]*.

Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 717 patients with multiple myeloma including 526 patients from two Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd, n=283; Study 3) or bortezomib (DVd, n=243; Study 4) and four open-label, clinical trials in which patients received DARZALEX either in combination with lenalidomide (n=35), or as monotherapy (n=156).

Combination Treatment with Lenalidomide

Adverse reactions described in Table 1 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study 3. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (12% vs Rd 10%), upper respiratory tract infection (7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 1: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm in Study 3

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.
[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
[c] cough, productive cough, allergic cough
[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-emergent hematology laboratory abnormalities in Study 3

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 3 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study 4. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

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Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 3: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm Study 4

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.
[b] edema peripheral, edema, generalized edema, peripheral swelling
[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
[d] cough, productive cough, allergic cough
[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 4.

Table 4: Treatment-emergent hematology laboratory abnormalities in Study 4

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 5. Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0

Table 5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg (continued)

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.
[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 6: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=717) the incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 72.8 hours). The incidence of infusion modification due to reactions was 41%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively.

Severe (Grade 3) infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions (any Grade, ≥5%) were nasal congestion, cough, chills, throat irritation and vomiting.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the randomized controlled combination therapy studies, herpes zoster was reported in 2% each in the DRd and Rd groups respectively (Study 3) and in 5% versus 3% in the DVd and Vd groups respectively (Study 4).

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively and 4% versus 3% of patients in the DVd and Vd groups respectively. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 1 (0.4%) of the 234 combination therapy patients, tested positive for anti-daratumumab antibodies. This patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

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DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding[1] *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations].* The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use

Of the 156 patients that received DARZALEX monotherapy at the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. Of 561 patients that received DARZALEX with various combination therapies, 40% were 65 to 75 years of age, and 9% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information].*

OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

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PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions and Adverse Reactions].*

Neutropenia

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions and Adverse Reactions].*

Thrombocytopenia

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions].*

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions and Drug Interactions].*

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions and Drug Interactions].*

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Patient Navigation in Immuno-Oncology

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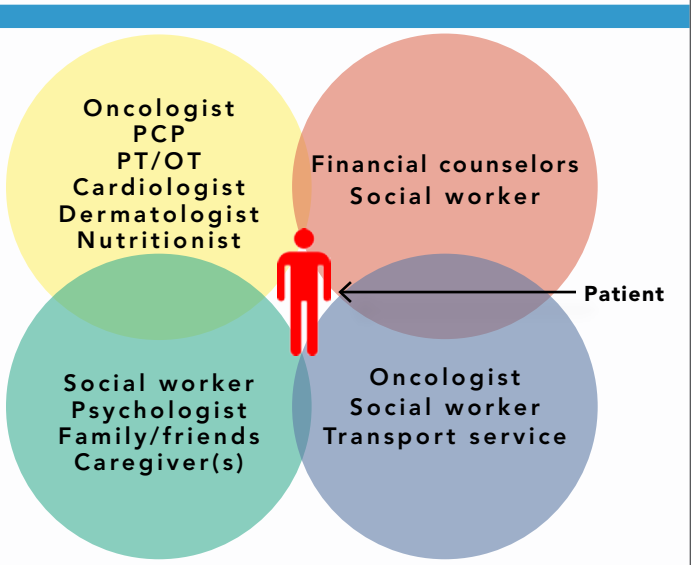
BEING DIAGNOSED WITH CANCER IS often the scariest news a patient will hear in his or her lifetime. In addition to the physical toll of the disease itself, there are numerous other factors associated with a cancer diagnosis that can be far too burdensome for a patient to handle alone. For this reason, care coordination for all oncology patients is critical in providing the best possible outcome. With disease treatment being the main focus, communication among primary care physicians, oncologists, and other specialists involved in patient care becomes very important. Patient comorbidities and treatment side effects often need to be addressed as well. This could require involvement of a range of subspecialty providers, including those in pulmonology, cardiology, dermatology, nutrition, and physical and occupational therapy (**Figure 1**).

Beyond these physical concerns, there is a large psychosocial burden associated with a cancer diagnosis. We know that psychosocial issues affect oncology patients regardless of stage and that the patient's emotional response to the diagnosis has an impact on both morbidity and mortality.[1] While many patients do eventually adjust effectively to their new circumstances without requiring intervention, more than one-third will experience significant distress requiring clinical support[2]; although many patients depend on family, friends, and religious leaders for support, others also need intervention in the form of a social worker or psychologist.

Beyond the clinical needs, there are also financial and logistical considerations when coordinating cancer care. Fighting cancer can be an expensive battle, and assistance from a financial counselor (either personal or assigned by the hospital) can prove beneficial. Patients also need to coordinate transportation to and from their (often multiple) appointments to receive care while deciphering the logistics to take time away from work if necessary. All of these factors combined make managing a cancer diagnosis a daunting task for any patient, and assistance from a navigator can help ease the burden (**Figure 2**). This is true for all oncology patients, but there are some unique challenges pertaining to the rapidly developing field of immuno-oncology (I-O).

FIGURE 1. Coordination of I-O Care in the Absence of Patient Navigation



Without patient navigation the full burden of care coordination falls on the patient, which can make it seem like the walls are closing in.

I-O indicates immuno-oncology; PCP, primary care physician; PT, physical therapist; OT, occupational therapist.

Educating Patients and Providers

The field of I-O has grown rapidly over the past 5 years, enough to now be considered the "fourth pillar" of oncology treatment,[3] along with surgery, radiation, and chemotherapy. One of the side effects of being a relatively new modality is that knowledge of the field is somewhat limited among patients and even some providers. A needs assessment conducted by the Association of Community Cancer Centers, in 2014, showed that only 7% of community clinicians reported being "extremely familiar" with emerging I-O therapies, while 39% responded that they were either "not at all familiar" or only "slightly familiar" with these therapies.[3] Thus, the very first piece of the puzzle in care coordination is to ensure providers are familiar with these treatments so they can discuss them with patients when appropriate. The patient must also be well informed to be effectively engaged in a shared decision-making process. However, with increasing demands on physicians' time, they may not be able to devote as much time as preferred on patient education. Therefore, a patient navigator who is knowledgeable of the field can be a great asset in answering patient questions and marshaling available resources as needed.

Not Your "Typical" Side Effects

Often times, when patients think about the side effects of cancer treatment they jump to horror stories they have heard about the hair loss, nausea, and vomiting, historically attributed to cytotoxic chemotherapy. While it is true that I-O drugs do not have these same side effects, significant toxicities can still occur. Because the goal of I-O drugs is to ramp up the immune response against cancer, it can also trigger unwanted autoimmune or inflammatory responses.[4] Common side effects associated with I-O are diarrhea, rash, and fatigue; additionally, I-O agents have been known to cause toxicity in the liver, thyroid, lung, and colon. Making patients aware of these adverse events should be a part of patient education, and patients should also have access to resources to help manage these side effects—access to dermatologists or gastrointestinal specialists who are familiar with the field of I-O. Coordinating appointments with these specialists, in addition to the regular treatments, is an important patient navigator function.

The Cost of Immunotherapy

An argument could be made that a patient navigator can have the most impact in the care coordination of I-O patients by helping them navigate financial assistance. By 2020, the cost of cancer care in the United States is expected to reach $157 billion.[5] This high cost could, in part, be attributed to I-O therapies, as the average cost for a course of this treatment in the United States is $120,000

to $150,000 per patient and could go higher if combination therapies are indicated.[6] Of note, some predict the market size for I-O agents alone will be over $30 billion by 2022, equal to the cost of all anticancer drugs in the United States for 2016.[4] With specialty tiers of insurance typically requiring patients to pay somewhere in the range of 20% to 25% of medication costs,[6] patient co-pays could range anywhere from $35,000 to $40,000. This can often lead patients to either refuse I-O therapy due to the high cost, or choose between treatment and other necessities in their lives. Adding in the fact that many patients can't work while undergoing treatment, and therefore may lose insurance, the problem becomes even more complex.

Data suggest that patients with cancer are roughly 2.5 times more likely to go bankrupt than those without cancer and that the severe financial distress caused by out-of-pocket expenses related to cancer treatment is associated with a 79% increased risk of death.[7] With such high stakes, the costs for which the patient may be held responsible should be part of the shared decision-making process regarding cancer treatment, although often that is not the case. The conventional decision flow when it comes to cancer treatment selection is drug effectiveness, followed by drug toxicity, and finally cost.[8] It is important for patients to be made aware of the expense they can expect to incur as a result of receiving I-O for cancer treatment, and what options are available for financial assistance. A patient navigator can play a huge role in this area.

Helping With the Cost of Treatment

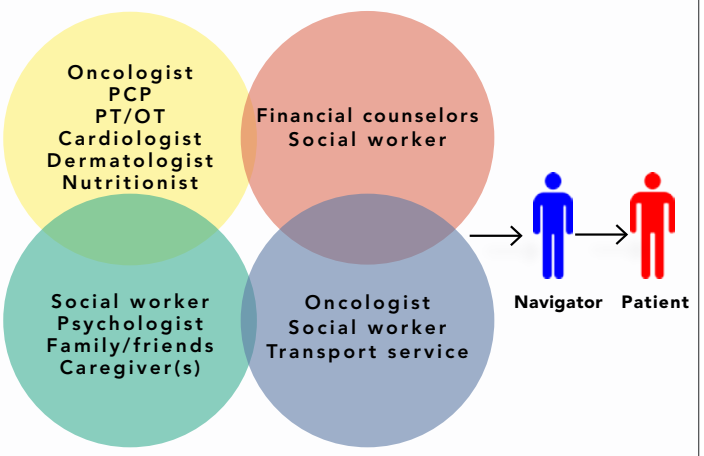
There are many options available to assist patients with the expenses associated with their oncology care. In addition to standard health insurance, these can include government programs, co-pay relief and patient assistance programs, assistance from volunteer organizations, and fundraising. However, it is not enough to simply notify a patient about these options; they also need guidance on whether they are eligible for this funding, and need to be informed of how to apply and obtain it. Patient navigators can connect with these different networks and help identify options that will generate the most benefit for the patient, and assist with the application process.

Because the cost of I-O therapies is high, and insurance companies often struggle to stay abreast and provide coverage for these rapidly emerging treatments,[3] many pharmaceutical companies offer assistance programs that can help patients with the cost of treatments, both beyond what their insurance will cover as well as for potential off-label use that most insurers will not cover. To apply, patients typically need to supply personal financial documents, including the previous year's tax returns, and/or a financial hardship statement attesting that even if they could "afford" the treatment, the burden of co-pays and other cost sharing would create a financial hardship. It is also important to note that while enrolling in such programs can lead to getting the treatment drug for free, the costs of the actual infusion (such as charges for supplies and intravenous catheter insertion) are still not covered. Navigators who are well educated in the field of I-O can be enormously beneficial when it comes to finding assistance programs like these.

Navigation Doesn't End When Treatment Does

As with all oncology care, the primary objective of coordinating care for patients receiving I-O therapy is to provide assistance throughout the care continuum. This includes survivorship, palliative, and hospice care, as applicable after treatment. Patients will continue to have follow-up visits, imaging, lab work, etc, and continue to require assistance in coordinating the care and costs. The benefits of survivorship programs have been well established, and there are often many questions and challenges associated with the transition to palliative and hospice care. Patient navigation should exist over this entire spectrum for oncology patients. Additionally, there are specific challenges associated with the rapidly evolving field of I-O that make having a patient navigator with extensive knowledge of the field a very valuable resource. ◆

FIGURE 2. Role of a Patient Navigator in I-O Care



Having a patient navigator with I-O experience coordinate the patient's care relieves much of the burden and allows the patient the ability to go to 1 person for all their questions/concerns.

I-O indicates immuno-oncology; PCP, primary care physician; PT, physical therapist; OT, occupational therapist.

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CAR-T Cells: The Next Era in Immuno-Oncology

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FOR THE THIRD CONSECUTIVE YEAR, the editors of *Evidence-Based Oncology* (*EBO*)™ are dedicating the February issue to immuno-oncology (I-O), and Cardinal Health has been a part of the conversation in each of the 3 issues. We marvel at the fact that it is a mere 5 years since the FDA approval of the first I-O of the modern era, the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor ipilumumab[1]; 2 years since the approval of the first 2 programmed death-1 (PD-1) inhibitors (nivolumab and pembrolizumab)[2,3]; and just months since the approval of the first programmed death-ligand 1 (PD-L1) antagonist (atezolizumab).[4] In such a relatively short time, these I-O therapies have:

- Garnered FDA approvals in 6 tumor types
- Received indications for adjuvant, first-line metastatic, and salvage disease
- Been combined for dual I-O therapy
- And, are likely to receive 5 additional tumor type approvals in the proceeding 12 to 18 months.

Key opinion leaders and subject matter experts openly conjecture the end of the chemotherapy era while the silence around precision medicine is deafening. More than half of all actively accruing cancer therapeutic trials involve I-O across 52 different malignancies as single agents, dual I-O regimens, and I-O in combination with chemotherapy and targeted therapy.

Our 2016 *EBO*™ article concluded with the statement: "Stakeholder adoption of I-O is no longer a question of 'IF' but a question of 'WHEN.' Who will be treated, with 'what' types of cancer, in 'which' stage and for 'how' long remain unanswered questions."[5] A year later, many of these questions are already being answered as new ones emerge, as I-O is poised to become the backbone of modern cancer treatment. Chief among these questions is 'What lies beyond CTLA-4, PD-1, and PD-L1 in the future of I-O therapeutics?' Most I-O treatments do not directly attack the tumor, rather, they mobilize the immune system to recognize and destroy the tumor. This can be achieved using various approaches, including antibodies, peptides, proteins, small molecules, adjuvants, cytokines, oncolytic viruses, bispecific molecules, and cellular therapies.

We believe the next I-O frontier to move from the bench to the bedside is cellular therapy in the form of chimeric antigen receptor (CAR)-T cells. In the first published trial from the University of Pennsylvania (U-Penn), 27 of 30 (90%) relapsed and refractory (R/R) patients with acute lymphoblastic leukemia (ALL) experienced complete remission 1 month after CAR-T infusion—22 (73%) of them had no evidence of minimal residual disease (MRD).[6] Rapid, complete, and durable responses in highly refractory patients make CAR T a potential game-changer for cancer therapy, but the issues impacting stakeholder adoption for ex-vivo activated cellular I-O are significantly more complex than anything we've seen before.[7]

History and Development of CAR-T Technology

First and foremost in the discussion is recognizing that CAR T does not represent a drug, but, rather, a complex therapeutic process. Whereas most of the previously commercialized I-O interventions—from interferons to interleukins to checkpoint inhibitors—are essentially drug therapies, CAR T is operationally more similar to hematopoietic stem cell transplantation (HSCT). In fact, the concept of CAR T has its origin in the allogeneic bone marrow transplantation (BMT) of ALL. More than a quarter century ago, observations of durable remissions in patients with ALL, post BMT, who suffered graft versus host disease (GVHD) led to the understanding that donor or grafted T-cell recognition of malignant host lymphoblasts could impart long-term disease control (graft versus leukemia effect).[8] The hypothesis generated was: if autologous T cells could be conditioned/manipulated to recognize malignant cells, then tumor control could be achieved without the negative consequences of GVHD.

When mild, GVHD is a complex chronic disease in which the grafted immune system is at war with the host organs; however, GVHD is life-threatening when severe. It would be critical to solve the problem of GVHD should any immune cellular therapy be successful. One method developed to create tumor recognition without the complications of GVHD involved reprogramming autologous T cells to identify and eliminate malignant cells through tumor-specific antigen recognition. The reprogramming required harvesting T cells from the patient via apheresis, transporting the cells to a wet lab where they could be chemically modified, and then altering the cells by linking the extracellular antigen recognition domain from a monoclonal antibody fragment to the T cell's intracellular signaling domains.[9] This newly modified autologous T-cell antigen receptor complex would then be a fusion, or chimera, of 2 proteins, or CAR. While still in the lab, the newly created CAR-T cells could then be incubated, or more technically, activated, to expand their number. Once adequately expanded, the CAR-T cells could be re-infused into the patient, but only after the patient is primed with chemotherapy to deplete their own circulating lymphocytes, which might dilute the CAR-T cells' effectiveness. T cells engineered to express such CARs engage an antigen on a tumor cell through the extracellular antibody domain, thereby activating the T cells in a major histocompatibility complex–independent manner.[8] Stated less scientifically, CAR-T cells can stimulate potent cytotoxic immune responses without the negative consequences of GVHD.

Early Clinical Experience: Efficacy

In **Table 1**, we have summarized selective data from completed or ongoing phase I/II CAR-T trials, which have been published and presented. This early research has focused on cancers in which the malignant cells express CD19—an antigen expressed

TABLE 1. Summary Table of Published/Presented Data

INSTITUTION	DISEASE	CHEMOTHERAPY (LYMPHODEPLETING AGENTS)	NUMBER OF PATIENTS	OUTCOMES	CRS RATE	NEUROTOXICITY RATE
U-Penn[6,19]	ALL	Various	30 (25 pediatric and 5 adult)	CR: 90%	Total: 100% Severe: 27%	Total: 43% Encephalopathy, seizure (1 patient)
MSKCC[20,21]	ALL	Cyclophosphamide	16 adults	CR: 88%	43% severe	Grade 3/4: 25% Encephalopathy and seizures
NCI[22]	ALL	Fludarabine and cyclophosphamide	21 pediatric and adults	CR: 67%	Total: 76% Severe: 28%	Total: 29% Hallucinations, dysphasia, and encephalopathy
FHCRC[23]	ALL	Cyclophosphamide and fludarabine or cyclophosphamide	29 adults	CR: 93%	Total: 83% Severe: 23%	50% severe
NCI[14,24]	CLL/NHL	Fludarabine and cyclophosphamide	7 CLL 14 (9 DLBCL or PMBCL)	CLL: (CR: 43%, PR: 43%) Other NHL (CR: 36%, PR: 36%)	Severe: 27%	Total: 40% Encephalopathy, aphasia, and ataxia
U-Penn[13]	CLL	Various regimens	14	CR: 29%, PR: 28%	Total: 64% Severe: 36%	Total: 43% Grade 4: 1 patient
MSKCC[25]	CLL	3 with nothing, 5 with cyclophosphamide, and 1 not evaluable	8 evaluable	No CR,1 PR	Fever in 8 and 1 patient died	Not reported

ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; FHCRC, Fred Hutch Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NHL, non-Hodgkin's lymphoma; PR, partial response; U-Penn, University of Pennsylvania.

only on malignant and normal B cells. CAR-T cells expressing anti-CD19 recognize and kill CD19-expressing malignant cells.[10] Among the CD19-expressing malignancies, pediatric R/R ALL has garnered the most attention. CAR-T treatment of pediatric R/R ALL has resulted in remarkable clinical benefit and fewer severe adverse events (SAEs) than adult R/R ALL treated with CAR-T cells, making pediatric ALL the leading candidate for the first FDA-approved indication.

Stakeholder adoption will likely be brisk for the same reasons, but the overall healthcare impact might be limited given the nature of this disease and the relatively small number of eligible patients; 2500 to 3500 new pediatric ALL in the United States are diagnosed annually, 80% of which are of B-cell lineage (CD19-positive); current 5-year survival is 85%, and treatment-related mortality is 1% to 3%.[11] While responses are attained with blinatumomab in the small number of R/R patients, they are rarely durable and less than one-third of pediatric patients with R/R ALL are cured with allogeneic HSCT.[11,12]

Analogous to ALL, other CD19-expressing hematologic malignancies have been targeted with CAR-T cells. While the CAR-T cells used in these studies target anti-CD19, they are not all identical. The methodology to develop the fusion protein that makes a CAR T is unique to each manufacturer and represents 1 variable that may be responsible for differing efficacy and toxicity outcomes. The U-Penn group reported an overall response rate (ORR) of 57% (complete response [CR], 29%) in a cohort of patients with R/R chronic lymphocytic leukemia (CLL).[13]

The National Cancer Institute (NCI) reported on 15 patients: 9 with R/R diffuse large B-cell lymphoma (DLBCL), 2 with R/R indolent lymphoma, and 4 with R/R CLL.[14] Of the entire NCI cohort of 15 patients, 8 achieved CRs; 4, partial remissions (PRs); and 1, stable disease. Investigators at the Fred Hutchinson Cancer Research Center (FHCRC) reported on 34 R/R non-Hodgkin lymphoma (NHL) patients, 18 of whom had DLBCL; 6, follicular lymphoma (FL); 6, CLL; and 4, mantle cell lymphoma (MCL).[15] CRs in studied subtypes were: 38% in DLBCL, 67% in FL, and 50% in CLL.

Another study by the U-Penn group included 38 R/R patients who had either FL (14), DLBCL (21), or MCL (3).[16] The median number of prior therapies was 4 (range: 1-10) and 32% of patients had prior autologous HSCT. ORR among 22 evaluable patients at 3 months was 54% in DLBCL, 100% in FL, and 50% in MCL. The 3-month ORR was 54% in DLBCL, 100% in FL, and 50% in MCL.[16] The ZUMA-1 study confirmed multi-center CAR-T treatment feasibility, with the following reported results on 51 relapsed/refractory DLBCL patients treated with KTE019; Orr was 76% with CR in 47%.[17] Finally, preliminary data also support activity in myeloma where studies are ongoing to explore how this strategy is best positioned among other recently approved novel antimyeloma agents.[18]

A critical component of the CAR-T treatment is the preinfusion conditioning regimen to reduce the circulating and competing T-cell population. Conditioning regimens varied in published studies suggesting that the conditioning program could be another factor impacting differential efficacy and toxicity. It is becoming increasingly clear that the selection of the conditioning program will be essential to optimize clinical outcomes, especially SAEs. Some patients in the trials presented were treated »

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TABLE 2. Phase 2 Trials Evaluating CAR-T Treatment in CD19–Expressing Hematological Malignancies

RANK	TITLE	RECRUITMENT	CONDITIONS	SPONSOR / COLLABORATORS	AGE	NUMBER OF PATIENTS	PRIMARY COMPLETION DATE
37	Study evaluating the efficacy and safety of JCAR015 in adult B-cell acute lymphoblastic leukemia	Recruiting*	ALL	Juno Therapeutics, Inc	Adult, senior	110	May 2018
67	Study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR and 4-1BB signaling domains in patients with chemotherapy-resistant or refractory ALL	Recruiting	Patients With B-cell ALL, relapsed or refractory, with no available/curative treatment options (such as autologous or allogeneic stem cell transplantation) who have limited prognosis (> 12 weeks survival expectancy) with currently available therapies.	University of Pennsylvania	Adult, senior	24	July 2017
76	Study of efficacy and safety of CTL019 in adult DLBCL patients	Recruiting	DLBCL	Novartis	Adult, senior	118	May 2022
86	CART19 in patients with ALL	Recruiting	Leukemia, ALL	University of Pennsylvania	Adult, senior	24	April 2018
121	A Phase 2 multicenter study evaluating subjects with relapsed/refractory MCL	Recruiting	Relapsed/refractory MCL	Kite Pharma, Inc	Adult, senior	70	

ALL indicates acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma.
*Trial has been halted as of December 2016 due to treatment-related deaths, and a clinical investigation is ongoing.

NABHAN

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with fludarabine plus cyclophosphamide conditioning, while others received cyclophosphamide monotherapy. In one study, the combination regimen resulted in a higher CR (42% versus 8%), positioning it as a benchmark, if not a standard, in this nascent field of research.[15]

Early Clinical Experience: Toxicity

The rapidity with which CAR-T treatment has become the standard of care in pediatric R/R ALL, as well as expanded indications across R/R B-cell CD19–expressing malignancies—such as CLL, DLBCL, MCL, and others—may have more to do with managing SAEs than with efficacy. The SAE that has garnered the most attention is cytokine release syndrome (CRS) because it is the most dangerous toxicity, usually occurring shortly after infusion although it can be delayed up to 3 weeks after.[26] Cytokines are immune cell signaling proteins that we associate with flu-like symptoms, which, if released into the circulation rapidly and in large amounts (cytokine storm), can be physiologically overwhelming and lead to vascular collapse and possible death.[26]

Grading of CRS toxicity has not been uniformly agreed upon. Severe CRS occurred in 7/16 (44%) patients in the Memorial Sloan Kettering Cancer Center (MSKCC) trial, 8/30 (27%) at U-Penn, 6/21 (29%) at the NCI, and 7/30 (23%) at FHCRC.[27] Deaths attributed to CRS have been suggested in only 2 out of 97 pediatric patients with R/R ALL (2%). The Juno Rocket trial has been held twice by the FDA due to SAE-related deaths, albeit not necessarily CRS-related. Observations that CRS may be mediated by IL-6 led to tocilizumab (Genentech anti–IL-6) and etanercept (anti–TNF) use.[26] IL-6 rescue appears to be an intriguing strategy to manage CRS, but its standardization and overall impact on treatment remains to be determined as patients who do not have CRS are unlikely to respond. The strongest predicting factor to developing severe CRS is the leukemia burden.[26] Guidelines are being developed to manage CRS—most require that C-reactive protein (CRP) be monitored daily to identify patients becoming at risk, while tocilizumab and/or steroids are recommended for high-risk patients.[26]

SELECTION OF THE CONDITIONING PROGRAM WILL BE ESSENTIAL TO OPTIMIZE CLINICAL OUTCOMES, ESPECIALLY SERIOUS ADVERSE EVENTS.

Fevers, hypotension, and a variety of neurological symptoms (confusion, obtundation, myoclonus, and aphasia) have been frequently reported, as have fatigue, diaphoresis, anorexia, and diarrhea. Neurotoxicity deserves special mention, as it is a potentially lethal toxicity and appears unrelated to CRS. Neurotoxicity, its prevention, and its relationship to tumor response are not well understood. Tumor response is clearly the basis for tumor lysis syndrome, which can occur even 3 weeks following infusion; it was noted as late as day 22 in a CLL patient in the first published CAR-T report.[10] The research into predictability, prevention, and management of SAEs without abrogating the clinical benefit of CAR-T therapy will be a critical element to the success of this I-O intervention.

An Expanding Therapeutic Platform

Although the salvage therapy of B-cell malignancies may become the earliest FDA-approved indications for CAR-T therapy, long term commercial success will require broader disease indications and labeling for use at earlier stages of disease. Methodologically, chimeric fusion protein design against antigens other than CD19, is not a limitation, nor do such antigens need to be associated with blood cells. A review of the active and accruing clinical trials provides insight into this possibility. Of the 57,889 oncology trials listed on ClinicalTrials.gov, 777 matched for checkpoint inhibitors

and 121 matched for CAR T. Of these 121 CAR-T trials, 58 are being conducted in China. Of the remaining 63 trials conducted in the United States and/or the European Union, 39 are phase 1, 14 are phase 1/2 hybrid, and 5 trials are phase 2; the phase is not identified for the remaining 5 (**Table 2**). The phase 2 trials all focus on hematologic malignancies expressing CD19. Of the 40 trials with a projected completion date before 2019, the CAR-T platform is being tested in melanoma, sarcoma, ovarian cancer, and brain tumors based on targetable antigens other than CD19. Of particular note are 6 trials involving brain malignancy, specifically glioblastoma multiforme, a disease with limited therapeutic progress over the preceding 30 years and for which CAR-T success could lead to a fast-track FDA approval and a frontline indication.

Potential for Commercial Success

The complexities of CAR-T synthesis and delivery make clinical benefit just one aspect of commercial viability. FDA approval of CAR-T treatment is just the first barrier to overcome in their incorporation into routine cancer therapeutics. Manufacturers need to prepare to scale these products and develop wrap-around services to ensure that their unique characteristics are not a barrier to adoption. Some of these characteristics include site of care, fragility of the patient, apheresis, cryogenic transport, and cost of the therapy. Today, CAR-T treatment is only available in clinical trials through a limited network of specialized centers. This limited network will likely be maintained upon approval since the manufacturers and FDA will want to ensure that the administering center is accredited in a similar fashion to the Foundation for the Accreditation of Cellular Therapy (FACT).

Travel and boarding for very sick patients and their caregivers should be an important consideration, along with referral to these sites from regional hematologists and oncologists. Educational platforms on the referral process, side effects, and relapse management are needed for all stakeholders. The delay between apheresis and the infusion of the CAR-T therapy also represents a possible barrier. Manufacturing cannot begin until the successful completion of an apheresis process, which some patients may not tolerate, while for others the manufacturing time may be clinically impractical. Allogeneic CAR-T alternatives that avoid the logistical complexities of apheresis and patient-specific manufacturing are under active investigation but appear years behind in clinical development. Finally, only a handful of vendors offer cryogenic transport.

Despite numerous uncertainties that can impact the commercial potential of CAR-T therapy, it is noteworthy that the leading compounds are supported by well-capitalized and committed companies. A conservative industry assessment of the commercial potential of this novel therapy puts the total market for CAR-T therapy in excess of $1.5 billion by 2020. Based on projected study completions and FDA filings, the first approved indication will likely be pediatric and young adult R/R ALL, followed by R/R DLBCL. Market models also expect commercially viable approvals for R/R MCL and R/R CLL, although some of these likely depend on the postapproval success of the initial indications.

The actual cost of therapy remains to be determined, but patient-specific manufacturing is costly and not easily scalable. In determining the cost, it is important to note that all steps in the CAR-T process require a Good Manufacturing Practice (GMP) facility or similar accredited environment. The highly trained physicians and nurses, the specialized facilities for manufacturing and administration, and the ongoing research and development will dictate that the cost of this therapy will be well north of 6 figures and likely benchmarked against allogeneic HSCT with which it will compete in many indications. The additional cost of transportation and boarding during the side-effect period and care between apheresis and infusion would challenge traditional payment and reimbursement models. Once CAR-T treatment is FDA-approved and used commercially, reimbursement strategies for institutions and physicians will be among the most significant questions to impact adoption. One possibility is a bundled payment approach, wherein a limited number of institutions will be allowed to administer therapy with payments based on predefined contractual agreements that include outpatient apheresis, inpatient hospitalization, and post discharge toxicity monitoring. There is precedent for such an approach as this is standard practice for HSCT reimbursement.

Discussion

Preliminary results from the Novartis Eliana global study, conducted in 25 centers across 8 countries, which were presented at the American Society of Hematology annual meeting in December 2016, illustrate the complexity, excitement and caution surrounding CAR T. The trial enrolled 87 pediatric and young adult patients with CD19-positive R/R B-ALL (average age, 12 years; range, 3-23 years). There were 5 manufacturing failures, 6 patients died before undergoing infusion, and 3 patients discontinued therapy before infusion because of AEs. A total of 62 patients underwent infusion. Efficacy data on the first 50 patients revealed that 41 patients (82%) achieved CR and were found to be negative for MRD at 3 months. AEs of grade 3 or 4, suspected to be product-related, were seen in 74% of patients in the first 8 weeks and in 10% of patients after 8 weeks. CRS was observed in 79% of patients (grade 3 in 27% and grade 4 in 27%), with average onset on day 3 (range, 1 to 22 days) and an average duration of 8 days (range, 1 to 36 days). More than half (59%) of the 49 patients who developed CRS were admitted to the intensive care unit, 20% underwent invasive ventilation, and 10% underwent dialysis. No treatment-related deaths were observed.[28]

THE LARGEST DRIVER OF MARKET UPTAKE [OF CAR-T TREATMENTS] MAY BE TIMING TO FIRST APPROVAL AND INITIAL EXPERIENCE WITH A COMMERCIAL PRODUCT.

CAR-T treatment, specifically Novartis CTL-019, will likely get FDA approval for R/R ALL in the pediatric population. Label restrictions requiring failing blinotumumab are unlikely, as this treatment is not "curative" and both treatments may be a bridge to an allogeneic HSCT—a known curative treatment.[11] Label restrictions might also include site-of-care restrictions, (eg, FACT-accredited networks). Such site-of-care restrictions are unlikely to be a barrier in the pediatric ALL population as these patients are currently treated in academic institutions, most already FACT-accredited for HSCT; however, the majority of eligible adult patients with hematologic malignancies and solid tumors would require referrals to such centers, often from the community. »

Logistical, operational, and financial aspects of such referrals become significant in managing a population of fragile patients with advanced malignancy and the significant CAR-T production variables.

As with any new drug or medical device, there are a myriad, and mundane, issues related to launch. CAR-T treatment, being a complex process, complicates this considerably because the apheresis center, CAR-T manufacturing, preparatory chemotherapy for lymphocyte depletion, intensive care management post CAR-T reinfusion, and postprocedure surveillance all need to be considered in logistics and pricing. We suspect that akin to HSCT, payment bundling will be the method of choice; patients, providers, and treatment centers will need education and coordination in reimbursement from payers. Monitoring patients after completion of therapy for possible late complications will likely be part of a mandatory phase 4 research program required by the FDA given the likely fast-track status of first indications. Manufacturers might need help in disseminating information regarding "centers of excellence for CAR-T" to community oncologists so that eligible patients are identified and referred.

Although a number of the factors described will contribute to the commercial success of these compounds, including final label, pricing, and clinical data, the largest driver of market uptake may be timing to first approval and initial experience with a commercial product. Once approved, CAR-T therapy will likely continue the trend of I-O therapeutic success. On the heels of CTLA-4, PD-1, and PD-L1, activated cellular therapy in the form of CAR-T cells will further the transformation of systemic cancer care from a chemotherapy to an I-O platform. However, the expansion of I-O platforms across an increasing number of malignancies, their indication in earlier lines of treatment, the anticipated use of I-O in combination, and trial designs that treat until progression may quickly erode the enthusiasm over their clinical benefit as stakeholders become mired in the debate over their cost. ◆

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EFFECTIVE JANUARY 1, 2017

PERMANENT J-CODE J9352 NOW AVAILABLE FOR YONDELIS® (trabectedin)

Effective on January 1, 2017, YONDELIS® may be reported using the permanent J-Code **J9352 (Injection, trabectedin, 0.1 mg)**.[1]

- J9352 replaces J9999 (Not otherwise classified antineoplastic agent) and C9480 (Injection, trabectedin, 0.1 mg), previously used to report YONDELIS® on claims.[1,2] It also requires billing in units consistent with the new code's descriptor.*
- J9352 applies to most commercial and Medicare patients in both hospital outpatient and physician's office settings.

Please note, the fact that a drug, device, procedure, or service is assigned an HCPCS code and a payment rate does not imply coverage by the Medicare program. An HCPCS code and a payment rate indicate only how the product, procedure, or service may be paid if covered by the program. Fiscal Intermediaries/Medicare Administrative Contractors determine whether a drug, device, procedure, or other service meets all program requirements for coverage.[3]

Please see Important Safety Information on reverse side. Please see full Prescribing Information for YONDELIS® (trabectedin) available from your sales representative.

The information provided represents no statement, promise, or guarantee of Janssen Biotech, Inc., concerning levels of reimbursement, payment, or charge. Please consult your payer organization with regard to local or actual coverage, reimbursement policies, and determination processes. Information is subject to change without notice. Nothing herein may be construed as an endorsement, approval, recommendation, representation, or warranty of any kind by any plan or insurer referenced herein. This communication is solely the responsibility of Janssen Biotech, Inc.

Information is valid as of November 22, 2016, and is subject to change.

* Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug.

1. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs; Office of the Federal Register. https://www.federalregister.gov/documents/2016/11/14/2016-26515/medicare-program-hospital-outpatient-prospective-payment-and-ambulatory-surgical-center-payment. Published November 14, 2016. Accessed November 22, 2016.
2. YONDELIS® Reimbursement and Access Guide. Published August 2015.
3. Medicare National Coverage Determinations Manual. Centers for Medicare & Medicaid Services (CMS); May 16, 2016.

Yondelis® (trabectedin)

INDICATION

YONDELIS® (trabectedin) is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS — YONDELIS® (trabectedin) is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378). Median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). Median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%). Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%). Assess neutrophil count prior to administration of each dose of YONDELIS® and periodically throughout the treatment cycle. Withhold YONDELIS® for neutrophil counts of less than 1500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS® for life-threatening or prolonged, severe neutropenia in the preceding cycle.

Rhabdomyolysis — YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS®, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS® with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). Median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). Median time to complete resolution was 14 days (range: 5 days to 1 month). Assess CPK levels prior to each administration of YONDELIS®. Withhold YONDELIS® for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS® for rhabdomyolysis.

Hepatotoxicity, including hepatic failure, can occur. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x ULN were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378). Median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3 to 4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. Assess LFTs prior to each administration of YONDELIS® and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality.

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS® and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS® and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS® and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS® was 5.3 months (range: 26 days to 15.3 months). Assess left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS® and at 2- to 3-month intervals thereafter until YONDELIS® is discontinued. Withhold YONDELIS® for LVEF below lower limit of normal. Permanently discontinue YONDELIS® for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks.

Extravasation Resulting in Tissue Necrosis — Extravasation of YONDELIS®, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS®. Administer YONDELIS® through a central venous line.

Embryofetal Toxicity — Based on its mechanism of action, YONDELIS® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS®. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS®.

Adverse Reactions — The most common (≥20%) adverse reactions are nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%), and headache (25%).

The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia (43%), increased ALT (31%), thrombocytopenia (21%), anemia (19%), increased AST (17%), and increased creatine phosphokinase (6.4%).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors — Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS®. Avoid taking grapefruit or grapefruit juice. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS® infusion, and discontinue it the day prior to the next YONDELIS® infusion.

Effect of Cytochrome CYP3A Inducers — Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS®.

Please see full Prescribing Information for YONDELIS® (trabectedin) available from your sales representative.

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Yondelis® (trabectedin)

 2/17 066465-170201

YONDELIS (trabectedin) for injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

YONDELIS® is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen *[see Clinical Studies (14) in Full Prescribing Information]*.

CONTRAINDICATIONS

YONDELIS is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

WARNINGS AND PRECAUTIONS

Neutropenic Sepsis: Neutropenic sepsis, including fatal cases, can occur with YONDELIS. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, in patients receiving YONDELIS was 43% (161/378). The median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%) treated with YONDELIS. Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%).

Assess neutrophil count prior to administration of each dose of YONDELIS and periodically throughout the treatment cycle. Withhold YONDELIS for neutrophil counts of less than 1,500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS for life-threatening or prolonged, severe neutropenia in the preceding cycle *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Rhabdomyolysis: YONDELIS can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients receiving YONDELIS. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). The median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). The median time to complete resolution was 14 days (range: 5 days to 1 month).

Assess CPK levels prior to each administration of YONDELIS. Withhold YONDELIS for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS for rhabdomyolysis *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Hepatotoxicity: Hepatotoxicity, including hepatic failure, can occur with YONDELIS. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x upper limit of normal were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (LFTs; defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378) in patients receiving YONDELIS. The median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3-4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months).

In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378) in patients receiving YONDELIS. ALT or AST elevation greater than eight times the upper limit of normal occurred in 18% (67/378) of patients receiving YONDELIS.

Assess LFTs prior to each administration of YONDELIS and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality *[see Dosage and Administration (2.3) in Full Prescribing Information and Use in Specific Populations]*.

Cardiomyopathy: Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS was 5.3 months (range: 26 days to 15.3 months).

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS and at 2- to 3-month intervals thereafter until YONDELIS is discontinued. Withhold YONDELIS for LVEF below lower limit of normal. Permanently discontinue YONDELIS for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Extravasation Resulting in Tissue Necrosis: Extravasation of YONDELIS, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS. Administer YONDELIS through a central venous line *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Embryofetal Toxicity: Based on its mechanism of action, YONDELIS can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling: • Anaphylaxis *[see Contraindications]* • Neutropenic Sepsis *[see Warnings and Precautions]* • Rhabdomyolysis *[see Warnings and Precautions]* • Hepatotoxicity *[see Warnings and Precautions]* • Cardiomyopathy *[see Warnings and Precautions]* • Extravasation Resulting in Tissue Necrosis *[see Warnings and Precautions]*

Adverse Reactions in Clinical Trials: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to YONDELIS in 755 patients with soft tissue sarcoma including 197 (26%) patients exposed to YONDELIS for greater than or equal to 6 months and 57 (8%) patients exposed to YONDELIS for greater than or equal to 1 year. The safety of YONDELIS was evaluated in six open-label, single-arm trials, in which 377 patients received YONDELIS and one open-label, randomized, active-controlled clinical trial in which 378 patients received YONDELIS (Trial 1). All patients received YONDELIS at the recommended dosing regimen of 1.5 mg/m² administered as an intravenous infusion over 24 hours once every 3 weeks (q3wk, 24-h). The median age was 54 years (range: 18 to 81 years), 63% were female, and all patients had metastatic soft tissue sarcoma.

Tables 1 and 2 present selected adverse reactions and laboratory abnormalities, respectively, observed in Trial 1, an open-label, randomized (2:1), active-controlled trial in which 550 patients with previously treated leiomyosarcoma or liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) received YONDELIS 1.5 mg/m² intravenous infusion over 24 hours once every 3 weeks (n=378) or dacarbazine 1000 mg/m² intravenous infusion over 20 to 120 minutes once every 3 weeks (n=172) *[see Clinical Studies (14) in Full Prescribing Information]*. All patients treated with YONDELIS were required to receive dexamethasone 20 mg intravenous injection 30 minutes prior to start of the YONDELIS infusion.

In Trial 1, patients had been previously treated with an anthracycline- and ifosfamide-containing regimen or with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. The trial excluded patients with known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, such as cirrhosis or active hepatitis, and history of myocardial infarction within 6 months, history of New York Heart Association Class II to IV heart failure, or abnormal left ventricular ejection fraction at baseline. The median age of patients in Trial 1 was 57 years (range: 17 to 81 years), with 69% female, 77% White, 12% Black or African American, 4% Asian, and <1% American Indian or Alaska Native. The median duration of exposure to trabectedin was 13 weeks (range: 1 to 127 weeks) with 30% of patients exposed to YONDELIS for greater than 6 months and 7% of patients exposed to YONDELIS for greater than 1 year.

In Trial 1, adverse reactions resulting in permanent discontinuation of YONDELIS occurred in 26% (98/378) of patients; the most common were increased liver tests (defined as ALT, AST, alkaline phosphatase, bilirubin) (5.6%), thrombocytopenia (3.4%), fatigue (1.6%), increased creatine phosphokinase (1.1%), and decreased ejection fraction (1.1%). Adverse reactions that led to dose reductions occurred in 42% (159/378) of patients treated with YONDELIS; the most common were increased liver tests (24%), neutropenia (including febrile neutropenia) (8%), thrombocytopenia (4.2%), fatigue (3.7%), increased creatine phosphokinase (2.4%), nausea (1.1%), and vomiting (1.1%). Adverse reactions led to dose interruptions in 52% (198/378) of patients treated with YONDELIS; the most common were neutropenia (31%), thrombocytopenia (15%), increased liver tests (6%), fatigue (2.9%), anemia (2.6%), increased creatinine (1.1%), and nausea (1.1%).

The most common adverse reactions (>20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities (>20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

Table 1: Selected Adverse Reactions[a] Occurring in ≥10% of Patients Receiving YONDELIS and at a Higher Incidence than in the Control Arm - Trial 1

System Organ Class Adverse Reaction	YONDELIS (N=378)		Dacarbazine (N=172)	
	All Grades[b] (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Nausea	75	7	50	1.7
Vomiting	46	6	22	1.2
Constipation	37	0.8	31	0.6
Diarrhea	35	1.6	23	0
General disorders and administration site conditions				
Fatigue[c]	69	8	52	1.7
Peripheral edema	28	0.8	13	0.6
Metabolism and nutrition disorders				
Decreased appetite	37	1.9	21	0.6
Respiratory, thoracic and mediastinal disorders				
Dyspnea	25	4.2	20	1.2
Nervous system disorders				
Headache	25	0.3	19	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	8	1.2
Myalgia	12	0	6	0
Psychiatric disorders				
Insomnia	15	0.3	9	0

[a] Limited to adverse reactions at a rate of ≥10% in the trabectedin arm and at a rate higher in the trabectedin arm compared with dacarbazine arm by ≥5% in overall incidence or by ≥2% for Grade 3-4 adverse reactions.
[b] Toxicity grade is based on NCI common toxicity criteria, version 4.0.
[c] Fatigue is a composite of the following adverse event terms: fatigue, asthenia, and malaise.

Other clinically important adverse reactions observed in <10% of patients (N=755) with soft tissue sarcoma receiving YONDELIS were:

Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia.

Respiratory, thoracic, and mediastinal disorders: pulmonary embolism.

Table 2: Incidence of Selected Treatment-Emergent Laboratory Abnormalities[a] - Trial 1

Laboratory Abnormalities	YONDELIS		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	90	31	33	0.6
Increased AST	84	17	32	1.2
Increased alkaline phosphatase	70	1.6	60	0.6
Hypoalbuminemia	63	3.7	51	3.0
Increased creatinine	46	4.2	29	1.2
Increased creatine phosphokinase	33	6.4	9	0.6
Hyperbilirubinemia	13	1.9	5	0.6
Hematology				
Anemia	96	19	79	12
Neutropenia	66	43	47	26
Thrombocytopenia	59	21	57	20

[a] Treatment-emergent laboratory abnormalities including those higher in the trabectedin arm compared with the dacarbazine arm by ≥5% (all Grades) or by ≥2% (Grade 3-4). Incidence based on number of patients who had both baseline and at least one on-study laboratory measurement.

YONDELIS group (range: 373 to 377 patients) and dacarbazine group (range: 166 to 168 patients).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors: Coadministration of YONDELIS with ketoconazole, a strong CYP3A inhibitor, increased systemic exposure of trabectedin by 66%. Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS. Avoid taking grapefruit or grapefruit juice during YONDELIS treatment. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS infusion, and discontinue it the day prior to the next YONDELIS infusion *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Effect of Cytochrome CYP3A Inducers: Coadministration of YONDELIS with rifampin, a strong CYP3A inducer, decreased systemic exposure of trabectedin by 31%. Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data with the use of YONDELIS during pregnancy. Animal reproductive and developmental studies at relevant doses have not been conducted with trabectedin; however, placental transfer of trabectedin was demonstrated in pregnant rats. Advise pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population are unknown; however, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Lactation: Risk Summary: There are no data on the presence of trabectedin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions from YONDELIS in breastfed infants, advise a nursing woman to discontinue nursing during treatment with YONDELIS.

Females and Males of Reproductive Potential: Contraception: ***Females:*** Advise female patients of reproductive potential to use effective contraception during and for 2 months after the last dose of YONDELIS *[see Use in Specific Populations]*. ***Males:*** YONDELIS may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 5 months after the last dose of YONDELIS *[see Nonclinical Toxicology (13.1) in Full Prescribing Information]*. **Infertility:** YONDELIS may result in decreased fertility in males and females *[see Nonclinical Toxicology (13.1) in Full Prescribing Information]*.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of YONDELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Hepatic Impairment: The mean trabectedin exposure was (97%) higher in patients with moderate (bilirubin levels 1.5 to 3.0 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal) hepatic impairment compared to patients with normal (total bilirubin ≤ the upper limit of normal, and AST and ALT < the upper limit of normal) liver function. Reduce YONDELIS dose in patients with moderate hepatic impairment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Do not administer YONDELIS to patients with severe hepatic impairment (bilirubin levels above 3 times to 10 times the upper limit of normal, and any AST and ALT) *[see Warnings and Precautions]*.

Renal Impairment: No dose adjustment is recommended in patients with mild (creatinine clearance (CLcr) 60-89 mL/min) or moderate (CLcr of 30-59 mL/min) renal impairment.

The pharmacokinetics of trabectedin has not been evaluated in patients with severe renal impairment (CLcr <30 mL/min) or end stage renal disease *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

There is no specific antidote for YONDELIS. Hemodialysis is not expected to enhance the elimination of YONDELIS because trabectedin is highly bound to plasma proteins (97%) and not significantly renally excreted.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression: Inform patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider for fever or unusual bruising, bleeding, tiredness, or paleness.

Rhabdomyolysis: Advise patients to contact their healthcare provider if they experience severe muscle pain or weakness.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for yellowing of skin and eyes (jaundice), pain in the upper right quadrant, severe nausea or vomiting, difficulty in concentrating, disorientation, or confusion.

Cardiomyopathy: Advise patients to contact their healthcare provider for new onset chest pain, shortness of breath, fatigue, lower extremity edema, or heart palpitations.

Hypersensitivity: Advise patients to seek immediate medical attention for symptoms of allergic reactions including difficulty breathing, chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash.

Extravasation: Inform patients of the risks of extravasation and to notify their healthcare provider for redness, swelling, itchiness and discomfort or leakage at the injection site.

Embryofetal toxicity: Advise pregnant women of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with YONDELIS *[see Warnings and Precautions and Use in Specific Populations]*.

Females and males of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 2 months after last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 5 months after the last dose *[see Warnings and Precautions and Use in Specific Populations]*.

Lactation: Advise females not to breastfeed during treatment with YONDELIS *[see Use in Specific Populations]*.

Manufactured by:
Baxter Oncology GmbH
Halle/Westfalen Germany

Manufactured for:
Janssen Products, LP
Horsham, PA

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From Bench to Community Oncology Clinic: The Promise of Immunotherapy

Sumeet Chandra, MD

IMMUNOTHERAPY AS A TREATMENT modality for cancer has been studied for over 5 decades. However, with the recent surge in new treatment options, immunotherapy seems to have come of age. An increasing number of immunotherapy agents have been approved for multiple tumor types over the past few years, bringing the promise of a more effective and less toxic form of cancer treatment. As these agents are increasingly making their way from the bench to the clinic, we, as community oncologists, will have to learn how costly new immunotherapy agents will be incorporated into the changing reimbursement landscape.

The cost of cancer care in the United States is growing rapidly and currently represents 5% of total healthcare spending.[1] These costs are estimated to grow from $158 billion to $173 billion by 2020, reflecting an increase of 27% to 39%. Drug costs are a key driver of oncology spending, including immunotherapy and targeted agents—the per patient per year spending on chemotherapy has increased from 15% to 20%. The response to rising costs by both Medicare and commercial payers has been to explore various payment models including clinical pathways, the oncology medical home model, bundled payments, and the Oncology Care Model. The overhanging question is how will these new and potentially beneficial therapies be incorporated into payment models that are designed to contain the cost of cancer care?

Is QALY the Answer?

There is no question that those of us in community practice have seen some remarkable responses to immunotherapy. Pembrolizumab was first approved in 2015 for the treatment of metastatic melanoma based on improved overall survival (OS) and progression-free survival.[2] Subsequently, nivolumab received approval for non–small cell lung cancer (NSCLC), and more recently, atezolizumab received approval for platinum-resistant metastatic bladder cancer, also based on a significant survival benefit. The cost of pembrolizumab before discount is $12,500 per patient per month, or approximately $150,000 per year. Similarly, both nivolumab and atezolizumab cost approximately $150,000 per year.[3]

The Institute for Clinical and Economic Review (ICER) recently evaluated the cost-effectiveness of all 3 approved immunotherapies targeting programmed death-1 (PD-1) (nivolumab) or programmed death-ligand 1 (PD-L1) (pembrolizumab and atezolizumab).[4] The report, which analyzed the clinical benefit of each drug against cost and health-system affordability, found that that a "substantial minority" of patients had gained clinical benefit, but for those patients who did respond, there was a substantial improvement in OS. In terms of cost-effectiveness, ICER estimated that atezolizumab cost $219,179, pembrolizumab cost $240,049, and nivolumab $415,950 per quality-adjusted life year (QALY) gained. The report placed a benchmark of $100,000 to $150,000 per QALY. To reach this benchmark, ICER estimated that atezolizumab would require a reduction in its wholesale acquisition price (WAC) of 31% to 53%; pembrolizumab, a reduction of 39% to 61%; and nivolumab a reduction of 57% to 68%.

How do we, as community oncologists, manage the financial burden of these costly medications in our current buy-and-bill model? The current unit cost for pembrolizumab is $4650, and for nivolumab it is $3000. As community practitioners, we need to be very diligent about obtaining preauthorization and documentation to ensure timely payment. As the indications for immunotherapies expand, the financial burden on practices is expected to substantially increase. The out-of-pocket costs associated with these treatments can be prohibitive for many patients. Practices will need a robust financial assistance program to help with patient co-payments, either through foundation programs or through the pharmaceutical companies themselves.

Bristol-Myers Squibb started a direct-to-consumer marketing campaign for nivolumab, in 2015, that has cost approximately $125 million.[5] The drug maker has stated that this aggressive direct-to-consumer approach is a way to facilitate discussions regarding immunotherapies between healthcare providers and patients.[5] This approach has received a fair amount of criticism from academic and community oncologists, as well as patient advocates. We have definitely noticed the effects of this marketing campaign in our practice. In our experience, many patients have a misconception that these therapies represent a "miracle cure." Marketing campaigns have certainly influenced patient opinions about immunotherapy. As community oncologists, the onus is on us to temper patient expectations about these treatments and to bring up cost-benefit discussions with patients.

Looking Ahead

So, where are we in this age of immunotherapy? I think we would all agree that this new treatment modality has the potential to revolutionize the practice of oncology. We are now seeing immunotherapies gaining wider use in the frontline setting in both metastatic melanoma and NSCLC. However, using these new therapies in the clinic has shown that they are far from a "miracle cure." Many patients fail to respond to immunotherapy.

Oncology, as a whole, must shift away from the one-size-fits-all treatment model. As newer therapies emerge, resources must be directed to identify those patients who would actually benefit from newer treatment modalities, allowing both patients and practitioners to make more informed treatment decisions. With the expansion of big data, the oncology community should anticipate a shift in focus toward patient outcomes, because in the coming years, both payers and patients will demand treatments based on value. We will be on the frontline of this changing landscape. In our current »

MITIGATING PATIENT EXPECTATIONS REGARDING IMMUNOTHERAPY AND HONEST DISCUSSIONS REGARDING THE COST OF THESE AGENTS COMPARED WITH POTENTIAL BENEFITS ARE A MUST.

CHANDRA

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structuring of oncology care, immunotherapies will not remain an affordable treatment modality in the future.

There are several important questions that we must ask ourselves going forward, a key one being "How will community oncologists be able to incorporate emerging therapies and maintain financial viability?" As I have previously mentioned, mitigating patient expectations regarding immunotherapy and honest discussions regarding the cost of these agents compared with potential benefits are a must. We also need to advocate for more research into identifying markers that would predict benefit, allowing practitioners and patients to have informed discussions about the treatment plan.

Community oncologists will be at the forefront in this emerging age of immunotherapies and will need to be strong advocates for greater information and affordability of these new and potentially groundbreaking therapies. ◆

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PATIENT PERSPECTIVE

Managing Patient Expectations With Immuno-Oncology

Surabhi Dangi-Garimella, PhD

THE PROMISE OF IMMUNOTHERAPY IS fraught with challenges. With an increase in indications for these immuno-oncology (I-O) agents, healthcare providers and patients are slowly realizing the balance they must strike with I-O. At the 5th annual Patient-Centered Oncology Care® (PCOC®) meeting, held November 17-18, 2016, in Baltimore, cancer research advocate Debra L. Madden discussed the importance of educating patients and caregivers on the variety of adverse events associated with I-O.

Being a systemic treatment, I-O agents provide a significant boost to the patient's immune system and impact its long-term memory and duration of response, Madden told the audience. While they have the potential to benefit patients across a variety of cancer types, managing patient and family expectations on these treatments is crucial. She emphasized that patients should understand the limitations of this treatment. "Those who have an autoimmune disorder, have undergone an organ transplant, or need to be on steroid treatment, for example, are not ideal candidates for immunotherapy," she said.

Debra L. Madden shares the side effects associated with immunotherapy.

Despite all the necessary exclusions and precautions, translating trial results into the clinic often yields unexpected patient responses, which makes it imperative to consider each patient on a case-by-case basis. Although patients with autoimmune disorders are excluded from receiving immunotherapy—due to concerns of a bigger flare-up (see **Table**)—a recent study[1] has raised some hope for these patients, Madden said. The study, conducted in Australia, found that patients with advanced melanoma who had preexisting autoimmune disorders or those who had a major immune-related adverse event (irAE) with the early next-generation immunotherapy ipilimumab, could potentially be treated with a programmed death ligand-1 (PD-1) inhibitor, with manageable immune toxicities.

Madden heard the presentation from that study's senior author, Alexander M. Menzies, PhD, at the 2016 annual meeting of the American Society of Clinical Oncology. "Dr Menzies said that the results of their study could be applied to other cancers, as well, that are now treated with I-O drugs," she told the audience at PCOC®. This study has raised hopes of cancer clinicians who can now expand the population of patients that receive treatment with PD-1 inhibitors. Madden believes that a cautious approach, which includes considering the individual patient characteristics and an open discussion with the patient, can make immune-based treatments available to those patients who did not qualify to participate in the clinical trial.

TABLE. Specific Immune-Related Adverse Events Associated With Immunotherapy

TOXICITY	SYMPTOMS
Dermatologic toxicity	Rash, skin blistering or peeling, dry mouth, mouth sores, and vitiligo.
Colitis	Abdominal pain, diarrhea, increased frequency of bowel movement, dark stools, and bloody stools.
Endocrine toxicities	Persistent headaches, fatigue, nausea, vision changes, weight gain, dizziness, fainting, and mood and behavioral changes.
Eye inflammation	Double vision, blurry vision, eye pain, eye redness, sensitivity to light, and dryness of the eyes.
Renal toxicities	Bloody urine, reduced urination, loss of appetite, and swollen ankles.
Pneumonitis	New or worsening cough, shortness of breath, chest pain, and decrease in oxygen saturation.

Madden also drew attention to the fact that patients may have a variable response (time to response, type of clinical response, etc) to I-O and some may experience a phenomenon described as "pseudo-progression." Pseudo-progression is the initial period following treatment initiation when a tumor might actually grow in size before it shrinks. "These variations in response led to the creation of new immune-related response criteria for I-O agents. The criteria require confirmation of suspected disease progression about 4 weeks following treatment initiation, with subsequent radiographic testing," she added.

"HEALTHCARE PROVIDERS SHOULD URGE THEIR PATIENTS TO MONITOR FOR ANY SIDE EFFECTS DURING AND IN THE MONTHS FOLLOWING IMMUNOTHERAPY."

—Debra L. Madden

Madden then walked the audience through some of the most commonly observed adverse effects with immunotherapy, emphasizing the importance of a thorough explanation of these for the patients and family members. "It is critical for healthcare providers to urge their patients to monitor for any side effects during and in the months following immunotherapy and to report all symptoms no matter how subtle they may seem," she added. ◆

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Getting Insured Could Reduce Cancer-Related Deaths Among Minorities

Surabhi Dangi-Garimella, PhD

A NEW REPORT FROM THE AMERICAN CANCER SOCIETY (ACS) indicates that while the cancer-related death rate was higher among blacks than whites in 2014, this racial gap could narrow as minority patients increasingly gain access to insurance and healthcare. The claim is based on the fact that the number of uninsured black Americans fell by 50% between 2010 (21%) and 2015 (11%). A similar trend was noted among Hispanic Americans; the group saw a decrease from 31% to 16%. The authors noted the effect of the Affordable Care Act (ACA) on these improvements.

ACS collected incidence and mortality data from 1930 to 2014 from the National Center for Health Statistics. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program and CDC's National Program of Cancer Registries are the sources for long-term cancer incidence data. Long-term incidence and survival trends were based on data from 9 SEER areas representing 9% of the US population; 18 SEER registries were used to gather data on the lifetime risk of developing cancer, stage, distribution, and survival by stage, as well as data on children and young adults, which covered 28% of the population. The report projects a daily diagnosis of 4600 new cancer cases in 2017, which would lead to 1,688,780 new cases of cancer in 2017; this includes 63,410 cases of breast carcinoma in situ among female patients and 74,680 cases of melanoma in situ. More women (852,630) are estimated to be diagnosed with cancer in 2017 than men (836,150); however, mortality is estimated to be higher among men than women. Of the nearly 601,000 cancer-related deaths in the coming year, 318,420 deaths are forecasted to be among men diagnosed with cancer and 282,500 among women.

More men than women are expected to be diagnosed with specific cancer types in 2017, and the trend holds across subtypes, except for breast cancer. With more than 250,000 women expected to receive a breast cancer diagnosis in 2017, women surpass men in overall cancer incidence. As for the death rate, the report states that cancers of the genital system and endocrine system will see more deaths among women than men—all other cancer types are predicted to increase mortality in men.

Among the states, California and Florida lead the tally on new cases in 2017, with both expected to have a high rate of female breast cancer incidence. Florida also has a high projected rate of new lung and bronchial cancers. Cancers of the lung and bronchus, colorectum, and prostate in men and lung and bronchus, breast, and colorectum in women will be the most common causes of cancer deaths in the country in 2017.

The report notes an overall upward trend in the 5-year survival rate over the past 30 years: survival has increased by 20 percentage points among whites and 24 percentage points among blacks, with the most pronounced improvements seen in the 50-to-64 age group. Hematologic malignancies have seen rapid progress due to better treatment protocols and the discovery of targeted therapies, the report states.

Another important finding of the report is the closing gap in racial disparity. The difference in the cancer death rate was at a peak in 1990, with the excess risk growing to 47% in black men compared with white men, the report states. It dropped to 21%, however, in 2014, which could be due to a sharp decline in smoking initiation in the black population overall. A similar trend was observed in women of both races. The authors note that after the ACA took full effect, the number of uninsured among the minority population dropped. "If maintained, these shifts should help expedite progress in reducing socioeconomic disparities in cancer, as well as other health conditions," they wrote. ◆

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REPEALING AND REPLACING THE AFFORDABLE CARE ACT
HEALTHCARE INSURANCE. © KAREN ROACH/FOTOLIA

Will the Absence of Certain Cancer Centers on Insurance Exchanges Impact Outcomes?

Surabhi Dangi-Garimella, PhD

THE AFFORDABLE CARE ACT WEAVED IN several provisions to improve access to health insurance within the United States—Medicaid expansion, online exchanges, and allowing young adults (until 26 years) to remain on their parents' plans, among others. However, narrow provider networks within these federal exchanges have raised questions about access to care. According to new study results from The University of Texas, a majority of these exchanges do not include National Cancer Institute (NCI)-designated centers, which, the authors believe, might create a barrier for access to clinical trials and specialized care.[1]

Studies have shown that federal exchanges either have narrow provider networks or there are restrictions on certain categories of physicians or hospitals, if the regional provider network is broad, which can be a barrier for patients with complex care needs for diseases such as cancer. Although health plans are required to cover the costs of participating in a clinical trial, they are not bound to do so for out-of-network costs. Under these circumstances, the absence of NCI-designated cancer centers from exchanges could prevent patients from receiving innovative treatments currently under development in oncology.

For their study, the researchers extracted provider network data for the 2016 enrollment year, available as of December 2015. They characterized the networks that included Commission on Cancer (CoC)-accredited hospitals and NCI-designated cancer centers. Of the 4058 individual plans, network data were available for 3637 (90%) and hospital information for 3531 (87%). Of the 295 unique networks that were identified, 95% included at least 1 CoC-accredited hospital, but only 41% included NCI-designated centers. The plan type was also a determinant of whether an NCI-designated center would be included in the network: 31% of health maintenance organizations and 49% of preferred provider organizations included them, independent of the metal level of an individual plan. As the authors expected, networks available in states and counties where the NCI-designated cancer centers were located were more likely to include the center, although only half did so.

The authors feel that their findings indicate lack of access to cancer care, and they reinforce the need to promote access to specialized care and clinical trials at community sites.While the question about access might hold true, do accredited cancer centers really improve patient outcomes? Not according to study results that were published in 2014,[2] which showed that whereas accredited cancer centers performed better on most process and patient experience measures, they came up short on most outcome measures. So, when policy makers consider improving access for patients enrolled on marketplace exchanges, they need to be aware of the differences in outcomes among the various sites of care. ◆

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Patient and Provider Education on Pain in Cancer: A Cost-saving Intervention

Surabhi Dangi-Garimella, PhD

AN EXPERIMENT BY AN integrated healthcare delivery system to document personalized pain management goals (PPGs) for patients in oncology clinics lowered documented pain and simultaneously reduced treatment costs. While achieving a pain level of 0 may not be possible, the authors suggest that achieving the patient's PPG is a good start.

As part of Park Nicollet Health Services quality-improvement course, a team that included a medical oncologist, oncology nurse practitioner, oncology nurse, pharmacist, statistician, computer programmer, and quality-improvement leaders documented pain values from the electronic health records (EHRs) of oncology patients in the outpatient clinics. This information included:

- Pain levels during a predetermined 18-month period
- Reporting and achievement of PPG
- Monthly tabulation of opioid prescriptions

Following analysis of this data, the researchers introduced a pain intervention that included patient education on pain management (using a handout), clinician education on opioid cost-effectiveness, and instituting a nursing protocol to document PPGs. The patient education handout detailed appropriate opioid use and the complications associated with using opioids, such as constipation. Physician education included a combination of a discussion with a palliative care physician and cost information data on various opioids extracted from a hospital pharmacy.

The study determined that 15% of patient encounters reported moderate to severe pain. Whereas PPGs were marked at 16% prior to the pain intervention, in June 2014, they crossed the 70% mark 1 year after its introduction in the oncology clinic, in June 2015. The authors write that the actual achievement of a PPG per EHR data was at 84% at the time.

Prescribing practices saw a simultaneous change, too, with a significant downturn observed in the prescription of high-cost opioids following clinician education on their cost. While low-cost and high-cost opioids were prescribed at the same rate prior to the intervention, June 2015 saw double the number of low-cost opioid prescriptions (n = 71) compared with high-cost prescriptions (n = 35)—a 10% drop in the prescription of high-cost opioids.

The authors believe that a PPG is a much better strategy over the standard pain measure that is commonly used in oncology clinics, considering that each patient will have unique pain thresholds, writing that PPGs can improve patient satisfaction because they signify to the patient that their physician is listening to their concerns and is focused on providing them with personalized quality care. The authors also note an indirect impact of the intervention on workflow efficiency and a shift in the nurses focus away from prior-authorization requests (due to the use of low-cost opioids) toward patient care. An average saving of 90 minutes that a nurse has to spend on processing prior authorizations (at least 3 of these each week) is 90 minutes added to patient care, the authors point out.

The researchers plan to track patient-reported outcomes through a symptom-assessment tool that exports data to the patient's EHR for use at the point of care and to auto-generate flags on uncontrolled pain and underlying causes for why patients need to continue treatment on high-cost medications. ◆

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NCI Formulary a Big Support for Cancer Moonshot

Surabhi Dangi-Garimella, PhD

DESCRIBED AS A PUBLIC–PRIVATE PARTNERSHIP BETWEEN the National Cancer Institute (NCI) and pharmaceutical and biotechnology companies, the NCI Formulary[1] has been created with the expectation that it will provide researchers rapid access to anticancer drugs for use in clinical trials. This resource would be particularly valuable for researchers trying to use combination therapies that incorporate agents manufactured by different pharmaceutical companies, which, in turn, can have a big impact on patient outcomes and help get drugs to patients much faster—one of the objectives of former Vice President Joe Biden's Cancer Moonshot Program.[2]

The NCI has developed a process that will eliminate the often lengthy negotiations that occur between academic researchers and pharmaceutical manufacturers. Investigators at NCI-designated cancer centers can use the agents within this formulary to conduct clinical trials on investigator-held investigational new drugs and for pre-clinical research. NCI's mediation is expected to streamline and smoothen the process for these researchers. Currently, 6 pharmaceutical companies have partnered with NCI and contributed 15 targeted anticancer agents to the formulary (**Table**).

TABLE. Drugs Currently Included in the National Cancer Institute Formulary

DRUG NAME	COMPANY	TARGET(S)
Alectinib (Alecensa)	Genentech	ALK
Atezolizumab (Tecentriq)	Genentech	PD-L1
Bevacizumab (Avastin)	Genentech	VEGF
Cobimetinib (Cotellic)	Genentech	MEK
Ensartinib	Xcovery Holding Company LLC	ALK, TrkA, TrkC, ROS, EphA2, c-MET
Ipilimumab (Yervoy)	Bristol-Myers Squibb	CTLA-4
Larotrectinib (LOXO-101)	Loxo Oncology	NTRK-1, NTRK-2, NTRK-3 fusion proteins; TrkA/B/C proteins
LY3039478	Eli Lilly and Company	Notch
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD-1
Obinutuzumab (Gazyva)	Genentech	CD20
Pertuzumab (Perjeta)	Genentech	HER2/neu
Prexasertib	Eli Lilly and Company	CHK1
Trastuzumab (Herceptin)	Genentech	HER2/neu
Vemurafenib (Zelboraf)	Genentech	BRAF V600 mutant, CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, FGR
Vismodegib (Erivedge)	Genentech	Smoothened
ACK1	Activated CDC42 kinase 1	
ALK	Anaplastic lymphoma kinase	
CD20	Cluster of differentiation 20	
CHK1	Checkpoint kinase 1	
CTLA-4	Cytotoxic T-lymphocyte associated protein 4	
EphA2	Ephrin receptor A2	
FGR	Gardner-Rasheed feline sarcoma viral	

(table continued on SP66) »

*For your members with advanced ovarian cancer after **2 or more** chemotherapies*

IF

BRCA^{mut+}

INDICATION

Rubraca™ (rucaparib) is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.

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

SELECT IMPORTANT SAFETY INFORMATION

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

AML was reported in 2 (<1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1).

Monitor complete blood count testing at baseline and monthly thereafter. For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Based on its mechanism of action and findings from animal studies, Rubraca can cause fetal harm when administered to a pregnant woman. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Most common adverse reactions (≥ 20%; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities (≥ 35%; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Clovis Oncology, Inc. at 1-844-258-7662.

Please see Brief Summary of Prescribing Information on adjacent pages.

CLOVIS ONCOLOGY

THEN

Rubraca™ (rucaparib) tablets

Rubraca is the first and only FDA-approved PARP inhibitor that treats patients with deleterious *BRCA* mutation (germline and/or somatic) advanced ovarian cancer

54%

Objective response rate

Rubraca demonstrated an objective response rate of 54%*†‡§‖ (44, 64)[1]¶

9.2 months

Median duration of response

The median duration of response was 9.2 months*‡§‖ (6.6, 11.6)[1]¶

10%

Discontinuation rate

10% of patients discontinued treatment with Rubraca due to adverse reactions[1]#**

600 mg BID

Dosing

The recommended starting dose of Rubraca is 600 mg (two 300 mg tablets) taken orally twice daily with or without food. Continue treatment until disease progression or unacceptable toxicity[1]

62%

Dose modification

62% of patients had dose reductions or interruptions as a result of adverse reactions[1]**

Please visit Rubraca.com for more information

BID=twice daily; *BRCA*=BReast CAncer susceptibility gene; PARP=poly (ADP-ribose) polymerase.

*The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with advanced *BRCA*-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and independent radiology review (IRR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[1]

†Complete response = 9% and partial response = 45%.[1]

‡Response assessment by independent radiology review was 42% (95% CI [32-52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]).[1]

§Efficacy outcome measure.[1]

‖Pooled analysis of Study 1 and Study 2 (N=106).[1]

¶95% CI.[1]

#The safety analysis was based on a pooled patient population of 377 patients with advanced ovarian cancer who received Rubraca 600 mg twice daily.[1]

**Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%).[1]

Reference: 1. Rubraca [package insert]. Boulder, CO: Clovis Oncology; 2016.

Rubraca™ (rucaparib) tablets

RUBRACA™ (rucaparib) tablets, for oral use

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1) in the full prescribing information]*.

This indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14) in the full prescribing information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the AUC in patients receiving the recommended dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197).

Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

Table 2 and Table 3 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with Rubraca.

Table 2. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Ovarian Cancer Patients (N = 377) %	
Adverse Reaction	**Grades[a] 1-4**	**Grades 3-4**
Gastrointestinal Disorders		
Nausea	77	5
Vomiting	46	4
Constipation	40	2
Diarrhea	34	2
Abdominal Pain	32	3
General Disorders		
Asthenia/Fatigue	77	11
Blood and Lymphatic System Disorders		
Anemia	44	25
Thrombocytopenia	21	5
Nervous System Disorders		
Dysgeusia	39	0.3
Metabolism and Nutrition Disorders		
Decreased appetite	39	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	21	0.5

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus generalized) (9%), Palmar-plantar erythrodysaesthesia syndrome (2%), and febrile neutropenia (1%).

Table 3. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Patients with Ovarian Cancer (N = 377) %	
Laboratory Parameter	**Grade 1-4 [a]**	**Grade 3-4**
Clinical Chemistry		
Increase in creatinine	92	1
Increase in ALT[b]	74	13
Increase in AST[b]	73	5
Increase in cholesterol	40	2
Hematologic		
Decrease in hemoglobin	67	23
Decrease in lymphocytes	45	7
Decrease in platelets	39	6
Decrease in absolute neutrophil count	35	10

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.

[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily *[see Data]*. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a dose range-finding embryo-fetal development study, pregnant rats received oral doses of 50, 150, 500, or 1000 mg/kg/day of rucaparib during the period of organogenesis. Post-implantation loss (100% early resorptions) was observed in all animals at doses greater than or equal to 50 mg/kg/day (with maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$).

Lactation

Risk Summary

There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed infant. Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca.

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Rubraca.

Pediatric Use

The safety and effectiveness of Rubraca in pediatric patients have not been established.

Geriatric Use

One hundred and sixty (42%) of the 377 ovarian cancer patients in clinical trials of Rubraca were 65 years of age or older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The effectiveness of Rubraca in patients with *BRCA*-mutant ovarian cancer who were 65 years of age or older could not be assessed due to the small number of patients (N=38).

Hepatic Impairment

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation of starting dose adjustment is available for patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

Renal Impairment

No starting dose adjustment is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method). There is no recommended starting dose for patients with CLcr less than 30 mL/min or patients on dialysis due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

OVERDOSAGE

There is no specific treatment in the event of Rubraca overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions and Use in Specific Populations]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations]*.

Dosing Instructions: Instruct patients to take Rubraca orally twice daily with or without food. Doses should be taken approximately 12 hours apart. Advise patients that if a dose of Rubraca is missed or if the patient vomits after taking a dose of Rubraca, patients should not take an extra dose, but take the next dose at the regular time *[see Dosage and Administration (2.1) in the full prescribing information]*.

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« (table continued from SP61)

RAF	Rapidly accelerated fibrosarcoma
HER2	Human epidermal growth factor receptor 2
MAP4K5	Mitogen-activated protein kinase kinase kinase kinase 5
RAF	Rapidly accelerated fibrosarcoma
HER2	Human epidermal growth factor receptor 2
MAP4K5	Mitogen-activated protein kinase kinase kinase kinase 5
MEK	MAPK/ERK kinase
c-MET	c-Mesenchymal epithelial transition factor
PD-L1	Programmed death ligand-1
SRMS	Src-related kinase lacking c-terminal regulatory tyrosine and N-terminal myristylation sites
TrkA/B/C	Tropomyosin receptor kinase A/B/C
VEGF	Vascular endothelial growth factor

"The agreements with these companies demonstrate our shared commitment to expedite cancer clinical trials and improve outcomes for patients," James Doroshow, MD, deputy director for clinical and translational research, NCI, said in a press release.[3] "It represents a new drug development paradigm that will enhance the efficiency with which new treatments are discovered."

6 PHARMACEUTICAL COMPANIES HAVE CONTRIBUTED 15 TARGETED ANTICANCER AGENTS TO THE FORMULARY.

The formulary has drawn inspiration from NCI's Cancer Therapy Evaluation Program and the NCI-MATCH trial. The study design of NCI-MATCH requires agents from multiple drug manufacturers, tested alone or in combination after matching a patient's mutation pattern. Doroshow expects the number of pharmaceutical partnerships and drugs to double by the end of 2017.

A report developed by the blue-ribbon panel of experts appointed by Biden had identified a lack of collaboration and the slow dissemination of discoveries and clinical data as some of the barriers to improving cancer delivery in the United States. Partnerships spearheaded by institutions like the NCI could help overcome some of them. ◆

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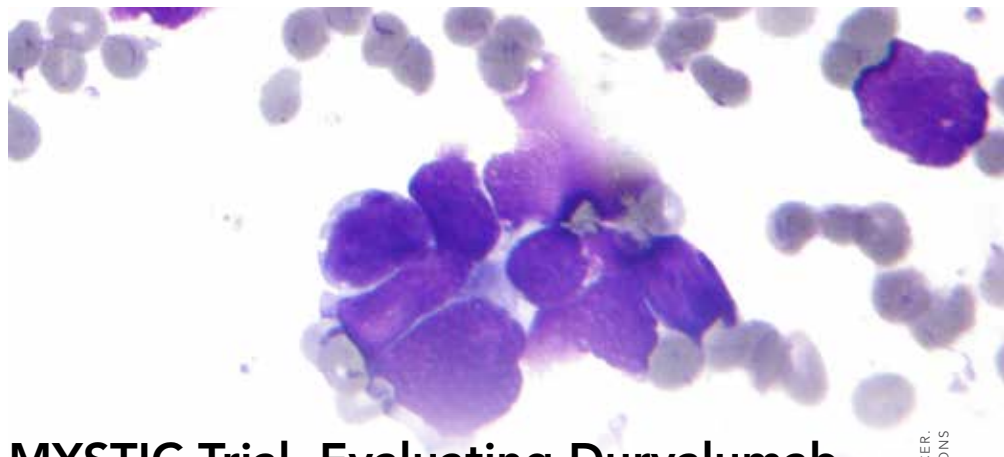

SMALL CELL LUNG CANCER. © NEPHRON (OWN WORK) VIA WIKIMEDIA COMMONS

MYSTIC Trial, Evaluating Durvalumab as First-line Treatment in NSCLC, Adds OS Endpoint

Surabhi Dangi-Garimella, PhD

A PHASE 3 TRIAL EVALUATING THE effect of durvalumab, the programmed death ligand-1 (PD-L1) inhibitor, alone or in combination with tremelimumab, versus platinum-based chemotherapy has refined its endpoints to include overall survival (OS) and progression-free survival (PFS).

The randomized, multi-center, open-label MYSTIC trial was designed to test whether durvalumab can be used as front-line treatment in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) who express wild-type epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and PD-L1. The original primary outcome measure was PFS at 3 years, while secondary outcome measures included health-related quality of life, pharmacokinetics of the drugs, and immunogenicity of the biologicals durvalumab and tremelimumab.

In a press release, AstraZeneca, which is developing the drug, said that the decision to include OS as an endpoint "is based on recent internal and external data, including durvalumab's strong efficacy as monotherapy presented at recent medical meetings, as well as significant opportunities in the competitive landscape." This update will extend OS data collection to 2018, while PFS data and several interim analyses for OS are expected in mid-2017.

The company is simultaneously testing durvalumab as monotherapy (PEARL trial) or in combination with tremelimumab (NEPTUNE trial) against standard-of-care platinum-based chemotherapy in patients with EGFR and ALK wild-type advanced or metastatic NSCLC. "The MYSTIC trial amendments, the NEPTUNE trial expansion, and initiation of the new PEARL trial are all designed to enhance our options in first-line NSCLC for immuno-oncology (IO—as monotherapy or combination with another IO agent. We continue to follow the science through both internal and external sources for the benefit of patients and look forward to sharing our first pivotal data in mid-2017," Sean Bohen, MD, PhD, executive vice president, Global Medicines Development, and chief medical officer at AstraZeneca, said in the press release.

Durvalumab is a PD-L1 inhibitor that received a breakthrough designation for use in bladder cancer in early 2016. By interacting with both, the programmed death-1 receptor and CD80 on T cells, it boosts the immune system's tumor-detecting capacity. AstraZeneca is also evaluating this antibody in head and neck cancer, liver cancer, and blood cancer. ◆

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Produced by Nicole Beagin and Laura Joszt

David Fabrizio Suggests Advantages of Genomic Profiling for Payers

Payers have been slow to adopt new technologies, but they are starting to be more proactive in seeking out genomic profiling companies, according to David Fabrizio of Foundation Medicine, Inc. These molecular diagnostic tools make the healthcare process more efficient by performing a comprehensive test at the point of diagnosis.

What specific challenges does the molecular diagnostics industry face with respect to insurance coverage for their products?

There is a challenge associated with getting coverage for molecular diagnostics. For the most part, payers have been slow to adopt new technologies, and really, they haven't been incentivized to do so, up until recently. However, what we're starting to see is that payers are being more proactive, certainly, in seeking out companies like Foundation Medicine that are building these comprehensive genomic profiling assays to understand what's going on inside a patient's tumor at the molecular level, and these are encouraging signs.

I think that they're starting to understand the implication of using these molecular diagnostics up front, at the very point of diagnosis, because it can remove a lot of the ambiguity associated with following that trail of breadcrumbs about understanding what is really contributing to a patient's disease, and what is the best course of therapy. So, rather than doing 1 test and getting 1 answer and then trying a treatment that doesn't work and then trying another test, you do a comprehensive test, like a FoundationOne test, for instance, up front, and it makes the healthcare process more efficient, and that's a benefit to patients and payers.

Dr David L. Porter: Combining CAR-T Cells With Other Immunotherapies, the Next Logical Step

David L. Porter, MD, of the University of Pennsylvania Health System, explains why treating tumors with a combination of CAR-T cells and other immune-stimulating agents is a logical next step for investigators.

Can CAR-T cells be combined with other immunotherapies or targeted agents?

There is no doubt that CAR-T cells will ultimately be combined with other immunotherapies and other agents. There are years and years of precedent for combining different types of anticancer therapy. I do think there will be some cases where CAR-T cells are sufficient by themselves. We've seen that already in some of these B-cell malignancies and ALL [acute lymphoblastic leukemia] and some people with non-Hodgkin's lymphoma or CLL [chronic lymphocytic leukemia].

But there will be situations where the CAR-T cells may not be effective by themselves, and there are some natural combinations one can start thinking of. For this to be effective, the T cell has to be active, so combining the CAR-T cells with immune-stimulating agents will be very, very logical—some of the checkpoint inhibitors, for instance.

There are also clinical trials currently ongoing combining CAR-T cells with medications like ibrutinib. Ibrutinib's a very common therapy for CLL and some B-cell malignancies, and there is now good laboratory data [showing] that ibrutinib may make the CAR-T cells more effective at killing their target, at killing CLL cells for instance. And there's data in the laboratory that it may make the CLL cells better targets for the T cells to kill them. It's another natural combination that, I think, investigators are thinking of testing.

And there are a number of other agents that one can think of to try and activate the T cells when perhaps the body's natural defenses are designed to keep the T cells from becoming activated, or the cancer's defenses are designed to keep the T cells from getting into the tumor or from being activated. So, I think there are a lot of possibilities, and we will see these trials being done over the next few years, combining CAR-T cells with other agents, as well.

Debra L. Madden on Unrealistic Expectations for Immuno-Oncology Treatments

Many patients have learned about the advances in immunotherapy treatments for cancer, but the media may not fully portray all the complexities and potential harms of these agents, according to Debra L. Madden, cancer research advocate and patient representative. Madden mentioned that biomarker research could help determine which patients are most likely to benefit from immuno-oncology.

What is the current level of knowledge most cancer patients have regarding immunotherapy risks?

If they're interested in information about cancer treatments, they will have noticed that there's all sorts of announcements about immunotherapy overall and what an important advance it is and how it's the most exciting breakthrough that we have seen in cancer treatment in decades. And for some patients, that's true.

But, again, I worry sometimes about how important and complex medical topics are presented in the popular media, because there's not always discussion about some of the adverse effects, and some of the potential harms, as well as the potential benefits. However, a couple areas aren't mentioned as much in the popular media. And that's the fact that, yes, there are some patients who have done extremely well with traditionally very difficult-to-treat cancers and advanced cancers. However, unfortunately, that's the minority of patients. Most patients do not have a response to these immuno-oncologic agents. One of the most important research questions that we have, »

at this point, is determining what biomarkers can we look at that will indicate who are these patients who are most likely to respond, so we can have more patients ultimately benefit.

Dr Carrie Stricker Discusses the Importance of the Patient Voice in Oncology Treatment Decisions

Oncologists must recognize the importance of the patient voice when making treatment decisions so that the treatment plan can be adapted to each patient's goals and desires, said Carrie Stricker, PhD, RN, AOCN, chief clinical officer and co-founder of Carevive Systems.

What is the importance of including patient voices when providing decision support to clinicians?

The attention to the patient voice at the time of treatment decision making, in clinical decision making, is thankfully increasing by leaps and bounds. I'll highlight for a moment—I am a volunteer for the American Society of Clinical Oncology (ASCO)—I'll highlight for a moment ASCO's value framework as one of the proliferating models for helping to ensure that clinicians can make evidence-based and very person-centered decisions at the point of care. And one of the 3 major factors that are included in that value framework is the patient's voice and the patient's preferences.

If we don't ask a patient what their goals are, what's valuable to them, and reflect that in our decision making, we could have a patient who really wants to have, as their primary goal, adequate quality of life and survival to make a significant wedding or other family event without their hair or with enough functional status intact to be present physically and emotionally for that event. We could end up giving them a highly toxic regimen that they would not want had they known that that would be the outcome for them.

So, it's absolutely crucial, and studies have shown, again and again, that we must get also at the patient's understanding of what the goals of that treatment are for them. Some studies have shown that more than half of patients may think treatment is curative when, in fact, it's intended to control, perhaps for long periods of time, but control and not cure disease. And we know from many case examples, analyses, and studies that patients say they would have made very different decisions had they known that information and had an opportunity to have an active voice in that treatment decision making and have it adapted to their preferences and goals and concerns.

Jonathan Hirsch on Making Data Usable for Oncologists at the Point of Care

Oncology care is often spread out across multiple facilities and providers, so health information technology (IT) innovators use software to integrate data from these many locations and deliver it to the point of care, according to Jonathan Hirsch, founder and president of Syapse.

How can health IT be used to transform oncology care?

Oncology is an incredibly complex domain, and it involves many different providers who may be at different practices, different health systems. It involves not just the medical professionals, but it also involves supportive care, like care coordinators, navigators, etc. And with oncology, you have this interesting dynamic where the care is highly longitudinal, it's spread out across multiple facilities, and having access to the right information at the right point in time is truly the way to make progress in the fight against cancer.

So that's really the job of software. It's to bring all the information together and make it usable for the provider of oncology care to help that patient. When we think about how we use software to appropriately direct care and help in the fight against cancer, it's really bringing the right information to the right person at the right point in time, but also having robust outcomes tracking capability so that the providers are not operating in isolation. You want to help the providers learn from the experiences of every other cancer case and every other provider facility.

One of the things that we've done to achieve this vision is we've partnered with a number of leading health systems, Intermountain, Stanford, and Providence Health & Services, to launch the Oncology Precision Network. This is an effort to use software and large data sets to really fight cancer by bringing the aggregate data and learnings from that network to the point of care, and this wouldn't be possible without a robust software platform.

Dr Sean Khozin Discusses How the FDA Regulatory Process Helps Advance Precision Oncology

FDA's regulatory science activities are working to advance the field of precision oncology, in part by using predictive analyses to identify patients that may be good candidates for certain therapies, according to Sean Khozin, MD, MPH, senior medical officer at the FDA.

How does the FDA encourage advances in precision oncology?

If we look at the definition of precision oncology, as we all know, we can best describe it as delivering the right drug to the right patient at the right dose. If you look at the FDA's approval mechanism, you'll notice that the policies and procedures that have been put into place, in fact, are based on that very precise definition of precision medicine.

In essence, when we review a marketing application, when we analyze the data, and do labeling negotiations, we ensure that the data support the indication, the population of patients who are supposed to be treated, at the right dose. So, that system has already been built into the approval process and the mechanism at the FDA.

Now, precision is a moving target and it's driven by science. And it's a very rapidly evolving field in oncology. Obviously, drugs are getting more targeted and more precise. One of the ways, and one of the primary ways, that the FDA has been contributing to the advancement of the field is through its regulatory science activity. What we have been doing more, especially more in recent years, is looking at our own internal data and doing our own analyses, aggregated analyses on primary research to be able to identify, for example, populations of patients who may have certain characteristics that may make them a good candidate for certain types of therapies. We're doing predictive analytics.

So, that's become part of the regulatory science process where we are doing primary research using our own data and also in collaboration with outside entities to contribute in a very proactive fashion to the advancement of the field of precision oncology. ◆

ADDITIONAL RESOURCES

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Advanced APMs and the Emerging Role of Immuno-Oncology Agents: Balancing Innovation and Value

Michael V. Seiden, MD, PhD; Marcus Neubauer, MD; and Diana Verrilli

(continued from cover)

categories of spend: avoidable hospital admissions and variations in treatment protocols, with a particular focus on clinical pathways and drug costs. Although no drugs are singled out in the OCM model, the rapid increase in the use of immuno-oncology (I-O) agents—programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitors—in oncology suggests that the expanding use of these agents will provide specific challenges to practice success in this program and will likely present both operational and moral challenges for physicians attempting to succeed in the OCM.[3]

The Opportunity Offered by I-O in 2016 and Beyond

In recent years, a deeper understanding of how the immune system works and how cancer disarms typical immune effector functions has led to advances in ways to improve the function of specialized immune cells, called T cells.[3] While many strategies are under development, this review will focus on antibodies that bind chimeric T-lymphocyte associated protein 4 (CTLA-4), PD-1, or PD-L1 in such a way that they interfere with the binding of these cell surface proteins with their natural ligands.[1] Vaccines, chimeric antigen receptor (CAR)-T cells, and small molecules that interfere with or augment other immune functions will pose similar challenges in the future, but still require further development and will not be discussed further, except to emphasize, *in toto, that* the development of I-O agents, either alone or in combination strategies, will likely dominate therapeutic advances in oncology for the next 10 years.

CTLA-4, PD-1, and PD-L1–Targeted Agents

Antibodies that bind CTLA-4 (ipilimumab), PD-1 (nivolumab and pembrolizumab), and PD-L1 (atezolizumab) successfully reactivate an exhausted or deactivated immune response.[3] Once reactivated, some tumors will demonstrate an expansion of activated immune cells within the tumor with rapid, cancer cell destruction. Single-arm and randomized studies in melanoma, lung cancer, renal cell carcinoma, head and neck cancer, bladder cancer, and Hodgkin's disease have demonstrated clinical activity of many of these agents.[4-10] Whereas the activity in Hodgkin's disease and melanoma has been dramatic, and in the case of melanoma, often very durable (measured in years), the findings in solid tumors have demonstrated a few key themes as reviewed in **Table 1**.

What is most intriguing is not the response rate associated with I-O, but the tail of the survival curve (**Figure 1**). In essentially all the studies that used I-O agents, there is a subset of 10% to 20% of patients who demonstrate durable responses with marked clinical improvement persisting more than a year after treatment. Some studies with longer follow-up have demonstrated multi-year responses.[4-11] Durable responses are distinctly unusual in patients treated with standard chemotherapy or molecularly targeted agents that inhibit nonimmune targets.

For patients with advanced cancers being treated with palliative (noncurative) intent, despite the wealth of data suggesting a very guarded prognosis, their primary question is "can my cancer be cured?" or, as a compromise, "Can my cancer be treated so I can live *a lot* longer?" If I-O provides hope for multi-year and perhaps decade-plus remissions, even if that likelihood is low (say 10%), all patients will want a chance at winning what has been described as an "I-O lottery." Further, patient and physician preference for I-O is also influenced by the fact that, compared with many alternative therapies, I-O is less toxic for most patients than chemotherapy. Thus, PD-1 inhibitors gain a strong acceptance based on slightly superior response rates, the important "tail of the curve" comprising the "I-O lottery winners," and decreased toxicity.

TABLE 1. Key Characteristics of CTLA-4 and PD-1/PD-L1 Agents in Solid Tumors

KEY VARIABLE	COMPARISON
Delivery of chemotherapy vs I-O	Chemotherapy delivered IV or orally by variable schedules. I-O agent delivered IV every 2-3 weeks.
Response rate	Response rates typically marginally higher with I-O agents.
Time to tumor progression	For the average patient, time to tumor progression is very similar between chemotherapy and I-O agents.
Overall survival	I-O typically yields more long-term survivors.
Toxicity	I-O agents can cause immune-related adverse events, but, on average, are better tolerated than chemotherapy.
Cost	I-O agents are dramatically more expensive than generic chemotherapy and similar in cost to other biologic and targeted oral agents. Most agents typically include substantial out-of-pocket patient expenses.

CTLA-4 indicates cytotoxic T lymphocyte-associated protein-4, I-O indicates immuno-oncology; IV, intravenous, PD-1, programmed death-1; PD-L1, programmed death ligand-1.

I-O at the Center of the Clash of Innovation and Value

The management of cancer is complex and expensive. The use of sophisticated imaging, molecular diagnostic tests, and the frequent use of expensive therapeutic modalities, including surgery, radiation, chemotherapy, biologics, and supportive drugs, can easily lead to courses of therapy that exceed $100,000 in the first year of a cancer diagnosis. Similar or even greater expenses are often also seen in the last year of life for patients who can't be offered curative therapy. Cancer spending was estimated to be $130 billion in 2010 and is expected to be between $170 billion and $180 billion in 2020.[1]

Figure 2 demonstrates the rough breakdown of annualized costs from patients with cancer. As seen in the graph, a significant expense is the office-based drug costs. »

McKesson Specialty Health

SEIDEN

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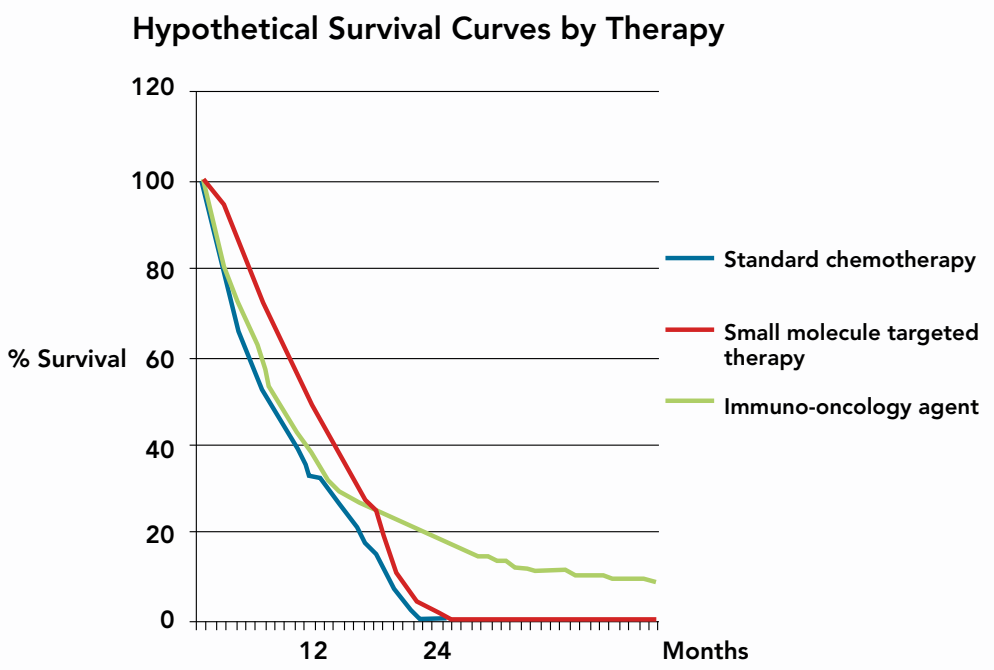
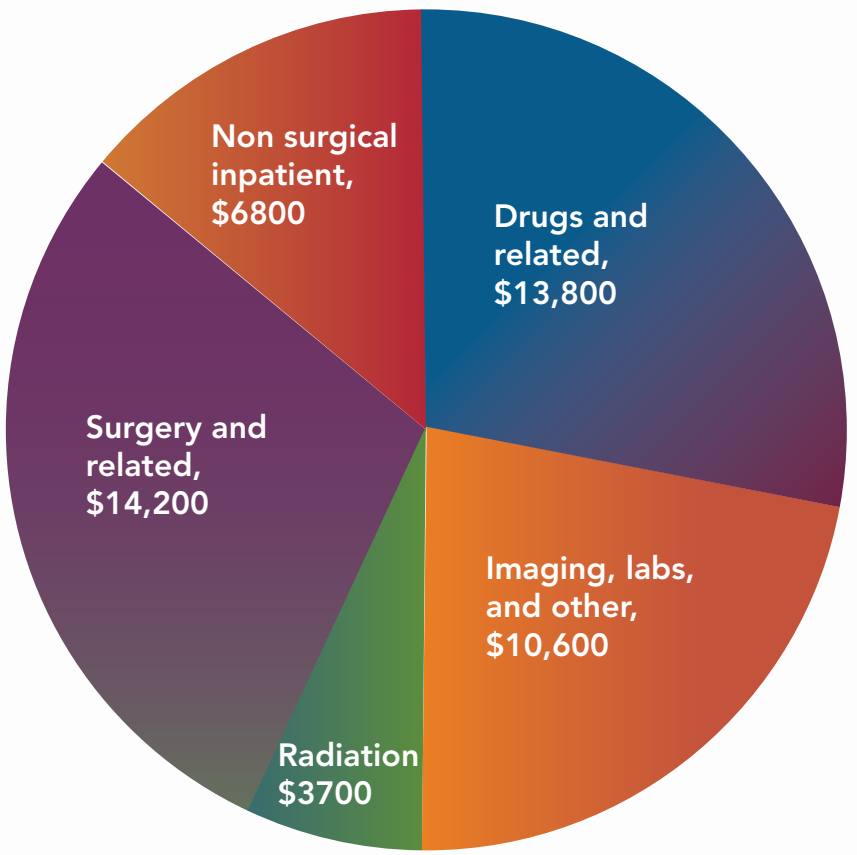
FIGURE 1. Immuno-Oncology Agents Differ From Other Therapies at the Tail of the Curve



Source: Fitch K, Pyenson B. Benefit designs for high cost medical conditions. Milliman website. http://us.milliman.com/uploadedFiles/insight/research/health-rr/benefit-designs-high-cost.pdf. Published April 22, 2011. Accessed January 9, 2017.

FIGURE 2. Annual Cancer Costs Among Medicare Patients on Active Oral or Intravenous Therapy for Cancer



Source: Fitch K, Pyenson B. Benefit designs for high cost medical conditions. Milliman website. http://us.milliman.com/uploadedFiles/insight/research/health-rr/benefit-designs-high-cost.pdf. Published April 22, 2011. Accessed January 9, 2017.

Cancer drugs (oral plus intravenous) and hospitalization make up almost two-thirds of the spend; thus, it will be hard to ignore these categories of expense as the provider community is challenged to participate and ultimately take risk in the quest to decelerate the increasing spend on cancer care. A special area of focus will be the PD-1 and PD-L1–inhibitors, which have gone from investigational agents to one of the top 5 oncology drugs in terms of costs in the community, in the last 2 years, with year-over-year growth of 300%. With the recent approval of pembrolizumab in a subset of individuals with newly diagnosed metastatic lung cancer, the country's most common lethal malignancy, it is likely even more patients will be getting this therapy, with their time on therapy being potentially longer. In addition, it is likely that in 2017, we will see additional inhibitors of PD-1 and PD-L1 approved, and potentially the combination of these agents with ipilimumab or other CTLA-4–binding agents. By some estimates, I-O drugs already represent 18% of the drug spend. As the principal APM in cancer, the OCM is due to pilot through 2021, and it is likely that I-O drugs will represent the principal driver of cancer drug costs, which, as a class, may represent 50% of the oncology drug spend towards the end of the OCM pilot trial.

Alternative Payment Models

I-O innovation arrives concurrently with the rapid roll-out of APMs. Both government and commercial payers are exploring novel, alternative payment strategies that will compel physicians to pay considerably more attention to the total cost of the cancer treatment and evaluation they prescribe. As the average age of cancer incidence is adults in their 60's, Medicare is the single most dominant payer of cancer expenses in this country. Thus, it is instructive to consider the Medicare Access and CHIP Reauthorization Act (MACRA) and the OCM to illustrate how these programs will impact oncology care and the oncology practitioner.

In 2015, Congress repealed the long-standing CMS program called the Sustainable Growth Rate program and replaced it with MACRA, which includes a performance-based adjustment to a practice's Medicare payment, under the acronym of MIPS (Merit-Based Incentive Payment System). This program, which took effect in January 2017, requires the submission of quality data from the practices and claims data from CMS. Practices will be scored on clinical quality metrics, cost of care, and practice improvement. CMS will provide 0.5% annual increases in total payouts through 2019 and will then keep payouts flat (budget neutrality), but will rank practices based on the above metrics to pick winners and losers. Those who outperform their peers will receive bonus payments of up to 9% while those that significantly underperform will see their payments drop by 9%. Of note, a well-run oncology practice in the community might expect a margin of 12% to 18% of revenue; thus, a 9% gain or loss will have extraordinary effects on the bottom line of the clinic, especially when one considers that overachieving on quality metrics might take incremental investments. Practices that invest wisely and over perform can expect at least some financial reward. Those that lack efficiency, scale, or a focus on quality will likely face extreme challenges in the MACRA-MIPS environment. Data will be sent to CMS in 2017, with bonuses or penalties being delivered in 2019.

A practice can gain additional benefits and risks by entering an advanced APM, such as the "2-sided risk" version of the OCM, which includes some of the same quality metrics of MACRA and MIPS along with additional responsibilities in transforming the care delivered to the patient. Practices participating in the OCM are compared with their baseline performance prior to program initiation, along with a number of adjustments and trend factors. The trend factor, still poorly defined, is proposed to correct for inflation and take into account the realization that innovation will

likely increase costs. Of note, the global baseline cancer spending calculated by CMS preceded the approval of all the PD-1 and PD-L1 checkpoint inhibitors.

Defining Value in Healthcare

In healthcare, value is often defined as quality divided by cost—increasing quality and/or decreasing costs offers the chance of increasing value. Indeed, in theory, one could still achieve an increase in value with higher costs if the quality of care improved dramatically. Economists often refer to value from the patient perspective. Measuring cost, the denominator of the value equation, is not as simple as it seems because it includes not just the direct cost of care, but also opportunity costs for the patient from lost time at work, or perhaps for the caregiver who left work to support the patient. Quality is an order of magnitude more challenging to convert into a number. From the patient's perspective, quality could include several concerns:

- Do I feel well?
- Can I live independently?
- Is my anxiety and/or pain relieved?
- Do I feel cared for?
- Can I return to work?

Obviously, how an individual patient scores these issues, numerically, is a daunting proposition and likely is very individualized. One patient might emphasize that value centers predominantly around their ability to live independently, while another might ascribe value just to surviving to a key milestone such as a wedding or delivery of a grandchild. It should be apparent that these types of value determinations are qualitative and precise measurement is aspirational. As a poor substitute, organizations have proposed various statistical standards such as cost per quality-adjusted life-years that a certain therapy provides, or costs to prevent a single death.

Within the US Oncology Network—a national collection of 1400 cancer caregivers including over 800 medical and gynecologic oncologists—much of the decisions around drug use are guided by well-conducted and peer-reviewed clinical trials that are vetted by the National Comprehensive Cancer Network and then further scrutinized by a Pathway Committee of the US Oncology Network. Selected drug regimens are defined by a combination of clinical efficacy and cost. Typically, costs are simply the drug costs since there is little data of costs of supportive care, in particular, the likelihood that a specific regimen will require urgent care, emergency care, or hospitalization. Developing such databases personalized to an individual's age, gender, comorbid disease, and performance status is an important goal for the future.

Ethical Issues of Society Versus the Individual and Models Around the Drug Value Proposition

The I-O agents, specifically the PD-1 and PD-L1 inhibitors, pose a particular set of challenges. Although sweeping generalizations are hazardous, a high-level summary of the data around these agents is as follows:

1. Compared with chemotherapy or other targeted agents, I-O agents are marginally more effective in many patients, and moderately to markedly more effective in a small minority of patients.
2. These agents are, in general, less toxic than most chemotherapy agents used in late stage cancer.
3. I-O agents are moderately or markedly more expensive than standard chemotherapy.
4. There is little guidance in the current literature on how long to continue these agents in patients with durable responses or how much emphasis to place on PD-L1 tumor expression.

Thus, the cost calculation of the value equation is high. However, since the toxicity is less (on average) than chemotherapy and the clinical outcome is improved, the quality (numerator) of the value equation is also higher. However, its impact on the overall value depends on how much an individual patient benefits, which, of course, is hard to predict a priori.

To make issues a bit more complicated, APMs, in general, and the OCM, in particular, don't really reward value as described above. It does include quality metrics, but doesn't include response, survival, or toxicity. The calculation of shared savings that would be delivered to the practice is equal to a quality score multiplied by a cost saving score. Consider, as an example, a practice that doubled its quality score from 50 to 100 while its healthcare costs increased 10%. In this hypothetical case, there was a marked improvement in quality and perhaps even survival, with a simultaneous increase in costs. Although the improvement in quality would exceed the cost increase (and thus improved "value"), the cost-saving equation would yield no financial return for the practice (reward in the OCM = quality score x cost savings). In the event the practice made a significant financial investment to transform clinical care through investment in information technology, staff, and processes, it could easily have overspent their monthly management fee. This highlights an important discordance with value and shared savings that dominates APMs.

In reality, while quality improvements are important, the dominant factor in the model is a reduction in costs. This puts the physician in a challenging position, especially in a society with direct-to-consumer marketing and the increasing awareness and hype around the potential of immunotherapy. For a patient with recurrent cancer of the lung, kidney, bladder, head and neck region, Merkel cell tumor, melanoma, or Hodgkin's disease, there is a growing body of literature that supports considering I-O agents. There are currently hundreds of clinical trials evaluating PD-1 and PD-L1 agents alone or in combination with other I-O agents. It is almost certain that during the tenure of the OCM project, PD-1 and PD-L1 agents will gain approval in many additional malignancies, including in patients with locally advanced or newly diagnosed metastatic disease, as was recently witnessed in melanoma, and a subset of patients with non–small cell lung cancer.[12]

BEARING RISK IN COMMUNITY ONCOLOGY PRACTICES TRANSLATES INTO RISKS TO PERSONAL INCOME AND A PRACTICE'S VITALITY.

In an environment that is without fiscal restraints, patients are offered such therapies with risk falling to the payer (government, insurer, employer, and, to a lesser extent, the patient). In the OCM world, such behavior adds risk to the participating practice. In addition, in the setting of higher patient co-payments, the patient now bears more of the risk. Bearing risk in community oncology practices translates into risks to personal income and the practice's vitality, challenging the physician to weigh personal interests against patient interests. While capitated contracts and risk-bearing contracts have existed in the past, particularly in healthcare systems and primary care practices, the scale of the OCM and the prices associated with these agents provide very broad risk corridors not typically seen in primary care or pediatrics practices.

Challenges in Delivering I-O Therapy Rationally

It is a physician's obligation to deliver therapy that will benefit the patient, and the current data supporting I-O therapy provide compelling evidence that it should be part of the therapeutic ar-

(continued on SP77)

#1 PRESCRIBED ORAL CLL THERAPY.*
MORE THAN 20,000 PATIENTS TREATED SINCE APPROVAL[1†]

MAKE IMBRUVICA® YOUR FIRST STEP

Approved in frontline CLL with or without 17p deletion[2]

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for:

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 9%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

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janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3]
Patients with 17p deletion were not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

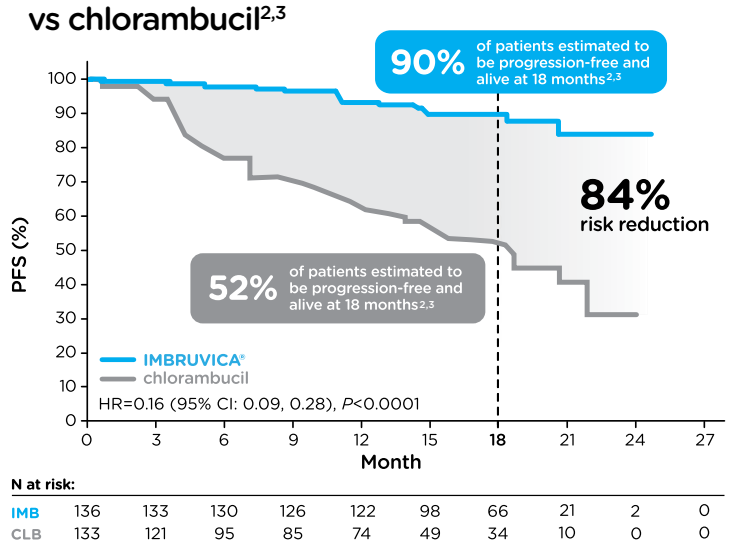
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil[2,3]



N at risk:

IMB	136	133	130	126	122	98	66	21	2	0
CLB	133	121	95	85	74	49	34	10	0	0

PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months[3]
- IMBRUVICA® median PFS not reached[2]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[2]
- PFS was assessed by an IRC per revised IWCLL criteria[3]

Adverse reactions ≥20% across CLL/SLL registration studies[2]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia‡ (64%), thrombocytopenia‡ (63%), diarrhea (43%), anemia‡ (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

‡Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

*Based on market share 2016 July YTD data from IMS.
†Based on IMS data February 2014 to date.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, IWCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic leukemia.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary disorders: hepatic failure (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data].* If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception:

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA *[see Clinical Studies (14.2) in Full Prescribing Information].*

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial fibrillation:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

(continued from SP71)

mamentarium in a variety of malignancies. Unfortunately, we are missing several important pieces of data that might help physicians deliver these therapies rationally. **Table 2** lists questions that might help moderate the costs of I-O.

TABLE 2. Questions to Help Moderate the Costs of I-O Agents

QUESTION	IMPACT
Are all PD-1 and PD-L1 agents equivalent?	If these agents are all equivalent, payers and physicians can expect the manufacturers to compete on price.
Would payers allow therapeutic interchange?	If the I-O agents are equivalent, can we use a more economical PD-1 or PD-L1 antibody and be reimbursed, even if the specific drug is not approved for that specific clinical indication?
Can we identify patients who will not benefit from I-O therapy?	If we can identify patients who do not stand a chance of benefiting from these therapies, we may confidently tell them this therapy is inappropriate.
Can we stop these agents early in responders?	If a patient has a partial or complete response to therapy at 6 months, can treatment be stopped or should it continue potentially for a year or more?
If a patient starts I-O therapy, can we be clear when to stop?	Particularly in a patient whose tumor does not express PD-L1, how short should the I-O course be to exclude potentially clinically meaningful benefit, if a benefit is not seen within a defined period of time?

I-O indicates immune-oncology; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

While there is an unprecedented number of I-O trials actively enrolling patients, essentially, all of these trials are looking for expanded use of PD-1, PD-L1, or CTLA-4–binding agents or novel I-O agents, either alone or with the approved agents. These trials, if positive, will only accelerate the rise of I-O use and costs in cancer care.

MANUFACTURERS OF IMMUNO-ONCOLOGY AGENTS SHOULD SHARE THE RESPONSIBILITY OF SUPPORTING VALUE-BASED PRICING.

Conclusion

Ideally, a society should support an environment of innovation that improves the lives of its citizens and simultaneously permits the astute use of its limited resources. Improving the value of the care we deliver to patients with cancer is important. The shift to value-based care, concurrent with the innovations in immunology and the rapidly growing indications for I-O agents, will create significant challenges for the physicians and healthcare systems in the near term. Community-based oncologists will need to be particularly savvy in meeting the operational and financial demands of clinical transformation prescribed by value-based care, while maintaining the financial viability of their practices. Finally, manufacturers of I-O agents should share the responsibility of supporting value-based pricing. The market is becoming more crowded with duplicate I-O agents, and competitive pricing will lower the tension that these treatments inflict on the value equation. ◆

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**The views and opinions expressed are those of the authors and do not reflect those of McKesson Specialty Health, the US Oncology Network, or McKesson Corporation.*

DISCLOSURES

Marcus Neubauer, MD, and Diana Verrilli are employees of McKesson Corporation. Michael V. Seiden, MD, PhD, is an employee of the McKesson Corporation and The US Oncology Network. Their views are their own and do not necessarily reflect the views of the McKesson Corporation, McKesson Specialty Health, or The US Oncology Network.

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PATIENT EDUCATION

Helping Cancer Patients and Caregivers Navigate Immunotherapy Treatment

Claire Saxton, MBA; Joanne Buzaglo, PhD; Sue Rochman, MA; and Alexandra Zaleta, PhD

(continued from cover)

SAXTON

BUZAGLO

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Methods Used to Gather Patient Insights on Immunotherapy

Quantitative data were obtained from an online survey and analysis of 367 evaluations of in-person immunotherapy workshops. Qualitative data and insights were gathered from a 2-day Immunotherapy Patient & Caregiver Summit.

The Cancer Support Community (CSC) is the largest professionally led nonprofit network of cancer support worldwide, reaching more than 1 million people annually. CSC is dedicated to ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community. These aims are met through direct service delivery, research, and advocacy. CSC's educational programs, which incorporate and reflect research and advocacy, are designed to help patients with cancer make treatment decisions that align with their goals and values (**Table**).

CSC's Frankly Speaking About Cancer (FSAC) series provides an in-depth coverage of topics relevant to those affected by cancer that are not otherwise available in a comprehensive format.[4] The series—delivered through in-person workshops, print publications, online content, webinars, and a radio show—addresses topics such as cancer treatments, side effects, and coping with the cost of care. Series topics are based on identified areas of need.

Results

An online survey that CSC conducted, in 2014, found that 34.8% of cancer survivors knew the term immuno-oncology and 64.9% had heard of immunotherapy. The survey also showed that 84% of respondents were interested in learning more about these topics. In response, CSC developed FSAC: Your Immune System and Cancer Treatment for cancer patients and their caregivers. Thus far, FSAC has developed educational content on immunotherapy as a cancer treatment and immunotherapy options by cancer type, which is accessible on the CSC website (www.CancerSupportCommunity.org/immunotherapy) and through 4 print/downloadable booklets, 3 webinars, 22 in-person workshops, and a 2-day immunotherapy patient and caregiver summit.

EVEN AFTER RECEIVING TREATMENT, PATIENTS AND CAREGIVERS REMAIN CONFUSED ABOUT WHAT IS IMMUNOTHERAPY AND WHETHER THEY HAVE RECEIVED IMMUNOTHERAPY.

Data From in-Person Workshop Evaluations

FSAC: Your Immune System and Cancer Treatment workshops provide an opportunity for patients and caregivers to obtain comprehensive information about immunotherapy, as well as to learn how to communicate with their healthcare team about immunotherapy treatment options. In 2014-2015, local CSC/Gilda's Clubs across the United States hosted 532 attendees at 11 in-person immunotherapy workshops. Of these 532 attendees, 367 completed evaluations that included personal demographics and self-reported pre- and postworkshop comparisons—72.5% of respondents were individuals with cancer, 20.5% were caregivers, and 5.8% were healthcare professionals. After the workshop, most respondents felt better equipped to discuss potential side effects (86.8%), have a conversation with their healthcare provider on treatment options (91.5%), and make treatment decisions in tandem with their doctors (87.9%). These findings were presented at the 2016 American Psychosocial Oncology Society Annual Conference.[5]

Strikingly, even though many workshop attendees described themselves as "partners" with their healthcare team when making decisions, many had no idea whether immunotherapy was an option for them. These and other findings reaffirmed the need for patients with cancer to receive clear, relevant, and comprehensive information about immunotherapy. The findings also underscored the importance of promoting proactive communication between patients and their healthcare team about whether or not immunotherapy is, or might soon be, a treatment option.

Insights From Patient and Caregiver Summit

In November 2016, CSC held a 2-day Immunotherapy Patient & Caregiver Summit specifically for cancer patients who have received immunotherapy treatments, and their caregivers. The summit provided a unique opportunity for immunotherapy patients to share their experiences and for CSC to identify specific needs and concerns of patients who are on these treatments. The summit was attended by 30 individuals—18 patients and 12 caregivers from throughout the United States who had been selected through an online application process. Eight of the patients had blood cancers, and 10 had solid tumors.

Even after receiving treatment, patients and caregivers remain confused about what is immunotherapy and whether they have received immunotherapy or other novel therapies. Tellingly, over half of the patients and caregivers who applied to participate in CSC's immunotherapy summit did not understand that they were ineligible for the summit because they or their loved one had not been treated with an immunotherapy.

CSC gained insight into how cancer patients and caregivers perceive the challenges, and hope, unique to immunotherapy from summit participants by using focus group formats, collecting written comments, and through discussions in workshops on topics such as side effects, self-advocacy, and storytelling. The insights gathered also helped to identify gaps in immunotherapy patient education. Before arriving at the summit, the 30 participants were asked to review several of CSC's FSAC immunotherapy materials. Utilizing a focus group format, participants also provided specific feedback on these materials.

Many of the participants had received or were receiving immunotherapy through clinical trials. Most knew very little, and some knew nothing, about immunotherapy before starting treatment. Discussions revealed that some patients and caregivers were not initially aware that immunotherapy differed from, and was not a type of, chemotherapy, while others didn't

know they would be receiving an infusion. For some, treatment also entailed learning to navigate the multiple campuses and buildings that comprise many large cancer centers. Patient experience was also complicated by the fact that many accessed these new treatments through clinical trials, which made it difficult for them to learn from others' experiences on treatments and side effects.

Side effects alone posed a unique concern. Some participants feared that telling their healthcare team about the side effects they were experiencing would result in their having to withdraw from an immunotherapy trial that was their only treatment option. This concern appeared to be compounded by the fact that patients and caregivers expected immunotherapy to be easier to tolerate than chemotherapy and to result in fewer side effects. This left them unprepared for the severe flu-like symptoms, overwhelming exhaustion, diarrhea, sleep disturbances, and endocrine problems many experienced. It also left them concerned about what these more severe side effects might portend.

After receiving immunotherapy, most patients and their caregivers understood the need for managing side effects quickly. Throughout the summit, patients and caregivers expressed a need for more detailed educational content on side effects and which symptoms they should immediately report to their healthcare team. Patients reported that the drug information they did receive was hard to understand and did not make a distinction between symptoms of their disease and symptoms that may be side effects.

Patients and caregivers reported high levels of distress associated with balancing their life, an advanced-stage disease, and treatment. Only a few patients and caregivers stated being offered psychosocial resources to mitigate their distress. Patients also said they had anxiety about living with uncertainty, as well as some cognitive distress because they did not "look sick" on immunotherapy even though they were often very fatigued and medically fragile.

Another important theme that emerged from the summit was the need for patients and caregivers to have more clarity on how immunotherapy might impact other aspects of routine care from a primary care provider or another specialist or in an emergency department setting. For example, it surprised patients that their other health providers might not know that they had to avoid live vaccines. To address this need, patient and provider educational materials and communication tools must be developed that guide patient and provider communication on what drugs, vaccines, or treatments can and cannot be used by patients with cancer on immunotherapy.

Cost of Care

No discussion of immunotherapy would be complete without mentioning the total cost of new cancer treatments. The summit underscored the high degree of distress patients experience around the cost of cancer in general and immunotherapy treatments in particular, even within the context of a clinical trial. As many have previously noted, the total annual cost of care for immunotherapy and other novel treatments can exceed $100,000.[6] The patient burden, through co-payments and co-insurance, can be tens of thousands of dollars. When patients do not have access to or do not know how to access patient assistance programs, these costs can quickly contribute to what is now widely referred to as the financial toxicity of cancer care.[7]

CSC's Support Services for Patients and Caregivers

In June 2016, CSC launched its *F*rankly Speaking About Cancer Clinical Trials program (www.CancerSupportCommunity.org/ClinicalTrials). This landmark education series aims to build awareness among patients and caregivers about the importance of clinical trials as a viable treatment option. This program will be especially important for patients as the number of new experimental immunotherapy treatments increases. CSC provides services that can help patients and caregivers understand and manage their treatment, mitigate distress, and get help assessing and managing cancer costs. These include:

TABLE. Education Programs and Information Created for Cancer Patients and Caregivers

PROGRAM/ MATERIALS	SERVICES
Telephonic and chat support on managing all aspects of living with cancer.	Toll-free Cancer Support Helpline. Counselors are available by phone, or can chat online.
Evidence-based program to help patients better communicate with their doctor around treatment decisions.	Open to Options program available through the Cancer Support Helpline and at local CSC/Gilda's Club affiliates.
In-person workshops and support at over 200 locations worldwide, including 50 local CSCs, Gilda's Clubs, and healthcare partnerships.	http://www.CancerSupportCommunity.org/find-affiliate
Web-based information on immunotherapy, cancer treatment and side effects, managing the cost of care, clinical trials, health insurance, employment and cancer, making treatment decisions, and more.	www.CancerSupportComunity.org (click on "Learn about Cancer" and "Living with Cancer," view webinars)
Print and digital Frankly Speaking About Cancer materials.	Print books available to order online at Orders.CancerSupportComunity.org. E-books available for iBook, Nook, Kindle, and Google Play.

CSC indicates Cancer Support Community.

Conclusion/Future Directions

Analysis of survey data and immunotherapy workshop evaluations, along with insights from CSC's Immunotherapy Summit demonstrate that patients, caregivers, and even primary care and emergency healthcare providers need education on immunotherapy treatment. This education needs to be bolstered with patient–provider communication support and tools to ensure that patients, caregivers, and all healthcare team members are working together to improve patient health. Finally, patients and caregivers need referrals to psychosocial support and »

PATIENTS AND CAREGIVERS REPORTED HIGH LEVELS OF DISTRESS ASSOCIATED WITH BALANCING THEIR LIFE, AN ADVANCED-STAGE DISEASE, AND TREATMENT.

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educational resources, like those available from CSC, to help them understand their disease and treatment, reduce distress, manage the total cost of care, and improve quality of life.

Over the next few years, findings from clinical trials that are now underway will shed light on the increased impact of immunotherapy on cancer—from prevention through treatment. In preparation for potential advances as well as inevitable setbacks and disappointments, new content needs to be developed to help cancer patients and caregivers navigate immunotherapy treatments. CSC is very close to releasing immunotherapy content for 3 additional tumor types, material in Spanish, and video testimonials from patients and caregivers who have experienced immunotherapy treatment. Our quantitative data and qualitative insights reinforce the need for more content to be distributed to additional patients and caregivers, as well as the need for continued improvement of this content over time.

CSC is also engaging in conversations with policy makers and other patient advocacy organizations on the impact of the total cost of these treatments on patients as our healthcare system braces for changes. This is a time in cancer care in which high hopes meet unknowns. As we move forward, it will be critical to include the voices of cancer patients and caregivers in the development of new immunotherapy educational programs, as well as in finding solutions to the impact of systemic changes. ◆

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PROVIDER INTERVIEW

Q&A With Dr Jae Park on the Promise of CAR-T Cells in Cancer Care

Surabhi Dangi-Garimella, PhD

Memorial Sloan Kettering Cancer Center

PARK

(continued from cover)

the challenges that the field is currently faced with, and predicted what the future holds for CAR-T cells.

***EBO™*: Can you explain the leukapheresis process that is necessary for CAR T-cell treatment?**

PARK: CAR is an artificial T-cell receptor that is genetically engineered by combining a binding domain from a monoclonal antibody that is fused to a T-cell receptor. So, the chimera binds like an antibody but acts like a T cell, and that's where the name "chimeric antigen receptor" originates. It allows the T cell to recognize and bind a tumor, just like an antibody would. It then allows a universal applicability of this type of therapy; so, once you create a CAR against a specific tumor antigen, you can modify the T cells—either the patient's own T cells or donor T cells—to express the CAR, which is now reeducated or reengineered to recognize a specific tumor antigen on a cancer cell better.

Once infused into the patient, these T cells traffic to the site of the tumor and they start eradicating the tumor cells. That's the basic mechanism by which CAR-T cells function.

Leukapheresis, which is sometimes called apheresis, is the process of collecting white blood cells (WBCs). The process is very similar to that of platelet donation: the patient is hooked up to a machine with 2 catheters, 1 in each arm. The machine filters and collects only the WBCs while the rest of the blood components are returned to the other arm. The entire process can last between 2 and 4 hours, the rate-limiting steps being the rate of blood flow and the volume of blood that needs to be collected.

Autologous or patient-derived T cells are the most commonly used form of CAR-T cells, so the patients are the ones who undergo leukapheresis.

***EBO™*: Cytokine-release syndrome, a typical reaction to CAR T-cell treatment, can drain a patient—both physically and emotionally. Can you explain why the patient's immune system generates this massive response? How is it typically managed?**

PARK: Cytokine-release syndrome, or CRS as it is commonly called, is the body's response to the T cells attacking the tumor cells. As the T cells are getting stimulated, and expand upon recognition of cancer cells, they release inflammatory proteins called cytokines—this is our body's typical immune response to fight off infection. Just as a viral or bacterial infection results in fever or issues with breathing or blood pressure, where the T cells release pro-inflammatory cytokines as a way to alert or recruit the body's endogenous immune cells to fight the infection.

Similarly, in this case, as the T cells are infused and are trafficked to the site of the tumor, they recognize the cancer cells, are activated, and they release pro-inflammatory cytokines. The body's reaction to this is the patient gets a high fever, and experiences low blood pressure or breathing difficulties. If the reaction is very severe, the patient may need to be managed in an intensive care unit.

CRS is typically managed using anti-inflammatory agents—one very specific way of treating these patients is by using an IL-6 inhibitor called tocilizumab, which has been approved for the treatment of rheumatoid arthritis. IL-6 levels are elevated during CRS, so by blocking this specific cytokine, you can dramatically, and very quickly, reverse the patient's symptoms. If this treatment is not sufficient, then we do use corticosteroids—a more general way to suppress the overall immune response. And these are mostly reversible. So, a patient may get sick for a time with high fever and such, but once they receive the treatment, these symptoms reverse very quickly. However, CRS can be fatal, so special attention is needed to prevent and effectively manage this unique side effect.

***EBO™*: In your experience, are all patients equally susceptible to CRS following CAR-T treatment?**

PARK: We do see a range in the severity of patient responses. We have developed a grading system—mild CRS or severe CRS—to document the severity of patient response. Sometimes, we can predict how severe CRS may be in a patient, which is dictated by the patient's disease burden. A higher disease burden means more antigens for the T cells to interact with, they get activated faster and expand to a greater degree, and the more severe the CRS. So it really depends on how much disease you have, what type of T cells, and what dose of T cells is infused—which matters as well.

So, there's a host of factors that can affect the degree of CRS.

***EBO™*: Which types of cancers has this treatment been tried in, overall, and at MSKCC in particular?**

PARK: At MSKCC, we have used CAR T-cell treatment in patients with ALL, CLL, and non-Hodgkin's lymphoma, including diffuse large B-cell lymphoma. We also have a trial for solid tumors, specifically for mesothelioma, which is a type of lung cancer, for breast cancer, and for ovarian cancer. So, these trials treating these disease types are currently enrolling patients. We also have a pediatric ALL trial that is treating younger patients with CAR-T cells.

***EBO™*: CAR T-cell treatment is very expensive. When do you anticipate this treatment to be used in mainstream cancer care?**

PARK: Right now, the treatment is expensive, but hopefully the cost of treatment with CAR-T cells will come down. Compared with a transplant or where you need repetitive treatments with a drug, such as an oral targeted drug, the advantage with CAR T-cell treatment is that 1 infusion of the drug can induce a great degree of remission. So, although the upfront cost may be high, downstream costs associated with this treatment likely decrease over time.

***EBO™*: This form of T-cell treatment could be considered an 'N-of-1' trial. Will the FDA evaluate this treatment differently, compared with the regular drug approval process?**

PARK: I think the FDA is viewing this therapy quite favorably because it recognizes that for some of the diseases that are being studied, there currently are no good alternatives for treatment. There are some regulatory processes involved because this treatment is categorized as a gene therapy due to the use of a retroviral or lentiviral vector for modifying the genetically engineered T cells. But the treatment has already received a breakthrough treatment designation for ALL and is close to being approved, as long as its efficacy and safety are confirmed in the ongoing large phase II clinical trials.

> **"THERE'S MORE WORK NEEDED TO OVERCOME SOME OF THE CHALLENGES, AND COMBINING CAR T-CELL TREATMENT WITH ONE OF THE IMMUNE CHECKPOINT INHIBITORS MIGHT BE ONE WAY."**
>
> –Jae Park, MD

***EBO™*: Are combination trials of CAR-T cells with immune checkpoint inhibitors being planned in the near future?**

PARK: CAR T-cell therapy, especially in ALL, is very effective and patients can get into remission 80% to 90% of the time, which is why we are so excited about this treatment. But it's not perfect, and not all patients benefit from it, and even after the initial respons, relapses do occur. So, there's more work needed to overcome some of these challenges, and combining CAR T-cell treatment with one of the immune checkpoint inhibitors might be one way. It could help prolong the immune response, prolong the persistence of the T cells, and hopefully prolong the duration of response.

These treatments are being evaluated at some of the centers around the country. Currently, we do not have enough data to draw conclusions on whether the combination of CAR-T cells with immune checkpoint inhibitors will be effective or whether it would result in more side effects. There are some safety mechanisms and management guidelines with these type of trials, but it's definitely a natural next step that we are currently exploring.

Next-generation CAR-T cells are also being explored in clinical trials—these cells are made stronger even without the immune checkpoint inhibitors.

***EBO™*: What is your prediction about where the future lies for CAR-T cells in oncology care?**

PARK: We are obviously very excited about the tremendous impact of immunotherapy in cancer care. Moving from chemotherapy, which is very nonspecific, to oral targeted treatments that target specific pathways—cancer cells do become resistant to these treatments. With immunotherapy, we are not targeting any particular signaling pathway; rather, we are manipulating the body's immune system to better recognize and kill cancer cells.

So, the future, I think, is very bright, and we are very close to getting this therapy approved in patients with ALL, using CD19-targeted CAR T-cells. We do have a lot of unanswered questions, such as whether treatment efficacy will remain the same with solid tumors and if not, whether we can improve efficacy with next-generation CARs or by combining the treatment with immune checkpoint inhibitors or with oral-targeted therapy.

A lot of efforts are being invested to improve the safety and efficacy of CAR-T cells, so we do expect the emergence of better and safer therapies in the future, either in combination treatments or by further modification of CAR-T cells, to hopefully lead us to a "cure" for cancer. I believe CAR-T cells is one of the ways by which we can get there. ◆

OncLive PRESENTS

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

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PROGRAM OVERVIEW

- Nominations are open through March 20, 2017.
- Domestic and international nominations will be accepted. Self-nominations are permitted and encouraged.
- The *Giants of Cancer Care*® Advisory Board will vet all nominations to determine finalists in each category.
- A selection committee of 90+ oncologists will vote to determine the 2017 inductees.
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