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Evidence-Based Oncology

THE IMMUNO-ONCOLOGY SPECIAL ISSUE

Provider Perspective

Immuno-Oncology 2016 and Beyond: *The Opportunities, Challenges, and Risks*

MICHAEL V. SEIDEN, MD, PHD

HISTORICAL PERSPECTIVE

In the late 18th century, a young surgeon at Memorial Hospital, Dr William Cooley, learned of a patient with locally recurrent sarcoma of the head and neck that developed a raging local erysipelas infection caused by *Streptococcal pyogenes* arising in the necrotic tumor. According to the report, with each wave of fever, the tumor shrank and ultimately disappeared. Cooley searched the boroughs of New York and found the patient alive and well 7 years after his infection, with a large tumor-free scar on his face. Subsequently, Cooley developed various concoctions of bacteria and intentionally infected scores of patients with these toxins, which caused numerous untoward events and even deaths in patients. Curiously, his treatments also led to a collection of dramatic responses and, in some cases, cures.[1]

Fast forward to experiences with high-dose interleukin 2 (IL-2) and interferons for the treatment of individuals with renal cell carcinoma and melanoma.[2] Although the clinical use of high-dose cytokines has led to important clinical insights and, in the case of high dose IL-2, a modest niche in the management of young individuals with cancer, it is reasonable to state that they have not changed the landscape of cancer therapeutics in a material way. Instead, they provide tantalizing clues that, if the immune system could be primed, expanded, and directed to the target (ie, the tumor), the patient might benefit. Their use also highlighted a few simple yet profound questions

(continued on SP67)

Cancer MoonShot

Cancer MoonShot 2020 Proposes a Collaborative Precision Cancer Care Model

SURABHI DANGI-GARIMELLA, PHD

A collaboration among the who's who of healthcare was announced on Monday, January 12, 2016, at the annual JP Morgan Healthcare Conference. Seeking to accelerate the development of next-generation immunotherapy in oncology, The National Immunotherapy Coalition (NIC) has coalesced leaders from large pharma (Celgene and Amgen), biotech (NantWorks, NantKwest, Etubics, Altor Bioscience, and Precision Biologics), academic cancer centers, community oncologists, and the health plan Independence Blue Cross. This coalition forms the basis of Cancer MoonShot 2020, which boasts the following key attributes:

- The nation's first insurance coverage of next-generation whole genome sequencing and proteomic diagnostic platform in cancer patients
- Next-generation sequencing and precision medicine evolving from research to the clinical trial and cancer care setting
- Coalition to design, initiate, and complete randomized clinical trials at all stages of cancer in up to 20 tumor types in as many as 20,000 patients in multiple phase 1 to 3 trials by 2020
- Beneficiaries and patients will undergo next-generation molecular sequencing and gain access to over 60 novel and approved molecules to be tested as immunotherapy combinations in 20,000 cancer patients with cancer across all tumor types under the QUantitative Integrative Lifelong Trial (QUILT) Program

(continued on SP71)

Clinical Integration of I-O

Evolving Practices in Managing Costly Immunotherapy

CARINA VERDIER DOLAN, PHARMD, BCOP

The high cost of cancer therapy frequently appears in the headlines of mainstream news outlets, such as *The Wall Street Journal*, *Forbes*, and CBS News. These reports juxtapose the new, and potentially life-saving drugs with the financial toxicity experienced by patients and their family members due to the significant cost of new therapies. Hospitals are also feeling the effects of rising drug costs and are similarly characterized as struggling with soaring medication budgets and physicians outraged at the cost of chemotherapy.

The class of drugs stirring these discussions about high cost and medicinal advancement is immunotherapy. This revolutionary therapy involves enlisting the immune system to enhance its effect against neoplastic cells.

While the concept of immunotherapy is well established in the treatment of cancer, recent enhancements to this core principal have expanded our capabilities to create novel subcategories, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), program cell death-1 (PD-1) inhibitors and bi-specific T-cell engagers (BiTEs). The most recognized for their unique feature are the PD-1 inhibitors and the targeting of co-inhibitory signaling receptors, discovered to play a major role in the activation and regulation of tumor-combating T-cells. These signaling receptors serve as checkpoints and are a major component in eliciting an immune response.

A handful of immunotherapy agents have recently been approved by the FDA, including nivolumab (Opdivo; Bristol-Myers Squibb), blinatumomab (Blincyto; Amgen), pembrolizumab

(continued on SP73)

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Also In This Issue...

A YEAR IN REVIEW

With nearly daily updates on immuno-oncology (I-O) drugs moving from salvage therapy to first-line or adjuvant care, there is no doubt about their impact on patient outcomes. **Bruce A. Feinberg, DO,** provides an overview of the progress in I-O over the past year, and addresses some of the challenges the field currently faces **(SP40)**.

POLICY DECISIONS TO IMPROVE PATIENT ACCESS

The European Expert Group on Immuno-Oncology has developed a framework to guide policy makers to develop tangible measures that would allow rapid and appropriate access for cancer patients in Europe to these expensive treatments. **Suzanne Wait, PhD,** explains the framework and other efforts in Europe to integrate immuno-oncology agents into clinical care **(SP47)**.

IMPORTANCE OF PATIENT ADVOCACY

Bonnie J. Addario, founder of the Bonnie J. Addario Lung Cancer Foundation, and a survivor, shares the Foundation's efforts to promote research in lung cancer—particularly in personalizing care based on a patient's genetic profile—and to help patients gain access to new life-saving treatments **(SP56)**.

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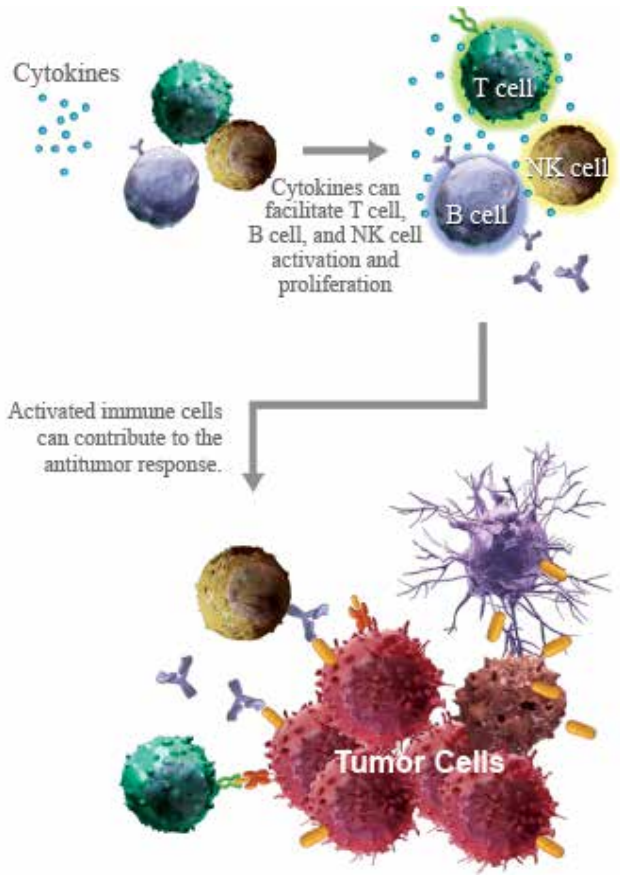

SOURCE: IO educational resources. Bristol-Myers Squibb website. http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources.

The Push–Pull of Tweaking the Immune System in Cancer Care

Expanded indications of approved drugs, encouraging data from drugs currently in the developmental phase, and the high cost of treatment—immuno-oncology (I-O) therapies are proving a bittersweet experience for patients, providers, and payers alike. Following the approval of ipilimumab in melanoma, we have seen vigorous activity in the development of monoclonal antibodies that manipulate the immune systems, vaccines, and chimeric antigen receptor T cells. Despite the advances and expanded indications for approved I-O agents, complications remain, including "pseudoprogression," developing combination treatments, sequencing of treatments in care pathways, and the absence of companion diagnostics.

However, the progress is real, as discussed by Bruce Feinberg, DO, vice president and chief medical officer at Cardinal Health. In this issue, Dr Feinberg provides an update on the clinical progress in I-O over the past year, following his review on this subject in the February 2015 issue of *Evidence-Based Oncology*. Assessing several options that could help find a place for the new treatments in value-based care delivery models, he writes, "Stakeholder adoption of I-O is no longer a question of "if," but "when." Who will be treated with "what" types of cancer in "which" stage and for "how" long, remain unanswered questions at the start of 2016."

As a medical oncologist leading an extensive network of integrated, community-based oncology practices in the country, Michael Seiden, MD, PhD, shares his views on the opportunities that the new I-O drugs have brought to the table, and some of the challenges that the community, and the healthcare system, as a whole, might face in the coming years. Dr Seiden explains that, while patients and providers recognize the potential of these agents, access is currently restricted through clinical trials, and the risk of not being reimbursed for these drugs is also a challenge. While the pharmaceutical industry is heavily invested in the development of I-O treatments, paying for them will prove a daunting task, he writes, "with the market size of I-O agents, alone, in 2022, predicted to be in excess of $30 billion."

MIKE HENNESSY, SR

Thinking ahead, especially with respect to patient access, Europe has developed a Policy Action Framework for Immuno-Oncology to guide policy makers to develop tangible measures that would allow rapid and appropriate access to I-O within the European Union member states. Suzanne Wait, PhD, director of The Health Policy Partnership, in the United Kingdom, explains the operation of the European Expert Group on Immuno-Oncology, which developed the framework, as well as other regulatory and access pathways being created to integrate I-O into clinical pathways and payment schemes.

We also hear from, Carina Verdier Dolan, PharmD, BCOP, senior clinical manager at Vizient, Inc, a healthcare services company. While providing a summary of a panel discussion on present-day challenges and future opportunities within the oncology environment, held during Vizient's Oncology Pharmacy Summit, she also describes strategies that oncology clinical pharmacists can implement to mitigate some of the high costs associated with using immunotherapies.

From the patient's perspective, monetary assistance could provide a big push to gaining access to I-O. Program coordinators who manage The Oncology Medication Assistance Program at the Smilow Cancer Hospital at Yale-New Haven provide insight into their program and the value it affords to patients who face the financial burden of drug-related expenses.

This issue provides well-rounded information on efforts to integrate this potentially revolutionary treatment into clinical practice. Please visit our website, www.ajmc.com, for additional updates on clinical and managed markets research and news.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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.

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- A 71% reduction in duration of severe neutropenia vs placebo (1.1 days vs 3.8 days, $p<0.0001$)[2]
  - Efficacy was evaluated in a multinational, multicenter, randomized, controlled, Phase III study of chemotherapy-naïve patients with high-risk breast cancer receiving doxorubicin (60 mg/m^2 IV bolus)/docetaxel (75 mg/m^2)[2]
- The safety of GRANIX was established in 3 Phase III trials, with 680 patients receiving chemotherapy for either breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL)[2]
- Offering a presentation for self-administration

- GRANIX is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- **Capillary leak syndrome (CLS):** CLS can occur in patients receiving hG-CSFs and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.
- **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

References: 1. This information is an estimate derived from the use of information under license from the following IMS Health Information Service: IMS National Sales Perspective, GRANIX micrograms by non-federal hospital channel September 2015. IMS expressly reserves all rights, including rights of copying, distribution, and republication (micrograms calculated as eaches x strength). **2.** GRANIX® (tbo-filgrastim) Injection Prescribing Information. North Wales, PA: Teva Pharmaceuticals; 2014.

TEVA Oncology

GRANIX®
(TBO-FILGRASTIM)
Injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
GRANIX® (tbo-filgrastim) injection, for subcutaneous use
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving human granulocyte colony-stimulating factors and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following potential serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [*see Warnings and Precautions (5.1)*]
- Acute Respiratory Distress Syndrome [*see Warnings and Precautions (5.2)*]
- Serious Allergic Reactions [*see Warnings and Precautions (5.3)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Capillary Leak Syndrome *[see Warnings and Precautions (5.5)]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.6)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

6.1 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 clinical practice.

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^6/L) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

Additional Adverse Reactions

Other adverse reactions known to occur following administration of human granulocyte colony-stimulating factors include myalgia, headache, vomiting, Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis and thrombocytopenia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of GRANIX in pregnant women. In animal reproduction studies, treatment of pregnant rabbits with tbo-filgrastim resulted in increased spontaneous abortion and fetal malformations at systemic exposures substantially higher than the human exposure. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In an embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

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

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

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GRX-40580 January 2015

This brief summary is based on TBO-004 GRANIX full Prescribing Information.

Shaping the Future of Immuno-Oncology

ABOUT THE EDITOR IN CHIEF

JOSEPH ALVARNAS, MD

Dr Alvarnas is associate clinical professor and director of medical quality and quality, risk, and regulatory management, City of Hope, Duarte, CA.

For decades, cancer treatment largely consisted of using varying combinations of surgery, radiation therapy, and chemotherapy. Throughout this period, research focused on using each of these therapeutic modalities in increasingly aggressive ways in an attempt to cure more patients. Unfortunately, the use of increasingly intensive chemotherapeutic regimens and aggressive surgical procedures failed to provide proportionate improvements in patient outcomes or overcome the enhanced toxicity and costs of these approaches.[1]

As early as the 1970s, however, investigators began to postulate that the immune system might be able to provide a fourth therapeutic avenue for improving cancer care outcomes. Based upon the early experience with interferon, in 1980, a *Time* magazine cover story heralded a new era of "magic bullets" for treating cancer.[2] Whereas the initial public enthusiasm for interferon quickly waned in the face of marginal cancer response rates and significant treatment-related toxicities, the belief persisted that immunologically-based therapeutics could significantly impact cancer. This belief was reinforced by data showing that immuno-stimulatory cytokines, like interleukin-2, could produce significant tumor responses in chemotherapy-refractory diseases (like renal cell carcinoma and metastatic melanoma) and that donor-derived T-cell infusions could produce significant disease responses in patients who had relapsed following prior allogeneic hematopoietic cell transplant.[3] The subsequent finding that 2 monoclonal antibody-based therapeutics could dramatically improve response rates and overall survival for patients with aggressive B-cell non-Hodgkin lymphoma (rituximab) and *Her2-neu*–expressing breast cancer (trastuzumab), respectively, firmly embedded immuno-oncological therapeutics within the anticancer armamentarium.[4]

Over the past 15 years, the number and diversity of immunologically-based anticancer agents have increased dramatically. Immuno-oncological therapeutics now include numerous monoclonal antibodies, monoclonal antibody–drug conjugates, bispecific antibody–like moieties, and gene-engineered cytotoxic T-cells. The armamentarium of these agents is growing rapidly. Patients affected by refractory-aggressive cancers, like acute lymphoblastic leukemia, now benefit from the availability of potent, highly-effective immunotherapeutic agents, with the promise of more to come.[5,6] These novel therapeutics, however, have provoked a number of challenging questions: how do we best use them? How do we sequence them with existing treatment regimens? How do we more carefully select those patients who might benefit from treatment? How do we use these agents in an economically sustainable way? Moreover, how do we ensure equitable patient access to these game-changing therapeutics?

This issue of *Evidence-Based Oncology* looks carefully at the immuno-oncology (I-O) revolution and its attendant issues. Bruce Feinberg, DO, of Cardinal Health provides his perspective on advances in I-O and the evolution of immunologically-based therapeutics and their clinical use. Suzanne Wait, PhD, of The Health Policy Partnership Ltd, United Kingdom, provides a policy perspective on how to ensure equitable patient access to these therapeutics. Carina Dolan, PharmD, of Vizient Inc, shares the findings of a panel discussion on how these agents can be used in a patient-centered, economically-sustainable way.

In his recent State of the Union address, President Obama spoke of his commitment to pursuing a new "moon shot" for achieving a cure for cancer. Although rhetorically, the image of a "moon shot" may embolden us as a nation to invest more aggressively in pursing new technical avenues in the war on cancer, the growing availability of effective immunotherapeutic agents shows us that the solutions are much closer to home. I-O is the fruit of decades of investment in immunology and cancer research that has translated into meaningful improvements in many patients' hopes for a cure for their cancer. Ensuring that we continue to develop these agents and make best practice–based use of existing agents is a far more prosaic, but essential, next step. **EBO**

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Where Does Immuno-Oncology Fit in a Value-Based Care Delivery Model?

BRUCE FEINBERG, DO

ABOUT THE AUTHOR

CardinalHealth

BRUCE A. FEINBERG, DO

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A year ago, the editors of *Evidence-Based Oncology* dedicated an issue to the rapidly expanding field of immuno-oncology (I-O). I was among the authors published in the issue with an article focused on challenges to stakeholder adoption of the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) antagonist class of drugs.[1] I concluded that article with the following thought: "The potential for broad antitumor activity agnostic to histology or complex genotype, rapid onset of clinical response, the relatively low toxicity profile of PD-1 and PD-L1 antagonists, and the possibility of T-cell memory resulting in durable responses differentiate this third generation of I-O agents from the preceding ones. We must remember, however, that these agents have toxicities, are prohibitively expensive, and are not currently curative. Informed stakeholders are likely to carefully weigh all these factors in their decision to adopt I-O drugs."

One year later, the challenges to stakeholder value remain at the forefront of the discussion. An additional year's knowledge and experience has resulted in:

- Expanded treatment areas
- FDA-approved indications beyond salvage therapy to first-line metastatic and adjuvant treatment
- Validation of I-O drugs in combination
- The possibility of curative treatment in select patients with metastatic disease.

Our increased understanding of immune regulation is defining a taxonomy of I-O that thus far includes checkpoint blockade, chimeric antigen receptor T cells (CAR-T cells), and vaccines. Clinical observations have created challenges to longstanding research paradigms, as phenomenon like "pseudoprogression" complicate the response evaluation criteria in solid tumors during trial design. Advances made in the field in 2015 have greatly expanded our understanding of I-O and added more complexity to its value assessment.

2015: A REMARKABLE YEAR FOR I-O

One might say that I-O was not just the oncology story but rather the medical story that went viral in 2015. Of the 10 most-read Medscape stories by oncologists in 2015, 5 were I-O–related. I-O stories were also 3 of the top 5 read by dermatologists on *NEJM* Journal Watch. Medscape's top stories for the American Society of Hematology and San Antonio Breast Cancer Symposium (SABCS) included I-O.

The interest among oncologists, hematologists, dermatologists, other physicians, and the media might be explained by the prevalence of I-O research. A search on the American Society of Clinical Oncology (ASCO) Universityweb site suggests that more than 10% of the abstracts, posters, and presentations published by ASCO in 2015 were I-O–related, with search terms yielding astounding numbers: PD-1 = 846, PD-L1 = 498, and CTLA-4 = 101. The *New England Journal of Medicine* (*NEJM*) has published articles on I-O clinical trials with positive results in melanoma, lung cancer, colon cancer, Hodgkin's disease, and renal cell cancer. If we extend the I-O discussion beyond *NEJM* and include CAR-T cells and vaccines, the list of published articles in 2015 for diagnoses favorably impacted by I-O therapy expands to include leukemia, lymphoma, glioblastoma multiforme (GBM), breast cancer, ovarian cancer, sarcoma, and more. At least one positive I-O trial was published in a high impact value medical journal and covered by major media outlets every month in 2015.

At the onset of 2016, the I-O market (excluding vaccines) is characterized by 3 marketed drugs while the pipeline features 37 drugs in clinical development; these include 2 cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), 9 PD-1/PD-L1, and 26 novel immune checkpoint inhibitors. The impact of I-O on the treatment of cancer is of tsunami proportions—by some estimates, half of all current cancer clinical trials involve some form of immunotherapy.

EFFICACY

Efficacy assessments that consider the time, depth, and duration of response remain the most critical determinant of value. Contrary to traditional cytotoxic chemotherapy, objective response rate (ORR) (both complete and partial) has not been the most remarkable feature of I-O treatment. This may be further complicated by what has been termed "pseudoprogression," or the early and transient apparent increase in bi-dimensional tumor mass due to an inflammatory infiltrate. Originally described in the setting of GBM, it is now routinely observed in melanoma and lung, so much so that multiple web videos can be found on a YouTube search in which prominent I-O researchers explain the phenomenon to patients and physicians unfamiliar with the class of drugs. Rather than objective bi-dimensional radiographic response, it is the rapidity of clinical benefit and, more importantly, the durability of tumor control and increase in overall survival (OS) that differentiates I-O from prior therapeutic drug classes.

One might say that [immuno-oncology] was not just the oncology story but rather the medical story that went viral in 2015.

Treatment of metastatic disease is rarely curable, but in 2015, we learned that in the continued follow-up of melanoma patients treated with ipilimumab, approximately 20% of responders had survived for several years; more remarkable is that some patients are now 10 years without recurrence—truly raising the possibility of cure.[2] Flattened slopes at the tail of survival curves have been seen in many of the I-O trials, but their significance remains uncertain given the short follow-up time in nearly all reported trials. Cancer researchers addressing OS have for years posited, "It's all about the tail of the curve." This common refrain has never been more compelling than with I-O; the possibility of cure may be the most provocative aspect of I-O value assessment.

Efficacy across a wide range of histologies was also established in 2015. Two checkpoint blockade drugs gained FDA approval for non–small cell lung cancer (NSCLC). The first was based on a study showing that patients previously treated with chemotherapy who received nivolumab had a 1-year OS of 42% compared with a 24% one-year survival rate for patients treated with docetaxel, a standard chemotherapy drug.[3] Similarly significant results were noted in a study of pembrolizumab in NSCLC.[4] Demonstration of superiority of I-O to standard salvage treatment was also confirmed in 2015 for renal cell carcinoma (RCC)[5] and for Hodgkin's disease.[6] Additionally, in a triumph of bench-to-bedside research to be discussed a bit later, significant anti-tumor activity was demonstrated in selected patients with colon cancer.[7] Three abstracts presented in 2015 at SABCS and at the annual meeting of the American Association for Cancer Research confirmed activity of I-O in the difficult-to-treat histology of triple negative breast cancer.[8,9,10] The possibility of I-O having first-line indications for breast, lung, and colon cancer seems just over the horizon.

Rare, Refractory Tumors

Some of the phase 2 clinical trials published in 2015 warrant specific mention, as they raise the possibility of new treatment paradigms for rare and refractory tumors. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma published in *NEJM* is just such a study.[6] Of the 23 study patients, 78% were enrolled in the study after a relapse following autologous stem-cell transplantation and 78% after a relapse following treatment with brentuximab vedotin. Grade 3 drug-related adverse events (AE) occurred in 22% of patients, but no grade 4 AEs were reported. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression-free survival (PFS) at 24 weeks was 86%.

In another study, a relatively rare and refractory tumor, sarcoma, was the I-O target. The study, Human Epidermal Growth Factor Receptor 2 (HER2)-Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-

Positive Sarcoma, published in the *Journal of Clinical Oncology*,[11] is the first published trial that evaluated the activity of CAR-T cell treatment in a solid tumor.[11] Nineteen patients with HER2-positive tumors (16 osteosarcomas, 1 Ewing sarcoma, 1 primitive neuroectodermal tumor, and 1 desmoplastic small round cell tumor) received HER2–CAR-T cell infusions, which were well-tolerated with no dose-limiting toxicity. Of 17 evaluable patients, 4 had stable disease for 12 weeks to 14 months. Three of these patients had their tumor removed, with 1 showing ≥90% necrosis. The median OS of all 19 infused patients was 10.3 months (range, 5.1 to 29.1 months).

Efficacy beyond salvage therapy and first-line metastatic disease was established in 2015 with the first I-O drug to have an adjuvant indication in its label. The FDA approved an expanded label indication for ipilumimab based on results from EORTC 18071, a randomized, double-blind trial conducted in 951 high-risk patients with stage 3 melanoma who had undergone a complete lymph node dissection. Recurrence-free survival was significantly higher in the ipilimumab group compared with the placebo group at 1 year (63.5% vs 56.1%), at 2 years (51.5% vs 43.8%), and at 3 years (46.5% vs 34.8%). Patients in the ipilimumab group also were 25% less likely to experience melanoma recurrence than those in the placebo group (HR, 0.75; 95% CI, 0.64-0.90; $P = .0013$). Median recurrence-free survival was also better in the ipilimumab group (26.1 vs 17.1 months). Forty-nine percent of participants taking ipilimumab had a recurrence after an average of 26 months compared with 62% percent of those receiving a placebo. The analysis of OS data is pending.[12]

I-O VERSUS TARGETED THERAPY

Whereas efficacy may be measured in the absolute criteria of a clinical trial's primary endpoints (eg, PFS, OS, etc), value is both more complex and relative as a drug or regimen assessed in the context of a broad therapeutic arsenal—especially a rapidly expanding arsenal. I-O is not only competing against the standard of care in trial design, but also against other novel therapeutics, the most compelling of which are the growing number of precision/targeted therapies. These new therapeutic classes (I-O and targeted therapies) are being tested against standards of care, with respective head-to-head testing likely years off. However, stakeholder value assessments will not patiently wait for such clinical research. They will more likely use new tools, such as value calculators, to make the cross trial comparisons that health economists have historically refused to validate.

Such comparisons may be done to compare the value of I-O versus targeted therapy in RCC using similarly designed clinical trial results published in 2015.[5,13] Nivolumab and cabozantinib (an oral, small-molecule tyrosine kinase inhibitor that targets the vascular endothelial growth factor receptor, MET, and AXL) were each compared against everolimus in randomized trials of advanced RCC. OS was longer (25 months vs 19.6 months) and fewer grade 3 or 4 AEs occurred with nivolumab (19%) than with everolimus (37%). PFS was longer with cabozantinib (7.4 months) than with everolimus (3.8 months). The conclusion of an accompanying editorial stated: "Without a significant overall survival benefit and with significant side effects necessitating dose reduction in 60% or more of patients, cabozantinib will not precede nivolumab in the therapeutic sequence."[14]

COMBINATION THERAPY

Researchers are also studying how checkpoint inhibitors can most effectively be used in combination with each other or other cancer therapies. For example, the results of a 2015 study of 945 patients with previously untreated metastatic melanoma showed that nivolumab alone or combined with ipilimumab produced longer PFS than ipilimumab alone.[15] For patients with tumors positive for expression of PD-L1, there was no difference in the overall median survival rate for nivolumab or nivolumab and ipilimumab combined. However, among patients with PD-L1–negative tumors, PFS was longer with the combination therapy than with nivolumab alone. Combination therapy will likely extend beyond combining CTLA-4 and PD-1 class drugs.

A boost in the I-O response with enhanced tumor immunogenicity has laid the groundwork for combination trial design. One such observation is that an immunotherapy drug is more likely to be effective in tumors that harbor greater number of mutations. Research suggests that tumors with multiple genetic mutations create more antigens that attract T cells.[16] One study determined that 78% of patients with colorectal tumors with mutations of the mismatch repair gene had PFS at 20 weeks after treatment with pembrolizumab compared with only 11% of patients with colorectal tumors without the mutation.[7] The theory is that a mutation in the mismatch repair gene results in a greater number of mutations, which itself results in more antigens on the tumor cells that attract T cells. Another study found that patients with NSCLC with high levels of mutations in their tumors linked to smoking were more likely to have a durable clinical response to nivolumab than patients with a low level of mutations in their tumors: 73% compared with 13%.[17]

Related research suggests the both radiation and chemotherapy may enhance immunotherapy response due to the DNA damage that the treatments cause. This possible relationship has been demonstrated in murine models and has been extended to a variety of clinical trials. Although the standard notion of whole-body radiation therapy is that it is immunosuppressive, there is growing evidence toward the contrary for focal radiation therapy.[18] The potential of chemotherapy and radiation therapy to enhance immunogenicity will become an increasing focus of I-O clinical research.

TOXICITY

The value-based care assessment is a 3-legged stool that cannot stand on efficacy alone, even when efficacy is supported by such compelling biology. Toxicity is the second leg of the stool and warrants increasing attention as our industry shifts philosophically toward a more patient-centered approach to medicine. Although ipilimumab achieved primary endpoints, and was granted FDA label expansion for stage 3 melanoma, the toxicity observed in the trial is noteworthy. The most common side effects reported in this study were rash, diarrhea, fatigue, itching, headache, weight loss, and nausea. AEs led to discontinuation of treatment in 245 (52%) of 471 patients who started ipilimumab, including 182 (39%) during the initial treatment period of 4 doses. In addition, 5 patients (1%) died due to drug-related AEs.[12] Such toxicity is also a profound concern for combination trials of CTLA-4 and PD-1 drugs as observed in the melanoma trial—36.4% patients in the combination group, 14.8% in the ipilimumab group, and 7.7% in the nivolumab group dropped out because of adverse drug reactions. One patient in the nivolumab study died from drug-related AEs, as did 1 patient in the ipilimumab group.[16]

Although efficacy and toxicity results are compelling for PD-1 and PD-L1 immunotherapy, cost weighs heavily on the value assessment.

PD-1 and PD-L1 drugs have clearly demonstrated less toxicity, but unique features of their toxicity may still impede adoption. Appropriate provider and patient education of the heretofore uncommon autoimmune complications associated with I-O is prudent, with the following caveats often noted by researchers:

- AEs associated with checkpoint-blockade immunotherapy can occur during both the treatment phase and after treatment
- AEs can present insidiously, but if recognized early, they can be reversed successfully in most cases
- Delay in intervention can result in significant morbidity, even mortality
- Judicious use of immune suppression appears to be the cornerstone of AE management
- Appropriate antibiotic prophylaxis should be considered for patients on long-term immune suppression to prevent opportunistic infections.[19]

COMPANION DIAGNOSTICS AND COST

Although both the efficacy and toxicity results are particularly compelling for PD-1 and PD-L1 immunotherapy, cost weighs heavily on the value assessment. I-O treatment courses routinely run in the 6 figures for single agents. Given the less predictable nature of objective bi-dimensional tumor shrinkage as a response criteria, stakeholders responsible for this cost are keenly interested in early identification of nonresponders. Such interest places I-O at the intersection of precision medicine as molecular profiles are sought to differentiate probable responders from likely nonresponders. The level of circulating PD-L1 has been proposed as a molecular target that differentiates potential treatment candidates, and research published in 2015 sheds further light on this important topic.[4]

Garon et al used immunohistochemical analysis to assess PD-L1 expression in the tumor samples of 495 patients with NSCLC receiving pembrolizumab. Response was assessed every 9 weeks by central review, and results were reported as the percentage of neoplastic cells that stained for membranous PD-L1 (proportion score). In the overall patient population, the ORR was 19.4%, median PFS was 3.7 months, and median OS was 12 months; however, among patients with a proportion score of at least 50%, the ORR was 45.2%, median PFS was 6.3 months, and median OS was not reached at the time of analysis.[4]

Whether used to differentiate responders from nonresponders, as in Garon's study or to determine benefit of combined versus monotherapy, as in Larkin's observations, a confounding observation is that although low PD-L1 expressors may be less likely to respond, those that do respond often have remarkable OS curve tails. One explanation for such results has been the lack of standardization of PD-L1 assays.

Pharmaceutical companies have independently established partnerships with diagnostic companies to co-develop PD-L1 assays. Individual assays differ in the context of specific immune

(continued on **SP46**)

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DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (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. 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.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

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%) occurred in patients treated with 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, 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. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

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®. 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.

IMBRUVICA® (ibrutinib) is the first and only FDA-approved therapy for use in patients with Waldenström's macroglobulinemia (WM)

IMBRUVICA® is approved for use in 4 indications

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.

Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia* (57%, 52%, 43%), neutropenia* (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia* (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%†, NA‡), bruising (30%, 12%†, 16%†), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%†, 22%†).

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

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

The most common Grade 3 or 4 non-hematological 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), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse events.

Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid co-administration 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 review the Brief Summary of full Prescribing Information on the following pages.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

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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: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) 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 (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.

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 26% of patients. *[See Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

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%) occurred in patients treated with 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, 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. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Second Primary Malignancies: Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

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.

Clinical Trials Experience: 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)

System Organ Class	Preferred Term	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
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

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

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
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: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

**One patient death due to histiocytic sarcoma.*

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	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.

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

System Organ Class ADR Term	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				
Fatigue	28	2	30	2
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

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 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

System Organ Class	Preferred Term	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

IMBRUVICA® (ibrutinib) capsules

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
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 terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 8: 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.

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.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: 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: Pregnancy Category D *[see Warnings and Precautions].*

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. 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.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral 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 post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL 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 animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Nursing Mothers: It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

(continued from **SP41**)

checkpoint inhibitors and their unique pharmacology, biological hypothesis, clinical development, and registration strategy.[19] The most critical difference between these tests is the definition of PD-L1 positivity, which depends on the cells, tissue compartments, and staining thresholds for the PD-L1 assay. Consequently, PD-L1 assays are not currently interchangeable, results cannot be compared, and the broad application of PD-L1 as a predictive and prognostic diagnostic test remains lacking.[20]

CONCLUSION

2015 was a remarkable year in the development of I-O as a foundational therapeutic in the cancer arsenal. Stakeholder adoption of I-O is no longer a question of "if," but "when." Who will be treated with "what" types of cancer in "which" stage and for "how" long remain unanswered questions at the start of 2016. How I-O will further alter treatment paradigms and, as a result of those alterations, impact the global cost of care of the treated patient will be critical to the value assessment process. Traditional clinical research seems ill-designed to address the many questions surrounding I-O value assessment, necessitating a rapid expansion of health economics and outcomes research in this nascent field. **EBO**

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Access to Immuno-Oncology Therapies—European Policy Perspective

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Immuno-oncology (I-O) therapies are expected to transform the treatment landscape for many forms of advanced cancer in years to come. The pace of development of these agents is remarkable, with multiple agents targeting different immune mechanisms being investigated for the treatment of some of the most common and most difficult-to-treat cancers.[1]

Understandably, patient groups are urging policy makers to make these innovative treatments available to patients as quickly as possible. However, the price tag for these new drugs is high, and policy makers have to find ways to accommodate these new agents within financially constrained healthcare budgets.[2]

It was in light of these political realities that the European Expert Group on Immuno-Oncology, an independent network of patient representatives, cancer clinical experts, scientists, and policy makers, issued the Policy Action Framework for Immuno-Oncology in 2014,[3] with the aim to guide policy makers toward concrete steps that may create an enabling policy environment for rapid and appropriate access to I-O drugs across Europe.[4] The Framework proposed 5 concrete steps that policy makers may take to foster access to I-O treatments (**FIGURE 1**). One year after its publication, we look at how some of these proposals have unfolded across Europe.

MORE FLEXIBLE, AND MORE EFFICIENT, REGULATORY AND ACCESS PATHWAYS

The science of I-O is continually evolving, and experts have called for adaptation to clinical development pathways[5] and trial endpoints[6,7] to best reflect the clinical patterns observed with I-O agents and capture their full benefits.[8] Experts have also called for greater flexibility in regulatory pathways for promising new cancer drugs, including I-O agents, to ensure they are made available to patients as quickly as possible.[9] With this goal in mind, the European Medicines Agency (EMA) is piloting a number of adaptive licensing schemes, which allow approval decisions to be based on an evolving set of data for drugs that show promising results in early phase clinical trials, with an ultimate aim to make them available to patients more quickly.[10,11]

Accelerating the drug approval process, however, is only one part of the access equation. In Europe, although drug approval is centralized with the EMA, each country maintains jurisdiction over the financing of its healthcare system. Access frameworks vary considerably across the member states, with some including a formal health technology assessment (HTA) and others relying on pricing and reimbursement mechanisms. Each access process also has its own evidentiary requirements. As a result, there are significant differences in the time it takes new drugs approved by the EMA to become available to patients in different European countries.[12]

The most important recommendation of the Action Framework is that evaluation of [immuno-oncology] drugs be based on what matters most to patients: long-term, quality survival.

These disparities in access have drawn considerable attention from patient groups and politicians alike.[13] In 2012, a European Commission Directive reduced the limit for the duration of pricing and reimbursement process-

FIGURE 1. Recommendations of the Policy Action Framework on Immuno-Oncology

es in member states from 180 days to 120 days.[14] The European Network for Health Technology Assessment has also tried to harmonize evidence requirements for new drugs across countries.

Despite these efforts, significant delays in access still remain in many countries, particularly in Eastern Europe.[12] This is illustrated in the case of trastuzumab for the treatment of metastatic cancer in **FIGURE 2**.[15]

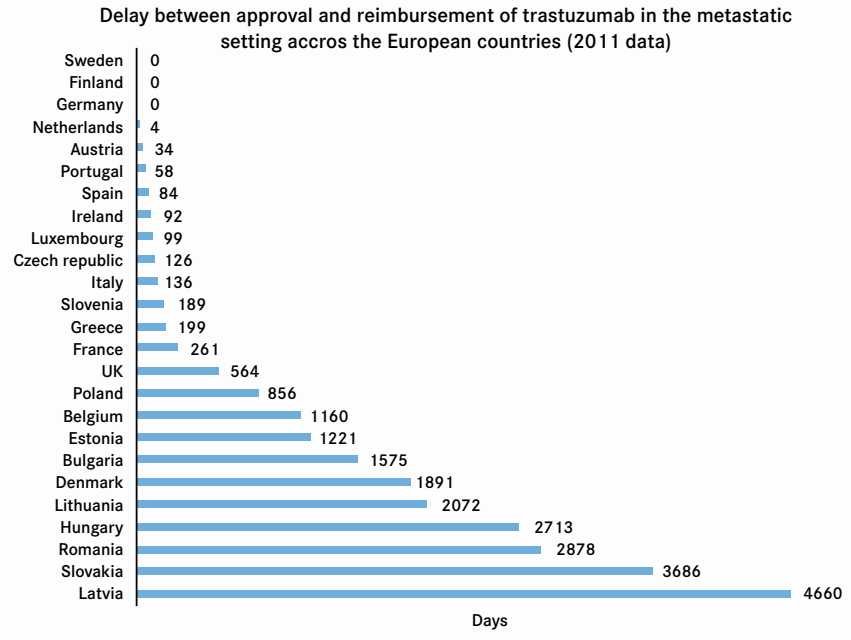
National-level reimbursement or coverage is critical; however, it does not necessarily result in patients having access to new drugs, as funding decisions are increasingly decentralized to the regional and sometimes the individual hospital level.[2] Inequities in access to all aspects of cancer care are widespread and are potentially increasing with the recent austerity measures introduced in a number of European countries.[13] Out-of-pocket payments are also increasing in light of limited public funding for new drugs in many countries, posing important ethical questions for societies whose healthcare systems are historically based on principles of solidarity and universal access.

INTEGRATING CANCER INNOVATIONS INTO FUNDING STREAMS AND TREATMENT PATHWAYS

To secure access to innovative, but high-priced, drugs, a number of countries have chosen to create special funds to finance these drugs outside of the mainstream drugs budget. In Italy, an "innovation fund" exists, which grants potentially innovative drugs preferential treatment in terms of adoption and pricing. The fund is partially financed from savings from expired patents on older drugs. The United Kingdom created the Cancer Drugs Fund (CDF) in 2011 in response to significant pressure from patient groups and the general public to provide access to several cancer drugs that were already available in other European countries. The CDF has thus far allowed up to 74,000 cancer patients access to drugs that were either not considered suitable for public funding by the National Institute for Health and Clinical Excellence (NICE) or that were still awaiting review by the Institute and not yet available for use in patients. However, NICE has been criticized on many grounds and its future remains uncertain.[16,17]

Another trend being extended to I-O agents is the increased adoption of managed-entry agreements (or risk-sharing schemes)[18] between payers and drug manufacturers. The taxonomy of these agreements varies. However, they are all based on the principle of conditional access: payers may grant access to a new drug based on a rebate or price discount, with the expectation of achieving a certain level of performance or outcomes (performance-linked payments) or while waiting for future evidence of the drug's impact on clinical practice (coverage with evidence). Thus, access decisions are no longer a one-off, but become dynamic and evolve over time. Under the conditional reimbursement scheme in the Netherlands, for example, a price for certain innovative drugs prescribed in hospitals is set based on international reference prices, and conditional access is given up front.[19] Outcomes, including patient

FIGURE 2. Delay in Access to Trastuzumab in Metastatic Breast Cancer Across Europe, 2011 Data



SOURCE: W.A.I.T. Indicator

adherence and cost-effectiveness, are then tracked for 4 years in select care settings against pre-established criteria. If, after 4 years, these criteria are not met, manufacturers must retroactively pay back the associated drug sales to the healthcare system.[20]

The above schemes may be seen as a pragmatic way for payers to grant rapid, albeit limited, patient access to potentially innovative drugs while they wait for real-world data to be collected that can demonstrate the effectiveness of these new drugs in clinical practice.[21] However, risk-sharing schemes are often adopted at a local or regional level and can be complex and resource-intensive to implement, making widespread implementation difficult.[21] Also, no evaluation of the impact of existing schemes currently exists.[18] As a result, it remains largely unknown whether existing schemes have improved access and outcomes for patients or led to overall long-term savings for payers.

MEASURING WHAT MATTERS TO PATIENTS

The most important recommendation of the Action Framework is that the evaluation of I-O drugs be based on what matters most to patients: long-term, quality survival.[6] Recently, the American Society of Clinical Oncology and the European Society for Medical Oncology have focused their attention on how to best measure benefits of new cancer drugs within clinical trials, proposing new scales that may form the basis for evaluations of all new cancer drugs.[22-24] However, these scales are insufficient in themselves to assess the "value" of new drugs, as they do not include any consideration of costs, patient preferences, or quality of life.[25] Thus, how they may help improve current methodologies used in access decisions—for example, by HTA agencies—still remains to be seen.

The evaluation of I-O drugs should be based on their impact—clinical and economic—on the entire cancer pathway and care experience for patients.[25] For example, the increased drug acquisition costs of I-O drugs should be weighed against their impact on the whole care pathway, such as reducing the need for hospitalization or other types of care. Also, the potential for long-term survival—in terms of reduced morbidity, extended life, and enhanced productivity over many years—should be factored into the evaluation of all new I-O agents.

We need to find equitable and financially sustainable ways of integrating the most valuable innovations in cancer care into our treatment pathways and healthcare budgets.

In conclusion, with ever-present pressures on our healthcare system, researchers, industry, regulatory agencies, and payers need to work together to try to continually improve outcomes for cancer patients despite financial pressures. To achieve this, we need to find equitable and financially sustainable ways of integrating the most valuable innovations in cancer care into our cancer plans, treatment pathways, and healthcare budgets. **EBO**

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Patient Access to Immuno-Oncology Agents—A US Policy Perspective

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Developments in the field of immuno-oncology (I-O) have ushered in a new era of hope in cancer care. This new concept has forced scientists and clinicians to think beyond the organ of origin of the tumor and wonder about the dynamic interaction between the tumor and its environment.

A significant advantage of I-O, unlike chemotherapy or some of the targeted agents, is the lasting memory created by immunomodulatory drugs on the individual's immune system. The idea of targeting the host's immune system evolved from an improved understanding of cancer—the realization that cancer is not an individual disease arising from a single, clonal cell harboring mutations—but rather, cancer can be defined as multiple diseases with a systemic rather than a clonal origin.

THE HISTORY

Pioneering work by cancer surgeon, William B. Coley, who demonstrated the importance of activating the immune system in a cancer patient (by injecting a live culture of bacteria into the tumor), generated clues leading to the important discovery of the immune system's role in cancer.[1] Subsequent animal models documented tumor rejection, rather than tumor immunity, which misled scientists resulting in a loss of faith in tumor immunology, until the development of the syngeneic mouse model—where tumors were derived from mice with the same genetic background. This subsequently laid the groundwork for the important role of immune surveillance in cancer.[2]

The entire immune system participates to help defend the body from the tumor; this includes innate immunity initiated by a cacophony of natural killer cells or NK cells, macrophages, dendritic cells, T- and B cells, and cytokines. The adaptive immune system, which includes the $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and antibodies, help with the complete elimination of the tumor and help develop the body's immune memory against tumor components to prevent tumor recurrence.[3]

TODAY

The armamentarium of immune defense against cancer has been growing: monoclonal antibodies, tumor vaccines, CAR-T or chimeric antigen receptor-T cells, and the new stream of immune activators. An overview of recent progress with the new I-O agents, including programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), can be found on **SP40** of this issue. Overall, these agents have been deemed game changers in oncology care, alone or in combination, over the standard of care.

So far, FDA approvals have been restricted to melanoma, non–small cell lung cancer, and renal cell carcinoma, but numerous studies are testing these agents in a variety of solid, as well as, liquid tumors.

AND THE ISSUE SEEMS TO BE?

There's little question that the cost of these drugs, and the resulting copayments and high deductibles, will be a barrier to patient access. Over the years, the oncology drug cost increase has had a steep slope. Given that some of the new drugs provide significant survival outcomes (months, instead of weeks); however, cancer drugs averaged at less than $10,000 annually prior to 2000, while 12 of 13 anticancer agents approved in 2012 were priced over $100,000 annually.[4] Ipilimumab, a CTLA-4 inhibitor developed by Bristol-Myers Squibb and approved for treatment of patients with advanced melanoma, costs $130,000 for a 12-week course. Nivolumab, developed by the same company is estimated to cost $150,000 annually ($12,500 per month). Pembrolizumab, developed by Merck, costs the same.[5]

High Patient Cost-Sharing

Financial toxicity, in oncology, is not a new phenomenon. In the December 2015 issue of *Evidence-Based Oncology*, we heard from patients, patient advocacy groups, and health policy experts about the economic impact of cancer, in addition to the physical and emotional cost, on the patient and their family. A recent study in 100 insured patients, who were already receiving treatment for multiple myeloma, between August 2014 and January 2015, found that:

- 59% of patients were surprised by the cost of their care
- 71% felt a small amount of financial burden
- 36% applied for assistance to pay their bills[6]

Another study, investigating the financial outcomes of 550 colon cancer patients, found nearly 40% of patients reported experiencing at least one of the following, after cancer diagnosis:

- Borrowing money from family or friends
- A minimum of 20% income decline
- Accrual of debt
- Selling their primary residence[7]

HOW CAN WE IMPROVE PATIENT ACCESS TO THESE TREATMENTS?

The cost issues are real, but so is the value that the new anticancer treatments bring to the table. If not "cure," I-O, at the least, has the potential to transform the discussion on cancer outcomes into one of a chronic disease, similar to what the newer treatments have done for hepatitis C.

We need a multi-faceted approach to help patients gain access to I-O and future revolutionary oncology treatments. To guide policy changes, policy makers in Europe have formed the European Expert Group on Immuno-Oncology to encourage rapid and appropriate access to I-O therapies across Europe. You can read more on the group's proposed framework on page **SP47**.

Here are a few proposed changes that could eliminate barriers to patient access to I-O, within the United States:

Clinical

1. Surrogate Markers

Need to develop surrogate intermediate markers in clinical trials that can predict long-term survival outcomes.

2. Adaptive Trials

Wider use of adaptive clinical trials that have interim analysis points, to balance safety and efficacy while accelerating patient access to life-changing medications.

a. Need for an early "adaptive licensing" plan that matches adaptive frameworks for reimbursement and health technology assessment decisions. Adaptive licensing places emphasis on early access, post-authorization, and real-world effectiveness studies.[8]

3. Trial Design

a. Head-to-head trials between competitor products could yield more value, especially in the case of drugs that yield improved outcomes over the standard of care.

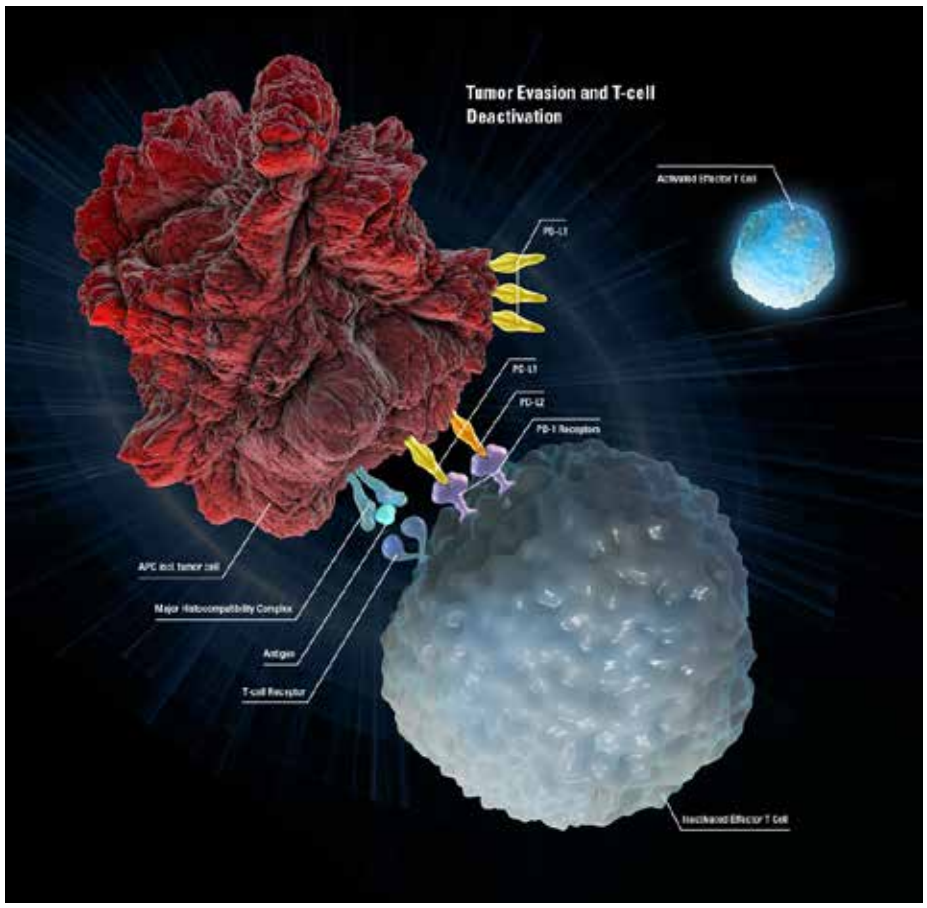
b. Another important point, with respect to trial design, is to make the trials inclusive and diverse, with respect to the patient population.

c. There is also a need to identify predictive biomarkers to choose the right patient population for treatment with a specific agent.

4. Real-World Evidence

Once a product is launched, real-world evidence should be collected and ana-

(continued on **SP51**)



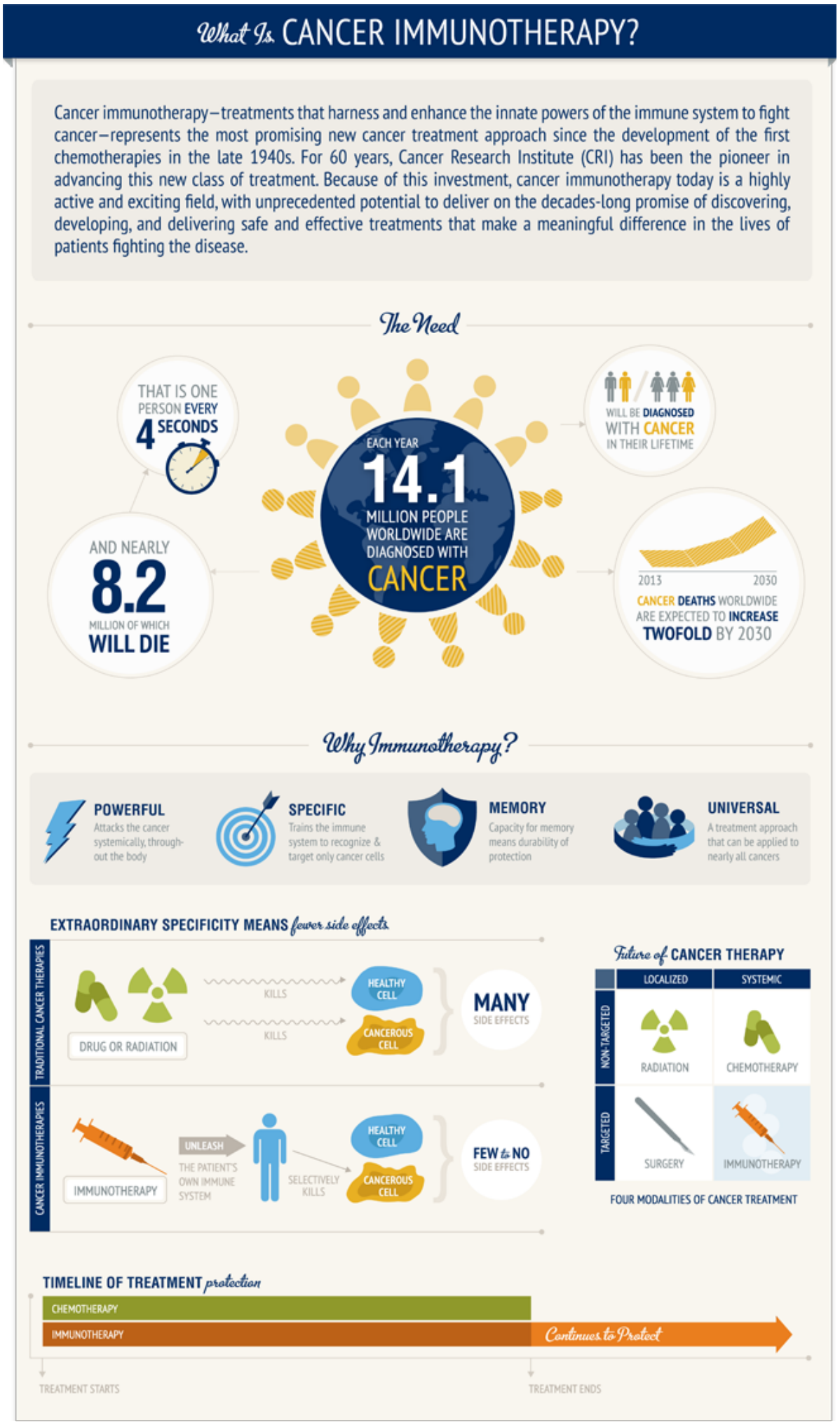
Mechanism of action of immuno-oncology agents.
SOURCE: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. All rights reserved.

While European policy makers grapple with developing a framework that can ensure patients receive appropriate and sustainable access to new immuno-oncology (I-O) agents, efforts are ongoing in the United States to eliminate barriers for patient access to I-O treatments. The Association of Community Cancer Centers, for example, has launched the Institute for Clinical Immuno-Oncology (ICLIO) to raise I-O awareness among community oncologists. ICLIO, which held its first annual meeting in Philadelphia in 2015, presents an ideal platform for payers, oncologists, patient advocacy groups, reimbursement and patient assistance specialists, and the pharmaceutical industry to share challenges and possible solutions for efficient adoption of I-O drugs.

With the cost of these agents being an important barrier for clinical adoption, establishing the value of I-O to patients and the healthcare system as a whole could flip the switch.

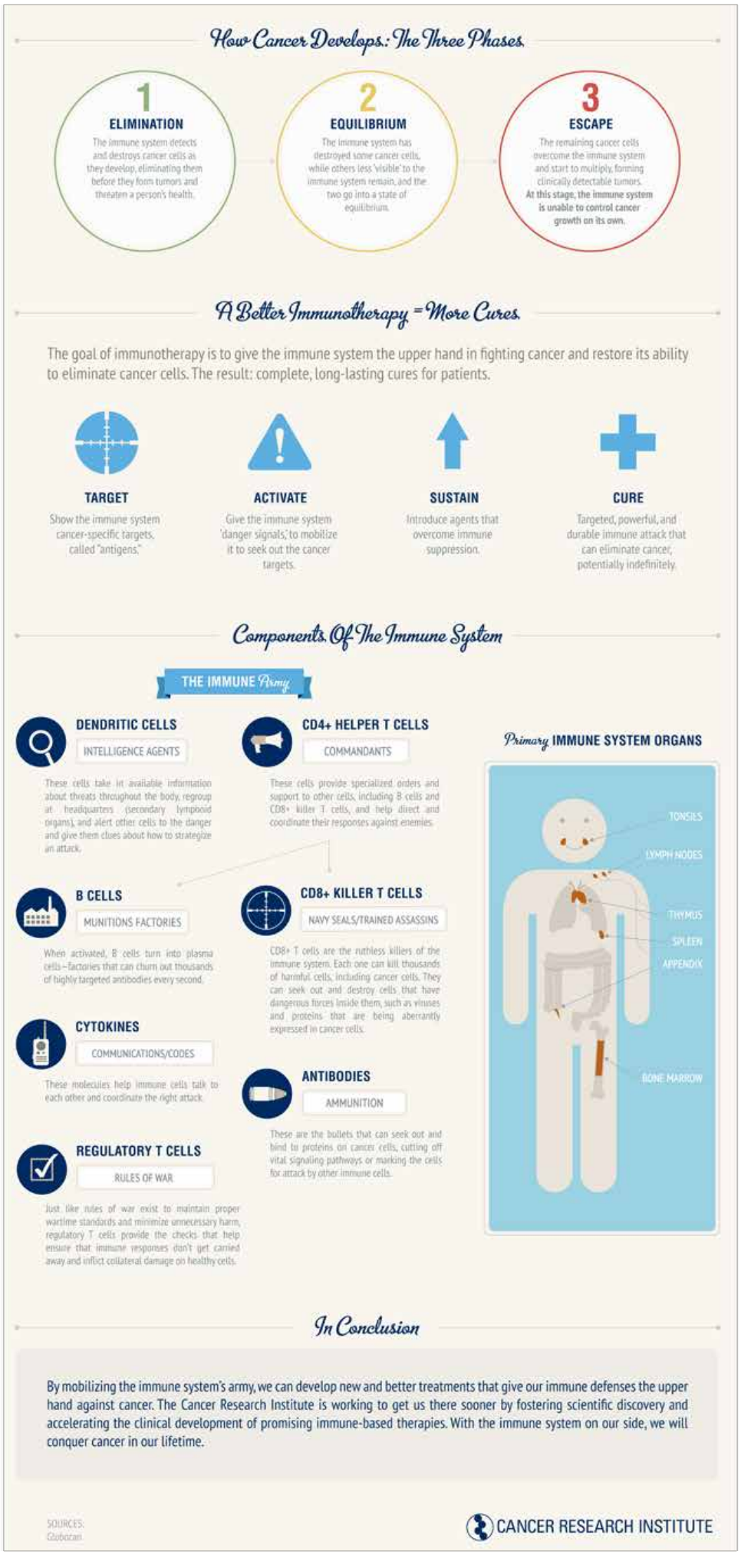
SOURCE: Bristol-Myers Squibb.

SOURCE: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. All rights reserved.



SOURCE: Cancer Research Institute

THE AMERICAN JOURNAL OF MANAGED CARE



SOURCE: Cancer Research Institute

(continued from **SP49**)

lyzed to understand outcomes in the larger population. This information should then be made easily accessible (eg, by updating information on the trial database ClinicalTrials.gov) to healthcare providers and payers to help them develop a prescription and coverage strategy, respectively.

5. Care Coordination and Clinical Trials

There's a definite need for rapid referrals and connectivity between physicians. Additionally, providers should be aware of clinical trials, in which their patients can participate, to help boost the current, dismal rate of trial participation.

Health Policy

1. Raising Awareness

Spread awareness and understanding on what I-O is and how it is distinguishable from the standard of care or other targeted therapies. Patients, payers, providers, and health policy makers in oncology should all be involved in this discussion.

2. Clinical Pathways

Health plans and individual care institutions have been developing and implementing clinical pathways to streamline treatment plans and make them cost-effective. Clinical pathways mirror, either the National Comprehensive Cancer Network Guidelines, or are developed based on existing medical evidence. This approach may not be the most flexible or accommodating of newly approved medications, such as I-O, but they need to be.

3. Value-Based Payments and Risk-Sharing Agreements

Risk-sharing agreements between drug manufacturers and health plans can provide the true assessment of value of a treatment, since the agreements use evidence from the real-world performance of drugs.[9] The opportunity for outcomes-based agreements, between drug developers and payers/pharmacy benefit managers, could help expensive drugs gain coverage or inclusion on formularies, which, in turn, will improve patient access.

4. Medicare Part D

With cost being a major barrier to access, Medicare should be allowed to negotiate with pharmaceutical manufacturers on brand name drugs covered under its prescription drug benefit program (Part D), just as Medicaid does. According to a brief published last year, if Medicare could secure the same prices as Medicaid does for brand-name drugs, it would result in annual cost savings of between $15.2 and $16 billion.[10]

5. PCORI

The Patient-Centered Outcomes Research Institute (PCORI) was established to fund comparative-effectiveness research (CER) that can then be disseminated to patients and clinicians for meaningful clinical decisions. However, Medicare has been prevented from using the CER data that PCORI-funded research generates. This barrier should be eliminated.

6. Competition

Encourage competition to drive down drug prices.

7. Importing Cheaper Drugs

If production costs in the United States and the FDA approval process add to a drug's development cost, could importing cheaper drugs be an answer? But this could stifle innovation and may not be the most viable alternative.

With growing healthcare cost concerns in the United States, constructive solutions, that are a win-win for all stakeholders, are the need of the hour. **EBO**

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ANNOUNCING

A Permanent J-code for: OPDIVO® (nivolumab) – J9299

J-code for OPDIVO

HCPCS Code	Description	Effective
J9299[1]	Injection, nivolumab, 1 mg	January 1, 2016

J9299 replaces HCPCS code C9453, injection, nivolumab, 1 mg, and also miscellaneous codes J9999, J3590, and J3490.[1-5]

NDC Codes for OPDIVO[6]

0003-3772-11, 00003-3772-11	40 mg/4 mL (10 mg/mL) solution in a single-use vial
0003-3774-12, 00003-3774-12	100 mg/10 mL (10 mg/mL) solution in a single-use vial

For more information:

- Contact your Area Reimbursement Manager for assistance and to schedule an office visit
- Contact Bristol-Myers Squibb Access Support® at **1-800-861-0048**, Monday-Friday, 8 AM to 8 PM ET
- Visit **www.bmsaccesssupport.com** for resources to help your patients with access to Bristol-Myers Squibb Oncology products

The accurate completion of reimbursement- or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol-Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item. This coding guidance is not intended to provide specific directions on requesting prior authorization or submitting claims for OPDIVO and does not provide a guarantee of receiving prior authorization or reimbursement. Coding for OPDIVO is dependent on the insurer and the care setting in which the drug will be administered. Oncology practices need to make coding decisions based on the diagnosis and treatment of each patient and the specific insurer requirements.

Indication[6]

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

Select Important Safety Information

OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryofetal toxicity.

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

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis
Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO® (nivolumab) treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred with OPDIVO. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold until resolution for Grade 2. In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO: Grade 3 (n=5), Grade 2 (n=2), and Grade 1 (n=3).

Immune-Mediated Colitis
Immune-mediated colitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. In Checkmate 057, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: Grade 3 (n=3), Grade 2 (n=2), and Grade 1 (n=2).

Immune-Mediated Hepatitis
Immune-mediated hepatitis can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 057, one patient (0.3%) developed immune-mediated hepatitis.

Immune-Mediated Endocrinopathies
Hypophysitis, adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, thyroid function prior to and periodically during treatment and hyperglycemia. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Administer insulin for type 1 diabetes. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia. In Checkmate 037, 066, and 057, <1.0% of OPDIVO-treated patients developed adrenal insufficiency. In Checkmate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated TSH occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients.

Immune-Mediated Nephritis and Renal Dysfunction
Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, withhold OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO. In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients receiving OPDIVO.

Immune-Mediated Rash
Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4. In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO, including four Grade 3 cases.

Immune-Mediated Encephalitis
Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Across clinical trials of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, <1.0% of patients were identified as having encephalitis. In Checkmate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO.

Other Immune-Mediated Adverse Reactions
Based on the severity of the adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. The following clinically significant immune-mediated adverse reactions occurred in <1.0% of OPDIVO-treated patients: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism, and systemic inflammatory response syndrome. Across clinical trials of OPDIVO as a single agent administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions
Severe infusion reactions have been reported in <1.0% of patients in clinical trials of OPDIVO as a single agent. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In Checkmate 057 and 066, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO.

Embryofetal Toxicity
Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an OPDIVO-containing regimen and for at least 5 months after the last dose of OPDIVO.

Lactation
It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO-containing regimen, advise women to discontinue breast-feeding during treatment.

Serious Adverse Reactions
In Checkmate 057, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure.

Common Adverse Reactions
In Checkmate 057, the most common adverse reactions (≥20%) reported with OPDIVO were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%), and constipation (23%).

Please see brief summary of Full Prescribing Information on following pages.

OPDIVO® (nivolumab) injection, for intravenous use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO *[see Clinical Studies (14.2) in full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.3% (5/1590) of patients. All five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

In Trial 3, pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO. Of these 10 patients, there were five patients with Grade 3, two patients with Grade 2, and three patients with Grade 1 immune-mediated pneumonitis. The median time to onset was 7.2 months (range: 2.7 to 13.1 months). All five patients with Grade 3 and one of two patients with Grade 2 pneumonitis received high-dose corticosteroids and permanently discontinued OPDIVO; two of these seven were documented radiographically to have complete resolution of pneumonitis. One patient with Grade 2 pneumonitis had OPDIVO temporarily withheld, received low-dose corticosteroids, experienced complete resolution and was retreated without recurrence of pneumonitis.

Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.4) in full Prescribing Information]*.

In Trial 3, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: three patients with Grade 3, two patients with Grade 2, and two patients with Grade 1. The median time to onset in these seven patients was 2.7 months (range: 4 weeks to 19 months). All seven patients received corticosteroids; six of these seven received high-dose corticosteroids for a median duration of 2.9 weeks (range: 1 week to 2.1 months). One patient with Grade 3 colitis permanently discontinued OPDIVO. All seven patients experienced complete resolution. Five of the seven patients were retreated after complete resolution without recurrence of diarrhea or colitis.

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.4) in full Prescribing Information and Adverse Reactions]*.

In Trial 3, one patient developed immune-mediated hepatitis (0.3%) after 7.8 months of OPDIVO exposure. The event resolved following temporary withholding of OPDIVO and high-dose corticosteroid therapy. Immune-mediated hepatitis recurred following resumption of OPDIVO, resulting in permanent discontinuation.

Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) and permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

Adrenal Insufficiency

Adrenal insufficiency can occur with OPDIVO treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.4) in full Prescribing Information]*.

In Trials 1, 3, and 5 (n=761), less than 1.0% of OPDIVO-treated patients developed adrenal insufficiency.

Hypothyroidism and Hyperthyroidism

Thyroid disorders can occur with OPDIVO treatment. Monitor thyroid function prior to and periodically during treatment. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

In Trial 3, Grade 1 or Grade 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) of patients receiving OPDIVO and 0% (0/268) of patients receiving docetaxel, while elevated TSH occurred in 17% of patients receiving OPDIVO and 5% of patients receiving docetaxel. The median time to onset of hypothyroidism/thyroiditis was 2.9 months (range: 1.4 to 11.8 months). All 20 patients received levothyroxine. Two patients received corticosteroids; one of whom received high-dose corticosteroids. Complete resolution of hypothyroidism occurred in one patient. OPDIVO was temporarily withheld due to hypothyroidism/thyroiditis in three patients; no patients discontinued OPDIVO due to hypothyroidism/thyroiditis.

Grade 1 or Grade 2 hyperthyroidism occurred in 1.4% (4/287) of patients. The median time to onset was 2 months (range: 4.1 weeks to 2.8 months). Two of four patients received methimazole and one patient also received treatment with high-dose corticosteroids. All four patients experienced complete resolution.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus can occur with OPDIVO (nivolumab) treatment. Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO. Permanently discontinue OPDIVO and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.4) in full Prescribing Information and Adverse Reactions]*.

In Trial 3, immune-mediated renal dysfunction (Grade 2) occurred in 0.3% (1/287) of patients. The time to onset in this patient was 1.5 months. The patient permanently discontinued OPDIVO, received high-dose corticosteroids, and experienced complete resolution.

Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash *[see Dosage and Administration (2.4) in full Prescribing Information]*.

In Trial 3, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO. Grade 3 rash developed in four patients (1.4%), of whom one discontinued treatment.

Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

Across clinical studies of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, less than 1.0% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO after 7.2 months of exposure. OPDIVO was discontinued; corticosteroids were administered.

Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.4) in full Prescribing Information]*.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1.0% of patients receiving OPDIVO as a single agent or in combination with ipilimumab in Trials 1, 3, 4, 5, and 6 (n=1261): uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, and systemic inflammatory response syndrome.

Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of OPDIVO as a single agent. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

In Trials 3 and 5, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO.

Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions]*
- Immune-Mediated Colitis *[see Warnings and Precautions]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions]*
- Immune-Mediated Rash *[see Warnings and Precautions]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions]*
- Infusion Reactions *[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.

The data in the Warning and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1590 patients enrolled in Trials 1, 3, 5, 6, a single-arm trial in NSCLC (n=117), or an additional dose-finding study (n=306) administering OPDIVO as a single agent at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions]*.

The data described below reflect exposure to OPDIVO as a single agent in Trial 3, which is a randomized trial in patients with metastatic non-squamous NSCLC.

Metastatic Non-Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO (nivolumab) was evaluated in Trial 3, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.2) in full Prescribing Information]*. Patients received 3 mg/kg of OPDIVO (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 2.6 months (range: 0 to 24.0+) in OPDIVO-treated patients and was 2.3 months (range: 0 to 15.9 months) in docetaxel-treated patients. In this trial, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

The median age of all randomized patients was 62 years (range: 21 to 85); 37% of patients in the OPDIVO group were ≥65 years of age and 47% of patients in the docetaxel group were ≥65 years of age, 55% were male, and 92% were white. Twelve percent of patients had brain metastases and ECOG performance status was 0 (31%) or 1 (69%).

OPDIVO was discontinued in 13% of patients, and was delayed in 29% of patients for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. Table 1 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

Table 1: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 3)

Adverse Reaction	OPDIVO (n=287)		Docetaxel (n=268)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	30	0.3	25	0
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.7	22	1.5
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.7
Skin and Subcutaneous Tissue Disorders				
Pruritus	11	0	1.9	0

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (49% Grade 1-4, 6% Grade 3-4), musculoskeletal pain (36%), pleural effusion (5.6%), pulmonary embolism (4.2%), urticaria (1.4%), and polymyalgia rheumatica (0.3%).

Table 2: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 3)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Docetaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Chemistry				
Hyponatremia	35	6	32	2.7
Increased AST	28	2.8	14	0.4
Increased alkaline phosphatase	27	1.1	18	0.4
Increased ALT	23	2.4	15	0.4
Increased creatinine	18	0	13	0.4
Increased TSH[b]	17	N/A	5	N/A

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 280 to 287 patients) and docetaxel group (range: 252 to 262 patients); TSH: OPDIVO group n=209 and docetaxel group n=207.
[b] Not graded per NCI CTCAE v4.0.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 639 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 73 patients (11.4%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in five patients (0.8%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-nivolumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]* and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *[see Data]*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO (nivolumab) are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is 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.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Lactation

Risk Summary

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, OPDIVO 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 with OPDIVO and for at least 5 months following the last dose of OPDIVO.

Pediatric Use

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

Geriatric Use

Of the 292 patients randomized to OPDIVO in Trial 3, 37% of patients were 65 years or older and 7% were 75 years or older. In this trial, no overall differences in safety or efficacy were reported between elderly patients and younger patients.

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There is no information on overdosage with OPDIVO.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*.
- Rash: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions]*.
- Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions]*.
- Females of Reproductive Potential: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO *[see Use in Specific Populations]*.
- Lactation: Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations]*.

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The Fight of Our Lives: *Confronting the Unmet Need in Lung Cancer*

BONNIE J. ADDARIO

ABOUT THE AUTHOR

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Ms Addario is a stage IIIB lung cancer survivor and founder of the Bonnie J. Addario Lung Cancer Foundation (ALCF) and the Addario Lung Cancer Medical Institute (ALCMI).

For more information please visit **www.lungcancerfoundation.org**.

Medical advancements, over the past year, have been game changing for lung cancer patients. In 1971, President Richard Nixon declared war on cancer, and now, we finally have a war on lung cancer.

In 2015, the FDA approved 7 new treatments for lung cancer patients, and 5 of these approvals came over a 2-month period. FDA programs, such as the Breakthrough Therapy, Accelerated Approval, Priority Review, and Fast Track designations, have allowed the expedited approval of life-saving lung cancer medicines that address unmet medical needs and provide clinical benefit to patients.

As we march into the era of personalized precision medicine and improved clinical trial design, genomic profiling allows us to target and treat specific cancer mutations, by identifying and prescribing the right drug to the right patient, at the right time. Another fantastic addition to our armamentarium is, immuno-oncology (I-O), a therapy that completely upends traditional treatment options using medicines to boost a patient's own immune system to fight their disease.

Many of us now have a second chance because of the doctors, scientists, and medical researchers working on our behalf, to provide new medicines and treatments for lung cancer patients.

MY STORY

Eleven years ago, I was at the peak of my career as a CEO when my world came crashing down around me. After 14 hours of surgery, a battery of nurses and doctors, an army of radiation and chemotherapy treatments, blood clots, procedures, and tubes, I lost my right lung to cancer. I am a survivor.

Today, we not only have new treatments; we have new surgical approaches; new medicines, and skilled, passionate researchers fighting for people with lung cancer; we have information, patient resources, and collaboration among patients, researchers, clinicians, and physicians. It is finally the century of patient-driven lung cancer research!

Throughout my diagnosis and treatment, I realized the huge unmet need for patient resources and information on lung cancer. Survival gave me a new goal: address a deficiency in lung cancer healthcare resources and research initiatives.

In 2006, my family and I founded the Bonnie J. Addario Lung Cancer Foundation (ALCF), where we work with patients to support research and advocate for innovative lung cancer medicines and treatments. In 2008, we started another nonprofit, Addario Lung Cancer Medical Institute (ALCMI), a global consortium dedicated to facilitating and driving research. We work with thousands of patients and families worldwide, providing free education and support programs, connecting patients with doctors and clinical trials, and funding innovative research where the need is greatest.

THE PROMISE OF IMMUNOTHERAPY

Clinical research holds the key to discovering the causes of lung cancer, developing effective treatment options, and delivering those treatments to patients, in a timely manner. What can we do to predict lung cancer risk, detect the disease at early onset, and prevent it? Are there novel drug combinations to pre-empt and overcome cancer cells? How can we personalize and provide targeted treatment for each individual patient?

For the first time in decades, we have momentum and hope in the progress made with immunotherapy and companion drug trials. Timely approval and availability of breakthrough therapies allow more families to think of lung cancer survival in terms of years, not just months, and provide hope to make lung cancer a chronic, manageable disease by 2023. It can't get more personalized than using your own immune system to fight your cancer!

Immunotherapy is a game-changer; a breakthrough that oncology desperately needs. Now, for the first time, we can begin to talk about long-lasting effects, even a *cure*. Unlike other therapies, immunotherapies afford a sustained, durable response that continues even after treatment is stopped—a first for diseases like lung cancer that have had poor prognoses.

This is a quantum leap forward—a moonshot. Before now, patients had limited options, especially after their disease progressed beyond the current standard of care therapies.

Unfortunately, immunotherapy does not work with every patient, every time. Approximately 70% to 80% of cancer patients do not respond to immunotherapy treatments, which may be an outcome of clinical trial design, including selection of the appropriate patient population.

Among patients who do respond to immunotherapy, not all have dramatic, long-lasting effects. Several patients present with pseudoprogression, meaning the disease appears to get worse before it gets better. Physicians, patients, and their caregivers need to be prepared for this to avoid discontinuing a potentially effective therapeutic regimen.

THE NEED TO REDESIGN CLINICAL STUDIES FOR MAXIMAL BENEFIT

On a broader level, we also need to examine clinical trial design in order to change the current dismal patient accrual rates of 3% to 5%. Clinical trial design needs an overhaul that would allow trials to be more inclusive, patient friendly, and easier to access, so that precious research dollars can be maximized to speed up the development of newer diagnostics, prognostics, and therapeutics. We need clinical trial data that is publicly available, so that it may advance the current state of lung cancer science and research, and inform the design of future clinical trials.

At ALCMI, we have successfully implemented a remote clinical study participation platform that allows young, lung cancer patients, from countries around the world—Italy, Turkey, Brazil, and New Zealand—to participate in the Genomics of Young Lung Study (GoYLC) trial[1] that is investigating mechanisms of tumor initiation and progression in patients under 40 years old. It is important that the field continues to change paradigms of how trials and studies are run, so that patients can look forward to better outcomes and more hope.

Not only do we need the clinical medicine ecosystem to change and adapt in order to bring newer treatments forward, we also need the patient to take a seat at the table, join clinical trials, and provide valuable data to drive faster cures.

Take Jeff Julian. Diagnosed in 2015, the 39-year-old former Olympic Trials finalist and Rose Bowl Aquatics head coach was shocked when he found out he had stage IV lung cancer. Because of his participation in a clinical trial for nivolumab, a breakthrough I-O drug, his tumors have significantly regressed and his disease is under control. Jeff knows, firsthand, that innovative treatments save countless lung cancer patients' lives.

Jeff Julian

This year alone, more than 200,000 people in the United States received a lung cancer diagnosis.[2] Innovative medicines, like immunotherapy drugs, have and will save countless lung cancer patients' lives. We need to continue to support the researchers and doctors pushing the envelope, and seeking new approaches and treatments to cure lung cancer.

Medical innovation works best when patients, donors, clinicians, pharma, biotech, payers, government, public, and private enterprise all take a seat at the table to collaboratively drive research. The lives of patients, around the world, are possible because of the stream of new research and novel drugs that help us fight lung cancer. It is a promising time for lung cancer patients and we are just getting started.

PERSONALIZED MEDICINE SHOULD LEAD THE WAY

Across the board, we see a heightened focus on precision medicine and personalized medicine, from President Obama's Precision Medicine Initiative[3] to the FDA's Breakthrough Therapy and Fast Track approval process.[4] Precision

medicine empowers oncologists to test, profile, and target genomic mutations that cause cancer to grow and spread. Personalized medicine takes a step back and looks at the whole person, his or her age, medical history, ethnicity, and other factors that might influence treatment decisions.

As an advocate for personalized medicine, the ALCF has established 20 Centers of Excellence in community hospitals, nationwide, to ensure all patients receive genomic testing that can guide the treatments they receive. The ALCF also collaborated with 16 other lung cancer organizations on the Don't Guess.Test. campaign[5] to expand awareness and educate patients about the importance of comprehensive genomic testing in lung cancer, so that each patient receives the right treatment at the right time. We have created both, an online patient portal and an app for lung cancer patients; we fund research initiatives, such as the GoYLC study and the Clinical Trials Innovation Prize. We are working hard to move the dial to improve the 16% survival rate for lung cancer patients.

We now have an arsenal of new resources for lung cancer patients who are living well longer than previously imagined; yet, in the United States alone, 450 patients die from lung cancer every day.[2] Lung cancer is the top cancer killer of men and women, killing almost twice as many women, as any other cancers. It accounts for 27% of all cancer deaths and is the second leading cause of all deaths in the country.

As a lung cancer patient and a patient advocate, I know the stakes have never been higher for patients waiting for new medicines that could improve treatment, save lives, and offer hope to families. Supporting, funding, and protecting the research and development of new medicines and new treatments is more critical, now than ever, to provide better treatments and better outcomes to all cancer patients. Patients deserve it. **EBO**

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PATIENT ASSISTANCE PROGRAMS

Patient Assistance: *Implementing Preventative Steps to Ensure Financial Wellness*

JACQUELINE CABÁN AND CHARLES LYNCH

OVERVIEW OF THE ONCOLOGY MEDICATION ASSISTANCE PROGRAM

The Oncology Medication Assistance Program (MAP) at Smilow Cancer Hospital at Yale-New Haven was created with a 2-fold vision model. The purpose was to help patients with elevated drug cost expenses associated with chemotherapy treatments while also protecting the hospital from potential write-offs. The current model utilizes manufacturer-sponsored drug replacement and co-pay assistance programs in an attempt to reduce the financial burden of drug-related expenses for patients and providers.

The uninsured patient, or off-label–use patient, being treated with the newer immuno-oncology (IO) drugs can easily have a negative impact on a hospital's pharmacy budget. The use of pharmaceutical-sponsored drug-replacement programs can offset the potential write-offs by aiding in the recovery of medications. The resulting win-win effect of drug recovery is one in which both the patients and providers have no financial drug liability and the patient is treated with the provider's preferred course of therapy.

In an innovative attempt to create a best practice model, Smilow Cancer Hospital at Yale-New Haven has reached out to pharmaceutical industry leaders to enlighten and educate them on real-life patient experiences and obstacles. Removing barriers and enhancing financial eligibility criteria has remained one of our priorities. The utilization of co-pay programs designed for community practices has always been a unique challenge within major institutions. One such innovative practice model was the use and acceptance of the hospital-based explanation of benefits (EOBs) form. These forms can be used in place of the patient's mailed EOB, which essentially removes the liability from patients having to manage on their own. Institutional EOBs usually can be generated the day the payer's reimbursement has been processed. This best-practice model has eliminated patient responsibilities and has assisted in expediting the turnaround times for payment processing with co-pay assistance.

REIMBURSEMENT OBSTACLES

The fast-pace challenge that comes from utilizing the new IO drugs can be observed through payer reimbursements. Some of these newly approved medications do not require prior authorization (PA) and the misconception is that they are being covered. Months later, however, the business office realizes that the payer has not covered the claim. The appeal process is initiated, and the patient continues treatment while in financial limbo. One way to avoid this situation is to use the Industry Sponsored Benefits Verification (BV) Form prior to treatment. Utilization of BV forms would identify drug coverage and patients' out-of-pocket (OOP) costs. Medicare patients are also identified for foundation co-pay assistance, such as through the Patient Advocate Foundation and Patient Access Network Foundation. Best-practice models would be to enroll all patients with financial issues into these sponsored programs as a precautionary measure, considering the programs have limited look-back periods, some as little as 30 days.

With more patients facing OOP expenses since the implementation of the Affordable Care Act, there has been a greater need for patient assistance. The 2015 Genentech Oncology Trend Report noted that only 26.7% of patient OOP expenses were collected in the oncology setting.[1] The remaining 73.3% of unrecovered co-pays can represent a significant financial burden on an institution's financial reports. Financial losses to the institution, as well as patient financial toxicity, could become greater if OOP expenses continue to increase in the coming years.

FINANCIAL BARRIERS

Today's oncology patient has many cost barriers that can easily affect their financial stability at the very beginning of their treatments. Being aware of your patient's financial health during treatment is important because it can have a significant impact on their compliance with respect to medication and the continuation of care. In 2013, the average

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OOP expense of a commercially insured patient's intravenous oncology medication was $5643 and the oral oncolytic OOP expense was $2838.[2] Additionally, when a patient begins treatment, there are additional nonmedical financial expenses that can add to the financial stress, such as costs associated with transportation, gas, and parking. Additional costs to consider are possible child or adult care, meals, nutritional modifications, and reduced employment wages. By themselves, these nonmedication stressors can cause a patient and family to slide into a state of financial vulnerability.

REAL LIFE EXAMPLES

The new reality of healthcare coverage cost and large OOP expenses are changing the financial landscape for many middle class Americans. Let's take a look at the costs associated with a new exchange patient in the state of Connecticut. The scenario is a family of 4 (consisting of 2 adults and their 2 teenage children). The family has an annual income of $60,625, which is equivalent to 250% of the 2015 federal poverty level (FPL). The plan purchased is an Anthem Blue Cross Blue Shield Silver PPO Pathway X Multi State Plan. The monthly premium cost is $458.46[3] or $5501.52 annually, representing 8.8% of the family's gross income. The newly insured member also has a maximum family deductible and OOP cost of $9400 per calendar enrollment year, which is 15% of their gross income.

The family may feel protected until a single or series of events challenges that perspective. With an unexpected cancer diagnosis along with other unanticipated events, it would be easy for this family to reach their maximum deductible and OOP expenses in just a few months. The annual cost of premiums, in addition to the OOP, could easily become 23.8% of the family's gross income. If one of the family members commences treatment or there are additional family events in the last quarter of the year, it is possible for them to reach $18,800 in deductibles and OOP expenses in a 5-to-6 month time frame. This financial threat is a real-life scenario that can undoubtedly cause financial toxicity to a patient in a relatively short period of time. The trickle-down effect on the provider will then become evident in the form of uncollected and/or unpaid debt, as patients have a greater cost share being added to their policies each year. On a broader scale, the term "institutional toxicity" might be the new phrase on the horizon.

Access to patient assistance programs (PAPs) can sometimes be hindered by the patient's ability to fit into a particular company's income criteria. There are some oncology drug companies that have a 400% FPL for the uninsured or off-label–use patient. The 400% FPL for a family of 2 is $63,720 dollars.[4] This income figure would be equivalent to both family members earning $15.32 an hour. Patients whose income exceeds this FPL would not have access to this program's medications. There are geographical areas within the United States, such as the Northeast and the San Francisco Bay area, where it is not difficult to exceed this FPL income level.

One of our biggest obstacles with PAPs in the Northeast is that the income criteria set in place by some of the industry players are not reflective of the cost of living within that region. When looking at one of the preferred drug combination therapies, the drug costs can exceed $50,000 per treatment. The costs associated with this therapy would not be affordable for the average middle class patient living in these regions, as the patient's elevated income would disqualify them from many drug assistance programs. The patient may now feel penalized for making an income that reflects the region where they reside. Most pharmaceutical companies like to state, however, that accesses to their medications are available to all who need it.

In oncology, it becomes apparent that access may be inhibited by a patient's income; in certain circumstances, income increases the chances of becoming a self-pay patient. The patient who makes $152,000 would have to use their entire annual gross income to receive 3 treatments worth about $50,000 each. They would need a rainy day fund to afford such a therapy and would need additional funds for the remaining cycles. This creates an unrealistic ability for any patient to receive therapy unless the institution decides to write off the cost or negotiates a reduced drug charge per treatment for the self-pay patient. There is a need for greater standardization between industry-sponsored programs' financial criteria to ensure that more patients have access to the preferred courses of therapy.

PATIENT ACCESSIBILITY

Cash-paying patients may have difficulties accessing medications that are marked as "limited distribution." When a patient has barriers obtaining high-cost medications from their mandated channels, they may have the option to utilize some of the benefits of the 340B program by purchasing the medication directly from an institution's specialty pharmacy at 340B cost.

Limited distribution can also cause confusion when patients are prescribed combination therapies. In using a combination therapy where the drugs are both limited-distribution and open-access, the entire regimen may not be filled at the same location, which can potentially cause a delay in therapy.

Lack of basic knowledge regarding the availability of industry sponsored PAPs is another hindering obstacle. Patients and providers are usually unaware that MAPs exist. Patients may be weighed down by daily stressors in addition to their health concerns, preventing them from diligently seeking out information. Additionally, the lack of PAP information available to the patient in a provider's office may be due to internal policies that prohibit branded industry information from being displayed.

A recent shift has become visible in the senior citizen patient population. Today's seniors have slightly higher incomes in relation to their predecessors. With the inception of 401K plans in 1978, we now see seniors who are collecting social security benefits, pensions, and their 401K distributions. These can all create incomes higher than the financial criteria currently established by the pharmaceutical industry PAPs. Increasing the financial criteria would reduce some of the accessibility barriers. We find that most patients who live within their income and their savings can support a small emergency, but a cancer diagnosis can bring in a prevailing financial toxicity. The ongoing need to advocate for higher-income-limit criteria needs to be addressed at the national level. A senior patient who may now enjoy survivorship might not have financial security in the future, having exhausted their limited assets.

There is a need for a more efficient, navigable, and universal platform for a patient assistance website. This would create value and be a streamlined utilization process formatted for both patients and providers. The fruition of a common application website would assist by reducing the need to fill out poly-pharma applications and, in turn, create a more streamlined process. The concept of this platform would be similar to the Common Application used by colleges. This website would have the patient or an advocate pre-populate demographics, in addition to medications and diagnosis codes. The portal could then triage a fully completed application to the appropriate PAP.

IMPLEMENTATION

Pharmaceutical companies have provided tools by which significant financial liabilities of many stakeholders can be eliminated. These programs are underutilized and undervalued. A field reimbursement manager can assist many practices in understanding why implementation of these tools is so critical. The knowledge of industry-sponsored programs can initiate the epiphany of potential savings for both patients and providers, although assuming ownership of such a robust program may raise some queries.

Collaborations among internal departments are critical for a program's overall success, which requires direct patient contact and maintenance of inventory levels, ordering processes, billing functions, application processes, and overall program management. MAP implementation could assure that both the patient and provider establishments would benefit by minimizing patient financial liability while having greater access to the preferred course of therapy. The internal program start-up could begin small and grow as the need and the financial benefits are recognized. Personnel can be assigned from among current oncology pharmacy team members, patient account representatives, financial counselors, or social services departments. In the absence of an assigned individual or team, word-of-mouth advice to a patient to navigate a company's website for assistance would bring great value.

We live in a world where coupons and promo codes are frequently used on items such as food, concert tickets, and even free shipping, so why not inform a patient of a coupon that could potentially save them thousands of dollars? The potential savings of millions of dollars for patients and the provider establishments tend to be a no-brainer in a climate of lower reimbursements and greater acquisition supply costs. **EBO**

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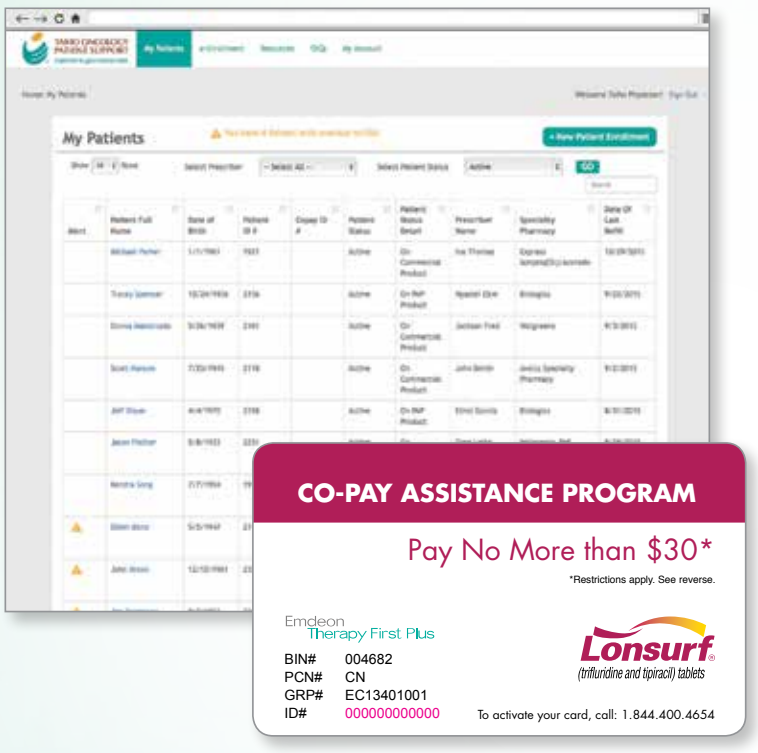

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Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild type, an anti-EGFR therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see brief summary of Prescribing Information on the following pages.

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

Brief Summary of Prescribing Information
For complete Prescribing Information, consult official package insert.

1 INDICATIONS AND USAGE
LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Myelosuppression
In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery resume LONSURF at a reduced dose. *[*see *Dosage and Administration (2.2) in the full Prescribing Information]*

5.2 Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[*see *Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information]*

6 ADVERSE REACTIONS
6.1 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.

The data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
Gastrointestinal disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders and administration site conditions				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)
† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treatment patients (2%) compared to no patients on placebo.

Additional Clinical Experience
Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

7 DRUG INTERACTIONS
No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

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.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifuridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. *[*see *Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. *[*see *Nonclinical Toxicology (13.1) in the full Prescribing Information]*

8.4 Pediatric Use

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

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m^2 per day.

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[*see *Warnings and Precautions (5.1)]*

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[*see *Adverse Reactions (6.1)]*

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. *[*see *Dosage and Administration (2.1) in the full Prescribing Information]*

Advise the patient that anyone else who handles their medication should wear gloves. *[*see *References (15) in the full Prescribing Information]*

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[*see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3)]*

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. *[*see *Use in Specific Populations (8.2)]*

TAIHO ONCOLOGY, INC.

Amgen's Carfilzomib Approved for Multiple Myeloma

SURABHI DANGI-GARIMELLA, PHD

Carfilzomib, a proteasome inhibitor, has been approved by the FDA for use in combination with dexamethasone or lenalidomide, in patients with relapsed/refractory multiple myeloma (RRMM) who have previously received 1 to 3 lines of therapy.[1] Also, the drug's accelerated approval as a single agent has now been converted to a full approval—carfilzomib can be used alone in previously treated patients with RRMM.

The approval is based on phase 3 results of the ENDEAVOR study that were presented at the annual meeting of the American Society of Hematology[2] and simultaneously published in *Lancet Oncology*. The randomized phase 3 study evaluated 929 adult patients with refractory multiple myeloma (RMM) who had received 1 to 3 prior lines of therapy. The study demonstrated that the doublet of carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with bortezomib and dexamethasone (Vd) (median PFS, 18.7 vs 9.4 months; HR, 0.53; 95% CI, 0.44–0.65; *P* <.0001) in relapsed multiple myeloma. Bortezomib and dexamethasone are the current standard of care in multiple myeloma.

Grade 3 and greater adverse events (AEs) were significantly higher with Kd compared with Vd: 69.8% and 63.9%, respectively, in patients with 1 prior treatment, and 76.6% and 69.9%, respectively, in patients with at least 2 prior treatments. Grade 3 or higher hypertension, dyspnea, and cardiac failure were more common in the Kd group.

Now that the treatment is approved, cost will be the next big question for payers to develop coverage policies for the combination. Carfilzomib alone is estimated to cost $10,000 for a 28-day cycle in an average-sized patient.[3] A recent health economic analysis of combination treatments commonly used in multiple myeloma by researchers at Novartis compared bortezomib plus dexamethasone; panobinostat, bortezomib, and dexamethasone; lenalidomide plus dexamethasone; lenalidomide, bortezomib, and dexamethasone; carfilzomib; carfilzomib, lenalidomide, and dexamethasone; and pomalidomide plus dexamethasone.[4] The study examined the expenditures for drugs and their administration, for prophylaxis and adverse event monitoring, and for the treatment of grade 3 or 4 AEs.

The authors concluded that the combination of carfilzomib, lenalidomide, and dexamethasone was the most expensive, because regimens that included lenalidomide were the most expensive (range was $126,000 to $256,000). The combination of bortezomib with dexamethasone and the combination of panobinostat, bortezomib, and dexamethasone, cost the least (less than $125,000). Quite importantly, the authors found that combining carfilzomib, lenalidomide, and dexamethasone incurred the highest medical costs. Since one of the regimens that has now been approved by the FDA is carfilzomib and dexamethasone, the safety and cost-effectiveness of this combination in the real world remains to be seen. **EBO**

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Updated USPSTF Breast Cancer Screening Guidelines Remain Controversial

SURABHI DANGI-GARIMELLA, PHD

The US Preventive Services Task Force (USPSTF) has released an updated recommendation for breast cancer screening calling for an individualized approach to screening mammograms for women less than 50 years of age and biennial screening for women between 50 and 74 years. However, radiologists and breast cancer specialists disagree with raising the age of screening from 40 years to 50 years.

The updated Recommendation Statement[1] includes the following advice:

- Biennial screening mammography for women 50 to 74 years old (**Grade B**)
- Individualized approach to screening for women between 40 and 49 years old (**Grade C**)
- Insufficient data to assess benefits or harm of screening mammography in women over 75 years (**Grade I**)

According to the USPSTF, screening with film mammography results in an absolute reduction in breast cancer mortality for women between 50 and 74 years old, and the strongest evidence for the greatest benefit is in women 60 to 69 years old. Further, the Task Force did not find evidence to support reduced mortality as a result of breast self-examination (BSE) or any benefit of digital mammography and magnetic resonance imaging of the breast.

In an opinion piece for Morning Consult, Michelle L, Rivera, MD, a diagnostic radiologist, writes that the absence of a radiologist or a breast cancer specialist on the Task Force bothers her.[2] Taking note of some of the outdated evidence from Sweden and Canada reviewed by the Task Force, Rivera points out, "the largest and longest running breast cancer screening studies in history reconfirm that regular screening cuts breast cancer deaths by roughly a third in all women over age 40—including those aged 40 to 49."

The American College of Radiology and the Society of Breast Cancer Imaging have issued a joint statement that supports annual mammography screening in women beginning at age 40. "Following these USPSTF recommendations would result in lethal consequences for thousands of women each year," the statement reads.

Coverage decisions for screening might be at stake if these recommendations pass Congress. The Affordable Care Act mandates private payer coverage for grade "A" and "B" recommendations by the USPSTF, without a copay. So for women younger than 50 years, who have a "C" grade for screening per the current recommendations, may have to bear the cost out-of-pocket, as will women in the 50 to 74 year age group who might prefer an annual examination versus the recommended biennial screen. However, the Protecting Access to Lifesaving Screenings Act or PALS Act, introduced in Congress in July last year,[3] could help protect these women—at least till January 1, 2018. The PALS Act recommends continuing Medicare coverage for screening mammography without coinsurance, including digital screening.

Rivera firmly believes in the positive impact of early screening mammography in reducing breast cancer deaths. "We know that women who develop breast cancer between the ages of 40 and 49 often develop more aggressive types of cancer with a worse prognosis," she writes. "Given all of the data showing that routine screening beginning at age 40 save the most lives, I cannot understand why the USPSTF would deny women a fighting chance." **EBO**

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MANAGED CARE UPDATES

MedPAC Recommends Congress Cut Part B Reimbursement for 340B Entities

SURABHI DANGI-GARIMELLA, PHD

A proposal to reduce Medicare Part B payment rates for participants in the 340B Drug Pricing Program has been approved 14-3 by the Medicare Payment Advisory Commission (MedPAC). A non-partisan agency, MedPAC, provides policy advice to the Congress on issues that affect the Medicare program.

In its January 14, 2016 vote, the Commission recommended the Congress to:

1. Reduce Medicare Part B drug reimbursement for 340B hospitals by 10% of average sales price, which would cut the amount a hospital saves on a Part-B drug by about 30%, and result in savings to the tune of $300 million.
2. Transfer the savings into the Medicare-funded hospital uncompensated care pool.
3. Distribute payments from the pool on the basis of data from the Medicare cost report's worksheet S-10, phased in over 3 years.

Initiated in 1992, the 340B Drug Pricing Program[1] requires pharmaceutical manufacturers participating in the Medicaid Drug Rebate Program to negotiate a drug pricing agreement with HHS—the manufacturer will provide specified discounts on "covered outpatient drugs" to government-supported facilities. The program enables covered entities to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services.


TED OKON

"MedPAC's decision to address the 340B drug discount program is yet another signal that the program is unsustainable and putting profits ahead of patients. The MedPAC decision follows work by government watchdogs, OIG [Office of Inspector General], and, GAO [Government Accountability Office], in documenting the excesses of 340B in the hospital sector," wrote Ted Okon, executive director of the Community Oncology Alliance, in an e-mail to *The American Journal of Managed Care*. "However, in order to ensure that 340B is being used as a true safety net by hospitals, Congress will have to act way beyond the MedPAC recommendations. Legislation is needed to better define patient eligibility and to require transparency and accountability of how hospitals are using 340B profits. 340B needs to be about patients in need, and not letting them fall between the treatment cracks, rather than about making money off of what has become an enormous government loophole."

Just a week before this recommendation, the American Hospital Association (AHA) had urged MedPAC to withdraw its draft recommendation to cut payment rates to the 340B-participating hospitals. "This recommendation is outside of the scope of MedPAC's mission, lacks a clear purpose and penalizes certain hospitals for their ability to obtain discounts on the items and services they purchase," wrote Ashley Thompson, AHA senior vice president for public policy analysis and development, in the letter.[2]

Reacting to the vote, 340B Health, a not-for-profit organization of over 1100 public and private hospitals and health systems, said in an e-mail, "We are concerned about MedPAC's recommendation to Congress on the 340B program approved by the panel this morning. MedPAC's proposal would fundamentally change the 340B program and there has not been enough analysis about how hospitals would be affected. 340B hospitals provide significantly more uncompensated care than non-340B hospitals. The proposal would harm hospitals that provide high levels of care to Medicaid patients even though Congress set the 340B eligibility criteria to explicitly include high-volume Medicaid hospitals. This is not the time to make fundamental changes to the 340B program, especially as 340B hospitals struggle to meet the needs of their low-income and underserved populations in an era of rapidly increasing drug costs." **EBO**

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Study Identifies Disparity in Survival of AYA Hodgkin Lymphoma

SURABHI DANGI-GARIMELLA, PHD

Mortality in adolescent and young adult (AYA) Hodgkin lymphoma patients is significantly affected by ethnic and socioeconomic factors, as well as insurance status, according to a new study published in *Cancer Epidemiology, Biomarkers & Prevention*.[1]

The collaborative study, led by authors at the University of California Davis Comprehensive Cancer Center, gathered data for 9353 AYA patients with Hodgkin lymphoma from the California Cancer Registry. These patients were between 15 and 39 years of age when diagnosed during the period between 1988 and 2011. The primary variables impacting survival that were analyzed were sociodemographic characteristics [race/ethnicity, neighborhood socioeconomic status (SES), and health insurance], initial combined-modality treatment, and subsequent cancers on survival.

> **"Hodgkin lymphoma is thought of as a curable cancer. However, the impressive survival gains have not been shared uniformly across the AYA population."**
>
> —THERESA H.M. KEEGAN, PHD, MS

"Hodgkin lymphoma is thought of as a curable cancer. However, the impressive survival gains have not been shared uniformly across the AYA population," said lead author Theresa H.M. Keegan, PhD, MS, in an associated press release.

The study found that Hodgkin lymphoma–specific survival was worse for Black AYA patients diagnosed at both early stage [hazard ratio (HR), 1.68; 95% CI; 1.14-2.49) and late stage disease (HR, 1.68; 95% CI, 1.17-2.41), compared with White AYA patients. Also, Hispanic AYA patients diagnosed at late-stage had worse survival compared with White AYA patients (HR, 1.58; 95% CI, 1.22-2.04). Further, AYA patients diagnosed at an early stage did much worse if they lived in lower SES neighborhoods (HR, 2.06; 95% CI, 1.59-2.68), the study found.

Insurance status was another determinant of survival, according to the authors. Survival in AYA patients who were newly diagnosed with Hodgkin lymphoma was worse if they were uninsured or if they were covered by public health insurance (HR, 2.08; 95% CI, 1.52-2.84).

According to Keegan, some patients who may have initially been declared cancer-free may not have continued medical care, leaving them susceptible to secondary cancers or other complications and late effects. "Identifying and reducing barriers to recommended treatment and surveillance in these AYAs at much higher risk of mortality is essential to ameliorating these survival disparities," she added.

Study limitations included lack of information on follow-up treatment, lack of insurance information on patients diagnosed prior to 2001, and lack of information on changes in insurance status if it occurred after their initial treatment. **EBO**

REFERENCE

Keegan TH, DeRouen MC, Parsons HM, et al. Impact of treatment and insurance on socioeconomic disparities in survival after adolescent and young adult Hodgkin lymphoma: a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2015;25(2):1-10.

(CONTINUED FROM COVER)

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that required further research: namely, why don't tumors more readily activate the immune system? Or, if they do lead to immune activation, how do these tumors escape destruction by the immune system?

Several recent developments in immuno-oncology (I-O) offer great opportunities and challenges for all stakeholders in the war on cancer. These include:

- The approval of a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)–binding antibody (ipilimumab)
- The recent approval of 2 programmed cell death protein 1 (PD-1)–targeted antibodies (nivolumab and pembrolizumab) and the rapid development of other PD-1 and programmed cell death protein 1 ligand (PD-L1)–targeted agents
- Interesting results with genetically engineered chimeric antigen receptor T cells (CAR-T cells)

These agents, along with a very long list of vaccines, antibodies, and small molecules that trigger immune cell activation, elimination of regulatory cells, or signals that extinguish the immune response, are likely to dominate therapeutic advances in oncology for the next 10 years.

Whereas results supporting the role of the immune system in treating cancer are actually a rediscovery of the work of Cooley, the profound impact of the most recent work is the likelihood that these agents, either alone or in combination (more likely), will democratize the delivery of effective immunotherapy for potentially millions of individuals worldwide in short order—something that neither Cooley nor those who developed high-dose cytokine therapy achieved. This democratization of therapy, with its potential for fantastic benefits in a subset of patients, will raise significant challenges for the healthcare community.

IMMUNOLOGY 101 AND CANCER

Life in our natural environment is not possible without a well-functioning immune system. The body is marvelously designed to recognize things that are foreign and then amplify a specific set of immune cells in concert with a variety of other inflammatory *aide de camps* to assist in the elimination of the invading bacteria, yeast, or viruses. Several sophisticated mechanisms exist to extinguish this immune response when the invading beast is eradicated, as ongoing inflammation and immune amplification are neither energy-efficient nor safe. Individuals born with or acquiring immune defects are prone to infection. Those with deregulated immune systems suffer the ravages of their own immune system directed against their normal tissues and joints with attendant disability.

Cancer arises from the accumulation of at least one, and typically multiple, mutations, which then translate into changes in the structure of key proteins, thus changing the function and the biology of the affected cell and converting the protein into a foreign protein, much like a virus carries proteins on its surface that are recognized as foreign. These mutations provide the cell with a growth advantage, as well as an ability to escape the bounds of its normal anatomical home.[3] So why don't these mutated tumors, which are now at least partially foreign, attract attention and ultimate destruction by the immune system?

A wealth of studies, well outside of the scope of this review, have demonstrated 3 interesting observations.[3,4]

- Some tumors effectively shield themselves from the immune system through a variety of mechanisms and can be considered camouflaged.
- Some tumors do activate the immune cells, but have developed mechanisms to exclude these cells from entering their tumor nests, with the malignant cells essentially residing and expanding in an immune-free fortress.
- Some tumors express cell surface molecules that deactivate immune cells that have managed their way into the "fortress," essentially defusing what had been an activated cell poised to eliminate the tumor cell.

Two of the key interactions that defuse the active immune cell are CTLA-4 and PD-L1, found on tumor cells and other inhibitory cells in the tumor microenvironment (the fortress). The CTLA-4 inhibitor, ipilimumab, has demonstrated remarkable activity in a subset of melanoma patients, leading to responses that often take a few months to appear, presumably due to the time it takes to reawaken the immune response to melanoma cells. A second and similar approach is accomplished by antibodies that interrupt the linkage of the PD-1 molecule on the immune cell (the off switch) to the PD-L1 protein on the tumor cell, interrupting the trigger that defuses and thereby extinguishes the immune response.

CTLA-4, PD-1, and PD-L1 are not the only key proteins that modulate the immune system, however. Cells in the tumor microenvironment carry a host of other regulatory molecules that might augment the effectiveness of PD-1. Not surprisingly, pharmaceutical and biotechnology companies are working hard to evaluate whether these targets and agents that bind these targets might enhance the effectiveness of PD-1 agents or prove effective in those patients for whom the PD-1/CTLA-4 agents are not effective.

Although a bit earlier in development, CAR-T cells (genetically modified T cells created and partially expanded in a test tube) can be engineered toward a specific molecule restricted to a specific cancer cell–type of interest.[5] One of the major advancements of this field, compared with earlier trials of transferring immune cells (termed "adoptive immunotherapy") is the ability to expand these cells in the test tube and to provide them with potent activating signals that aid in their expansion and persistence once infused back into the patient. This approach helps to solve 2 of the problems listed above: namely, the ability to develop immune cells against camouflaged tumors and make them resistant to inactivation of exhaustion.

HOW EFFECTIVE ARE PD-1/PD-L1–TARGETED AGENTS AND CAR-T CELLS?

The research efforts with CTLA-4 largely focused on persons with advanced melanoma.[6] Although clearly an important new drug, ipilimumab impacted only a small portion of those individuals with cancer. The impending democratization of immunotherapy in the last year arises from a number of high-profile clinical trials that have demonstrated activity of PD-1– and PD-L1–binding antibodies in a variety of tumor types, including melanoma; essentially all types of lung cancer, kidney cancer, and bladder cancer; and Hodgkin's disease.[7-13] While the results are most impressive for Hodgkin's disease,[13] with an 87% response rate (most after an unsuccessful bone marrow transplant), immunotherapy's major impact will likely be in patients with high-risk solid tumors. Studies in melanoma, lung cancer, bladder cancer, and kidney cancer demonstrate that although only 1 in 5 (20%) patients had a reduction in tumor volume, a larger portion have stable disease.[7-12] Not yet reported in detail, early anecdotal evidence demonstrates similar activity in a variety of other malignancies, including head and neck cancers; certain types of colon, breast, and ovarian cancer; Merkel cell tumors; and esophageal cancer.

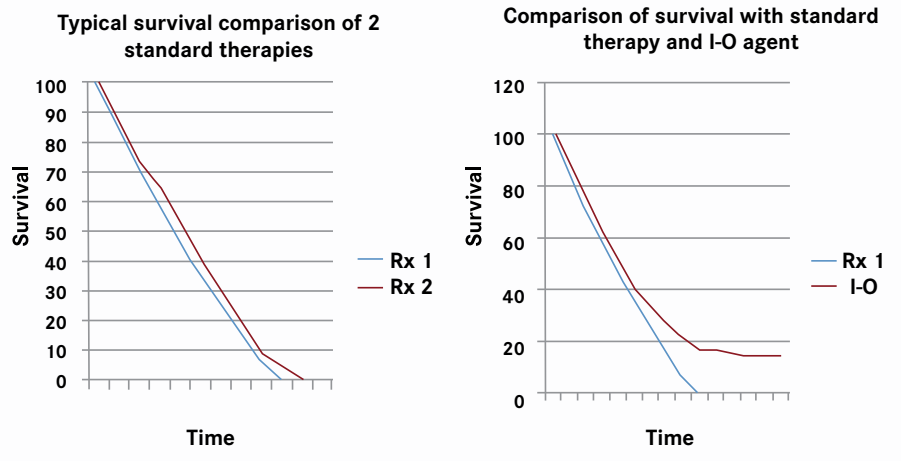
What is most intriguing, however, is not the response rate or the average time to tumor progression, but instead the tail of the curve (**FIGURE**). In all the studies looking at these contemporary I-O agents, there is a subset of 10% to 20% of patients who are doing remarkably well more than a year after treatment. Some studies with longer follow-up have demonstrated multi-year responses.[6-12] This is distinctly unusual from standard chemotherapy or molecularly targeted agents that inhibit nonimmune targets.

THE TAIL OF THE SURVIVAL CURVE

Patients treated with these I-O agents had widely metastatic and often drug-resistant diseases, with a predicted survival of usually less than a year.

(continued on **SP70**)

FIGURE. Difference in Tail of the Survival Curve With Immuno-Oncology Agents



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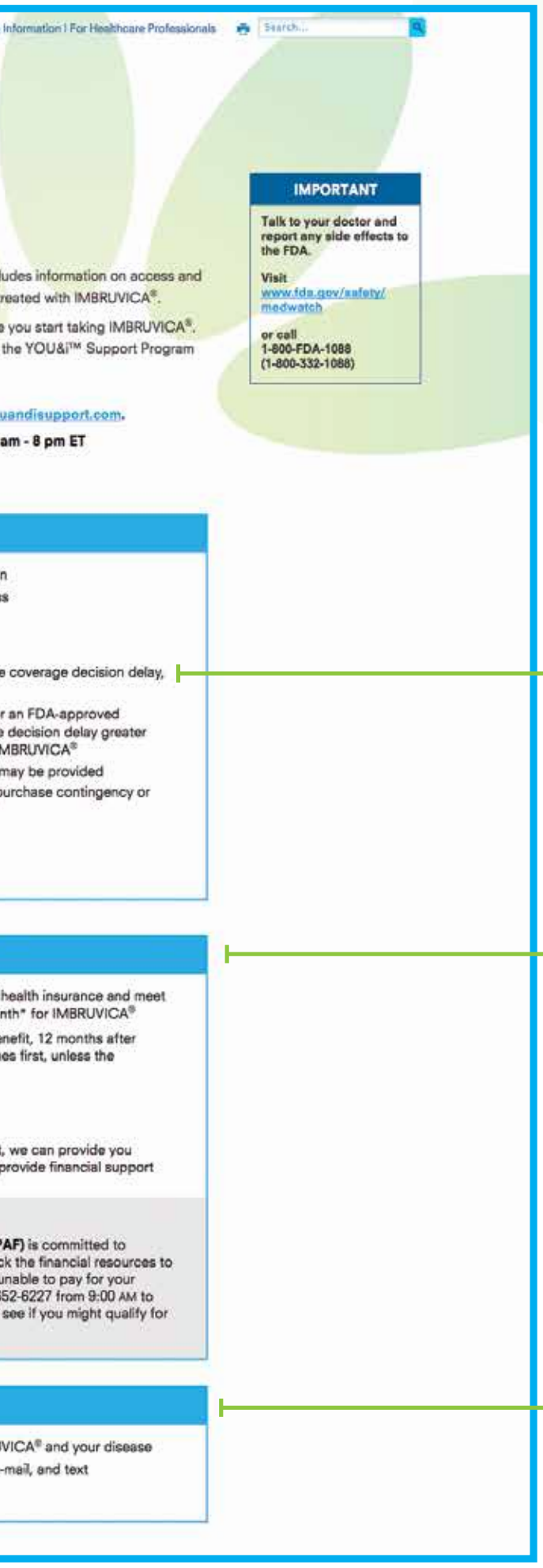

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(continued from **SP67**)

In melanoma, where some of the data with ipilimumab is most mature, a subset of patients are 10 years out from therapy, raising the specter that some of these individuals might be cured.[6] Although these results are striking, perhaps even more remarkable is that the combination of ipilimumab and nivolumab may provide even more striking long-term survival.[7]

For patients with advanced cancers that are currently treated with palliative (noncurative) intent, their primary question is, "Can my cancer be cured?" Indeed, other endpoints typically deemed important by oncologists, such as response rates, are low priority in comparison. If these therapies provide multi-year. and perhaps decade-plus remissions, even if that likelihood is low (say 10%), all patients will want a chance at winning on what might be considered a life-saving I-O lottery ticket, compared with the alternative—almost certain death in a year or two with what was until very recently considered best therapy. Interestingly, in a few studies, the toxicity associated with relatively ineffective chemotherapy (the previous standard) was more toxic then the PD-1 inhibitor.[10] Thus, PD-1 inhibitors gain a strong foothold based on response, the important "tail of the curve," and toxicity, and therefore deliver a proverbial "trifecta."

CAR-T cells involve considerably more time and attention to create and are still being made 1 patient at a time. These therapies will be more challenging to democratize although hundreds of millions of dollars are being invested in automating what for now is a partially manual process.[5] The effort has been deemed worthwhile by large pharmaceutical companies and some new biotechnology companies that have garnered huge investments from a variety of stakeholders following dramatic responses in children with acute lymphoblastic leukemia (ALL) and some other leukemias and lymphomas. The broad-scale applicability of CAR-T to leukemia and lymphoma or, more importantly, to solid tumors, is uncertain. One important challenge outside of manufacturing is the significant and, at times, lethal toxicity of this treatment. There can be sizable hospital costs associated with considerable inflammatory responses soon after administration of CAR-T cells. Nevertheless, it is possible that this therapy will provide cures for otherwise incurable conditions, which might support very significant price points with manufacturing. If better strategies are not developed to mitigate clinical costs, the total healthcare cost of this therapy might be very significant.

THE PATIENT AND PHYSICIAN PERSPECTIVES

I-O has had a singular impact on patients and providers. Patients have a growing recognition of the potential of I-O agents, including advertisements on national television. Currently, ipilimumab is approved for use in various stages of melanoma, pembrolizumab is approved for use in melanoma and lung cancer, and nivolumab is approved for use in melanoma, lung cancer, and metastatic renal cell carcinoma. With these approvals, patients with a variety of metastatic malignancies are, or soon will be, hearing of interesting results in their tumors. For now, access for these patients is largely through clinical trials, although there is some anecdotal evidence of patients receiving these agents off trial and outside their FDA indications. As these drugs are expensive, the risk of not being reimbursed is real, particularly for physicians in the community who bear the financial risks of unreimbursed drug expenses.

A second challenge for physicians is the management of toxicity. Although hair loss, nausea, and vomiting, all vexing issues associated with chemotherapy, are not issues with I-O drugs, the drugs are far from being free of toxicities. Most notable is that these immune activators can generate unwanted immune or inflammatory responses.[7-13] To date, the principal toxicities have been diarrhea (sometimes severe and long lasting), rash, and fatigue. Less common side effects have included dysfunction of the kidneys and liver; more worrisome, a variety of endocrine effects causing abnormalities in the thyroid, pancreas, and pituitary gland that sometimes require long-term hormone replacement. The latter is a new set of toxicities for oncologists who will need to quickly learn to keep these toxicities "top of mind" and become facile at evaluating and managing them. Many of the tissue toxicities, such as colitis, require steroids and occasionally other expensive and toxic agents. Endocrine abnormalities must first be recognized and then managed with hormone replacement therapy, which will require oncologists to either form closer relationships with endocrinologists or take the time to brush up on their endocrinology.

THE PHARMACEUTICAL AND BIOTECHNOLOGY PERSPECTIVE

The response by pharmaceutical companies has been dramatic. While Bristol-Myers Squibb and Merck are the early leaders, AstraZeneca, Roche, and others are not far behind. In addition, dozens of pharmaceutical and biotech companies have complementary agents, including vaccines and other small and large molecules. Investments into these ancillary initiatives are moving at full speed. CAR-T cells may either stand alone as a single modality or they might be combined with the above list of novel agents. A quick review of the ClinicalTrials.gov website reveals well over 100 trials underway in this space, including many large or randomized phase 2 or 3 trials and a large proportion in combination with vaccines and other novel immune-modulatory agents. A small army of medical oncologists is being recruited to pharma to help conduct these trials, and there is a growing concern that the clinical research infrastructure will be strained in an attempt to find the tens of thousands of patients needed to fill the current phase 1 through 3 portfolio of I-O trials.

THE PAYER PERSPECTIVE

The implications for those who pay the healthcare bill (insurance companies, employers, and now patients) are likewise daunting. Whereas a course of ipilimumab (4 doses) retails at about $130,000, it's important to note that the PD-1 inhibitors have an undefined duration of treatment, with some patients on therapy for over a year. A 1-year course of a PD-1 inhibitor is approximately $180,000.[14] If early results on the aforementioned cancers pan out, it is possible that 250,000 to 500,000 patients per year might be eligible to receive a course of an I-O agent or agents in the United States.

Of note, studies in melanoma and early results in other tumors suggest that a CTLA-4–binding antibody is likely to work better in combination with a PD-1 inhibitor than either drug alone.[7] Indeed, this combination was recently approved by the FDA in melanoma.[7] Although a person's size would determine the total costs associated with treatment with I-O agents, pricing of currently approved drugs, of those expected to be approved soon, and associated healthcare costs will all be very significant. If current drug prices are any indication, it is not hard to imagine that a significant proportion of cancer patients will be prescribed a regimen with a price tag in excess of $200,000 if they remain on therapy for a year. For example, 4 doses of ipilimumab and a year of a PD-1 inhibitor for an 80-kg individual cost $250,000 (note: the dose of nivolumab is lower when combined with ipilimumab). The market size of I-O agents alone in 2022 is predicted by some to be in excess of $30 billion.[15] Of note, the total dollars spent on anticancer drugs in the United States is currently about $30 billion.

It is important to appreciate that the I-O market is very young, and it is possible that the approval of multiple PD-1 and PD-L1 inhibitors might allow for intra-class price competition, as witnessed with the emerging market of hepatitis C drugs. While first-in-class agents generated a hefty price tag, the entrance of alternative curative therapies led to marked price concessions by manufacturers. The same may happen with I-O agents, largely driven by a consolidating payer landscape.

WHAT ARE THE IMPLICATIONS FOR SOCIETY?

With FDA approval for lung cancer, melanoma, and renal cell carcinoma, it is reasonable to predict that I-O agents, including additional monoclonal antibodies, CAR-T-cells, and various vaccines or immune-modulatory agents, will be approved in a variety of malignancies. This repertoire could include ALL, Hodgkin's disease, bladder cancer, head and neck cancer, breast cancer, gastric cancer, Merkel Cell tumors, and specific subtypes of colon[16] and endometrial cancers. Furthermore, all potential lethal cancers will be under evaluation by one or more pharmaceutical and/or biotechnology companies. If combinations are advanced, it is likely they will combine multiple novel agents, with the price tag for each agent in excess of $100,000. Whereas a few large pharmaceutical companies might have diverse I-O portfolios that allow them to co-market a drug cocktail at a less astronomical aggregate price, in many circumstances, these agents will come from different companies. The total price tags for these therapies—including monitoring, hospitalizations, and other components of care—could, therefore, easily exceed $200,000 per patient treated.

Assuming the I-O market reaches $30 billion in the next decade, how should we frame this expense? This expense would double the oncology drug spend and increase the oncology total cost by about 20%, but add only a miniscule amount to the multi-trillion dollar healthcare spend. Assuming the full potential of I-O drug cost is realized, will this cost be accretive? The total cost of oncology care was estimated to be $130 billion in 2010, with about one-third of that cost during the last year of a cancer survivor's life.[17] Much of this expenditure is on futile care. Is it possible that these therapies will provide benefits that will reduce hospitalizations and deaths? Can we estimate savings that such therapies might provide to the subset of patients who have long-term benefit? In the absence of such data, it is likely that society will focus on drug price as it grapples with the rising cost of healthcare. We might be in a quandary of having effective drugs, with evidence-based clinical criteria to support appropriate prescribing, at a difficult-to-afford price.

Although ultra-high drug costs have been the norm for rare diseases, the new I-O therapies have the potential to be useful in several hundred thousand patients annually. It is likely something will need to be done to manage this expense. An ideal solution is to identify a biomarker that can distinguish between responders and nonresponders. Early attempts in select tumors may have found a group that has a 40% to 60% chance[8,12] of winning the I-O lottery

compared with a 10% chance. While this is a start, it is likely that patients with desperate cancer conditions will gladly accept—and perhaps demand—a lottery ticket even if the odds of "winning" are only 10%!

Other possibilities might include variable pricing, for example, dependent on a priori chance of response in a specific tumor, or "indication-based pricing." Perhaps negotiating early cycles of therapy at deeply discounted prices, with only the full price paid if the therapy is effective (pay-for-performance)? Another option is to consider PD-1 and PD-L1 drugs as a single interchangeable class and having payers, group purchasing organizations, or pharmacy benefit managers limit their formularies for their prescribers based on price. It is conceivable that a multi-tier structure could be developed in which the wealthy can have unfettered access and those less fortunate might have limited access based on age, lottery, or some other yet-to-be-determined system. Even more Draconian strategies include having the government buy a portfolio of I-O agents or companies and provide them to citizens at "cost" (similar to how the CDC provides childhood vaccines to underserved communities). All of the above would require a major legislative overhaul or changes in how we manage the price, prescribing, and delivery of innovative therapies still under patent protection, not to mention a shift of our capitalistic healthcare market to a government service. It is conceivable that if these agents lead to the democratization of a highly effective therapy for a broad swath of the cancer population, the unthinkable may become thinkable.

In summary, it is likely that the translation of I-O from the research to the practice arena may provide significant clinical benefit to patients with difficult-to-treat malignancies, as well as considerable and well-deserved enthusiasm in our efforts to prevail over cancer. The further development and marketing of these agents might also serve as a lightning rod to escalating the discussion of how to equitably deliver important, innovative, and costly medical breakthroughs to a very large population of individuals in a time of constrained resources.

ACKNOWLEDGEMENTS

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CANCER MOONSHOT

Cancer MoonShot 2020 Proposes a Collaborative Precision Cancer Care Model

(CONTINUED FROM COVER)

To further discuss this venture, Patrick Soon-Shiong, MD, founder and CEO of NantWorks, and the brains behind this entire operation, invited Dan Hilferty, president and CEO of the Independence Health Group (parent company of Independence Blue Cross), and Paul Black, CEO, Allscripts Healthcare Solutions Inc, to participate on a panel at the Healthcare Conference on January 13, 2016.

PAUL BLACK

"The president mentioned MoonShot in his State of the Union speech, which has put us on the stage and in the news," said Soon-Shiong. "The opportunity to change healthcare forever, in the face of immunotherapy use, is upon us. It's taken us 15 years to get here." Explaining that our body has the innate capacity to immunize itself against infections, as well as abnormal growth, he added, "I have personally struggled with the fact that we destroy our immune system with chemotherapy and then boost the immune system with checkpoint inhibitors."

DAN HILFERTY

He acknowledged the fact that this dogma is influenced by factors beyond research, such as marketing plans and business decisions. "We know that when you create a blockbuster, it treats only 20% of those who receive it…this is well known." When a physician prescribes this treatment, Soon-Shiong added, he goes in blindly without knowing whether you fall under the responsive 20% or the unresponsive 80% of patients.

Another important aspect of the failure to treat is the dearth of patient participation in cancer clinical trials. Most trials are primarily conducted in academic centers, not in the community; community doctors often do not send their patients to these academic centers because of fear of losing them. "That is why only 4% of cancer patients are enrolled in clinical trials. But I firmly believe in measurement to improve health outcomes. We have to understand each of the 3 billion base pairs in every genome, which is an expensive proposition." That's where the health plans come in. "It will be paid for by pulling in the health plans," he said.

COMPLIMENTS AND CONTROVERSY

Hilferty acknowledged being a part of the group, "As part of MoonShot, we are working closely with the team." With heavy accolades for Soon-Shiong, Hilferty said he was the only individual who could pull together the financers, the pharmaceutical industry, the scientific heavyweights, the regulators, and the government for this project.

There is, however, some controversy associated with Soon-Shiong's claims. According to an article in *The Cancer Letter*, officials from the National Cancer Institute (NCI) and the FDA are not in partnership with NIC[1]; in fact, government officials asked Soon-Shiong to remove federal agencies from the press release announcing the partnership,[2] the article claims.

PATRICK SOON-SHIONG, MD

Explaining his company's decision to approve whole genomic testing for beneficiaries receiving treatment for cancer, Hilferty added, "We serve 3 million people in 5 counties in the Philadelphia region. [The trials] will include a small pool numbering in the hundreds, but it's a start. We want to prove that working together with whole genome testing will improve the quality of care and outcomes, as well as the service we deliver. This can serve an example for care providers across the country. With outcome-based practice of medicine, we can show that we can improve outcomes and reduce costs, as well. From an insurance point of view, this is the future." Hilferty said that they will be working to convince other insurers to get on board as well.

Black had similar praise for Soon-Shiong—for his vision and his leadership in marshalling competitors to collaborate on this project. "We have faith that the monstrous amount of data resulting from the sequencing can be applied and translated by community oncologists even in rural areas to improve outcomes," Black said, emphasizing the need to connect individuals with their data and their information. "We are thrilled to be a part of this project," he added.

According to Soon-Shiong, the platform they plan to develop can also help reduce the toxicities and avoid unnec-

essary treatment with chemotherapy agents. Introducing the concept of "targeted chemotherapy," he said clinical trials will be designed to conduct a micro laser dissection on tumor samples and measure resistance patterns of the tumor to different chemotherapy agents. "We can measure the resistance factor before treating patients with the drug…similar to how we measure antibiotic resistance in patients before starting them on an antibiotic." This can put an end to the trial-and-error empiric treatment.

> **"We want to prove that working together with whole genome testing will improve the quality of care and outcomes, as well as the service we deliver. This can serve as an example for care providers across the country. With outcome-based practice of medicine, we can show that we can improve outcomes and reduce costs, as well."**
>
> —DAN HILFERTY

"We also need to empower the patient with his medical records…think about a patient controlling his own medical records and giving the doctor the privilege to access it," said Soon-Shiong. "We want to create a predictive learning model, which makes real-time analysis vital. But analyzing and computing this huge amount of data in real-time requires enormous computing capacity." He said they plan to use the fiber optic cable that was earlier used by scientists working on the Large Hadron Collider, which has the capacity to compute data at the rate of 10 Gb/sec. "This is what we mean by analyzing tumor data in real time. We are not talking about retrospective claims data; it's tumor data that we now have the capability to analyze in 47 seconds."

Sharing his experience of meeting Vice President Biden and his staffers recently, Soon-Shiong said, "We explained this science to them, and we wanted to help them understand the problem and ask them for their support—regulatory and otherwise. Robert Califf and Janet Woodcock were there as well."

White House insiders have denied official support of the project. According to *The Cancer Letter*,[1] although Biden and his staff have participated in listening sessions with Soon-Shiong, neither the vice president nor any federal agencies are involved with the MoonShot program. In fact, Francis Collins, MD, PhD, director of the National Institutes of Health, said that the program described by Soon-Shiong at the Healthcare Conference does not involve the NCI or the FDA.

BACK TO MOONSHOT 2020

"The concept of immunotherapy as the backbone is the only way to fight this disease. My only concern is with wiping off the immune system," Soon-Shiong said, introducing the QUILT program as a part of Cancer MoonShot 2020. QUILT is designed to harness and orchestrate all the elements of the immune system (including dendritic cell, T-cell, and NK cell therapies) by testing novel combinations of vaccines, cell-based immunotherapy, metronomic chemotherapy, low-dose radiotherapy, and immunomodulators—including check point inhibitors—in patients who have undergone next-generation whole genome, transcriptome, and quantitative proteomic analysis, with the goal of achieving durable, long-lasting remission for patients with cancer.[2] **EBO**

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Evolving Practices in Managing Costly Immunotherapy

(CONTINUED FROM COVER)

(Keytruda; Merck), and ipilimumab (Yervoy: Bristol-Myers Squibb), for the treatment of various types of cancers. Beyond their remarkable survival rates, in comparison to traditional treatments and standard of care, these therapies are most recognized for their unsustainable price tags. Since their approval, healthcare systems across the country have struggled to determine the most effective strategy to incorporate these important agents into practice, while mitigating their cost.

PANEL DISCUSSION AT THE ONCOLOGY PHARMACY SUMMIT

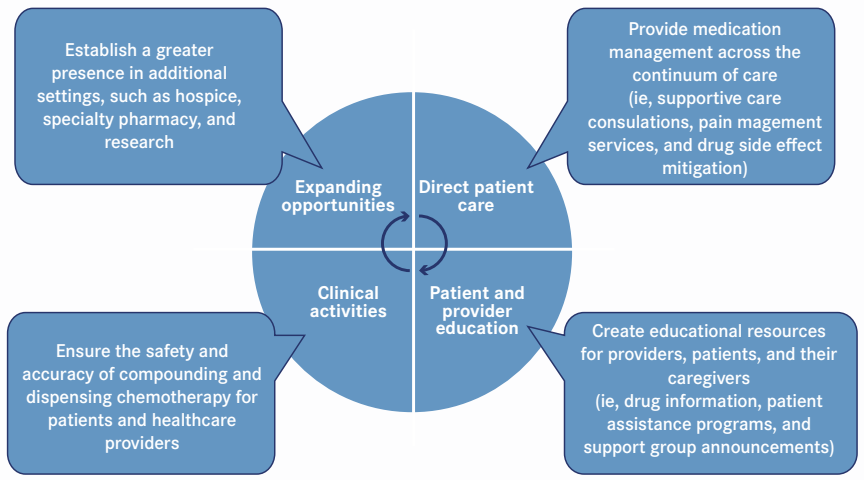
To address this nationwide concern, Vizient, Inc (the new brand identity for the organizations formerly known as, VHA Inc, UHC, and Novation), hosted a roundtable discussion, during its 4th annual Oncology Pharmacy Summit, on member strategies to manage immuno-oncology (I-O). The Oncology Pharmacy Summit is intended to provide a forum for member organizations, particularly those with large oncology patient populations, to discuss current critical issues and future opportunities within the cancer care environment.

The roundtable discussion started with most participants describing the overwhelming speed with which these agents have hit the market. Pembrolizumab was the first agent to be approved on September 4, 2014, for the treatment of patients with advanced or unresectable melanoma who had progressed on previous therapy and were no longer responding to other drugs.[1] In just 15 months, the PD-1 inhibitor has received 2 additional indications: for advanced non-small cell lung cancer (NSCLC), and most recently, an expanded indication to be included as first-line treatment in patients with unresectable or metastatic melanoma.[2,3]

The second agent in this class, nivolumab, was originally approved on December 22, 2014, for advanced melanoma. In just one year, it has achieved 4 additional indications including use in previously-treated squamous and non-squamous NSCLC, as part of a combination regimen with ipilimumab for untreated or unresectable advanced melanoma, and renal cell carcinoma in patients who have received prior therapy.[4-7] The work the FDA has accomplished in approving 8 indications between 2 agents for 3 different cancer types has been impressive, but has left insurance providers struggling to keep up with the labeled indications of these products, much less the off-label circumstances in which they are currently being considered.

Panelists also noted the rapid release of preliminary clinical trial announcements of I-O agents. These therapies are currently being tested in several different conditions, such as ovarian cancer, Hodgkin's lymphoma, and head and neck cancer, and are likely to yield results in the near future. Research is also being conducted on the sequence of combined modalities including surgery, radiation, traditional chemotherapy, and other new targeted drugs. The use of this innovative group of drugs will continue to surge as study results are confirmed and applications broaden. Therefore, the need to define effective strategies to evaluate and monitor use of these drugs will only continue to expand. One particular program was universally endorsed by all panelists as an essential component of managing these therapies—the employment and placement of clinical pharmacists in ambulatory clinics and in-patient service lines to assist physicians with appropriate dosing and monitoring of cancer patients.

FIGURE 1. The Role of Hematology/Oncology Pharmacists[9]



THE ROLE OF ONCOLOGY CLINICAL PHARMACISTS

Clinical pharmacists are the frontline defenders in effective medication utilization and are paramount in the therapeutic decision-making process. One study has shown that adding a clinical oncology pharmacist to a community oncology clinic resulted in a cost saving of $210,000 in patient charges by preventing drug waste, reducing chemotherapy dosages, and rounding to the nearest vial size, where appropriate.[8] Clinical pharmacists function as gatekeepers, actively reviewing patients' medical records to determine acceptable medication use in compliance with the health system pharmacy and therapeutics (P&T) formulary management, as well as employing dose-rounding strategies to ensure a reduction in drug waste (FIGURE 1).

A strategy in place at many institutions—and imperative to a health system—in managing this class of drugs is inpatient and outpatient drug formulary management. Policies to evaluate each medication, and resulting reimbursement for inclusion on the formulary, can greatly impact the economic bearings to the healthcare system and assist in dictating patient-specific utilization.

Inpatient and outpatient practices significantly differ in their reimbursement methods. Below are additional strategies for mitigating the cost of immunotherapy categorized by site of administration.

Managing the high cost of cancer therapy requires a dedicated multidisciplinary team of physicians, pharmacists, social workers, and finance to learn, organize, and execute strategies for a successful program.

INPATIENT PRACTICES FOR MITIGATING THE COST OF IMMUNOTHERAPY

It is not unusual for physicians to request a continuation of medication that the patient is receiving, on an outpatient basis, while that patient is admitted to the hospital. Moreover, when a cancer patient is admitted to the hospital for emergency care, new treatment options can be prescribed and administered as a matter of convenience. However, some medications require administration inside a hospital to ensure close monitoring by healthcare professionals. Without a proactive and comprehensive approach to medication management via P&T formulary policies, pharmacists will be hard-pressed to balance true patient considerations with the economic consequences of medication administration outside of the most cost-effective setting.

Expert Committees to Oversee Approval of Drug Use

To assist in the system-wide organization and coordination of policies and procedures, designated committees, involving key stakeholders and experts within the institution, must be created to facilitate the approval of processes surrounding these expensive items.

1. High Drug Cost Committee

This multidisciplinary committee is formed in alliance with the P&T committee to evaluate medications that cost the healthcare system a large amount of money. The committee should include physicians, pharmacists, finance or reimbursement specialists, and administrator champions to set policies and procedures documenting which marketed drugs will be evaluated using a scoring system to grade each medication, including available clinical data and pricing information. Additional factors, such as limited distribution channels and specialty pharmacy should also be considered. Each evaluation will determine the medications that will be allowed to be administered in-house as compared with those restricted to outpatient use only. It is important to remember that there remains no universal definition of a "high cost" drug. Rather, each organization must define the threshold above which this additional level of scrutiny will be applied.

2. Off-label Use Committee

Frequently, medications are studied in supplemental disease states beyond the conditions for which they were initially approved. The Off-label Use Committee is designed to approve

(continued on SP79)

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vizient

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ZARXIO™
(filgrastim-sndz)

Subcutaneous or Intravenous Injection
300 mcg/0.5 mL | 480 mcg/0.8 mL

NOW AVAILABLE

Supported by the totality of evidence for biosimilarity and the expertise of Sandoz, a Novartis company[1,2]

- First FDA-approved biosimilar[2]
- Approved in Europe in 2009[3]
- More than 7.5 million patient-exposure days outside of the US[3]
- Confirmed biosimilarity to Neupogen® (filgrastim)[2,3]

PRODUCT ATTRIBUTE	ZARXIO[1,4]	Neupogen[4]
Identical routes of administration	✓	✓
Identical dosing schedule	✓	✓
Identical dosage strengths	✓	✓

For the ZARXIO prefilled syringe, direct administration of less than 0.3 mL is not recommended due to potential for dosing errors.

Important Safety Information

CONTRAINDICATIONS

- ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

WARNINGS AND PRECAUTIONS

- Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Patients who report left upper abdominal or shoulder pain should be evaluated.
- Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Patients who develop fever and lung infiltrates or respiratory distress should be evaluated. Discontinue ZARXIO in patients with ARDS.
- Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions.
- Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.
- Glomerulonephritis has occurred in patients receiving filgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.
- Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.
- Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate treatment.
- Confirm the diagnosis of severe chronic neutropenia (SCN) before initiating ZARXIO therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Abnormal

ZARXIO™ shares the following 5 indications with Neupogen® (filgrastim)[1,4]

1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

ZARXIO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

ZARXIO is indicated to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3 Patients with Cancer Undergoing Bone Marrow Transplantation

ZARXIO is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

ZARXIO is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5 Patients with Severe Chronic Neutropenia

ZARXIO is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Important Safety Information (cont'd)

cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing ZARXIO should be carefully considered.

- Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.
- Leukocytosis:
  - Patients with Cancer Receiving Myelosuppressive Chemotherapy: White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy.
  - Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy: During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to >100,000/mm^3.
- Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.
- The possibility that filgrastim acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. Available data is limited and inconclusive.
- The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.
- Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes on nuclear imaging.

ADVERSE REACTIONS

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥5% difference in incidence compared to placebo) are thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, blood lactate dehydrogenase increased and blood alkaline phosphatase increased
- With AML (≥2% difference in incidence) are epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥5% difference in incidence) are rash and hypersensitivity
- Undergoing peripheral blood progenitor cell mobilization and collection (≥5% incidence) are bone pain, pyrexia, blood alkaline phosphatase increased and headache
- With severe chronic neutropenia (SCN) (≥5% difference in incidence) are arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia

Please see the Brief Summary on the following pages.

References: 1. Zarxio Prescribing Information. Sandoz, Inc. August 2015. **2.** Data on file. Sandoz Inc, Princeton, NJ. **3.** US Food and Drug Administration. Christi L. Overview of the regulatory pathway and FDA's guidance for the development and approval of biosimilar products in the US (approved in European Union under the trade name Zarzio). **4.** Neupogen® Prescribing Information. Amgen, Inc. July 2015.

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ZARX 0045 09/2015

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a Novartis company

ZARXIO™ (filgrastim-sndz) BRIEF SUMMARY OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of ZARXIO is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting ZARXIO therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping ZARXIO if the ANC increases beyond 10,000/mm^3 [*see Warnings and Precautions*].

Administer ZARXIO at least 24 hours after cytotoxic chemotherapy. Do not administer ZARXIO within the 24-hour period prior to chemotherapy [*see Warnings and Precautions*]. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of ZARXIO therapy. Therefore, to ensure a sustained therapeutic response, administer ZARXIO daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of ZARXIO therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

ZARXIO prefilled syringe with BD UltraSafe Passive® Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of ZARXIO less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.

ZARXIO is supplied in single-dose prefilled syringes (for subcutaneous use) [*see Dosage Forms and Strengths*]. Prior to use, remove the prefilled syringe from the refrigerator and allow ZARXIO to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any prefilled syringe left at room temperature for greater than 24 hours. Visually inspect ZARXIO for particulate matter and discoloration prior to administration (the solution is clear and colorless to slightly yellowish). Do not administer ZARXIO if particulates or discoloration are observed.

Discard unused portion of ZARXIO in prefilled syringes. Do not save unused drug for later administration.

Administration Instructions for the Prefilled Syringe

Persons with latex allergies should not administer the ZARXIO prefilled syringe, because the needle cap contains natural rubber latex (derived from latex).

Dilution

If required for intraveneous administration, ZARXIO may be diluted in 5% Dextrose Injection, USP to concentrations between 5 mcg/mL and 15 mcg/ml. ZARXIO diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP, or 5% Dextrose plus Albumin (Human), ZARXIO is compatible with glass, polyvinylchloride, polyolefin, and polypropylene.

Do not dilute with saline at any time, because the product may precipitate.

Diluted ZARXIO solution can be stored at room temperature for up to 24 hours. This 24 hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

CONTRAINDICATIONS

ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions. ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

Sickle Cell Disorders

Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.

Glomerulonephritis

Glomerulonephritis has occurred in patients receiving filgrastim. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.

Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Patients with Severe Chronic Neutropenia

Confirm the diagnosis of SCN before initiating ZARXIO therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing ZARXIO should be carefully considered.

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.

Leukocytosis

Patients with Cancer Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy [*see Warnings and Precautions*]. Dosages of ZARXIO that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell Collection and Therapy

During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to > 100,000/mm^3.

Cutaneous Vasculitis

Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

Potential Effect on Malignant Cells

ZARXIO is a growth factor that primarily stimulates neutrophils. The granulocyte-colony stimulating factor (G-CSF) receptor through which ZARXIO acts has also been found on tumor cell lines. The possibility that ZARXIO acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied, and the limited data available are inconclusive.

Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy [*see Dosage and Administration*].

The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.

Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

ADVERSE REACTIONS

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

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy

The following adverse reaction data in Table 2 are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, methylprednisolone, and methotrexate ("VIM3") (Study 3).

A total of 451 patients were randomized to receive subcutaneous filgrastim 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in Filgrastim Compared to Placebo)

System Organ Class Preferred Term	**Filgrastim (N = 294)**	**Placebo (N = 157)**
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%
Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%
Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

*Percent difference (Filgrastim – Placebo) was 4%.

Adverse events with ≥ 5% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day filgrastim (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in filgrastim patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment controlled study in patients with Hodgkin's disease (HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4 hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24 hour infusion (Study 6) filgrastim (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection

The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of filgrastim ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in Filgrastim Patients)

System Organ Class Preferred Term	**Mobilization Phase (N = 166)**
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving filgrastim (Study 7). 123 patients were randomized to a 4 month observation period followed by subcutaneous filgrastim treatment or immediate subcutaneous filgrastim treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of filgrastim was determined by the category of neutropenia.

Initial dosage of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response. Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory

tract infection and urinary tract infection were higher in the filgrastim arm, total infection related events were lower in filgrastim treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving filgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using filgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, timing of sampling, sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim reported in this section with the incidence of antibodies in other studies or to other filgrastim products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. The potential risk to the fetus is unknown. Reports in the scientific literature have described transplacental passage of filgrastim products in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

Nursing Mothers

It is not known whether filgrastim products are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if ZARXIO is administered to women who are breastfeeding.

Pediatric Use

ZARXIO prefilled syringe with BD UltraSafe Passive™ Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL is not recommended due to the potential for dosing errors.

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 – 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous filgrastim at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim. In this population, filgrastim was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

The safety and effectiveness of filgrastim have been established in pediatric patients with SCN [*see Clinical Studies*]. In a phase 3 study (Study 7) to assess the safety and efficacy of filgrastim in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 -17) [*see Indications and Usage, Dosage and Administration, and Clinical Studies*].

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown [*see Warnings and Precautions, Adverse Reactions*].

Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of filgrastim treated-patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Clinical studies of filgrastim in other approved indications (i.e., BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

OVERDOSAGE

The maximum tolerated dose of filgrastim products has not been determined. In filgrastim clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

Pharmacokinetics

Specific Populations

The pharmacokinetics of filgrastim were studied in pediatric patients with advanced neuroblastoma [*see Use in Specific Populations*], in subjects with renal impairment, and in subjects with hepatic impairment.

Pediatric Patients: The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim products.

Renal Impairment: In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end stage renal disease (n=4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment: Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, dose adjustment for ZARXIO in patients with hepatic impairment is not necessary.

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(continued from **SP73**)

the use of medications for an off-label indication. The team can be comprised of prominent chief medical officers and high-ranking pharmacy administrators, including a drug information officer. Physicians who submit an application for off-label administration should also be required to provide evidence-based proof of therapeutic validity. A decision on the submission-for-use should be reported to the applicant within 48 hours to provide real-time support and feedback.

3. Oncology Subcommittee

As a division of the formal P&T Committee, the oncology subcommittee includes lead oncology physicians and pharmacists throughout the healthcare system. This group convenes to discuss the clinical and operational aspects of oncolytics and supportive care medications used to treat cancer. They can make recommendations on agents to be added to the formulary or non-formulary, as well as participate in quality assurance, informatics, and therapeutic equivalence activity. Given the anticipated product pipeline, this group could help lead an organization's initial level of understanding and familiarity with the biosimilar pipeline.

OUTPATIENT PRACTICES FOR MITIGATING THE COST OF IMMUNOTHERAPY

In contrast to the inpatient diagnosis-related group codes for the purposes of hospital payment, the primary mechanism in ambulatory settings for authorization of drug regimens is the approval by a patient's insurance company. Multiple services can be used to ensure accurate payment for drugs and to improve the overall fiscal responsibility of an infusion clinic (**FIGURE 2**).

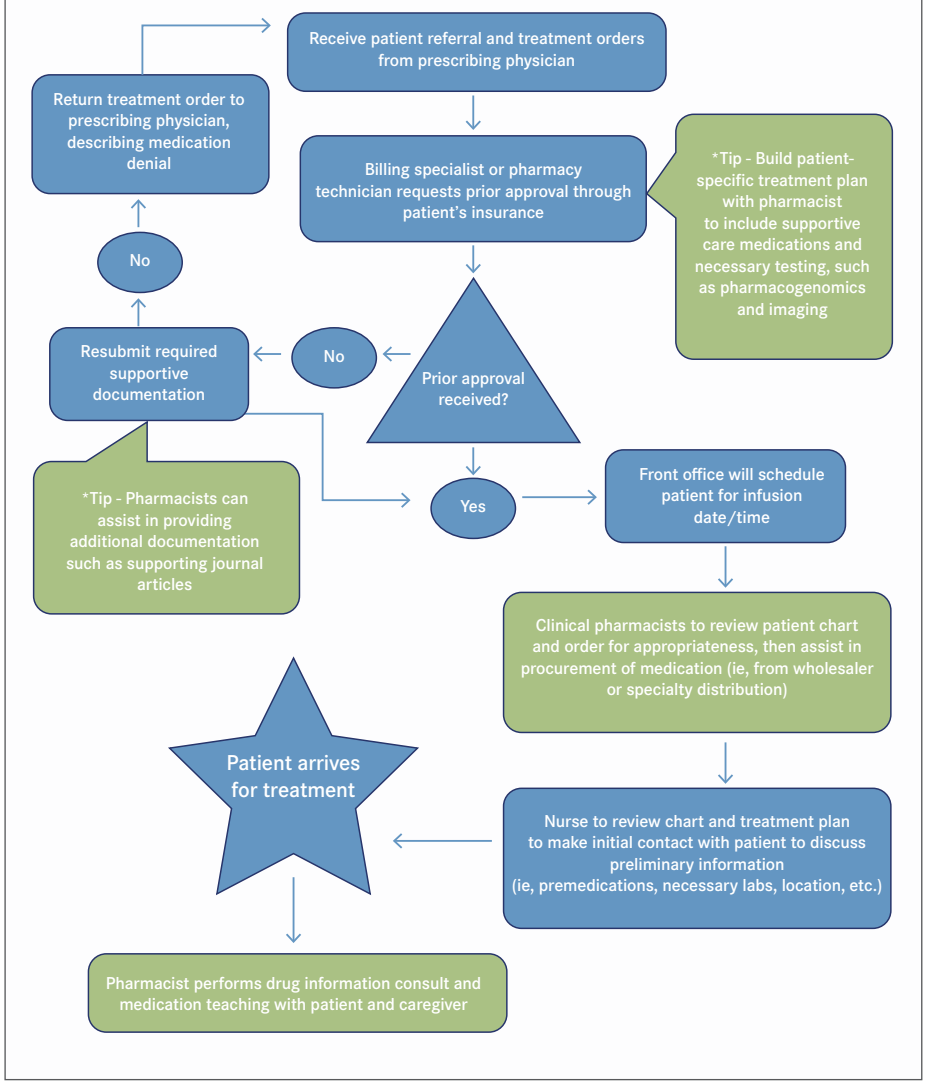
1. Insurance Approval

Receiving prior authorization on a patient's medications and services, prior to delivery, is an excellent method of verifying reimbursement for the patient. Employment of a billing specialist, with support provided by a pharmacist or pharmacy technician, can capture drug payments and prevent loss of significant revenue to the infusion clinic. While this service may incorporate additional steps, it can provide a preventive measure to ensure maximum allowable compensation.

2. Patient Assistance Programs

Patient assistance programs originated to provide a means to supply medications to patients with low income, a lack of health insurance, or a gap in prescription plan coverage. These programs are often funded by drug manufacturers and require the patient to meet an eligibility criterion to be accepted in the program. This avenue can provide auxiliary medications to the pharmacy that would have otherwise been a cost to the pharmacy budget. Participating in medication replacement programs are a cost-effective measure for the infusion clinic, and the patients they serve.

FIGURE 2. Infusion Clinic Prior Approval Process



3. Medication Billing

Depending on the services and infusions the clinic provides, it may be necessary to adopt a multi-billing system approach to maximize reimbursement. Outpatient account billing is an intricate process of submitting national drug codes with correct billing units and physician services in correlation with documentation. One step during the submission process is accounting for the amount of drug used for treatment. During the compounding process of intravenous medications, it may be necessary to dispose of a portion of unused drug. Insurance providers may allow for compensation of this remaining portion. It is important to have regular discussions with the finance department with regards to multi-billing approaches, including but not limited to, appropriateness of billing for waste, previously rejected claims, and updated code and billing unit information.

CONCLUSION

Cancer immunotherapy has the potential to produce lifesaving treatments for patients, but at a great expense. Managing the high cost of cancer therapy requires a dedicated multidisciplinary team of physicians, pharmacists, social workers, and finance to learn, organize, and execute strategies for a successful program. The programs suggested above are pertinent, not only to costly oncology therapies, but also to other disease states that require expensive treatments. Such programs must be present and highly functional in order to address the staggering cost of today's medications and to prepare for the clinical future of I-O with combination therapy. To continue to provide patients with contemporary treatment options, healthcare providers must remain at the leading edge of cost-containment approaches.

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