Bridging the gap between payer and provider perspectives

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Evidence-Based Oncology

THE COST AND VALUE ISSUE

340B Policy

Three Proposals to Reform the 340B Drug Discount Program

RENA M. CONTI, PHD; PETER B. BACH, MD, MAPP; MICHAEL KOLODZIEJ, MD

WHAT IS 340B?

Section 340B of the Public Health Service Act, passed by the Congress in 1992, was intended to provide assistance to medical providers who serve poor, underinsured patients.[1] The 340B Program provides enrolled hospitals and other providers (340B-qualified entities) with deep discounts on the acquisition costs of outpatient drugs, whether those drugs are later administered by physicians or dispensed by pharmacies.[2] Reports suggest the original program has substantially expanded in recent years via newly qualified entities, affiliated clinics, and contract pharmacy relationships.

Through deep acquisition cost discounts, the original intent of the 340B program was to enable underfinanced medical providers (a variety of safety net clinics and selected hospitals and their affiliated clinics and pharmacies) to purchase otherwise expensive drugs for the outpatient treatment of their patients. By statute, the program does not require 340B entities to pass on the drug discounts to the patients they treat, nor to the insurance plans that cover those patients.[2] Neither does it require these entities to limit the patients who receive the discounted drugs to those who are poor and in need. Instead, 340B entities, alone or via their contract pharmacies, can dispense discounted drugs to all their patients (except in some cases those insured by Medicaid), and keep the profits they make when they bill insurers and patients for the drugs as if they had purchased them at full price.[1]

(continued on page SP576)

Patient Advocacy

Eliminating a Barrier to Cancer Care through Universal Fair Access to Oral Chemotherapy Medications

CHRISTOPHER HANSEN

A cancer diagnosis can generate a host of fears, including fear about the availability and cost of the recommended treatment for a particular diagnosis. Cancer patients and their families, although rightly concerned about whether a treatment has been discovered for their particular cancer, also worry about their ability to afford those lifesaving cancer treatments.

To reduce death and suffering from cancer, we need a balanced approach that fosters continuous innovation in the development of cutting-edge cancer treatments that will save more lives and is affordable for those who need it. With increasing attention being paid to the rising cost of prescription medicines, one aspect of this issue that has seen visible progress in terms of accessibility is oral chemotherapy fairness.

Historically, the majority of frontline cancer chemotherapy treatments were administered intravenously to patients in their physician's office. However, scientific advancements over the past several years have brought forth effective oral medications for cancer that are convenient to self-administer, require less time off from work and less travel time to and from medical facilities, and, in some cases, come with fewer side effects (see Sidebar). Today, oral chemotherapies account for about 10% of available chemotherapies and roughly 25% of the medications in the oncology development pipeline, indicating a growing role for oral chemotherapy in cancer treatment.[1]

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PBM Commentary

Managing Costs and Enhancing the Value of Oncology Care

SURYA SINGH, MD; CHRISTINE SAWICKI, RPH, MBA; KEN VANDER PYL; ALAN LOTVIN, MD

SUMMARY

Management of high and rising costs in oncology requires a multifaceted approach using both innovative strategies and pragmatic tools. Increased spend is often attributed by plan sponsors to factors including the growing number of novel oncology therapies and expanded indications for previously approved therapies. In this article, we discuss these and several additional factors also influencing costs of oncology care, including improved patient survival, regulatory changes, increasing drug utilization, off-label drug use, and provider consolidation.

Current management methods in oncology include prior authorization, pharmacy and medical claims editing, restructured plan designs, and pharmacist- and nurse-led care management. The use of alternate sites of care for select therapies and the increased availability of genomic and other advanced molecular diagnostic testing are newer additions to the portfolio of management tools.

Value-based cancer care models are emerging and represent a significant evolution of the oncology payment model. In these new models, providers are rewarded for providing cost-effective and higher quality patient care. With respect to management in these new models, the focus shifts away from individual point-of-care activities and instead recalibrates on a holistic view defined by episodes of care. Several prominent organizations in oncology, including the Centers for Medicare and Medicare Services (CMS), the Na-

(continued on page SP583)

Also in this issue...


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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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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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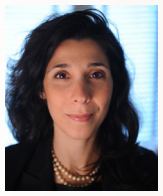
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Healthcare's Journey to the Fulcrum That Balances Cost and Value


MIKE HENNESSY, SR

The drug price discussion, rather than debate, has worked its way into business, social, and political conversations around the nation. Some pharmaceutical sympathizers/lobbying groups would argue that the percentage of drug spending has remained stable over time when adjusted for inflation and that healthcare costs have risen, overall; but, the bottom line is still the significant growth in healthcare spending.

So why are we so sensitive to healthcare costs? The primary reason is the uncertainty of healthcare outcomes. Human health, and its care, are a gamble—considering the wide variability in response to a particular treatment regimen, uncertainty looms large. Going back several decades, healthcare costs were paid directly by patients or consumers, while health plans and managed care were still gaining a foothold. As the managed care industry grew, however, the healthcare industry, as a whole, observed a cost shift from the patient to the health plans. Today, we are witnessing a shift back to the patients. Increasing drug prices, the Affordable Care Act, and alternative payment models are just some of the factors shifting the cost back to the patient, either via higher deductibles or greater out-of-pocket costs.

However, in a move to balance the pushback from health plans, as well as pharmaceutical benefit managers, the pharmaceutical industry is developing risk-sharing models, such as pay-for-performance where reimbursement for a drug is determined by the plan member's response to treatment. These, and other healthcare models, are all a part of the growing inclusion of "value" talks in the healthcare industry. As you'll read in this year-end issue of *Evidence-Based Oncology*, value is a variable that includes much more than just the cost of a commodity or service.

For Debra Madden, a 2-time cancer survivor and patient advocate, it's about receiving the care prescribed by her oncologist without going bankrupt. "Since cancer is an expensive disease, shouldn't the costs be covered by insurance for those of us who are insured?" Debra asks. Patient advocacy groups, like the American Cancer Society Cancer Action Network (ACS CAN), would like to see changes in oral parity, among other things, and ACS CAN has been helping 40 states pass oral chemotherapy fairness laws since 2007. Veena Shankaran, MD, MS, medical oncologist at the University of Washington School of Medicine, believes that addressing the financial burden faced by some of her cancer patients requires efforts at the policy, payer, and clinic levels.

A successful alliance between 21st Century Oncology and the Lee Memorial Health System in Florida resulted in a new breast cancer clinic that would effectively integrate radiation oncology, surgery, and medical oncology. The integrated care delivery reduced the "screening-to-call back" average, as well as the "screening-to-diagnosis" average, the author reports.

In terms of healthcare coverage, decision-support tools and consumer education can help patients look beyond premiums offered by health plans, especially with respect to the state healthcare exchanges, write Caroline F. Pearson and Deirdre B. Parsons, MPP, MPH, MS, of Avalere Health. Raising awareness can influence patient understanding of access to services and cost of care, and, consequently, reduce their out-of-pocket costs.

Several organizations have developed value calculators that touch on different aspects of care held valuable by each stakeholder. These models—Evidence Blocks, DrugAbacus, and the Value Framework—have been reviewed by experts at Cardinal Health Specialty Solutions and the University of Texas School of Public Health. To complement the movement toward value-based care, a huge shift in policy may be vital, and we hope to see some of these changes reflected in clinical practice in the coming years.

As always, we appreciate your interest in our publication. Don't forget to visit our website, www.ajmc.com, for healthcare news updates and conference coverage.

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.

The Struggle Between Oncology Care Cost and Value

Since the passage of the Affordable Care Act (ACA), there has been a push by numerous stakeholders to reduce healthcare costs while enhancing value delivery to patients. In many areas of medicine, both goals can be achieved by reducing inter-physician variability in care delivery and giving providers incentives to consistently apply best practices on a population basis. The cancer care model, however, is different and far less amenable to this approach. For many patients with advanced-stage or high-risk cancers, there is no clear standard of care. For others, the emergence of genetic and molecular testing has shown that what was previously believed to be one type of cancer may represent dozens of molecular subtypes, each requiring a profoundly different therapeutic approach.

Additional factors that contribute to rising cancer care costs include the aging population, astronomical increases in pharmaceutical costs, increasingly complex multimodality care, and advances in surgical and radiotherapeutic technology. Costs are further inflated through non–value-added care delivery mismatches, and increasingly expensive end-of-life care. As a result, the National Cancer Institute projects that cancer care costs will increase by 27% between 2010 and 2020, rising to an estimated $158 billion annually.[1] The implications of these rising costs are beyond societal—they have an increasingly personal impact on patients. The rising burden of cancer care costs shouldered by patients and their families has led to the coining of the term "patient financial toxicity."[2]

The tension between controlling rapidly-growing cancer care costs and the need to enhance oncology value-delivery has, therefore, been escalating. Numerous stakeholders, including patients, families, physicians, payers, managed care plans, pharmacy benefits managers, employers, and the government, are deeply invested in trying to navigate this conundrum. Each has a unique perspective that may not be fully informed by that of the other stakeholders, and the task is rendered all the more difficult by 3 key factors:

- The standard of care for treating patients with cancer is a rapidly moving target.
- There is no clear consensus on what constitutes value in cancer care.
- Information is siloed and frequently inaccessible; as such existing metrics for cancer care performance and patient outcomes are very poor indicators of actual value delivery.

While most stakeholders are willing to accept that cost is not the sole determinant of value delivery, both our language and tools for fully defining what constitutes value-based cancer care are in their infancy. This process is further challenged by the fact that data collection by billing codes provides vanishing little information regarding the appropriateness, effectiveness, or patient-centeredness of care. Electronic medical records have also been of limited use in accessing essential care data, because much of that data remains trapped within paper records that can only be mined at enormous cost and inconvenience. The way out of this conundrum begins with robust, multi-stakeholder deliberations on ways to contain costs and promote healthcare innovations while creating a system that allows for the economically sustainable practice of personalized medicine.

Given the breadth of stakeholders and the complexity of cancer care in the United States, cost-effective care that is robust enough to empower personalized medicine solutions can only be achieved by engaging stakeholders in a process that increases the "systemness" of care.

A number of stakeholders have made important forays toward addressing these complex issues. These include the National Comprehensive Cancer Network (NCCN), whose Evidence Blocks provide a formulation for comparing the relative effectiveness and value of differing therapeutic regimens,[3] and the American Society of Clinic Oncology's (ASCO) Value Framework, which includes an important acknowledgment of a patient's financial toxicity as a risk of cancer care.[4] On the data side of the equation, Flatiron is one of several companies attempting to convert all of the data contained in healthcare records into information that can effectively inform stakeholder discussions.[5]

Evidence-Based Oncology's mission is to further advance the conversation among stakeholders, so that we can create effective responses to the cancer cost/value conundrum. In this issue, Dr Bruce Feinberg of Cardinal Health reviews some of the new value calculators related to the cost versus value debate. Dr Veena Shankaran of the University of Washington and Dr Jonas de Souza of the University of Chicago review the patient burden of cancer care costs. Dr Constantine Mantz reviews the importance and effectiveness of developing a greater collaboration between providers and cancer care facilities.

While cost is an important component of value, it tells only a small part of the cancer care story. By focusing on issues of payment and cost alone, we miss our opportunity to engage cancer care stakeholders in the process of creating a more effective system of care. Given the breadth of stakeholders and the complexity of cancer care in the United States, cost-effective care that is robust enough to empower personalized medicine solutions can only be achieved by engaging stakeholders in a process that increases the "systemness" of care.[6] The term "systemness" refers to a model of care in which all of the constituent parts function with maximum transparency, efficiency, effectiveness, and patient centeredness. It is this quest for perfect alignment of people, resources, information, and capital that forms the basis for a sustainable care delivery system.[7]

At the recent Patient-Centered Oncology Care meeting in Baltimore,[8] *hosted by The American Journal of Managed Care*, stakeholders had an opportunity to gather and discuss these issues from a multi-stakeholder perspective that provided an excellent foundation for understanding the cost conundrum, and also pointed a way forward. What we ultimately seek is a cancer care delivery system that places patients' risk-adapted care needs first, creates systems to ensure economically sustainable care delivery, and provides each stakeholder with the information necessary to bring such a system to life. **EBO**

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Is There a Mathemetical Resolution to the Cost-Versus-Value Debate?

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The projections for the rising cost of cancer care have spurned robust dialogue from every sector of the healthcare economy.[1] Among the many targets for cost control are the rising cost of cancer specialty drugs—drugs distinguished by their route of administration, synthesis or bioengineering, mechanism of action, cost, etc.[2] Although there are examples of market forces and competition emerging to tamp down prices to more acceptable levels (eg, pharmacy benefit manager negotiations for hepatitis C drugs), stakeholders seem impatient for these market-based solutions.[3]

Payer approaches to specialty drug cost control have included, but are not limited to:

- Bundled reimbursement
- Episode-of-care reimbursement
- Restricted clinical pathways
- Product tiering
- Step edits.

Proposed policy approaches to specialty drug cost control have included, but are not limited to:

- Empowering Medicare to negotiate drug prices (as the Veteran's Administration does)
- Allowing the importation of drugs for personal use
- Reforming the patent system to combat so-called pay-for-delay settlements between brand and generic drug makers.

Solutions proposed by patient advocates and physicians aim to control costs by providing standardized approaches to valuing new drug/treatments compared with 1 or several prevailing standards of care. Increasingly, the debate over cost is transitioning to a debate over value, but the value of cancer drugs—in what is often a complex multi-modality treatment of a terminal disease—is complicated to say the least.[4,5]

VALUE CALCULATORS

Thus far 2 provider organizations, one a professional society and the other a cancer center, have developed a value-based cancer care model geared to the patient and the provider. These models were recently made available for peer and public review. A third was previewed with limited content restricted to 2 less-prevalent cancer diagnoses.

The American Society of Clinical Oncology (ASCO) announced its Value Framework in June 2015, which is designed to help physicians and patients assess specialty drug treatments based on their clinical benefit, side effects, and cost. ASCO's approach is thus far unique, released to the public and professional community using a peer-reviewed publication that included extensive background and content on methodology. Schnipper et al have detailed the nuances of the Value Framework, developed by ASCO's Value in Cancer Care Task Force, in the *Journal of Clinical Oncology*.[6] The framework is expected to be applied by medical oncologists to assess the relative value of cancer therapies, in various clinical scenarios, as an element in the shared decision-making process with their patients.

In the same week, an interactive online tool developed by Peter B. Bach, MD, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center (MSKCC), was also made public. The DrugAbacus calculator attempts to place drug costs in line with their overall value (**FIGURES 1** and **2**). The calculator has primarily been developed as a tool for research and information only, but critics and supporters believe it "may be utilized by physicians to start a conversation discussing the value of chemotherapy agents with their patients." However, the authors clearly state it is purely informational and should not be used to guide decision making.[7]

More recently, the National Comprehensive Cancer Network (NCCN) provided a preview of its Evidence Blocks via mainstream media and its website. The Evidence Blocks, for now, are limited to multiple myeloma (MM) and chronic myeloid leukemia (CML). The NCCN Evidence Blocks are published in a new version of the NCCN Guidelines and are intended as a visual representation of 5 key value measures: efficacy, expected associated toxicities, and the quality, quantity, and consistency of the evidence that provide important information about specific NCCN Guidelines recommendations (**FIGURE 3**).[8]

Other strategies aiming to gauge cancer-drug value are under development by the European Society of Medical Oncology and the Boston-based Institute for Clinical and Economic Review (ICER). ICER recently announced it had received a $5.2 million grant from the Laura and John Arnold Foundation to produce 15 to 20 reports on the value of major new drugs approved by the FDA.[9] Understanding the similarities, differences, and potential limitations of these approaches to calculate cancer-drug value will be critical to their adoption and appropriate use.

VALUE AND QUALITY

Interpreting value relative to cost, what is often also referred to as cost-effectiveness, is not a new concept in healthcare. For over 2 decades, cost-effectiveness analyses, particularly in the United States, have used a figure of $50,000 per life-year or quality-adjusted life-year (QALY) gained as a threshold for affirming the cost-effectiveness of an intervention. The history of this practice is ill defined, although it has been linked to the end-stage renal disease kidney dialysis cost-effectiveness literature that dates back to 1968.[10] The use of $50,000 as a benchmark for assessing the cost-effectiveness of an intervention first emerged in 1992 and became widely used after 1996.[11] Critics have argued that this figure is arbitrary, that its appeal lies more in the convenience of a round number rather than in the current value of renal dialysis or in stakeholder assessment.[12] Nonetheless, cost-effectiveness or value analyses of healthcare interventions have an extensive history.

The confusion inherent to the casual interchangeable use of terms like quality, value, and cost-effectiveness was clarified in a seminal report published in 2002 by the Institute of Medicine (IOM), Crossing the Quality Chasm.[13] This influential work framed all future discussions of quality healthcare. In the report, IOM outlined 6 specific aims that a healthcare system must fulfill to deliver quality care:

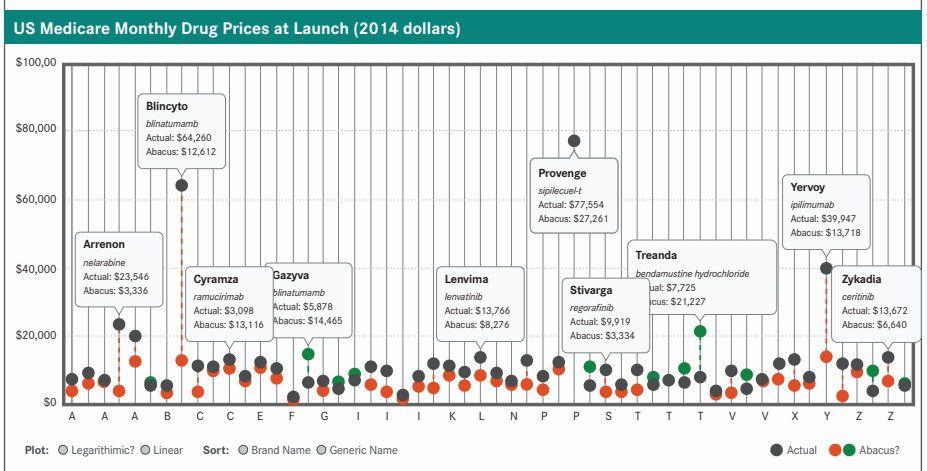
1. **Safe:** care should be as safe for patients in healthcare facilities as in their homes.
2. **Effective:** the science and evidence behind healthcare should be applied and serve as the standard in the delivery of care.
3. **Efficient:** care and service should be cost-effective and waste should be removed from the system.
4. **Timely:** patients should not experience waits or delays in receiving care and service.
5. **Patient-centered:** the system of care should revolve around the patient, respect patient preferences, and put the patient in control.
6. **Equitable:** unequal treatment should be a fact of the past; disparities in care should be eradicated.

Although the focus of the IOM report was not the medical intervention itself, but the healthcare system delivering it, its conclusions broadened value concepts for interventions beyond safety and efficacy. Cancer-care value assessments, which historically have focused on efficacy and toxicity, have been informed by this seminal work. Patient-centered aspects of treatment value like route, frequency, and site of administration are now routinely considered. The IOM's report on quality and the legacy of research using QALYs serve as a foundation on which these new value tools can be evaluated.

METHODOLOGY USED BY THE VALUE CALCULATORS

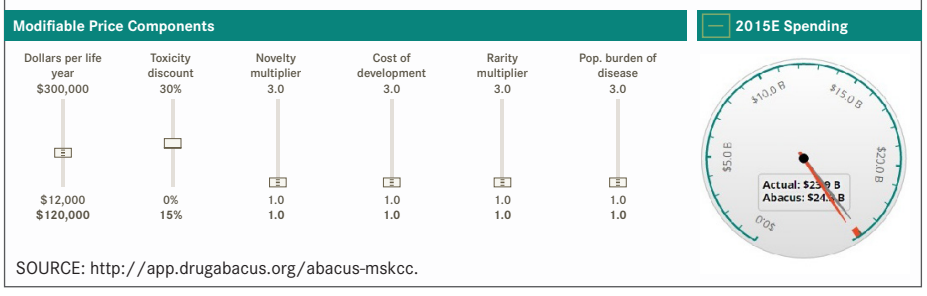
The authors of the ASCO Value Framework have attempted to define value in terms of 3 of the 6 IOM elements of quality healthcare delivery: efficacy (clinical benefit), safety (toxicity), and efficiency (cost). They have chosen to use "net health benefit" (NHB), which is the dif-

FIGURE 1. Actual and DrugAbacus-Calculated Medicare Monthly Drug Price of Oncology Agents



SOURCE: http://app.drugabacus.org/abacus-mskcc.

FIGURE 2. Modifiable Inputs That Determine Drug Cost Using DrugAbacus



SOURCE: http://app.drugabacus.org/abacus-mskcc.

ference in mean effectiveness of a new treatment compared with a standard, as the aggregated metric for a value assessment in this tool. NHB is composed of 3 elements: clinical benefit (max 80% contribution), toxicity (+/- 20% contribution), and bonus points (maximum, 30). Clinical benefit is assigned a score between 1 and 5 based on the fractional improvement in overall survival (OS) or if not available, progression-free survival (PFS) based on a specific clinical scenario comparator. The clinical benefit score is then multiplied by a weighting factor (16 for OS and 11 for PFS). Toxicity is also assigned a categorical value ranging between –20 and +20 based on fractional decrease or increase in grade 3 to grade 5 toxicities of the comparator. Finally, bonus points can be awarded for differential symptom palliation or treatment-free interval.

The task force has decided to display NHB as a separate calculation without the cost factored in so that physicians and patients can view the clinical information independent of the cost. Although this methodology deviates significantly from formal economic analysis, it may feel more realistic to both the physician and the patient who are focused on a very specific clinical scenario.

The DrugAbacus uses 4 of the 6 parameters outlined by the IOM for quality healthcare delivery: efficacy (clinical benefit), safety (tolerability), efficiency (cost), and equity (rarity and population burden). Only timeliness and patient centeredness are not considered.

The 6 specific attributes that DrugAbacus does consider in value determination, include: efficacy, toxicity, novelty, development cost, disease rarity, and population burden—all at the individual drug level. In this tool, as in the ASCO framework, efficacy is measured in terms of OS; if OS is not available, then PFS or response rate are used as a surrogate, but modified by a level of evidence grade into an estimated OS benefit. Toxicity scoring has 2 components: differential proportion of grade 3 to 4 adverse events (AE) and differential probability of drug discontinuation due to AE. The user determines the weight of each of the components. For example, the user must determine the value of efficacy in order to output a price, and can also manipulate the weight of the other factors. The output is dependent solely on how the user values each of those 6 attributes.

The NCCN Evidence Blocks are in development, but from the information currently available, value determination is regimen-based, rather than drug-based, and comprises the following:

- Efficacy of regimens
- Safety of regimens
- Quality and quantity of evidence for regimens
- Consistency of evidence for regimens
- Affordability of regimens

Each of the attributes is graded 1 to 5 and presented to the user in a visual 5 x 5 grid of 25 squares, with the X axis having 5 columns, 1 for each attribute, and the Y axis having 5 rows for low to high assessment. The higher the value, the more opaque the grid. The affordability measurement represents an estimate of overall total cost of a therapy, including, but not limited to, acquisition, administration, in-patient versus out-patient care, supportive care, infusions, toxicity monitoring, anti-emetics and growth factors, and hospitalization. Although a detailed methodology that explains the process used to assign grade is not yet available on the NCCN website, a list of the criteria used by the panel members to score the measures is elaborated, suggesting that as per the historical guidelines, the Evidence Block grading system will be by subjective consensus among panel members.

EFFICACY

In regard to efficacy determinations, the tools use significantly different approaches, as evidenced by their use to assess systemic treatment value in stage IV, or metastatic, non-small cell lung cancer. The Value Framework presents 4 different clinical scenarios, 2 comparators at a time, which may include as many as 5 drugs incorporated into treatment cocktails or regimens.

In the DrugAbacus, the comparison is made at the single-drug level even when the drug is only administered as one component of a regimen. Although DrugAbacus currently has information pre-populated for 54 different chemotherapeutic agents, all information is based on the drug's first approved indication and monotherapy, neither of which may apply to the specific clinical scenario of interest.

NCCN's approach to MM and CML suggests that an efficacy grade of 1 to 5 will be assigned based on panel consensus for each regimen and comparator. Although all tools limit comparisons to prospective published peer-reviewed study data comparing the new agent or specific regimen of interest with known comparator(s) of interest, NCCN offers some redress by addressing quality, quantity, and consistency of evidence.

TOXICITY

In regard to redress of toxicities, the approaches are again different. ASCO's Value Framework limits AE inclusion to those grade 3 to 5 only and treats all of them equally. The DrugAbacus also limits to higher grade (3 and 4) AE, then augments that number by determining their influence on value by including toxicities that impact discontinuation rates or impact resource utilization. NCCN takes a more inclusive approach grading toxicity from 1 (not meaningful) to 5 (severe, life threatening). Despite such thoughtful and varied approaches to the impact of safety/toxicity on value, AE burden remains incredibly subjective for most patients.

Despite such thoughtful and varied approaches to the impact of safety or toxicity on value, AE burden remains incredibly subjective for most patients. Alopecia is unlikely to result in treatment discontinuation or acute care intervention cost, but it is a deciding factor in some patients' treatment selection. Severe neutropenia has a real mortality risk yet can be effectively prevented, but only at a potentially significant cost. Intermediate grade neuropathy may neither incur acute care intervention cost nor impact treatment intensity, but physicians are all too aware it may become a lifelong disability.

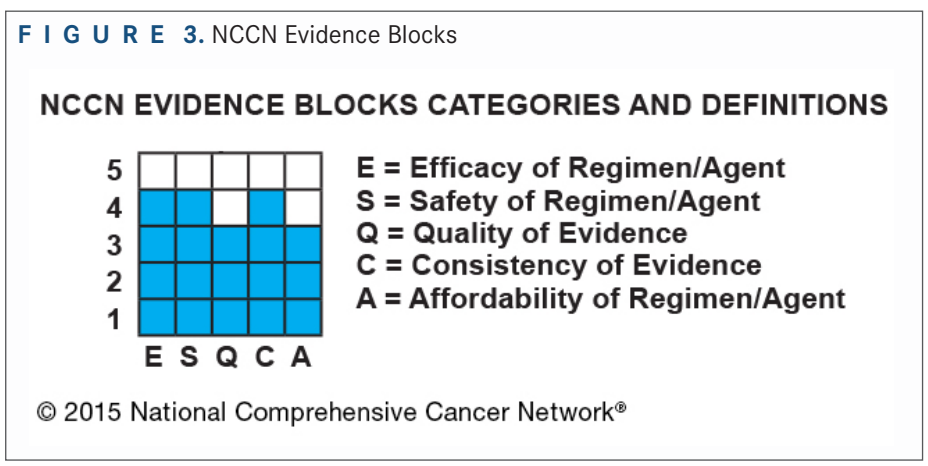
EFFICIENCY

These approaches have their greatest differentiation in the assessment of their cost-effectiveness. The Value Framework separates the clinical assessment from the economic, asking the user to determine value. The DrugAbacus incorporates cost based on Medicare reimbursement, but provides significant latitude for user discretion through the use of price (or value) modifiers. NCCN uses a 1-to-5 grading system incorporated into the visual Evidence Block, but we currently lack insight into their approach to affordability grading (whether it uses absolute dollar thresholds of cost or relative to comparators). Regardless of approach, the inclusion of cost represents a sea change from prior approaches to cancer treatment valuation and selection.

CONCLUSIONS

The ASCO Value Framework, DrugAbacus, and NCCN Evidence Blocks provide opportunities for discussions about the financial costs and associated value gained from the various treatments of oncology patients. By the authors' own accounts, the ASCO tool is designed as

FIGURE 3. NCCN Evidence Blocks



a patient decision-support tool, DrugAbacus is research-focused and informational, and the stated goals of the NCCN are to provide the healthcare provider and patient information to make informed choices.

These tools are not completely intuitive, suggesting providers and patients will need experience or training to optimize them. ASCO clearly states their vision is to preload comparisons into user-friendly software. The DrugAbacus has default values if modifiers are not specified. NCCN's panel consensus may suffer for subjectivity. Critical evaluations of these approaches to value assessment provide a telescopic view into the existing gaps in evidence and literature, and provide additional opportunities for research.

The complexity of cancer treatment and the related design of clinical trials further complicate tool design. Use of drugs in combination rather than as monotherapy, mandatory or reflexive use of supportive care drugs, crossover trial design, prevailing therapeutic, or best supportive care comparator, are but a sampling of the intricacies of oncologic research that may bedevil any approach to value calculation. Traditional clinical research may itself be problematic in value determination, as declining single-digit participation of adult oncology patients who are often younger and healthier and less diverse than their real-world counterparts may be less than representative of the target population.

Conversations on costs and value at both the patient and population levels may provide insights into areas for improvement in medical education and training. Lastly, it behooves all stakeholders to give consideration whether this is a discussion best conducted at the patient, policy, or payer level as we move toward considering both value and costs in our medical decision processes. **EBO**

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PROVIDER COMMENTARY

ABOUT THE AUTHOR

21st Century Oncology

CONSTANTINE MANTZ, MD

Dr Mantz is chief medical officer of 21st Century Oncology.

The venture discussed in this article is a successful collaboration of 21st Century Oncology with the Lee Memorial Health System.

Maximizing Value of Freestanding and Outpatient Hospital Setting in Cancer Care Delivery

CONSTANTINE MANTZ, MD

The cancer care environment today is defined largely by medical innovations. No matter the setting, patients are exposed to physicians using pioneering treatments. As a result, health outcomes are better than ever and survival rates are rising for almost every form of the disease. The 5-year survival rate for all cancers has increased by 20% over the past 4 years.[1] Such positive statistics, which manifest themselves in the form of lives saved, suggest something quite vital: When it comes to cancer, we are finally getting the science and subsequent therapies right. And with each subsequent biomedical discovery, we put ourselves on a path towards solutions once thought impossible.

Even as science races forward, breakthroughs still take time. Therefore, it is imperative that we supplement critical areas like biomedical innovation with equivalent advances in care delivery to reform the way physicians operate—anticipating powerful outcomes. Perhaps most importantly, changes to the efficiency of cancer care—unlike changes to the medicine or technology we use—can be implemented immediately. In the short run, structural and procedural changes are the most effective tools to improve health outcomes and could do the most to provide better value and low-cost cancer treatment.

Ultimately, there is a simple way to bolster the efficiency of cancer care: collaboration. Although this may seem obvious, collaboration in healthcare is no simple task. In most cases, oncologists, treating the same patient, operate across a myriad of specialties in disparate settings, resulting in minimal communication and lack of a unified vision for a patient's course of care. Additionally, there are consistent gaps in care coordination among cancer specialists, diagnostic radiologists, and pathologists. This system leads to obvious inefficiencies, such as repeated and unnecessary tests. It also prevents patients from receiving the highest quality care following a cancer diagnosis.

Quite simply, collaboration would eliminate inefficiencies—saving critical time, improving patient outcomes, and cutting system costs. Therefore, over the past 4 years, we at 21st Century Oncology and Lee Memorial Health System have put ideas into action, working together to establish a multidisciplinary breast cancer clinic in Lee County, Florida.

Our goal was to eliminate the clutter of cancer care and create a single, unified breast cancer treatment center that combined the best parts of a freestanding oncology setting and the outpatient hospital environment. Just 2 short years after initiating the project, we were able to achieve a National Accreditation Program for Breast Centers certification. Our hope is that our experience can generate a replicable model of collaboration across all spectrums of cancer care.

IMPROVING QUALITY OF CARE THROUGH COLLABORATION

The process began with the creation of a multidisciplinary Breast Program Leadership Team Committee, composed of physicians (including radiation oncologists), breast fellowship–trained surgeons, general surgeons, and radiologists. It also included a chief administrative officer, a medical director, 2 breast cancer navigators, and a cancer registrar. Following multiple rounds of deliberations, experts experienced with the local patient population drafted comprehensive plans for a new breast cancer clinic that would effectively integrate radiation oncology, surgery, and medical oncology.

Thus far, the results have been very encouraging and measurable in key areas. Since the establishment of the clinic, we have witnessed a significant reduction in the "screening to call back" average, which essentially measures the time patients wait for test results. Before oncology services were unified in the multidisciplinary clinic, patients were forced to wait an average of 12.5 days for screening results; subsequently, the average fell to 6.5 days. We witnessed an even more dramatic reduction in the "screening to diagnosis" average—9.55 days compared with a staggering 34 days prior to unification. In other words, even in its nascent stages, patients were reaping the rewards of integrated care.

In addition to strengthening quality

(continued on **SP546***)*

THE AMERICAN JOURNAL OF
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CALL FOR PAPERS

HCV Special Issue

The American Journal of Managed Care (*AJMC*) is issuing a call for papers for a special issue on the hepatitis C virus (HCV), set to be published in March 2016. This issue will feature scholarly articles and perspectives from a range of stakeholders and researchers, with the goal of defining the impact, innovations, and challenges related to HCV.

We are seeking a limited quantity of original research papers and informed commentary on HCV-focused topics in the following areas:

- New innovations for interventions and the diagnosis and treatment of HCV
- Post-marketing outcomes for new agents in HCV
- The evolving role of quality measures for management of HCV
- Effects of healthcare reform on HCV care
- Challenges and best practices in providing access to the entire continuum of care
- Impact of plan design on patient access to appropriate therapies
- Barriers to patient adherence
- Improving coordination of care
- Methodologies for provider and payer accountability
- Innovative partnerships between payers, providers, and manufacturers
- Effects of changing capitation and reimbursement on healthcare delivery
- Cost of new therapeutic agents and their impact on utilization
- Balancing cost silos—medical versus pharmacy spend
- Best practices in cost sharing
- Comparative effectiveness research and methodologies
- Examples of integrating evidence-based guidelines into practice
- Implications of HCV coverage decisions for other disease areas and patient populations

Due to space constraints, we request that you limit your manuscript's text to 2500 words or less (excluding references) and its graphic elements to 3 figures and/or tables total. The final decision regarding a paper's acceptance will be made by the editors; each accepted paper will be peer-reviewed. Your paper will have its best chance for inclusion if you submit it before **January 13, 2016**. High-quality papers not selected for publication in the special issue will be considered for one of the regular monthly issues of *AJMC*.

Please submit all manuscripts through *AJMC*'s online submission system at **http://mc.manuscriptcentral.com/ajmc** using the category "**Special Issue**."

If you have questions or wish to speak to an editor, please e-mail: **nbeagin@ajmc.com**

(continued from SP544)

of care, we have been able to conduct 2 quality improvement studies in the multidisciplinary setting. We first evaluated genetic testing and clinical management in the community hospital setting among breast cancer patients less than 40 year. The results ultimately signaled a need for increased referrals to genetic counselors for women under age 40 years, a change that we subsequently integrated within our treatment process. The second study indicated that magnetic resonance imaging (MRI) plays a fundamental role in detecting additional disease in biopsy-proven breast cancer. Based on the results, we have now ensured that all appropriate clinic patients will have a breast MRI prior to surgery. Once again, patients gained an immediate benefit from innovations in the care setting.

These developments in the efficiency of care delivery and effectiveness of treatment significantly bolster the value of cancer care and allow patients to seek much improved treatment, faster. Notably, multidisciplinary care also has the potential to reduce costs through reductions in avoidable medical events. Whereas the available data is not sufficient to conduct a cost-benefit analysis of the quality improvement program (cost analysis requires 2 years to allow medical events and their related costs to fully declare themselves), this type of analysis is definitely planned.

In the end, our model of collaboration and innovation was effective for treating a specific class of cancer in a narrow geographic region. However, our experience suggests that expanding multidisciplinary care could make a difference for countless Americans. Thus, in our opinion, it is time to invest in greater care coordination in oncology, as a whole, and facilitate a dynamic path towards better, cost-effective cancer care. **EBO**

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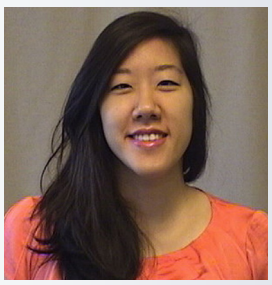
HEALTH OUTCOMES

Measuring Financial Toxicity in Cancer Patients

PAULINE LEE, PHARMD, AND JONAS A. DE SOUZA, MD

ABOUT THE AUTHORS



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Financial toxicity is an emerging and growing problem for many patients. To keep pace with the rising costs of medical care in the United States, insurance companies have increasingly shifted the economic burden to patients in the form of higher premiums or co-payments. A 2015 survey by the Kaiser Family Foundation showed that worker contributions to premiums have increased by about 296% and deductibles have almost doubled.[1] Patients diagnosed with cancer, which is one of the most expensive diseases to treat in the United States, are at risk of experiencing significant financial burden.[2] These patients, in general, pay more out of pocket for their healthcare compared with those suffering from other chronic conditions,[3,4] which, in turn, can harm the quality of cancer treatment. For example, financial burden could be a risk factor for nonadherence,[5] as patients with higher co-payments were shown to be more likely to discontinue therapy in the first 6 months of treatment. In order to understand how financial toxicity affects cancer patients, it is important to identify effective methods to measure it.

MEASURING FINANCIAL TOXICITY

There is increasing evidence that higher financial burden is correlated with poorer quality of life. Both objective and subjective measures to determine the financial condition of individuals and families have been studied extensively; however, there is no consensus on the best tool to measure financial distress in cancer patients. A common objective measure is defined as health-related spending in terms of the total family income, with 20% used as a common threshold for burden.[6-8] However, objective measures such as insurance co-payments or household income may not capture an individual's feelings about the situation or their impact on a patient's quality of life. In addition, health-related expenses are usually difficult to access and collect.

Shankaran and colleagues[9] considered patients to have experienced financial burden if they accrued debt, sold, or refinanced their home, borrowed money from friends or family, or experienced a 20% or greater decline in their annual income as a result of treatment-related expenses. Zafar and colleagues[10] enrolled colorectal and lung cancer survivors to assess financial burden and whether patients reported difficulties living on their household income or whether the quality of their insurance had changed. In this study, high financial burden was associated with lower household income, younger age, and poorer quality of life. The authors confirmed that financial burden is prevalent among cancer survivors and is correlated with patients' health-related quality of life (as measured by the EuroQol or EQ-5D).

Knowing that cancer care costs are rapidly increasing and may yield negative financial consequences, evidence-based and validated tools can assist physicians to screen patients for financial toxicity.

In another study, Fenn and colleagues[11] examined the association between financial problems caused by cancer and reported quality of life in a sample of cancer survivors. Over 2000 cancer survivors participated in a survey in which they were asked, "To what degree has cancer caused financial problems for you and your family?" Possible responses were "a lot," "some," "a little," or "not at all." About 30% of patients reported some degree of financial problems. Those who reported "a lot" of financial distress (8.6%) were more likely to rate their physical health, mental health, and satisfaction with social activities and relationships as poor. They were also 4 times less likely to rate their quality of life as "excellent," "very good," or "good." The authors concluded that increased financial burden from cancer care costs was the strongest independent predictor of poor quality of life among survivors compared with other factors such as age, race, education, insurance status, and family income. Delgado-Guay and colleagues[12] interviewed patients with advanced cancer to assess their subjective experience of financial distress on a numeric scale (0 = best, 10 = worst). Findings showed financial distress was very prevalent (90% of patients) and was more severe than physical distress, distress about physical functioning, social or family distress, and emotional distress.[9] These studies underscore the prevalence of financial distress among many cancer patients and illustrate its close association with a poor quality of life and difficulties living on household income.

Others have focused on developing and validating patient-reported outcome measures (PROMs) in order to assess financial burden experienced by patients. de Souza and colleagues[13] developed a comprehensive score for financial toxicity (COST)-PROM, which was applied to advanced cancer patients and demonstrated validity.[13] A follow-up study showed that COST correlated with the Functional Assessment of Cancer Therapy-General (or FACT-G) questionnaire, which is a quality of life instrument that can be used with a variety of chronic conditions originally validated in the general cancer population.[14] Huntington and colleagues[15] utilized the COST tool to measure the financial toxicity of 100 patients with multiple myeloma. In that population, worse financial toxicity was correlated with lower patient-reported income, higher use of savings, borrowing of money, and treatment delays (P <.001). Veenstra and colleagues[16] aimed to derive and validate a patient-reported measure of personal financial burden in

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stage III colorectal cancer (CRC) patients during treatment. A survey was created to query patients on the financial impact of CRC treatment. A composite measure of financial burden, with a range of 0 to 6, was developed—higher scores denote increased financial burden. The authors found the mean financial burden score among all respondents was 1.72. Eighty-five percent of patients who reported chemotherapy use had significantly higher financial burden scores than those who did not (mean burden score 1.88 vs 0.88, $P < .001$).

Although not specifically developed for the cancer patient population, The Personal Financial Well-Being Scale (PFWBS),[17] a brief and cursory framework to evaluate the general population's reactions to their financial situation, has also been utilized. In fact, items from the PFWBS were used in early stages of the COST development but not retained by cancer patients in final development stages. We hypothesize that the main reason for the difference in elements between the COST and the PFWBS instruments is that concerns elicited by the general population (such as "go out to eat or go to a movie") were ranked lower by cancer patients relative to other items in the earlier development stages of the COST instrument. Finally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30),[18] another prominent quality of life instrument developed in 1993 with a focus on cancer patients, does include 1 item that qualitatively assesses financial impact of the disease ("Has your physical condition or medical treatment caused you financial difficulties?").

FUTURE DIRECTIONS

In this article, we have listed different methods that have been utilized to measure the financial burden in cancer patients—from single questions to elaborated PROMs—and included very objective measures, such as the percentage of healthcare costs related to a household income. We strongly believe standardization of these measures will allow further comparisons among different groups and facilitate clinical utilization. Eventually, selection of the instrument should be based on evidence, which can be gathered from the instrument's developmental data, the instrument's association with meaningful health outcomes, and its ease of use in clinical practice.

Knowing that cancer care costs are rapidly increasing and may yield negative financial consequences, evidence-based and validated tools can assist physicians to screen patients for financial toxicity. Once identified, physician referrals to financial assistance, switching to a less expensive medication, decreasing the number of tests, and decreasing the number of doctor visits can possibly prevent the impact of financial distress. Finally, similar to any other side effect, it is imperative that healthcare providers clearly inform patients about the possibility of financial toxicity when receiving cancer treatment and be more cognizant of cost-effective cancer treatment when making clinical decisions. **EBO**

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The Financial Impact of Cancer Care: *Implications and Potential Solutions*

VEENA SHANKARAN, MD, MS

A 56-year-old insured woman with metastatic colorectal cancer presents to you for consultation. She has received multiple prior therapies since her diagnosis 2 years ago, but has continued to experience progression of disease and deterioration in functional status. She sees you in consultation and is eager to "try anything" that might allow her to have more time with her children. You recommend an oral multikinase inhibitor, which has been shown to improve median survival by close to 6 weeks in a randomized phase 3 study of patients with refractory metastatic colorectal cancer. She agrees to this approach, and you prepare a prescription. Unbeknownst to you, the pharmacist, or your clinic staff, she goes to fill the prescription and discovers that her out-of-pocket responsibility for a month's supply of medication is $1870. She charges the initial payment to 3 different credit cards, including one belonging to her 24- year-old son. After 3 months of treatment (and $5610 paid out-of-pocket), she develops significant toxicities and progressive disease, at which point she is enrolled in a hospice care program.

This clinical vignette highlights many flaws with the way treatment cost information is handled in most oncology practices in the United States. First, this example illustrates a failure of the shared decision-making model. Neither the patient nor the treating physician was aware of the high out-of-pocket cost associated with the prescribed drug; therefore the treatment decision was made in the absence of complete information. Next, lack of transparency about costs may have led to missed opportunities for financial assistance. While upfront knowledge of the $1870 per month coinsurance may not have changed the physician's recommendation or the patient's decision, it might have prompted the care team to look for patient assistance resources to reduce or eliminate the out-of-pocket payment. Finally, lack of a mechanism to identify and address this patient's financial concerns, in real time, may have prevented the patient from planning in advance for her bereaved children's financial well-being.

In this article, we will address the growing problem of "financial toxicity" in cancer care, the impact of financial toxicity on a patient's well-being, and potential strategies at the patient and clinic or hospital level to mitigate the financial burden of cancer treatment.

RISING COST OF CANCER CARE

As the cost of cancer care in the United States continues to rise at an unprecedented rate, cancer patients are strug-

(continued on **SP550***)*

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FRED HUTCH CURES START HERE™

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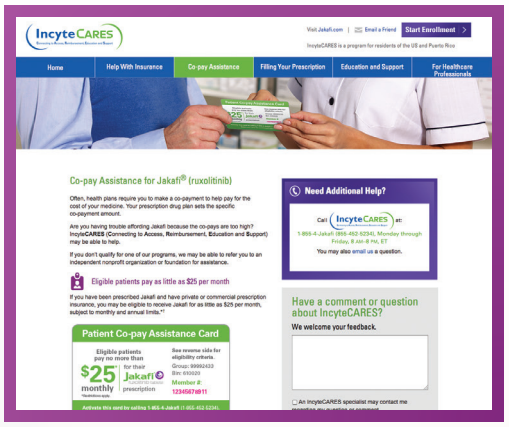
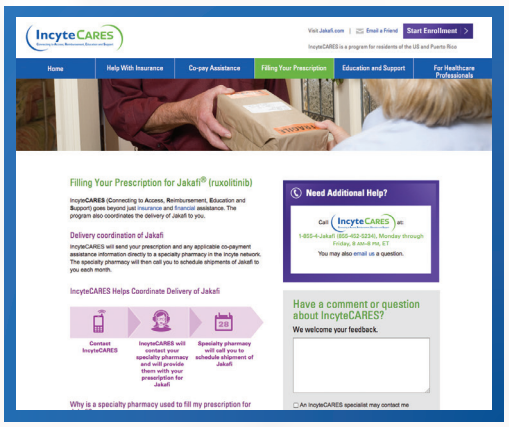
IncyteCARES (Connecting to Access, Reimbursement, Education and Support) can help with more than just prescription assistance for Jakafi® (ruxolitinib). Trained IncyteCARES specialists work with physicians' offices to help address questions and concerns about patients' insurance coverage related to access to Jakafi.



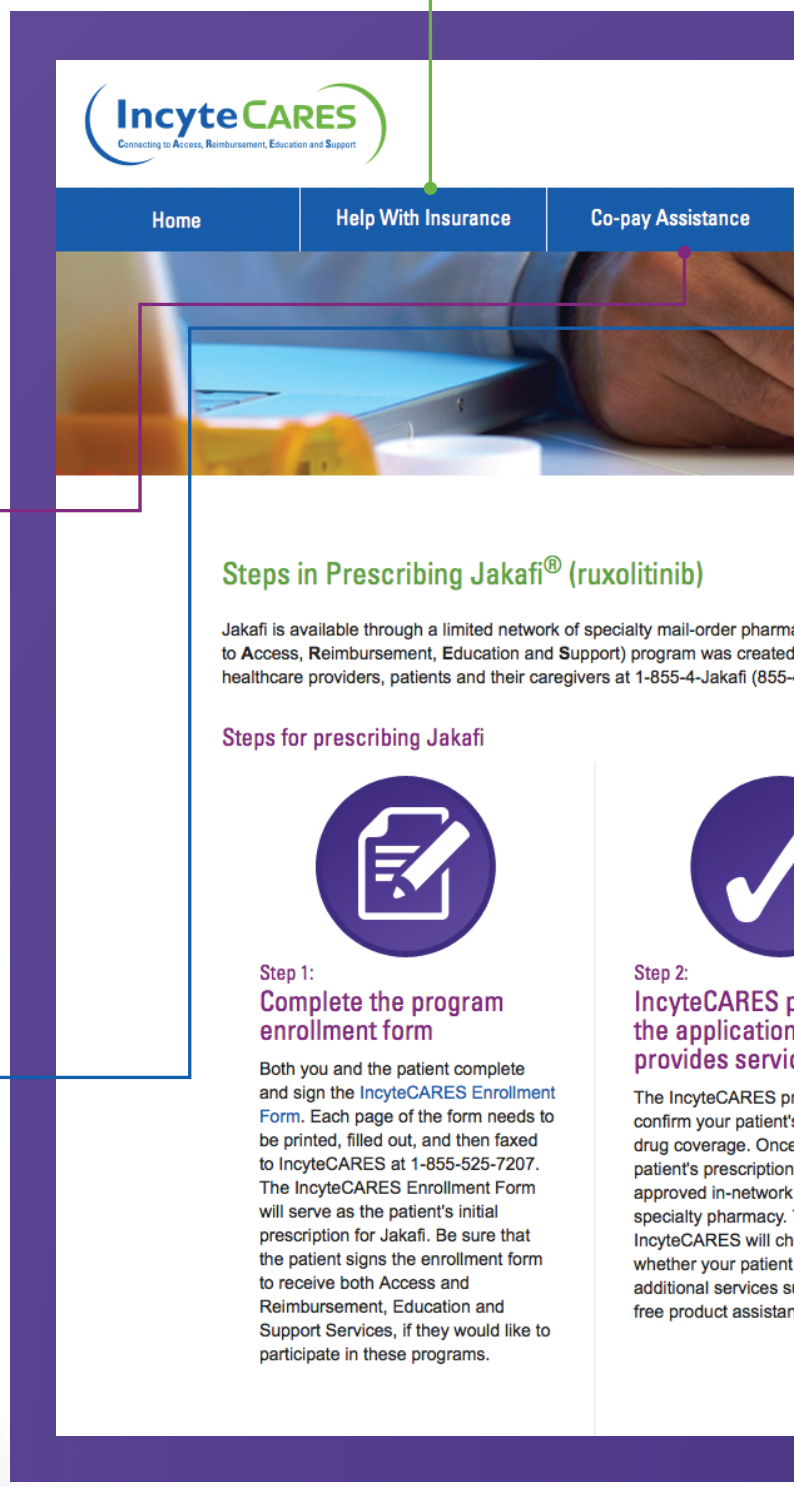
Co-pay Assistance

Help eligible patients who have been prescribed Jakafi to enroll for co-pay assistance by encouraging them to contact IncyteCARES (Connecting to Access, Reimbursement, Education and Support) at 1-855-4-Jakafi to activate their patient co-pay assistance card.



Filling Your Prescription

Jakafi is not available through local retail pharmacies. To help patients locate a specialty pharmacy, download a current list of specialty pharmacies that are authorized to dispense Jakafi. IncyteCARES (Connecting to Access, Reimbursement, Education and Support) can also help coordinate delivery of Jakafi by sending patient prescription information and applicable co-payment assistance information directly to a specialty pharmacy in the Incyte network. The specialty pharmacy will contact the patient to schedule monthly shipments of Jakafi.



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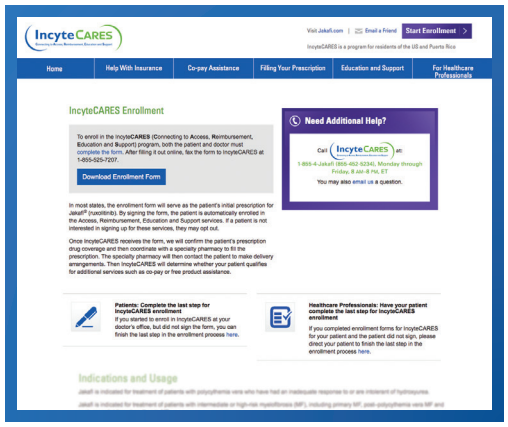
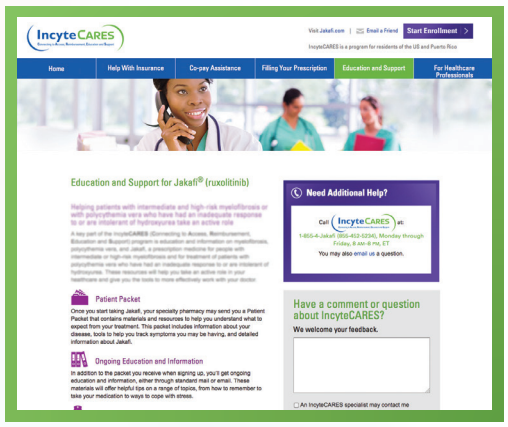


Enrollment

To enroll patients in the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program, both the patient and doctor must complete an enrollment form. Download a copy of the enrollment form, fill it out with the patient, and fax the form to IncyteCARES at 1-855-525-7207.

For Healthcare Professionals

Learn the necessary steps that must be taken when prescribing Jakafi to patients, and discover the resources that the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program makes available to you and your patients.



Education and Support

Discover how the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program provides education and information on Jakafi to help patients take a proactive approach in their care and work more effectively with their doctors.

Jakafi™ ruxolitinib (tablets)

IncyteCARES
Connecting to Access, Reimbursement, Education and Support

(continued from **SP547**)

gling to pay their share of the bill. Cancer care represents one of the fastest growing segments of healthcare spending; median cancer drug prices alone have risen from $962 in 1989 to $7112 in 2009.[1,2] In response to rising cancer care costs, many health plans have shifted some costs to patients in the form of higher co-payments, deductibles, and premiums. The proportion of employee health plans with multitiered prescription formularies (3 or 4 tiers) has steadily increased from roughly 25% in 2000 to nearly 80% in 2013.[3] Estimates from the 2014 Commonwealth Fund Biennial Health Insurance Survey indicate that 23% of adults aged 19 to 64 years were underinsured, meaning that out-of-pocket costs (excluding premiums) equaled 10% or more of household income.[4] The 2010 Patient Protection and Affordable Care Act (ACA) has increased access to quality health insurance, but has not removed financial risk in the context of a major health shock like cancer.

FINANCIAL TOXICITY

With respect to rising cancer treatment costs, increased cost-sharing schemas, and economic instability in recent years, many reports have shown that patients with cancer are facing a variety of financial challenges following diagnosis. In a recent study investigating financial outcomes of 550 colon cancer patients in western Washington state, nearly 40% 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, or selling their primary residence.[5] In another study linking US Bankruptcy Court records with records from the Western Washington Surveillance, Epidemiology, and End Results registry, patients with cancer were found to file for bankruptcy at significantly higher rates than similar patients without cancer (hazard ratio [HR], 2.65; 95% CI, 2.51-2.80).[6]

Importantly, financial problems following diagnosis may be critical, but underappreciated drivers of observed disparities in treatment adherence and health outcomes among cancer patients. In a follow-up to the bankruptcy study discussed above, bankruptcy filing was associated with a higher risk of death among cancer patients, after adjusting for age, gender, cancer stage, and treatment using propensity score matching (HR, 1.79; 95% CI, 1.64-1.96).[7] Studies have also shown an association between high co-payments for cancer drugs and lower adherence to therapy. Among Medicare Part D enrollees, a $10 incremental increase in oral cancer drug co-payment was associated with a 13% to 20% increased likelihood of treatment discontinuation.[8] High monthly co-payments for tyrosine kinase inhibitors have also been shown to be associated with a greater risk of treatment discontinuation compared with low co-payments (relative risk [RR], 1.42; 95% CI, 1.19-1.69).[9] While not specifically addressed in these studies, nonadherence likely translates into poorer clinical outcomes.

Patients who face major financial hardships, such as personal bankruptcy during cancer treatment, typically exhibit some earlier signs of financial vulnerability or strain. Yet, financial strain is rarely measured in clinical oncology practice on a routine and prospective basis.

POTENTIAL SOLUTIONS

Addressing the problem of financial toxicity requires a comprehensive approach with commitment from multiple stakeholders. In recent years, the oncology community has come together to lobby for lower pharmaceutical prices, a crucial step in addressing the growing financial burden faced by cancer patients and their families.[10,11] We propose several other potential strategies at the patient and clinic or hospital level to address the problem, focusing on missed opportunities highlighted in the earlier clinical vignette.

Improve Cost Transparency

The shared decision-making model is based on full disclosure of risks, benefits, and alternatives to a particular treatment strategy.[12,13] In oncology, patients are often given very thorough information about physical side effects and clinical benefit (usually in terms of median survival). However, patients are often unaware of their financial liability for treatment until well after a clinical decision has been made, often at the pharmacy window or after receiving a bill in the mail. We argue that upfront information about out-of-pocket treatment costs might help patients make more informed decisions, including decisions to forgo subsequent-line palliative chemotherapy when clinical benefit is low and financial burden is high. True cost transparency requires engagement from payers and a system, not only to generate real-time cost estimates, but to deliver these estimates in an appropriate context to physicians and/or patients.

Improve Access to Financial Assistance

Identification of high copayments and coinsurance before a prescription is filled or a treatment is administered not only informs the clinical decision-making process, but may also allow the clinic staff and pharmacy billing specialists to identify sources (through foundations or pharmaceutical companies) for co-payment assistance or provision of free drug.[14,15] Opportunities for assistance should be identified early and should be offered to all patients regardless of their perceived ability to pay, as financial circumstances can change quickly during the course of treatment.

Measure Financial Burden in Real Time

Patients who face major financial hardships, such as personal bankruptcy during cancer treatment, typically exhibit some earlier signs of financial vulnerability or strain. Yet, financial strain is rarely measured in clinical oncology practice on a routine and prospective basis. We argue that a proactive approach of measuring financial status, early and often, can help align patients with appropriate resources before they face more devastating financial consequences. In the era of widespread mobile phone and smartphone use across all racial and income groups, leveraging mobile technology to measure out-of-pocket expenses and financial vulnerability would be an appealing approach.

Provide Access to Financial Planners

Some of the strategies (eg, asset management, debt consolidation), which could help prevent cancer patients from facing devastating financial consequences, fall outside the purview of the healthcare profession. Oncology practices can help by connecting patients with trained financial planners who can help them budget for upcoming out-of-pocket expenses or plan for their family's financial future.

CONCLUSION

Addressing the financial burden of cancer treatment requires efforts at the policy, payer, and clinic level to control soaring drug prices, improve cost transparency, measure financial toxicity, in real time, and align patients with financial assistance or counseling. Implementation of these strategies, in clinical practice, requires commitment from various stakeholders and a recognition that addressing the problem of financial toxicity is as important as addressing other side effects of cancer treatment. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE 20 ANNIVERSARY

Patient Access to Oncology Care in ACA Exchange Plans

CAROLINE F. PEARSON AND DEIRDRE B. PARSONS, MPP, MPH, MS

INTRODUCTION

Innovations in cancer treatment and health insurance markets present new opportunities for patients. Advances in medical treatment today give more patients reason to hope for a cure and reduce some of the devastating adverse effects long associated with cancer therapy. However, such treatments can often be costly to insurers and to patients.

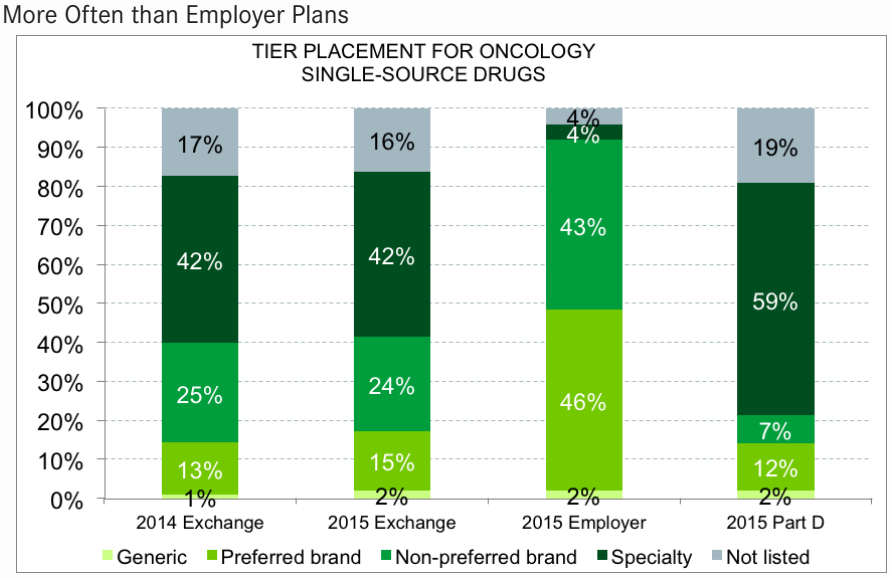
The Affordable Care Act (ACA) significantly broadened insurance coverage by ensuring that all individuals, even those with pre-existing diagnoses, can purchase insurance. The law also caps maximum out-of-pocket (MOOP) spending for individuals at $6600, which offers important protection for cancer patients against high costs and possible medical bankruptcy. Meanwhile, insurers are responding to pressure from individuals and employers to reduce monthly premiums. Each of these advances in healthcare coverage will benefit cancer patients. However, they also have required changes to benefit designs that may impact patients.

In order to manage costs in the face of more expensive therapies and new coverage and benefit requirements, health plans have revised their insurance products to include narrower provider networks and increased cost sharing for some services and medications before consumers reach their MOOP spending. Exchange markets are leading the way in these innovations, although these benefit designs are likely to spill over into other sources of insurance—like the employer market.

Access to oncology care through exchange plans will vary depending on the plan level purchased and the specific design of each product. On average, individuals with exchange coverage face higher levels of cost sharing for services and for medications compared with traditional commercial or Medicare markets.

This article reviews plan designs and network breadth for oncology patients who have exchange coverage. Successful exchange innovations that are popular with consumers and effective at reducing premiums are likely to spread into other markets, including employer coverage. As such, it is important to understand these exchange benefit designs and what they will mean for cancer patients.

FIGURE 1. Exchange Plans Tend to Place Oncology Drugs on Specialty Tiers More Often than Employer Plans



Coverage is weighted according to unique plan-state combinations. Sample includes silver plans in 6 states (Florida, Georgia, Illinois, North Carolina, Pennsylvania, and Texas) relying on HealthCare.gov, as well as California and New York. Managed Markets Insight & Technology (MMIT) uses universal tier status rather than "raw" tier numbers to facilitate comparisons across plans and markets. Avalere uses universal tier status for tiering analyses and raw tier status for cost-sharing analyses. For the purpose of this analysis, "coverage" means formulary inclusion. Avalere excluded physician-administered drugs from this analysis, except when comparing with state benchmark minimums.

Source: Avalere Health analysis of 2015 exchange formularies using the PlanScape database. Avalere analyzed formularies for silver plans participating in 8 states (California, Florida, Georgia, Illinois, New York, North Carolina, Pennsylvania, and Texas) using data from MMIT, LLC and the 2015 HHS Individual Market Landscape File.

THE AFFORDABLE CARE ACT

Along with the many changes it brought about in health insurance markets, the ACA also expanded access to patients who previously could not afford healthcare or who were denied access due to pre-existing conditions. Since 2010, health plans subject to ACA requirements have adjusted to operate under the new rules and regulations. The downstream effect of complying with the new regulations has been that plans have been more constrained in some ways—such as the amounts by which they can raise premiums and the scope of services they offer. However, that has given rise to innovation focused on network and benefit design.

The insurance exchanges created by the ACA also offer a new, centralized way for consumers to shop and compare health plans. Thus far, enrollees in these markets have been extremely price-sensitive—overwhelmingly choosing plans with lower premiums. Insurers that want to win enrollment have sought to keep premiums low by limiting provider networks and shifting more cost sharing onto enrollees, resulting in increased costs for some patients before they reach their MOOP limit. We have seen this dynamic unfold in several specialties, including oncology.

ONCOLOGY BENEFITS IN EXCHANGE MARKETS

Exchange markets are leading the way in developing benefit designs that seek to contain costs. Access to oncology care through exchange plans will vary depending on the plan level purchased and the specific design of each product. On average, individuals with exchange coverage face higher levels of cost sharing for services and for medications compared with traditional commercial or Medicare markets. In 2014, almost two-thirds of enrollees selected silver tier plans, which are designed to cover an average of 70% of consumers' healthcare costs.[1]

Most exchange plans feature high deductibles that result in front-loaded costs in the benefit year. High deductibles have been shown to have the effect of reducing spending, even for very sick patients.[2] In 2015, silver tier plans had an average deductible of $2658, which usually includes prescription drugs. Patients are responsible for 100% of applicable healthcare costs until the deductible is fulfilled.

Once the deductible is met, patients will be responsible for cost sharing for drugs and services they receive before reaching the MOOP limit. For oncologist visits, the average co-pay for a silver plan in 2015 was $52 if the physician was included in the plan's network. However, if a patient seeks care from a non-network provider, he/she will be responsible for the full cost of the visit unless the exchange plan includes out-of-network coverage. Of the 40% of plans that offered out-of-network coverage for specialists in 2015, 49% was the average coinsurance for an out-of-network specialist for plans offered through Healthcare.gov.[3]

The diagnosis and monitoring of cancer may also require patients to share in the costs for those services, such as CT and MRI scans. In 2015, imaging services had an average cost share of $234 or 27% in-network.

Most patients who have cancer receiving active treatment will incur enough

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FIGURE 2. Network Breadth Varies Between Exchange and Commercial Plans and Across Regions

EXCHANGE NETWORK AVERAGE AS PERCENT OF COMMERCIAL NETWORK AVERAGE

Rating Regions	Commercial: Oncology Providers	Exchanges: Oncology Providers	Exchange Coverage as Percent of Commercial
Florida (Jacksonville)	226	142	63%
California (Los Angeles)	592	332	56%
Texas (Dallas)	830	492	59%
Georgia (Atlanta)	585	354	60%
North Carolina (Charlotte)	393	207	53%
Average	525	305	58%

NETWORK COVERAGE OF ONCOLOGY PROVIDERS COMPARED WITH AVERAGE AMONG COMMERCIAL PLANS IN SAME RATING REGION

	Florida	California	Texas	Georgia	North Carolina
Broadest Network	Aetna, 70%	Health Net, 75%	Aetna, 80%	Humana, 70%	Humana, 63%
Narrowest Network	UHC, 45%	Kaiser, 3%	Molina, 4%	Ambetter (Centene), 15%	UHC, 25%

UHC indicates UnitedHealthcare.
Avalere Health analysis of 2015 exchange network designs using its proprietary PlanScape database. Avalere analyzed exchange and commercial plan networks in the largest cities in the 5 states with the largest 2015 exchange enrollment (FL, CA, TX, GA, and NC) using data provided by Strenuus (proprietary information).

costs to reach their MOOP. Many plans sold in the higher gold and platinum tier feature reduced MOOP spending, which may reduce patients' total costs despite having higher monthly premiums. In 2015, the average MOOP for platinum plans was $2145 compared with $6381 for bronze plans.[4]

COST SHARING FOR SERVICES AND DRUGS IN EXCHANGE MARKETS

Oncology patients may also find themselves with high levels of cost sharing for their drugs in addition to access to their providers. As insurers look for ways to contain healthcare costs, utilization management (UM) of and cost sharing for prescription drugs has increased, especially as competition within therapeutic classes—through new molecules being released to the market, existing products gaining approval for new indications, and patents of pharmaceuticals and biologics expiring—has heightened the ability for payers to more tightly manage prescription drugs.

Plans are aggressively managing access to drugs through UM. Not only are rates of UM higher in exchanges than in employer plans, but the use of UM has been increasing in the market. Rates of UM for oncology medicines rose from 34% of drugs in 2015 to 50% in 2016.[5]

After meeting any UM requirements, patients in exchanges may also face high cost sharing for oncology drugs. An Avalere analysis of drug coverage in exchange plans found that coverage of oncology products within exchanges closely mimics trends seen in Medicare Part D, while employer plans tend to list these drugs on formulary and preferred tiers more frequently.[5] In exchanges, 42% of oncology products are placed on the specialty tier compared with only 4% in employer plans (**FIGURE 1**).

Specialty tiers disproportionately use coinsurance, often requiring patients to pay a greater share of the cost of the drug than a flat dollar co-pay. As such, nearly half of oncology therapies are subject to coinsurance in exchange plans, averaging 37% of the cost of the drug.[4] Although the majority of individuals enrolling through the exchanges opt for silver tier plans, individuals with serious conditions, such as cancer, should consider choosing plans with richer benefits to reduce their out-of-pocket (OOP) costs and spread their expenses more evenly throughout the year.

ONCOLOGY NETWORKS IN EXCHANGE MARKETS

In addition to benefit design, provider networks can have a significant impact on consumer costs and access. The ACA sets minimum standards for network adequacy in exchange plans but leaves significant discretion to those plans. Insurers have leveraged provider networks to reduce premiums by limiting participating providers to higher-value or lower-cost providers.

Because coverage for out-of-network providers is limited, cancer patients will benefit from ensuring their preferred physicians and hospitals are included in the network when choosing a plan. However, individuals given a recent diagnosis may find they have chosen plans with narrow provider networks and high cost sharing for out-of-network providers.

After evaluating how the oncology provider networks in exchange plans compare with networks in traditional commercial plans, an Avalere analysis of exchange plans found 42% fewer oncology providers in exchanges.[4] This disparity in access to oncology providers within exchange networks also varies by region: for example, in Charlotte, North Carolina, and Jacksonville, Florida, exchange networks for oncology are 53% and 63%, respectively, the size of traditional networks in the same region.[4] Individual plans within each region also vary by the breadth of their oncology networks (**FIGURE 2**).

Furthermore, the results of a survey conducted in partnership between Avalere and the National Comprehensive Cancer Network of 20 National Cancer Institute–designated cancer centers revealed that some leading cancer centers have been excluded from exchange networks:

- Five centers (in Florida, Missouri, New York, Texas, and Washington) were excluded from the networks of the exchange plans offered by the majority of the state's exchange carriers.
- Thirteen centers indicated they were excluded from some networks despite their attempt to be in network.
- Six centers reported they opted out of exchange contracts due to low reimbursement rates.[6]

These data demonstrate that access to oncologists and hospitals may be much more limited for exchange enrollees than for those in other markets. As such, it is critical that patients carefully examine the details of the plan prior to purchasing coverage.

THE FUTURE OF ONCOLOGY CARE FOR EXCHANGE PATIENTS

Going forward, oncology patients may have more tools to choose coverage that meets their needs, but some gaps could remain. For the 2016 plan year, issuers of exchange plans will be required to provide increased transparency for consumers in at least 3 ways:

1. Plans will be required to publicly post a complete list of all covered drugs on an up-to-date formulary, including tiers and restrictions on drug access.
2. Issuers must publish machine-readable formularies, which can support a range of interactive consumer shopping tools. Links to formularies must be updated frequently so that consumers will be able to obtain accurate information on drug coverage.
3. Issuers must provide up-to-date and complete provider directories, which should be accessible to consumers even prior to enrolling in a plan.[7]

The growth of decision support tools and consumer education can also help combat the tendency for patients to pick plans based on the premium alone. Some states have developed their own consumer support tools. California, for example, has developed an OOP calculator and Idaho factors average "estimated expenses" associated with each plan. CMS has developed its own cost calculator, which include a provider and formulary search and estimates total OOP spending.

Beginning in 2016, the ACA will also require HHS to release an enrollee satisfaction survey to assess consumer experience with exchange plans.[8] The information collected from the surveys will be publicly displayed to allow individuals to compare satisfaction across plans. The survey will include questions on access to specialists and cost sharing for medications.

As we enter 2016, patients with cancer who are enrolling in coverage through the exchanges need to recognize the unique characteristics of this market that may impact their access to services and the costs associated with treatment. Careful selection of a health plan can help consumers anticipate and minimize their OOP costs. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE

"Financial Toxicity": *A New Term, but Not a New Reality for Many Cancer Patients*

DEBRA MADDEN

I've never been one who appreciated the portrayal of cancer as "a battle to be fought," since the expression implies that the cancer patient either wins or loses that battle. This becomes uncomfortably close to "blaming the victims" if their condition deteriorates. With that said, however, I do not shy away from using battle terminology to describe the experiences I had with my insurance company during treatment for my first cancer, Hodgkin's lymphoma, when I was in my early 20s.

Soon after graduating from college, I was diagnosed with stage III Hodgkin's lymphoma. Due to having extremely bulky disease, my treatment required grueling chemotherapy (8 cycles of MOPP [nitrogen mustard, Oncovin (vincristine), procarbazine, prednisone]) and ABVD (adriamycin, bleomycin, vinblastine, and darcarbazine), followed by 6 weeks of high-dose radiation. I had been having symptoms for at least a year before finally receiving my diagnosis, and I was extremely ill by that point. (Constant coughing, difficulty catching my breath, painfully itchy skin, drenching night sweats, weight loss, and exhaustion: I later learned that, taken together, my symptoms were highly suggestive of Hodgkin's lymphoma.) During my biopsy, the surgical team also found that one of my lungs had collapsed from the cancer. And then my chemotherapy began—and I felt even worse. This was back in the 1980s, well before the effective antiemetic drugs we have today. Every other Friday for more than 8 months, I received my chemotherapy, was brutally sick for hours (and hours), slowly regained my strength over the next 2 weeks, and then started the same cycle all over again. With each treatment, my exhaustion worsened, and as time went on, my red and white blood cells had more and more difficulty bouncing back. The entire experience was absolutely horrific.

But dealing with my health insurance company? That proved even worse. Shortly after graduating from college, I started a new job at a local newspaper—a job that I quickly grew to dislike. However, since this was my first "real job" as an adult, I thought it was important to stay and give it more of a chance—despite the devil on my shoulder that kept whispering, "Quit this lousy job. Quit, quit, quit! What are you waiting for?" Fortunately, I didn't listen to this temptation—because I soon desperately needed the health insurance that I received as a job benefit, being diagnosed just a few months after starting with the newspaper.

As I struggled to come to terms with my diagnosis, I took comfort from the fact that I had this insurance, thinking that I didn't need to worry so much about the costs of my treatment. But I was quickly, rudely shaken out of my naiveté. One of my first memories of chemotherapy was stepping out of my infusion room, walking by my oncologist's office, and being unable to ignore the phone conversation he was having. My oncologist was a gentle soul: a highly religious, warm, compassionate man who was loved by his patients. I cannot imagine surviving the rigors of treatment without his care and ongoing support. But on that day, I saw a side of him that I hadn't previously witnessed. He was talking with one of his patient's insurance companies and his voice was growing louder and louder until he seemed nearly frantic. It became clear that he was calling on behalf of a critically ill patient, whose insurance company had improperly, repeatedly refused to cover the cost of one of his chemotherapy drugs.

Since cancer is an expensive disease, shouldn't the costs be covered by insurance for those of us who are insured? Today, for many, the concern is that although insurance is "paying" for cancer care, insured patients are facing ever increasing out-of-pocket costs.

As my doctor repeatedly explained, this drug was an absolutely critical part of his patient's treatment, it was considered standard-of-care for this type of cancer, the company had always paid for the entire regimen in the past, and their refusal today was unacceptably delaying treatment that his patient desperately needed. This gentle man's voice continued to increase in volume until he was nearly shouting into the phone. He then went completely silent, took a deep breath, and concluded with words to the effect, "You are absolutely, dangerously wrong. You WILL pay for this for my patient. I WILL continue treating him with this medically necessary drug. And you WILL make this ridiculous problem go away." He slammed down the phone and immediately sank his head into his hands. I looked up at the receptionist, and I obviously appeared extremely concerned, because she immediately reassured me. She explained that the doctor would be okay, that the only time anyone ever saw him become upset was when he had to deal with "some of the worst insurance companies," and that, most importantly, his patient WOULD continue receiving the treatments he needed.

In just a few months, I knew exactly how my doctor had felt in that moment—because I was the one who was slamming the phone down, again and again and again. I was now the patient for whom an insurance company was consistently initially denying payment for cancer treatments. So, just as with my chemotherapy, I'd entered into a vicious cycle where my insurance company was the toxic agent.

It always went the same way: I would have the distinct pleasure of calling the insurance company to explain that they had (once again) made a mistake, that all my chemotherapy drugs were covered, and that they had improperly denied payment. I would then be transferred at least 2 or 3 times, with each transfer requiring that I launch into the same explanation all over again. The bulk of these calls consisted of my waiting on hold for yet another person, anxiously peering at the clock every few minutes, then every few seconds. I always called when the lines opened first thing in the morning, in an ineffective effort to avoid lengthy hold times, since I was doing my best to work through my treatment. The irony was never lost on me that my (insert expletive here) insurance company was again making me late for a job I strongly disliked—yet one I *had* to keep in order to continue *having* this coverage and to stay with an insurance company that fought against paying for my treatments…every…single…step…of the way.

After experiencing this same scenario half a dozen times, my hands started to visibly shake every time I received a piece of mail from my insurance company—because it would inevitably be another denial and I'd need to start my insurance battle cycle all over again. As noted above, I was exhausted, usually felt terrible, and was trying to put in as many hours at work as I could. Adding to that the constant stress of the continued denials, the enormous loss of time fighting for rightful payment, the fear that I could lose the little money that I had if they never did make these payments…all of this was taking a heavy toll. And then, once again, it became even worse.

It began the same way that it always did. My insurance company—which had repeatedly denied and then finally paid for the same chemotherapy drugs cycle and after cycle—was saying once again that these very same drugs were not covered. On this morning, I had been on hold for nearly an hour and a half, listening to the same cycle of music over and over, waiting for someone, anyone, to take my call. Finally, a woman came on the line and I launched into an explanation of my issue. I'd managed to speak just a few words, when she began to interrupt me. I'd try again and she'd interrupt me again. Out of desperation, I finally said, "I'm sorry, but it's *my* turn to speak now" and she interrupted me *again*. But this time, she was interrupting me to say that there "was nothing she could do." I pushed back and said that "of course there was!," emphasizing that this had happened with *every single cycle* of my chemo and that they always ultimately paid. Interrupting yet again, she said that if I "wouldn't listen to her," she would just have to transfer me to someone else. As I rushed to say, "Please do NOT put me back on hold again…," she did just that: she transferred me. Once again, I was back in purgatory

(continued on **SP556***)*

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Ms Madden is a 2-time cancer survivor and a cancer research advocate.

Photo accredited to Danielle Abraham.

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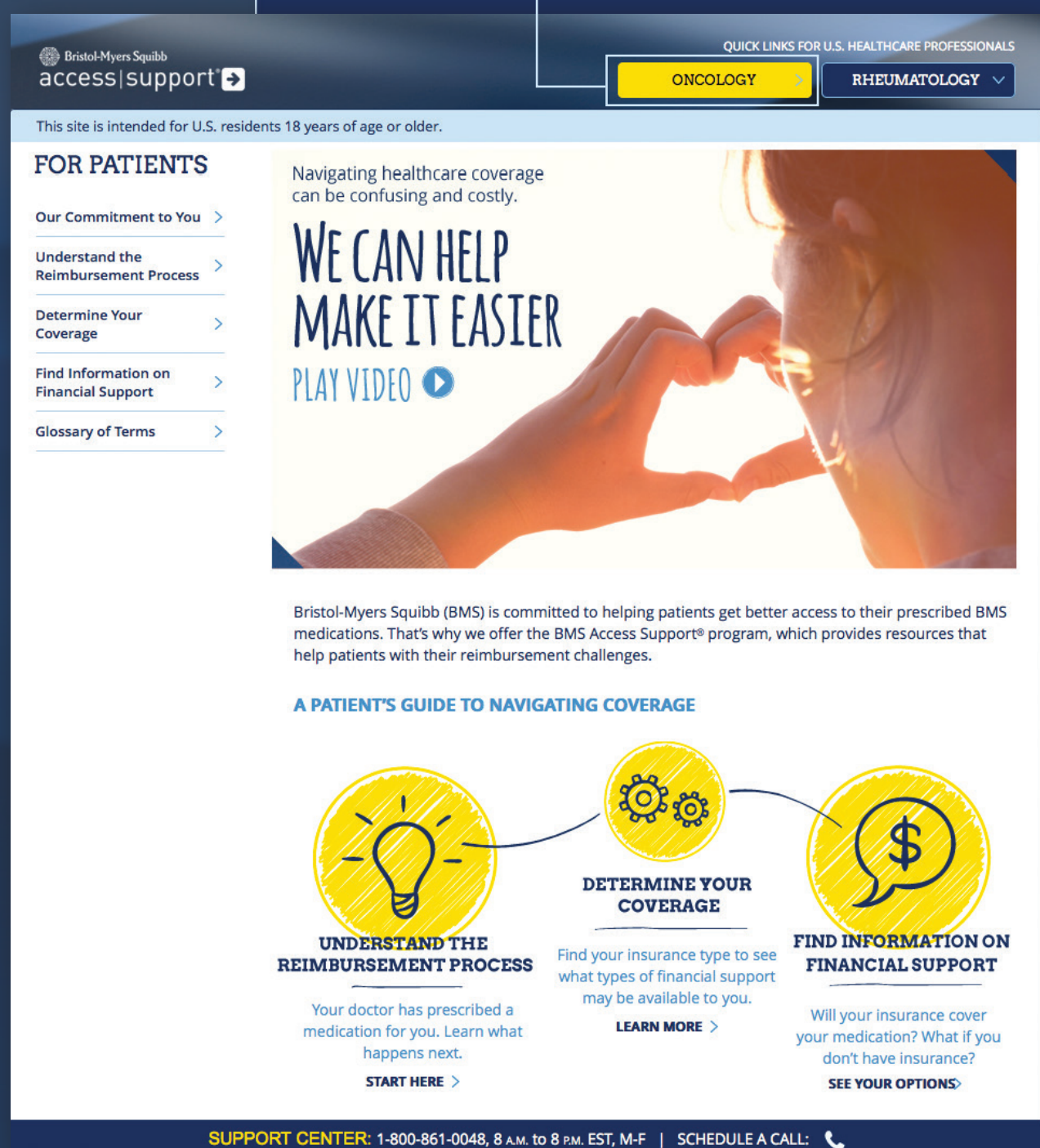

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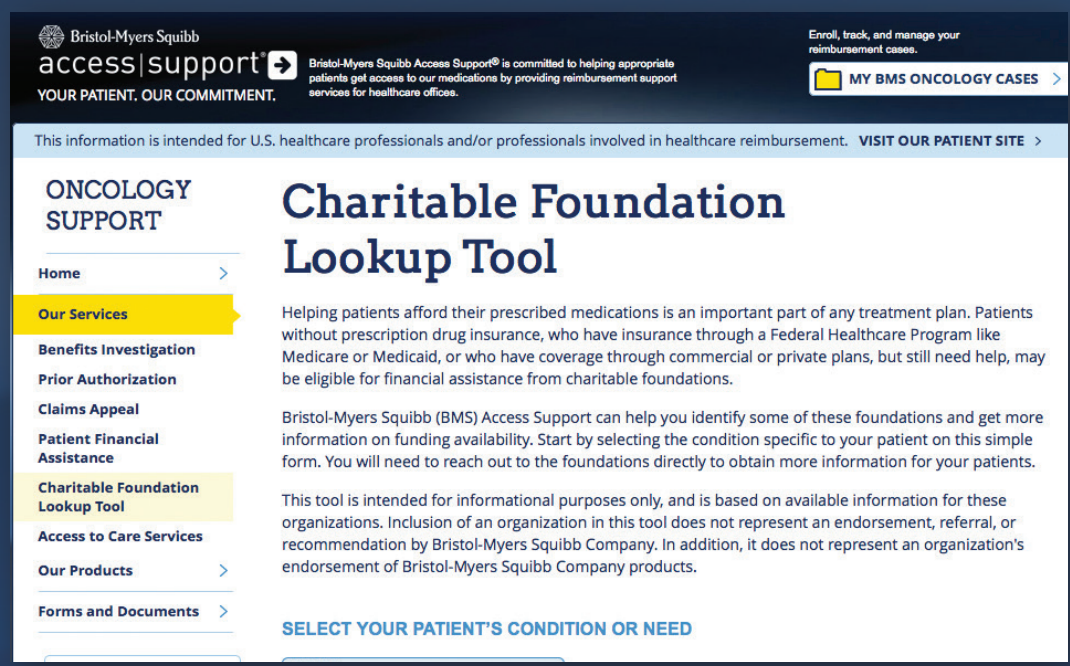
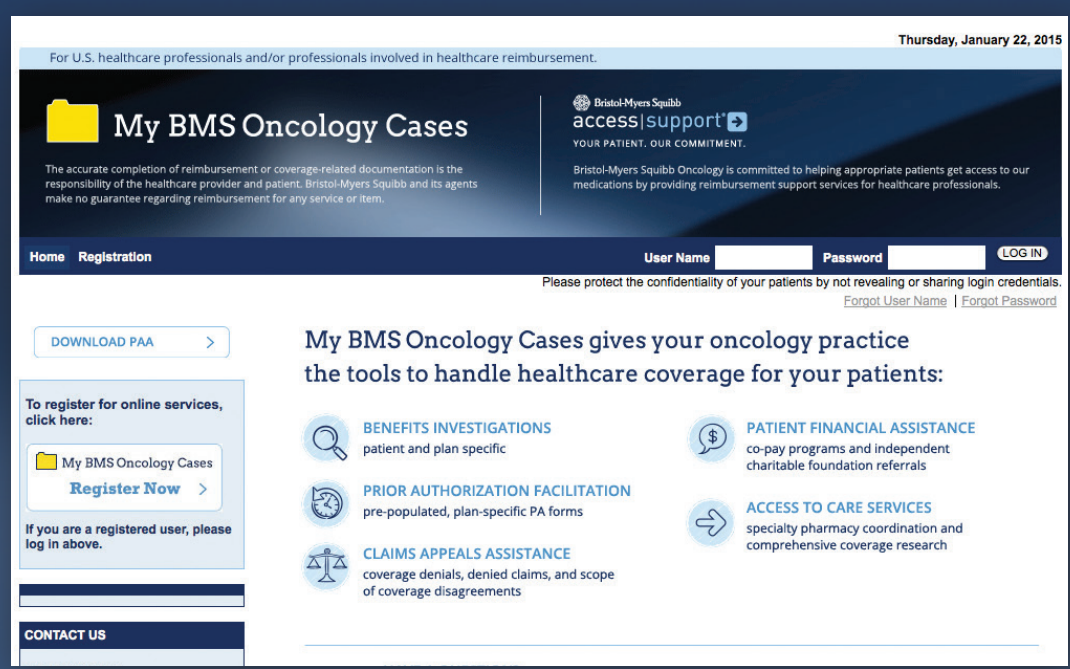
Single enrollment form for HCP and patients to enroll in the services below for BMS oncology medications. Download, select requested services, complete, and fax this form. If you have any questions, contact us at **1-800-861-0048**.

- **Benefit Investigation**
- **Prior Authorization & Appeals Assistance**
- **Comprehensive Coverage Research**
- **Co-Pay Assistance Referrals**
- **Information About Independent Foundation Assistance Programs**



Charitable Foundation Lookup Tool

For patients who need additional assistance affording their BMS medicines, BMS Access Support® can help identify charitable foundations that may provide more information on funding availability. Utilize the ***Charitable Foundation Lookup Tool*** feature to access information on organizations that may be able to help.



Manage BMS Oncology Cases

The My BMS Oncology Cases program gives your oncology practice the tools to enroll, track, and manage your cases online through an HCP portal.

ONCUS15UB00228-01-01 03/15

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(continued from **SP553***)*

hold, right where I'd started, listening to the same cycle of music. The clock continued its ceaseless ticking, my head began to throb, and my hands wouldn't stop shaking, as I remained tethered to the phone for another 20 minutes. And it was then that the unthinkable happened: I was *disconnected*! I stared at the phone in disbelief. I stood there in shock for several seconds—and then very methodically began to slam the phone's receiver onto the body of the phone over and over again, as hard as I could. The tears started streaming and I started screaming, "No, no, noooo!!!" My parents came running and watched while I fell completely apart. I was screaming over and over that they'd hung up on me, that I couldn't take it anymore, and that I was done.

It was one of the few times that I completely lost control after my diagnosis, and it was because of what was a faceless entity to me—an amorphous "insurance" company that insured absolutely nothing, yet had such a hold on me because of my fear of losing everything I had because of their actions (or inactions) and the reality that their decisions could literally alter the course or even, in some cases, the length of one's life.

And then my father, with righteous anger, took matters into his own hands. I'll never know how he did it, but he managed to get a member of upper management on the line almost immediately. And he promptly, loudly, and heroically gave them a piece of his mind. I remember him saying something along the lines of, "My daughter is extremely ill. You *know* this because of the types of drugs you're *supposed* to be paying for. Every 2 weeks, she has to go through grueling chemotherapy, and every 2 weeks, she has to go through a grueling battle *with you* to get you to do your *jobs* and pay for her treatment appropriately. I swear that you're doing this on purpose: you immediately deny all claims, hoping that most people won't be patient enough to stay on hold for hours, repeat their stories 6 times, and have to deal with your extremely rude and callous employees. You hope that they'll just give up and pay it themselves rather than going through this type of torture. But my daughter is a young woman, with a bright future, and she cannot afford to pay for these extremely expensive chemotherapy drugs, NOR *should she have to do so*. After all, that's *why she has your insurance!* She will NOT go into bankruptcy making payments for which *you* are responsible. You WILL pay for this claim and for all the rest of her treatments, and you will NEVER put her through this again. Dealing with you people has been more painful for her than her chemotherapy."

God, I love my father. And I don't remember ever dealing with my insurance company again. From that point on, I believe that my parents gave me the wonderful gift of taking that on for me, worrying about the "PTSD-like" impact caused by that terrible episode. But here's the rub: as awful as that experience was, the fact is, so many cancer survivors have gone through—and are currently experiencing—*much* worse. A dear friend of mine was also diagnosed with Hodgkin's lymphoma as a young adult, but unlike me, she did not have health insurance. Fortunately, she did extremely well with her treatment. But she began her adulthood as a cancer survivor who was carrying the weight of tremendous debt—debt that haunted her for years until she finally paid everything she owed more than a decade later. We were both treated during the late 1980s, well before the era of genomic medicine, and the costs of cancer treatment were high even then.

THE COST DISCUSSIONS TODAY

Fast forward to today, and the costs of cancer treatment are even higher. During this year's American Society for Clinical Oncology (ASCO) Annual Meeting, I was struck by a new phrase that was on everyone's lips: financial toxicity. I appreciated that this very real adverse effect of cancer treatment finally had a name—but I also recall thinking that while the term was new, the condition was not. Yet, the crucial difference now is that more and more oncologists, other healthcare providers, patients, advocates, and other stakeholders are speaking openly about this and actively working on measures to "prevent or treat" this serious toxicity of cancer.

It's impossible to escape the fact that cancer treatments are becoming increasingly expensive, particularly for the novel targeted therapies that have emerged for many cancer types. According to a study published in the *Journal of Clinical Oncology,* targeted therapies accounted for 63% of all chemotherapy costs in 2011.[1] One relevant example is trastuzumab (Herceptin) and another is the more recently approved HER2+ targeted therapy, pertuzumab (Perjeta). In the CLEOPATRA clinical trial, first-line treatment with the chemotherapy drug docetaxel combined with trastuzumab and pertuzumab significantly improved overall survival in women with metastatic HER2+ breast cancer by an average of nearly 16 months. However, trastuzumab costs approximately $4500 each month and pertuzumab, the newer agent, about $6000 per month. Depending on the duration of treatment and the taxane chemotherapy agent used, it is estimated that the total cost can run as high as $195,000.[2]

Worry about financial distress has been associated with changes in treatment-related decision making, such as deciding against a recommended treatment course due to cost and higher rates of nonadherence with oral chemotherapy drugs and hormonal medications.

Since cancer is an expensive disease, shouldn't the costs be covered by insurance for those of us who are insured? In my 20s, my fear was that my insurance company was not acting in good faith, was playing games, and was a bad actor who would not appropriately pay for treatment costs that were rightfully covered by my insurance plan. But today, for many, the concern is different: that although insurance is "paying" for cancer care, insured patients are facing ever increasing out-of-pocket (OOP) costs. As the societal costs of cancer care increase—due to our aging population, an increased risk of developing cancer with older age, improved access to cancer care, and access to more expensive treatments that may have minimal effect or be inappropriately used contrary to the evidence—an increasingly significant portion of these rising costs have shifted to the patient.[3] Insurance premiums, deductibles, and specialty visit co-pays continue to rise, as have prescription drug co-pays; in fact, high OOP costs are most frequently due to prescription medications, followed by outpatient care and hospitalizations.

A growing percentage of insurance companies now divide specific drugs into different tiers, including a "specialty tier," which typically comprises the most expensive and innovative agents, where patients are required to pay a percentage of the drug cost that may be as high as 33%.[4] Further complicating the problem is the disparity in insurance coverage between intravenous treatments and orally administered anticancer agents (oral parity). If patients' oral chemotherapy drugs are associated with high OOP costs, this may increase the risk for nonadherence, where patients skip pills to make their prescriptions last longer or do not get refills because they cannot afford the cost. Private health plans may have a cap on the maximum OOP expense for patients, but there is no maximum OOP expense for Medicare enrollees.

ASCRIBING VALUE TO CANCER CARE

Compared with patients affected by other chronic diseases, those with cancer have higher OOP costs. Their concerns over the financial burden can be likened to the physical toxicities associated with cancer treatment, negatively affecting quality of life and preventing optimal care. A significant percentage of insured patients may spend their savings, work additional hours, cancel vacations, and cut back on other expenses whenever possible to afford their cancer treatment and in an effort to avoid going into debt. In addition, worry about financial distress has been associated with changes in treatment-related deci-

THE AMERICAN JOURNAL OF MANAGED CARE 20 ANNIVERSARY

sion-making, such as deciding against a recommended treatment course due to cost and higher rates of nonadherence with oral chemotherapy drugs and hormonal medications.

According to Gary Lyman, MD, MPH, oncologist at Fred Hutchinson Cancer Research Center in Seattle, health economist, and co-director of the Hutchinson Institute for Cancer Outcomes Research (HICOR; Seattle), "For many, the indirect and out of pocket expenses for cancer care are more than they can handle, leading to interruption or even cessation of potentially lifesaving treatment…We know that cancer is one of the most, maybe the most, common causes of bankruptcy in the country." In his role as HICOR's co-director, he notes that "We're trying to bring a greater awareness and a high level of science to the discussion of the cost and overall value of cancer care." He explained that, in many cases, oncologists and their patients frequently have choices concerning which specific cancer treatment can be used. "We may have 2 treatments that give you the same overall benefit, but one is much less costly," he stressed. "Therefore, it has a great value in the sense that you're going to get to the same place, but you don't need to go into bankruptcy or create enormous financial distress for yourself or your family."[5]

The good news is that the discussion of value in cancer care is a crucial one that is taking place with more frequency. A growing number of oncologists have begun to push back, being vocal about not prescribing new "me too" cancer drugs that are extremely costly yet provide little or no benefit for patients. Peter Bach, MD, director of Memorial Sloan Kettering's Center for Health Policy and Outcomes in New York, and 2 physician colleagues announced to *The New York Times* that the hospital would not be offering Zaltrap (ziv-aflibercept), an angiogenesis inhibitor that was newly FDA approved for the treatment of metastatic colon cancer. Sanofi, the manufacturer of the drug, later cut the drug price in half.

Per Dr Bach, "There are drugs that don't make much sense given how much they cost, given their small benefits. There are drugs that can cost up to $10,000 a month that provide, at the median, a few weeks or less than a month of additional life, but with substantial toxicity."

The good news is that the discussion of value in cancer care is a crucial one that is taking place with more frequency. A growing number of oncologists have begun to push back, being vocal about not prescribing new "me too" cancer drugs that are extremely costly yet provide little or no benefit for patients.

In announcing their decision, Dr Bach and colleagues wrote the following: "At Memorial Sloan-Kettering Cancer Center, we recently made a decision that should have been a no-brainer: we are not going to give a phenomenally expensive new cancer drug to our patients. The reasons are simple: the drug, Zaltrap, has proved to be no better than a similar medicine we already have for advanced colorectal cancer, while its price—at $11,063 on average for a month of treatment—is more than twice as high. When choosing treatments for a patient, we have to consider the financial strains they may cause alongside the benefits they might deliver. This is particularly the case with cancer, where the cost of drugs, and of care overall, has risen precipitously."[6]

VALUE CALCULATORS

Fortunately, several groups are facing the reality of financial toxicity head on and developing tools to help prevent this serious adverse effect of cancer. For example, in June 2015, ASCO released its Value Framework[7] for assessing the value of new cancer treatments based on benefits, toxicities, and costs. Developed by the ASCO Value in Cancer Care Task Force, this conceptual framework will be used to establish standardized tools for oncologists, assisting them in discussing the relative value of specific new cancer therapeutics in comparison with established therapies. In addition, just last month, the National Comprehensive Cancer Network (NCCN) unveiled its new value initiative: the NCCN Evidence Blocks will be published within new versions of the NCCN Clinical Practice Guidelines in Oncology for chronic myelogenous leukemia and multiple myeloma. The costs and affordability of treatment will be included, in addition to the NCCN Guidelines' standard measures of efficacy, toxicity, and quality of associated clinical research data. Per Robert W. Carlson, MD, CEO of NCCN, "NCCN Evidence Blocks will educate providers and patients about the efficacy, safety, and affordability of systemic therapy, serving as a starting point for shared decision making based on the individual patient's value system."[8]

As Dr Bach eloquently stated, "If we link drugs' prices to their value, we can continue the vital quest to lengthen and improve people's lives. We can draw a bulls-eye around the places where innovation is needed most, and we can mandate that treatments be affordable for patients. This last, vital part of the formula would require insurers to jettison the multi-thousand-dollar co-payments they often tack on to expensive specialty drugs."[9]

To conclude, Oscar Wilde famously wrote the following in his masterpiece, *The Picture of Dorian Gray,* "Nowadays, people know the price of everything and the value of nothing." But today, we as patients, advocates, caregivers, clinicians, and all other stakeholders, are beginning to take the necessary steps to change that. **EBO**

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Challenges With Transforming Into an Oncology Medical Home

SURABHI DANGI-GARIMELLA, PHD

"We have come a long way—3 years since the concept of an Oncology Medical Home (OMH) was generated," said Daniel McKellar, MD, who chairs the Commission on Cancer (CoC), a consortium of 56 diverse professional organizations (including clinical registry organizations and patient advocacy groups) that sets and monitors quality standards to ensure improved outcomes and quality of life for cancer patients. Speaking at the Payer Exchange Summit on Oncology Payment Reform, hosted by the Community Oncology Alliance (COA) on October 27, 2015, in Tysons Corner, Virginia, McKellar insisted on meaningful feedback from the community to ensure adequate transformation of practices into a medical home.

McKellar created a case for why CoC is the right body for OMH accreditation. "CoC has significant experience accrediting cancer programs. We are leaders in quality metric development and implementation, and we have a significant infrastructure in place," he said.

McKellar informed the audience that the OMH work group, which includes participation by COA, the National Comprehensive Cancer Network, and the COME HOME group, has developed various standards and quality measures. With 10 pilot surveys completed, a standards manual has been finalized, he said, adding, "So far, we have 10 Oncology Medical Homes accredited by CoC, and we have plans to open up accreditation to 20 to 30 practices in 2016."

McKellar insisted that payers have to be a part of the conversation to ensure these standards and quality measures are meaningful to them, as well. The accreditation process, he said, includes surveyor teams consisting of medical oncologists, and collecting feedback and input from participants on the standards will be an ongoing process. "This will not only further refine the standards, but it will also help develop education programs that can be disseminated within the community," McKellar said.

> **"So far, we have 10 Oncology Medical Homes accredited by Commission of Cancer, and we have plans to open up accreditation to 20 to 30 practices in 2016."**
>
> —DANIEL MCKELLAR, MD

DANIEL MCKELLAR, MD

In an article published in *Evidence-Based Oncology* earlier this year, McKellar described the various domains that CoC uses to measure compliance (**FIGURE**).[1] The process itself includes the following steps:

- Practice submits application
- Practice completes survey application record
- Survey practices reviewed by surveyor on-site
- Report submitted by surveyor staff
- Performance report will be generated.

Clinics are expected to resolve any deficiencies within 12 months of receipt of the performance report. The duration of accreditation is 3 years.

McKellar said that CoC is providing education and support for the community through various means, including developing the standards manual, an OMH accreditation 101 seminar, webinars, and examples of best practices. "CoC is also training—but not promoting—consultants to assist practices in transforming into an OMH."

"Accreditation does matter. It demonstrates that the practice believes in raising its standards of care for patients and their commitment to quality of care. It also improves patient satisfaction," McKellar concluded.

In a subsequent panel discussion, McKellar was joined by representatives from several practices who have received their OMH accreditation. The panelists provided feedback on their experience with the program and the challenges they had to surmount to bring about the transformation.

"We have multiple sites of service, and wanting to provide the same level of care at all of those sites was a challenge. Trying to centralize things is a challenge," shared Charles Bane, MD, Dayton Physicians Network in Ohio.

Pointing to the financial challenges associated with this massive change, Brian Borbeau, Oncology Hematology Care, Ohio, said that transformation has a price associated with it. "Transformation can prove expensive while we are adapting to it, but once we reach the other side, it's easier," he said.

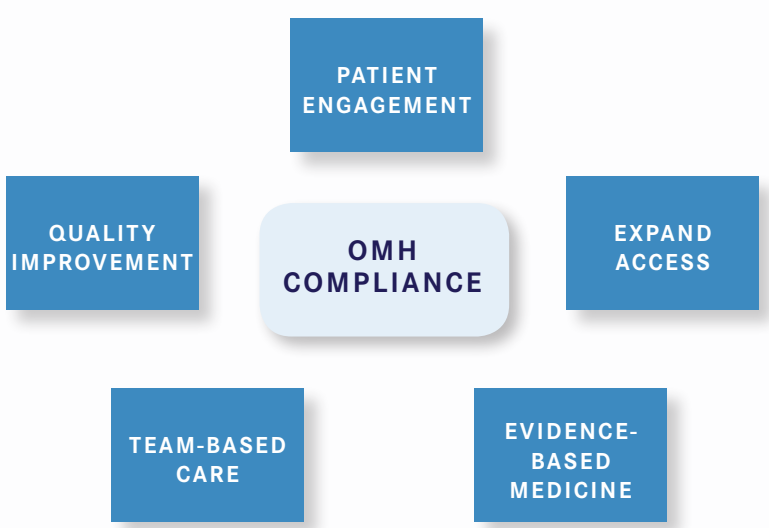
Tammy Chambers of The Center for Cancer and Blood Disorders, acknowledged the support they received from COME HOME. "We had a grant to help us through the cost of transformation Also, Aetna and UnitedHealthcare helped us participate in the shared-savings program, and those savings were fed back into the practice to offset the increased costs we faced during the transformation."

Insisting that the accreditation helped them tell their story, Chambers added that their clinic was practicing evidence-based quality care all along. She told the audience that the transformation, although a lot of work, eventually helps strengthen the practice. "Payers will eventually recognize the value of the accreditation," she claimed.

When asked by Bo Gamble, director, Strategic Planning Initiatives, COA, what their advice would be for other practices who would want to follow the OMH route, panelists had the following responses:

- Identify a physician surveyor
- It will help payers notice you
- The entire staff should be on board
- Every new process needs a cultural or a mindset change, and this must be reinforced with both staff and patients. **EBO**

FIGURE. Compliance Standards for Commission on Cancer Accreditation of Oncology Medical Home (OMH)



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ZYTIGA® + prednisone achieved a median OS of almost 3 years (34.7 months) after a median 4 years (49 months) of follow-up†

- **4.4 months improvement in median overall survival—34.7 months** with ZYTIGA® + prednisone vs **30.3 months** with placebo + prednisone (active compound)‡
  - **Co-primary end point**—median OS: hazard ratio (HR)=0.81; 95% CI: 0.70, 0.93; ***P*=0.0033**
- **Co-primary end point**—at the prespecified rPFS analysis, median not reached for ZYTIGA® + prednisone vs a median of 8.28 months for placebo + prednisone; HR=0.425; 95% CI: 0.347, 0.522; ***P*<0.0001**§‖

MEDIAN 4 YEARS (49 MONTHS) OF FOLLOW-UP

IMPORTANT SAFETY INFORMATION

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Drug Interactions—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

Use in Specific Populations—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

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

ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS

Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS

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

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.

Clinical Trial 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.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy: Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

	Abiraterone (N=791)		Placebo (N=394)	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy: Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2 (continued)

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=540) All Grades %	 Grade 3-4 %
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N=542) Grade 1-4 %	 Grade 3-4 %	Placebo (N=540) Grade 1-4 %	 Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. 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.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category X *[see Contraindications].:* ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate 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 ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

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

Geriatric Use: Of the total number of patients receiving ZYTIGA in Phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment: The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions,* and *Clinical Pharmacology (12.3)] in full Prescribing Information.*

Patients with Renal Impairment: In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

Storage and Handling: Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations]*.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA should not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

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Payment Reform Pilot Updates at the COA Payer Summit

SURABHI DANGI-GARIMELLA, PHD

An aging population, technological innovation, increased awareness resulting in earlier screening, and improved treatment regimens that have made cancer a chronic disease in some cases—all of these factors together have a significant impact on the growing cost of oncology care. In an attempt to curb this increasing financial burden on the US healthcare system, several payment reform pilots are being evaluated by payers in collaboration with their clinical care partners. At the third Payer Summit hosted by the Community Oncology Alliance (COA), payers and providers took to the stage to provide a progress report and discuss challenges and lessons learned along the way.

BARBARA MCANENY, MD

The first case study was presented by Michael Kolodziej, MD, national medical director, Oncology Solutions, Aetna, and Russell Hoverman, MD, vice president, Quality Programs, Texas Oncology. They provided an update on the clinical pathways pilot program at Texas Oncology. Kolodziej said that he had played a significant role in developing the pathways program while he was still with US Oncology to evaluate its impact on cost of care. "We were successfully able to show that pathways can reduce cost while maintaining the quality of care," he said. After joining Aetna, "We convinced Texas Oncology to let us try the pathway in the Medicare Advantage program (MA)." The Aetna Teacher Retirement System MA Innovent Oncology Program[1] has yielded about $4180 savings per patient in the first year, Kolodziej said, with total savings of $765,000 among 183 members. "The second year savings are even better," he added.

MICHAEL KOLODZIEJ, MD

The pathways program is still a product in evolution, according to Hoverman. "When we tied income to pathways performance, we saw a tremendous improvement in performance," he said. In his opinion, pathways and guidelines, tiered drug fee schedules, care management and patient support services, advance care planning, and payment structure all contribute toward bending the cost curve while helping deliver quality cancer care. Support tools such as "Clear Value Plus have tremendously improved data compliance, which, in turn, has improved pathway performance," Hoverman told the audience.

LEE NEWCOMER, MD, MHA

Pointing out that being responsible for the total cost of care is a whole new arena, Hoverman thinks that hospital-generated data can be pooled with the data generated in smaller physician practices for improved progress. "The cost of drugs and cost of care means we have to change," he said.

The next pilot program introduced was UnitedHealthcare's episode payment program that was piloted at 5 medical groups, including Northwest Georgia Oncology Centers. Lee Newcomer, MD, MHA, senior vice president at UnitedHealthcare, explained that the episode model was rooted in rewarding performance and cutting back dependency on drug volume and sales. A gain-sharing model, the participating clinics registered all patients with breast, colon, and lung cancer and provided clinical data to the payer. A single-episode payment was made at the initial visit and drugs were reimbursed at the average sales price rate. All physician services continued to be reimbursed as fee-for-service (FFS). "Episode payments remained unchanged with drug changes," Newcomer explained.

Measurement of annual performance found that the episode payment model resulted in tremendous cost savings. Newcomer then showed data, now been published in the *Journal of Oncology Practice*,[2] showing that although the FFS cost for the 810 patients from the 5 practices was expected to be $98,121,388, the actual cost was $64,760,116; a huge saving of $33,361,272 in total medical costs. However, drug costs increased, said Newcomer, from $7,519,504, to $20,979,417 during the period of data collection between October 2009 and December 2012.

"The program has since expanded; Texas Oncology started in January. We now have a third wave of practices joining in, but we have frozen participation right now. Since the first wave of pilots was so successful, we need to see them duplicated before we move forward."

"We are very encouraged by this project…that there are opportunities for savings," said Newcomer. "No matter the approach, community oncologists have the opportunity to be rewarded for the value they bring."

RUSSELL HOVERMAN, MD

According to Scott Parker, executive director of Northwest Georgia Oncology Centers, the essential requirements of a successful reform pilot are a cohesive practice group, strong analytics capacity (either in-house or outsourced), strong reimbursement, a strong clinical manager, a strong treatment planning approval procedure, and active collaboration with customer service for patients. "From our standpoint, these key components—though obvious and simple in concept—are critical to develop an innovative payment model," said Parker.

STEVE D'AMATO, BSPHARM, BCOP

Another pilot program that was discussed was the COME HOME project that has been the brainchild of Barbara McAneny, MD, who leads New Mexico Oncology Hematology Consultants.

Steve D'Amato, BSPharm, BCOP, executive director of New England Cancer Specialists, shared the adaptation of the COME HOME project at his practice. "It transformed and positioned us for the future," D'Amato said, adding that it required commitment, buy-in, and a lot of energy.

In his experience, COME HOME requires a triage system, and urgent care was a major component of it. It was key, he said. "Clinicians participating in the COME HOME program have their own set of pathways—that's another essential component. At our clinic, we extended our daily clinic hours and began operating even on weekends—which was quite essential," D'Amato said. He explained that although it did not directly impact cost, "patient satisfaction was through the roof." This helped patients bypass visits to the emergency department (ED), which is an overall cost saving to the healthcare system, he said. "COME HOME also positioned us for the Oncology Care Model (OCM)," the initiative proposed by CMS.[3] "The infrastructure costs, though, are real to run this project. To transform the clinic into an OCM was huge, but COA and Barbara provided us with tremendous support," D'Amato indicated.

McAneny said, "When we started COME HOME, we were only thinking of patients and doctors. Most of my patient population is poor. So the point was to keep them out of the ED and from being admitted to a hospital. The triage pathways that we created solidified what we were doing. We had to educate our patients and ask them to call us first rather than 911. This took a lot of educating our practice staff on how to handle these patients and them to teach patients to call us rather than ED." She explained that the complexities of the healthcare system should be the least of a sick patient's worries, so "we took care of navigating the healthcare conundrum for the patients."

She acknowledged that working with COA and the Commission on Cancer for the accreditation worked very well for the project. "We have seen significant impact on total cost of care and reduced the number of days of hospitalization." At the end of the day, McAneny wants to see a restructuring of payments "so physicians have the flexibility to do what they want to do while keeping patients happy with the quality of care they get." **EBO**

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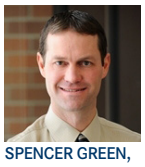
Who Pays for Immuno-Oncology?

SURABHI DANGI-GARIMELLA, PHD


NIESHA GRIFFITH, MS, RPH, FASHP


SPENCER GREEN, MS, MBA


STEVE D'AMATO, BSPHARM, BCOP

Immuno-oncology clinical trials have transformed the cancer treatment landscape. Nearly every week we hear about improved trial outcomes across a broad range of tumor types. However, challenges remain with clinical integration of these revolutionary agents into mainstream cancer care. To discuss existing challenges and possible solutions, the Association of Community Cancer Centers hosted the first annual conference of the Institute for Clinical Immuno-Oncology (ICLIO) on October 1, 2015, in Philadelphia. ICLIO launched as an immuno-oncology resource for community oncologists earlier this year.[1]

Among the sessions was a presentation by Niesha Griffith, MS, RPh, FASHP, administrator of Oncology Pharmacy and Infusion Services at the James Cancer Hospital, Ohio State University. Griffith provided insight into administrative challenges with immuno-oncology agents, existing coverage policies, and reimbursement concerns. She ended with suggestions on the best practices for successfully using these agents in practice.

The primary challenges for her as an administrator, said Griffith, included:

1. **Patient and staff education.** Identify a point person to be a resource for immuno-oncology and a core group to manage patient education. This requires proactive staff education on immuno-oncology updates.
2. **Patient triage,** especially with respect to unfamiliar adverse events. Staff attending patient phone calls should be aware of potential adverse effects that demand immediate attention. Develop protocols for patient triage/management.
3. **Navigating financial challenges** for these high dollar agents.
4. **Reimbursement concerns with new-to-market agents.** Assign a dedicated financial or reimbursement staffer—familiar with manufacturer programs, co-pay foundations, and patient assistance programs—to focus on immuno-oncology agents.
5. **Off-label use may cause reimbursement concerns.** Each institution needs a policy in place to ensure best practices with off-label use, with patients being kept well-informed on financial challenges with reimbursing off-label use.

Griffith pointed out that her cancer center moved reimbursement specialists to the pharmacy department to handle high-dollar approvals, and also developed a work flow to ensure a smooth process for both on-label and off-label immuno-oncology agent use—a staff-intense process that would need additional hands on board. Several oncologists attending the session pointed out that this would be a difficult proposition for an already resource-stretched community oncology practice.

"Payers need to keep up with accelerating evidence-based new indications," said Griffith. She believes that as marketplace competition increases, payers may include step therapy in precertification requirements to specify preferred agents.

During a subsequent panel discussion, Spencer Green, MS, MBA, business operations manager, Bozeman Deaconess Cancer Center, said, "By entering into an alliance with organizations like the ACCC, community centers can gain access to experts for the necessary information on these novel treatment options. Company sales representatives are an additional resource to understand the program—it can help avoid back-end issues with billing and reimbursement." This can also prevent delays in patient access to care, he added.

Steve D'Amato, BSPharm, BCOP, executive director, New England Cancer Specialists, and current president of ACCC, insisted on including payers in the conversation. "We have a good relation with our payers," he said. "We have shared some of our data with Anthem on new therapies, cost implications, and what we are doing as beneficiaries. Both Aetna and Anthem have been quite supportive of the programs in place at our clinic with these agents." Keeping payers informed on policies being developed at our institutions and clinics can have a huge impact on reimbursement, and can also help payers understand the challenges we face with using these agents, added D'Amato. **EBO**

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Patient Assistance Programs Ensure Affordable and Quality Cancer Care

SURABHI DANGI-GARIMELLA, PHD

Oncologists are increasingly aware of the hardships patients face as they choose newer oncolytic agents that promise better outcomes. The financial toxicity of healthcare, particularly in oncology, is not lost on anyone, and drug companies have renewed their efforts with patient assistance programs, ensuring that physicians,as well as patient support groups,are aware of the financial resources that patients can access. "We work extensively to provide clarity around our programs to clinicians," shared Frank Marra, executive director, Patient Affordability and Executive Services at Bristol Myers Squibb.

Marra was part of a panel discussion at the first national meeting of the Institute for Clinical Immuno-Oncology, an initiative of the Association of Community Cancer Centers, held October 2, 2015, in Philadelphia. The panel followed a presentation by Linda House, RN, BSN, MSM, president, Cancer Support Community (CSC). According to House, the patients open up to CSC more than they do with their oncologists. "We try to work on psychosocial aspects of the patient's care," she said. In an 8000-patient registry, CSC has observed that 75% of cancer patients follow their clinician's advice when making health decisions. So with respect to newer, more expensive immuno-oncology agents, the quality of patient care is closely associated with reimbursement. And to be able to afford this expensive care, patients and their families sacrifice vacations, social events, and skimp on groceries, House said.

"Many live with chronic toxicities, and need follow-up care; 36% do not return to work." Mental health conditions are an important sideeffect associated with their suffering and "depression in cancer patients is estimated to cost about $8400 per patient," said House, adding that the pharmaceutical industry is actively partnering with organizations like CSC to understand the needs of patients and to provide improved support. "We have 1-800 helplines at CSC, with mental health counselors on call," and CSC's partnership with Onyx Pharmaceuticals allows their support line to transfer callers to CSC's helpline.

During the subsequent panel, Delali Attiogbe, site manager for BioOncology Managed Markets, Genentech, said that her company understands that patients do hold financial conversations with their treating physician, and so her company is ensuring physician awareness on patient support programs. "We are also partnering with groups like CSC, arranging warm transfers of patients. There are dedicated groups within the company to help the process," said Attiogbe.

Charles Lynch, program coordinator of the Oncology Medical Assistance Program at Yale-New Haven Hospital, said, "We have a support system at Yale that various health service providers are involved in, including clinicians, nurses, and social workers." After the treatment clinic works out a treatment plan, his department calculates the patient's out-of-pocket expenses and also evaluates the available alternatives on drug lists, Lynch explained. "We explore PAN [Patient Access Network] and PAF [Patient Advocate Foundation] grants and co-pay cards…all the information is assessed to support care."

When asked if the newer immuno-oncology agents have created unique challenges for patient assistance programs, Marra said that while similar challenges have persisted over the years, newer products have only amplified the problem. "We work extensively to provide clarity around our programs to clinicians and we are striving to enroll every patient in the program. Each patient is different and the program tries to adapt around their needs," said Marra. **EBO**

Tagrisso Approved, but Can Patients With EGFR-Mutant NSCLC Afford It?

SURABHI DANGI-GARIMELLA, PHD

AstraZeneca's epidermal growth factor receptor (EGFR) inhibitor, osimertinib (Tagrisso), was recently approved in patients harboring T790M-mutated non-small cell lung cancer (NSCLC) who have regressed following treatment with other EGFR inhibitors.[1] The approval comes within 3 years of the company having launched drug trials for osimertinib, which showed an objective response rate of 59%, and a sustained response of over a year.

Having specifically developed the drug for a subset of NSCLC patients, AstraZeneca collaborated with Roche Diagnostics to develop a companion diagnostic, the cobas EGFR Mutation Test v2, which detects EGFR mutations in NSCLC tissue samples.

While oncologists, including Pasi A. Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute, have hailed osimertinib to have the potential to be the standard of care in EGFRm T790M NSCLC, the question now is how much will it cost the patient and the healthcare system overall, and, will this cost add value?

According to a company spokeswoman, a 1-month supply of this oral medication is estimated to cost nearly $13,000[2]—quite comparable with Pfizer's Xalkori (prices at $11,500 a month) and Zykadia by Novartis ($13,200), both approved for treating Alk-mutated lung cancer. And, we have not yet started talking about the cost of the companion diagnostic test that will determine patient eligibility for osimertinib.

While previous estimates from AstraZeneca projected a $3 billion annual market for the drug, the news of Clovis Oncology's competitor product hitting a snag in their FDA review could further open up the market for AstraZeneca. CO-1686 or rociletinib, which has shown promising results in EGFR-mutated (T790M) NSCLC patients, now needs additional data for FDA review.

Meanwhile, Diplomat Pharmacy, the largest independent specialty pharmacy in the country, has announced plans to offer osimertinib to a few select patients. "Diplomat is proud to support patient adherence and compliance with therapy through enhanced clinical outreach programs, with customized messaging, developed in collaboration with AstraZeneca, to patients through various stages of treatment," said Gary Kadlec, president of the company, when making the announcement.[3] **EBO**

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Daratumumab Approval Yields the First Monoclonal Antibody, and Another Option, in Multiple Myeloma

SURABHI DANGI-GARIMELLA, PHD

The FDA has approved daratumumab for patients with multiple myeloma who have previously been treated with at least 3 regimens.[1] Daratumumab, which received breakthrough status 2 years ago, is the first monoclonal antibody approved for multiple myeloma.

RICHARD PAZDUR, MD

The approval follows review of 2 open-label studies that included 106 and 42 participants. The first study (phase 2 MMY2002) saw 29% of patients with a complete or partial reduction in tumor burden that was sustained for at least 7.4 months. These patients had received a median of 5 lines of prior therapy. The second study (phase 1/2 GEN501) saw a complete or partial reduction in tumor burden of 36% of patients. These patients had received a median of 4 lines of prior therapy. Today's approval is the first for a CD38 antibody and comes just 2 months after the drug was submitted for priority review.

Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research, hailed daratumumab as another option for patients to turn to when their disease has developed resistance to all other existing therapies.

Some of the side-effects associated with the drug include infusion-related reactions, fatigue, nausea, back pain, fever, and cough. Daratumumab may also result in low counts of infection-fighting white blood cells (lymphopenia, neutropenia, and leukopenia) or red blood cells (anemia), and low levels of blood platelets (thrombocytopenia).

Daratumumab, approved under the FDA's accelerated approval program, had an orphan drug designation. **EBO**

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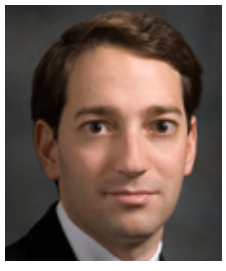
A Cancer Prevention Trial Identifies Predictive Biomarker in Oral Cancer Development

SURABHI DANGI-GARIMELLA, PHD


WILLIAM N. WILLIAM JR, MD

Oral premalignant lesions (OPL) can be risk factors for oral cancer, and chemoprevention strategies can be developed to stop or reverse the cancer. A trial designed to test one such strategy—the Erlotinib Prevention of Oral Cancer (EPOC)—evaluated whether inhibiting the epidermal growth factor receptor (EGFR) could reduce oral cancer development in patients with high-risk OPLs. While the EGFR inhibitor being evaluated, erlotinib, did not improve cancer-free survival (CFS), the trial validated loss of heterozygosity (LOH) as a marker of oral cancer risk and was associated with increased copy number of the EGFR gene.

The EPOC study, conducted between November 2006 and July 2012, recruited 395 participants with OPL in 5 academic institutions in the United States. Following LOH profiling, 379 patients were classified as high-risk (LOH-positive) or low-risk (LOH-negative). Treated with 150 mg/day erlotinib or placebo for 12 months, the trial followed patients for 35 months. One hundred and fifty of the 254 LOH-positive patients were randomized—75 received erlotinib and 75 were on placebo. The 3-year CFS rate was 70% and 74%, respectively, when comparing these 2-patient cohorts. However, 3-year CFS of LOH-negative patients was much better than that of LOH-positive patients—87% versus 74%, respectively. Further, the authors deduced a correlation between EGFR gene copy number and LOH-positive status, as well as EGFR gene copy number and lower CFS. A serendipitous finding of the trial was that patients who developed a skin rash, a side-effect of erlotinib, had better CFS.[1]

According to study author William N. William Jr, MD, associate professor at MD Anderson, "One of the greatest challenges in developing chemopreventive agents is to identify the population at highest cancer risk. Not all patients with an oral premalignant lesion will develop cancer. By developing a molecular test that can identify those at highest risk, we hope to focus future preventive efforts on these specific individuals."[2]

The authors write that, while their results support using LOH testing as a prognostic tool in routine clinical practice, they do not support erlotinib use in this setting. Another feather in the cap of personalized medicine in the preventive setting. **EBO**

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Exceptional Response in Brain Tumor Patient Instills Confidence in Personalized Medicine

SURABHI DANGI-GARIMELLA, PHD

A young man, less than 40 years old, with recurrent craniopharyngioma (pituitary tumor) harboring a BRAF V600E mutation, showed a dramatic response when treated with BRAF V600E inhibitors—85% reduction in tumor volume. This case has the "potential of completely changing the management of papillary craniopharyngiomas," according to study author Priscilla Brastianos, MD, of the Massachusetts General Hospital (MGH) Cancer Center.[1]

The study, published in the *Journal of the National Cancer Institute*,[2] reports on the case study of a patient who came to the emergency department at MGH, 7 months after having undergone surgery to excise a brain tumor. A CT scan of the patient, who complained of confusion, impaired vision, severe headaches, and vomiting, revealed a 4-cm cystic tumor. Six weeks following partial removal of the tumor, the patient was brought back and underwent additional surgery. At this point, the tumor was confirmed to carry a mutant BRAF. Another unsuccessful surgery and a recurrence in 2 weeks prompted the providers handling the case to treat the patient with the BRAF-V600E inhibitor dabrafenib, currently approved for the treatment of patients with unresectable or metastatic melanoma harboring the BRAF-V600E mutation.

A dramatic response was seen within 4 days of treatment, with a 25% tumor shrinkage, the authors report. Following a 50% shrinkage in tumor by day 17, the authors added a MEK inhibitor, trametinib, which has been approved for use in patients expressing a mutant BRAF (V600E or V600K).[3] When the tumor reduced to 80% its original size, another surgery removed any accessible tumor at day 38 and drug treatment was stopped a week later, followed by radiation. The patient has been reported to be symptom–free for a year. Another extremely important outcome of the study was the ability to detect circulating tumor cells, which carried the BRAF mutation, using a blood-based assay. For patients with a brain tumor, a noninvasive test can be a tremendous advantage and can significantly reduce patient morbidity.

"It is quite remarkable how quickly we have been able to go from identifying the genetic driver of papillary craniopharyngiomas to testing the idea in a patient that needed help. It was only last year that, along with Dr Brastianos and colleagues, we first described in Nature Genetics that nearly all papillary craniopharyngiomas have mutations in BRAF," said co-senior author Sandro Santagata, MD, PhD, of Brigham and Women's Hospital's Pathology Department. **EBO**

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Another First for Nivolumab: *Approved as Frontline for BRaf Wild Type Melanoma*

SURABHI DANGI-GARIMELLA, PHD

The new class of immuno-oncology molecules are definitely keeping up with their promised potential. Nivolumab was approved as first line for treatment-naïve melanoma patients whose tumors express a wild type (WT) BRaf V600.[1] The approval follows 5 months after Bristol-Myers Squibb submitted phase 3 results of the Checkmate-066 trial for FDA review.

JEFFREY S. WEBER, MD, PHD

With overall survival (OS) as the primary endpoint, Checkmate-066 evaluated nivolumab as a single agent in treatment-naïve patients with unresectable or metastatic BRaf WT melanoma. Patients received either nivolumab (n = 210; 3 mg/kg intravenously, once every 2 weeks) or dacarbazine (n = 208; 1000 mg/m2, once every 3 weeks). Progression-free survival (PFS) and objective response rate (ORR) were the secondary endpoints.

Interim trial analysis showed a superior OS with nivolumab compared with dacarbazine. Median OS was not reached for nivolumab at the time of analysis; for dacarbazine, it was 10.8 months (95% CI, 9.3-12.1). Nivolumab significantly improved PFS: 5.1 months (95% CI, 3.5-10.8) compared with 2.2 months (95% CI, 2.1-2.4) for patients treated with dacarbazine (Hazard ratio [HR], 0.43; 95% CI, 0.34-0.56; P <.0001), and ORR was 34% (4% complete response rate [CRR], 30% partial response rate [95% CI, 28-41]) compared with 9% with dacarbazine (1% CRR, 8% partial response rate [95% CI, 5-13]). Nearly 88% of patients had ongoing responses at the time of analysis, about 68% of whom had at least a 6-month response.

Jeffrey S. Weber, MD, PhD, deputy director of the Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center who has been actively involved with Checkmate-066, said, "Advanced melanoma continues to be one of the deadliest and most challenging cancers to treat, and ongoing research in immuno-oncology from clinical trials like CheckMate -066 shows the potential to provide improved overall survival for newly diagnosed patients with BRAF wild-type metastatic melanoma. This important news means that we now have another new option to offer patients with BRAF wild-type metastatic melanoma."

Grade 3 and 4 adverse events (AE) were observed in 43% of patients treated with nivolumab, the most common being gamma-glutamyltransferase increase and diarrhea. AE resulted in permanent discontinuation of nivolumab treatment in 7% of patients and dose interruption in 26% of patients. Other documented AE included fatigue, musculoskeletal pain, rash, and pruritis. **EBO**

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Nivolumab Approved for Third Indication: *Advanced Renal Cell Carcinoma*

SURABHI DANGI-GARIMELLA, PHD

Two months after being granted a Breakthrough Therapy designation by the FDA for metastatic renal cell carcinoma (mRCC), nivolumab was today approved by regulators for treating mRCC patients who have failed a certain type of prior therapy.

The approval[1] was based on the results of a phase 3 trial published earlier this month in the *New England Journal of Medicine*, which compared nivolumab with everolimus in 821 patients with advanced clear-cell renal-cell carcinoma who had received prior treatment with 1 or 2 antiangiogenic agents. The randomized trial assigned patients to receive either an intravenous infusion of nivolumab (3mg/kg) every 2 weeks or oral everolimus (10 mg tablet, once daily). The secondary endpoints were objective response rate and safety, and the primary trial endpoint was overall survival. The study design allowed dose modification for everolimus but not for nivolumab.

This international study, dubbed Checkmate-025, recruited patients at 146 sites across 24 countries in 5 continents (North and South America, Australia, Asia, and Europe). Only 803 of the 821 patients were treated, with 406 in the nivolumab group and 397 in the everolimus group. By data cutoff in June 2015, 17% (67) of patients in the nivolumab group and 7% (28) in the everolimus group continued to receive treatment. Minimum follow-up period was 14 months and disease progression as the primary reason for discontinuation of treatment (observed in 70% of nivolumab-treated patients and 69% of everolimus-treated patients).

Patients in the nivolumab group had significantly better overall survival (25 months; 95% confidence interval (CI), 21.8 to not estimable) compared with those treated with everolimus (19.6 months; 95% CI, 17.6 to 23.1). Nearly 45% of patients (183 of 410) in the nivolumab cohort died, as opposed to 52% (215 of 411) in the everolimus group. The hazard ratio for all-cause death was 0.73 (98.5% CI, 0.57 to 0.93; P = .002) for nivolumab versus everolimus.

In the press release announcing the drug's approval, Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said, "Opdivo [nivolumab] provides an important therapy option for patients with renal cell carcinoma. It is one of few therapies that have demonstrated the ability to extend patients' survival in treating this disease. Additionally, Opdivo's extended indication, from melanoma and non-small cell lung cancer to renal cell cancer, demonstrates how immune therapies can benefit patients across a wide range of tumors." **EBO**

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Smoking Rates Declining but Disparities Evident: *CDC Report*

SURABHI DANGI-GARIMELLA, PHD

Whether you are privately or federally insured is an important determinant of whether you smoke, according to CDC's recently released *Morbidity and Mortality Weekly Report*.[1]

Results based on the 2014 National Health Interview Survey show that 27.9% of uninsured adults and 29.1% of Medicaid enrollees smoke, compared with 12.9% of privately insured adults and 12.5% of Medicare enrollees who are smokers. Another important finding, other than the insurance-based disparity, is the steady decline in the rate of smoking over a decade (2005 to 2014), from 20.9% to 16.8%—these numbers seem well on target to achieving a smoking rate of 12% or lower by 2020, per the Healthy People 2020 targets.[2] The average number of cigarettes smoked per day dropped by about 3 percentage points, from 16.7% to 13.8% during the study period.

The highest smoking rates were observed among:

- Males
- Young adults
- People below the poverty line
- People with a disability
- People with a General Education Development certificate
- People who are lesbian, gay, or bisexual.

A press release announcing the results of the study, from the Campaign for Tobacco-Free Kids, says that while the results prove that the fight against this devastating habit has made huge strides, there's much work needed to meet the goals of "protecting Americans from the number one cause of preventable death." The organization urges continued national efforts on multiple fronts, including higher taxation on tobacco products, smoke-free laws, and barrier-free health insurance for smoking cessation treatments, among others.


TOM FRIEDEN, MD, MPH

Smoking cessation treatments have gained improved coverage, especially under the Affordable Care Act. A recent report by the CDC, addressing cessation coverage, found that only 9 states cover all 9 evidence-based cessation treatments (individual counseling, group counseling, nicotine gum, nicotine patches, nicotine lozenge, nicotine nasal spray, nicotine inhaler, bupropion, and varenicline).

Praising the findings from the report, CDC Director Tom Frieden, MD, MPH, said, "Smoking kills half a million Americans each year and costs more than $300 billion. This report shows real progress helping American smokers quit and that more progress is possible." **EBO**

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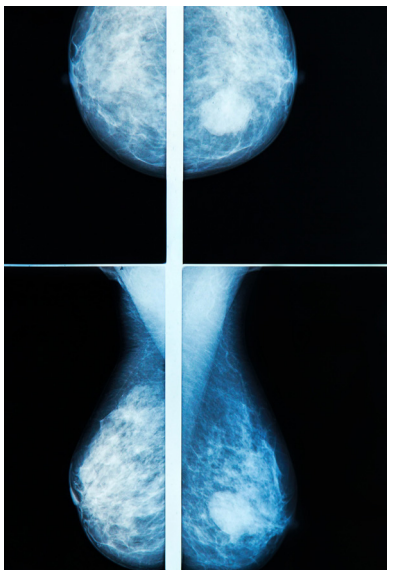
Should We Trust Screening Age Recommendations in Cancer?

SURABHI DANGI-GARIMELLA, PHD

Initiate an active discussion with your clinician about screening at age 40 years if you have an average risk of developing breast cancer, but regular screening mammograms can wait till age 45 years. This is the new evidence-based guidance update provided by the American Cancer Society (ACS), published yesterday in *JAMA Internal Medicine*.[1]



The leading cause of cancer death in women in the United States, second to lung cancer, nearly 240,000 women are expected to be diagnosed with the disease this year. Despite increased disease awareness and rapid strides in research and drug development, mortality among breast cancer patients remains high.

The previous ACS recommendations for breast cancer screening were published more than a decade ago and recommended that women at average risk should begin screening at age 40 years.[2] A periodic, preferably annual, breast exam was recommended for women 40 years and older. Women at an increased risk of breast cancer, the guidelines recommended, should be offered an earlier screening, shorter screening intervals, and the inclusion of ultrasound or magnetic resonance imaging, along with a physical exam and a mammogram, to their screening modalities.

The updated guideline for women with an average risk of developing breast cancer (ie, women without a personal history of breast cancer, a suspected or confirmed genetic mutation that can increase risk, or a history of chest radiotherapy at a young age) are:

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (Strong Recommendation)
   - 1a. Women aged 45 to 54 years should be screened annually. (Qualified Recommendation)
   - 1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. (Qualified Recommendation)
   - 1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (Qualified Recommendation)
2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. (Qualified Recommendation)
3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. (Qualified Recommendation)

The article emphasizes the need for a discussion of personal and family medical history with the individual's physician and a periodic evaluation of whether the risk profile has altered. Additionally, the ACS recommends that women should be informed on the risk factors, risk reduction, benefits, and harms, associated with mammography screening. **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 treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred in 0.5% (5/978) of patients receiving OPDIVO as a single agent. In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO including five Grade 3, two Grade 2, and three Grade 1 cases. 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.

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 including three Grade 3, two Grade 2, and two Grade 1 cases.

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, and thyroid disorders can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, and thyroid function prior to and periodically during treatment. 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. Adrenal insufficiency occurred in 1% (n=555) of patients receiving OPDIVO as a single agent. 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.

Immune-Mediated Rash
Immune-mediated rash can occur with OPDIVO treatment. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 rash. In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including 4 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% 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 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 <2% (n=555) of single-agent OPDIVO-treated patients: uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy. 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: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

Infusion Reactions
Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO. In Checkmate 057, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. 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.

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 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 breastfeeding 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 0.5% (5/978) 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 (2.3) 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 (2.3) 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 (2.3) 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 (nivolumab) 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 (2.3) 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 (2.3) in full Prescribing Information]*.

In Trials 1 and 3 (n=555), 1% 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.

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 (2.3) 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. 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 (2.3) 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 serve 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 (2.3) in full Prescribing Information]*.

Across clinical studies of 8490 patients receiving OPDIVO, less than 1% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO (nivolumab) 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 (2.3) in full Prescribing Information]*.

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=555): uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy.

Across clinical trials of OPDIVO administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

Infusion Reactions

Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO as a single agent. In Trial 3, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. 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.

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 for clinically significant adverse reactions in 978 patients enrolled in Trials 1, 3, a single-arm trial in NSCLC, 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 in Trial 3, which is a randomized trial in patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

Metastatic Non-Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO 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 (nivolumab) 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 532 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 67 patients (12.6%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in five patients (0.9%). 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 (nivolumab) 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 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 (nivolumab) 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 interruption 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, and hyperthyroidism *[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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FDA Regulation of LDTs:

A Report Justifies the Need for It

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Medicare covers them, private payers cover them, and providers and patients make clinical decisions on the results they generate—isn't it time to regulate laboratory-developed tests (LDTs), which cost Medicare $9.7 billion in 2012 alone?[1] The FDA believes so and, in preparation, has issued a report that details the potential harm to patients resulting from false-negative or false-positive test results.[2] This follows a draft guidance issued in October 2014 that included a risk-based framework to define regulatory oversight of LDTs for the clinical laboratories that develop them.

By definition, an LDT is an in vitro diagnostic that is designed, manufactured, and used within a single laboratory. A test that is even partially designed outside the laboratory that offers or uses it no longer falls within the class. This definition is site-restricted. For example, if several clinical labs form a network within an entity, an LDT developed by one of these laboratories cannot be used by another lab within that network. If a component used within the test is manufactured for the lab by a third party, the FDA will cease to consider the device an LDT.

Lakshman Ramamurthy, PhD, vice president at Avalere Health, wrote in a blog that LDTs, also known as "home-brewed" tests, are created in response to unmet clinical needs. However, the tests have come a long way. "LDTs have expanded in their reach and are purchased by and shipped to nationwide laboratories and utilized across the country," he writes.[3]

The new FDA report provides case studies that underscore the importance of regulating LDTs beyond the current requirements of the CMS-developed Clinical Laboratory Improvement Amendments (CLIA) and the Federal Food, Drug, and Cosmetic Act. The report claims that events associated with 20 case studies presented in the report resulted from adherence of the test developers to the minimum requirements of CLIA. The following **TABLE** includes a few examples from the report.

"As this report demonstrates, strengthening the FDA's oversight over LDTs is critical to protect both patients and the public health," wrote Peter Lurie, MD, MPH, the FDA's associate commissioner for public health strategy and analysis, in his blog post published November 16, 2015.

In April of this year, the FDA and CMS announced the formation of a task force to avoid duplication of efforts by the agencies.[4] Although CMS, through CLIA, ensures quality of the lab processes used to develop the tests, the FDA plans to enforce the premarket review requirements to confirm both the analytical and clinical validity of the tests. **EBO**

TABLE. Examples of Problematic Laboratory-Developed Tests Included in the FDA Report

LDT NAME	PURPOSE	PROBLEM	CLINICAL CONSEQUENCE	COST IMPACT OF INACCURACY
OvaCheck	Screen and detect ovarian cancer	Lack of validation that test detects ovarian cancer; inflated accuracy claims	False-positive results could result in unnecessary removal of ovaries	Not yet known
Whooping Cough (Pertussis) PCR Test	Rapid and improved diagnosis of whooping cough	False-positive results	Incorrect diagnosis resulting in incorrect treatment	Not estimated
Oncotype DX HER2 RT-PCR	Use HER2 receptor expression level to guide treatment	Poor sensitivity	False-negative results because of low sensitivity can result in disease progression due to lack of treatment	$775,278 estimated per false-negative case
KIF6 "Statincheck" Genotyping Assay	Predict risk of heart disease and response to statin therapy	Biomarker not validated to predict coronary heart disease or statin response; incorrect validation; unproven product claims.	Over- or under-treatment with statins	Not estimated

HER2 indicates human epidermal growth factor receptor 2; KIF6, kinesin family member 6; LDT, laboratory-developed test; PCR, polymerase chain reaction; and RT-PCR, reverse transcription polymerase chain reaction.

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Absence of Prescription Coverage Could Prove Catastrophic in Cancer, Study Shows

SURABHI DANGI-GARIMELLA, PHD

A study conducted among patients who had breast cancer found that in the absence of prescription drug coverage, patients—especially from the low-income strata—make harmful clinical decisions.[1] Published in *Breast Cancer Research and Treatment*,[2] the study involved a retrospective analysis based on surveys filled out by 712 women diagnosed with breast cancer. The women were approached by the researchers 9 months following their diagnosis and again at the 4-year mark. The primary outcome being evaluated was initiation and continuation of prescribed hormonal therapy (usually administered for 5 to 10 years), which reduces the risk of cancer recurrence in women with estrogen- or progesterone-positive breast cancer by as much as 50%.

The study's results showed that 90% of women who were eligible for prescription drug coverage started their recommended hormonal treatment as prescribed; however, that number dropped to 81% by the end of the study period. Of the cohort whose insurance plan did not include prescription drug coverage, 82% started hormonal therapy (requiring them to cover the cost out-of-pocket), but by 4 years, only 66% remained on the treatment. Overall, the authors observed a significant influence of family income on the women's decision to initiate and continue hormonal therapy. Women with an annual household income of less than $40,000 were about 40% as likely as women with an annual household income of more than $70,000 to continue treatment.

Lead author Cathy J. Bradley, PhD, said in a press release, "What this research says is that general health insurance isn't enough. You have to have prescription drug coverage."[1] Bradley is associate director for Population Studies at the CU Cancer Center and professor in the Colorado School of Public Health. "When someone thinks about coverage for high-cost care, they're usually thinking about that trip to the hospital that costs $80,000 that could leave them bankrupt. But, the fact is that the cost of prescription medicines—even fairly low-cost medications—can also be 'catastrophic.'"

With President Obama's renewed attention to precision medicine and provisions of the Affordable Care Act, changes within insurance benefits are imminent. However, there are certain caveats. For example, in addition to being expensive, many of the targeted agents are oral medications to be self-administered at home, as opposed to an infusion that requires a patient to visit the

clinic. This can result in adherence issues. Patients can skip doses or not fill a prescription, which can result in poor outcomes.

Pointing out that there's plenty of evidence showing that if people feel that a drug is too expensive, they stop taking it, Bradley says, "This study suggests that reluctance to insure prescription drugs may result in increased recurrence and poor survival among women with breast cancer, one of the largest groups of cancer survivors." **EBO**

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Because the discounts pertain to drugs delivered to all of a qualified entity's patients, whether they are poor or have terrific insurance, 340B-qualified entities make money by treating patients who reimburse for drugs at rates well above the discounts mandated by the 340B program.

The 340B program is overseen by Health Resources and Services Administration (HRSA), which falls within the purview of the Secretary of HHS. Under current rules, HRSA requires qualified safety net clinics to report the volume of patients served, their vulnerability, and how specific revenue streams are being used to increase access to medical care or improved quality of care. However, other qualified entities—including hospitals and contract pharmacies—that make up the vast majority of the program's current scope, do not face these same reporting requirements.

WHAT ARE THE PROBLEMS WITH 340B?

Critics speculate that the opportunity to profit from this provision has created an impetus for 340B-qualified hospitals to push the envelope on the program's intent—by opening outpatient clinics or pursuing affiliations with outpatient clinics in affluent communities where most patients will be well-insured. By so doing, hospitals increase their opportunity to profit from dispensing discounted drugs while being reimbursed at retail rates, but divert from the goal of the program, which is to provide services to the poor. Two of us (Conti and Bach) empirically evaluated this contention, using nationally representative data on program participants in 2012, matched to US Census Bureau data on local communities' socioeconomic characteristics. We found that 340B-qualified hospitals are expanding their base into communities that tend to be affluent and well-insured, consistent with the most profitable expansion strategy that counters the objectives of the program.[4] It is uncertain whether these affiliations and mergers improve the outpatient care patients receive. It is clear, however, that these activities drive up costs of providing care—and ultimately, commercial insurance premiums—since hospital outpatient contracts tend to be much more generous than physician office contracts and charge facility fees on top of service charges to payers and patients.

Other work has examined how 340B qualification influences prescription drug dispensing patterns. If 340B hospitals are aiming to conserve resources and deliver high-value, low-cost care, prescribing should favor low-cost (often generic) drugs. But if 340B hospitals are aiming to maximize profits, they will tend to prescribe more expensive (often branded) drugs, because the profits from each prescription are based on the retail cost of the drug, with larger profits coming from more expensive drugs. These studies have shown that, in fact, contract pharmacies for 340B hospitals disproportionately favor branded, patent-protected drugs over generic therapeutic substitutes, overall, and within a therapeutic class—a pattern that does not appear to be driven by a patient's clinical complexity alone.[4] A 2015 Government Accountability Office (GAO) report corroborated these findings. In both 2008 and 2012, GAO estimated per beneficiary Medicare Part B drug spending, including oncology drug spending, was substantially higher at 340B hospitals compared with non-340B hospitals. On average, beneficiaries at 340B hospitals were either prescribed more drugs or more expensive drugs than beneficiaries at other hospitals.[5]

The scope of the program is currently so vast that drug prices are also driven up for all consumers. By definition, branded manufacturers hold monopoly power, and recent consolidation in the generics market has similarly concentrated pricing power. As these manufacturers face significant and expanding demand for discounts on the acquisition prices of these drugs, they are able to pass the costs of these discounts onto other payers.

In August 2015, HRSA released its' proposed "mega" guidance regarding manufacturer and qualified entity participation in the 340B drug discount program.[6] The proposal recommends several changes to the program, including tightening the definition of which patients are eligible for treatment with drugs acquired at 340B prices, and which physicians are eligible to administer or prescribe drugs acquired at 340B prices. However, the actual impact of this proposal remains uncertain, particularly because recent court rulings have created doubts regarding HRSA's authority to implement their new standards.[7]

PROPOSED 340B REFORM STRATEGIES

Given that empiric evidence suggests that the pattern of the program's expansion has been both, towards affluent populations of patients and more expensive drugs—which run contrary to the program's goals of enhancing access for poor patients to cost-effective, high-value care—we believe it is a good time to consider revising the program. We have contemplated 3 possible steps that would enhance the program's function and be more consistent with Congress' original intent to enhance access for the poor to essential medical services.[8]

1. ***Redefine 340B qualification for hospitals and affiliated clinics based on the vulnerability of their outpatient population.*** This would address the logical contradiction embedded in the current qualification criteria for disproportionate share hospitals and their affiliated clinics, which is that eligibility is based on the insurance status of their *inpatient* population, but the 340B discounts apply to drugs administered or dispensed in the *outpatient* setting. This disconnect creates the perverse incentive for hospitals to expand their reach away from poor patients even as they qualify for discounts, and therefore profits, that are intended to help them serve the poor.
2. ***Pass the 340B discount through to payers and patients, regardless of their insurance status.*** The majority of patients currently being treated as outpatients at qualified entities are, in fact, insured. But 340B discounts, enjoyed by these entities, are not translated into discounts for their patients or for payers. If these discounts were passed along to the insurer and to the patient, both would benefit. This reform would improve access, lower patient out-of-pocket expenses, and lower health insurer costs, including those of Medicare. By requiring facilities to pass through the discounts, the profit potential of the program, which is driving rapid program expansion and medical practice consolidation, would be diminished while not disrupting the ability of the hospital to acquire drugs needed to treat poor patients at reduced costs.
3. ***Limit the distribution of discounted drugs to those patients who are of limited means, irrespective of their medical provider's qualification for "safety net" status.*** This reform would essentially transfer 340B eligibility from providers to patients. Patients could qualify for a 340B discount based on personal economic circumstances, irrespective of whether they are insured. This approach could employ tools currently used to qualify patients for discounted coverage in exchange plans and other types of government or private-assistance programs. Depending on need, the discounted pricing could be coupled to the current patient-level financial assistance in a single program, providing added help to those who need it the most. By tying the benefit to the patient most in need, the benefits could also travel with them, meaning that they would not be constrained to receive care at specified "qualified" providers if other medical providers in their communities are better for them.

Although the 340B program's intent was clearly well meaning, and many 340B providers are doubtless pursuing

the goals of the program, it is also clear that the program has become a profit center for participating hospitals, clinics, and contract pharmacies, distorting where patients receive care and driving up care costs, without any demonstrated improvement in quality of care. Given the distortions in the market, altering the program in the manners we have described: outpatient eligibility criteria, pass through of the discounts to patients, and portability of eligibility, are all sensible approaches that should be considered by policymakers. **EBO**

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PATIENT ADVOCACY

Eliminating a Barrier to Cancer Care through Universal Fair Access to Oral Chemotherapy Medications

(CONTINUED FROM COVER)

Although intravenous (IV) medications are typically covered under a health plan's medical benefit, health plans have often required higher cost-sharing for oral cancer medications rather than those administered intravenously by a doctor because they are included in the plan's drug benefit. This disparity can influence patient and physician decision making about treatment options and may lead patients to forgo the best treatment for their situation in favor of a treatment they can afford. In addition, research suggests high cost-sharing for oral chemotherapy medications may lead patients to abandon treatment altogether.[1]

ORAL PARITY, THE AFFORDABLE CARE ACT, THE AMERICAN CANCER SOCIETY CANCER ACTION NETWORK

The Affordable Care Act (ACA) mandates the inclusion of prescription drug coverage as an essential health benefit that must be offered in new insurance plans; however, it does not dictate the specific details of that coverage other than the number of drugs per therapeutic class that must be offered.[2] Many cancer drugs are placed on "specialty" tiers, which typically have the highest patient out-of-pocket (OOP) costs, some as high as 50% of a drug's cost.

A 2014 analysis of drug formularies in marketplace plans revealed, for example, that Tarceva, a treatment for advanced-stage non-small cell lung cancer and advanced-stage pancreatic cancer, although included on all health insurance marketplace plans evaluated, was listed on the highest tier between 50% and 100% of the time.[3] In the case of drugs that are offered in both oral or IV form, the difference in OOP costs can influence a patient's decision to choose the IV version of a therapy even though doing so could be significantly more burdensome from a nonfinancial standpoint in terms of time away from work, transportation, etc.

Under the ACA, states must also pick a benchmark for the minimum level of coverage all healthcare plans must provide in that state—most states select the largest small group insurance plan as the benchmark. If a state passes a mandate that goes above and beyond the benefits included in the benchmark plan, then the state is responsible for footing the bill for that extra coverage.

A guidance issued by HHS in 2012 states that oral chemotherapy fairness policies did not constitute an additional benefit beyond the established essential health benefit package. Thus, if plans already cover the IV counterpart medication as part of their essential benefit, parity policies limiting OOP costs for oral chemotherapy can be applied without the state incurring additional costs. Eliminating this state budget implication opened the floodgates for states to pass oral chemotherapy fairness laws that include oral chemotherapy medications under the state's benchmark health plan and, in many cases, eliminated the disparity with IV medications. The American Cancer Society Cancer Action Network (ACS CAN) has been a driving force in helping 40 states pass oral chemotherapy fairness laws since 2007.

There are 3 types of laws that states have passed to address oral chemotherapy fairness:

1. The first type creates parity for OOP costs for IV chemotherapies and oral chemotherapies. These laws fix the problem on the surface. However, insurers in some states (eg, Hawaii) have been quick to react by increasing the cost of IV medications, forcing organizations like ours to work to tighten the laws.
2. The second type of law caps the monthly OOP costs for oral chemotherapy medications. Whereas this action might control costs, it could also fail to create true parity with IV medications, which may continue to carry lower OOP costs.
3. The most recent laws mandate coverage with capped co-payments or coinsurance per prescription per month for specialty tier drugs, which includes medications for other conditions in addition to chemotherapies.

IN THE TRENCHES

ACS CAN and the Leukemia & Lymphoma Society recently led a coalition of public health groups in Mississippi to pass a law that would create fairness between oral chemotherapy medications and IV chemotherapies. The successful, coalition-driven campaign is a prime example of the power of advocacy. The bill, first introduced in January 2015 by Rep. Charles Busby (R-Pascagoula), received great bipartisan support from the start, passing the House with a vote of 117:1. However, once the legislation reached the state Senate, the opposition geared up its fight.

ACS CAN and the coalition intensified their campaign to ensure that this bill passed and gave patients equal access to the chemotherapies they need. ACS CAN hosted a Day at the Capitol during which volunteers from across the state met with their legislators and discussed the oral chemotherapy fairness legislation. In collaboration with its coalition partners, ACS CAN hosted a press conference and had volunteers send in letters and e-mails to their legislators throughout the campaign to remind them of the importance of this legislation. All of this hard work paid off and the bill passed the full Senate and was eventually signed into law by Governor Phil Bryant on April 23, 2015.[4]

Passing state laws is only one part of a 3-pronged approach to ensuring oral chemotherapy fairness. We must ensure these laws are implemented and enforced appropriately so they work as intended. Although some are concerned that parity will lead to increased costs for insurance plans, data show that health benefit plan prices increase less than one-tenth of 1%.[5] In spite of the evidence, efforts to find loopholes in oral chemotherapy fairness laws continue so these medications will not have to be covered on the same level as IV chemotherapies. ACS CAN is committed to working to tighten any regulations that would guarantee equal, affordable access to oral chemotherapy medications for patients with cancer.

(CONTINUED ON SP582)

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imbruvica®
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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)
IMBRUVICA® (ibrutinib) capsules, for oral use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

Chronic Lymphocytic Leukemia: 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 Nausea Stomatitis* Gastroesophageal reflux disease	37 21 16 13	0 0 0 0
Skin and subcutaneous tissue disorders	Rash* Bruising* Pruritus	22 16 11	0 0 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 Arthropathy	21 13	0 0
Infections and infestations	Upper respiratory tract infection Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 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.

Eliminating a Barrier to Cancer Care through Universal Fair Access to Oral Chemotherapy Medications

(CONTINUED FROM SP577)

Because of the variability in the state laws, there is strong desire for a federal bill that would set a level playing field among the states.

Sen. Mark Kirk (R-IL), Sen. Al Franken (D-MN), Rep. Leonard Lance (R-NJ,) and Rep. Brian Higgins (D-NY) have taken up the charge and earlier this year introduced the Cancer Treatment Parity Act of 2015.[6] Like much of the state legislation, the federal bill would require private health insurance plans that cover traditional chemotherapy to provide equally favorable coverage for orally administered anticancer medications. It would set a national maximum OOP cost for patients with private insurance on oral chemotherapy medications. By removing barriers to critical treatments, this bill has the potential to ensure that patients and their oncologists can choose a course of treatment based on what is in the best health interest of the patient, rather than by what a patient will have to pay under an insurance plan.

The larger issue of drug costs needs a balanced, comprehensive approach that could take some time to develop; however, oral chemotherapy fairness is one issue we can tackle now. It's an issue that is important in the states, with 40 states having passed legislation to address it. It's an issue that is important to lawmakers on both sides of the aisle, with federal legislation introduced in both the House and the Senate. Most importantly, it's an issue that is important to patients because it can mean a significantly improved quality of life while dealing with one of the most feared diseases.

We've achieved significant strides in developing oral chemotherapy regimens that are improving survivorship along with the patient's quality of life and ability to continue working. However, the advances in research mean nothing if patients lack access to these life-saving treatments. Oral chemotherapy fairness should be the standard practice in every insurance plan, not a luxury based on where a patient lives or what they can afford. **EBO**

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Impact of Oral Parity: A Personal Story

CHRISTOPHER HANSEN

ALEXANDER (XAN) HARWOOD-KARLIK

Alexander (Xan) Harwood-Karlik was 29 years old when he was diagnosed with stage 3 pancreatic cancer in November 2014. Living in Portland, Oregon, and working as a recruiter for a higher education company, he started to feel abdominal pain that would intensify each afternoon and evening. Initially he was diagnosed with pancreatitis, but given Xan's active lifestyle and healthy diet, a persistent primary care doctor was not satisfied with that diagnosis. Further tests revealed a walnut-sized tumor on his pancreas—devastating news to learn that he had been diagnosed with one of the most aggressive types of cancer at such a young age.

After a very difficult couple of weeks, his family and his oncologist were able to figure out a treatment plan that started with intravenous (IV) chemotherapy administered continuously through a pump for 4 treatments of 55 hours each, over 8 weeks. The pump came with many side effects, including pain at the port site, inability to exercise, stress over protecting the pump line, and anxiety over hearing the sound of the medicine dripping into his system every 45 minutes.

When it came time to discuss the next phase of his treatment plan that would involve over 5 weeks of a combination of chemotherapy and radiation, Xan's oncologist and the director of the clinical trial he had enrolled in fought hard to make sure Xan could get the oral equivalent of his chemotherapy, because it would immensely improve his quality of life. Oregon was the first state to pass a law requiring insurers cover oral chemotherapy drugs just as they would IV chemotherapies, so Xan received no push back from his insurance company when his doctors prescribed him the oral chemotherapy medication. Although the oral chemotherapy had some traditional effects of chemotherapy—namely nausea and fatigue—the ability to take this medication orally meant "a major improvement in my ability to move around and conduct my daily life," said Xan.

Following surgery in May 2015 that removed a significant portion of the tumor and other cancerous tissue in his abdomen, doctors saw no trace of cancer. In November, a scan showed cancer in Xan's liver. Doctors are working to again balance an aggressive cancer treatment plan with as little interruption as possible in Xan's daily routine. **EBO**

tional Comprehensive Cancer Network (NCCN), Memorial Sloan-Kettering Cancer Center (MSKCC), and the American Society of Clinical Oncologists (ASCO) have created and launched new tools and initiatives intended to help facilitate the adoption of value-based cancer care models.

BACKGROUND

Cancer care represents a central source of growth in spending on specialty medications. Approximately 29% of health care costs in the United States stem from oncology, which has seen spending grow at a rate of 15% annually.[1] Despite the prominence of oncology, however, the marketplace has not coalesced around a unified, effective, and scalable approach to oncology trend management. It is clear that a multifaceted and adaptable approach is necessary to help ensure that patients have access to high-quality compassionate cancer care that minimizes waste and inappropriate use of resources, while simultaneously taking full advantage of ongoing scientific advances and multidisciplinary, well-coordinated care.

DIAGNOSIS OF INFLATION

The high and rising cost of oncology medications is buoyed by several factors (**FIGURE 1**), which include:

- Drug development pipeline
- Improved rate of survival
- Regulatory process changes
- Drug utilization variation
- Off-label drug utilization
- Oncology practice and hospital consolidation

Drug Development Pipeline

The robust drug development pipeline includes more than 5400 products in clinical development, with an estimated 55% for use in oncology. This includes both new molecular entities and expanded indications based on additional clinical studies of approved drugs or combinations of drugs. Approximately 45% of new molecular entities are first-in-class therapies, with 80% of these for use in oncology.[2] The number and breadth of oncology medications entering the market each year continues to expand, with many more drugs currently in various phases of development (**FIGURE 2**).[3,4]

Improved Rate of Survival

Survival rates for several cancer subtypes, including some in breast and lung cancer, have increased in recent decades. The overall 5-year relative survival rate for female breast cancer patients has improved from 75% in the 1970s to 90% in the 2000s.[5] This increase in survival is largely attributed to improvements in treatment (hormonal treatment and molecularly targeted therapies) and earlier diagnosis from screening (driven by the widespread use of mammography).[6] The 1-year relative survival for all lung cancers combined increased over the same 30-year time span from 34% to 45%, largely due to improvements in surgical techniques and combined therapies.[7]

Regulatory Process Changes

In recent years, the pipeline has delivered new oncology treatments, almost all of which have been "targeted therapies," or drugs aimed at a specific molecular target within tumor cells. The speed with which some novel treatments and expanded indications have reached the market has been quickened by the "Breakthrough Therapy" designation created by the U.S. Food and Drug Administration (FDA) in 2012, further increasing the total spending on oncology (**FIGURE 3**).[8,9] The advocacy group Friends of Cancer Research reports that 133 of the 304 total requests between 2013 and 2015 for breakthrough status have been granted by the FDA. Of these 133, there have been 30 approvals, 14 of which are cancer treatments (46.1%).[10] Looking forward, there are 36 anticipated approvals for cancer treatments in the remainder of 2015 and 2016, 3 of which are for breakthrough-designated treatments.

Drug Utilization Variation

The high degree of drug-utilization variation between oncology practices is another factor driving the cost of cancer care. In a study of 2012 data for Medicare beneficiaries, researchers analyzed administrative claims to evaluate variation in the use of chemotherapy and supportive care agents, acute hospitalizations, and advanced imaging among 1534 oncology practices. Between the practices at the 25th and 75th percentiles, there was a $3866 (26%) difference in the cost of drugs used for cancer treatment (inclusive of chemotherapy, supportive care, and administrative fees for infusions). Cost variation for acute medical hospitalizations (surgical ones were excluded) and imaging were slightly larger on a percent basis; however, as the authors pointed out, on an absolute basis, the drug cost variation was by far the largest and most meaningful.[11]

Off-Label Drug Utilization

While off-label use of chemotherapy is permitted by the FDA, treatment usually includes newer higher-cost therapies and may be administered after completion of an approved protocol. Off-label use is often a major focus of attention in discussions of cancer care economics, but there have been few large-scale published analyses quantifying the degree of this use. In one of the largest such studies to date, a group from MSKCC used prescribing data for 19,500 cancer patients treated by 570 oncologists, and categorized the utilization of 10 chemotherapy agents into "on-label," "off-label and National Comprehensive Cancer Network (NCCN) supported," and "off-label and NCCN unsupported." Based on this sample, they found 30% of the utilization was off-label, split into 14% NCCN supported and 16% NCCN unsupported.[12]

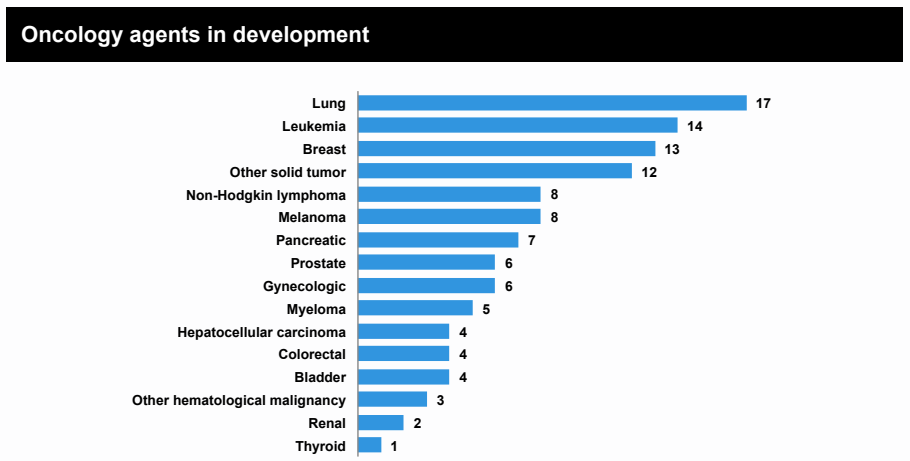
Oncology Practice and Hospital Consolidation

Consolidation of providers in the cancer care delivery system has caused many stakeholders to raise concerns about both access and cost. First, consolidation often leads to a reduction in the available options for patients to access care. Secondly, the comparatively high cost of care in hospital outpatient centers is likely a driver of this cost trend. In October 2014, based on 6 years of monitoring, the Community Oncology Alliance reported that 544 oncology practices have been acquired by hospitals and 313 outpatient clinics have closed.[13] Hospital acquisition of practices results in immediate revenue growth based on the typically higher reimbursement rates for oncology services that hospitals have in place with payers.

FIGURE 1. Drivers of Oncology Drug Costs

Cost driver	Description
Robust pipeline[3]	Estimated ~3000 oncology drugs in development
Improved or longer survival[4]	Longer overall survival based on diagnostic and therapeutic advances in major cancer types, including breast and lung
Regulatory changes and expedited approvals[8]	Introduction of Breakthrough Therapy designation by the FDA in 2012, and faster approvals
Practice variation[11]	Large interpractice variation in cost of drugs utilized for similar patients
Off-label utilization[12]	Often prescribed after use of an on-label regimen or treatment
Provider consolidation[13]	Leads to an increased portion of care delivered in the typically higher-cost hospital outpatient center site of service

FIGURE 2. Oncology Drug Pipeline[4]



MANAGEMENT APPROACHES

Against this evolving array of cost drivers, managed care organizations and pharmacy benefit managers have created a portfolio approach to oncology management in which 1 or more of several approaches are applied in an effort to increase the value of cancer care delivered to patients. These approaches include the following and have been listed in **FIGURE 4**:

1. Prior authorizations are increasingly applied to chemotherapeutic medications in an effort to reduce off-label prescribing of these drugs and utilization that is not supported by the NCCN guidelines. During the prior authorization process, in addition to addressing the indication for use of a specific agent, the duration of therapy is also typically addressed, rather than granting long or open-ended authorization intervals.[14]
2. Claims editing is another approach that is used to ensure payment for on-label dosing and indications. While not uniformly adopted, to

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be most effectively implemented, edits must be deployed against all oncology drugs whether they are infused, injected, or orally administered, or adjudicated under the pharmacy or medical benefit.

3. Plan design is playing an increasingly significant role in oncology management. Recent years have seen the introduction of some frequently prescribed generic drugs in oncology (e.g., capecitabine in colon and breast cancers), and there is accelerating activity in this area. Coupled with the first biosimilar Zarxio (filgrastim)[15] in 2015, there is likely to be an increased need for multi-tiered plan design and potential formulary exclusions (with appropriate medical exceptions) in oncology.
4. Care management of oncology patients can be quite complex, but essential to achieve high-quality care. During this time, patients rely heavily on their health care providers. Further, disease progression and response to treatment vary, which leads to highly individualized patient needs. These complexities necessitate a sophisticated nurse-led care management approach, which provides support to patients in several areas, including, but not limited to: assessment and management of side effects, compliance with nutritional plan and recommendations, interventions for reducing infection risk, and facilitation of end-of-life care discussions.
5. Adherence to oral and infused treatments in oncology can be optimized through proactive consultation to identify and address potential barriers to compliance and persistence. A comprehensive nurse-led care management approach also includes tools and resources to address root causes that may lead to non-adherence, such as unrealistic patient expectations, inadequate levels of health literacy, existence of comorbid conditions, concurrent drug therapies, and the need for assistance with financial concerns.

FIGURE 3. FDA Expedited Drug Review Programs[9]

Approach	Description
FAST TRACK	A process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
BREAKTHROUGH THERAPY	A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
ACCELERATED APPROVAL	Regulations that allow drugs that fill an unmet need for treatment of serious conditions to be approved based on a surrogate endpoint.
PRIORITY REVIEW	A Priority Review designation means the FDA's goal is to take action on an application within 6 months.

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FIGURE 4. Existing Cost Management Approaches

Existing approaches to managing oncology drug costs	
Management approach	**Cost drivers impacted**
Prior Authorization of selected drugs	• Pipeline • Inter-practice variation in drug utilization • Off-label drug utilization (dose, duration, and indication)
Claims editing to ensure payment for on-label dosing and indications	• Inter-practice variation in drug utilization • Off-label drug utilization
Plan design and formulary management	• Pipeline • Regulatory changes and expedited approvals • Off-label drug utilization
Care management for advanced-stage patients	• Improved or longer patient survival • Off-label drug utilization
Adherence support for patients receiving oral oncolytics	• Pipeline • Improved or longer patient survival
Site-of-service management for selected supportive care agents	• Interpractice variation in drug utilization • Provider consolidation
Optimizing the use of molecular diagnostic testing (personalized medicine)	• Improved or longer patient survival • Interpractice variation in drug utilization

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The treatment of cancer frequently requires medication infusion and/or injection by a clinician, for which a site of care must be selected. This decision is usually made based on the preference of the treating medical oncologist. For some aspects of patient care—including supportive drugs, such as antiemetics and blood cell growth factors—an alternative site of care for drug administration can be offered, such as home or ambulatory infusion centers. These sites offer greater comfort and convenience to certain patients, while also being cost effective.

Personalized medicine is an evolving field in which physicians use diagnostic tests to determine which treatments will work best for each patient.[16] In breast cancer, a recurrence score based on a 21-gene assay ("Oncotype DX") has been shown to determine whether chemotherapy, in addition to hormone therapy, will be incrementally beneficial in lymph-node negative, hormone-receptor positive patients. In essence, Oncotype DX allows physicians to identify those patients in the relevant subpopulation who would best respond to chemotherapy (in addition to well-tolerated and relatively inexpensive hormone therapy). This may also help reduce the unnecessary cost of treating non-responders.[17] Recently published results from the prospective TAILORx trial of this assay demonstrate that women with low recurrence scores (16% of the studied population) had a 98% survival with hormone therapy alone, as well as a rate of freedom from cancer recurrence of almost 99%, providing support for the clinical validity of this test, and its ability to lower the cost of care when used appropriately.[18]

EMERGENCE OF VALUE-BASED CANCER CARE MODELS

Sustainably addressing the oncology cost drivers also requires new approaches that not only incorporate traditional management approaches, but also go beyond the existing methods. Some degree of redesign in how cancer care is delivered is necessary in order to enable the iterative enhancement and measurement of value through new approaches. If providers are expected to meaningfully alter their practice patterns, they must be rewarded for higher quality and/or more efficient care. Instead of simply paying more for greater volume for individual point of care activities, the focus should be more holistic, at the patient or episode level. While experimentation with 2 such models—cancer care pathways and bundled payments for cancer episodes of care—have been most popular, other models and tools aimed at enhancing the value of oncology care are emerging.

Cancer care pathways aim to reward providers for performance, offering greater reimbursement for following established, evidence-based care recommendations. Some payers have seen measurable success with pathways while others have experienced barriers in pathways adoption. Aetna and The US Oncology Network's cancer-care management program is one such example of a pathways program that reported a modest reduction in hospitalizations and treatment costs for lung, breast, and colorectal cancers, but the firm evidence for substantial impact on costs attributable to oncology pathway programs has been minimal.[19]

Payers continue to experiment with bundled payments for all care delivered to patients. Such an approach offers a single payment for the full episode of care, creating incentives to reduce total health care costs. UnitedHealthcare recently reported the results of such a study in 5 medical groups, and their intervention also featured a stronger data feedback loop to providers to improve care management. The experiment led to substantially reduced health care

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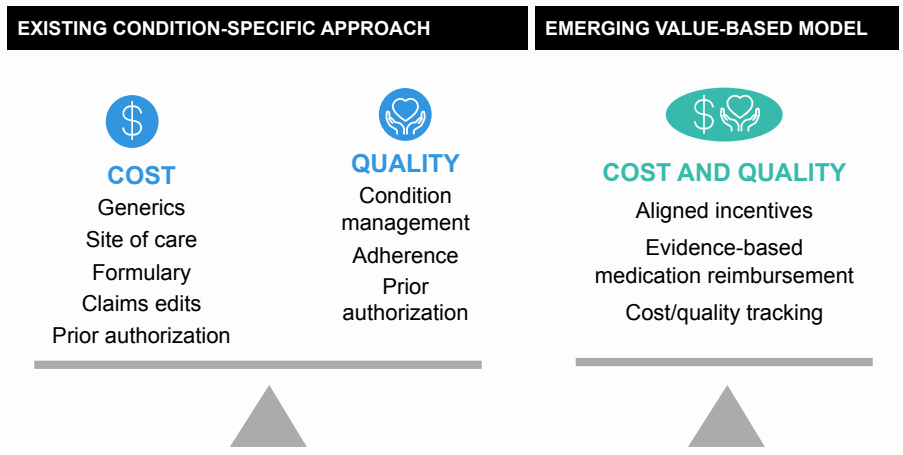
costs, but paradoxically led to increases in prescription drug spending.[20]

Meanwhile CMS, the nation's largest payer, has announced its intention to test a value-based approach.[21] While it will be challenging for a single commercial insurer to create sufficient incentives to encourage practice change in a given provider community (because any 1 plan only impacts a modest proportion of a provider's population), CMS is the exception. Due to its enormous market share, particularly for Medicare beneficiaries (where the greatest cancer burden is found), CMS has the ability to promote meaningful change. As part of the value-based approach being pursued, CMS plans to evaluate a model that offers bundled payments for oncology episodes of care. The test, a product of the CMS Innovation Center, will be implemented and evaluated, offering the US Department of Health & Human Services Secretary the opportunity to scale the program, nationwide, if there is evidence of cost savings without compromising the quality of care delivered. CMS' Oncology Care Model also offers a monthly care coordination payment to practices to support the complex care coordination needs of their cancer patients. Further, CMS has encouraged commercial payers to participate in the model, with the goal of reducing fragmentation of incentives. Of note, Medicare's decision to leave out prescription drugs from total cost-of-care calculations that determine provider payments may weaken incentives to impact prescribing practices (**FIGURE 5**).[22]

FIGURE 5. Emerging Value-Based Focus to Oncology Management



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Beyond cancer care pathways and bundled payments, additional efforts are underway to help determine the value of cancer care with a focus on assessing cancer drugs and regimens. With patients bearing more of the cost of care, these new efforts seek to provide increased physician and patient education in order to allow for more informed treatment decisions. NCCN, MSKCC, and ASCO have recently introduced tools and frameworks for assessing cancer drugs to determine the best overall value—value is assessed differently within each tool or framework.

The NCCN Evidence Blocks were published in the NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia and Multiple Myeloma in October 2015. This tool determines value based upon assigning scores to each drug in 5 areas—price, effectiveness, safety, quality, and consistency of clinical data.[23,24] The tool is meant to supplement the widely used NCCN guidelines for oncology care. The ASCO tool is a points-based framework that defines value based on 3 elements articulated by the Institute of Medicine: clinical benefit (efficacy), toxicity (safety), and cost (efficiency). ASCO believes the 3 elements are readily measured and ascertainable.[25] The MSKCC published a web-based comparative cancer care pricing tool called the DrugAbacus, which provides drug pricing by episode of care based on several attributes and treatment needed to achieve outcomes in published clinical studies. Currently, DrugAbacus includes 54 cancer drugs (approved between 2001 and 2013) with a list of comparative features that include drug efficacy, toxicity, novelty, research and development costs, disease incidence, population health burden, treatment duration, and total sales. The DrugAbacus price is a calculation based on values for each comparative feature. Expansion of the drug list, provider, and expert feedback will continue to be incorporated in future enhancements to the tool.[26]

While it may be too soon to fully understand how these new tools for assessing value can be used directly or indirectly to inform patient and physician care decisions or shape reimbursement policies, they, along with the other approaches described, must be iteratively refined if we are to truly create a system that supports and incents value-based oncology care. **EBO**

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- Visit **www.youandisupport.com** and click the "Enroll Here" button
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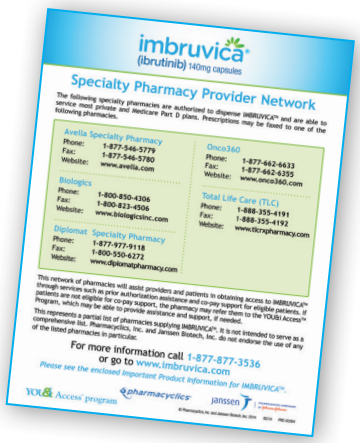
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The following specialty pharmacies are authorized to dispense IMBRUVICA® and are able to service most private and Medicare Part D plans. Prescriptions may be faxed to one of the following pharmacies.

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Fax: 1-877-546-5780
Website: www.avella.com

Biologics
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Fax: 1-800-823-4506
Website: www.biologicsinc.com

Diplomat Specialty Pharmacy
Phone: 1-877-977-9118
Fax: 1-800-350-6272
Website: www.diplomatpharmacy.com

Onco360
Phone: 1-877-662-6633
Fax: 1-877-662-6395
Website: www.onco360.com

Total Life Care (TLC)
Phone: 1-888-355-4191
Fax: 1-888-355-4192
Website: www.tlcrxpharmacy.com

This network of pharmacies will assist providers and patients in obtaining access to IMBRUVICA® through services such as prior authorization assistance and co-pay support for eligible patients. If patients are not eligible for co-pay support, the pharmacy may refer them to the YOU&i Access™ Program, which may be able to provide assistance and support, if needed.

This represents a partial list of pharmacies supplying IMBRUVICA®. It is not intended to serve as a comprehensive list. Pharmacyclics, Inc. and Janssen Biotech, Inc. do not endorse the use of any of the listed pharmacies in particular.

For more information call 1-877-877-3536 or go to www.imbruvica.com

Please see the enclosed Important Product Information for IMBRUVICA®.

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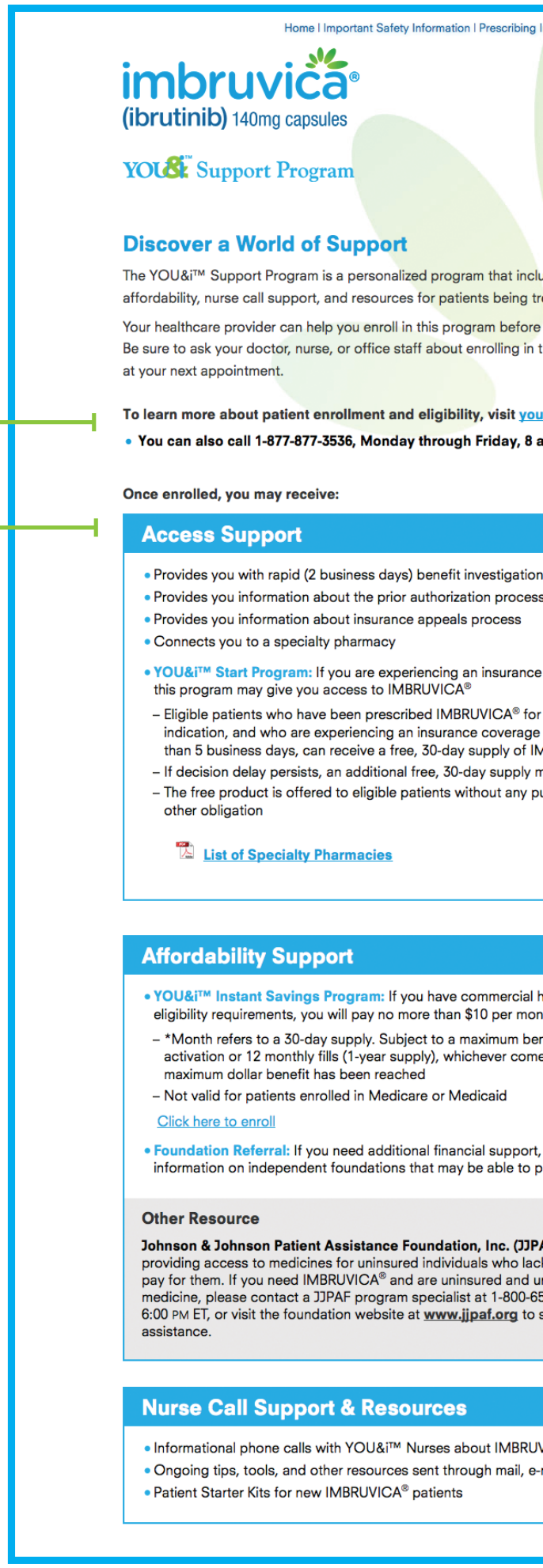
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affordability, nurse call support, and resources for patients being tr

Your healthcare provider can help you enroll in this program before
Be sure to ask your doctor, nurse, or office staff about enrolling in t
at your next appointment.

To learn more about patient enrollment and eligibility, visit you

- **You can also call 1-877-877-3536, Monday through Friday, 8 a**

Once enrolled, you may receive:

Access Support

- Provides you with rapid (2 business days) benefit investigation
- Provides you information about the prior authorization process
- Provides you information about insurance appeals process
- Connects you to a specialty pharmacy
- **YOU&i™ Start Program:** If you are experiencing an insurance this program may give you access to IMBRUVICA®
  - Eligible patients who have been prescribed IMBRUVICA® for indication, and who are experiencing an insurance coverage than 5 business days, can receive a free, 30-day supply of IM
  - If decision delay persists, an additional free, 30-day supply m
  - The free product is offered to eligible patients without any pu other obligation

List of Specialty Pharmacies

Affordability Support

- **YOU&i™ Instant Savings Program:** If you have commercial h eligibility requirements, you will pay no more than $10 per mon
  - *Month refers to a 30-day supply. Subject to a maximum ben activation or 12 monthly fills (1-year supply), whichever come maximum dollar benefit has been reached
  - Not valid for patients enrolled in Medicare or Medicaid

Click here to enroll

- **Foundation Referral:** If you need additional financial support, information on independent foundations that may be able to p

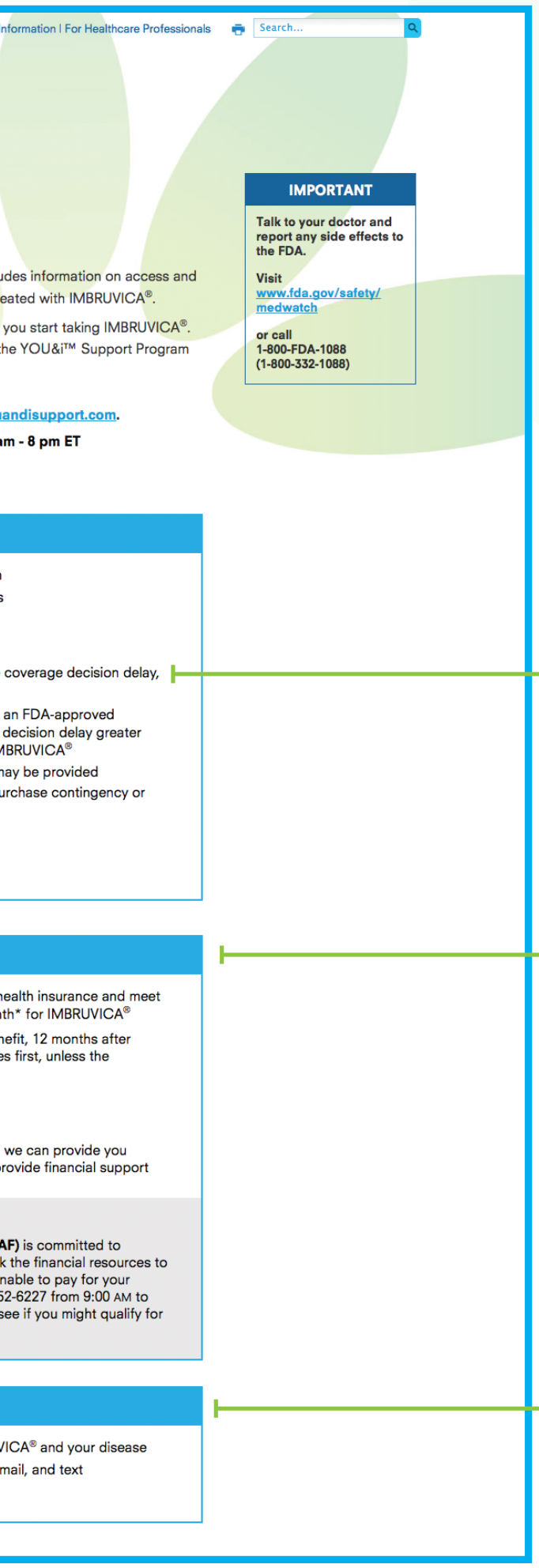
Other Resource

Johnson & Johnson Patient Assistance Foundation, Inc. (JJPA
providing access to medicines for uninsured individuals who lack
pay for them. If you need IMBRUVICA® and are uninsured and u
medicine, please contact a JJPAF program specialist at 1-800-65
6:00 PM ET, or visit the foundation website at **www.jjpaf.org** to s
assistance.

Nurse Call Support & Resources

- Informational phone calls with YOU&i™ Nurses about IMBRUV
- Ongoing tips, tools, and other resources sent through mail, e-r
- Patient Starter Kits for new IMBRUVICA® patients

Program Mapped!®



YOU&i™ Start Program

Learn about providing eligible new patients with access to IMBRUVICA® during an insurance coverage decision delay.

Affordability Support

Discover the benefits of the YOU&i™ Instant Savings Program, and help enroll patients in the program. Eligible patients will receive instant savings on private insurance co-pays, deductibles, and co-insurance for IMBRUVICA®. Not valid for federal and state healthcare program beneficiaries.

Nurse Call Support & Resources

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Ongoing tips, tools, and other resources about IMBRUVICA® are sent through mail, e-mail, and text. Patient Starter Kits for new IMBRUVICA® patients are also available.

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