SPECIAL ISSUE: **HEALTHCARE POLICY AND ONCOLOGY**

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ALSO IN THIS ISSUE

NOBEL FOR IMMUNOTHERAPY. James P. Allison, PhD, and Tasuku Honjo, MD, PhD, were awarded the 2018 Nobel Prize in Medicine or Physiology for basic research conducted in the 1990s that led to the development of checkpoint inhibitors, a new pillar of cancer treatment, SP496.

GRAPPLING WITH THE OCM. Today's oncologists get competing messages from CMS: they are told to move forward with value-based payment, perhaps through the Oncology Care Model. But they face a myriad of rule changes that would diminish revenue to make the transition, SP482.

VERMA

OPPORTUNITIES TO BOOST SCREENING. Results of a new survey highlight how nurse practitioners can play a key role in increasing screening rates for colorectal cancer, which has been identified as a public health priority, SP485.

MOVING TO PROSPECTIVE RISK. Moving to the next phase of value-based care in oncology requires the right technology to provide data to make decisions, as well as levels of trust between payers and providers, SP493.

CMS UPDATES, FDA APPROVALS, AND MORE. Medicare Advantage will allow step therapy, ivosidenib is approved for treatment of certain patients with relapsed or refractory acute myeloid leukemia, and other managed care and clinical news, SP503-SP507.

PROVIDER PERSPECTIVE

The Financial Impact of the Sequester Cut to Medicare Part B Drug Reimbursement in Community Oncology

Lucio Gordan, MD; Cass Schaedig; and Susan Weidner, MBA, MS

MEDICAL EXPENDITURES FOR CANCER care are estimated to top $158 billion (in 2010 dollars) in 2020, representing nearly a 30% increase compared with 2010.[1]

Adequate access to cancer care continues to be a challenge due to the closing of community-based cancer practices in the United States. The 2018 Community Oncology Alliance (COA) Practice Impact Report stated the following facts from the last 10 years: 423 individual clinics have closed, 658 practices have been acquired by hospitals, 359 practices have reported significant financial instability, and nearly 50 practices sent Medicare patients to receive chemotherapy elsewhere.[2] Causes of cessation of operations of many community-based oncology practices include:

(a) Misuse and lack of transparency of the 340B drug discount program by hospital systems. This has led to unfair competition and market control,
(b) Application of sequester to Part B drugs,
(c) Burden and risks of running a private community practice in a climate of significant regulatory constraints and increased reporting requirements,
(d) Lack of adequate site-of-care reimbursement parity between community-based clinics and outpatient hospital settings,
(e) Decreased reimbursement for oncology care and treatments over the past decade.[3]

CONTINUED ON SP515

BENEFIT DESIGN

Survey of NCI-Designated Cancer Centers Finds Most are Out-of-Network on Exchanges

Alyssa Schatz, MSW, and Katy Winckworth-Prejsnar, MPH

Introduction

The Patient Protection and Affordable Care Act (ACA) of 2010 created numerous protections for patients with cancer, including mandatory coverage for people with preexisting conditions and an array of essential health benefits. But these requirements may have inadvertently accelerated the use of narrow networks to control health plan costs on the ACA marketplace. Despite shifting federal health policies, state marketplace health plans insure nearly 12 million Americans in 2018.[1] To understand the composition of narrow networks on the exchange, the National Comprehensive Cancer Network (NCCN), in collaboration with Avalere Health, examined network exclusions for high-quality academic cancer centers and the potential health implications for enrollees with cancer. This paper will present survey results examining the experiences National Cancer Institute (NCI)–designated cancer centers have had with the marketplaces, the implications for patients' access to cancer care, and proposed policy solutions.

CONTINUED ON SP517

DRUG POLICY

Medical Marijuana in Cancer Treatment: No Standards of Care, and So Far, No Coverage

Samantha DiGrande

OVER THE PAST DECADE, both recreational and medical marijuana use in the United States has grown tremendously.[1] However, disputes surrounding the legal and ethical implications, safe administration, dispensing, health consequences, and therapeutic indications—albeit based on very limited clinical data—related to its usage abound.

Medical marijuana has gained traction specifically in patients with cancer to treat a variety of adverse effects associated with treatment, such as pain, nausea, and lack of appetite. However, major cancer

CONTINUED ON SP519

Most major cancer organizations have not taken a position on putting medical marijuana in clinical guidelines, although the American Cancer Society has called for more research.

AJMC® Managed Markets Network®
ACCC Association of Community Cancer Centers
AJMC® THE INSTITUTE FOR VALUE-BASED MEDICINE
COMMUNITY ONCOLOGY ALLIANCE COA

YES CAR T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*[1]

// PROVEN EFFICACY

51%

Patients achieved a best response of complete remission (CR) (52/101)

NR

Response duration was not reached at a median follow-up of 7.9 months in patients who achieved CR

// CYTOKINE RELEASE SYNDROME

13%

Grade ≥3 incidence

94%

Overall incidence

// NEUROLOGIC TOXICITIES

31%

Grade ≥3 incidence

87%

Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time†

99%

Manufacturing success of CAR T cells engineered and expanded ex vivo

VISIT YESCARTAHCP.COM/CENTERS TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2 x 10^6 viable CAR T cells/kg body weight (maximum of 2 x 10^8 viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

†The median time from leukapheresis to product delivery.

INDICATION

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®. Do not administer YESCARTA® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA®. Provide supportive care and/or corticosteroids as needed.**
- **YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS.**

Important Safety Information continued on adjacent page.

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with ≥ Grade 3. Among patients who died after receiving YESCARTA®, 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA®. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA® REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS. The required components of the YESCARTA® REMS are: Healthcare facilities that dispense and administer YESCARTA® must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA®.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with ≥ Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA® infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA® infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA® infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA® infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA® treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages.

Reference: 1. YESCARTA™ [package insert]. Santa Monica, CA: Kite Pharma; 2017.

Kite
A GILEAD Company
Santa Monica, CA

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA®
(axicabtagene ciloleucel) suspension for intravenous infusion

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)]*.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)]*.**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient *[see Dosage and Administration(2.2.3)]*.

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. *Pre-treatment:* Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA. *Premedication:* Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.

Table 1. CRS Grading and Management Guidance (continued)

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014, (b) Refer to Table 2 for management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (6)]*. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated *[See Dosage and Administration (2.3)]*.

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor

patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly *[see Management of Severe Adverse Reactions (2.3); Neurologic Toxicities]*.

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. *Viral Reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based *[see Clinical Trials (14)]* . Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was 43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Cardiac disorders	Tachycardia	57	2
	Arrhythmia	23	7
Gastrointestinal disorders	Diarrhea	38	4
	Nausea	34	0
	Vomiting	26	1
	Constipation	23	0
	Abdominal pain	14	1
	Dry mouth	11	0
General disorders and administration site conditions	Fever	86	16
	Fatigue	46	3
	Chills	40	0
	Edema	19	1
Immune system disorders	Cytokine release syndrome	94	13
	Hypogammaglobulinemia	15	0
Infections and infestations	Infections-pathogen unspecified	26	16
	Viral infections	16	4
	Bacterial infections	13	9
Investigations	Decreased appetite	44	2
	Weight decreased	16	0
	Dehydration	11	3

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1 (continued)

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Musculoskeletal and connective tissue disorders	Motor dysfunction	19	1
	Pain in extremity	17	2
	Back pain	15	1
	Muscle pain	14	1
	Arthralgia	10	0
Nervous system disorders	Encephalopathy	57	29
	Headache	45	1
	Tremor	31	2
	Dizziness	21	1
	Aphasia	18	6
Psychiatric disorders	Delirium	17	6
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	11
	Cough	30	0
	Dyspnea	19	3
	Pleural effusion	13	2
Renal and urinary disorders	Renal insufficiency	12	5
Vascular disorders	Hypotension	57	15
	Hypertension	15	6
	Thrombosis	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxemia, renal insufficiency, and hypotension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%, Thrombocytopenia 58%, Hypophosphatemia 50%, Hyponatremia 19%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Risk Summary*: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation: *Risk Summary*: There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential: *Pregnancy Testing*: Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. *Contraception:* See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. *Infertility:* There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]*. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion *[see Warnings and Precautions (5.2)]*, Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.

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FROM THE EDITOR-IN-CHIEF


ALVARNAS

Getting to *The Prestige* in Cancer Care

"Every great magic trick consists of three parts or acts. The first part is called 'The Pledge.' The magician shows you something ordinary. ...The second act is called 'The Turn.' The magician takes the ordinary something and makes it do something extraordinary. Now you're looking for the secret, but you won't find it, because of course you're not really looking...Every magic trick has a third act, the hardest part, the part we call 'The Prestige.'" — Christopher Priest, *The Prestige*

I WOULD BE LOATH to equate the domain of cancer care delivery and reimbursement with the fascinating world of magic, but the analogy is not so bizarre as it might first appear. We have gone through an extraordinary period of change in oncology; during this time, standards of care in cancer have been upended by unprecedented innovations in diagnosis and treatment that have changed much of what we know about the care of many patients. Patients with metastatic melanoma and advanced stage non–small cell lung cancer now enjoy a breadth of previously unimaginable effective treatment options that have transformed the meaning of those diagnoses. We now bear witness to countless survival stories from patients who show us how historical outcomes have yielded to truly extraordinary advancements in care. *The Washington Post* recently featured a story on former President Jimmy Carter whose life and tirelessness, despite a diagnosis of metastatic melanoma, is a graphic example of the human impact of emerging therapeutic advances.[1] The challenge now is that of getting to *j* portion of this profound paradigm shift. It means creating systems of care and crafting healthcare policy that will support these advances becoming equitably, routinely, and economically sustainably available to those in need.

We are in a time of strange paradoxes, when life-saving therapeutics are available but inaccessible to patients in need.[2] Inasmuch as scientific innovation in oncology has led to previously unimaginable advances in cancer therapeutics, our health policy, reimbursement models, and conceptual constructs of value have not kept up with these advances. This failure of our cancer care delivery system to evolve at the same breakneck pace as our diagnostic and therapeutic armamentarium is creating deep disconnects in patient access, sustainable reimbursement, and the quest by government and private payers to move toward value-based pay for performance.[3,4] I do not believe that we will come to a resolution with any of these issues quickly or easily. To accomplish these goals, healthcare payers, government, patients, health systems, and oncology practitioners need to commit innovative ideas, talent, resources, comprehensive clinical data sets, and a willingness to partner closely to create a deeper and profoundly more transparent understanding of clinical risk, therapeutic opportunity, care effectiveness, and economic sustainability around care delivery than we have ever seen. It means a rejection of zero-sum thinking when it comes to the economics of healthcare reimbursement.

It means refocusing on the ideal of patient centricity in care delivery and therapeutic outcomes.

This grand process begins slowly, sometimes in relatively prosaic ideas and models. And so we begin down this road in this issue of *Evidence-Based Oncology*™ with a series of conversations on the ways in which healthcare policy might evolve. Lucio Gordan, MD, and co-authors on behalf of the Community Oncology Alliance evaluate the impact of sequester cuts upon reimbursement for chemotherapeutic drug administration in the community setting. Alyssa Schatz from the National Comprehensive Cancer Network provides an organizational perspective on the impact of narrow networks upon cancer care delivery. We also feature an overview of how a series of proposals from CMS will affect oncologists in their daily practice, the most recent being whether reimbursement for chimeric antigen receptor T cells should reflect patient-reported outcomes.

As our increasingly effective suite of anticancer therapeutics evolves further, I hope that conversations such as these and a meeting of the minds between the respective cancer care stakeholders can eventually lead to the creation of a comprehensive system of care delivery that ensures that patients get sustainable, equitable access to the care that they need when they need it. This third act in the evolution of our care delivery system is inevitably the hardest part. This is why they call it The Prestige. ◆

Joseph Alvarnas, MD
EDITOR-IN-CHIEF

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

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SPECIAL ISSUE / Healthcare Policy and Oncology
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The Oncology Care Model is design not just to eliminate waste but to create a change of culture, according to experts who appeared at the Institute for Value-Based Medicine on September 27, 2018, in New York City.

FEATURES

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continued on SP481

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everyday
Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets
twice a day

Along the MBC journey*– explore Verzenio[1]

Verzenio is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (MBC):

- In **combination with fulvestrant** for women with disease progression following endocrine therapy
- In **combination with an aromatase inhibitor (AI)** for postmenopausal women as initial endocrine-based therapy
- As a **single agent** for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

*Patients who received prior therapy with a CDK4 & 6 inhibitor were excluded from the MONARCH trials.[2-4] There are currently no data regarding the use of Verzenio following use of another CDK4 & 6 inhibitor.

For patients with HR+, HER2– MBC, including those with **concerning clinical characteristics**[1-14†]

†Disease characteristics that typically confer a less favorable prognosis. Visceral disease and progression on ET and prior chemotherapy in the metastatic setting were concerning clinical characteristics in MONARCH 1. Primary resistance and visceral disease were concerning clinical characteristics in MONARCH 2. Liver metastases and treatment-free interval <36 months were concerning clinical characteristics in MONARCH 3. Exploratory subgroup analyses of PFS were performed for patients with liver metastases and for patients with a treatment-free interval <36 months.[2-14]

CDK4 & 6=cyclin-dependent kinases 4 and 6; ET=endocrine therapy; PFS=progression-free survival.

Select Important Safety Information

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for Verzenio on the following pages.

Lilly

For women with HR+, HER2– MBC

Verzenio + AI as first-line endocrine-based therapy[1,3]

>28-month median PFS as initial endocrine-based therapy[1]

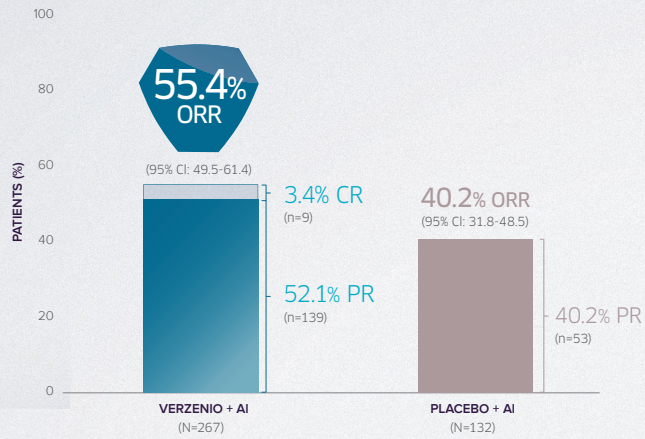
ITT[1]

28.2 months mPFS

(95% CI: 23.5-NR) vs **14.8 months** with AI alone (95% CI: 11.2-19.2)
HR=0.540 (95% CI: 0.418-0.698)
P<.0001[1]

- The percentage of events at the time of analysis was 42.1% (n=138) and 65.5% (n=108) in the Verzenio + AI and AI alone arms, respectively[1]
- At the time of the PFS analysis, 19% of patients had died, and overall survival data were immature[1]

ORR in patients with measurable disease[1,3*†‡]



- ORR was defined as the proportion of patients with CR + PR and does not include stable disease[1]

*In patients with measurable disease; N=267 for the Verzenio + AI arm, N=132 for the AI alone arm.[1]
†Based upon confirmed responses.[1]
‡PR defined as ≥30% reduction in target lesion size per RECIST 1.1.[3,15]

Exploratory subgroup analyses

PFS results in women with concerning clinical characteristics were consistent with the ITT population[1,3,9-14§]

§Disease characteristics that typically confer a less favorable prognosis. Liver metastases and treatment-free interval <36 months were concerning clinical characteristics in MONARCH 3.

Liver metastases[13]

15.0 months

(95% CI: 7.4-23.7) (n=47) vs **7.2 months** median PFS with AI alone (95% CI: 2.1-14.0) (n=31)
HR=0.477 (95% CI: 0.272-0.837)

Treatment-free interval <36 months[14]

29.5 months

(95% CI: 11.6-NR) (n=44) vs **9.0 months** median PFS with AI alone (95% CI: 3.7-14.2) (n=32)
HR=0.441 (95% CI: 0.241-0.805)

- Exploratory subgroup analyses of PFS were performed for the subgroups of patients with liver metastases or with treatment-free interval <36 months after completion of adjuvant ET. Estimated HRs and CIs for the within group analyses that were adjusted for treatment interaction are shown. The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + AI among subgroups.[13,14]

MONARCH 3 was a multicenter trial that enrolled 493 patients with HR+, HER2– locoregionally recurrent or MBC in combination with a nonsteroidal AI as initial endocrine-based therapy. The median patient age was 63 years (range, 32 to 88 years). Forty-seven percent of patients had received prior ET and 39% of patients had received chemotherapy in the adjuvant setting. Patients were randomized 2:1 to Verzenio + AI or placebo + AI. Patients received either letrozole (80%) or anastrozole (20%). Verzenio was dosed continuously until disease progression or unacceptable toxicity. The primary endpoint was PFS. Key secondary endpoints were ORR and DoR.[1,3]

CI=confidence interval; CR=complete response; DoR=duration of response; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; ORR=objective response rate; PR=partial response; RECIST 1.1= Response Evaluation Criteria in Solid Tumors version 1.1.

Select Important Safety Information (cont'd)

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Grade ≥3 increases in **alanine aminotransferase (ALT)** (6% versus 2%) and **aspartate aminotransferase (AST)** (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.

For women with HR+, HER2− MBC

Verzenio + fulvestrant in patients who recurred or progressed on or after ET[1]

>16-month median PFS in women who recurred or progressed on or after ET[1]

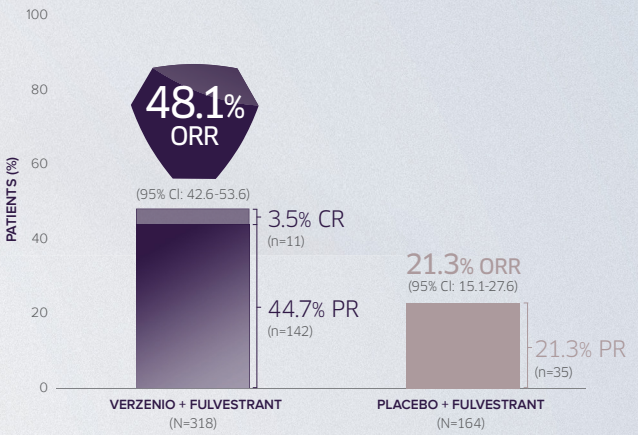
ITT[1]

16.4 months mPFS

(95% CI: 14.4-19.3) vs **9.3 months** with fulvestrant alone (95% CI: 7.4-12.7)
HR=0.553 (95% CI: 0.449-0.681)
P<.0001[1]

- The percentage of events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio + fulvestrant and fulvestrant alone arms, respectively[1]
- At the time of the primary analysis of PFS, overall survival data were not mature (20% of patients had died)[1]

ORR in patients with measurable disease[1,2*†]



- ORR was defined as the proportion of patients with CR + PR, and does not include stable disease[1,15†]

*N=318 for the Verzenio + fulvestrant arm; N=164 for the fulvestrant alone arm.[1]
†PR defined as ≥30% reduction in target lesion size per RECIST 1.1.[2,15]

PFS results in women with concerning clinical characteristics were consistent with the ITT population[1,2,5-8‡]

‡Disease characteristics that typically confer a less favorable prognosis. Primary resistance and visceral disease were concerning clinical characteristics in MONARCH 2.

Primary resistance[16]

15.3 months

(95% CI: 12.4-24.1) (n=111) vs **7.9 months** with fulvestrant alone (95% CI: 5.7-11.4) (n=58)
HR=0.454 (95% CI: 0.306-0.674)

- Primary resistance is defined as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer[1]

Visceral disease[16]

14.7 months

(95% CI: 13.0-17.4) (n=245) vs **6.5 months** with fulvestrant alone (95% CI: 5.6-8.7) (n=128)
HR=0.481 (95% CI: 0.369-0.627)

- Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement[17]

- Preplanned subgroup analyses of PFS were performed for stratification factors of disease site, including visceral disease, and endocrine resistance, including primary resistance. The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups[16]

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2− MBC who progressed on ET. Patients were randomized 2:1 to Verzenio + fulvestrant or placebo + fulvestrant. Verzenio was dosed on a continuous dosing schedule until disease progression or unacceptable toxicity. The primary endpoint was PFS. Key secondary endpoints were ORR, overall survival, and DoR.[1,2]

Select Important Safety Information (cont'd)

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential **hepatotoxicity,** monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for Verzenio on the following pages.

everyday Verzenio® abemaciclib
50 | 100 | 150 | 200 mg tablets
twice a day

For heavily pretreated women with HR+, HER2− MBC

The only CDK4 & 6 inhibitor approved as a single agent[1]

ORR[1]

19.7% ORR

(95% CI: 13.3-27.5) per investigator assessment[1]
ORR was defined as the proportion of patients with CR + PR, and does not include stable disease[1,15]*

- 17.4% ORR (95% CI: 11.4-25.0), per independent review[1]

MONARCH 1 was a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2− MBC whose disease progressed during or after ET, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. Patients had an Eastern Cooperative Oncology Group Performance Status of 0 (55% of patients) or 1 (45% of patients). Patients took 200 mg of Verzenio orally twice daily on a continuous schedule unless disease progression or unacceptable toxicity occurred. The primary endpoint was ORR. A key secondary endpoint was DoR.[1,4]

Median duration of response (mDoR)[1†]

- **3.7-month** median time to response (range: 1.1-14.2 months)[4,18]
- **7.2-month mDoR** (95% CI: 5.6-NR), per independent review[1]

*PR defined as ≥30% reduction in target lesion size per RECIST 1.1.[4,15]
†Among 26 patients (investigator assessed) and 23 patients (independent review) who had a PR.[1]

Select Important Safety Information (cont'd)

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole** and **≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were diarrhea (81% vs 30%), neutropenia (41% vs 2%), fatigue (40% vs 32%), infections (39% vs 29%), nausea (39% vs 20%), abdominal pain (29% vs 12%), vomiting (28% vs 12%), anemia (28% vs 5%), alopecia (27% vs 11%), decreased appetite (24% vs 9%), leukopenia (21% vs 2%), creatinine increased (19% vs 4%), constipation (16% vs 12%), ALT increased (16% vs 7%), AST increased (15% vs 7%), rash (14% vs 5%), pruritus (13% vs 9%), cough (13% vs 9%), dyspnea (12% vs 6%), dizziness (11% vs 9%), weight decreased (10% vs 3%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 1** with Verzenio were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), leukopenia (17%), constipation (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 3** were neutropenia (22% vs 2%), diarrhea (9% vs 1%), leukopenia (8% vs <1%), ALT increased (7% vs 2%), and anemia (6% vs 1%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 2** were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** from **MONARCH 1** with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%).

Abemaciclib (Verzenio®): recommended by the National Comprehensive Cancer Network®(NCCN®)[19]

Abemaciclib (Verzenio): the only CDK4 & 6 inhibitor recommended by NCCN in combination with fulvestrant or an AI and as a single agent[19]

CATEGORY 1*

Abemaciclib (Verzenio) + fulvestrant[19†]

Recommended option for the treatment of postmenopausal women with HR+, HER2− MBC after disease progression on prior ET

Abemaciclib (Verzenio) + an AI[19†]

Recommended option for the treatment of postmenopausal women with HR+, HER2− MBC as initial endocrine-based therapy

CATEGORY 2A‡

Abemaciclib (Verzenio) as a single agent[19†]

Recommended option for the treatment of postmenopausal women with HR+, HER2–MBC after disease progression on prior ET and prior chemotherapy in the metastatic setting

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[19]
†If there is disease progression while on CDK4 & 6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4 & 6–containing regimen.
‡Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[19]
NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Select Important Safety Information (cont'd)

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 3 in ≥10% for Verzenio plus anastrozole or letrozole and ≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were increased serum creatinine (98% vs 84%; 2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs <1%), anemia (82% vs 28%; 2% vs 0%), decreased neutrophil count (80% vs 21%; 22% vs 3%), decreased lymphocyte count (53% vs 26%; 8% vs 2%), decreased platelet count (36% vs 12%; 2% vs <1%), increased ALT (48% vs 25%; 7% vs 2%), and increased AST (37% vs 23%; 4% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (98%; <1%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

Strong CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Patients should avoid grapefruit products.

Avoid concomitant use of strong CYP3A inducers and consider alternative agents. Coadministration of Verzenio with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis **is unknown.** No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30-89 mL/min).

AL HCP ISI 26FEB2018

Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.

everyday
Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets
twice a day

DISCOVER MORE DATA AT
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Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.

References: 1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018. **2.** Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35:2875-2884. **3.** Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35:3638-3646. **4.** Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res.* 2017;23:5218-5224. **5.** Imkampe A, Bendall S, Bates T. The significance of the site of recurrence to subsequent breast cancer survival. *Eur J Surg Oncol.* 2007;33:420-423. **6.** Largillier R, Ferrero JM, Doyen J, et al. Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol.* 2008;19:2012-2019 **7.** Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat.* 2000;59:271-278. **8.** Cardoso F, Costa A, Senkus E, et al. 3rd ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Breast.* 2017;31:244-259. **9.** Gerratana L, Fanotto V, Bonotto M, et al. Pattern of metastasis and outcome in patients with breast cancer. *Clin Exp Metastasis.* 2015;32:125-133. **10.** Vogel CL, Azevedo S, Hilsenbeck S, East DR, Ayub J. Survival after first recurrence of breast cancer: the Miami experience. *Cancer.* 1992;70:129-135. **11.** Chang J, Clark GM, Allred DC, Mohsin S, Chamness G, Elledge RM. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. *Cancer.* 2003;97:545-553. **12.** Yamamoto N, Watanabe T, Katsumata N, et al. Construction and validation of a practical prognostic index for patients with metastatic breast cancer. *J Clin Oncol.* 1998;16:2401-2408. **13.** Data on file. Lilly USA, LLC. ONC20180108a. **14.** Data on file. Lilly USA, LLC. ONC20180328a. **15.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247. **16.** Data on file. Lilly USA, LLC. ONC20180103a. **17.** Data on file. Lilly USA, LLC. ONC20171128a. **18.** Data on file. Lilly USA, LLC. ONC20171201a. **19.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed March 22, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.

Lilly

Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets

VERZENIO™ (abemaciclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Diarrhea

Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of VERZENIO dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose.

Neutropenia

Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Hepatotoxicity

In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the VERZENIO and placebo arms, respectively. In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the VERZENIO and placebo arms, respectively.

In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism

In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies 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.

MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy
Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus anastrozole or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 13% of patients receiving VERZENIO plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. VERZENIO dose reductions due to neutropenia of any grade occurred in 11% of patients receiving VERZENIO plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anemia, rash, weight decreased and thrombocytopenia (each 0.3%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of VERZENIO plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving VERZENIO plus an aromatase inhibitor included: 3 (1%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm and ≥2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia (Table 6). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia. Diarrhea incidence was greatest during the first month of VERZENIO dosing. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grades 2 and for Grade 3 were 11 days and 8 days, respectively. Most diarrhea events recovered or resolved (88%) with supportive treatment and/or dose reductions. Nineteen percent of patients with diarrhea required a dose omission and 13% required a dose reduction. The median time to the first dose reduction due to diarrhea was 38 days.

Table 6: Adverse Reactions ≥10% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	81	9	0	30	1	0
Nausea	39	<1	0	20	1	0
Abdominal pain	29	1	0	12	1	0
Vomiting	28	1	0	12	2	0
Constipation	16	<1	0	12	0	0
Infections and Infestations						
Infections[a]	39	4	<1	29	2	<1
Blood and Lymphatic System Disorders						
Neutropenia	41	20	2	2	<1	<1
Anemia	28	6	0	5	1	0
Leukopenia	21	7	<1	2	0	<1
Thrombocytopenia	10	2	<1	2	<1	0

Table 6: Adverse Reactions ≥10% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3 (Cont.)

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions						
Fatigue	40	2	0	32	0	0
Influenza like illness	10	0	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	27	0	0	11	0	0
Rash	14	<1	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1	0	9	<1	0
Investigations						
Blood creatinine increased	19	2	0	4	0	0
Alanine aminotransferase increased	16	6	<1	7	2	0
Aspartate aminotransferase increased	15	3	0	7	1	0
Weight decreased	10	<1	0	3	<1	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	<1	<1	6	<1	0
Nervous System Disorders						
Dizziness	11	<1	0	9	0	0

[a] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Additional adverse reactions in MONARCH 3 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, and pelvic venous thrombosis), which were reported in 5% of patients treated with VERZENIO plus anastrozole or letrozole as compared to 0.6% of patients treated with anastrozole or letrozole plus placebo.

Table 7: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
Laboratory Abnormality	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	2	0	84	0	0
White blood cell decreased	82	13	0	27	<1	0
Anemia	82	2	0	28	0	0
Neutrophil count decreased	80	19	3	21	3	0
Lymphocyte count decreased	53	7	<1	26	2	0
Platelet count decreased	36	1	<1	12	<1	0
Alanine aminotransferase increased	48	6	<1	25	2	0
Aspartate aminotransferase increased	37	4	0	23	<1	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. Across the clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

MONARCH 2: VERZENIO in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 8). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 8: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal Pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

[c] Includes neutropenia, neutrophil count decreased.

[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[e] Includes leukopenia, white blood cell count decreased.

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 9: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)
Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2- metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 10). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 10: Adverse Reactions (≥10% of Patients) in MONARCH 1

	VERZENIO N=132		
	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0

Table 10: Adverse Reactions (≥10% of Patients) in MONARCH 1 (Cont.)

	VERZENIO N=132		
	All Grades %	Grade 3 %	Grade 4 %
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.

[b] Includes neutropenia, neutrophil count decreased.

[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[d] Includes platelet count decreased, thrombocytopenia.

[e] Includes leukopenia, white blood cell count decreased.

Table 11: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

	VERZENIO N=132		
	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

DRUG INTERACTIONS

Effect of Other Drugs on VERZENIO

Strong CYP3A Inhibitors
Strong CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Patients should avoid grapefruit products.

Strong CYP3A Inducers

Coadministration of VERZENIO with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong CYP3A inducers and consider alternative agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was

teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*see* Data). 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

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

OVERDOSAGE

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

Additional information can be found at www.verzenio.com.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

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What's the Value of Innovation Without Access?

THERE ARE MANY WAYS we measure success in our long fight against cancer. In clinical trials, we record additional months of overall survival, and we look at scans that tell us tumors are shrinking or have disappeared. Then there are the less scientific, but not less meaningful signs: our new Nobel Prize winner James Allison, MD, told the story of shedding tears upon meeting one of the first patients treated with ipilimumab, a young woman who'd been headed for hospice but was now one year cancer free. Last month, the story of a couple who married on the grounds of St. Jude Children's Hospital, where they met years ago as childhood cancer patients, gained attention for what this told us about changing expectations for survival.

So many things we thought were impossible in cancer care are now possible, thanks to the arrival of new classes of treatments like targeted therapies, checkpoint inhibitors, and now chimeric antigen receptor (CAR) T-cell therapies.

But the possibility of a miracle matters little if the cost of treatment is beyond one's reach. St. Jude's commits to treating every child regardless of a family's ability to pay. But most children, teenagers, and adults are treated closer to home. Can we call cancer care a "success" if it means a future filled with medical bills that can never be paid or retirement funds that are wiped out? Should young adults be forced to choose between treatment and college education or owning a home someday?

For some time, we have heard about the fallout of "financial toxicity" on patients. Today, we are hearing more about efforts to contain cancer costs that are adversely affecting the doctors and practices that deliver life-saving care. This issue features research from Lucio Gordan, MD, and co-authors on the long-term effects of the federal sequester on community oncology practices, as well as an overview of a series of proposals from CMS that are straining oncologists as they strive to move from a fee-for-service system to value-based care. Oncologists who believe they have commitments within the Oncology Care Model to adjust for rising therapy costs, regional pricing differences, or the use of new treatments that didn't exist a year ago report that the model simply isn't keeping up and the most innovative practices are hurting. This issue also features the next installment of our series from the Institute for Value-Based Medicine, where experts dig deeply into the challenges at the practice level.

Meanwhile, CMS pursues policies such as step therapy, which calls for patients to accept a "fail first" strategy in cancer care even if their oncologist believes a more expensive therapy is the better option. And Medicare unraveled the value-based agreement to pay for CAR T-cell therapy and went back to the drawing board, creating uncertainty for patients and the institutions that administer these treatments.

Patients and families will only tolerate a wall between innovation and access for so long. The public will demand policies that connect people who need treatment with the best that science has to offer. ◆

Sincerely,

Mike Hennessy, Sr

CHAIRMAN AND CEO

ajmc.com
EBOncology

CONTENTS (CONTINUED)

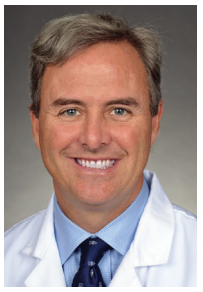
OCTOBER 2018, VOLUME 24, ISSUE 12

Measuring patient satisfaction is a priority for the National Community Oncology Dispensing Association.

REIMBURSEMENT

Squaring Value-Based Payment With Innovation in Oncology

Mary Caffrey



PATTON
Jeffrey F. Patton, MD, is CEO of Tennessee Oncology.

ALVARNAS
Joseph Alvarnas, MD, is vice president of government affairs and seniormedical director for employer strategy, City of Hope.

LYSS
Aaron Lyss is director of value-based care, Tennessee Oncology.

IN SEPTEMBER, CMS ADMINISTRATOR Seema Verma, MPH, described the giant footprint her agency has in the US healthcare system as the nation's largest insurer. "Everything we do has a large effect on every American," she told an audience at a September conference. "In every action we take, we examine the impact it will have on the entire healthcare system."

Few healthcare stakeholders would argue her first point. On the second one, many physicians, especially oncologists, would disagree. Oncologists hear the frustration from patients about what they pay out of pocket for cutting-edge therapies. They know a transition away from old reimbursement models is inevitable, and many are working to adapt. But in court filings, in regulatory comments, and in responses to ever-changing payment rules, oncologists are sounding the alarm: Many say government efforts to rein in Medicare spending will squeeze their margins and push more practices out of existence, instead of taking on the costs of drugs or the byzantine system that rewards pharmacy middlemen.

"For long-term success, Medicare must change course and develop payment policies to support, rather than weaken, the provision of cancer care in the United States," American Society of Clinical Oncology (ASCO) president Monica M. Bertagnolli, MD, FACS, FASCO, wrote in a September letter that accompanied a regulatory comment to CMS. "We urge CMS to refrain from finalizing any proposals that would result in any cuts in payments for cancer services and to work collaboratively with ASCO to implement global payment reforms, including the development and implementation of new [alternative payment models] that are widely available to all cancer professionals."[1]

That last part is the rub: As Bertagnolli's statement attests, CMS, on one hand, asks oncologists to move toward quality-based models that demand more risk, but at the same time it seeks to disrupt payment streams that practices need to make the transition. Reimbursement challenges and shrinking payments from Medicare are happening at a time when clinical breakthroughs give oncologists new opportunities to extend life. Oncologists who took part in a panel discussion hosted in June by *The American Journal of Managed Care®* (*AJMC®*) said that although the transition to value-based reimbursement is the right thing to do, many practices that were already efficient saw red ink during the first year of Medicare's Oncology Care Model (OCM), a 5-year alternative payment model set to run through 2021.[2,3]

"We are in the midst of a perfect storm, in which there is a constant down pressure on reimbursement while oncologists are being asked to immerse themselves in genomics, become effective stewards of emerging therapeutics, and magically lead efforts to control anticancer pricing," said Joseph Alvarnas, MD, a hematologist/oncologist who is vice president of government affairs and senior medical director for employer strategy at City of Hope in Duarte, California, and editor-in-chief for *Evidence-Based Oncology™* (*EBO*). "There is much talk about a move toward reimbursement based on the value of healthcare without clear evidence that there is a consistent, coherent model for what that is and little evidence that economic incentives are being realigned to support these activities."

For the OCM in particular, there's a difference between the financial challenges of the model and what it has done for patients, said Jeffrey F. Patton, MD, CEO of Tennessee Oncology, and Aaron Lyss, who is the practice's director of value-based care, in an interview with *EBO*. "We're very happy with the program in general," Patton said. "CMS has been very open to feedback, and it's working out to the point that we would not consider pulling out," he said. Tennessee Oncology has produced savings in the area of post–acute emergency readmissions, and the navigator and palliative care programs have been huge successes. Relative to other government agencies, Patton and Lyss have found the Center for Medicare and Medicaid Innovation (CMMI) within CMS to be responsive.

"The big problem is the drugs," Patton said. And that's not all CMMI's fault. The model started just as new, expensive immunotherapies and a new class of breast cancer drugs—the CDK4/6 inhibitors—were being approved and reaching patients. Given that the pricing elements of the model were necessarily retrospective, "The timing was about as bad as it could have been," Patton said.

"CMS has been very open to feedback, and it's working out to the point that we would not consider pulling out. ... The big problem is the drugs."

—Jeffrey F. Patton, MD, CEO of Tennessee Oncology

CMS has acknowledged that pursuing high-cost therapies is a balancing act for the 179 practices and 13 payers taking part in this payment model, but that's by design.[3] At the June policy summit of the National Comprehensive Cancer Network (NCCN), Ron Kline, MD, said that if figuring out how to pay for innovation in cancer care was easy, it would have happened already. "We know it's hard. We know it's going to take a while," said Kline, medical officer in the Patient Care Models Group for CMMI.[4]

But data produced by the Community Oncology Alliance (COA) suggest that some members don't have time to wait. COA's annual Practice Impact Report, released in April, found that 1653 practices have closed, merged, or reported financial problems over the past decade.[5] The COA report cited the "push and pull" of recent healthcare policy, as well as the effects of the ongoing federal sequester and the 340B drug discount program, which CMS has taken steps to reform.

Proposals for Medicare Part B Draw Fire

On May 11, 2018, President Donald Trump presented a blueprint that offered more than 4 dozen ideas for trimming out-of-pocket costs for prescription drugs, but the document did not recommend direct negotiations between Medicare and pharmaceutical companies, something Trump called for as a candidate. Instead, the blueprint proposed merging Medicare Part B, which pays for office-administered drugs, like chemotherapy, and Medicare Part D, which pays for prescription drugs patients take at home.[6]

This proposal and others have alarmed ASCO and COA, who say the plans being discussed could undermine quality care and harm patients.[7-9] However, COA has endorsed steps to rein in rebating practices by pharmacy benefit managers (PBMs).[10]

Since Trump's proposal, oncology groups have responded to federal actions past and present:

- In May, COA sued in US District Court, seeking to end application of the 2% federal sequester to Medicare Part B drugs, which COA argues have cost practices $78 million.[11] (See **Cover**.)
- In August, ASCO voiced opposition to a plan by CMS to allow Medicare Advantage plans to employ step therapy across Medicare Part B and Part D, which oncologists said could cause cancer to progress if patients cannot immediately access an appropriate therapy.[12]
- In September, ASCO and other physician groups filed regulatory comments protesting CMS' proposal to collapse multiple Medicare rate tiers for evaluation and management into just 2 tiers. Physician groups could cause financial harm for practices; ASCO additionally opposed a plan to cut by half an add-on charge for Medicare Part B.[1,13]

As part of its regulatory comment, ASCO called on CMS to allow more flexibility with payment models beyond the OCM that began last year. ASCO developed the Patient-Centered Oncology Payment (PCOP) Model[14] to qualify as an Advanced Alternative Payment Model under the Medicare Access and CHIP Reauthorization Act,[15] but it remains unapproved. COA has worked with the Commission on Cancer to launch the Oncology Medical Home recognition process, which seeks to reward practices that deliver efficient, measurable, evidence-based care.[16]

HHS Secretary Alex Azar, JD, explained the rationale for the step therapy plan this way: "By allowing Medicare Advantage plans to negotiate for physician-administered drugs, like private-sector insurers already do, we can drive down prices for some of the most expensive drugs seniors use."[17]

Patton agreed that merging Medicare Part B and Part D would be "disaster," as would be collapsing the E/M tiers. COA executive director Ted Okon, MBA, took special aim at the administration's plan for step therapy, including ideas for patients to be encouraged to use less expensive treatments with rewards programs, such as gift cards. "Does CMS truly believe that Medicare seniors will be enticed away from their physician-recommended treatment with the promise of a $50 Amazon gift card?" he asked. "Allowing middlemen to profit [from] denying cancer patients needed medications is immoral and cruel."[18]

Factoring in Rising Prices for Cancer Therapies

The OCM does try to account for innovation and high-cost drugs. The episode-based reimbursement model includes both a trend factor and a novel therapy adjustment:

- The trend factor accounts for the model's reliance on historical prices as oncology practices continue to see new therapies introduced at higher prices. This factor compares OCM participants with nonparticipants and it examines how costs are changing for each group. The trend factor allows CMS to look at specific attributes in the claims data—such as age, gender, and type of cancer—and make adjustments at the practice level based on the claims mix. Prices are also factored by hospital referral region to account for geographic differences.
- The novel therapy adjustment, an element of the trend factor, works similarly. This measure seeks to avoid penalizing early adopters of new cancer treatments. Practices benefit if they end up treating more than the anticipated number of patients with a certain cancer or more patients than would be expected to use a newly approved treatment. Prices for novel therapies inside the OCM are compared with prices outside the OCM: Practices within the OCM are paid in full to the point that they match what is being spent across the country, and then they are paid 80% of the remaining target price.

"We are in the midst of a perfect storm, in which there is a constant down pressure on reimbursement while oncologists are being asked to immerse themselves in genomics, become effective stewards of emerging therapeutics, and magically lead efforts to control anticancer pricing."

—Joseph Alvarnas, MD, vice president of government affairs and senior medical director for employer strategy, City of Hope

Participants in the *AJMC*® panel discussion questioned whether the novel therapy adjustment adequately compensates OCM participants.[2] "For an academic medical center, we use a lot of the drugs as they come out, if not before [in clinical trials] the approval. So, one of the things we expected was that we would probably get that back," said Mark Liu, MHA, director of strategic initiatives for the Mount Sinai Health System. "We did get some adjustment, but not nearly as much as we would have expected."

In the interview, Patton agreed with the panel participants that, "As early adopters of novel therapies, in the current system we are penalized by the novel therapy adjustment," since it stops paying at 80% of the target price. Innovative practices are never going to withhold the best therapy for cost reasons, Patton said, but there is a penalty.

The Challenge of CAR T-Cell Therapy

A session of the NCCN summit, Paying for Innovation, asked how oncologists could continue to offer game-changing treatments, like chimeric antigen receptor (CAR) T-cell therapy, if payers cannot figure out how to fund them.[4] CAR T-cell therapy offers a textbook case, because Novartis initially reached a value-based payment agreement with CMS when the first therapy, tisagenlecleucel (Kymriah), was approved. But then CMS changed course and launched a national coverage analysis for the therapies, in response to a request from UnitedHealthcare.[19]

The August 22, 2018, meeting of the Medicare Evidence Development and Coverage Advisory Committee endorsed 4 tools to measure patient-reported outcomes (PROs), as part of the national coverage determination for CAR T-cell therapy pricing. A Novartis representative said the process could lead to a slowdown in access to CAR T-cell therapy and asked that the process be withdrawn. Others asked whether PROs could be applicable to CAR T-cell therapy, which is known to have side effects that include cytokine release syndrome.[19]

Because of the unique administration requirements of CAR T-cell therapy—each treatment must be manufactured individually from a patient's cells—it is only administered at select centers. Leaders from cancer centers who attended the NCCN summit and those who spoke earlier this year with *EBO* said the enormous financial risk demands intense involvement from senior officials at institutions. Tisagenlecleucel has a list price of $475,000, and the second approved therapy, axicabtagene ciloleucel (Yescarta), lists at $373,000; with the cost of administration and treatment of side effects, some estimates put the full cost of a treatment at $1 million. But unlike earlier therapies that could shrink tumors or delay disease progression, CAR T-cell therapies offer the promise of curing disease.

How does the OCM handle CAR T-cell therapy, which had not been approved when the model began in 2016? OCM participants can still receive the $160 monthly payment for each patient, but the total cost of care is not counted within the performance element. In August, CMS finalized rules that included an extra $72 million for CAR T-cell payments for 2019, based on increased Medicare technology add-on payments and a higher diagnostic-related group weighting, similar to transplants. But experts who spoke with *EBO*™ say under the current reimbursement structure, institutions will lose money on this treatment process.[19]

"With the current CMS reimbursement models for both the [Prospective Payment System (PPS)] and PPS-exempt centers, those who provide inpatient CAR T-cell treatments to patients assume enormous financial risks around the product acquisition costs and are at further risk for losses related to the clinical care of patients following the infusion of the products," Alvarnas said.

Moving to Two-Sided Risk

Verma stirred debate with an August 9, 2018, post on the *Health Affairs* blog, when she wrote that accountable care organizations (ACOs) that only accept 1-sided risk are not saving Medicare enough money and proposed rules will push ACOs into 2-sided risk more quickly.[20] Many disagree, as expressed by Kip Sullivan, JD, who chairs the »

policy advisory committee for Healthcare for All - Minnesota. Sullivan said Verma's own numbers show that the difference between ACOs taking 1-sided or 2-sided risk have been so small they matter little within the context of what Medicare spends.[21]

Oncologists who spoke with *EBO* took exception to Verma's remarks in late July at the Commonwealth Club in California, where she implied that doctors are part of the problem in the high cost of prescription drugs in Medicare Part B. "Today, Medicare is a price taker in our Part B program, we don't negotiate, and manufacturers can charge whatever they want. And Medicare incentivizes them to charge more, because doctors that prescribe their drugs are paid on a percentage of the cost of the drug," Verma said. "So, the more the drug costs, the more the doctor gets. This is another example of misaligned financial incentives in Medicare that are driving up costs."[22]

The underlying assumption, that health systems aren't trying hard enough, falls apart when experts report on the complexity of CMS programs and the OCM, in particular. Darcie Hurteau and Alyssa Dahl of DataGen, writing earlier this year in *EBO*, said CMS' initial release of OCM reconciliation data revealed administrative headaches that could make a move to 2-sided risk burdensome. DataGen and others had to tell CMS about errors in an initial data, and CMS had to send the data a second time. Hurteau and Dahl also reported that some providers received far less from the novel therapy adjustment than they had anticipated. Other participants were pleasantly surprised. However, Hurteau and Dahl wrote that it's already time for those who didn't see savings to start thinking about downside risk, even though they won't have to decide until the middle of 2019.[23]

The first evaluation report on OCM is expected before the end of 2018, according to a calendar outlined by CMS officials. Bruce Feinberg, DO, of Cardinal Specialty Solutions, and Bruce Gould, MD, of Northwest Georgia Oncology Centers, who also took part in the *AJMC*® panel discussion, said there are many financial details that need to be worked out, including implementation of the 13-point care plan from the Institute of Medicine. The plan requires practices to discuss treatment goals, develop a treatment plan that anticipates response to treatment, assess psychosocial needs, and develop a survivorship plan.[2,23]

Lyss said that although CMMI is more flexible relative to other government agencies, it still must move more quickly to keep pace with the science. He and Patton agreed that the "cliff" will come when it's time for practices to decide whether to move to 2-sided risk. They agreed that the challenges with the novel therapy adjustment are fixable, and CMMI will have to fix them—because it's not in the agency's interest for practices to drop out of the program. Lyss said there are some examples of models in the commercial sector that could offer a guide for where CMMI should go. There's no single right way to account for rapidly rising drug costs, he said. "It's far from a settled issue," he added, and Medicare's population is older with more comorbidities. But the commercial sector does offer ideas.

If practices use innovative therapies, Lyss said, "they are going to be more expensive, and we've got to find a way to account for that."

"We appreciate CMS' stated efforts in wanting to move toward value-based care delivery," Alvarnas said. "In order to get to this aspirational state, we need to have robust engagement between CMS and the key stakeholders in the cancer care domain to ensure that value-based care ensures that patients and families receive the care they need without unnecessary delays, excessive patient-borne costs, or unsustainable payments to physicians and healthcare systems." ◆

Aaron Lyss of Tennessee Oncology said that although the Center for Medicare and Medicaid Innovation is more flexible relative to other government agencies, it still must move more quickly to keep pace with the science. The "cliff" will come when it's time for practices to decide whether to move to 2-sided risk. It's not in the agency's interest for practices to drop out of the Oncology Care Model, he said.

With reporting by Allison Inserro and Samantha DiGrande.

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Nurse Practitioners Can Lead the Way in Affecting Colorectal Cancer Screening

Philip Parks, MD, MPH

NURSE PRACTITIONERS (NPS) PLAY an increasingly important role in healthcare. Not only is the NP population growing at a rapid rate—the American Association of Nurse Practitioners (AANP) reports that the number of licensed NPs nationwide has doubled since 2007 to nearly 250,000—but their practice style is also particularly effective. NPs are often distinguished by their ability to engage with patients and embrace shared decision making. Offering patients active roles in their healthcare decisions can improve outcomes and decrease medical costs.

The results of a recent study[1] reveal that in US rural areas, NPs account for 1 in 4 healthcare providers, a 43.2% increase from just 10 years ago. This increase is linked in part to changes in state regulations that favor direct access by patients to NPs. Currently, 22 states and the District of Columbia offer "full practice" authority for NPs, whereby they can practice independently of a physician. The reliance on NPs to meet healthcare needs is expected to continue, as the US Bureau of Labor Statistics projects a nearly 19% growth in NP licensure by 2020.[2]

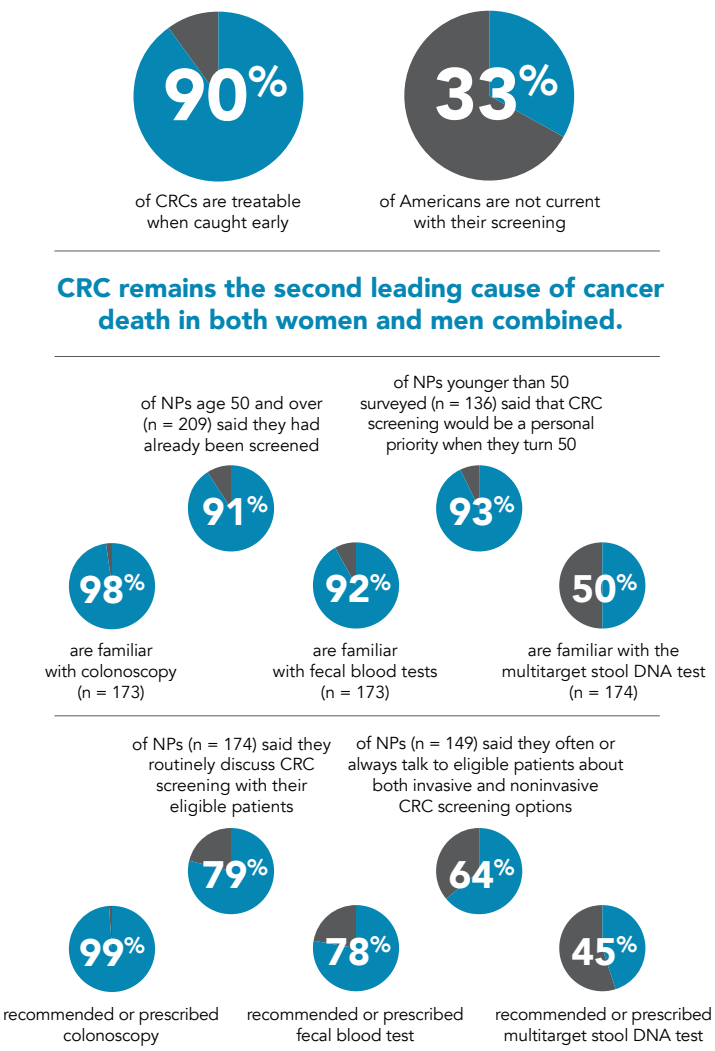
Preventive health strategies, such as colorectal cancer (CRC) screening, are an example in which patient involvement and shared decision making can make a significant difference in getting more individuals screened. The AANP, in partnership with the independent nonprofit organization HealthyWomen, recently conducted a survey designed to examine NPs' knowledge and practice patterns around CRC screening. The survey found that CRC screening is a personal priority for NPs: 91% of respondents eligible for screening reported they had been screened. For respondents younger than 50 years, 93% reported that CRC screening would become a priority when they turn 50.

The survey results also revealed an opportunity for the majority of participating NPs to educate their patients about the risks and benefits of all CRC screening options. The United States Preventive Services Task Force gave CRC screening an "A" rating for individuals aged 50 to 75 years and recommended 7 screening options.[3] However, most NPs who responded to the AANP survey indicated they were not familiar with every screening option. Given the recent update to the American Cancer Society's CRC screening guidelines,[4] there is heightened awareness around this healthcare issue. The updated guidelines endorse a range of CRC screening options, noting that the "initial test does not have to be a colonoscopy… Instead, it could be one of several other tests, including home stool tests available by prescription." Now is the time for NPs to leverage their ability to engage and educate their patients about all screening options to increase CRC screening rates.

Brenda Boutin of Savannah, Georgia, is one patient whose life was significantly impacted by her NP's knowledge. Boutin's NP, Mary McCourt, recommended Cologuard, the noninvasive home stool DNA test, for CRC screening to accommodate Boutin's busy lifestyle. Together they discussed this option, along with others, and Boutin agreed to take the Cologuard test. A positive result necessitated a follow-up colonoscopy, which revealed early-stage, yet treatable, CRC.

Now healthy, active, and free of cancer, Boutin credits McCourt for helping her decide which CRC screening test was best for her. NPs are in the position to guide their patients through learning and shared decision making by offering up-to-date health information. The current and future growth in the NP population means that there are hundreds of thousands of NPs like McCourt who can encourage patients to engage in preventive health decisions and empower them to take charge of their health. ◆

FIGURE. Colorectal Cancer Screening: SNAPP Survey Results



CRC indicates colorectal cancer; NP, nurse practitioner; SNAPP, the CRC Screening Knowledge and Practice Patterns

Sources: American Association of Nurse Practitioners, Healthy Women, and Exact Sciences.

PARKS

Philip Parks, MD, MPH, is the senior director of medical affairs, Exact Sciences. He is a board-certified practicing physician who served in the US Navy and has clinical, corporate medicine, and managed care experience.

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Rubraca® (rucaparib) tablets:

TWO INDICATIONS. MORE PATIENT TYPES.

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for the **maintenance** treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and

for the **treatment** of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca

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MAINTENANCE

Debra, 67

- *BRCA* wild-type
- Taking Rubraca to maintain response to most recent platinum-based chemotherapy

These individuals are not actual patients.

*In the ARIEL3 trial of Rubraca as maintenance therapy, investigator-assessed median progression-free survival (PFS) in the overall study population was 10.8 months in the treatment group versus 5.4 months in the placebo group (HR=0.36 [95% CI, 0.30, 0.45], *P*<0.0001).[1]

Study design: The efficacy of Rubraca for maintenance treatment was investigated in a randomized, placebo-controlled, double-blind, multicenter clinical trial of 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had a response to platinum-based chemotherapy. The efficacy of Rubraca was evaluated in 3 prospectively defined molecular subgroups in a step-down manner: 1) *BRCA* mutation-positive patients, 2) patients with homologous recombination deficiency (HRD), and 3) all randomized patients.[1]

Select Important Safety Information

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur uncommonly in patients treated with Rubraca, and are potentially fatal adverse reactions. In approximately 1100 treated patients, MDS/AML occurred in 12 patients (1.1%), including those in long term follow-up. Of these, 5 occurred during treatment or during the 28 day safety follow-up (0.5%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 28 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing regimens and/or other DNA damaging agents.

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

Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose (see Dosage and Administration (2.2) in full Prescribing Information) and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

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

Most common adverse reactions in ARIEL3 (≥ 20%; Grade 1-4) were nausea (76%), fatigue/asthenia (73%), abdominal pain/distention (46%), rash (43%), dysgeusia (40%), anemia (39%), AST/ALT elevation (38%),

CLOVIS ONCOLOGY

Reference: 1. Rubraca [package insert]. Boulder, CO: Clovis Oncology; 2018.

In a phase 3 study for maintenance treatment, Rubraca significantly extended progression-free survival versus placebo, **regardless of *BRCA* status**[1]*

constipation (37%), vomiting (37%), diarrhea (32%), thrombocytopenia (29%), nasopharyngitis/upper respiratory tract infection (29%), stomatitis (28%), decreased appetite (23%), and neutropenia (20%).

Most common laboratory abnormalities in ARIEL3 (≥ 25%; Grade 1-4) were increase in creatinine (98%), decrease in hemoglobin (88%), increase in cholesterol (84%), increase in alanine aminotransferase (ALT) (73%), increase in aspartate aminotransferase (AST) (61%), decrease in platelets (44%), decrease in leukocytes (44%), decrease in neutrophils (38%), increase in alkaline phosphatase (37%), and decrease in lymphocytes (29%).

Most common adverse reactions in Study 10 and ARIEL2 (≥ 20%; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities in Study 10 and ARIEL2 (≥ 35%; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, which may increase the risk of toxicities of these drugs. Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing frequency of international normalized ratios (INR) monitoring.

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

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

Please see Brief Summary of Prescribing Information on the following pages.

Rubraca® (rucaparib) tablets

RUBRACA® (rucaparib) tablets, for oral use

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

INDICATIONS AND USAGE

Maintenance Treatment of Recurrent Ovarian Cancer

Rubraca is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies

Rubraca is indicated for the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur uncommonly in patients treated with Rubraca, and are potentially fatal adverse reactions. In approximately 1100 treated patients, MDS/AML occurred in 12 patients (1.1%), including those in long term follow-up. Of these, 5 occurred during treatment or during the 28 day safety follow-up (0.5%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 28 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose according to Table 1 *[see Dosage and Administration (2.2) in the full Prescribing Information]* and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during the period of organogenesis resulted in embryo-fetal death at exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended human dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full Prescribing Information]*.

ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

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.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of Rubraca for the maintenance treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer was investigated in ARIEL3, a randomized (2:1), double-blind, placebo-controlled study in which 561 patients received either Rubraca 600 mg BID (n=372) or placebo (n=189) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.3 months (range: < 1 month to 35 months) for patients who received Rubraca and 5.5 months for patients who received placebo.

Dose interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving Rubraca and 10% of those receiving placebo; dose reductions due to an adverse reaction occurred in 55% of Rubraca patients and 4% of placebo patients. The most frequent adverse reactions leading to dose interruption or dose reduction of Rubraca were thrombocytopenia (18%), anemia (17%), nausea (15%), and fatigue/asthenia (13%).

Discontinuation due to adverse reactions occurred in 15% of Rubraca patients and 2% of placebo patients. Specific adverse reactions that most frequently led to discontinuation in patients treated with Rubraca were anemia (3%), thrombocytopenia (3%) and nausea (3%).

Table 1. Adverse Reactions in ARIEL3 Occurring in ≥ 20% of Patients

	Rubraca N=372		Placebo N=189	
Adverse reactions	**Grades[a] 1-4 %**	**Grades 3-4 %**	**Grades[a] 1-4 %**	**Grades 3-4 %**
Gastrointestinal Disorders				
Nausea	76	4	36	0.5
Abdominal pain/distention[b]	46	3	39	0.5
Constipation	37	2	24	1
Vomiting	37	4	15	1
Diarrhea	32	0.5	22	1
Stomatitis[b]	28	1	14	0.5
General Disorders and Administration Site Conditions				
Fatigue/asthenia	73	7	46	3
Skin and Subcutaneous Tissue Disorders				
Rash[b]	43	1	23	0
Nervous System Disorders				
Dysgeusia	40	0	7	0
Investigations				
AST/ALT elevation	38	11	4	0
Blood and Lymphatic System Disorders				
Anemia	39	21	5	0.5
Thrombocytopenia	29	5	3	0
Neutropenia	20	8	5	1
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis/Upper respiratory tract infection[b]	29	0.3	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	23	1	14	0

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

[b] Consists of grouped related terms that reflect the medical concept of the adverse reaction.

Adverse reactions occurring in < 20% of patients treated with Rubraca include headache (18%), dizziness (19%), dyspepsia (19%), insomnia (15%), dyspnea (17%), pyrexia (13%), peripheral edema (11%), and depression (11%).

Table 2. Laboratory Abnormalities in ARIEL3 Occurring in ≥ 25% of Patients

	Rubraca N=372		Placebo N=189	
Laboratory Parameter[a]	**Grade 1-4 %**	**Grade 3-4 %**	**Grade 1-4 %**	**Grade 3-4 %**
Chemistry				
Increase in creatinine	98	0.3	90	0
Increase in cholesterol	84	4	78	0
Increase in ALT	73	7	4	0
Increase in AST	61	1	4	0
Increase in Alkaline Phosphatase	37	0.3	10	0
Hematology				
Decrease in hemoglobin	88	13	56	1
Decrease in platelets	44	2	9	0
Decrease in leukocytes	44	3	29	0
Decrease in neutrophils	38	6	22	3
Decrease in lymphocytes	29	5	20	3

[a] Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

Treatment of BRCA-mutated Recurrent Ovarian Cancer After 2 or More Chemotherapies

Rubraca 600 mg twice daily as monotherapy has also been studied in 377 patients with epithelial ovarian, fallopian tube or primary peritoneal cancer who have progressed after 2 or more prior chemotherapies in two open-label, single arm trials. In these patients, the median age was 62 years (range: 31 to 86), 100% had an ECOG performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range: 6 to 197).

Table 3. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL2

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

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

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

Table 4. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL2

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

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.
[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

DRUG INTERACTIONS

Effect of Rucaparib on Cytochrome p450 (CYP) Substrates

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*, which may increase the risk of toxicities of these drugs.

Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing the frequency of international normalized ratio (INR) monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Pediatric Use

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

Geriatric Use

In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anemia, fatigue/asthenia, and ALT/AST increase. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies.

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions (6.1) in the full Prescribing Information]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations (8.2) in the full Prescribing Information]*.

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

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Patient Satisfaction Surveys: A Continuous NCODA Initiative for Improvement Within the Oncology Dispensing Practice

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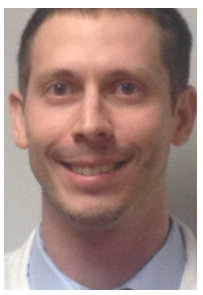

BUDGE

Aaron Budge, PharmD, was a clinical pharmacist of Tri-County Hematology & Oncology when this article was drafted. He is a practicing pharmacist in Northeastern Ohio.

PATIENT SATISFACTION is an essential metric in the growing trend of value-based care within the oncology community. The National Community Oncology Dispensing Association (NCODA), in conjunction with Syracuse University's Maxwell School of Citizenship and Public Affairs' Community Link Program, has developed and distributed a patient satisfaction survey to its practice members. NCODA practices have held the high standard and goal of providing the best patient care to their respective communities, and surveys are one method by which NCODA has been able to provide its members a platform to display the benefits and value of their practice.

As of spring 2018, NCODA had collected over 700 patient responses from across the country, which were evaluated by Syracuse University's Community Link Program. The satisfaction metric was separated into 4 core categories: time, convenience, staff interaction, and overall satisfaction. These data were subsequently stratified over multiple demographic groups for additional analysis such as gender, patient usage between mail order and in-office dispensing, financial assistance, and future patient use of dispensing. For NCODA practices, the overall satisfaction measured approximately 95% for patients who reported they were satisfied or very satisfied. From that subset, 92% reported being very satisfied overall. Moving forward, we aim to display this measure as an advance in value-based care within NCODA member practices. This aim is consistent with improvement of survey utilization and increased distribution. Reports such as these can be deemed beneficial for practices that are looking to exhibit and leverage these data to create a dialogue among various stakeholders for continued sustainability as well as to self-audit their own pursuit of excellence in oncology patient care.

Patient Satisfaction Surveys in the Medically Integrated Dispensing Practice: Issues and Observations

Data are a real and valuable commodity in most industries. We use data of all kinds, relevance, lot size, and accuracy as we try to proactively manage this historicly elusive wealth of information. Monetizing these data is quite another matter. In our business space, what specific data should we obtain, analyze, and operationalize?

Some say that improving the US healthcare system requires simultaneous pursuit of 3 aims: "improving the care experience, improving the health of populations, and reducing per capita costs of healthcare. Preconditions for this include the enrollment of an identified population, a commitment to universality for its members, and the existence of a care provider organization that accepts responsibility for the 3 aims for that population. The healthcare organization's role includes at least 5 components: partnership with individuals and families, redesign of primary care, population health management, financial management, and macro system integration."[2]

When discussing patient satisfaction, 3 fundamental questions emerge: "Is it worth measuring? How can it best be measured? How are we to use the results? These 3 questions—1 philosophical, 1 empirical, and 1 practical—form a framework for evaluating the place of patient satisfaction within the patient outcomes movement."[3]

Patient satisfaction can carry strategic weight beyond the traditional objectives of other patient surveys for medically integrated dispensing (MID) practices. Under current circumstances, would it be more appropriate to address the patients as "consumers"? Today, patients are guided to see themselves as buyers of health services. "Once this concept is accepted, there is a need to recognize that every patient has certain rights, which puts emphasis on the delivery of quality healthcare."[4]

Private MID practices are at the intersection of healthcare, technology, and human service We all have data dashboards, laws, regulations, and policies to guide our decisions on every aspect of the business. These data are usually timely and valid, and we can reasonably rely on them. What we do not have are data that are just as valid and reliable to help us better manage the business with the goal of an optimal, at least a favorable, patient experience.

It is important to recognize that a satisfaction score is a perspective, not the truth, about a physician's ability to deliver quality care. It is information that reflects a subset of daily interactions, and it is dependent on the number of variables involved.

Patient satisfaction surveys have evolved into a full-fledged data set and platform. From large health systems to the smallest private medical practice, obtaining, analyzing and responding (or not) to results can certainly provide benefits. They can also serve as a management tool to better align management's goals, marketing messages, and process design based upon survey results. The practice of medicine has evolved over centuries. There are certain significant developments that have taken place in health systems in recent times, chief among them being:

1. Establishment of high-cost corporate-style hospital systems equipped with the latest facilities.
2. Strategic integration of third-party payers, insurance companies, specialty pharmacies (SPs), pharmacy benefit managers (PBMs), government entities, distributors, and companies on the periphery of the doctor–patient relationship.
3. Availability of information through the internet, and higher expectations of patient care.[5]
4. Increasing litigation methods from delay in diagnosis to breakdowns in communication[6] and other consequences of unsatisfactory results such as financial distress/toxicity.[7]

All of these factors have resulted in a challenging environment for the healthcare industry, with a movement away from the traditional concept of a noble profession toward more of a service industry.

In a major report published in 2001, the Institute of Medicine, now the National Academy of Medicine, set forth 6 aims for quality and patient safety in a healthcare system[1]:

1. Safe
2. Equitable

3. Evidence-based
4. Timely
5. Efficient
6. Patient-centered

Factors 4 through 6 directly influence patient satisfaction.

The NCODA Patient Satisfaction Survey

The NCODA Patient Satisfaction Survey was developed in conjunction with Syracuse University in 2016 with the purpose of measuring qualitative differences within the pharmacy-dispensing space. NCODA created a template that allows practices to add their own brand details that could be sent to a central location for aggregation. The Community Link Program has a process where the data can be coded and accounted for future analysis, which is then presented to the membership in multiple channels such as at national conferences and webinars. Practices utilizing the surveys have the ability to account for areas of high satisfaction and possible improvement, which is paramount to the NCODA foundation and quality standards. The goal of the surveys is to create a quantitative narrative based on the positive influence that MID practices can provide by virtue of being at the cross-section of clinical and operational responsibilties. NCODA members strive to focus on creating better quality interventions within the continuity of care for the patient, and the surveys allow for that collective voice to be heard.

The MID Patient as a Consumer

Patients with cancer, as a population within the healthcare environment, present with certain issues and characteristics that can be well managed in the MID space, and at an overall lower cost than what is found in larger systems. Further exacerbating the higher costs and challenges to timeliness and quality of care are the payer/SP/PBM demands and constraints placed upon the MID practice. However, these issues are outside the scope of this article to develop more fully.

The NCODA survey is meant primarily as a tool to prove to legislators, regulators, insurance companies, SPs, PBMs, employers, and patients that the MID practice has real value in the cancer care continuum. The survey is intentionally brief. Most MID practices conduct other patient surveys besides the in-office dispensing (IOD) service line. Numerous surveys are available to obtain a picture of satisfaction and other metrics across all organizational aspects. The NCODA survey is given exclusively to IOD patients, usually at their second visit, the reason being that at the first visit, patients are bombarded with information about treatment decisions, drug interactions, studies, imaging, and other ancillary services. Survey fatigue can be a real issue for patients with cancer, over half of whom are over age 65 and suffer from comorbidities. Also, for MID practices that are in the Oncology Care Model or other government advanced payment models, those patients receive lengthy surveys already. The MID practice must be sensitive to this reality.

The NCODA Patient Satisfaction Survey is straightforward and easy to complete. No personally identifiable information, such as name, address, or social security number—is collected. The 1-page survey mainly includes check-box questions, and the hard copy surveys are collected, scanned, and sent to NCODA headquarters for coding and accounting. Summaries are available for either the individual practice submitting the data or the NCODA-wide summary data. When evaluating the data, NCODA believes that service excellence revolves around 3 factors: doctor, patient, and a medically integrated organization.

The Medical Oncologist/Hematologist

"Undoubtedly, physicians have the twin responsibilities of giving the best healthcare to the patient and leading the MID practice in attaining the goal of satisfying the patient," Bhanu Prakash writes.[4] Listed below are a few "house rules" to handle patients so as to have all satisfied:[4]

1. Break the ice: Make eye contact, smile, call patients by name, and express words of concern.
2. Show courtesy: Kind gestures and polite words make patients very comfortable.
3. Listen and understand: Encourage patients to narrate their problem. Invite and answer their questions.
4. Inform and explain: These promote compliance. People are less anxious when they know what's happening.
5. See the whole person: Envision the whole person beyond the illness.
6. Share the responsibility: Risks and uncertainty are facts of life in medical practice. Acknowledging risks builds trust.
7. Pay undivided attention: This reduces distractions and interruptions as much as possible.
8. Secure confidentiality and privacy: Watch what you say, where you say it, and to whom you say it to.
9. Preserve dignity: Treat patients with respect. Respect modesty.
10. Remember patients' families: Families feel protective, anxious, frightened, and insecure. Extend yourself, reassure, and inform.
11. Respond quickly: Keep appointments, return calls, and apologize for delays.

From a healthcare provider's perspective, specifically a pharmacist, there are gaps and scenarios where patient satisfaction surveys are underutilized. For example, in one participating practice, surveys are considered beneficial primarily from a business and operations perspective. However, they should also be considered valuable for patient outcomes, because continuous quality improvement is a vital aspect of any dispensing service and healthcare practice. From a pharmacy and dispensing outlook, it is often difficult to distinguish and visualize the impact of the pharmacist and staff. At some practices, physicians and nurses are strained for time and often are unable to spend as much time with a patient as they would prefer. This gap, which in the past has gone unmeasured, could potentially be covered by pharmacists and the auxiliary staff (ie, pharmacy technicians, nurses, patient financial advocates, etc),. The NCODA Patient Satisfaction surveys help to validate the continuity of care to help transverse the different disciplines involved.

There are also other opportunities where assessing patient satisfaction can be implemented at a practice, such as in an oral chemotherapy follow-up program, where a pharmacist can initiate education around a new oral chemotherapy drug with a patient. Patients who are part of an MID practice are also contacted at predetermine intervals, in addition to their office visits, to assess adherence and drug toxicity. Education and reinforcement are provided as needed.

Questions to always ask:

1. Does the patient walk away feeling more comfortable with the information they need to begin taking the medication?
2. Does the patient fully understand how to take their medication and why they are taking it?
3. Does the patient feel that their adverse effects are under control?
4. Does the patient feel they have the support they need if there is cognitive impairment or they face financial issues?

Anecdotal evidence suggests many patients are unaware of their diagnosis, why they are on a certain medication, or why their particular medication was discontinued, held, or switched. The MID is a service of the practice that can provide clarity and relieve fears about adverse effects.

When a patient understands and trusts the healthcare providing team and their decisions, they can be much more satisfied knowing that they are being taken care of on a personal level.[8] For example, in a scenario involving a personal exchange between a patient and pharmacist, a patient mentions that she does not trust the drug companies. The pharmacist then shows a study that found that adding a particular drug improved progression-free survival by 10.2 months. Through data and a friendly and understanding healthcare provider, the patient is able to visualize the effectiveness and see that the practice had her best interests in mind.

For drugs that are filled at SP, the MID practice's responsibility as the patient's healthcare provider is often mixed, given certain circumstances that disallow continued refills at the practice. Even in those situations, the burden may still be placed on the MID practice to ensure that the patient receives their medication on time. For certain restricted drugs in a practice, for example, prescriptions are not permitted to have refills. The physician must sign a new prescription every cycle and an authorization number must be obtained from the manufacturer.

MID practices can also help patients who cannot afford their medications by connecting them with charitable foundations that provide financial assistance. Without oversight, numerous patients may not get their medication on time especially during long events, such as holidays. For example, what if a patient needed an early refill/vacation override prior to embarking on a month-long vacation? A vacation override would be needed for the manufacturer, their specialty pharmacy, and their insurance provider. Patient satisfaction is readily apparent when they receive assistance in such scenarios. Patients are extremely grateful and happy that MID practices can provide this kind of service. »

Utilizing Survey Data

How can these patient satisfaction survey results be utilized? Many satisfaction batteries can reliably distinguish between physicians who are great communicators and those who are interpersonally challenged. Patient satisfaction is also related to a variety of possible downstream outcomes, such as the propensity to change health plans or to sue for malpractice. These results are clearly of interest to managers and marketers, but their relation to clinical quality improvement is tenuous. The important question is whether information on patient perceptions and values can stimulate genuine gains in patient-centered care. Providing physicians, payers, SPs, PBMs, employers, and staff with comparative quarterly satisfaction reports is likely to accomplish little except fuel resentment.

Accounting for all of these sources of variation, it is important to recognize that a satisfaction score is a perspective, not the truth, about a physician's ability to deliver quality care. It is information that reflects a subset of daily interactions, and it is dependent on the number of variables involved.

NCODA plans to continue building an inventory of survey responses to help members better manage their IOD and other internal processes. We also hope to apply this data as one more piece of evidence that we are a better alternative to the current restrictions and barriers to cost avoidance, waste reduction, and more timely care.

Conclusion

Patient satisfaction is an attitude. Patient satisfaction is an indirect, or a proxy, indicator of the quality of care, the provider, or their MID practice overall. Delivery of patient-focused care requires that we provide care in a particular way, always. It must be the best care for every patient every time. Ideally what is needed is for the MID pratice to have the ability to manage the patient with cancer in totality, unencumbered by interference from specialty pharmacies; incomplete payer or PBM formularies; and the complicated system of authorizations and financial support, policy changes, inadequate beneficiary education on the part of policy purchasers and sellers, and regulations that frustrate the realization of lower cost, same or better quality of care, and a higher patient satisfaction score. ◆

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Making the Leap to Prospective Risk in Value-Based Oncology Care

Mary Caffrey

AS PHYSICIANS, INCLUDING ONCOLOGISTS, gain comfort with payment for value, one question keeps popping up: What will it take to move from being rewarded for good results to accepting losses for bad ones?

The challenge in getting specialists to join the shift from 1-sided to 2-sided risk is the next big hurdle in healthcare transformation. In a *Health Affairs* blog post in August, CMS Administrator Seema Verma, MPH, made it clear that Medicare ACOs will no longer be allowed to linger indefinitely in 1-sided, or "upside-only", status.[1] But oncologists say their situation is different. For years their compensation has been tied to the price of drugs in Medicare Part B, a system they didn't invent.[2] So far, the hurdles found in being fairly compensated when using expensive cutting-edge therapies under CMS' Oncology Care Model (OCM) are very real.

Making this leap to 2-sided, or prospective, risk was the theme of "Future Perspectives on Oncology Value-Based Care," a September 27, 2018, presentation of the Institute for Value-Based Medicine (IVBM) that took place at the Sofitel Hotel in New York City. Serving as moderator was Andrew Pecora, MD, FACP, CPE, chief innovation officer, professor, and vice president of Cancer Services at John Theurer Cancer Center, Hackensack Meridian Health. Joining Pecora were:

- Lani Alison, BSN, MS-HCQ, PCMH, CCE, vice president of clinical affairs, Regional Cancer Care Associates, which has 30 locations in New Jersey, Connecticut and Maryland;
- Luis Isola, MD, director of cancer clinical programs at Mount Sinai Health System, New York City;
- Allen Karp, executive vice president of healthcare management and transformation for Horizon Blue Cross Blue Shield of New Jersey, which serves 3.8 million members.

Where the Money Is

As Pecora explained, there's a simple reason why payers, including Medicare, are taking aim at the waste in healthcare spending: That's where the money is. At $2.9 trillion a year in the United States, healthcare spending accounts for 17% of the US gross domestic product. When one considers estimates that 30% of this is wasted—on the order of $2.4 billion a day—that's too much to not find ways to deliver higher-quality care more efficiently. Like each of the speakers, he said that spending money wisely starts with learning what isn't working and then doing everything possible to minimize variation and maximize quality.

Pecora said looking backward at claims and outcomes to gain insights is hampered by billing codes that are overly broad and reveal too little about the specifics that affect outcomes, especially in cancer. Things like comorbidities, family history, genetic information—none of that is in the codes. Pecora then showed the attendees a picture of an apple with a grocery store bar code, which tracks where the apple was picked, its price, and where it was stored, as well as links to other databases. "When I saw this, it made me laugh," he said. "There's more information on the bar code of an apple than in your healthcare data."

At Hackensack Meridian, the quest has been to figure out how to build a bar code for oncology. Pecora explained that "bar code" is the foundation for COTA, the technology company that brings together oncologists and data scientists to build actionable data, which allows clinicians to make better decisions based on outcomes seen in similar patients. Key information from bulky records and physician notes is pressed into a numeric code, called the COTA Nodal Address,[3] or CNA. This becomes a precision medicine tool by folding in a patient's diagnosis, genomic status, tumor type, and the type of diagnostic test used. Using this tool, Hackensack has partnered with Horizon to develop a bundled payment model in oncology, which received overwhelming approval from the Physician-Focused Payment Model Technical Advisory Committee.[4]

Pecora walked the audience through examples from breast cancer to show how the tool allowed the health system to work with Horizon to produce data that identified the best treatments for certain types of patients, as well as outliers. "Once it's digitally mapped, it's not that hard," he explained. Yes, there are pathways for treating disease states but "not all diseases are the same. Not all patients are the same. Not all doctors treat the same disease the same way. And not all doctors treat the same disease the same way every time. The data show us this happens every day."

> **"Not all diseases are the same. Not all patients are the same. Not all doctors treat the same disease the same way. And not all doctors treat the same disease the same way every time. The data show us this happens every day."**
>
> —Andrew Pecora, MD, FACP, CPE,
> John Theurer Cancer Center, Hackensack Meridian Health

Finding where this occurs uncovers those human behaviors that lead to variation, deviations from quality care, and higher costs. "We're starting to think about this completely differently," Pecora said. As Karp would emphasize later, payers and health systems would rather not use tools, like prior authorization, to manage spending. "No one wants patients to not get the care they should get," Pecora said. "But can they do that and get care that's not wasteful?"

Creating a Change in Culture

Identifying where waste and poor-quality care are happening is only the first step. Preventing them demands a change to the organization's culture, which is what the OCM is designed to do, according to Alison. At its heart, she said, healthcare transformation is about developing a unified system of delivering care that ensures the integrity of the core processes, while finding efficiencies and lowering costs. Cancer care is constantly evolving, so transformation must do the same. "It is a journey, not a destination," she said. The components of the OCM demand that every person in the organization must be on board, from the leadership to the surgeons to the nursing staff to the front desk clerk who is trained to work with a patient who has just been told she has stage IV breast cancer.

A key feature of Regional Cancer Care Associates' (RCCA) implementation of the patient centered medical home is that it must »

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KARP

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be "payer agnostic," which means its care delivery model meets all the requirements of the OCM or other alternative payment models for commercial payers, as well as various accountable care organizations (ACOs) and other collaborative agreements. She showed a table with various measures from OCM, the Merit-based Incentive Payment System, the Oncology Medical Home from the National Committee for Quality Assurance,[5] and the Quality Oncology Practice Initiative from the American Society of Clinical Oncology.[6] RCCA met them all. This is essential given RCCA's footprint across 30 sites in 3 states. A single model of care "harmonizes not only the people of RCCA but promotes a common goal and objective of providing the highest and safest standardized care in the provision of oncology services outside the walls of the hospital," according to information from Alison's presentation.

As examples, Alison said she works with the staff on processes so that time with patients is not spent looking at the computer and updating the electronic health record. Because of the OCM's focus on palliative care, "We have trained our staff to state the conversation about the end of life and what their wishes are," Alison said. "It's our duty as clinicians to honor their wishes."

RCCA measures improvement with reductions in emergency department (ED) visits and readmissions, measurable improvements in patient experience, and increased bonus payments.

Consolidating the Data

Isola, from Mount Sinai, agreed that changing the culture starts with the faculty. "You need those faculty believing in the common mission," he said. Developing clinical ways, determining standards of care, establishing patient conferences, operating tumor boards, integrating clinical trials, and weaving information technology (IT) throughout mean the faculty must "buy in" to healthcare transformation from top to bottom. The role of IT in consolidation data and creating a dashboard to measure progress is crucial. "Data can standardize your operations and support your practices, projecting what your cost of delivering care is," he said, which leads to the development of contracts for value-based care.

He showed what color-coded dashboards under the OCM look like and how they helped Mount Sinai identify avoidable admissions among patients with cancer. Mount Sinai now directs patients with neutropenia into a 24-hour ambulatory care center instead of sending them to the ED, for example. Social determinants play a huge role in who ends up in the ED or the hospital. "Not that these are easy things to change, but they are easy to identify," Isola said. Data point out the need for more investment in social workers who can help these patients deal with housing, hunger, or other stressors.

Mount Sinai fell short of savings targets for the first 2 evaluation periods under the OCM, but the knowledge it gained from looking at data brought dramatic improvement between the second half of 2016 and the first half of 2017. "We're moving in the right direction," Isola said.

Making Payment Models Prospective

Payment on volume is not where healthcare wants to be, Karp said. But he acknowledged that having volume allows Horizon, New Jersey's largest insurer, with 50% of the market, to take on innovations that would not be possible without 3.8 million members. Today, around 4100 physicians and 800,000 members are in some sort of value-based arrangement, he said.

When Horizon embarked on its movement toward value-based care a decade ago, getting specialists to join the primary care physicians was not easy. The first step to bring the 2 groups together was bundled payments, which Karp said included an underlying fee-for-service payment with targets around quality and an upside bonus. Today, more than 1000 specialists have signed on and Horizon has seen $45 million in savings, with half going back to the physicians. Next came ACOs, and Horizon contracts with 8 throughout New Jersey.

The big step was the OMNIA Health Alliance,[7] a controversial step in which Horizon formed partnerships with 6 health systems and a large physician practice to enter into long-term value-based partnerships that included data sharing, along with financial terms that called for the partners to accept lower reimbursements in exchange for anticipated patient volume. "These were not standard hospital contracts," Karp told the IVBM audience. He said Horizon wanted partners with the same vision and that there's been significant progress.

How do Horizon's efforts apply to oncology? Karp began with a snapshot of spending trends by cancer type and the bad news that higher spending is not necessarily bringing better quality. Increased spending is being driven by demographic shifts, new treatments and genomic testing, and more imaging. According to his presentation, of the $2.8 billion that Horizon spent on oncology claims in 2017, breast cancer accounted for 17.4%, followed by skin cancer (11.5%), prostate cancer (9.3%), pulmonary (7.9%), and lymphoma (5.9%). There are still significant disparities in cancer screening, which Karp said Horizon is working to address through direct contact with employers by offering screenings at the workplace; Horizon does additional outreach through community relationships and through social media.

Karp also discussed the new payment models that will leverage the data gathered with COTA, which will take effect on January 1, 2019. "We have used claims data to build our bundles, but we didn't have the clinical data available to us," he said. "Now, we do." Combining the sets will provide "a much more sophisticated view of the of how the bundle was built."

But Karp said the better modeling is only one piece of convincing physicians to take on more risk. Building trust is just as important. "We can't do this if we have a relationship that we used to have, where we pay the bills and we argue over contract rates. That's not the way it works. We work collaboratively. We have meetings weekly, monthly. We develop things together with our provider partners. That's the only way it's going to work." ◆

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Nobel Prize Recognizes Discoveries With T Cells in Immunotherapy

Mary Caffrey

ALLISON

James P. Allison, PhD, is chair of the Department of Immunology, and director of the Parker Institute, and executive director of the Immunotherapy Platform, The University of Texas MD Anderson Cancer Center.

HONJO

Tasuku Honjo, MD, PhD, is a professor in the Department of Immunology and Genomic Medicine, Kyoto University, Japan.

TWO SCIENTISTS WHO SEPARATELY uncovered mechanisms that block key proteins and allow the immune system to attack cancer, creating a new way to fight the disease, were awarded the 2018 Nobel Prize in Physiology or Medicine on October 1, 2018.

James P. Allison, PhD, of The University of Texas MD Anderson Cancer Center, and Tasuku Honjo, MD, PhD, of Kyoto University in Japan, were honored by the Nobel Assembly at Karolinska Institute in Sweden for work performed in the 1990s, which has resulted in FDA-approved therapies in the last decade.[1]

Immunotherapy represents a new pillar in cancer treatment, alongside chemotherapy, surgery, and radiation. More than a century after scientists first conceived harnessing the body's immune system to attack cancer cells, Allison and Honjo pushed science past the tipping point to develop the first commercial treatments that rely on this idea.

What makes immunotherapy such a game-changer, Allison said during a news conference in New York City, is that when patients achieve a durable response, it can last for years. For some, he said, the word "cure" is appropriate.

Called checkpoint therapy, such treatments act as accelerators that activate T cells, the white blood cells that send the immune system into battle, or as brakes, blocking the proteins that stop the T cells in their tracks. As the Nobel Assembly discussed in its announcement, "This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues."[1]

Allison, then at the University of California at Berkeley, was among scientists studying cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). But while others looked at its potential in autoimmune disease, he looked at the potential in cancer. His lab resolved the issue of how the protein blocked the activation of T cells, which was by opposing the stimulation needed from CD28 proteins. In experiments with mice, Allison showed that blocking CTLA-4 could boost T-cell responses. At first, tumors in the mice appeared to be progressing, but as Allison told the *Journal of Clinical Investigation* in 2015, the tumors for some mice stopped growing. "In the ones that had stopped, some of the tumors started necrosing, and they just went away."[2]

His report in *Science* in 1996[3] eventually led to the development of ipilimumab. Allison worked with Princeton, New Jersey–based biotech firm Medarex to develop the human monoclonal antibody. Bristol-Myers Squibb (BMS) later acquired Medarex, and in 2011, the FDA approved ipilimumab, the first therapy of its kind.[4] Now sold as Yervoy, it was the first drug to extend the survival of patients with late-stage metastatic melanoma; study results show that 20% of the patients treated with ipilimumab live at least 3 years and many have lived 10 years.

Ipilimumab has been used in combination with therapies developed to target the protein that Honjo first studied in 1992, the programmed cell death protein 1 (PD-1), also expressed on the surface of T cells.[1] In a series of experiments at Kyoto University, Honjo showed that PD-1 also functions as a brake, but with a different mechanism. However, it took Honjo and his colleagues more than a decade to fully understand how this mechanism worked. In time, Honjo and a group led by Freeman et al, identified a ligand involved, programmed death-ligand 1 (PD-L1), raising the possibility that some tumors may use PD-L1 to inhibit an anti-tumor immune response. A 2005 paper by Honjo's group showed that PD-1 inhibition may produce antitumor effects that are even more efficient than CTLA-4 and with fewer adverse effects.[5]

The work by Honjo's team led directly to the development of nivolumab (Opdivo, BMS), which received approval in Japan in July 2014 and FDA approval in December 2014[6]; a second PD-1 inhibitor, pembrolizumab (Keytruda, Merck) received FDA approval in September 2014.[7] One famous patient treated with pembrolizumab is former President Jimmy Carter, who celebrated his 94th birthday the same day the Nobel Prize was announced.[8]

Checkpoint therapy involving PD-1 inhibition is now approved to treat several types of cancer, including lung and renal cancer and lymphoma, besides melanoma. Many more clinical trials are underway involving many cancer types, including trials involving combination therapy. The next frontier is finding biomarkers to help pair these therapies with patients who will respond best to the drugs and to develop strategies to avoid adverse effects.

From his earliest experiments, Allison has strived to understand why these therapies work in some patients and not others, and he does this today through MD Anderson's Moon Shots program, which analyzes tumor samples before, during, and after treatment.[9] Honjo's work also points out the importance of basic science, as his team was not searching for a pharmaceutical target when it discovered PD-1.

Allison was attending an immunotherapy conference when his son called at 5:30 AM with the news. He said the recognition of the Nobel Prize will spread the message to patients with cancer that while other forms of treatment are still viable, combining them with immunotherapy offers the possibility of a cure for more people, even though there's much work for scientists to do.

"We need these drugs to work for more people," Allison said. "One challenge is that the clinical success has outrun our scientific knowledge of how these drugs work and how they might best be combined with other therapies to improve treatment and reduce unwanted side effects. We need more basic science research to do that."

In a statement from MD Anderson,[9] Allison thanked the patients who took part in early clinical trials. "I never dreamed my research would take the direction it has," he said. "It's a great, emotional privilege to meet cancer patients who've been successfully treated with immune checkpoint blockade. They are living proof of the power of basic science, of following our urge to learn and to understand how things work." ◆

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The Long Road: Nobel Prize Winner James Allison, PhD, Highlights the Value of Research

Allison Inserro

NOBEL PRIZE WINNER James Allison, PhD, pioneering T-cell researcher, said the award represents the triumph of science and shows the value of research, even if that work does not immediately lead to a scientific or commercial success.

The soft-spoken researcher is sharing the award with Tasuku Honjo, MD, PhD. Both men were awarded the Nobel Prize for Physiology or Medicine on October 1, 2018, for their separate, but related, discoveries that uncovered mechanisms that block key proteins and allow the immune system to attack cancer, creating a new way to fight the disease.

Allison's work led to checkpoint therapy, treatments that act as accelerators that activate T cells, the white blood cells that send the immune system into battle, or as brakes, blocking the proteins that stop the T cells in their tracks. The 70-year-old scientist is chair of the Department of Immunology, the Vivian L. Smith Distinguished Chair in Immunology, director of the Parker Institute for Cancer Research, and executive director of the Immunotherapy Platform at The University of Texas MD Anderson Cancer Center.

The day the Nobel Prize was announced, Allison spoke at a press conference in New York City held during the second day of the 4-day International Cancer lmmunotherapy Conference, run by the Cancer Research Institute, the Association for Cancer lmmunotherapy, the European Academy of Tumor Immunology, and the American Association for Cancer Research (AACR). Allison is a fellow of the AACR Academy and a former board member.

Allison said there are "somewhere on the order of 2000 clinical trials going on now with checkpoint inhibitors in combination with something else. And that something else is usually chosen just because a company owns it." There are very few combinations based on data, he said.

There are also not enough patients in clinical trials, and given that, whether the result is a clinical signal or not, samples should be collected from every patient, he said. "You can understand something about a signal by knowing what didn't happen," he said.

He also noted that he thought there was too much emphasis in grantmaking for researchers to state "what the relevance is." "How do you know what's going to be relevant or not?" he asked. "I think you should pick your problem, work on it, do the best work you can."

He spent his career studying cytotoxic T-lymphocyte antigen 4 (CTLA-4). His former lab at the University of California at Berkeley resolved the issue of how the protein blocked the activation of T cells, which was by opposing the stimulation needed from CD28 proteins. In experiments with mice, Allison showed that blocking CTLA-4 could boost T-cell responses. His work eventually led to the development of ipilimumab, now sold as Yervoy by Bristol-Myers Squibb.

Allison, who was woken with the news at 5:30 in the morning when his son called him, said he first started studying T cells in an immunology undergraduate course in Texas, about 50 years ago, when T cells had just been discovered. He asked the professor more about them after class, intrigued, and the professor replied that they float around the body and "do stuff."

"I asked, 'Well, how do they know what to do?' He said, 'I don't know. I don't know if they even exist,'" Allison recalled.

For deciding to make T cells his life's work, Allison will split the $1-million prize with Honjo.

Joining Allison at the conference was Jill O'Donnell-Tormey, PhD, the chief executive officer and director of scientific affairs at the Cancer Research Institute, who called Allison a "dyed-in-the-wool" immunologist and noted that no one was interested in his work in the beginning.

Crystal Mackall, MD, conference scientific planning committee member and director of both the Stanford Center for Cancer Cell Therapy and the Parker Institute for Cancer Immunotherapy, called Allison a "role model for all of us" and said the average citizen needs to know more about why society needs to invest in basic science. "You make fundamental discoveries and it takes a long time," said Mackall. But in the end, "you can cure people who are otherwise incurable."

Allison, O'Donnell-Tormey, Mackall, and Nina Bhardwaj, MD, PhD, conference co-chair and director of cancer immunotherapy, professor of medicine, and Ward-Coleman Chair in Cancer Research at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai, also spoke at the press conference about the future of immunotherapy.

Mackall and Bhardwaj echoed Allison's comments about picking combinations to study based on data and science. Regarding chimeric antigen receptor technology, Crystal said, "We are just scratching the surface of what is possible" and thinks adoptive T-cell technologies will be able to treat solid tumors in the future.

Personalized immunotherapy will require biomarkers, O'Donnell-Tormey said. The expression of programmed death-ligand 1 on tissues as adjunct biomarkers for the intervention of antibodies is one such example, said Bhardwaj. Understanding the tumor environment and landscape will also be key, she said.

Another exciting future development, Bhardwaj said, is the discovery of neoantigens, arising from a patient's specific mutations, which could help propel the creation of cancer vaccines and perhaps lead to cancer vaccines being combined with other methods.

Researchers are also focusing on understanding more about the concept of resistance, specifically T-cell resistance, and why they stop functioning, Mackell said. Bhardwaj said another type of resistance happens at the level of the tumor cells, where they learn to escape recognition by T cells.

"There's an awful lot of biology that still needs to happen," said O'Donnell-Tormey. She said the reason patients in clinical trials are asked to give so many biopsies is so that researchers have a grasp of what is happening at all phases, including before, during, and after treatment.

As for other predictions, Allison thinks that within the next 5 years some cancers are headed towards a 100% patient response, if they are given the right combinations. "Not many, but at least a few," he said.

With immunology becoming the fourth pillar of cancer treatment, Allison said it "is the only one that can work nicely with the other ones," and that has led to a shift in thinking. Instead of killing every last cancer cell, "just kill enough to let the immune system take it out," he said.

The organizations did not have any warning that Allison would be awarded the Nobel, said O'Donnell-Tormey. "We've been anticipating for 3 years that he would get it," she said. ◆

TREATING MYELOMA CAN SEEM LIKE A MARATHON

WOULD YOU TAKE OFF YOUR SHOE WHEN RUNNING A MARATHON?

Continuous treatment with a proteasome inhibitor (PI)–based regimen is associated with clinical benefits.[1] However, most patients who have had 1 prior therapy only receive PIs for 4 to 7 months.[2-4]

The NINLARO® (ixazomib) regimen extended PFS by ~6 months (median: 20.6 vs 14.7 months) vs the placebo regimen in patients with multiple myeloma who have received at least 1 prior therapy.[1*†]

Prescribe the all-oral NINLARO regimen for long-term‡ proteasome inhibition.

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.[1]

Important Safety Information

Warnings and Precautions

- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs occurred between Days 14-21 of each 28-day cycle and typically recovered to baseline by the start of the next cycle.
- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.
- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.
- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO. Women using hormonal contraceptives should also use a barrier method of contraception.

Adverse Reactions

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

Special Populations

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
- **Lactation:** Advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

Drug Interactions: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The placebo regimen included placebo+lenalidomide+dexamethasone.
†95% CI, 17.0-NE and 95% CI, 12.9-17.6, respectively; HR=0.74 (95% CI, 0.587-0.939); *P*=0.012.
‡**Defined as treatment to progression or unacceptable toxicity.**
NE=not evaluable; PFS=progression-free survival.

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Please see accompanying Brief Summary.

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NINLARO® (ixazomib) capsules
4mg | 3mg | 2.3mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION
NINLARO (ixazomib) capsules, for oral use

1 INDICATION

NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm^3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm^3 during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs).The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions.

The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

5.6 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.7 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using NINLARO. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with NINLARO and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Thrombocytopenia [*see Warnings and Precautions (5.1)*]
- Gastrointestinal Toxicities [*see Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [*see Warnings and Precautions (5.3)*]
- Peripheral Edema [*see Warnings and Precautions (5.4)*]
- Cutaneous Reactions [*see Warnings and Precautions (5.5)*]
- Hepatotoxicity [*see Warnings and Precautions (5.6)*]

6.1 CLINICAL TRIALS EXPERIENCE

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

The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO + Lenalidomide and Dexamethasone N=360			Placebo + Lenalidomide and Dexamethasone N=360		
System Organ Class / Preferred Term	**N (%)**			**N (%)**		
	All	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Infections and infestations						
Upper respiratory tract infection	69 (19)	1 (< 1)	0	52 (14)	2 (< 1)	0
Nervous system disorders						
Peripheral neuropathies*	100 (28)	7 (2)	0	77 (21)	7 (2)	0
Gastrointestinal disorders						
Diarrhea	151 (42)	22 (6)	0	130 (36)	8 (2)	0
Constipation	122 (34)	1 (< 1)	0	90 (25)	1 (< 1)	0
Nausea	92 (26)	6 (2)	0	74 (21)	0	0
Vomiting	79 (22)	4 (1)	0	38 (11)	2 (< 1)	0
Skin and subcutaneous tissue disorders						
Rash*	68 (19)	9 (3)	0	38 (11)	5 (1)	0
Musculoskeletal and connective tissue disorders						
Back pain	74 (21)	2 (< 1)	0	57 (16)	9 (3)	0
General disorders and administration site conditions						
Edema peripheral	91 (25)	8 (2)	0	66 (18)	4 (1)	0

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

*Represents a pooling of preferred terms

(Continued on next page)

Table 5: Thrombocytopenia and Neutropenia (pooled adverse event and laboratory data)

	NINLARO + Lenalidomide and Dexamethasone N=360		Placebo + Lenalidomide and Dexamethasone N=360	
	N (%)		N (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Thrombocytopenia	281 (78)	93 (26)	196 (54)	39 (11)
Neutropenia	240 (67)	93 (26)	239 (66)	107 (30)

Herpes Zoster

Herpes zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the physician's discretion. Patients treated in the NINLARO regimen who received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy:

Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no human data available regarding the potential effect of NINLARO on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher then those observed in patients receiving the recommended dose. Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. *Animal Data:* In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic (≥ 0.3 mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.6 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

8.2 Lactation: No data are available regarding the presence of NINLARO or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because the potential for serious adverse reactions from NINLARO in breastfed infants is unknown, advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: *Contraception* - Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Advise women using hormonal contraceptives to also use a barrier method of contraception.

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

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and 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.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis

10 OVERDOSAGE: There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising.

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their physician if these adverse reactions persist.

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

Peripheral Edema: Advise patients to contact their physicians if they experience unusual swelling of their extremities or weight gain due to swelling.

Cutaneous Reactions: Advise patients to contact their physicians if they experience new or worsening rash

Hepatotoxicity: Advise patients to contact their physicians if they experience jaundice or right upper quadrant abdominal pain

Other Adverse Reactions: Advise patients to contact their physicians if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura

Pregnancy: Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO and for 90 days following the final dose. Advise women using hormonal contraceptives to also use a barrier method of contraception. Advise patients to contact their physicians immediately if they or their female partner become pregnant during treatment or within 90 days of the final dose.

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLARO-hcp.com.

SEPT 2017 USO/IXA/15/0123(4)

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Coverage by Allison Inserro, Laura Joszt, Samantha DiGrande, Jaime Rosenberg, Mary Caffrey, and David Bai, PharmD

Oncologists have raised concerns about the effect of proposed Medicare fee schedules on complex patients.

ASCO: Proposed Medicare Payment Changes Could Hurt Quality Cancer Care

A NEW RULE IN THE Medicare Access and CHIP Reauthorization Act's 2019 Quality Payment Program (QPP) and the proposed 2019 Medicare Physician Fee Schedule (MPFS) could negatively affect the quality of cancer care for Medicare beneficiaries, according to the American Society of Clinical Oncology (ASCO).

In order to address its concerns, ASCO sent a letter[1] to the US House of Representatives Energy and Commerce Committee. In it, ASCO President Monica M. Bertagnolli, MD, FACS, FASCO, explained how the changes could limit the ability of high-performing providers to receive bonuses. She wrote that the changes raise "several questions about how oncology practices will be able to continue to provide the highest quality care for Medicare beneficiaries."

The proposed QPP rule increases the weight for the cost category under the Merit-based Incentive Payment System (MIPS) from 10% to 15%, without an updated methodology. ASCO is calling for a risk adjustment that accounts for the severity and variation of high-cost therapies when treating patients with cancer, Bertagnolli explained.

The MPFS is proposing a 4% cut in reimbursement for oncology services, a decrease in reimbursement for new Part B drugs, and an overhaul of evaluation and management coding that "does not reflect accurately services and resources practices deliver to complex patients," she wrote.

She goes on to explain that the reimbursement cut could mean oncology practices reduce some of the unpaid or underpaid services they provide to patients with cancer. "ASCO opposes the cuts in the proposed MPFS and believes they will harm Medicare beneficiaries with cancer, impede MIPS implementation, and risk access to appropriate anti-cancer therapies."

The end result of these proposals would be that the best performers would only receive a 2% bonus, rather than the 4% bonus authorized by law. Even if they met all necessary quality improvement and value requirements, providers and practices would see a decrease in their overall reimbursement for 2019.

The comment period on the proposed QPP ended on September 30, 2018. The comment period on the MPFS ended on September 10, 2018. ◆

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As MACRA heads toward third year, Congress urged to consider how proposed CMS changes will impact Medicare beneficiaries with cancer. American Society of Clinical Oncology website. asco.org/advocacy-policy/asco-in-action/macra-heads-toward-third-year-congress-urged-consider-how-proposed. Published July 31, 2018. Accessed August 12, 2018.

CMS Will Allow Medicare Advantage Plans to Use Step Therapy to Negotiate Drug Prices

THE TRUMP ADMINISTRATION IS ALLOWING Medicare Advantage (MA) plans to negotiate prices for Part B drugs by providing them the opportunity to create plans that use step therapy.

During a press call, CMS Administrator Seema Verma explained that this new tool will bring down the cost of drugs for America's seniors. She pitched the plan as giving patients the option to choose a plan that has them try more cost-effective drugs first before moving onto more expensive drugs. She gave the example that the plan would ensure a patient starts with a more cost-effective biosimilar before going on to a more costly biologic, if necessary.

"By allowing Medicare Advantage plans to negotiate for physician-administered drugs, like private-sector insurers already do, we can drive down prices for some of the most expensive drugs seniors use," HHS Secretary Alex Azar said in a statement.[1]

Dan Best, senior adviser to Azar for drug pricing reform, explained that MA Part B drugs represented about $11.9 billion in spending in 2017. The administration does not expect all plans will use these tools, therefore savings would be similar to what the private sector sees for utilizing step therapy: between 15% and 20%, on average. MA plans that implement step therapy will be able to use the tool to negotiate better prices for more expensive treatments, and CMS will allow these plans to negotiate Part B drug prices against competitors in Part D. MA currently covers 33% of all Medicare beneficiaries.

"Step therapy has the potential to lower drug spending and beneficiary costs," said AARP in a statement to *The American Journal of Managed Care®*. "However, any implementation of this proposal must include robust consumer protections, including extensive beneficiary education and outreach and meaningful improvements to existing exceptions and appeals processes. It's also noteworthy that any savings would be substantially larger if the secretary were granted the authority to negotiate on behalf of all of Medicare."

Step therapy is not uncommon in private-sector plans, and physicians will be familiar with these policies, Verma said. "It's unique that Medicare Advantage has not used this," she added.

Step therapy in MA plans can only be applied to new prescriptions, Verma explained, so patients who choose one of these plans will not have medications they are actively receiving be affected by the policy. However, some in the healthcare industry believe that step therapy, also known as fail first, can have a negative impact on patients. The Community Oncology Alliance (COA) called step therapy "dangerous" for patients with cancer. Step therapy would require patients to try cheaper, and usually older, treatments before they can try novel therapies that are more expensive.

According to COA, step therapy can also delay delivery of care and leave patients facing a life-threatening disease without access to the most immediate and life-saving treatments. "Cancer treatment is becoming more personalized, and not all therapies produce the identical result from patient to patient. Having therapy options is imperative to successful treatment," Jeff Vacirca, MD, FACP, president of COA and CEO of New York Cancer and Blood Specialists, said in a statement.[2] "CMS' action is the antithesis of where personalized cancer treatment is going. It's old-school cookbook medicine that treats every patient as one-size-fits-all. It's telling me to effectively sit back and let some middleman make treatment decisions for my patients."

The savings that plans accrue through these plans will largely need to be passed on to patients, according to Verma. Patients will see these savings through lower coinsurance and rewards programs, such as gift cards to patients.

"Does CMS truly believe that Medicare seniors will be enticed away from their physician-recommended treatment with the promise of a »

$50 Amazon giftcard?" asked Ted Okon, executive director of COA. "Allowing middlemen to profit off denying cancer patients needed medications is immoral and cruel."

Since MA plans can start offering plans with step therapy in 2019, patients might also see savings returned to them through lower premiums in 2020. MA plans that use step therapy will also be required to provide care coordination services that include discussing medication options with beneficiaries, providing beneficiaries with educational material and information about their medications, and implementing adherence strategies to their medication regimen.

"We look forward to seeing the results of this step toward tougher negotiation within Medicare and will continue efforts to expand negotiation tools throughout our programs," Azar said. ◆

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Amgen AMG 420 Finds Early Success in Patients With Relapsed and Refractory Multiple Myeloma

AMG 420, A BISPECIFIC T-CELL ENGAGER (BITE) from Amgen for the treatment of patients with relapsed and refractory multiple myeloma (RRMM), has found positive preliminary results in a phase 1 trial. The development of AMG 420 adds another contender to the immunotherapy category for treating MM.

In 2016, Amgen bought the BiTE platform from Boehringer Ingelheim.[1] BiTE combats cancer by directing T cells to destroy cancer cells. It consists of 2 single chain antibodies: one specific for B-cell maturation antigen (BCMA), a tumor antigen, and the other specific for CD3, a protein on the surface of T cells. By binding to BCMA and CD3, BiTE technology forms a bridge between the T cell and the tumor cell. This lets the T cell target the tumor cell, resulting in tumor cell lysis and reduced tumor burden and therefore halting the progression of the cancer.[1-3]

By 2018, AMG 420, an anti-BCMA BiTE product, was considered potentially beneficial in patients with RRMM. Preliminary results were reviewed, and findings showed that 5 patients on AMG 420 were able to obtain stringent complete responses, with 4 of the patients having negative minimal residual disease exceeding 10 months.[2] AMG 420 is still in phase 1 trials, but the positive results may streamline AMG 420 ahead into future clinical trials.

Another drug that has entered the MM drug development market is bb2121, an anti-BCMA chimeric antigen receptor (CAR) T drug developed by Celgene with bluebird bio, Inc, also designed to treat patients with RRMM. Although it was created to target the same population as AMG 420, bb2121 is a gene therapy. T cells extracted from the white blood cells of a patient are collected and genetically modified to recognize BCMA. They are then returned to the body of the patient, so they can target MM tumor cells that express the BCMA.[4]

Results from phase 1 study of bb2121 were revealed at the annual meeting of the American Society of Clinical Oncology in June. The overall response rate in the 18 patients with RRMM was 94%, with 56% (10 patients) having complete response. Nine of the 10 patients were also MRD-negative. At 40 weeks, the median duration of response and progression-free survival were not reached.[5] Currently, bb2121 is in phase 2 and 3 trials, for which Celgene and bluebird bio, Inc, had begun testing the efficacy and safety of bb2121 and comparing it with other treatment options for MM (NCT03361748, NCT0365112).

Right now, there is reason to believe that AMG 420 may have similar efficacy to bb2121 for treating patients with RRMM. But this assumption will not be verified until the results of longer-term data are available. The development of these new drugs in the field of MM is groundbreaking, and it will be very interesting to see where these drugs will fit within MM treatment guidelines. ◆

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FDA Accepts First Allogeneic CAR T-Cell Therapy Trial

CELYAD, A BIOPHARMACEUTICAL COMPANY that focuses on the development of chimeric antigen receptor (CAR) T-cell therapies, recently announced[1] that the FDA accepted its investigational new drug (IND) application for CYAD-101, the first non–gene-edited allogeneic clinical program.

Traditionally, CAR T-cell therapies are created by genetically modifying a patient's immune cells to target specific cancer cells before injecting them back into the patient. However, this can be difficult because researchers aren't always able to collect enough cells from a patient to create the treatment. Conversely, in an allogeneic CAR T-cell therapy, immune cells are collected from healthy donors, rather than the patient.

The Allo-SHRINK trial looks to evaluate the safety and clinical activity of CYAD-101 in patients with unresectable colorectal cancer in combination with standard chemotherapy. "We are pleased to have achieved this important milestone. Celyad is the first company clinically evaluating a non–gene-edited CAR T candidate, which, we believe, offers significant advantages over gene-edited approaches," Christian Homsy, MD, CEO of Celyad, said in a statement.

CYAD-101 is based on features of the company's investigational autologous CYAD-01 CAR T with a novel peptide, TCR Inhibiting Molecule (TIM). This prevents the patients' immune system from recognizing the cells as foreign. The cells in CYAD-01 produce a chimeric receptor, called natural killer group 2D (NKG2D), that recognizes multiple tumor proteins.

Celyad's investigational autologous CYAD-01 treatment is currently being tested in 3 phase 1 trials for different cancers, including SHRINK,[2] which is investigating increasing doses of CYAD-01 with chemotherapy in patients with colorectal cancer whose liver metastasis can be removed by surgery; LINK,[3] which is examining increasing doses of CYAD-01 in patients with colorectal cancer with liver metastases that cannot be removed by surgery; and THINK,[4] which is evaluating CYAD-01 in 7 types of refractory cancers, including 5 solid tumors.

"Our non–gene-edited program consists of a family of technologies aimed at reducing or eliminating T-cell receptor (TCR) signaling without requiring genetic manipulation. CYAD-101 is part of a robust clinical development plan, establishing the foundations of next-generation CAR T products," said Homsy. ◆

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Coverage by Allison Inserro, Laura Joszt, Samantha DiGrande, Jaime Rosenberg, Mary Caffrey, and David Bai, PharmD

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Cancer Screening Rates in the US Fall Short of Healthy People 2020 Targets

WITH HEALTHY PEOPLE 2020 goals of achieving health equity, eliminating disparities, and improving the health of all groups, cancer screening plays an integral role in achieving these goals. However, cancer screening rates in the United States fall short of these targets and significant disparities exist among subgroups, according to CDC data.[1]

The agency's research focused on breast, cervical, colorectal, and prostate cancers, as these accounted for nearly 40% of new cancer diagnoses and close to 20% of cancer deaths in 2013. Among the goals of Healthy People 2020 are increasing the proportion of women aged 21 to 65 years screened for cervical cancer, women aged 50 to 74 years screened for breast cancer, and men and women aged 50 to 75 years screened for colorectal cancer. Their goals also include reducing prostate cancer deaths.

Although screening rates were high, they fell short of the Healthy People 2020 targets of 93% for Pap tests and 81% for mammography.

Using the National Health Interview Study, researchers collected data from participants on Papanicolaou (Pap) tests, hysterectomies, mammograms, prostate-specific antigen (PSA) tests, and endoscopic exams and fecal occult blood tests (FOBTs) screening for colorectal cancer. Women were considered to have been screened recently for breast cancer if they had a mammogram within 2 years and screened for cervical cancer if they had a Pap test within 3 years.

Having an FOBT within the past year, a flexible sigmoidoscopy within 5 years and an FOBT within 3 years, or a colonoscopy within 10 years signified a recent colorectal cancer screening. The authors noted that at the time of analysis, the US Preventive Services Task Force (USPSTF) was following its 2012 guideline that recommended against routine PSA screening.

Of the 83% of women who received a recent Pap test, women aged 21 to 30 and women aged 51 to 60 years were less likely to have been screened. More than two-thirds (71.7%) also reported having a recent mammogram. Similar to Pap testing, mammography testing was least likely among those aged 50 to 64 years. Although screening rates were high, they fell short of the Healthy People 2020 targets of 93% for Pap tests and 81% for mammography. For colorectal screening, 63.4% of women and 61.9% of men reported having a recent screening, falling below the target of 80%. Across the 3 screening methods, having less than a high school education, having no usual source of care, having public insurance, and being underinsured were associated with lower testing rates.

Among men, 35.8% reported having a recent PSA test in the past year.

Between 2000 and 2015, Pap test use declined by 4.3% among women with a usual source of care and mammography rates declined by 3%. Only use of colorectal cancer screening has increased significantly and consistently, rising 25.1% among women between 2000 and 2010. Rates stayed stable between 2010 and 2013 and then increased slightly in 2015. Colorectal cancer screening among men also increased significantly.

Use of a PSA test declined by 9.2% from 2008 to 2013 but remained stable between 2013 and 2015. The authors noted that this drop can be attributed to USPSTF's recommendation against routine screening and, subsequently, a drop in the test being offered by physicians and used by patients. Earlier this year, USPSTF updated their recommendation,[2] calling for men aged 55 to 69 years to make their own decision on whether to be screened periodically for prostate cancer after they have had a conversation with their physician on potential benefits and harms.

"One approach to improving screening use across all subgroups would be for physicians to recommend screening to all age-appropriate patients, including traditionally underserved groups," they wrote. They add that physician enthusiasm and outreach with tailored or innovative strategies to educate and inform may increase knowledge and intention to screen among these underserved groups. ◆

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PARP Inhibitor Increases PFS Over Chemotherapy in Advanced Breast Cancers, Study Finds

A RECENT STUDY[1] FOUND that the poly (ADP-ribose) polymerase (PARP) inhibitor talazoparib extended progression-free survival (PFS) and improved quality of life over chemotherapies for patients with metastatic human epidermal growth factor 2–negative breast cancer and mutations in the *BRCA 1/2* genes.

The results of the EMBRACA trial, an international randomized phase 3 study led by researchers at The University of Texas MD Anderson Cancer Center, were recently published in the *New England Journal of Medicine*. Researchers enrolled 431 patients with locally advanced or metastatic and hereditary *BRCA 1/2* gene mutations in the study. Participants were randomized 2:1 to receive either talazoparib (n = 287) or a physician's choice of single-agent therapy (n = 144), which was either capecitabine, eribulin, gemcitabine, or vinorelbine. Of the patients enrolled in the trial, 54% had hormone receptor–positive disease and 46% had triple-negative breast cancer; *BRCA 1* and *BRCA 2* mutations were split at 45% and 55%, respectively.

"The trial found that talazoparib provides a significant clinical benefit to all patient subgroups, including those with hormone receptor–positive and triple-negative disease," Jennifer Litton, MD, associate professor of breast medical oncology and the corresponding author of the study, said in a statement.[2] "The results of this trial are quite exciting and indicate talazoparib is a novel treatment option for patients with metastatic breast cancer and *BRCA* mutations."

Notably, the primary endpoint of PFS was met in the talazoparib arm, as the median PFS was 8.6 months in the talazoparib cohort and 5.6 months in physician's choice. Researchers evaluated time to deterioration of overall health as the secondary endpoint of the study. Patient-reported quality-of-life measures found a greater time to deterioration of overall health in the talazoparib arm compared with the physician's choice arm: 24.3 versus 6.3 months. »

"It is encouraging to see this oral PARP inhibitor was well tolerated and superior to chemotherapy alone," said Litton. To follow up the positive results of this trial, researchers have already begun a phase 1 study evaluating talazoparib combination treatment. ◆

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USPSTF Updates Cervical Cancer Screening Recommendations

WHAT TYPE OF CERVICAL cancer screening should a woman get, if any, and how often? The latest recommendation[1] from the United States Preventive Services Task Force (USPSTF) said in August that it depends on a woman's age and other factors, but those 30 or older have a new option.

The number of deaths[2] from cervical cancer in the United States has decreased since widespread cervical cancer screening began, falling to 2.3 from 2.8 deaths per 100,000 women. Still, 4170 will die from the disease this year, according to the American Cancer Society. Most will not have been adequately screened.

To update its 2012 recommendation, the USPSTF reviewed evidence on screening for cervical cancer, looking at clinical trials and cohort studies that evaluated screening with high-risk human papillomavirus (hrHPV) testing[3] alone or together with hrHPV using a cytology-based Papanicolaou (Pap) smear, where cells are scraped from the back of the cervix. The 2 tests together are called cotesting.

As over 99% of all cervical cancers are associated with HPV, testing for the infection has been touted as an alternate option for cervical cancer screening.

For women aged 30 to 65, there are 2 options: screening by either a Pap test every 3 years or a Pap and hrHPV test every 5 years. The recommendation is a slight change from draft guidelines, which recommended that women get just 1 test, instead of a co-test. Overall, the USPSTF gave an "A" recommendation to screening women aged 21 to 65 years, but did not recommend testing for those younger than 21 or older than 65. For women aged 21 to 30, screening should be done by a Pap test every 3 years.

Under current law, preventive services receiving an A or B grade must be covered by most private insurance plans, with no co-pay for patients. Other screening tests and services with different grades are up to the payer.

As over 99% of all cervical cancers are associated with HPV, testing for the infection has been touted as an alternate option for cervical cancer screening. Previous research has indicated that HPV testing alone or combined with a Pap smear is linked to increased detection of precancerous lesions in the first screening round, followed by a subsequent reduction in precancerous lesions.

In a joint statement, 3 of the nations' top women's healthcare groups called the recommendation "largely in line" with clinical guidance with their own.

"With a number of screening options now available, the new guidelines emphasize the importance of the patient–provider shared decision-making process to assist women in making an informed choice about which screening method is most suitable for them," said the statement[4] from the American College of Obstetricians and Gynecologists (ACOG), the Society of Gynecologic Oncology, and the ASCCP. "However, more importantly, there needs to be a continued effort to ensure all women are adequately screened, because a significant number of women in the country are not. It's also essential for women to have access to all of the tests and that they are appropriately covered by insurance companies."

Discussion about insurance coverage[5] of the tests based on USPSTF recommendations was a source of lively discussion at a session of the annual meeting of ACOG earlier this year.

Screening women who have had a hysterectomy with removal of the cervix for indications other than a high-grade precancerous lesion or cervical cancer does not offer any benefit, the USPSFT said. ◆

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Ivosidenib Is Approved for Relapsed, Refractory Acute Myeloid Leukemia in Patients With Genetic Mutation

THE FDA HAS APPROVED ivosidenib, the first targeted therapy for the treatment of relapsed or refractory acute myeloid leukemia (AML) in patients with specific mutations in the isocitrate dehydrogenase-1 (*IDH1*) gene. Ivosidenib, a tablet to be sold as Tibsovo by Agios Pharmaceuticals, was approved July 20, 2018, for use with an FDA-approved companion diagnostic.

"Tibsovo is a targeted therapy that fills an unmet need for patients with relapsed or refractory AML who have an *IDH1* mutation," said Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.[1] "The use of Tibsovo is associated with a complete remission in some patients and a reduction in the need for both red cell and platelet transfusions."

Ivosidenib is an IDH1 inhibitor, which means it works to decrease abnormal production of oncometabolite 2-hydroxyglutarate (2-HG), which causes the differentiation of malignant cells. Patients who are found to have the *IDH1* mutation in their blood or marrow sample would be considered for the therapy. The FDA also approved the RealTime IDH1 Assay to detect the genetic mutation.

Approval of ivosidenib was based on results from a single-arm trial of 174 patients, and those results showed that 32.8% of the patients had a compete response or a partial hematologic recovery that lasted a median of 8.2 months. Of the 110 patients who required blood or platelet transfusion due to AML when the study began, 37% went at least 56 days without needing a transfusion after taking the study drug.

Coverage by Allison Inserro, Laura Joszt, Samantha DiGrande, Jaime Rosenberg, Mary Caffrey, and David Bai, PharmD

Results were also presented at the June meeting of the American Society of Clinical Oncology and published in the *New England Journal of Medicine*,[2] which noted the drug had few adverse effects (AEs) of grade 3 or higher. Common AEs were fatigue, an increase in white blood cells, joint pain, diarrhea, shortness of breath, swelling in the arms or legs, nausea, and pain or sores in the mouth or throat.

AML forms in the bone marrow and progresses quickly to increase the number of abnormal white blood cells in the bone marrow and bloodstream. According to the National Cancer Institute, 19,520 patients will receive an AML diagnosis this year and 10,670 will die of it in 2018. ◆

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UK Knocks Down Yescarta as CAR T Therapy Gains European Authorization

CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy axicabtagene ciloleucel, sold as Yescarta, was authorized[1] in August 2018 by the European Commission (EC) as a treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy. This approval allows Yescarta to be available for use in the 28 countries of the European Union, as well as Norway, Iceland, and Liechtenstein.

The marketing authorization application was approved based on data from the ZUMA-1 trial that investigated axicabtagene ciloleucel in adult patents with refractory aggressive non-Hodgkin lymphoma. In the single-arm trial that enrolled 101 participants, 72% of patients (n = 73) who received a single infusion of axicabtagene ciloleucel responded to therapy, with 51% (n = 52) achieving a complete response.

There are currently 2 CAR T-cell therapies available on the market, and although both treatments have many benefits, they come at a steep price. Yescarta carries a US price tag of $373,000,[2] and tisagenlecleucel (Kymriah), which treats pediatric and adult B-cell acute lymphoblastic leukemia, comes at the hefty price of $475,000 for a 1-time dose.[3]

Just 1 day after the EC approved the treatments, the National Institute for Health and Care Excellence (NICE) deemed Yescarta too expensive to justify placing it on Britain's state-funded health service.[4] Although Yescarta was "an exciting innovation in very difficult to treat cancers, with a promise of a cure for some patients," the price was too high for it to be considered cost-effective, said Meindert Boysen, PharmD, MSc, director, Centre for Health Technology Evaluation at NICE. The United Kingdom list prices of the drugs have yet to be disclosed.

The developer of Yescarta, Gilead, said in a statement that it was in "ongoing discussions with NICE to identify appropriate treatment comparators which can clarify how cell therapy may be made available to patients in the [United Kingdom]." NICE's evaluation of the cost-effectiveness of Kymriah is still ongoing.

Kymriah was the first CAR T-cell therapy approved in August 2017,[5] and Yescarta followed shortly thereafter in October 2017.[6] ◆

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Abemaciclib Halts Tumor Growth in Ewing Sarcoma

A RECENT STUDY EVALUATED abemaciclib (Verzenio) in a preclinical model of Ewing sarcoma (ES), a rare and highly malignant cancer that occurs in the bone and surrounding tissue of children and adolescents.

Currently, abemaciclib is approved as a monotherapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 *(HER2)*-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy. It also holds indications to treat metastatic or advanced HR-positive, *HER2*-negative breast cancer in combination with an aromatase inhibitor; or plus fulvestrant. Now, researchers are looking to evaluate its effectiveness in ES.

Traditionally, ES treatment includes surgery, radiation, and high dose chemotherapy, which has improved outcomes for patients with localized disease and who have achieved a 5-year overall survival of 50% to 70%. However, in the recurrent or metastatic setting, the 5-year survival rate drops to below 30%.

Researchers characterized in vitro responses of ES cell lines to abemaciclib using various assays and high content imaging. After this was complete, abemaciclib was investigated in vivo in cell line–derived and patient-derived xenograft mouse models of ES as either a monotherapy or in combination with chemotherapy.

The study found that cancer cell lines most sensitive to abemaciclib were previously shown to have D-type cyclin activating features (DCAF). In a large cell line panel consisting of both adult and pediatric tumor cells, 50.0% of ES cell lines and 40.7% of other tumor cell lines with DCAF were highly sensitive to abemaciclib.

Additionally, abemaciclib inhibited tumor growth either alone or in combination with chemotherapy in multiple ES xenograft models. The researchers noted that abemaciclib exhibits a unique mechanism of action that spans cell cycle blockade, DNA demethylation, and activation of the adaptive immune response in an ES model.

"While our data strongly support evaluation of abemaciclib in immune-competent ES models, development of such models has proved elusive," the study authors wrote.

After the conclusion of this study, researchers recommended that future studies of abemaciclib should include additional preclinical models of adult and pediatric malignancies. ◆

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TIBSOVO® IS THE FIRST AND ONLY ORAL, NONCYTOTOXIC THERAPY THAT TARGETS MUTATED *IDH1* IN RELAPSED OR REFRACTORY AML

A single agent for a small population with high clinical unmet need

The pivotal trial for TIBSOVO was an open-label, single-arm, multicenter trial. Patients with R/R AML and an *IDH1* mutation were assigned a starting dose of TIBSOVO 500 mg daily and received treatment until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Efficacy was established based on the rate and duration of CR+CRh, as well as on the rate of conversion from transfusion dependence to transfusion independence.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 34 patients who experienced differentiation syndrome, 27 (79%) recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

agios

TIBSOVO (ivosidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

In a population with difficult-to-treat disease, TIBSOVO delivered strong and durable responses[1]

- **33%** of patients (57/174) achieved CR or CRh (95% CI, 25.8-40.3)
- Median duration of CR+CRh: **8.2 months** (95% CI, 5.6-12)[a]
- **37%** of patients who were transfusion dependent at baseline (41/110) became transfusion independent[b]

*Visit **TibsovoPro.com** to learn more*

[a]Duration of response was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.[1]
[b]Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO. Patients were defined as transfusion independent if they became independent of RBC and platelet transfusions during any 56-day postbaseline period.[1]
CR, complete remission, defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts >1000/microliter); CRh, complete remission with partial hematological recovery, defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and absolute neutrophil counts >500/microliter); RBC, red blood cell; R/R, relapsed or refractory.[1]

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) of any grade were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolonged (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%).
- The most frequently reported ≥Grade 3 adverse reactions (≥5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%).
- Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

Please see brief summary of full Prescribing Information on following pages, including Boxed WARNING.

Reference: 1. TIBSOVO [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

TIBSOVO® (ivosidenib) 250 mg tablets

TIBSOVO® (ivosidenib tablets), for oral use
BRIEF SUMMARY: Please see package insert for full Prescribing Information.

WARNING: DIFFERENTIATION SYNDROME
Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

INDICATIONS AND USAGE

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the treatment of AML with TIBSOVO based on the presence of IDH1 mutations in the blood or bone marrow. Patients without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse. Information on FDA-approved tests for the detection of IDH1 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage

The recommended dose of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Administer TIBSOVO with or without food. Do not administer TIBSOVO with a high-fat meal because of an increase in ivosidenib concentration. Do not split or crush TIBSOVO tablets. Administer TIBSOVO tablets orally about the same time each day.

If a dose of TIBSOVO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Monitoring and Dose Modifications for Toxicities

Assess blood counts and blood chemistries prior to the initiation of TIBSOVO, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Monitor blood creatine phosphokinase weekly for the first month of therapy. Monitor electrocardiograms (ECGs) at least once weekly for the first 3 weeks of therapy and then at least once monthly for the duration of therapy. Manage any abnormalities promptly.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dose modification guidelines.

Table 1. Recommended Dose Modifications for TIBSOVO

Adverse Reactions	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume TIBSOVO when signs and symptoms improve to Grade 2* or lower.
• Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved.
• QTc interval greater than 480 msec to 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt TIBSOVO. • Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.
• QTc interval greater than 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt TIBSOVO. • Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified.
• QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue TIBSOVO permanently.
• Guillain-Barré syndrome	• Discontinue TIBSOVO permanently.
• Other Grade 3* or higher toxicity considered related to treatment	• Interrupt TIBSOVO until toxicity resolves to Grade 2* or lower. • Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue TIBSOVO.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Dose Modification for Use with Strong CYP3A4 Inhibitors

If a strong CYP3A4 inhibitor must be coadministered, reduce the TIBSOVO dose to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: In the clinical trial, 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. Of the 34 patients who experienced differentiation syndrome, 27 (79%) recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Of the 258 patients treated with TIBSOVO in the clinical trial, 9% were found to have a QTc interval greater than 500 msec and 14% of patients had an increase from baseline QTc greater than 60 msec. One patient developed ventricular fibrillation attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes.

In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome occurred in < 1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

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

- Differentiation Syndrome
- QTc Interval Prolongation
- Guillain-Barré Syndrome

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 safety profile of single-agent TIBSOVO is based on experience in 179 adults with relapsed or refractory AML treated with 500 mg daily. The median duration of exposure to TIBSOVO was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to TIBSOVO for at least 6 months and 16 patients (9%) were exposed for at least 1 year.

Serious adverse reactions (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%), and dyspnea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%). Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

The most common adverse reactions (≥ 20%) of any grade were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation. Adverse reactions reported in the trial are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Relapsed or Refractory AML

	TIBSOVO (500 mg daily) N=179	
Body System Adverse Reaction	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood System and Lymphatic System Disorders		
Leukocytosis[1]	68 (38)	15 (8)
Differentiation Syndrome[2]	34 (19)	23 (13)
Gastrointestinal Disorders		
Diarrhea	60 (34)	4 (2)
Nausea	56 (31)	1 (1)
Mucositis[3]	51 (28)	6 (3)
Constipation	35 (20)	1 (1)
Vomiting[4]	32 (18)	2 (1)
Abdominal pain[5]	29 (16)	2 (1)
General Disorders and Administration Site Conditions		
Fatigue[6]	69 (39)	6 (3)
Edema[7]	57 (32)	2 (1)
Pyrexia	41 (23)	2 (1)
Chest pain[8]	29 (16)	5 (3)
Investigations		
Electrocardiogram QT prolonged	46 (26)	18 (10)
Metabolism and Nutrition Disorders		
Decreased appetite	33 (18)	3 (2)
Tumor lysis syndrome	14 (8)	11 (6)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[9]	64 (36)	8 (4)
Myalgia[10]	33 (18)	1 (1)
Nervous System Disorders		
Headache	28 (16)	0
Neuropathy[11]	21 (12)	2 (1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough[12]	40 (22)	1 (<1)
Dyspnea[13]	59 (33)	16 (9)
Pleural effusion	23 (13)	5 (3)
Skin and Subcutaneous Tissue Disorders		
Rash[14]	46 (26)	4 (2)
Vascular Disorders		
Hypotension[15]	22 (12)	7 (4)

[1] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[2] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[3] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[4] Grouped term includes vomiting and retching.
[5] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[6] Grouped term includes asthenia and fatigue.
[7] Grouped term includes peripheral edema, edema, fluid overload, fluid retention, and face edema.
[8] Grouped term includes angina pectoris, chest pain, chest discomfort, and non-cardiac chest pain.
[9] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[10] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[11] Grouped term includes ataxia, burning sensation, gait disturbance, Guillain-Barré syndrome, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, and sensory disturbance.
[12] Grouped term includes cough, productive cough, and upper airway cough syndrome.
[13] Grouped term includes dyspnea, respiratory failure, hypoxia, and dyspnea exertional.
[14] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.
[15] Grouped term includes hypotension and orthostatic hypotension.

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 3.

Table 3: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML[1]

	TIBSOVO (500 mg daily) N=179	
Parameter	**All Grades n (%)**	**≥ Grade 3 n (%)**
Hemoglobin decreased	108 (60)	83 (46)
Sodium decreased	69 (39)	8 (4)
Magnesium decreased	68 (38)	0
Uric acid increased	57 (32)	11 (6)
Potassium decreased	55 (31)	11 (6)
Alkaline phosphatase increased	49 (27)	1 (1)
Aspartate aminotransferase increased	49 (27)	1 (1)
Phosphate decreased	45 (25)	15 (8)
Creatinine increased	42 (23)	2 (1)
Alanine aminotransferase increased	26 (15)	2 (1)
Bilirubin increased	28 (16)	1 (1)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

DRUG INTERACTIONS

Effect of Other Drugs on Ivosidenib

Strong or Moderate CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of TIBSOVO with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations. • Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation.
Prevention or Management	• Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with TIBSOVO. • If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO to 250 mg once daily. • Monitor patients for increased risk of QTc interval prolongation.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of TIBSOVO with strong CYP3A4 inducers decreased ivosidenib plasma concentrations.
Prevention or Management	• Avoid co-administration of strong CYP3A4 inducers with TIBSOVO.
QTc Prolonging Drugs	
Clinical Impact	• Co-administration of TIBSOVO with QTc prolonging drugs may increase the risk of QTc interval prolongation.
Prevention or Management	• Avoid co-administration of QTc prolonging drugs with TIBSOVO or replace with alternative therapies. • If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Effect of Ivosidenib on Other Drugs

Ivosidenib induces CYP3A4 and may induce CYP2C9. Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease the concentrations of drugs that are sensitive CYP2C9 substrates. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during TIBSOVO treatment. Do not administer TIBSOVO with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy. Co-administration of TIBSOVO may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving TIBSOVO. If co-administration of TIBSOVO sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, TIBSOVO may cause fetal harm when administered to a pregnant woman. There are no available data on TIBSOVO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of ivosidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 2 times the steady state clinical exposure based on the AUC at the recommended human dose (*see Data*). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Ivosidenib administered to pregnant rats at a dose of 500 mg/kg/day during organogenesis (gestation days 6-17) was associated with adverse embryo-fetal effects including lower fetal weights, and skeletal variations. These effects occurred in rats at approximately 2 times the human exposure at the recommended dose of 500 mg daily.

In pregnant rabbits treated during organogenesis (gestation days 7-20), ivosidenib was maternally toxic at doses of 180 mg/kg/day (exposure approximately 3.9 times the human exposure at the recommended dose of 500 mg daily) and caused spontaneous abortions as well as decreased fetal weights, skeletal variations, and visceral variations.

Lactation

Risk Summary

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

Pediatric Use

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

Geriatric Use

One hundred and twelve (63%) of the 179 patients with relapsed or refractory AML in the clinical study were 65 years of age or older and 40 patients (22%) were 75 years or older. No overall differences in effectiveness or safety were observed between patients 65 years and older and younger patients.

PATIENT COUNSELING INFORMATION

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

Differentiation Syndrome

Advise patients of the risks of developing differentiation syndrome as early as 1 day after start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, decreased urinary output, low blood pressure, rapid weight gain, or swelling of their arms or legs, to their healthcare provider for further evaluation.

QTc Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc interval prolongation including dizziness, lightheadedness, and fainting. Advise patients to report these symptoms and the use of all medications to their healthcare provider.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products.

Guillain-Barré Syndrome

Inform patients of symptoms that may be indicative of Guillain-Barré syndrome, including new signs or symptoms of motor and/or sensory neuropathy, such as weakness or tingling sensation in the legs, arms, or upper body, numbness and pain on one side or both sides of the body, changes to any sensory function, or burning or prickling sensation, or difficulty breathing. Advise patients to report these symptoms to their healthcare provider.

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake, and the need for frequent monitoring of blood chemistry values.

Gastrointestinal Adverse Reactions

Advise patients on the risks of experiencing gastrointestinal reactions such as diarrhea, nausea, mucositis, constipation, vomiting, decreased appetite and abdominal pain. Ask patients to report these events to their healthcare provider, and advise patients how to manage them.

Lactation

Advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the final dose.

Dosing and Storage Instructions

- Advise patients to swallow tablets whole and not to split, crush, or chew TIBSOVO tablets.
- Advise patients to avoid taking TIBSOVO with a high-fat meal.
- Instruct patients that if a dose of TIBSOVO is vomited, not to take an additional dose, and wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, instruct patients to take the dose as soon as possible unless the next dose is due within 12 hours. Patients can return to the normal schedule the following day.
- Store TIBSOVO at room temperature from 20°C to 25°C (68°F to 77°F).

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Sara Tolaney, MD, MPH, instructor of medicine, Harvard Medical School, attending physician of medical oncology, Dana-Farber Cancer Institute

What challenges are there in the management of patients with *HER2*-positive breast cancer?

I think 1 particular challenge for patients with *HER2*-positive disease, unfortunately, is brain metastases. Approximately half of all patients who develop metastatic *HER2*-positive disease will die from progression in the brain, and so, there have been much efforts made to try to improve outcomes for these patients. One class of drugs that we've focused on for this patient population has been the use of tyrosine kinase inhibitors. These agents have a lower molecular weight than monoclonal antibodies and are able to penetrate through the blood–brain barrier.

There have been several trials done, looking at these agents, and [results from] a few trials would suggest that when you combine tyrosine kinase inhibitors with capecitabine [Xeloda], their response rates do seem to be much greater, and maybe as high as even 60%. So, now actually, the National Comprehensive Cancer Network has added it to their guidelines to consider the use of capecitabine and neratinib [Nerlynx] for patients who have progressive disease in the brain.

How do clinical trials provide another treatment approach for these patients?

I think clinical trials are a great opportunity for patients, because [they allow] them to get novel therapies before they get approved, and so it really gives them an opportunity to get a new agent that may have very promising activity earlier than they would normally have access to it. So, usually when I'm seeing a patient I like to always present what the standard option is so that they're very well aware of what they could get outside of a clinical trial. But [I] also discuss what the clinical trial option would be at that time and see what makes more sense at that particular moment, because it's not always that the clinical trial is the right decision for them, and so it's important to weigh the pros and cons of that approach. ◆

Tim Gronniger, MPP, MHSA, senior vice president of development and strategy at Caravan Health

What have been some of the biggest barriers for organizations trying to implement new payment models?

Relationships within an organization and with physicians in the community are [some] of the first things that you have to figure out, and a lot of that comes up under the rubric of governance structures. Who's going to be making the decisions about the ACO's [accountable care organization's] performance, and who's going to be making decisions about who's doing what about who the leaders of it are? And, then, technology ends up dominating a lot of discussion time as well. How are we getting all of our information in 1 data warehouse if we're building an ACO with our independent community network of physicians? Then there might be 50 EMO products in that network, so we have to find a way where can at least pull data from that set of vendors, if not push and pull that data. So, getting a good handle on IT and technology and analytics takes a lot of time early on in an ACO.

What changes do you think need to be made to improve the move to value-based payment models?

The changes that we need to see are really consistent policy direction from Washington around what they want the health system to do first. A way to enable providers who are working together on improving quality in trackable form ensure, that is going to continue into the future and avoid unforced errors, such as cancellation of a mandatory bundle payment programs last year, anything that would upset the apple cart in terms of the Medicare Shared Savings Program, where we could see a huge withdrawal if the agency moves to promote risk too aggressively. Now, I said earlier, we all know that risk-bearing models are the future and Medicare Shared Savings Program, but trying to make the future happen in 6 months is a recipe for confusion and turmoil, not a recipe for success. I'm all for the agency being aggressive on risk-bearing models, but it needs to be done in a stepwise fashion.

When working with hospital leaders, how do you discuss the future of ACOs in the United States?

That's a big question. We talk about a lot of different things with our clients, and the reading we're getting from Washington, very clearly, is that Medicare wants ACOs to take risk. So, a lot of our discussions lately have been around, how do you get ready for that world? What sort of systems and competencies do you need to put in place? What does your staffing model need to look like? What do you need to do to work more effectively with your physicians? And like we talked about a little bit earlier this morning, what do you need to do to make sure you're large enough to be able to take risk effectively?

What concerns are top of mind for the providers and hospital systems that you work with?

There's the joke that every health system CEO has a to-do list that's about 100 items long and they only get to the first 10 on the list. So, at any given day in my world, they're worrying about what's going to be happening with CMS policy. They're worrying about what's happening with their staff. They're worrying about what their performance is over the last month and over the last quarter on metrics that we track. And they're always planning for the next year as well. So, the initial work in our model is geared around getting ready to put in place practices, build up primary care capacity, and get hired and train the right kind of nursing support to deliver effective preventive and primary care, and then to track performance on metrics that will determine success in the ACO over time. ◆

Sally Okun, RN, MMHS, vice president, Policy and Ethics, PatientsLikeMe

How well informed do patients usually feel when they start treatment after a new diagnosis?

I'm not so sure I can point to any one data point that would say, "Well, this is how well informed they are." What I would say is that over the course of the last number of years, as we've created a framework for what we call "the patient and caregiver journey," we've identified different points in time across that journey and the kinds of questions that patients have, and the things that they are experiencing during those different stages. And so, we have again distilled that down to about 6 common questions that most anybody has. Regardless of what their condition is, they seem to pretty much all fall around the same 6 questions, and one of them that I thought was interesting, in light of your question, was, "What will this treatment do to me?" »

or "What will this diagnosis do to me?" or "What will this prescription drug that you're going to prescribe for me do to me?"

So, I think what we're finding is that when patients come into an environment like PatientsLikeMe and tell us about that journey they've been on, what we've learned is that they didn't have a good understanding in the beginning, and these are the kinds of questions that they needed to ask, and they didn't necessarily get the answers that they needed. So, when they come into an environment like ours and they start asking other patients, they're starting to get some information that they wouldn't previously have gotten maybe from the clinician. It's not that the clinician isn't giving it to them; they might be giving it to them in a form that isn't necessarily digestible for the patient. It's not as easily understood as another person telling them about what that treatment had done for them, not necessarily saying, "It's going to do the same for you, but these are the things that I experienced."

Your question made me pause, and I almost asked you not to ask me because I didn't have a data point I could point to, but I think the interviews that we do continuously reinforce that patients have many, many, many questions and they often are the kinds of things that don't necessarily get addressed. But that one question of, "What will this do to me?" is, I think, what gets the closest to what you're asking. And so, it's 1 of our 6 common questions that all patients ask, regardless, again, of the conditions they have, and they don't necessarily get it answered all the time.

What benefits does technology offer to gather and use real-world evidence? And what are the barriers preventing the use of real-world evidence in meaningful ways?

I think what we have ahead of us right now is a monumental amount of data. So, I think the real-world data [that're] being generated, from all different sources, whether that's from patients themselves and devices they may be using or electronic health records and claims data, it almost doesn't matter. The volume is just growing so exponentially that we, actually, are ahead of ourselves in thinking about how we can turn that into evidence.

I think we're a little ways from that, yet, so I think the benefits actually are that we should take a step back and recognize these digitally native data sets that we're collecting from many situations that never existed before. So we need to be thinking what are the ways that we can start to harness the power of the data, first [by] empowering the data, actually, to start answering questions that could be better understood once we know what the evidence is we're trying to generate.

So, I think we need to be careful not to suggest that real-world data [are] going to translate into real-world evidence without some fair amount of work in between. I think between the benefits of having more access, greater integration of a variety of different data sources coming together to really form a more holistic picture of a person is incredibly wonderful and I think people will welcome that. It's the other side of that to say, then, "How can all of that information become meaningful to me when I'm trying to make a healthcare decision or when my clinician is trying to help me with a healthcare decision?"

How has the understanding of the need for patient input changed over the years?

I think in light of where we are, at ISPOR [the Professional Society for Health Economics and Outcomes research], and the fact that there's been such huge advances in the last number of years in recognizing that people have preferences around [their] care—and not only the care, but also the research they want to participate in—I think what we're seeing here and recognizing here this year is that it's finally starting to resonate with the research and clinical community in a way that people are embracing it. They want that kind of partnership.

I was on a panel [at ISPOR] that asked whether or not we're at an inflection point, particularly around transforming digital health into something that can actually inform real-world evidence. And I do think we are. I think we've gotten to the point where patients and people are more engaged in their health. They've got more tools that can help them have that kind of experience with it.

Now, we really need to empower the data so that data become more meaningful in their daily lives. And I think that would be something that ISPOR as an organization can help advance in the kinds of work that it does and the research it supports. ◆

Ejim E. Mark, MD, MPH, MBA, Chief Executive Officer and founder of Access Healthcare Foundation

With increasing amounts of health data available as a result of new digital technologies, what challenges exist for providers and researchers to use that data in meaningful ways?

The data [are] not being collected in a similar manner, so you have a lot of data sets that are not connected. Because of that, analyzing such data can be challenging for researchers. But looking into the future, with things like artificial intelligence, or looking into things that analytics can actually do, we hope that we keep gathering data in anticipation that one day we can integrate all that data and be able to get better analysis around it.

Are consumers' personal data being adequately protected as more digital technologies collect and share health information?

We try as much as we can. The reality is that there are breaches all the time, and it's not about just single breaches. There can be breaches from the provider side and the user side as well. So, being able to stay on top of protecting or securing this data is something we should always think about. We shouldn't put it at the back of our mind, but we should be thinking about that, because I've heard about 2000 attacks in hospitals each day.

As systems are becoming more interconnected, how can they help protect that data while still allowing it to flow freely?

You have to determine who owns the data and where the data resides, because that's important. If the data resides in the cloud or if it's in servers that are within the hospital systems, then those are different protections that are needed. And that's why it's imperative to know who owns the data and where it resides and provide adequate security around that. ◆

Michael Thompson, MD, PhD, FASCO, Aurora Advanced Care

What challenges are associated with the mass adoption of electronic health records (EHRs) and precision medicine?

There are a number of issues around EHRs that are separate from just precision medicine. But for precision medicine, it's how do you get this 20-page PDF that has a dashboard summary, that has all this information? How do you get that into an electronic format with discrete variables that you can search and do something with? That is one of the challenges that we were recently discussing: How do you make all of that happen? And there are different companies trying approaches.

We have purchased, and are trying to implement, Syapse to do that, but within 1 molecular testing vendor, you can go to individual portals they have to find out some of that information, and sometimes they will give you downloads of electronic information. But I think the big idea is how do you get all of that information from 1 site, like our place, and share it across the country? And that's a part of the Biden Moonshot initiative, to try to break down the silos so we gain information faster, so we aren't making the same mistakes over years. We're learning in weeks and months what people are doing. So, I'd say that there are a variety of vendors and approaches trying to do this, but it's still very much a work in progress and it's still very early on.

I think we know a number of things [about precision medicine]: We know that precision medicine works and there're a lot of examples where it's standard of care. We know precision medicine doesn't work, including *BRAF* inhibition in colorectal cancer. We have to combine it with other therapies, and we know that there are a lot of problems with precision medicine and lots of areas that we need to define better. But that shouldn't stop us from moving forward and trying to optimize the care for our patients. And we realized that sometimes we don't have enough data, but we're trying to move as fast as we can to help people. ◆

PROVIDER PERSPECTIVE

The Financial Impact of the Sequester Cut to Medicare Part B Drug Reimbursement in Community Oncology

Lucio Gordan, MD; Cass Schaedig; and Susan Weidner, MBA, MS

CONTINUED FROM COVER

The Medicare Modernization Act of 2003 established that the rate for payment of Medicare Part B drugs is the average sales price (ASP) of the drug plus 6%.[4] However, this percentage was affected when the Balanced Budget and Emergency Deficit Control Act of 1985 was amended by the Budget Control Act (BCA) of 2011. BCA required payment reductions in federal expenses through a sequestration order then set by the Office of Management and Budget and subsequently mandated by President Barack Obama on March 1, 2013. On April 1, 2013, a 2% cut was implemented to Part B drug reimbursement. However, the sequester is taken off the top of the 80% paid by Medicare, bringing a drop in the ASP from 6% to 4.3% and a 28.4% drop in reimbursement for cancer medications (chemotherapy, immunotherapy, and supportive intravenous drugs) under Part B reimbursement.[5]

In this study, we report the financial impact of the sequester cuts to Medicare Part B drug reimbursement to community oncology practices of different sizes.

Methods

Data Source and Sample Selection. An aggregated database of medical claims from practice management systems used by community-based oncology practices was used to conduct this analysis. This deidentified patient information, which required no informed consent or institutional review board, was integrated with the practices' drug cost and Medicare ASP information at the individual-service-line level. Any services provided to any Medicare patient during the period of January 2016 to March 2018 were included in the analysis.

Statistical Analysis. Practices included in this analysis were categorized based on the number of full-time physicians to adjust for the potential differences associated with patient and treatment volume. The categories were defined as follows: small practices had 1 to 5 physicians; medium practices, 6 to 10 physicians; and large practices, more than 10 physicians.

Patients were summarized by age category, practice size, and geographic region. The portions of Medicare patients per quarter were compared to determine if significant differences existed between practice size categories.

All analyses of reimbursement and costs were conducted for each quarter during the observation period, starting with the first quarter of 2016 and ending March 2018. The full ASP reimbursement and the corresponding sequestration amount were calculated for each service line. The differences were assessed in order to reflect the losses experienced by each service line and the differences among them.

Each practice's drug-related operating margin was calculated based on the difference between their actual reimbursement and total Part B drug costs per quarter. The drug costs were based on invoice costs. The impact of sequestration was summarized as the percent of drug-related operating margin, which will adjust for potential differences in treatment use over time.

Results

This analysis was based on cancer care provided to 396,848 Medicare recipients with an active cancer diagnosis during the 27-month period. These patients were treated at 92 community oncology practices representing 33 states, geographically distributed across the United States over the observation period. There were 54 small, 19 medium, and 19 large practices included within the sample. The percentage of Medicare patients was consistent throughout the observation period for the small and medium-sized practices, ranging from 52% to 54%. However, the large practices saw a 10% increase from the first quarter of 2016 (45%) to the first quarter of 2018 (55%).

The **Table** summarizes key patient demographics. Fifty-seven percent of patients were between 65 and 75 years of age, and those over 80 accounted for 23%. Leading cancer diagnoses included breast (26%), lung (11%), and lymphoma (9%). Of the top 10 diagnoses, 26% were hematologic malignancies.

During the observation period, these patients generated approximately $4.9 billion in Medicare allowable for medical services rendered. This resulted in a $78 million loss due to sequestration, or an average of more than $847,000 per practice during this timeframe. The average quarterly loss increased from $67,243 to $124,902 per practice from the first quarter of 2016 to the end of 2017, or an 86% increase in lost revenue. Small and medium-sized practices experienced an increase in their losses of approximately 13% while large practices saw more than a doubling of their losses due to sequestration. The latter was largely due to increased patient volume.

Overall, Part B drugs accounted for 68% of the total Medicare allowable generated. However, smaller practices had a slightly higher rate: 76% of total Medicare allowable associated with buy-and-bill drugs compared with medium (62%) and large (67%) practices. The overall growth in quarterly Part B drug reimbursement was 91% from the beginning of 2016 to the end of 2017. The reimbursement for large practices tripled, while it only grew 16% and 9% for small and medium-sized practices, respectively. »

TABLE. Patient Demographics

Age Distribution	Number	Percentage (%)[a]
65-70 years	125,795	31.6
71-75 years	99,838	25.1
76-80 years	79,602	20.1
Diagnosis Distribution	**Number**	**Percentage (%)[a]**
Breast cancer	104,002	26.2
Lung cancer	42,434	10.6
Lymphoma	34,405	8.7
Colorectal cancer	22,800	5.7
Prostate cancer	21,120	5.3
Chronic leukemia	15,771	4.0
MDS	12,086	3.0
Multiple myeloma	10,073	2.5
Bladder cancer	8260	2.1
All others	118,890	30.0

MDS indicates myelodysplastic syndrome.
[a]Percentages rounded to the nearest tenth of 1%.

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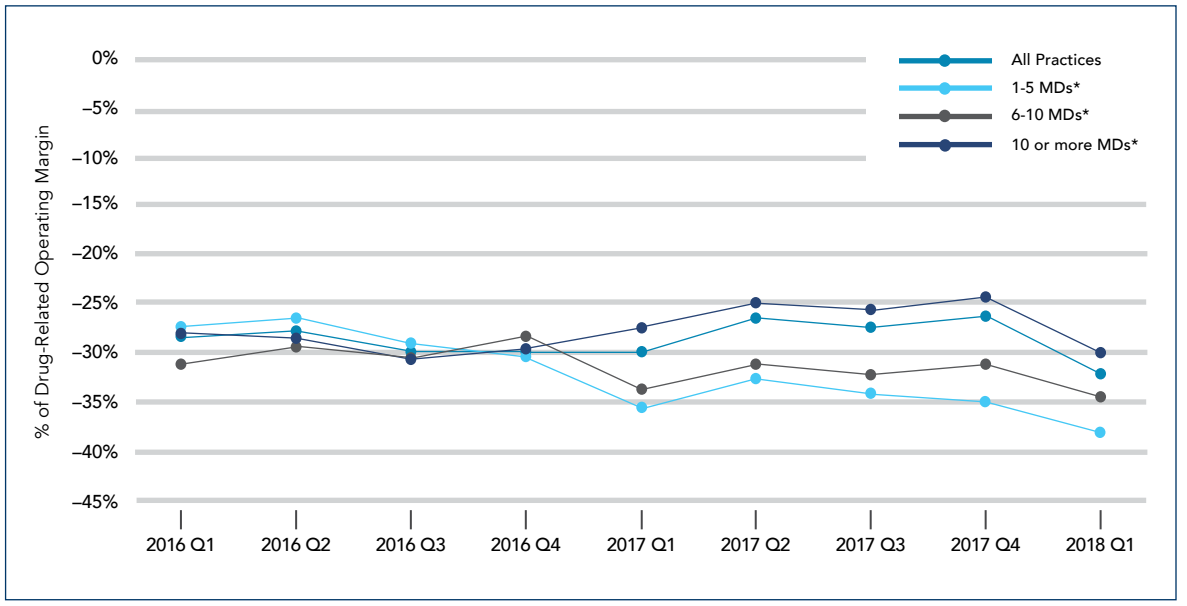
FIGURE. Effect of Sequester on Drug-Related Operating Margin



*MDs indicates physicians.

In parallel, the total quarterly drug costs increased 9% and 10% for small and medium-sized practices while they almost tripled in the large practices. Over the study period, the average quarterly drug costs to treat Medicare patients increased to approximately $1.9 million, $3.6 million, and $17.1 million per quarter for small, medium, and large practices, respectively.

The **Figure** displays the percent loss due to sequestration relative to drug-related operating margin. All practices experienced significant impact from sequestration over time. At the beginning of 2016, each practice, on average, experienced an approximate 28% to 31% loss due to sequestration. This remained steady for large practices while the small and medium practices began to experience more impact (38.4% and 34.7%, respectively). The overall average loss was 32% in the first quarter of 2018.

Discussion

In this study, we present data demonstrating the severe financial impact of sequestration applied to Medicare Part B reimbursement in practices of different sizes and geographic distribution, representing 396,848 patients. The drop in reimbursement from ASP+6% to ASP+4.3% has been temporally associated with an increased number of closings and rate of closure of community oncology practices in the United States.

The closure of community oncology practices represents a significant impediment to appropriate access to cancer care. Another negative consequence of the closure of community practices is the shift of site of care from the community setting to outpatient hospital systems. Other research has described the ominous financial impact of the site-of-care shift.[6-13] The cost of cancer in outpatient hospital systems is more expensive—an average of 38% higher costs than community oncology practices—without any evidence of superior quality-related outcomes.[14] More recently, we demonstrated a much higher cost of care in hospital outpatient settings with robust data, including a large number of patients treated with chemotherapy or immunotherapy for different cancer types. In addition, we also demonstrated 28% and 18% less emergency department visits within 72 hours and 10 days post chemotherapy, respectively.[15]

As the necessary debate about increasing healthcare costs continues and new proposals are made, including the blueprint to reduce the costs of prescription drugs,[16] it is imperative that Congress and the White House address multiple facets of our healthcare system.

The sequester to the Part B Medicare drug reimbursement program has contributed to the financial distress of community oncology practices, inadvertently contributing to the shift of care from the community setting, which is known to deliver efficient, and less expensive, patient-oriented care compared with other sites of care.

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BENEFIT DESIGN

Survey of NCI-Designated Cancer Centers Finds Most Are Out-of-Network on Exchanges

Alyssa Schatz, MSW, and Katy Winckworth-Prejsnar, MPH

CONTINUED FROM COVER

Background

Affordability is a key factor for many individuals shopping on the exchanges. More than 80% of individuals on the exchanges qualify for an advance premium tax credit, which requires an adjusted gross income of between 100% and 400% of the federal poverty level (incomes below 100% of FPL do not qualify).[2] One survey found that for most health insurance consumers, the most important factor in shopping for health insurance on the exchange is a low monthly premium.[3] Insurance plans that have narrow physician and hospital networks offer premiums that are, on average, 16% less expensive than broad-network plans, which may make them more appealing to consumers on the exchange.[4] But premiums are just 1 component of cost sharing and do not include deductibles, co-pays, and out-of-network costs. Considering the broader affordability of marketplace plans on the exchange is important because out-of-pocket medical costs have outpaced wage growth in recent years.[5]

About 21% of marketplace plans available in 2017 had narrow networks, defined as having 25% or fewer eligible physicians in a plan area.[6] Narrow-network plans are popular for their competitive premium pricing, but consumers may not fully understand what they are purchasing. Surveys by the Commonwealth Fund have shown that 20% to 25% of marketplace enrollees did not know that the plans have differing networks, while McKinsey & Company has found that more than 40% of new enrollees in 2015 were unaware of their plan's network configuration.[7] Understanding network design is particularly important for enrollees living with cancer or diagnosed during their time enrolled in an exchange plan.

In 2015, the Leonard Davis Institute of Health Economics at the University of Pennsylvania (Penn LDI) found that across insurance plans on the exchanges in 2014, network exclusions were particularly prevalent in oncology: 59% of plan networks of oncologists were classified as small (less than 25% of eligible physicians) or extrasmall (less than 10% of eligible physicians).[8] Analyses of narrow networks on the exchanges have found that NCI-designated cancer centers are more likely to be excluded from narrow-network plans.[9] Excluding academic cancer centers from narrow-network plans may inhibit access to high-quality cancer care for exchange enrollees.

Studies have found that treatment at academic cancer centers is tied to higher overall survival.[10,11] NCI-designated centers offer specialized services often unavailable elsewhere, including interdisciplinary team-based care, the latest therapies and advancements in cancer treatment, cutting-edge technology, and greater access to clinical trials. Patients on narrow-network plans that prohibit academic cancer centers may be less likely to access treatment at out-of-network centers because of higher cost sharing. This may be particularly problematic for patients with rare or advanced cancers, who could benefit from care at an academic cancer center.

Survey Methods

In 2015, NCCN and Avalere Health sought to better understand cancer centers' initial experiences with exchange plans.[12] In January 2018, NCCN and Avalere Health surveyed NCI-designated cancer centers to further understand their participation in the 2017 and 2018 exchange marketplace. Surveys were sent to directors or vice presidents of payer or managed care contracting and to individuals with similar titles at the 61 NCI-designated cancer centers. The survey was completed by 29 NCI-designated centers from 21 states and Washington, DC. Most respondents (82%) were from NCCN institutions.

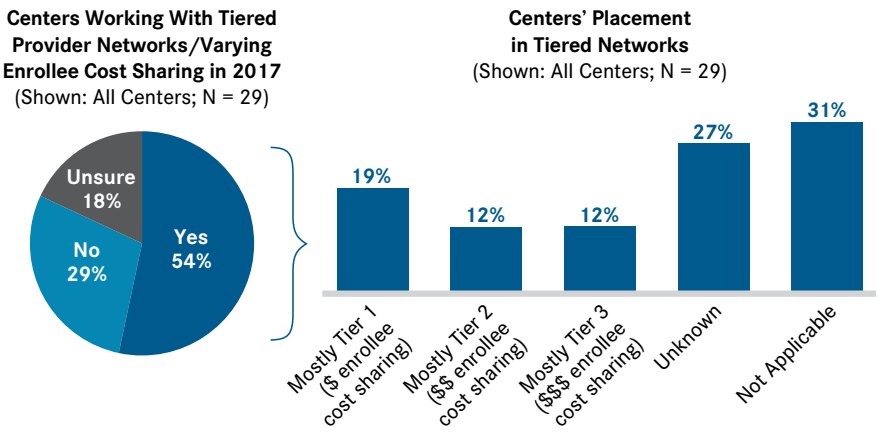
Survey Results

The survey found that 93% of cancer centers are out of network for some or all health exchange carriers in their state. Furthermore, the inclusion of major cancer centers on marketplace plans varies significantly. Some reported coverage in 100% of exchange plans in their state; others said they are out of network for all exchange plans. For example, centers in Connecticut and Maryland had less restrictive networks, while centers in Illinois, Minnesota, Nebraska, North Carolina, Pennsylvania, and Texas had more restrictive networks.

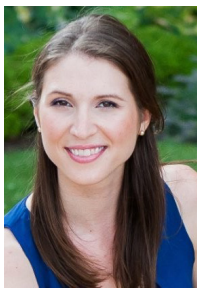
In addition to narrow networks, tiered networks also use higher or lower cost sharing to guide patient care. Under both, patients might incur higher out-of-pocket costs or reduce or delay necessary treatment.[13,14] For 2017, 55% of respondents said their states have tiered provider networks. Of those who were able to indicate their tier, more than half were in Tier 2 or 3, which would result in high enrollee cost sharing (**Figure 1**). For 2018, centers' placements in tiered networks was relatively consistent with 2017.

According to the National Cancer Database (NCDB), more than 250,000 Americans traveled more than 40 miles for cancer care in 2015.[15] For some patients, this included out-of-state travel, which poses network inclusion challenges. The majority of centers (59%) were unsure what percentage of their 2017 exchange patients were from out of state, and the majority of the remaining centers said that 10% or less were from out of state. Although 52% of centers said they were out of network for out-of-state plans, 26% were in network for plans in some border states and none were in network for all exchange plans from border states (**Figure 2**). »

FIGURE 1. Survey Findings



Q: Do any of the 2017 individual exchange plans in your state have tiered provider networks with different enrollee cost-sharing at each tier?
Q: For the 2017 individual exchange plans(s) with tiered networks, which tier are you in?



SCHATZ
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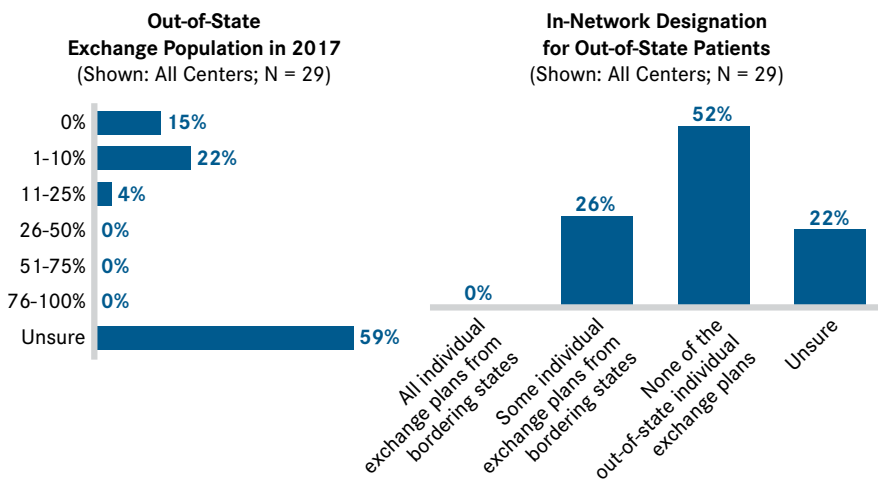
FIGURE 2. Survey Findings



Q: Do any of the 2017 individual exchange plans in your state have tiered provider networks with different enrollee cost-sharing at each tier?
Q: For the 2017 individual exchange plans(s) with tiered networks, which tier are you in?

The survey results expose marketplace challenges, including network variance across regions, high enrollee cost sharing under tiered networks, and network inclusion barriers for out-of-state patients.

Implications and Policy Solutions for Narrow Networks

Because more than 93% of responding NCI-designated cancer centers reported that they are out of network for at least some of their state's exchange plans, education on network configuration is needed for consumers to make informed purchasing decisions. Exchange enrollees may benefit from transparent, accessible, and user-friendly information on their plan's networks for specialists.

Further research is needed to determine the most effective mechanism to educate consumers about exchange networks. Some groups argue that state marketplace websites could include clearly marked labels for each plan's network size.[8] Recently, however, the Centers for Medicare and Medicaid Services (CMS) has dramatically reduced the role and funding for health care navigators. Exchange navigators have had their funding reduced by 84% since 2016, which may affect their ability to educate consumers about provider networks.[16] It remains to be seen how those significant gaps will be filled.

In addition, CMS has given states greater authority to oversee the network adequacy requirements on the exchanges. States already had significant authority to enforce network adequacy, which may explain why some state exchanges sell no plans with narrow networks and others comprise more than 80% narrow network plans.[17] The change increases state autonomy in reviewing the qualified health plan certification standards of network adequacy by allowing states to rely on state reviews or issuer accreditation.[18] This may result in wider disparities in network size.

Further research is needed into the impact narrow-network plans have on access to high-quality cancer care and overall health outcomes for enrollees with cancer. Surveys have reported that consumers are widely satisfied with narrow-network plans and that these plans have reduced consumers' out-of-pocket costs.[19] But these studies do not look specifically at enrollees with cancer, particularly enrollees with advanced or rare cancers, who are likely to have high out-of-pocket costs at out-of-network providers, face a delay or reduction in treatment, or seek care from a provider who may not be optimally equipped to treat all cancers. This survey focuses on narrow networks on state exchanges, but they are increasingly used in other markets, including Medicare Advantage plans, which are likely to have higher rates of beneficiaries with cancer. Further research is needed on the implications of narrow networks for beneficiaries with cancer in the broader insurance market.

Conclusions

Narrow networks and tiered networks have become popular ways of controlling costs on the exchange. But inclusion of academic cancer centers on these plans varies widely, which can impede enrollee access to needed care. Patients with cancer who do not have an in-network academic cancer center may be unable to access the latest treatment advances, clinical trials, or specialized care. Additional research is needed to better understand the health outcome and out-of-pocket-cost implications of narrow networks for enrollees with cancer, including patients with rare or advanced cancers. Finally, wide variance in center inclusion across exchange plans, coupled with reduced funding for navigator programs, indicates a need for increased consumer education efforts on exchange plan network design and breadth. ◆

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DRUG POLICY

Medical Marijuana in Cancer Treatment: No Standards of Care, and So Far, No Coverage

Samantha DiGrande

CONTINUED FROM COVER

organizations do not have any standards for marijuana use. With no guidelines, payers have yet to cover it as a treatment, citing this lack of acceptance, insufficient clinical data, and the lack of an FDA-approved product for cancer adverse effects that contains a marijuana-based ingredient.

According to the World Health Organization (WHO), cannabis is the most commonly cultivated, trafficked, and abused illicit drug worldwide, with annual consumption by nearly 147 million people, or 2.5% of the world's population as of 2016. In comparison, 0.2% of the world's population consumes opiates on a yearly basis.[2]

The legal status of marijuana has become increasingly complex. At the federal level, marijuana remains illegal. It is classified as a schedule 1 drug, defined as "drugs, substances, or chemicals with no currently accepted medical use and a high potential for abuse."[3] Other drugs in this class include heroin, lysergic acid diethylamide (LSD), methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote.

"My position is that [cannabis] is extremely safe and effective for multiple ailments, and ideal for patients who are on polypharmacy that can have risky drug interactions, potential for addiction, and [for] patients on medication doses that I don't feel comfortable with."

—Andrew Medvedovsky, MD,
New Jersey neurologist and pain management specialist

Despite this, many states have taken matters into their own hands **(Figure)**. To date, marijuana is legal for medical use in 22 states and for both medical and recreational use in 9 states and the District of Columbia. It remains illegal in Idaho, South Dakota, Nebraska, and Kansas. The remaining 15 states have some level of medicinal marijuana legalized, though it is only available as a "low THC, high CBD oil."[4] Scientists have identified many cannabinoids, the biologically active components in marijuana; the 2 most studied are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

In New Jersey, where medical marijuana is legal and the legislature is weighing recreational use, neurologist Andrew Medvedovsky, MD, began recommending cannabis in 2015, after completing an interventional pain fellowship. Prescribers need a special registration, so Medvedovsky often receives referrals from other physicians, including oncologists, when patients want to try cannabis to relieve pain and other symptoms. "My position is that [it] is extremely safe and effective for multiple ailments, and ideal for patients who are on polypharmacy that can have risky drug interactions, potential for addiction, or [for] patients on medication doses that I don't feel comfortable with," he said. Some patients already test positive for THC, "and we start this conversation."

"My goal for every patient is to reduce the need for such a load of medications, get them back to functional status, decrease side effects and [put them] at less risk of addiction," Medvedovsky said. "I find medical marijuana to be a great substitute for such patients, because we can manage severe pain, muscle spasms, sleep, anxiety, depression, and reduce the burden of pills and improve function."

Understanding Marijuana's Mechanisms

Marijuana primarily affects parts of the brain and the spinal cord by binding to 2 types of G-protein coupled receptors, CB1 and CB2. By acting on the CB1 receptor in the brain, marijuana overactivates the endo cannabinoid system within the body, alters the user's perceptions and mood, disturbs memory function and learning, and impairs judgement.[5]

The CB2 receptors, primarily found in peripheral tissues on cells in the immune system, hematopoietic systems, and the spleen may play a role in the immune-suppressive activity of cannabis.[6] Some research has even suggested that it may contain anticancer properties. In mouse models, cannabinoid administration was observed to reduce the expression of vascular endothelial growth factor and its receptors, leading to inhibition of angiogenesis. In another study involving mice, adding THC to temozolomide reinstated glioma suppression in tumors that had become resistant to chemotherapy. Cannabinoids also have anti-inflammatory and antioxidant properties that are beneficial in combatting cancer specifically,[6] although these studies were performed in laboratories with animal models rather than in human models.

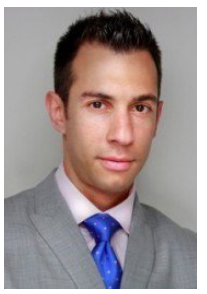
The effects an individual feels from marijuana also depend on how the compounds enter the body. When taken by mouth, such as in baked goods, THC can take hours to be fully absorbed. Once that occurs, marijuana is processed by the liver, which produces a second psychoactive compound, CBD, that acts on the brain and changes mood or consciousness. When marijuana is smoked or vaporized, THC enters the bloodstream and reaches the brain very quickly. The second psychoactive compound, CBD, is produced in small amounts, with fewer effects.[7] Medvedovsky discourages smoking because of the possibility of toxins and encourages vaping instead, although he finds that most patients still inhale by smoking.

Despite Need for Use in Cancer, Gaps in Research

In the United States, an estimated 1,735,350 people will be diagnosed with cancer this year.[8] Although nearly every state that has laws surrounding medical marijuana identifies cancer as a qualifying condition, little research has been conducted to support its use in oncology. In a study published in the *Journal of Clinical Oncology* in July 2018[9], researchers hypothesized that the discrepancy between medical marijuana laws and scientific evidence posed a clinical challenge for oncologists. The study authors mailed a survey to 400 medical oncologists across the nation that included questions surrounding whether physicians reported discussing medical marijuana with patients, recommended it clinically within the past year, or felt sufficiently informed to make such recommendations.

Researchers found that while only 30% of oncologists felt sufficiently informed to make recommendations regarding medical marijuana, nearly 80% conducted discussions about the treatment and 46% recommended it clinically. These findings shed light on critical gaps in research, medical education, and policies regarding medical marijuana.

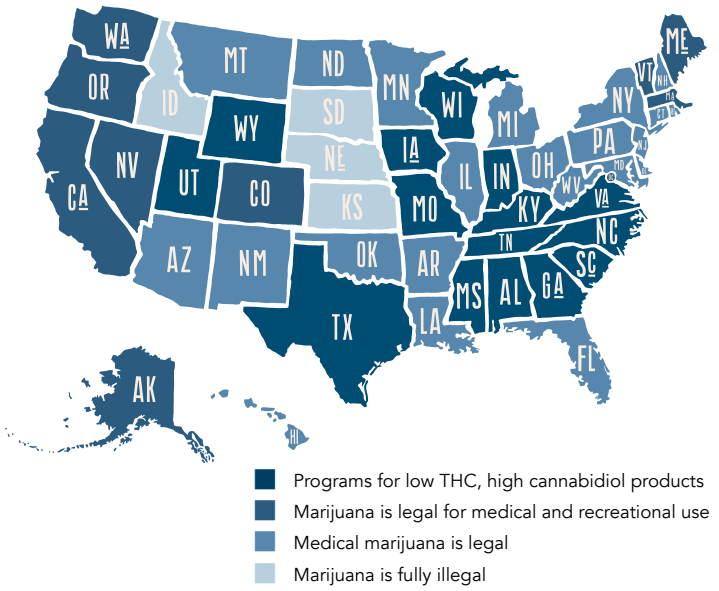
Despite the treatment becoming increasingly popular among patients with cancer, most major cancer societies have declined



MEDVEDOVSKY

Andrew Medvedovsky, MD, is a neurologist and pain management specialist who is authorized in New Jersey to prescribe medical marijuana.

FIGURE. Marijuana Laws State by State



THC indicates delta-9-tetrahydrocannabinol.

Source: Governing. State marijuana laws in 2018. Governing website. governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html. Published March 30, 2018. Accessed September 14, 2018.

to take positions on its use. When *Evidence-Based Oncology™ (EBO)* reached out to cancer organizations, here's what each had to say:

American Society of Clinical Oncology	"ASCO does not have an official position on the use of cannabis for pain management."
National Comprehensive Cancer Network	"The NCCN Adult Cancer Pain Panel has made no recommendation either for or against cannabis for pain management in cancer patients."
National Cancer Institute	"NCI does not take positions or make recommendations about this or other treatments but rather, as the federal government's principal agency for cancer research and training, provides scientific-based information for patients and healthcare providers."
Oncology Nursing Society	"ONS does not have a position statement related to medical cannabis."
American College of Obstetricians and Gynecologists	"ACOG doesn't have any specific guidance about cannabis use as a pain management tool for gynecologic cancers."

By contrast, the American Cancer Society stated that it supports the need for more scientific research around the treatments.

Absent Guidelines, Payers Stay on Sidelines

Some cancer groups provide guidelines[10] about how to administer the treatment to patients, but none has taken a stand to say it explicitly approves of or disapproves of the treatment. This can lead to confusion not only for patients and their oncologists, but for payers as well.

When *EBO* reached out to several major insurers about coverage for medical marijuana for pain management specifically in cancer, their answers were much of the same. A representative from Humana noted in an email to *EBO*, "As of right now, there is no FDA-approved marijuana product, and we therefore do not currently offer a prescription drug benefit for medical marijuana. If there were to be an FDA-approved medical marijuana product in the future, it may be covered depending upon the terms of the individual member's drug coverage." A representative from UnitedHealthCare echoed this, stating, "We do not cover medical marijuana at this time as it is not approved by the FDA."

However, in June 2018, the FDA approved Epidiolex (cannabidiol) oral solution for the treatment of seizures associated with 2 rare and severe forms of epilepsy. It was the first FDA-approved drug that contained a purified drug substance derived from marijuana.[11] Previously, the FDA had approved dronabinol (Marinol), a gelatin capsule containing a synthetic version of THC to treat nausea and vomiting associated with chemotherapy as well as weight loss and poor appetite in patients with AIDS, and nabilone (Cesamet), a synthetic cannabinoid that acts like THC to treat nausea and vomiting caused by chemotherapy.[12]

"We know that THC helps patients with nausea and appetite, which is why cancer patients receive the FDA-approved drug Marinol," Medvedovsky noted. "In my experience and from the cancer patients I have treated with cannabis, there was no negative effect of medical marijuana on their cancer treatment. It is usually the opposite—so many patients suffer with nausea, poor appetite, pain, depression, insomnia—and the medications they are prescribed are challenging to tolerate because of the nausea," he said.

"Cannabis allows patients to medicate naturally and find almost immediate relief of nausea symptoms during or after chemotherapy, improve appetite, sleep, mood, energy, and pain control naturally." He noted the emerging evidence of anticancer properties as well.

Many questions remain unanswered for medical marijuana in terms of insurance coverage, such as:

- Which conditions would be covered? Do health plans see a difference between covering medical marijuana to treat terminal cancer and covering it to treat chronic back pain?
- Will coverage extend to patients in taxpayer-funded programs, such as Medicare or Medicaid?
- Will state-level plans, such as the Blues, cover it?

In a recent case in New Jersey, *McNeary v. Township of Freehold,* a worker's compensation judge ruled for at least the second time in the state that an injured worker was entitled to coverage for medical marijuana.[13] Steven McNeary, a patient with muscular spasticity, sought a court order to require the insurance carrier for Freehold Township to pay for his medical marijuana treatment. The insurer refused, arguing that the Controlled Substances Act's (CSA) criminalization of marijuana supersedes state-level laws. New Jersey Workers' Compensation Judge Lionel Simon disagreed, ruling that New Jersey's medical marijuana statute is not pre-empted by federal law. In his decision, Simon stated that the CSA and the New Jersey Medical Marijuana Act both seek to deter the distribution and use of illicit drugs.

"I honestly don't feel in my heart of hearts that this is a conflict. Certainly, I don't understand how a carrier, who will never possess, never distribute, never intend to distribute these products, who will [merely] sign a check into an attorney's trust account, is in any way complicit with the distribution of illicit narcotics," Simon said.

He cited concerns that McNeary could instead become addicted to opioids should he not be able to obtain medical marijuana. He explained that the court is aware of the "explosion" of narcotics in the United States and the related deaths and addiction rates that follow. "I believe, and I think science supports this, that medical marijuana is safer, it's less addictive, it is better for the treatment of pain," he said.

However, the Maine Supreme Court reversed a lower court ruling to compel an insurer to pay for medical marijuana, citing the conflict with federal law.[14]

Evolving Law and Patient Access

The landscape and conversation around marijuana and its potential use for a multitude of treatments in many disease states is evolving in the United States. In 2018, more states have laws on the books that allow patients access to marijuana in some form than those that do not. While the future of such products remains uncertain, the FDA and the WHO have taken steps to further increase patient access.

WHO recently launched a review of the current international classification of marijuana, THC, CBD, and other related compounds and requested input from member nations.[15] The FDA has also requested that the public submit comments that can inform the country's position before provides its opinion to the WHO.[16] This public comment period has since closed. While the findings of the WHO's review were not released at the time of publication, the potential reclassification of marijuana could have implications both at the state and federal levels.

In addition, a panel in the US House of Representatives that reviews federal drug enforcement approved a bill on September 13 that will require the Department of Justice and Attorney General Jeff Sessions to begin issuing more licenses to grow marijuana for research. To date, 1 farm at the University of Mississippi can supply cannabis for research purposes.[17] This bill would increase the number of locations able to legally cultivate marijuana for research purposes to 3.

Prior to the vote, a debate broke out regarding a provision of the legislation that prevents anyone with a "conviction for a felony or drug-related misdemeanor"[18] from being affiliated with any kind of cannabis research cultivation. While legislation supporters sought to amend the bill to remove this distinction, House Judiciary Chairman Bob Goodlatte (R-VA) shot down a compromise that would have done away with the restrictions on people with drug misdemeanors while maintaining the ban on those with felony convictions. Instead, he made a commitment to work to revise the restrictions before the bill goes to the House floor and indicated that he would "probably not object" to a carve-out designation for individuals with drug possession convictions.

"While there are many varying opinions on the issue of marijuana, one thing we can all agree on is that we need qualified researchers to study the

science to determine if there are any potential medicinal benefits to chemicals derived from cannabis," said Goodlatte in a statement.[19]

Without insurance, cost considerations keep patients from using vapes, which Medvedovsky said are safer than smoking. Vapes cost $200 to $400, and a typical medical marijuana program will cost $300 to $400 to join and $150 to $200 per month after that for product.

More patients are asking for medical marijuana as the stigma around it has waned, Medvedovsky said. "By the time I see them, most patients are excited and ready to start. Many people are desperate for relief and will do anything to feel better, especially when dealing with the end of life." ◆

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Cancer Types Can Affect How Well Providers May Perform Under OCM

Laura Joszt

THE TYPE OF CANCER a provider treats can determine how well he or she performs under the Oncology Care Model (OCM), according to research from Avalere Health that was presented[1] at the American Society of Clinical Oncology Quality Care Symposium.

The Avalere researchers constructed and analyzed OCM episodes using Medicare Part A/B fee-for-service claims and Part D prescription drug event data. They then compared the average actual Medicare costs with the OCM predicted costs for each of the 21 types of cancer included in the OCM.

First, they found that 62% of the cancer episodes occurring during the OCM baseline period were either breast or prostate cancer. Although the average and predicted OCM episode for the baseline period was $20,900 across all cancer types, the average and predicted costs varied for individual cancer types. For instance, actual costs were an average 8% higher than predicted in lung and liver cancer episodes. Meanwhile, the actual costs for bladder and female genitourinary cancers other than ovarian were 5% lower on average compared with the predicted costs.

"As the shift toward value-based care continues, it is important to evaluate how new payment models, like the Oncology Care Model, may affect physicians and patients," Richard Kane, senior director at Avalere, said in a statement.[2] "Our research suggests that clinicians who treat certain cancer types may perform better under the Oncology Care Model."

Performance on quality scores also varied by cancer type, with acute leukemia and head-and-neck cancers performing worse; none of the possible quality points were achieved. However, in bladder cancers, 92% of the possible quality points were achieved, on average. According to the research, 8 cancer types that account for 80% of OCM episodes achieved, on average, more than 50% of possible quality points. In comparison, the 11 cancer types that account for just 20% of OCM episodes achieved, on average, less than 50% of possible quality points.

Overall, the Avalere researchers determined that the "ability of a participant to succeed in the OCM can vary depending on the types of cancers treated by the practice."

"Cancer episodes for which actual costs are greater than predicted costs and for which quality scores are low will adversely affect a participant's ability to earn performance-based payments," said Matt Brow, president of Avalere. "Identifying these types of challenges are essential to ensuring the Oncology Care Model succeeds in rewarding efficient and high-quality care."

Previously, Avalere found[3] that participation in the OCM may transform care more quickly for certain types of cancers, as participating doctors treat some types more than others. For instance, breast and lung cancers were the most common types of cancers treated by doctors in the OCM. ◆

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