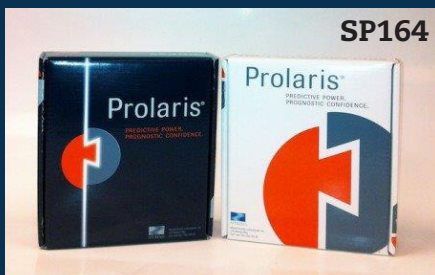


Evidence-Based ONCOLOGY™

JUNE 2018
VOL. 24 • NO. 6

ALSO IN THIS ISSUE

SP164



Myriad Genetics photo

BIOMARKERS IN PROSTATE CANCER

This spring, the National Comprehensive Cancer Network updated its prostate cancer guidelines to support the use of biomarkers, including Prolaris, in prostate cancer tumors. Molecular testing of prostate tissue helps physicians and patients decide between definitive treatment and active surveillance, [SP164](#).

DATA SKILLS IN CANCER CARE

When Richard Grenell was diagnosed with cancer, his partner, Matt Lashey, tapped into his experience in strategic research and data analysis to track how symptoms, diet, behaviors, and environment affected clinical outcomes. The result is an app, chemoWave, that can make more systematic use of patient-reported outcomes, [SP165](#).

GENETIC TESTS AND HEALTH PLANS

The role of diagnostic testing to guide clinical decisions will likely grow, and health plans would be wise to prioritize trustworthy experts to ensure that testing can deliver on its potential, [SP168](#).



ENGAGING IN THE OCM MODEL

A report from Orlando, Florida, where *The American Journal of Managed Care*®

convened its first meeting of the Institute for Value-Based Medicine to bring expert insights on implementing the Oncology Care Model (OCM), featuring Florida Cancer Specialists, Tennessee Oncology, and Southern Oncology Specialists, [SP169](#).



GORDAN CHAMPLAIN LYSS KEPINSKI

THE REGULATORY PROCESS

Perspective: FDA/CMS Parallel Review Advances Coverage for Cancer Comprehensive Genomic Profiling

Lakshman Ramamurthy, PhD; Kristi Maxwell, MS, CGC; Bethany Sawchyn, PharmD; and Rachel Anhorn, PharmD

FOUNDATION MEDICINE'S FOUNDATIONONE CDx was the second product to pursue FDA/CMS dual review, paving the way for comprehensive genomic profiling in advanced cancer patients.

Introduction

Keeping up with the ongoing changes in oncology is becoming a difficult task for clinicians and payers. New relevant biomarkers and biomarker-driven treatments are introduced each year, and many more are in late-stage development. For example, 8 new biomarker-driven oncology treatments were approved in 2017 alone.¹ Although many patients have benefited from this revolution in precision medicine by using comprehensive genomic profiling (CGP) of their tumors to help direct therapy, many others have missed this opportunity by receiving conventional testing or, worse, by failing to receive any molecular testing.

CGP refers to next-generation sequencing (NGS)-based testing of tumors that has been optimized to identify all types of cancer-relevant molecular alterations and complex genomic signatures in known cancer-related genes in a single test, using complex (often proprietary) bioinformatics. There has been substantial debate of the value of CGP in both the clinical oncology and managed care communities. Regardless, the demand for the technology exists among patients, providers, and biopharmaceutical companies alike.²

CONTINUED ON SP193



Foundation Medicine photo

TECHNOLOGY VIEWPOINT

A Retrospective on the Oncology Care Model

Ryan Holleran; Arif Gilani; Abigail Orlando; and Brenton Fagnoli, MD

IN SOFTWARE DEVELOPMENT, there's a concept of a "retro." Short for a retrospective, the process asks the engineering and product teams to review what's been working, what hasn't, and what they'll commit to improving in the future. As we near the 2-year mark of the Oncology Care Model (OCM),¹ we've had a chance to reflect on the results and reactions from the first performance period. The completion of the first performance period cycle presents an opportune time to step back to do a retro on how the model has reshaped participating practices and influenced the technology developers supporting them.

The OCM now covers 150,000 Medicare beneficiaries in 200,000 to 300,000 episodes per year,² and we believe the sustained success and potential expansion of the model can best be driven by incremental iteration that reflects ongoing stakeholder feedback. The OCM, or any future model, will continue to have significant implications for technology developers and participating practices, as requirements become

CONTINUED ON SP197

PROVIDER PERSPECTIVE

The Impact of New CMS Rules for Telehealth on Cancer Genetic Counseling

Heather Zierhut, PhD, MS, CGC, and Adam Buchanan, MS, MPH, LGC

TELEHEALTH, A UNIVERSAL term for the use of digital information and communication technologies to remotely¹ access healthcare services, is improving availability of healthcare services, particularly for patients in rural areas. Data from a wide range of medical specialties have demonstrated that telehealth can improve access while maintaining quality.²⁻⁴ Private payers have been influential in supporting telehealth initiatives, with more than 30 states mandating coverage.^{5,6} Yet limitations on Medicaid and Medicare reimbursement of telehealth have hampered broad implementation of this promising service delivery model.⁷⁻⁹

CONTINUED ON SP199

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% 94%

Grade ≥ 3 incidence

Overall incidence

// NEUROLOGIC TOXICITIES

31% 87%

Grade ≥ 3 incidence

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 2×10^6 viable CAR T cells/kg body weight (maximum of 2×10^8 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.

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with \geq 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 \geq 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 \geq 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.

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
<ul style="list-style-type: none">• 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/m² intravenously and fludarabine 30 mg/m² 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 <i>(a)</i>	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 <i>(b)</i> .	Administer tocilizumab <i>(c)</i> 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 <i>(a)</i>	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.

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

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)*].

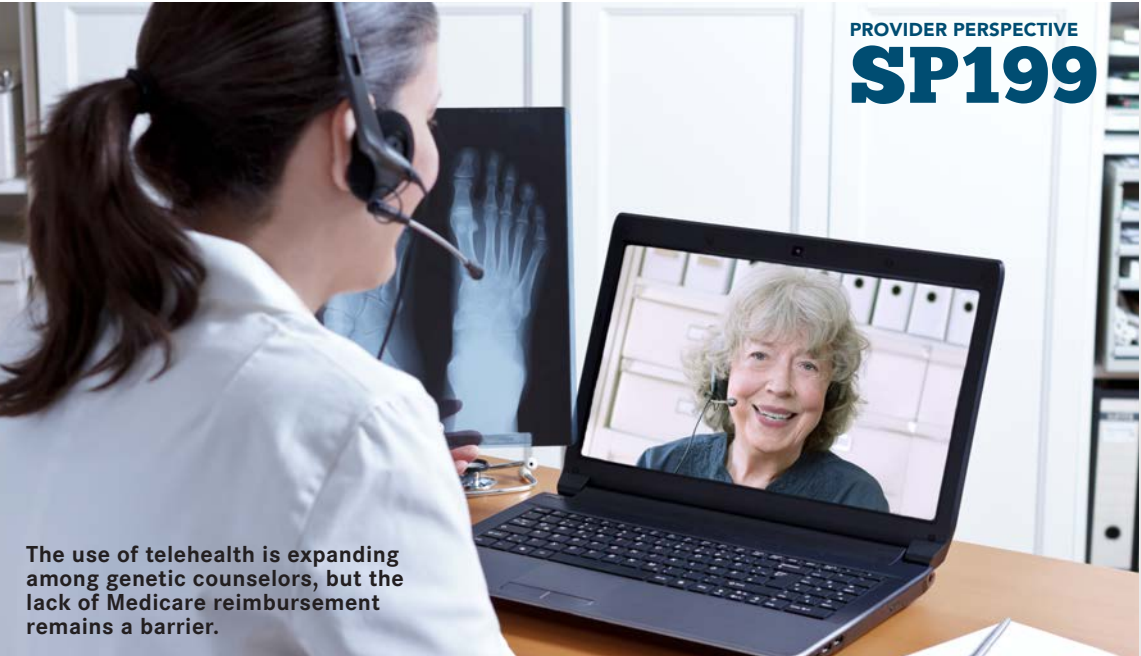
Manufactured by, Packed by, Distributed by: Kite Pharma, Inc., Santa Monica, CA 90404

US License No 2064

YESCARTA and KITE are trademarks of Kite Pharma, Inc.

© 2018 Kite Pharma | PRC-00428 03/2018

SPECIAL ISSUE / Point-of-Care Tools
JUNE 2018
VOLUME 24, ISSUE 6



The use of telehealth is expanding among genetic counselors, but the lack of Medicare reimbursement remains a barrier.

FEATURES

SP193
THE REGULATORY PROCESS
Perspective: FDA/CMS Parallel Review Advances Coverage for Cancer Comprehensive Genomic Profiling

LAKSHMAN RAMAMURTHY, PHD; KRISTI MAXWELL, MS, CGC; BETHANY SAWCHYN, PHARM D; AND RACHEL ANHORN, PHARM D

SP197
TECHNOLOGY VIEWPOINT
A Retrospective on the Oncology Care Model

RYAN HOLLERAN; ARIF GILANI; ABIGAIL ORLANDO; AND BRENTON FARGNOLI, MD

SP199
PROVIDER PERSPECTIVE
The Impact of New CMS Rules for Telehealth on Cancer Genetic Counseling

HEATHER ZIERHUT, PHD, MS, CGC, AND ADAM BUCHANAN, MS, MPH, LGC

INSIDE THE ISSUE

SP161
FROM THE CHAIRMAN
New Stakeholders at the Point of Care

SP162
FROM THE EDITOR-IN-CHIEF
Making Disruptive Technology Less Disruptive

JOSEPH ALVARNAS, MD

SP164
BIOMARKERS
National Comprehensive Cancer Network, American Association of Clinical Urologists, and Large Urology Group Practice Association Endorse Biomarkers in Prostate Cancer

ROBERT FINCH, MS, CGC

SP165
PATIENT-REPORTED OUTCOMES
Riding the Wave Through Chemo: Cancer Journey Leads to chemoWave App for Reporting PROs

MATT LASHEY, MBA

SP168
FROM OUR CONTRIBUTOR
How Managed Care Can Advance Responsible Genetic Testing

L. PATRICK JAMES, MD

PUBLICATION STAFF

SENIOR VICE PRESIDENT,
MANAGED MARKETS
Jeff Prescott, PharmD

COPY CHIEF
Jennifer Potash

ASSOCIATE EDITORIAL
DIRECTOR
Surabhi Dangi-Garimella,
PhD

COPY EDITORS
Maggie Shaw
Rachelle Laliberte
Paul Silverman

MANAGING EDITOR
Mary K. Caffrey

DESIGNER
Brianna Gibb

ASSISTANT EDITOR
Samantha DiGrande

SALES & MARKETING

DIRECTOR OF SALES
Gilbert Hernandez

NATIONAL ACCOUNTS
ASSOCIATE
Ryan O'Leary

OPERATIONS & FINANCE

CIRCULATION DIRECTOR
Jon Severn

VICE PRESIDENT OF FINANCE
Leah Babitz, CPA

CONTROLLER
Katherine Wyckoff

CORPORATE OFFICERS

CHAIRMAN AND CEO
Mike Hennessy, Sr

VICE PRESIDENT OF EDITORIAL
SERVICES AND PRODUCTION
Kerrie Keegan

VICE CHAIRMAN
Jack Lepping

VICE PRESIDENT OF
DIGITAL MEDIA
Jung Kim

PRESIDENT
Mike Hennessy, Jr

CHIEF CREATIVE OFFICER
Jeff Brown

CHIEF FINANCIAL
OFFICER
Neil Glasser, CPA/CFE

DIRECTOR OF HUMAN
RESOURCES
Shari Lundenberg

SENIOR VICE PRESIDENT
OF OPERATIONS
Tom Tolvé



Scan here to subscribe
ajmc.com/subscribe.



2 Clarke Drive, Suite 100
Cranbury, NJ 08512 • (609) 716-7777

Copyright © 2018 by Managed Care & Healthcare Communications, LLC

The American Journal of Managed Care® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512. Copyright © 2018 by Managed Care & Healthcare Communications, LLC. All rights reserved. As provided by US copyright law, no part of this publication may be reproduced, displayed, or transmitted in any form or by any means, electronic or mechanical, without the prior written permission of the publisher. For subscription inquiries or change of address, please call 888-826-3066. For permission to photocopy or reuse material from this journal, please contact the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923; Tel: 978-750-8400; Web: www.copyright.com. Reprints of articles are available in minimum quantities of 250 copies. To order custom reprints, please contact Jeff Prescott, The American Journal of Managed Care®, jprescott@ajmc.com; Tel: 609-716-7777. The American Journal of Managed Care is a registered trademark of Managed Care & Healthcare Communications, LLC. www.ajmc.com • Printed on acid-free paper.

New Stakeholders at the Point of Care

PRECISION MEDICINE, which calls for customizing healthcare delivery to meet individual needs, necessitates having 2 distinct information sets: First, the medical team needs details about the patient—from genetics, to lifestyle, to what other drugs the person is taking. Second, the team needs data on what treatments worked (or didn't) in patients similar to the person they are now treating. This second realm of information has typically been gathered slowly and less than methodically. One by one, doctors examined patients, they read journals, they talked with colleagues. They might see an unusual case; they might not.

Today, thanks to the digital revolution, the lessons of a thousand careers can be at one's fingertips, a prospect that is at once empowering and daunting. As we learn in this issue of *Evidence-Based Oncology™*, the revolution has given rise to a new group of stakeholders in cancer care: the data providers. This class can include genetic testing companies, creators of electronic health records or clinical pathways, and tools that help operate a clinical trial—or some that make sense of information from all of these.

For a time, digital entrepreneurs have navigated a landscape that lacked a roadmap. FDA Commissioner Scott Gottlieb, MD, has fully embraced their presence and is hard at work creating guidance for how they should operate. CMS, however, has taken a bit longer to figure out how they should be paid. This is changing, as the authors from Foundation Medicine so graciously share in describing the joint FDA/CMS process used to approve FoundationOne CDx, a next-generation sequencing test for comprehensive genomic profiling of tumors to direct therapy choices.

Clearly, this represents progress. But as authors from Flatiron Health describe, technology developers need equal seats at the table with providers and pharmaceutical companies when rules are developed, because they will be central to advancing the shift toward value-based care. Digital entrepreneurs say they can help CMS in its goal to reduce administrative burdens in alternative payment models, including the Oncology Care Model.

This issue reveals how entrepreneurs not only bring new solutions to cancer care but also inspire us with extraordinary stories of life after treatment. We feature chemoWave, an app designed by entertainment marketing executive Matt Lashey, who used his experience in data analysis to show how better care comes from systematically listening to consumers and tracking patient-reported outcomes. Lashey's app grew out of caring for his partner, Ric Grenell. Today, their experience is shared with patients with cancer who use the app and with all Americans who benefit from Ric's service as our new ambassador to Germany. We proudly wish Matt and Ric the best on their journey. ♦

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO



CONFERENCE COVERAGE

SP180

A study presented at the Society of Gynecologic Oncology found that fewer boys are vaccinated to protect against human papillomavirus because physicians don't discuss it.

SP169 VALUE-BASED MEDICINE With the Oncology Care Model, “Everyone Has to Be Engaged,” Including Patients

AJMC® Convenes First Gathering of Institute for Value-Based Medicine to Share Best Practices in New Payment Models in Cancer Care

SP171 POPULATION HEALTH Population Health Council Discusses Progress in Payment Reform, Ongoing Barriers in Oncology Care

SP178-SP180 AJMC® STAFF CONFERENCE COVERAGE SGO 2018 Study Models ASCO Alternative Payment Model in Advanced Ovarian Cancer Care

Deciding When to Use PARP Inhibitors, and Which One

Boys Don't Get HPV Vaccination Because Doctors Don't Recommend It, Study Finds

SP181-SP183 NCCN 2018 Oncologist Shares Lessons Learned From CAR T-Cell Therapy in ALL

Oncologists Must Weigh Risks, Benefits of Immune Checkpoint Inhibitors

Making Progress or Headed for Crisis? NCCN Keynotes Offer Contrasting Views of US Cancer Care

NCCN's New Guidelines Promote Better Cancer Care for People With HIV

SP184-SP186 COA 2018 Commissioner Gottlieb Updates Community Oncologists on the FDA's Mission to Improve Access

Gene Therapy in Community Practices—Administering CAR T Therapies

Avalere Consultants Untangle the MIPS Conundrum for Oncologists

Panelists Discuss Key Issues in Community Oncology Affecting Patients and Practices

Medical World News®

SP187 MANAGED CARE UPDATES FDA Grants Priority Review for Pembrolizumab, Chemotherapy Combination in NSCLC

Researchers Identify New Gene That Predisposes People to ALL

SP192 CLINICAL UPDATES New Test Could Make Multiple Myeloma Diagnosis as Easy as Drawing a Blood Sample

Novel Drug Shows Promise in Acute Myeloid Leukemia by Suppressing 2 Proteins

FROM THE EDITOR-IN-CHIEF



ALVARNAS

Making Disruptive Technology Less Disruptive

Film is truth 24 times a second, and every cut is a lie

— Jean-Luc Godard

WHILE GODARD’S pronouncement on the cinema may have been uttered with more than a hint of irony, the sensibilities he captured do have relevance in regard to the delivery of cancer care. When patients discuss what is of the greatest value in their care, many describe their relationship with their physician as an essential, indispensable part of their cancer journey. Similarly, most physicians describe their relationship with their patients as the grounding core of their profession. As the “truth” of these key human interactions are disrupted by the technical and workflow disruptions that, tragically, increasingly permeate and undermine the quality of the time spent in direct patient care, both physicians and patients note the toll that these disruptions take their experience of healthcare.

As cancer care becomes increasingly technology driven, the relationship between the patient and the physician is increasingly subject to “cuts” that undermine the patient centricity of care. In addition, as the increasing number of “cuts” become an inescapable part of the oncologist’s work day (including the innumerable clicks necessary to navigate electronic health records, the interruptions of having to obtain authorization for diagnostic studies, the paperwork associated with obtaining access to cutting edge oral therapeutics, interpreting genomic testing data, seeking clinical trials for patients), the complexity and work burdens of physicians are leading to greater clinician work stress and burnout. Inasmuch as advances in diagnostic technologies, such as genomic testing, promise to improve patient outcomes, the addition of reviewing, interpreting the results, developing care plans based upon genomic data further test the time limits and technical skills of many oncologists. In an article in Healthcare Informatics, the authors quote Jeremy Warner, MD, MS, in noting:

Integrating genomics into clinical workflow is a step into unknown territory, he added. Health systems have to make sure the report is not interruptive of the patient-doctor relationship. “I can’t imagine reading a 30-page PDF in front of a patient in the office.”¹

The importance of bringing effective point-of-care tools to the practice of oncology cannot be overstated. With the confluence of the increasing complexity of delivering state-of-the-art cancer care to patients and the

finite limits of physician time, focus, and human sustainability, the importance of more effective point-of-care resources seems to be self-evident. Advances in information technologies, coupled with greater engagement of an increasingly diverse set of health care stakeholders, has helped to grow point-of-care tools from a core suite of technologies that include evidence-based guidelines and clinical pathways tools to a growing breadth of assets that bring genomic information, reimbursement support, and patient education tools closer toward meeting the needs of the patient and the clinician. These tools may take the form of more effective authorization policies by private and government payers, telehealth support to ensure more effective patient engagement and education, and apps to assess patient-reported outcomes.

In this month’s edition of *Evidence-Based Oncology*[™], we review some of the point-of-care tools that may help to improve physician work life while also enhancing the patients’ care experience. Authors from Flatiron Health share offer an update on what is working and what’s not with the Oncology Care Model from the perspective of the technology provider and how changes could mitigate the burdens of the electron health record upon physicians’ time with their patients. Authors from Foundation Medicine describe how changes to the FDA/CMS approval process can reduce the pre-authorization burden imposed upon physicians seeking genomic testing for their cancer patients. Matt Lashey from chemoWave writes about how an app to track patient-reported outcomes can help empower better care. Heather Zierhut, PhD, MS, CGC, and Adam Buchanan, MS, MPH, LGC, explore how Medicare reimbursement for telehealth for genetic counseling could more effectively meet patient care needs while helping physicians bring additional expertise to the care of their patients. ♦

REFERENCE

1. Raths D. The ongoing struggle to get actionable genomic data to the point of care. Healthcare Informatics website. healthcare-informatics.com/blogs/david-raths/ongoing-struggle-get-actionable-genomic-data-point-care. Published October 26, 2016. Accessed May 8, 2018.

Joseph Alvarnas, MD
EDITOR-IN-CHIEF

EDITORIAL MISSION

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

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Clinical Care Targeted Communications, LLC, d/b/a Managed Care & Healthcare Communications, LLC, the editorial staff, or any member of the editorial advisory board. Clinical Care Targeted Communications, LLC, d/b/a Managed Care & Healthcare Communications, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this journal is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Clinical Care Targeted Communications, LLC, d/b/a Managed Care & Healthcare Communications, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

The content contained in this publication is for general information purposes only. The reader is encouraged to confirm the information presented with other sources. *Evidence-Based Oncology*[™] makes no representations or warranties of any kind about the completeness, accuracy, timeliness, reliability, or suitability of any of the information, including content or advertisements, contained in this publication and expressly disclaims liability for any errors and omissions that may be presented in this publication. *Evidence-Based Oncology*[™] reserves the right to alter or correct any error or omission in the information it provides in this publication, without any obligations. *Evidence-Based Oncology*[™] further disclaims any and all liability for any direct, indirect, consequential, special, exemplary, or other damages arising from the use or misuse of any material or information presented in this publication. The views expressed in this publication are those of the authors and do not necessarily reflect the opinion or policy of *Evidence-Based Oncology*[™].

EDITORIAL BOARD



EDITOR-IN-CHIEF
JOSEPH ALVARNAS, MD
Director of Value-Based Analytics
Director of Clinical Quality
Alpha Clinic, City of Hope
Duarte, CA



MICHAEL E. CHERNEW, PHD
Department of Health Care Policy
Harvard Medical School
Boston, MA



JESSICA DEMARTINO, PHD
Manager, Health Outcomes, Insights, and Solutions—Vaccines
Glaxo Smith Kline
Philadelphia, PA



JONAS DE SOUZA, MD, MBA
Medical Director, Office of the Chief Medical Officer
Humana
Louisville, Kentucky



JEFFREY D. DUNN, PHARM.D, MBA
Vice President, Clinical Strategy and Programs and
Industry Relations
Magellan Rx
Salt Lake City, UT



BRUCE A. FEINBERG, DO
Vice President and Chief Medical Officer
Cardinal Health Specialty Solutions
Atlanta, GA



A. MARK FENDRICK, MD
Professor of Medicine and Health
Management and Policy
Schools of Medicine & Health
University of Michigan
Ann Arbor, MI



JOHN L. FOX, MD, MS
Senior Medical Director and Vice President
of Medical Affairs
Priority Health
Grand Rapids, MI



DANA GOLDMAN, PHD
Director
Leonard D. Schaeffer Center for
Health Policy and Economics
University of Southern California
Los Angeles, CA



DAWN G. HOLCOMBE, MBA, FACMPE
DGH Consulting
South Windsor, CT



JOHN HORNBERGER, MD, MS
Cedar Associates, LLC
Menlo Park, CA



IRA M. KLEIN, MD, MBA
Senior Director Quality
Strategic Customer Group
Janssen Pharmaceutical Companies



DARIUS LAKDAWALLA, PHD
Director of Research, Schaeffer Center
Quantiles Chair in Pharmaceutical Development and
Regulatory Innovation, School of Pharmacy
Professor, Sol Price School of Public Policy
University of Southern California
Los Angeles, CA



KATHLEEN G. LOKAY
CEO of Via Technology
Pittsburgh, PA



ELLEN MATLOFF, MS, CGC
President and CEO
My Gene Counsel



JOSHUA J. OFMAN, MD, MSHA
SVP, Global Value and Access
Amgen, Inc
Thousand Oaks, CA



EBERECHUKWU ONUKWUGHA, PHD
Associate Professor
Department of Pharmaceutical Health Services Research
University of Maryland School of Pharmacy
Baltimore, MD



DEBRA PATT, MD, MPH, MBA
Texas Oncology Cancer Center
Austin, TX



ANDREW L. PECORA, MD, FACP, CPE
Chief Innovations Officer
Vice President of Cancer Services
John Theurer Cancer Center
Hackensack, NJ



ERIN SULLIVAN, MPH, PHD
Vice President, Health Economics and Outcomes Research
Avalere Health
Lexington, MA



MARK ZITTER, MBA
The Zetema Project
San Francisco, CA

Nominate a Rising Leader in Managed Care Research!



AJMC® Seema S. Sonnad
Emerging Leader
in Managed Care Research Award

The American Journal of Managed Care® (AJMC®)'s Seema S. Sonnad Emerging Leader in Managed Care Research Award was established to recognize an individual whose early achievements in managed care demonstrate the potential for making an exceptional long-term contribution as a leader in the field.

To commemorate Sonnad's exemplary leadership and the valuable mentoring she provided to her fellows and trainees, *AJMC®* has dedicated this award in her honor. Her countless contributions will continue to affect healthcare through her research, her many collaborations, and the generation of investigators she helped to train.

AJMC®
Managed Markets Network®

ELIGIBILITY

Award nominees must meet the following requirements.

NOMINEES MUST:

- Be less than 5 years from the receipt of their highest degree/ less than 7 years from their first full-time position.

**While not a requirement, the publication or acceptance of a paper in *AJMC®* will be positively noted.

NOMINATIONS

The nomination package should consist of a letter of recommendation outlining the nominee's contributions and merit (not to exceed 2 pages), CV, and *AJMC®* publications (if applicable).

Self-nominations are permitted.

Please visit www.ajmc.com/about/ajmc/ss-elmcr-award to submit a nomination.
Nominations close on July 31, 2018.

National Comprehensive Cancer Network, American Association of Clinical Urologists, and Large Urology Group Practice Association Endorse Biomarkers in Prostate Cancer

Robert Finch, MS, CGC



FINCH
Robert Finch, MS, CGC, is a medical science liaison at Myriad Genetics Laboratories.

PROSTATE CANCER IS the most common cancer diagnosed in men, second only to skin cancer.¹ However, the gravity of a diagnosis is highly variable and difficult to predict. Some men will have more aggressive disease and should receive definitive treatments, while many others will have indolent disease and may best be followed with active surveillance. Active surveillance, which is the careful observation of patients to make sure the cancer shows no signs of becoming more aggressive, is much less expensive than definitive treatments; however, scientific literature and guidelines to help physicians make this choice don't always agree. Historically, the decision whether to pursue treatment or active surveillance has relied solely on clinical and pathologic features, such as Gleason score, baseline prostate-specific antigen level, clinical stage, and extent of disease based on core biopsies. Clinical and pathologic features are important, but some of these features have been shown to be highly variable. The combination of these features to create nomograms, such as CAPRA (Cancer of the Prostate Risk Assessment),² improves upon the use of these features alone, but still leaves many men with inadequate information to make a treatment decision.³

Accurate prediction of the natural history of prostate cancer is necessary to avoid overtreatment, which increases the morbidity rate in men⁴ and is costly to the healthcare system. Biomarkers, or molecular testing of the prostate cancer tumor tissue, can more accurately predict the aggressiveness of prostate cancer and help physicians determine who needs definitive treatment and who can safely pursue active surveillance.³

Prolaris is a biomarker test that assesses the expression levels of 31 cell cycle progression (CCP) genes, normalized by 15 housekeeper genes. CCP genes are actively expressed during cell replication and division. The higher the expression of these genes, the more quickly tumor cells may be dividing. The expression levels of CCP genes are used to generate a CCP score, which is then combined with the clinical and pathologic features to create a Combined Clinical Risk (CCR) score that refines the risk of prostate cancer mortality. The Prolaris assay was found to be highly prognostic, with the combined score being a better predictor of disease-specific mortality than standard clinical and pathologic features alone.⁵

Of note, Prolaris is the only biomarker for prostate cancer that has been validated in patients who have not undergone immediate treatment, because they are being conservatively managed. Once validated in this group, CCR scores are evaluated to develop a threshold that can be used to guide patient selection for active surveillance. The chosen threshold was validated in a cohort of 585 conservatively managed men with low-, intermediate-, or high-risk features and a modified cohort of 284 men with high-risk features. There were no observed deaths in men with CCR scores at or below the threshold selected in either cohort.⁶

With 80% of prostate cancers diagnosed at a clinically localized stage and still treated with definitive surgery before the introduction of biomarkers, Crawford et al examined the clinical utility of Prolaris.⁷ In a prospective study of 305 patients with newly diagnosed prostate cancer, the authors sought to evaluate the impact of Prolaris on treatment decisions. Overall, 65% of cases showed a change between intended treatment prior to the Prolaris test and treatment recommendations following the test. In 37.2% of cases, men who were planning to have radical prostatectomy changed

to active surveillance. Prolaris helps to identify men who can safely pursue active surveillance, reducing the number of patients who pursue definitive treatment options and the healthcare costs associated with overtreatment.

In March of 2018, the National Comprehensive Cancer Network (NCCN) updated its Prostate Cancer Guidelines⁸ to support the use of biomarkers, including Prolaris, in prostate cancer tumors. The guidelines suggest that tissue-based molecular testing should be considered for low- and favorable intermediate-risk men who have a life expectancy of at least 10 years. The guidelines also suggest that germline testing should be considered for men with localized disease and a strong family history as well as men with high-risk or metastatic disease, irrespective of family history. Research suggests that up to 24.1% of men with prostate cancer may harbor germline mutations that contributed to the development of their disease⁹ and may have implications for the aggressiveness of the disease.¹⁰

Following the support of the NCCN, the American Association of Clinical Urologists (AACU) published a position statement with respect to genomic testing in prostate cancer.¹¹ AACU supports the use of tissue-based molecular testing for prostate cancer to help guide treatment decisions and strongly encourages providers to take a family cancer history and offer germline genetic testing for appropriate patients to help clarify hereditary cancer risk.

Most recently, the Large Urology Group Practice Association (LUGPA) acknowledged and endorsed the AACU position statement¹² and the NCCN Guidelines, providing more direction for LUGPA providers who utilize genomic and genetic testing for men with prostate cancer. Neal D. Shore, MD, FACS, LUGPA president, said in a statement, "LUGPA and AACU are proud to represent more than 6000 American urologists who strive to provide patients with quality, personalized care. Together our organizations are sending a message to policy makers, researchers, payers, and, most importantly, patients and their families, that we are committed to applying the best and most current science to the detection, risk stratification, and appropriate treatment of prostate cancer."¹²

The support of the NCCN and 2 prominent urologic professional societies represents the most direct guidance to date for practicing clinicians who treat prostate cancer on these 2 important components of risk stratification. With the utilization of a validated algorithm of clinical, pathologic and genomic variables, as well as a patient's germline genetic information, healthcare providers are poised to provide the best care to patients with prostate cancer. ♦

AUTHOR INFORMATION

Robert Finch, MS, CGC, is a certified genetic counselor specializing in the genetics and genomics of cancer. He currently serves as a medical science liaison at Myriad Genetic Laboratories, where he provides education and clinical support to healthcare providers treating men with prostate cancer.

REFERENCES

1. Key statistics for prostate cancer. American Cancer Society website. cancer.org/cancer/prostate-cancer/about/key-statistics.html. Updated January 4, 2018. Accessed April 17, 2018.
2. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment Score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol*. 2005;173(6):1938-1942.
3. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort.

CONTINUED ON SP166

AJMC

The Evolution of Biomarkers to Guide the Treatment of Metastatic Colorectal Cancer: ajmc.com/link/2900.

PATIENT-REPORTED OUTCOMES

Riding the Wave Through Chemo: Cancer Journey Leads to chemoWave App for Reporting PROs

Matt Lashey, MBA

IN 2013, MY PARTNER RIC was diagnosed with stage IIIA non-Hodgkin lymphoma. The pronouncement that we were facing a fast-growing cancer felt like a slow-motion nightmare; it was disorienting, devastating, scary, and completely out of nowhere. Cancer came crashing into our lives like a tsunami and we were left scrambling to find anything that might help us stay afloat.

Ric did not feel sick. He had been a vegetarian for more than 15 years, was feeling great, was running 5 to 6 miles a day, and was in great shape. We noticed a small lump on his neck but decided not to worry about it after consulting with a doctor who ordered a computed tomography (CT) scan and subsequently advised us that it was “nothing to be concerned about.” We tried to ignore it, but over the next few weeks it continued to grow and eventually became uncomfortable, so we scheduled an appointment to have it removed. At this second appointment, a different doctor inspected Ric’s neck, ordered a new scan, and soon after informed us that this “lump” actually was something to be very concerned about—we were facing cancer. Within days, we found ourselves in the hospital starting the first of 6 aggressive rounds of chemotherapy, rituximab with cyclophosphamide, hydroxydaunomycin, oncovin and prednisone, the regimen known as R-CHOP.

After the initial shock, we tried to educate ourselves. We dove into a sea of resources and information about Ric’s treatment options and potential side effects. We sorted through tips upon tips about what to expect and how to manage it all, but it was difficult to determine what would apply to Ric’s situation and even harder to reconcile so much contradictory information. We paid for apps and digital services that did not deliver the promised benefits. We sought advice from others who’d received a similar diagnosis and been through the same treatment; but time and again, Ric’s personal experiences did not resemble what these well-meaning acquaintances warned us to expect. And we began to get more confused. We soon realized that even though many of the cancer treatments and protocols are standard, every patient is unique.

Everyone’s Different

We now understand that most of the symptoms and side effects patients experience while undergoing chemotherapy can be managed, if not avoided all together. Throughout treatment, doctors ask patients questions about how they feel and patients do their best to remember what happened during the previous weeks. However, patients struggle to recall details of when they felt good and how long ago they felt poorly. It becomes increasingly difficult to remember the specifics of a skin rash or point to the exact moment of discomfort with nausea by the time a one-on-one visit with the doctor occurs. Patients’ memories fade. Or “chemo brain” takes over and patients can’t remember the details at all. Ric and I realized we needed to take daily notes to keep track of the details.

As we plodded through the ups and downs of Ric’s chemo treatment, I noticed that Ric’s various activities and encounters seemed to have an impact on his physical and emotional state from day to day.



chemoWave allows users to track and view water intake, among other things, in the form of a chart.

He clearly felt better on days after he’d been more physically active, and the benefits of visits or calls from Ric’s nephews and nieces were undeniable. He was more easily aggravated when he took certain medications and too much sleep seemed to make him feel worse.

Then something clicked for me. With a background in market research, I’d spent much of my career using data driven insights to help big companies identify opportunities, reduce risks, and become more efficient. I decided to use my research and data analysis skills to help Ric in his time of need. With a goal of helping Ric get through treatment, I created a system on my computer to keep a detailed record of Ric’s activities and experiences, which could help me identify things that might make him feel better or worse.

At first, Ric would get annoyed at my insistence to answer questions while he was struggling to not throw up his food. My constant inquiries seemed useless to him. And truth be told, I wasn’t sure if my system would help. But I was determined to help us regain control in what seemed like an uncontrollable situation and to give our doctor

information that would let him intervene earlier to resolve issues.

Our doctor quickly acknowledged the benefits of the system. During an appointment when Ric had been dealing with severe constipation, we shared charts that highlighted an anti-nausea drug might be related to the issue he was experiencing. Ric’s doctor saw what we did. He could see the exact day and time when the negative side effect started—and so he prescribed Ric a different anti-nausea medication. Almost immediately, Ric’s symptom was relieved. We were excited that our system helped to identify the relationship between the constipation and Ric’s anti-nausea medication. We also realized for the first time that we had medication options and that doctors had choices if they had enough data.

Ric was resigned to the fact that he would feel terrible throughout the process. After all, “I have cancer,” he would say. But having the doctor easily change a drug designed to manage one side effect that might be causing another was a real revelation—and motivation for both of us. He could depend on our information to determine if a drug was working as intended or if Ric was drinking enough water, doing enough physical activity, or taking his medications on time. We now felt like we had an advantage in this fight—and a purpose. We knew with greater accuracy what Ric experienced and when. We now had *individualized* information. And we could give »



A 4-year cancer survivor, **Richard Grenell** assumed office as the US Ambassador to Germany on May 8, 2018. He was previously the longest serving US spokesman in United Nations history and is a former partner with Los Angeles-based Capitol Media Partners. Grenell is also a former Fox News contributor.



LASHEY

Matt Lashey is the creator of chemoWave, the first free app from parent company Treatment Technology & Insights, Inc. Previously, Lashey served as an executive in various strategic research and data analysis roles for Discovery Networks, A&E/Lifetime Television, as well as the innovation consulting firm Maddock Douglas.



Users can allow the app to send a notification when it is time to take medications. Depending on the users' response, if they've taken the medication promptly, they have the ability to log what their symptoms are like after taking it.

our doctor actionable and *personalized* insights. So, we started tracking everything we could think of: visits from family members, sleep patterns, weather, moon phases, moods, activities, and more.

Patient Empowerment

We had discovered that far from being powerless throughout Ric's treatment, that we could play an active role. We later learned that some healthcare organizations had been exploring the benefits of tracking symptoms between doctor appointments. The industry calls this type of symptom tracking patient reported outcomes (PROs).¹ We also learned that while the industry talks a lot about PROs, some executives are reluctant to integrate this type of patient information into their current systems, despite the benefits that have been proven through clinical research. Their reluctance stems from the overwhelming government and legal requirements that have turned too much of their work into silly administrative tasks. Also, electronic health records (EHRs) have been dumped into doctors' files with little regard for the impact they have on patients. The doctor-patient relationship has greatly suffered because of the administrative tasks EHR systems have introduced into their face-to-face time. While many doctors feel the benefits of monitoring patient experiences or PROs are worth the added work, many hospital administrators have been reluctant to integrate PROs because this would add another layer to the record keeping process.

Less Trial and Error

But the valuable daily information patients have about their care cannot be ignored if providers want less trial and error and better outcomes. Results from a recent 7-year clinical trial revealed that a system that enabled patients to record and report symptoms to doctors in real time resulted in higher survival rates among patients and helped patients to live longer with an improved quality of life and less emergency department visits.² The healthcare industry is just beginning to realize the power of this immediate real-time tracking and monitoring of symptoms reported by patients. Many doctors see they can intervene with their patients when necessary, instead of allowing their patients to suffer in silence until their next in-person visit.

After Ric finished his treatment and was

pronounced cancer free, and at the encouragement of his doctor, we decided to take the analytics program I created and put it into an app that could be accessed by anyone. The lessons we learned through 6 rounds of R-CHOP in the summer of 2013 needed to be shared with others dealing with cancer. And we were committed to making our program available for free.

After consulting with digital experts and health-care professionals, I quit my full-time job, took money from our savings, and built a PROs system called chemoWave.³ After years of studying the technology options, hiring consultants, talking to researchers, and learning to comply with the Health Insurance Portability and Accountability Act, we are now harnessing the power of patient engagement and how they can drive better care using their own individualized information.

New Type of Precision Medicine

Today, our free app has gone through multiple upgrades and is now helping thousands of people. We've partnered with patient support groups such as the Look Good Feel Better Foundation and the CaringBridge non profit social network, and we have a resource collaboration with Cancer.net from the American Society of Clinical Oncology.⁴ We are working with major cancer hospitals to provide real-time, actionable chemoWave data to doctors and valuable aggregated/de-identified data to researchers. Our technology solution is less about the cancer diagnosis and more about identifying what makes each patient unique. An individual's DNA is important, but so are psychosocial factors, their support system, their activities, and lifestyle.

Technology advances have prompted patients to demand this more immediate give-and-take with their doctor. Cancer patients are currently not equipped to be active participants in their care, and many tell us they feel like guinea pigs relegated to deal with cancer's side effects on their own. They feel like they must put their heads down and endure it until their next face-to-face appointment with their doctor. But the more patients can get timely and accurate data to their healthcare team, the more likely the doctor can adjust treatment to significantly reduce or avoid side effects.

Today, chemoWave has learned much from the thousands of patients using our technology in all 50 states, representing 70 plus types of cancers.³ Some users have said, "This is the first time I understand what's going on with my body and my emotions," and "I am motivated to get up and do more by seeing how closely tied my activity levels are to feeling better." chemoWave is equipping patients and their caregivers with personal data-driven insights to better manage the physical and emotional rollercoaster of chemotherapy. And doctors who are treating patients using chemoWave are telling us that chemoWave has helped to improve their communication and made them feel more connected outside the office visit. This personal, real-time information on patient experiences means doctors can be more confident about their choices and spend less time on trial-and-error strategies.

chemoWave's timely and specific data, and its system of ongoing data collection represent an

Br J Cancer. 2015;113(3):382-389. doi: 10.1038/bjc.2015.223.

4. Cuzick J, Berney DM, Fisher G, et al; Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2012;106(6):1095-1099. doi: 10.1038/bjc.2012.39.
5. Brawer MK, Cooperberg MR, Freedland SJ, et al. Development and validation of a multivariate model combining cell cycle progression score with CAPRA to predict prostate cancer mortality in a conservatively managed cohort. *J Clin Oncol*. 2013;31(6 suppl):67. ascopubs.org/doi/abs/10.1200/jco.2013.31.6_suppl.67. Published February 23, 2013. Accessed April 17, 2018.
6. Lin DW, Crawford ED, Keane T, et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance [published online April 11, 2018]. *Urol Onc*. doi: 10.1016/j.urolonc.2018.03.011.
7. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Curr Med Res Opin*. 2014;30(6):1025-31. doi: 10.1185/03007995.2014.899208.
8. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer, version 2.2018. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published March 8, 2018. Accessed March 26, 2018.
9. Rosenthal E, Brown K, Kidd J, et al. Outcomes of clinical testing for 76,000 patients utilizing a panel of 25 genes associated with increased risk for breast, ovarian, colorectal, endometrial, gastric, pancreatic, melanoma and prostate cancers. Presented at: 2015 American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2015; Chicago, IL. Poster 338. ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.1515.
10. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. 2013;31(14):1748-1757. doi: 10.1200/JCO.2012.43.1882.
11. American Association of Clinical Urologists. Position statement: genomic testing in prostate cancer. AACU website. aacuweb.org/docs/position-statements/ps_genomic-testing-in-prostate-cancer.aspx. Accessed April 17, 2018.
12. LUGPA endorses AACU policy statement on genomic testing [press release]. Chicago, IL: LUGPA; March 7, 2018. lugpa.org/lugpa-endorses-and-supports-new-cancer-guidelines-from-nccn/. Accessed April 17, 2018.

underutilized trove of information not represented in the literature. Technology has revolutionized many industries, and it should be used to update patient protocols and their reactions to standardized healthcare. It is time for patients to have more control over what is prescribed to them and technologies like chemoWave are giving them that power. ♦

AUTHOR INFORMATION

Matt Lashey, MBA, is the CEO of Treatment Technologies and Insights, which distributes the mobile application chemoWave. He founded the company working as a leader in market research and branding in the entertainment industry.

REFERENCES

1. Basch E. The rise of patient-reported outcomes in oncology. American Society of Clinical Oncology website. am.asco.org/daily-news/rise-patient-reported-outcomes-oncology. Published May 26, 2016. Accessed April 6, 2018.
2. Basch E, Deal A, Dueck A, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017;318(2):197-198. doi:10.1001/jama.2017.7156.
3. chemoWave website. chemowave.com.
4. Our partners. chemoWave website. chemowave.com/partners. Accessed April 6, 2018.

ONCOLOGY

BEST PRACTICE™



Overview:

Oncology Best Practice™ brings recognized thought leaders directly to your institution. Our mission is to educate your oncology care team on the latest clinical data, guidelines, and best practices across a range of topics in cancer care. All programs are complimentary and logistically-supported by PER®, a leading CME/CE accredited provider of oncology-focused education for over 2 decades. **Oncology Best Practice™** is 60/90-minute CME accredited programs.

Oncology Best Practice™: Informed Decision Making in Advanced NSCLC: Matching Treatment to Patient

The program will address unmet needs that persist for patients with lung cancer, followed by current and emerging therapies to address these medical needs.

Chair: **David R. Gandara, MD**
UC Davis Comprehensive Cancer Center
Sacramento, CA

Oncology Best Practice™: Choosing Therapies for Patients with EGFR-Mutant Lung Cancers: More Options... More Decisions... Better Outcomes

This series is a synthesis of recent data sets on newly available and late-stage investigational strategies to manage *EGFR*-mutated, advanced NSCLCs, and who can help place new evidence in its proper context for the practitioner challenged to manage patients with these tumors.

Chair: **Mark Kris, MD**
Memorial Sloan Kettering Cancer Center
New York, NY

Oncology Best Practice™: Optimizing Outcomes When Quality Is Being Measured: A Focus on Evidence-Based Care for Gastric and GEJ Cancer Treatment

This is a synthesis of data sets on newly available and late-stage investigational strategies to manage advanced gastric cancers that can assist community practitioners in optimizing outcomes for their patients.

Chair: **Manish A. Shah, MD**
Weill Cornell Medical College/
New York-Presbyterian Hospital
New York, NY

Oncology Best Practice™: Decision Points in Advanced NSCLC: Assessing Treatment Options Beyond Disease Progression

This series will address the therapeutic needs that persist for patients with lung cancer, as well as current and emerging therapies to address these medical needs.

Chair: **David R. Gandara, MD**
UC Davis Comprehensive Cancer Center
Sacramento, CA

Oncology Best Practice™: Expert Perspectives to Incorporate Evidence on PARP Inhibitors into Practice and Optimize the Medical Management of Ovarian Cancer

This series program will address how to optimize sequencing treatment strategies and manage adverse events based on the current evidence in ovarian cancer.

Chair: **Michael Birrer, MD, PhD**
Massachusetts General Hospital
Boston, MA

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Physicians' Education Resource®, LLC, designates this live activity for 1.5 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Physicians' Education Resource®, LLC, is approved by the California Board of Registered Nursing, Provider #16669, for 1 to 1.5 Contact Hour.

For more information visit
gotoper.com/go/OBP

Call 609-325-4668 or
email SZelasko@gotoper.com

FROM OUR CONTRIBUTOR

How Managed Care Can Advance Responsible Genetic Testing

L. Patrick James, MD



JAMES

L. Patrick James, MD, is the chief clinical officer for health plans and policy, Medical Affairs, Quest Diagnostics.

WHEN THE HUMAN genome was first sequenced in the early 2000s, the president of the American College of Medical Genetics, R. Rodney Howell, MD, declared, “The implications for healthcare are tremendous...it will take time to gather the full benefit of the Human Genome Project, but this will no doubt change the practice of medicine in every way.”¹

More than a decade later, one filled with tremendous new discoveries in genetics, a survey in the *Journal of Family Medicine* found that a majority of primary care physicians (54%) felt that they were not knowledgeable about available genetic tests, and their perception of the utility of genetic tests varied wildly, depending on the disease state.²

Given slower adoption of genetic testing over more than a decade, diagnostic information service providers of laboratory genetic tests must take a critical look at why so many clinicians lack deep knowledge of advanced diagnostics involving genetic or molecular analysis. In many cases, the root cause is not the lack of clinical or economic utility of these services; it is physicians’ lack of practical knowledge about how and when to use genetic insights in care management and having confidence they’ll be reimbursed for patients.

In a perfect world, innovation, adoption, and reimbursement would develop and occur in lock step. Tests that provide clinically valuable insights to influence patient care would be developed and made available, physicians would use those tests in practice, and payers would cover much of the costs.

But healthcare is imperfect. Genetic tests and other advanced diagnostics are often introduced to a medical community with limited understanding about their potential applications and benefits. Health plans may be blindsided, too, unprepared to reimburse a new service based on limited research or, at least, research deemed credible by the plan.

It’s a Catch-22. Without clinical and economic evidence, payers are unlikely to issue favorable coverage and reimbursement decisions; without reimbursement or coverage, physicians may be less likely to order the tests.

Within this environment, the quality and innovativeness of the service provider can go a long way toward promoting appropriate use of genetic and other advanced diagnostic services. When evaluating a diagnostic provider and its services, health plans and physicians should carefully consider several factors that can influence quality and care:

Trustworthiness. At the 2012 “Reimbursement Models to Promote Evidence Generation and Innovation for Genomic Tests” workshop, Representatives from Palmetto GBA, a Medicare Administrative Contractor that is the national specialist in assessing molecular diagnostic technologies, emphasized the roles that labs can play in physician education: ensuring appropriate test use and assisting with test interpretation.³

Health plans and physicians, along with patients, need to know they can trust their diagnostic service provider. A genetic test is not always the best option. A comparatively less expensive routine blood test might be as effective in guiding care in some cases. Likewise, a panel of actionable, validated genes may produce fewer opportunities for confusion than a very large panel with genes that are not well characterized. Does the provider push for more or higher-priced services when something less expensive may be just as good?

It is not uncommon for physicians to mistakenly order genetic tests because they lack a complete family history for a patient. When we notice a pattern of inappropriate overutilization, Quest

Diagnostics arranges for genetic counselors to review members’ personal and family histories extending back generations. To reduce potential conflicts of interest, these patient counselors are not employed by Quest; access is provided through a third-party vendor. With this collected history, the physician is better informed and may opt to order fewer, but more appropriate, tests. There is great power in collaboration amongst trusted partners. This process has helped to reduce overutilization of services, benefiting the patients, physicians, and health plans.

Connects patients, payers, and physicians. When genetic testing is ordered for a patient, it may be under emotionally fraught circumstances, such as for evaluation for susceptibility to cancer. A diagnostic service provider should aim to connect patients, payers, and physicians to ensure a smooth testing process for all concerned.

Preauthorization is a case-in-point. A diagnostic service provider that can facilitate pre-authorization helps the patient and provider estimate the level of reimbursement and patient responsibility before testing occurs. In today’s era of high-deductible plans, such insights can be invaluable for patients. Pre-authorization can also reduce turnaround time to report results by ensuring the health plan has the documentation it needs before testing occurs. In working with 1 health plan to pre-authorize *BRCA1* and *BRCA2* testing, Quest Diagnostics reduced the average turnaround time from 40 days to 24 to 48 hours, largely by reducing the time needed by the payer to authorize testing.

Connecting patients, payers, and physicians also extends to the comprehensiveness of services. In many cases, one evaluation with a certain lab test leads to another episode of care with other tests. A provider that offers the gamut of diagnostic services may be better positioned to help the physician manage the patient across the care continuum. A specialty lab focused on noninvasive prenatal screening, for instance, may not offer confirmatory testing, such as chromosome analysis of amniotic fluid.

Scientific expertise. Genetics is a murky science, and discerning which discoveries are actionable and which are not requires significant expertise. A typical genome sequence has about 3.5 million differences from a reference genome, but only about 0.6 million are rare. Accurate identification and interpretation of the clinical significance of genetic variants is critical to quality testing. In this regard, the quality of the medical staff and the databases they refer to in order to determine variant classifications can influence whether testing is clinically actionable.

As genetic discoveries grow, the role of diagnostic testing to inform clinical decisions is likely to expand. Responsible stewards of genetic and other advanced diagnostic services are best positioned to favorably influence care. Health plans that prioritize trustworthy expert providers will be best positioned to ensure advanced diagnostics deliver on their potential to improve managed care and patient health. ♦

REFERENCES

1. Villano D. Human code. *University of Miami Medicine Online*. Winter 2001. miami.edu/ummedicine-magazine/winter2001/humancode.html. Accessed April 25, 2018.
2. Mainous AG, Johnson SP, Chirina S, Baker R. Academic family physicians’ perception of genetic testing and integration into practice: a CERA study. *Fam Med*. 2013;45(4):257-262.
3. Workshop Summary. Reimbursement models to promote evidence generation and innovation for genomic tests workshop. National Human Genome Research Institute website. genome.gov/27552210/reimbursement-models-to-promote-evidence-generation-and-innovation-for-genomic-tests/ National Institutes of Health, Bethesda, Maryland. October 24, 2012.

VALUE-BASED MEDICINE

With the Oncology Care Model, “Everyone Has to Be Engaged,” Including Patients

AJMC® Convenes First Gathering of Institute for Value-Based Medicine to Share Best Practices in New Payment Models in Cancer Care

Mary Caffrey

A GENERATION AGO, doctors made decisions and everyone else adapted. The rise of patient-centered care has changed the game, however, making medicine a team effort in which physicians collaborate with nurses, social workers, nutritionists, and other specialists. Most of all, physicians seek input from the patients themselves.¹ This is especially true in cancer care, where the advances have never been greater. And yet, as Lucio Gordan, MD, an oncologist with Florida Cancer Specialists, notes, the decline in cancer mortality over the past generation² has come with a caveat: The cost of care is rising.

“Because of cost, because of concerns about access to care, we started to transition away from fee-for-service to value-based care,” said Gordan, who welcomed a group of care administrators and fellow physicians to a unique gathering in Orlando, Florida, at Rosen Shingle Creek on April 5, 2018. Advancing Quality in Oncology Care was the first session of the Institute for Value-Based Medicine (IVBM), a new initiative of *The American Journal of Managed Care*®.

Taking part in the inaugural session were Gordan; Don Champlain, RN, MHA, associate director of care management for Florida Cancer Specialists; Aaron Lyss, MBA, director of value-based medicine at Tennessee Oncology; and Chris Kepinski, PharmD, clinical oncology pharmacy manager for Southern Oncology Specialists, based in North Carolina.

As Gordan explained, therapeutic advances have come alongside a growing senior population. Cancer death rates have fallen 23% over 20 years,² even among patients who have what Gordan called “bad cancers” like multiple myeloma. Census data show that when the first baby boomers turned 65 in 2011, they numbered 77 million.³ This means that “patients are staying alive and responding well to treatment,” he said, with much of this attributable to the rise of better therapies, including immunotherapies. Thus, cancer care costs, which reached \$87.8 billion in the United States in 2014,⁴ are not simply derivative of pharmaceutical costs, Gordan said, but reflect that cancer is being diagnosed at earlier stages across a much larger population, one that is living longer with the disease. Quality of life is improved, too. “Patients are tolerating therapy better,” he said.

Value-based medicine seeks to target resources where they will do the most good, while avoiding unnecessary spending on the emergency department (ED), hospital admissions, or therapies that won’t work or that patients won’t take. Deployment of these principles requires communication and coordination among all of the parts of the healthcare enterprise, the use of data-driven tools to guide decision making, and, most of all, listening to the patient’s needs. “Everyone has to be engaged,” Gordan said.

Most of all, new payment models must recognize a different way of doing business. As Gordan and Champlain would explain, Florida Cancer Specialists got a head start on the episode-based system that would become the CMS Oncology Care Model (OCM), which has now been embraced by 14 commercial payers and is in use by 187 practices.⁵ Gordan explained that the OCM blends the concept of the patient-centered medical home with bundled payments. Under the 5-year model, a triggering event creates



The Institute for Value-Based Medicine (IVBM) launched its inaugural Advancing Quality in Oncology Care program in Orlando, Florida. IVBM is dedicated to advancing education in oncology value-based medicine.

Our goal is to bring together experts from multiple disciplines to advance best practices. Our program includes leaders from leading community-based practices who shared their experiences implementing CMS’ Oncology Care Model, oral therapy adherence, and care management.

an episode that runs for 6 months. Practices are paid \$160 per member per month to provide care coordination and enhanced services, while achieving requirements that include 24/7 access to a clinician who uses a patient’s electronic health record. The OCM calls on practices to adhere to national clinical guidelines for use of therapies and, above all, to “adhere to a patient-centered approach,” Gordan said. “We can’t ever forget that.”

Opportunities and Barriers in Oral Chemotherapy

Kepinski followed with a presentation, “Best Practices: Treatment Planning and Management in Oral Therapies,” which highlighted the benefits of fully integrating the pharmacy into an oncology practice. While oral oncolytics can be convenient, they bring many challenges, too—which makes education essential, Kepinski said.

“Every year we know there are more and more oral chemotherapies coming out,” he said. “Drugs that are already approved have new indications,” perhaps with new dosing. Coordination with a patient’s primary care physician is essential to create a patient profile, which tells the pharmacist what other drugs the patient is taking. But avoiding drug interactions or allergies is just one element. Kepinski outlined the many steps that occur to make sure that patients can pay for their therapies, one of which may be help from a foundation. The rise of high-deductible plans is complicating the math for patients with high out-of-pocket costs. “Foundations may cover the co-pay, but that might not count toward the deductible,” he said. “This is going to be a hot topic in the near future.”

The transition of some cancers from a short-term event to a chronic condition, requiring treatment for years, has given rise to the term “financial toxicity,”⁶ referring to the burdens that patients with cancer and their families face from the cost of care. Kepinski sees it up close. “Often, I get calls that have nothing to do with the medication,” he said. A patient who initially says that he or she can afford a drug “can do it for a month, but they can’t do it every month.”

Thus, follow-up is essential. Patients need phone calls at least once a month to ensure they are still taking oral medications; these calls should be backed by lab reports and a discussion of any new adverse effects. Getting a count of remaining pills is a must, Kepinski said, and patients should be encouraged to bring up financial or insurance issues. Each phone call is an opportunity for education. “The back-and-forth helps involve the patient in their own care,” he said. »



GORDAN

Lucio Gordan, MD, is an oncologist with Florida Cancer Specialists.



CHAMPLAIN

Don Champlain, RN, MHA, is the associate director of care management for Florida Cancer Specialists.



LYSS

Aaron Lyss, MBA, is the director of value-based medicine at Tennessee Oncology.



KEPINSKI

Chris Kepinski, PharmD, is a clinical oncology pharmacy manager for Southern Oncology Specialists.

The Shift to Value Means Changing the Culture

In his presentation, “Culture Change and Process Improvement: Key Initiatives for Success in Value-based Payment,” Lyss said that for all of the unknowns about the move away from fee-for-service, this much is true. “The old world is not coming back,” he said. Oncology practices must adapt to a value-based climate, and the only decision is how far along that practice wants to be.

In 2015, Congress passed the Medicare Access and CHIP Reauthorization Act,⁷ giving physicians with any significant footprint in Medicare a choice of how they want to be paid: through the Merit-based Incentive Payment System or through an advanced alternative payment model (APM). The OCM gives practices the ability to meet advanced APM requirements in a way that many commercial payers have also pursued.

Lyss said the OCM allowed Tennessee Oncology to build on lessons it had gained from earlier value-based initiatives. This was no “box-checking” exercise, as doing so would call on the practice to improve its use of clinical pathways and its telephone triage system; a core feature of OCM is giving patients access to same-day appointments. Better access to palliative care and improvements in end-of-life discussions were musts. The shift to OCM required:

- Accurate tracking of the start and end of episodes
- Data management to report quality measures
- Patient safety steps that featured morning “safety huddles,” scheduled based on patient needs
- Adverse event reporting
- Better patient education and financial counseling
- Better pharmacy integration.

The best way to keep physicians on pathways is to report how much individual physicians adhere to them, Lyss said. So far, Tennessee Oncology’s adherence rate is about 80%. “Transparency keeps people on pathway,” he noted.

Tennessee Oncology is seeing improved response times to phone calls. So far there’s been a jump from 48% to 68% of symptom management calls being addressed within 2 hours and improvement to 73% following the implementation of a case management system. Before the start of case management, 35% of calls to the triage nurse were for items that belonged elsewhere in the system; that proportion has now shrunk to less than 1%.

A partnership with Aspire Health has embedded palliative care in outpatient clinics, and claims data show a drop in overall spending, with more spending on hospice care and less on hospitalization in the last 6 months of life. “It’s one thing to operationalize it; it’s another to make it seamless,” Lyss said.

Educating patients is part of the picture, too. A team at Tennessee Oncology’s Chattanooga location took part in a quality training pilot with the American Society of Clinical Oncology to train patients to call the office first. This brought a 30% reduction in ED visits, and the program is now being implemented elsewhere.⁸

But Lyss said that the shift to value-based medicine isn’t just about putting in new processes; it requires a



From left, Lyss, Kepinski, Champlain, and Gordan at the IVBM presentation in Orlando, Florida.

change of culture and takes clinician buy-in. Across 30 sites, there will be physicians at different ends of the spectrum: Some will be champions of change, and some will resist. “That’s one of the key strategies. We have to be sure we engage the early adopters,” he said. “They must have the respect of their colleagues in the office and help us operationalize this type of change.”

The Art and Science of Care Management

Value-based care has not achieved the uptake that experts and physicians predicted back in 2015. Not so at Florida Cancer Specialists. Champlain and Gordan’s presentation, “Development of Care Management at Florida Cancer Specialists and Leveraging Data with Payers,” opened with this statistic: In 2015, only 0.51% of payments were value based; in January 2018, 40.82% were. The OCM formally started later than other value-based models, but as Gordan explained, this 222-physician practice with 85 locations across Florida gets 51.84% of its payer revenue from Medicare, so it ramped up early.

To achieve OCM requirements, like 24/7 access and better care coordination, the practice turned to Champlain, who since 2015 has built a 75-person care management team of nurse navigators, nurse triage specialists, and others who coordinate services that range from nutrition to psychosocial care to survivorship. “From the time the patient leaves their visit until the next one, that’s care management,” Champlain said.

Care management starts even before the first visit to the oncologist. New patients are interviewed by phone before they come in, to review medical history and medications they are taking—while they can be retrieved from the cabinet. The central triage team handles calls all day so that messages do not pile up at individual sites. Besides the incoming calls, care managers call to check on patients. OCM requirements for a care plan are taken seriously. “It’s something we want them to use,” Champlain said.

Around-the-clock access is the key to keeping people out of the ED, he said. “A majority of the calls come later in the evening. Patients start thinking of things, and if you can’t talk to someone, that person is going to end up going to the [ED],” Champlain said. If a nurse can talk to the patient about adverse effects or offer a solution to constipation, that trip is avoided. “The patients appreciate being able to reach someone at 2 in the morning.”

For Champlain, those who come for care—and their families—are not simply “patients.” They are “consumers” and “customers,” and he says they have the option to go elsewhere. He is proud of his team’s 96% customer satisfaction rating and the fact that he is saving payers money. “I have some of the

best staff in the country,” he said. “We know we are making a difference.”

Gordan wrapped up the discussion with a review of how Florida Cancer Specialists has used data to hone in on where its hospitalization rates were high and for what types of cancer. Data allow a large practice to zero in on the practices or individual physicians who are outliers and identify cost-reduction strategies.

He shared results from 3 partnerships, including 2 unidentified payers (a third began in September 2017). Since the start of care management:

- The first partnership, which began July 1, 2015, has seen a 34% decrease in hospitalization stays.
- The second partnership, which began December 1, 2016, has brought a 17% decrease in hospitalization rates.
- The OCM population has seen a decrease in hospitalization rates of 16% since July 2016, when the program formally began.

Gordan hinted at the challenges ahead for large practices that are already efficient. For those practices that have already identified the “low-hanging fruit,” continuing to find major savings against an in-house benchmark will be difficult. “It’s very hard to repeat the same feat all the time,” he said.

Lyss agreed. CMS may have to look instead at practice spending relative to what is realistic for that market. “We need to talk about what is the sustainability and a reasonable expectation going forward,” he said. ♦

REFERENCES

1. Weissman JS, Millenson ML, Haring RS. Patient-centered care: turning the rhetoric into reality. *Am J Manag Care*. 2017;23(1):e31-e32.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30. doi: 10.3322/caac.21332.
3. Colby SL, Ortman JM. The baby boom cohort in the United States: 2012 to 2060: population estimates and projections. US Census Bureau website. census.gov/content/dam/Census/library/publications/2014/demo/p25-1141.pdf. Published May 2014. Accessed April 11, 2018.
4. The costs of cancer: addressing patient costs. American Cancer Society Cancer Action Network website. aacsn.org/policy-resources/costs-cancer. Published April 11, 2018. Accessed April 11, 2018.
5. Oncology Care Model. CMS website. innovation.cms.gov/initiatives/Oncology-Care. Updated April 5, 2018. Accessed April 11, 2018.
6. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. *Oncology (Williston Park)*. 2013;27(2):80-81, 149.
7. Quality Payment Program. CMS website. qpp.cms.gov. Accessed April 11, 2018.
8. Tennessee Oncology continually improves patient experience. Pilot study reduces ER visits in patients receiving IV chemo. Tennessee Oncology website. moncology.com/blog/2017/02/15/tennessee-oncology-continually-improves-patient-experience-pilot-study-reduces-er-visits-patients-receiving-iv-chemo. Published February 15, 2017. Accessed April 11, 2018.

POPULATION HEALTH

Population Health Council Discusses Progress in Payment Reform, Ongoing Barriers in Oncology Care

Mary Caffrey

THE SHIFT FROM managing “the patient in front of me” to populations with cancer is in full swing, and health systems have been adjusting to the presence of accountable care organizations (ACOs) and other value-based payment structures for some time.

More than a year into Medicare’s Oncology Care Model (OCM), and with changes to the 340B program on the horizon, *The American Journal of Managed Care*® convened a meeting of its Population Health Delivery Council on May 11, 2018, in San Diego, California. Chaired by Neil B. Minkoff, MD, the chief medical officer for EmpiraMed, Inc., the council featured Scott Maron, MD, medical director for Atlantic Health ACO; Deborah Welle-Powell, MPA, chief population health officer for Essentia Health; Bhavesh Shah, BPharm, director of specialty and hematology/oncology pharmacy services at Boston Medical Center Health System; Lynne Milgram, MD, MBA, chief medical officer, Sharp Community Medical Group; Debi Reissman, PharmD, senior pharmacy specialist, Sharp HealthCare; John Fox, MD, MHA, medical director, Priority Health; Dan Kus, vice president, pharmacy services, Henry Ford Health System; Despina Garalis, director, population health, Partners Physician Health Organization; Benjamin Kruskal, MD, PhD, medical director, New England Quality Care Alliance; Jonathan Jaffery, MD, senior vice president, chief population health office, UW Health; and Nirav Vakharia, MD, associate chief quality officer, Cleveland Clinic Medicare ACO.

Minkoff opened with a discussion of where ACOs are and how the movement toward population health is going as it relates to oncology. Health systems are still struggling to move oncologists or practices that have been acquired from a system of “everyone doing their own thing” to a standardized one. Pilot programs have helped, but they require significant investment. As health systems integrate with cancer centers, there are more opportunities for standardization. The panelists said the movement toward greater quality and measurement requires both leadership from the top and ownership from individual physicians. And this isn’t a one-and-done proposition. Implementation requires regular gatherings on different aspects of care, review of how the health system will implement clinical guidelines, use of technology, etc.

Early lessons. What has the movement toward population health taught us thus far in oncology? First, standardization has improved care, but it cannot always control costs. Oncologists who want to deliver the most cutting-edge therapies—to extend life by months or years—find that they cannot do so without high-cost therapies. Palliative care is getting more focus than it did in the past, but the council members agreed it’s not nearly enough. The shift from intravenous to oral oncolytic drugs has created a new challenge in oncology: adherence. Patients may not take all of their medication or may not purchase medication that is prescribed, due to cost.

Still a “revenue” item. While ACOs look to contain cancer care costs, most participants said cancer care is still seen by their health systems as a source of revenue—although one said that the “dogs ate our lunch” in a recent ACO contract. They see the tide turning slowly—from a focus on reducing oncology admissions and readmissions to putting a higher priority on care coordination; however, this last point remains challenging, since so many health systems still struggle with how to pay for a service that so clearly helps patients.

What will make care coordination easier without increasing costs? Some see hope in artificial intelligence while others point to better integration of specialty pharmacy into the rest of cancer care. Participants noted that the arrival of new value-based models is creating more reliance on midlevel practitioners, such as nurse practitioners and physician assistants. Recent efforts to reform the 340B drug discount program pose a threat to many hospitals’ bottom lines, the participants warned. Some cautioned that after years of seeing health systems



buy up oncology practices that could not compete due to the anticompetitive nature of 340B pricing, pending reforms could force health systems to cut oncologists loose—except their old practices are gone and they have nowhere to go. The “windfall” of 340B is “not what it was,” one said.

Shared decision making. Participants expect patients to have a stronger voice in care decisions, especially in the decision to withhold care. There’s more and more evidence being published on this topic, yet council members said they still see examples where patients are denied the chance to understand all of their options. Too often, the vow to “first do no harm” is interpreted as a call to intervene, one participant said.

But the bigger challenge to shared decision making is cost, which takes many choices off the table. And while drugs are a main culprit, they aren’t alone. Imaging, lost time at work for patient and caregiver, travel expenses, lack of disability coverage, it all adds up. Complex regimens can overwhelm patients, too.

Following guidelines. The National Comprehensive Cancer Network guidelines are increasingly complex, council members said. There are many malignancies for which more than 1 immunotherapy can work, and sometimes therapies can work together, at great cost. Different health systems may have different protocols as a result.

What does implementing the guidelines mean? In oncology, it doesn’t mean a hospital’s physicians follow guidelines 100% of the time—exceptions are expected. Sometimes there are target rates, such as 80%; sometimes systems find out a compliance rate and scale up over time. Then there’s the matter of matching adherence to guidelines with observance to what various payer guidelines and formularies require, and that’s when things get interesting. Tinkering with each payer’s “black box” can be baffling and problematic, and then doing multiple bundled payment programs within 1 hospital can be a nightmare.

Working together. What can payers do to make population health administration more seamless? Providers were unified: “Give us the data!” The government does a better job giving health systems Medicare data through the OCM than most commercial payers do sharing bundled payment data, yet providers can’t improve without it. Security concerns can be addressed, and they must, if the promise of value-based contracting is to succeed.

What’s ahead? Providers expect more indication-based pricing. The expect oncologists to control every cost they can—and for these costs to go down. ♦

#1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL^{1†}

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS²

¹Based on market share data from IMS from November 2016 to April 2017.

[†]Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)²
- CLL/SLL with 17p deletion²

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

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

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

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

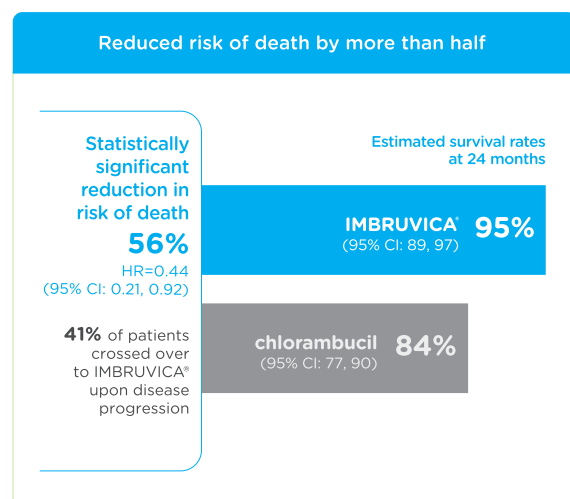
Monitor patients closely and treat as appropriate.

RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)^{2,3} Patients with 17p deletion were excluded³

EXTENDED OVERALL SURVIVAL²

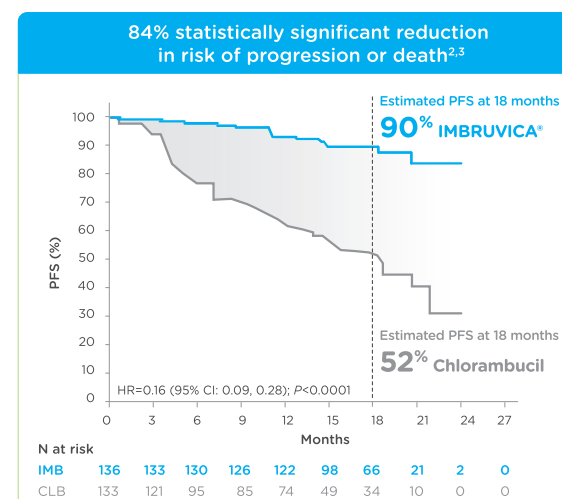
SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL



- Median follow-up was 28 months²
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm²

PROLONGED PROGRESSION-FREE SURVIVAL^{2,3}

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL



- Median follow-up was 18 months³
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil²
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria³

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

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

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%)*, neutropenia (61%)*, diarrhea (43%), anemia (41%)*, musculoskeletal pain (30%), bruising (30%), rash (30%), fatigue (29%), nausea (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%)*, thrombocytopenia (16%)*, and pneumonia (10%).

Approximately 6% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included hemorrhage (1.3%), pneumonia (1.1%), atrial fibrillation (0.8%), neutropenia (0.7%)*, rash (0.7%), diarrhea (0.6%), bruising (0.2%), interstitial lung disease (0.2%), and thrombocytopenia (0.2%)*. Seven percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

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

References: 1. Data on file. Pharmacyclics LLC. 2. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2018. 3. Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib)

560, 420, 280, 140 mg tablets | 70 mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

Waldenström’s Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström’s macroglobulinemia (WM).

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

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

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

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

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

ADVERSE REACTIONS

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

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

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

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

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

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

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

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

IMBRUVICA® (ibrutinib) capsules

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)			
Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)		
	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

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

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102			
Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102		
	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

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

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

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

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

* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE				
	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2				
Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)				
Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2

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

* Includes multiple ADR terms

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

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

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

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

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

The most commonly occurring adverse reactions in Studies 1118 and 1121 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 1118: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63)			
Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (N=63)

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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

* Includes multiple ADR terms.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions: Cardiac Arrhythmias: In randomized controlled trials (n=1227; median treatment duration of 13.1 months for patients treated with IMBRUVICA and 9.0 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.2% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 7% versus 1.5% and for Grade 3 or greater was 2.8% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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

- Hepatobiliary disorders: hepatic failure
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasia
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Animal Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

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

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

Contraception

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

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

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

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA.

Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

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

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

Active ingredient made in China.

Distributed and Marketed by:

Pharmacyclics LLC
Sunnyvale, CA USA 94085
and

Marketed by:

Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent <http://www.imbruvica.com>

IMBRUVICA® is a registered trademark owned by Pharmacyclics LLC

© Pharmacyclics LLC 2018
© Janssen Biotech, Inc. 2018

PRC-03818

CONFERENCE COVERAGE: SOCIETY OF GYNECOLOGIC ONCOLOGY

Coverage by Mary Caffrey, Kelly Davio, and Surabhi Dangi-Garimella, PhD



The American Society of Clinical Oncology continues to seek its own alternative payment model under the Quality Payment Program.

Study Models ASCO Alternative Payment Model in Advanced Ovarian Cancer Care

EACH YEAR, SURVEY results show more physicians are interested in alternative payment models (APMs); however, the risk and concerns about interoperability remain unknowns.¹

With practices anxious to meet the requirements of the Medicare Access and CHIP Reauthorization Act, the American Society of Clinical Oncology (ASCO) proposed the Patient-Centered Oncology Payment (PCOP) model in 2015 to help practices meet the requirements of an APM under the law.² ASCO continues to seek physician-designed APMs under its Quality Payment Program³ as options to the Oncology Care Model (OCM), which is promoted by CMS.⁴



MOSS

A group of researchers from Duke University Medical Center and the Duke Cancer Institute, led by Haley A. Moss, MD, MBA, sought to test the PCOP model. Their abstract, “Can the ASCO Patient-Centered Oncology Payment Model Achieve Cost Savings in Ovarian Cancer Care?”⁵ was part of session, “Reducing Cost and Pain,” held on March 26, 2018, at the Society of Gynecologic Oncology’s 2018 Annual Meeting on Women’s Cancer, in New Orleans, Louisiana.

Using Surveillance, Epidemiology and End Results data linked with Medicare claims, the Duke researchers identified more than 4600 women who were diagnosed with stage III to IV epithelial ovarian cancer between 2000 and 2012. The women received primary debulking surgery (PDS), followed by adjuvant (ACT) or neoadjuvant chemotherapy (NACT). With actual costs in hand, they modeled what costs would have been under the PCOP model compared with fee-for-service (FFS).

Like the OCM, the PCOP model sought to hold practices accountable by having them take on risk to avoid unnecessary hospital stays and trips to the emergency department (ED), unnecessary medication, and excessive end-of-life care. The PCOP model had unique features and created new payments for these key tasks previously not covered by FFS:

- New patient treatment planning, \$750
- Care management during treatment, \$200 per month
- Care management during active monitoring, \$50 per month
- Participation in clinical trials, \$100 per month

As Moss explained, the “carrots” of these new incentives, which offer new fees to encourage clinicians to provide more services, would be offset by “sticks” in the form of financial penalties for failing to meet quality standards.

The Duke study had a dual aim: (1) to compare the total cost difference in Medicare FFS with the PCOP model in patients with advanced ovarian cancer and (2) to gauge how much ED visits, hospitalizations, and imaging would need to be reduced to make the model achieve cost savings in ovarian cancer. The researchers calculated that the model provides approximately \$2600 per patient with ovarian cancer in additional practice payments.

Results showed that of the 4643 women who met the study criteria, 3777 underwent PDS followed by ACT and 866 followed with NACT. The mean cost of chemotherapy and surveillance was \$71,763 in the PDS group compared with \$90,058 in the NACT group.

For both groups, most FFS costs were related to chemotherapy or hospitalization. Patients in each cohort had similar numbers of hospitalizations (PDS, 62%; NACT, 60%). According to the abstract the PCOP would save money compared with the standard payment schedule, with an absolute drop of 8% in hospitalizations, to rates of 54% and 52% in PDS and NACT, respectively.

The study found that the PCOP model could achieve overall savings in advanced ovarian cancer, but that this would need to be achieved by reducing hospitalizations during the active treatment period, because reducing imaging or ED visits on their own would likely not be enough to offset increased practice fees.

Financial Toxicity in Gynecological Cancer: A Distress Score

Researchers from Columbia University Medical Center, Columbia University Medical College, Weill Cornell Medical College, and Columbia University College of Physicians and Surgeons collaborated on the abstract, “Evaluation of Financial Toxicity in Women with Gynecologic Malignancies: a Cross-sectional Study,”⁶ also presented at the “Reducing Cost and Pain” session. Sudeshna Chatterjee, MD, of New York-Presbyterian Hospital/Weill Cornell Medical College presented results for the group.

The term *financial toxicity* has become well known in cancer care, referring to the fact that medical costs are the leading driver of bankruptcy in the United States and that patients with cancer are 2.5 times more likely to file for bankruptcy than other Americans.⁷ The link between financial concerns and health outcomes is now well established. The study focused specifically on the effect of financial concerns on women with gynecological cancers, in the wake of a wave of FDA approvals for new chemotherapy agents and targeted therapies, including poly (ADP-ribose) polymerase inhibitors that can cost \$13,000 to \$20,000 per month.

Due to changing benefit designs, particularly the rise of high-deductible plans, more costs are being transferred to patients, resulting in higher out-of-pocket costs. Patients experiencing financial toxicity are known to have poorer adherence, especially to oral therapy, and are more likely to neglect general overall medical care, the researchers said. Their pilot study sought to quantify this problem in women with gynecological cancers.

Over 10 months, they administered a 35-item questionnaire to patients during treatment based on the Federal Reserve Board’s Survey of Household Economics and Decisionmaking (SHED). From this, they created an 11-item validated Comprehensive Score for Financial Toxicity, or COST measure, with financial toxicity defined as a score of at least 22. A total of 120 women completed the survey; their average age was 64 years, and 72 had an annual income less than \$60,000. One-third of the women (32%) reported a decline in income since diagnosis, with 10% earning less than half of their prior income.

Problems with insurance were significant: 37% reported at least 1 denial for a recommended treatment, including 24 for medications, 5 for imaging, and 3 for genetic testing. This meant 47% had out-of-pocket costs and 26% skipped some medical care due to cost concerns, with 22% saying they could not cover the cost of care.

As for scores, 43% of the survey takers had a score of 22 or higher, indicating distress from financial toxicity; 79% of these patients made \$20,000 a year or less, but 20% made \$100,000 a year or more. Risk factors for distress included being young, unmarried, or African American compared with white.

Notably, the researchers found that although financial toxicity hit harder on those at lower income levels, those at higher incomes were not immune. Most of all, the role of the physician in the conversation, “continues to evolve.” ♦

REFERENCES

1. Joszt L. Progress with risk-based agreements failing to keep pace with expectations. *The American Journal of Managed Care* website. April 10, 2018. ajmc.com/focus-of-the-week/progress-with-riskbased-agreements-failing-to-keep-pace-with-expectations. Accessed April 11, 2018.
2. ASCO’s alternative payment model takes important initial step towards QPP inclusion [press release]. Washington, DC: American Society of Clinical Oncology; May 16, 2017. asco.org/advocacy-policy/asco-in-action/ascos-alternative-payment-model-takes-important-initial-step-towards. Accessed April 13, 2018.

CONFERENCE COVERAGE: SOCIETY OF GYNECOLOGIC ONCOLOGY

3. Quality Payment Program. CMS website. qpp.cms.gov. Accessed April 11, 2018.
4. Oncology Care Model. CMS website. innovation.cms.gov/initiatives/Oncology-Care. Updated April 5, 2018. Accessed April 11, 2018.
5. Dinan M, Georgieva MV, Havrilesky LJ, Hendrix LH, Moss HA. Can the ASCO Patient-Centered Oncology Payment Model (PCOP) achieve cost savings in ovarian cancer care? Presented at: Society of Gynecologic Oncology 2018 Annual Meeting; March 24-27, 2018; New Orleans, LA. Abstract 34.
6. Chatterjee S, Gabor L, Hou JY, et al. Evaluation of financial toxicity in women with gynecological malignancies: a cross-sectional study. Presented at: Society of Gynecologic Oncology 2018 Annual Meeting; March 24-27, 2018; New Orleans, LA. Abstract 35. sgo.org/wp-content/uploads/2018/03/Abstracts-2018-SGO-Annual-Meeting-on-Womens-Cancer-1.pdf.
7. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. *Oncology (Williston Park)*. 2013;27(2):80-81, 149.

Deciding When to Use PARP Inhibitors, and Which One

NEW THERAPEUTIC OPTIONS, with more on the horizon, offer challenges and opportunities in the treatment of ovarian cancer. Understanding the set of decisions that surround poly (ADP-ribose) polymerase (PARP) inhibitors was the theme of a continuing education session presented on March 24, 2018, during the Society of Gynecologic Oncology's 2018 Annual Meeting on Women's Cancer, in New Orleans, Louisiana.

"Times are tricky," said Bradley Monk, MD, FACS, FACOG, Arizona Oncology, and professor of gynecologic oncology at the University of Arizona and Creighton University. "Targeted therapies are here" and choices are not as straightforward as they once were. "You have to make 2 decisions: are PARP inhibitors appropriate? Yes or no? And if it's yes, then you have to decide which one," he explained.



MONK

Monk was among 3 faculty to present "Show Me the Data: Levering Evidence to Optimize Applications of PARP Inhibitor Strategies in Ovarian Cancer," chaired by Robert L. Coleman, MD, FACOG, FACS, professor and executive director of the Cancer Network Research in the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas MD Anderson Cancer Center.

Also presenting were Michael J. Birrer, MD, PhD, director of the University of Alabama Birmingham Comprehensive Cancer Center and professor of medicine, Division of Hematology & Oncology, and Ursula A. Matulonis, MD, director of gynecologic oncology and professor of medicine at Harvard Medical School.

The interactive format used case scenarios to test participants' existing knowledge from key clinical trials involving the PARP inhibitors olaparib (Lynparza, AstraZeneca), rucaparib (Rubraca, Clovis Oncology), and niraparib (Zejula, Tesaro), before Monk, Birrer, and Matulonis each offered their perspectives on these critical questions:

- When are PARP inhibitors best used in the treatment paradigm?
- Which molecular markers can guide treatment decisions with PARP inhibitors?
- Who should get a PARP inhibitor?
- Which PARP inhibitor characteristics inform treatment choices?

Deciding to Use a PARP Inhibitor

"This is all about DNA repair," Monk said, in offering background on how PARP inhibitors came to be. Over time, DNA is constantly breaking down, and homologous recombination (HR) DNA repair seeks to repair double-strand breaks to avoid the genetic turmoil that leads to cancer. However, the presence of *BRCA* mutations interferes with this process and can cause errors in DNA repair that give rise to cancer. In 2005, scientists discovered an alternate method of repair of single broken strands of DNA: Blocking the protein PARP can cause double-strand breaks to form, killing dangerous cells but leaving healthy ones alone. PARP inhibitors have many potential uses, but ovarian cancer offers the most immediate application.

As Monk noted, in 40% to 50% of epithelial ovarian cancers, genetic alterations are responsible for the HR repair pathway. Thus, identifying the germline and somatic mutations involved in HR DNA repair helps guide decision making on when to use a PARP inhibitor. The 3 approved PARP inhibitors are not the same, he said, and each one must be assessed based on its indication and data.

"It's all about the sequencing," Monk said. Increasingly, interpreting a biomarker will depend on whether the therapy will be used in front-line or second-line treatment. He showed slides featuring trials that may soon give oncologists more choices in management of ovarian cancer, pending upcoming FDA decisions:

- Bevacizumab. The FDA accepted a supplemental biologics license for the angiogenesis inhibitor to be used as frontline therapy for women who have advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. A decision is expected June 25, 2018.¹
- Rucaparib. This is approved for treatment in active disease for patients with germline/somatic *BRCA* mutations who have received at least 2 lines of chemotherapy. The PARP inhibitor received FDA approval on April 6, 2018, for recurrent ovarian cancer maintenance treatment, based on results of the ARIEL 3 trial.²
- Olaparib is approved for treatment and maintenance of recurrent ovarian cancer³ and niraparib is approved for maintenance of recurrent ovarian cancer.⁴

Monk said key considerations include whether the benefit of PARP inhibitors will be greater if bevacizumab is used earlier and whether toxicity changes. He is also looking ahead to PARP inhibitor combinations: Trials are under way studying the class with bevacizumab, combining PARP inhibitors with immunotherapy, and even triplet therapy with PARP inhibitors, immunotherapy, and bevacizumab.

HRD Testing in Ovarian Cancer

"We're still trying to find the perfect biomarker," Birrer said, but short of that, there's a lot that can be done to connect patients with therapies for maximum efficacy. He discussed the complexities of homologous recombination deficiency (HRD) testing. Getting patients the right therapy starts with understanding starting that although *BRCA1* and *BRCA2* are still the most common mutations, they are far from the end of the story. Many more mutations have been identified, and within *BRCA1/2* there are distinctions between germline and somatic mutations.

Birrer discussed how the ARIEL 2 trial used a next-generation sequencing assay to examine how *BRCA1* and *BRCA2* mutations' genomic loss of heterozygosity (LOH) might also indicate HRD and response to rucaparib. Data show that those in the *BRCA*-mutant group had the best response (12-month progression-free survival) compared with *BRCA* wild-type with LOH high (5.7 months) and *BRCA* wild-type LOH low carcinomas (5.2 months).

In the NOVA trial, patients with *BRCA* mutations had the best results with niraparib, but patients with a non-*BRCA* mutation still had good results.

Birrer said although some patients still do not receive testing, "all patients with ovarian cancer should undergo genetic testing," and HRD assays are now available.

Which PARP Inhibitor to Select

Matulonis said there are multiple factors that can affect which PARP inhibitor is selected, from clinical trial results to other drugs the patient is taking to dosing schedules to insurance coverage. She presented tables summarizing clinical trial results, FDA approvals and dosing, HRD results (where applicable), drug-drug interactions, and which enzymes the various PARP inhibitors use to metabolize the drugs, as this can have a corresponding effect on certain cell transporters.

The challenge for physicians, she said, is that PARP inhibitors are so new that drug-drug interactions may not be flagged in some health system electronic health records. This is especially true "if a patient is on a complicated regimen," she said. Liver function tests are important to catch effects on cell transporters.

Hypertension and fatigue are legitimate concerns, but often patients work through these early side effects, and typically dose modification is all that is needed. She presented physicians with patient cases and a series »

CONFERENCE COVERAGE: SOCIETY OF GYNECOLOGIC ONCOLOGY

of decision-making scenarios that, like Monk, spoke to the challenge of sequencing, both in treatment and in maintenance, noting the ARIEL 3 data “are very convincing in the maintenance setting.”

The continuing education session was presented by Physicians’ Education Resource®, LLC, which is owned by the same company that owns *The American Journal of Managed Care*®, and the session was funded through educational grants from AstraZeneca, Clovis Oncology, Myriad Genetics, and Tesaro. ♦

REFERENCES

1. Syrop J. FDA agrees to review sBLA for reference bevacizumab. The Center for Biosimilars website. centerfor-biosimilars.com/news/fda-agrees-to-review-sbla-for-reference-bevacizumab. Published November 2, 2017. Accessed March 26, 2018.
2. FDA approves rucaparib for maintenance in recurrent ovarian cancer. *The American Journal of Managed Care*®. April 7, 2018. ajmc.com/newsroom/fda-approves-rucaparib-for-maintenance-in-recurrent-ovarian-cancer. Accessed April 7, 2018.
3. FDA approves olaparib for maintenance treatment in ovarian cancer [press release]. Silver Spring, MD: FDA; August 17, 2017. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm572143.htm. Accessed March 26, 2018.
4. Niraparib (Zejula). FDA website. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm548487.htm. Published May 30, 2017. Accessed March 26, 2018.

Boys Don’t Get HPV Vaccination Because Doctors Don’t Recommend It, Study Finds

VACCINATION RATES FOR the human papillomavirus (HPV) are not where public health officials would like them to be, especially for boys. The most common reason parents may not get their sons vaccinated is because their family doctors don’t recommend it, according to findings presented at the Society of Gynecologic Oncology 2018 Annual Meeting on Women’s Cancer, in New Orleans, Louisiana.

One in 5 parents does not plan to vaccinate their adolescent son compared with 1 in 10 parents of an adolescent daughter, according to Anna Beavis, MD, MPH, a gynecologic oncologist fellow at Johns Hopkins Hospital, who based her presentation on results from the 2015 National Immunization Survey-Teen. Survey data were used to calculate survey-weighted prevalence estimates of HPV vaccine initiation among boys and girls aged 13 to 17 years. Not only did the survey capture vaccination rates, but reasons parents gave for why they did or did not plan to get their children vaccinated.

In an interview with *The American Journal of Managed Care*® (AJMC®), Beavis noted that HPV vaccination rates are higher for African American and Hispanic youth at lower income levels than they are for white children at higher income levels, which further suggest that physician communication is at the root of the problem.

“It is clear that physicians need to give a strong recommendation to both parents of boys and girls,” Beavis said. “They also need to remind parents of the importance of getting all doses, which makes the vaccine the most effective in preventing HPV.”

The 3-dose HPV vaccine was introduced in 2006 for girls and 2009 for boys (both genders get the same vaccines), with the goal of reducing rates of cervical and vaginal cancer in women, penile cancer in men, and cancers of the mouth, throat, and anus in both genders. However, uptake of the HPV vaccine has never come close to reaching the Healthy People 2020 goal¹ of 80% completion in both boys and girls by age 15. In the interview with AJMC®, Beavis noted that although CDC data² show the rate for boys continues to climb incrementally, the rate for girls seems to be leveling off.

While a 2-dose version of the vaccine is now available, Beavis said this is only recommended for children aged 9 to 15, whose immune systems are stronger. Current CDC guidelines call for vaccinating children between ages 11 and 12, although catch-up doses can be given as late as age 26 for women and age 21 for men.

What the Data Show

According to Beavis’ abstract, in 2015, 63% of all girls aged 13 to 17 initiated the HPV vaccine compared with 50% of boys. When they did not get vaccinated, the most common reason cited was a perceived lack of necessity (21% in girls vs 22% in boys; $P = .6$). Both boys and girls reported lack of knowledge about the vaccine (13% and 14%, respectively; $P = .5$). However, parents of boys were significantly more likely to cite lack of HPV vaccine recommendation from a provider as a reason (19% vs 10%; $P < .001$) and were less likely to report concerns about safety and side effects (9% vs 14%; $P < .01$). Only 3% of parents of boys cited gender as their reason for lack of vaccination. Parents of girls were more likely to cite the girls’ lack of sexual activity as reason for lack of vaccination (15% vs 9%; $P < .01$).



BEAVIS

In the interview, Beavis said vaccination rates are uneven across the country, with the lowest rates seen in the Southeast. This is also the area with the highest rates of cervical cancer, although Beavis said this is not a “cause and effect.” When asked if cultural impediments prevented communication about the HPV vaccine, she said the data were not nuanced enough to confirm this, but some focus groups have suggested a reluctance to give the HPV vaccination to children who are not sexually active.

What is clear is that increasing the vaccination rate, for girls and boys, will take more than 1 response by states, communities, and health systems. Her own health system, Johns Hopkins, requires primary care providers to meet an 80% HPV initiation rate, for example.

Beavis said the communication issues in the United States surrounding the HPV vaccine put children and young adults with compromised immune systems or chronic health conditions at an especially high risk. In Australia, by contrast, recently published data show 78.6% of girls and 72.9% of boys have been vaccinated at age 15, Beavis said.

“Unfortunately, HPV vaccination rates in the United States continue to lag behind those of other Westernized nations,” she said. ♦

REFERENCES

1. Immunization and infectious diseases. HealthyPeople website. healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives. Accessed March 25, 2018.
2. Walker T, Elam-Evans L, Singleton J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years – United States 2016. Centers for Disease Control and Prevention website. cdc.gov/mmwr/volumes/66/wr/mm6633a2.htm. Accessed March 25, 2018.

Oncologist Shares Lessons Learned From CAR T-Cell Therapy in ALL

ON THE CLOSING day of the National Comprehensive Cancer Network (NCCN) 23rd Annual Conference in Orlando, Florida, Bijal Shah, MD, of Moffitt Cancer Center, presented on acute lymphoblastic leukemia (ALL) and on lessons learned from the application of chimeric antigen receptor (CAR) T-cell therapy in this indication.

First, said Shah, “Adult ALL doesn’t get enough attention, but it does account for nearly half of all of the all cases that we see.” Adult patients with ALL are more likely to relapse, and their outcomes are typically poor, with an average survival of roughly 40%. “I think we have a lot of room for improvement there,” said Shah.

Allogenic transplant may help these patients, and while inotuzumab does improve overall survival, “it’s not easy to get excited” about long-term survival improvements of only small percentages. With blinatumomab, a T-cell-directed therapy, “We did better than chemotherapy for a short while,” Shah explained; however, even with blinatumomab, long-term survival remains around 25%, “so we’re still having trouble getting past this hurdle.”

CAR T-cell therapies may provide an important improvement on these options. However, said Shah, after a patient has been identified as having relapsed/refractory disease, the time it takes to manufacture a therapy can »

CONFERENCE COVERAGE: NATIONAL COMPREHENSIVE CANCER NETWORK

stretch from weeks to months and it can be difficult to keep the patient's disease stable during this period. "We're not taking as many patients" because of manufacturing time, he said, and some patients will become very ill before a drug product can be made.



SHAH

In addition to the challenge posed by manufacturing time, data also show that adults had worse outcomes than children when treated with tisagenlecleucel,¹ and "That's disconcerting. As we decrease the age, we see better responses." This is discouraging for adult patients. "We are absolutely improving survival," said Shah. "But why do adults have to take the short end of the stick?"

Patients with higher tumor burdens also did significantly worse in trends, as did patients who were more heavily pretreated (having received 4 or more lines of therapy).² Furthermore, toxicity is a significant concern with CAR T-cell therapies. Severe neurotoxicity has been observed, although the mortality rate for these adverse events (AEs) remains low, at around 2% to 3% across the approximately 230 patients studied so far, said Shah. Interestingly, ALL seems to have a higher rate of neurologic toxicity with CAR T therapy than other cancers do, an observation that suggests that there are some disease features that are linked with AEs. Adults with ALL appear to have even more neurotoxicity than younger patients.³ "I have no explanation for this," Shah said.

Management of treatment-related toxicities is critical for patients with ALL receiving these therapies; among the toxicities of greatest concern is cytokine release syndrome (CRS). Tocilizumab is key to managing CRS, and it should be administered at the first signs of hypotension or fever. Tocilizumab, it is important to note, will not help with neurotoxicity, and it is important to watch the patient closely for infusion-related reactions or infections.

If fever and hypotension do not resolve with tocilizumab, "my own personal bias is that more tocilizumab won't help," said Shah, who would resort to steroids in this case. "They're bad, but they're not that bad." He urged clinicians not to be afraid to put a patient on steroids as long as they are willing to stop the course once CRS symptoms start to improve.

Cerebral edema is another challenging AE, and "the answer is nobody knows" why cerebral edema was observed among 6 patients treated in Juno's trial of its proposed CAR T-cell therapy, JCAR015, which resulted in multiple deaths. The mechanisms of this AE remain "elusive."

In looking to the future, Shah says that off-the-shelf CAR T-cell therapies will be key to treating more patients and that improving on current toxicities will be key. Finally, improving the durability of response will be necessary. "Post-CAR T therapy relapse is going to be a big problem, and I don't know how to solve it... We have to worry about the fact that response isn't durable." ♦

REFERENCES

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448. doi: 10.1056/NEJMoa1709866.
2. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):449-459. doi: 10.1056/NEJMoa1709919.
3. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR T-cells. *Cancer Discov*. 2017;7(12):1404-1419. doi: 10.1158/2159-8290.CD-17-0698.

Oncologists Must Weigh Risks, Benefits of Immune Checkpoint Inhibitors

AT THE NATIONAL Comprehensive Cancer Network (NCCN) 23rd Annual Conference in Orlando, Florida, John A. Thompson, MD, of the Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance, presented an overview of immunotherapy-related toxicities and their management.

The use of immune checkpoint inhibitors has revolutionized the treatment of melanoma and other cancers, said Thompson, but "with this good news has

come some not so good news": Immune-related adverse events (irAEs) can cause serious harm to patients receiving these drugs. In response to a growing need to standardize an approach to irAEs, the NCCN has collaborated with the America Society of Clinical Oncology on new guidelines for managing these toxicities.

High Risk of Toxicity

Thompson pointed to the CheckMate study,¹ which assessed nivolumab, ipilimumab, and nivolumab plus ipilimumab. The combination of the 2 drugs was more efficacious than either drug alone, he said. In addition, 59% of patients who received the combination experienced toxicities compared with 21% receiving only nivolumab and 28% receiving only ipilimumab.



THOMPSON

"In the clinic, if we start a patient on this regimen, there's a 50/50 chance that the patient will encounter serious toxicity. Some of the toxicities may occur very early, and there may be toxicities that occur way, way later, even after the completion of the study," he said.

When a toxicity emerges, said Thompson, "one of the first things to do is stop the therapy" to allow the toxicity to resolve. Although patients may be reluctant to temporarily discontinue their anticancer regimen, Thompson said that available data demonstrate no statistical difference in overall survival when therapy is discontinued to address a toxicity, and "we're not jeopardizing anti-cancer effect" by doing so.

Skin. Thompson said that among the first toxicities to appear in patients are those that are skin related. Maculopapular rash, vitiligo, and pruritus have all been observed. According to Thompson, while vitiligo may be distressing to a patient, its presence "sometimes confers a better outcome."

In cases of mild maculopapular rash, therapy can be continued with the addition of topical steroids, but moderate rash may warrant holding immunotherapy while the toxicity resolves. In cases of severe rash, therapy must be withheld. In bullous dermatitis, immunotherapy should be held even in mild cases.

Gastrointestinal. One of the next toxicities to emerge is gastrointestinal, manifesting as diarrhea or colitis. In even mild cases, clinicians should consider holding immunotherapy and administering steroids until the toxicity resolves. Patients have been observed to have durable, complete remission of cancer even after aggressive steroid treatment for colitis has been administered. If colitis cannot be controlled on steroids, infliximab may be warranted, and usually only a single dose is needed.

Liver. Immune-related hepatitis has been observed in some patients receiving checkpoint inhibitors. The NCCN does not recommend the use of infliximab for refractory hepatitis because of concerns about increased toxicity in this indication, but mycophenolate (CellCept) may be used as a second-line agent in life-threatening cases.

Pancreatic. Asymptomatic elevation of amylase and lipase may occur. Elevated levels of these enzymes may not require holding immunotherapy, but persistent high elevation would warrant looking at other potential causes of the toxicity. In cases of pancreatitis, high-dose steroids should be used and immunotherapy withheld until the toxicity resolves.

Endocrine. "One of the fortunately more rare, but very disturbing, toxicities is the development of type 1 diabetes," said Thompson. "It's hard to see this coming." Patients may present with acute diabetic ketoacidosis. "For the most part, this is not reversible." Oncologists must work closely with a diabetes team to control this toxicity so that treatment can continue.

Thyroid. Primary adrenal insufficiency is one potential irAE affecting the thyroid. "This can come on fairly insidiously, with a feeling of lassitude [or] fatigue." Periodically monitoring cortisol levels can be useful, and adrenal hormone replacement should be given before thyroid hormone replacement to prevent adrenal crisis.

Lung. Pneumonitis can be very serious, and prednisone may be useful, although steroids may have to be used for a long period of time to bring lung inflammation under control. However, "as far as we can tell, we are not abrogating the antitumor effect" by using a long course of steroids.

Ocular. Eye pain and proptosis warrant special concern, as retinal »

CONFERENCE COVERAGE: NATIONAL COMPREHENSIVE CANCER NETWORK

detachment and vision loss may result from swelling in the eye. Steroids may be indicated, and infliximab can be added if steroids are ineffective. The oncologist should “tread very cautiously” in cases of ocular toxicity, said Thompson, and ensure that the patient sees an eye specialist early.

Nervous System. Myasthenia gravis—which manifests as gait difficulty, dysphagia, ptosis, diplopia, and respiratory failure—is an irAE of special concern, and Thompson urged oncologists to be alert to these symptoms and involve neurologists and an intensive care unit if the condition is suspected. Peripheral neuropathy, encephalitis, meningitis, and transverse myelitis have also been observed in patients receiving checkpoint inhibitors.

Cardiac. “Cardiac toxicity is rare,” said Thompson, “but when it happens, it may be disastrous.” Abrupt and fatal myocarditis sometime arise, and “I don’t think any of us are skilled enough clinicians to see this coming.” Oncologists should exercise special caution with any patients who have a history of cardiac issues and should have “second thoughts” about using immune checkpoint therapy in these patients.

Overall, said Thompson, oncologists should weigh carefully the decision to use therapies that carry a high risk of serious toxicity. Patients should have a high level of suspicion that new symptoms are related to treatment, and patients and caregivers should receive education about potential toxicities. ♦

REFERENCE

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356. doi: 10.1056/NEJMoa1709684.

Making Progress or Headed for Crisis? NCCN Keynotes Offer Contrasting Views of US Cancer Care

THE SECOND DAY of the National Comprehensive Cancer Network (NCCN) 23rd Annual Conference in Orlando, Florida, on March 23, 2018, opened with a dual keynote presentation on transforming cancer care in the United States.



KLINE

Opening the presentation was Ron Kline, MD, FAAP, medical officer in the patient care models group at CMS’ Center for Medicare and Medicaid Innovation. Kline, a practicing pediatric oncologist, opened by assuring those participating in the Oncology Care Model (OCM) that their feedback on, and concerns about the OCM, are being heard, even if the agency has not directly replied to comments from individual practices: “We know you have to keep your doors open, [and] we know about the burdens. We do listen to you. Many of you acknowledged problems in the OCM. We’ve changed those things, and we’ve listened... If you hear nothing from us, that doesn’t mean we haven’t heard you.”

Kline also acknowledged that the OCM is a difficult program to implement, saying, “If the OCM was easy, someone would have done it 20 years ago.” Yet CMS has not instituted an unfunded mandate. With its monthly enhanced oncology services payments, “We put \$80 million of skin in this game. We’re giving you the tools to do these things.”

Despite the challenges of implementing the OCM, Kline says that preliminary results from the first reporting period show progress. Twenty-five percent of Medicare fee-for-service (FFS) chemotherapy-related cancer care—in 187 practices for 150,000 unique beneficiaries each year, representing approximately 200,000 episodes of care—is now given under the OCM, and 14 commercial payers are also now participating in the model.

The Institute of Medicine (IOM)’s Care Management Plan is having a positive impact on patient care, says Kline. Some oncologists have argued that the 13 components of the plan are tasks they are already undertaking, only without

documentation. Kline agrees that “the 13 components of the [IOM] care management plan are things that a good oncologist should be doing anyway.” However, some oncologists have had to be pushed to talk to patients about prognosis, as they felt that it was too depressing for patients to know their likelihood of survival. Implementing the IOM plan has compelled them to have these difficult discussions with their patients.

Furthermore, Kline says that some practices are beginning to provide the enhanced services of the OCM, such as around-the-clock patient access to an appropriate clinician, to all of their oncology patients, regardless of their health plan, as a means of streamlining processes and improving care. “When we hear that, that’s music to our ears,” said Kline. “One of the nice things we hear from practices is, ‘You know what, we’re providing the care we always wanted to provide.’ That’s where you want to be.”

Following Kline was Lee N. Newcomer, MD, MHA, a private consultant who recently retired from his position as senior vice president of oncology and genetics at UnitedHealthcare. Newcomer gave a sobering statistic: The medical expenditure of the United States is equal to the fifth largest national gross domestic product (GDP) in the world. What the United States spends on health care is, in fact, larger than the GDP of France. “If we don’t fix this problem, we’re going to have a crisis, and a big one,” he said.



NEWCOMER

Newcomer cautioned that reimbursement strategies alone will be insufficient to solve this problem. Roughly 80% of this growth in spending, he said, is not driven by providing more care but by rising prices. “It is a failed system,” he said, that is driving an interest in value-based bundles.

Working with the MD Anderson Institute in Houston, Texas, UnitedHealthcare attempted a pilot bundle for the treatment of head and neck cancers and used treatment strategy (eg, surgery, radiation, surgery plus radiation) as the basis for the bundle. Each bundle had a different dollar amount attached to it, with the same profit margin for all categories.

“The purpose of the program was [to see] if we could even do it.” The answer, said Newcomer, was “yes, but not without a lot of extra resources” to coordinate. “There were too many resources for too little gain. Not that it was a bad idea. What we learned is we have to have something we can spread over thousands of patients.”

In a UnitedHealthcare trial of a gain-sharing arrangement in patients with cancer, 810 patients were matched with a cohort of FFS patients. In total, it cost \$99 million to treat the FFS group and \$65 million to treat the gain-sharing arrangement group. Hospitalizations declined, and survival curves in lung cancer were the same in both groups. “A huge, whopping win,” Newcomer said. Unfortunately, in a second instance of the program, there were no differences in costs between groups. These experiences proved, said Newcomer, that leadership is essential and internal controls and timely data are critical. “Without those elements, things tend to fall apart.”

Newcomer argued that, in order to make a real difference in costs, “We have to get rid of the mandates that require every payer in the United States to pay for any drug that has an FDA cancer approval.” The mandate is well intended, said Newcomer, “[but] the unintended consequence is that it’s limiting access to cancer care...making it too expensive.” With no ability to negotiate, there’s nowhere for prices to go but up, putting a high burden on vulnerable patients with cancer.

Newcomer welcomes the advent of more data in oncology and says that, in the coming years, practices will be able to see more clear information on which therapies cost more without providing substantial benefit. Newcomer pointed to the cost of zoledronic acid versus the cost of denosumab as a prime example of the kind of data that clinicians need for better decision making. “Are we really getting \$25,000 worth of benefit” from denosumab versus the far cheaper zoledronic acid? “I would argue no,” said Newcomer.

Yet these data will only be useful if clinicians use them to make prescribing choices that optimize value in oncology care. Newcomer ended with a challenge to oncologists to take charge of the cost of care. “You have the power to do something about this. The people who will make this happen are sitting right out there. I’m looking at you.” ♦

NCCN's New Guidelines Promote Better Cancer Care for People With HIV

AT THE NATIONAL Comprehensive Cancer Network (NCCN) 23rd Annual Conference March 22-24 in Orlando, Florida, Gita Suneja, MD, Duke Cancer Institute, presented the NCCN's new guidelines on treating cancer in people living with HIV.

"The story of HIV in America began in June of 1981," said Suneja, with the CDC's *Morbidity and Mortality Weekly Report*¹ that described 5 young men with biopsy-confirmed *Pneumocystis carinii* pneumonia. Although the CDC would not name AIDS-defining cancers (Kaposi sarcoma [KS], non-Hodgkin lymphoma, and cervical cancer) until 1993, Suneja said, "Cancer was a part of the story from the very beginning." As early as July 1981, KS was described together with pneumonia among homosexual men.

Today, Suneja said, we understand that people with HIV have a higher incidence of many cancers—not only AIDS-defining cancers—compared with the general population. Some factors involved are coinfection with oncogenic viruses and a higher incidence of smoking within this population. Aging, too, is playing a role. Antiretroviral therapy (ART) has increased survival of people living with HIV, and "HIV has really been converted over to a chronic disease. Not only is the US HIV population growing over time, they're also aging."

While the incidence of AIDS-defining cancers is on the decline due to patients' improved immune function with ART, the incidence of non-AIDS-defining cancer is rising among people with HIV. Some potential explanations include complications with AIDS, advanced cancer stage at diagnosis, decreased immune surveillance, and more biologically aggressive disease.

Concerningly, people living with HIV are also significantly less likely to receive cancer treatment compared with patients without HIV. Suneja pointed to a 2015 survey that she and her colleagues conducted among 500 US oncologists. Among the respondents, 20% to 25% said that they would not offer standard cancer therapy to a patient who had HIV, 70% said that sufficient guidelines for treating these patients were not available, and 45% said that they rarely or never discussed a management plan with an HIV specialist.

Further compounding the problem is the fact that patients with HIV are routinely excluded from clinical trials, so there is a knowledge gap about how best to treat them. Suneja likens such a practice to excluding people with cardiovascular disease, something that wouldn't really be done. "HIV status alone should not be used for cancer treatment decision making," said Suneja. Instead, clinicians should bear in mind unique considerations for patients who have HIV.

Cancer Work-up

Because imaging may reveal lymphadenopathy with nonmalignant etiology, clinicians should consider a lower threshold to perform a nodal biopsy to determine whether cancer is involved. Lesions of the brain, bone, lung, spleen, liver, or gastrointestinal tract may be noncancerous in nature, especially if a patient's CD4+ T-cell count is low.

General Management

Poor performance status could be from HIV, cancer, or other causes, and drug-drug interactions among oncology and HIV therapies are possible. It is key to consult an HIV specialist and a pharmacist, said Suneja, before initiating therapy. Co-management between the oncologist and HIV specialist is critical.

While publications from the pre-ART era showed increased toxicity from cancer therapies in patients with HIV, modern data do not demonstrate the same results in patients who have a CD4+ T-cell counts above 200 cells/ μ L. Conformal radiotherapy techniques can be used to reduce the dose to bone marrow, skin, and mucosa, and there is no difference in clinical outcomes or complications for patients with HIV who undergo surgery compared with patients without HIV.

Kaposi Sarcoma

The risk of KS may have declined by 90% with better HIV management, but patients with HIV are still at elevated risk for this cancer. It is important to understand that individual lesions may be distinct clones that arise from persistent immunosuppression and human herpesvirus 8 infection, so treating

existing disease may not prevent future lesions.

In AIDS-related KS, in patients who are asymptomatic and find their condition cosmetically acceptable, "sometimes we don't need to do any cancer-related therapy. ART is really the backbone of treatment for KS," Suneja said.

Patients who are symptomatic or find their condition cosmetically unacceptable should receive ART with topical drugs, systemic therapy, radiation therapy, intralesional chemotherapy, or local excision or attempt to qualify for a clinical trial. Patients with advanced disease should receive ART with treatment in a clinical trial, if eligible.

Because reconstitution of immune function is important for the control of KS, clinicians should be aware of immune reconstitution inflammatory syndrome, during which glucocorticoids may become necessary; their use is generally avoided, as they may promote KS. Potential lymphedema should also be closely monitored.

Cervical and Anal Cancers

The NCCN recommends that patients who have cervical cancer or anal cancer be treated in line with existing NCCN guidelines for these conditions. In the case of anal cancer, patients should receive more frequent surveillance, with anoscopy every 3 to 6 months for 3 years.

Lung Cancer

The most common non-AIDS-defining cancer in people with HIV is lung cancer. Even after controlling for increased levels of smoking in the HIV population, people with HIV still have an increased risk for this disease. The NCCN says that patients with HIV should receive treatment per its guidelines for non-small cell lung cancer, and smoking cessation support should be offered.

Hodgkin Lymphoma

Ninety percent of cases of Hodgkin lymphoma in people with HIV are related to the Epstein-Barr virus, and many patients with HIV present with more advanced disease. The preferred treatment regimen in this population is doxorubicin hydrochloride, bleomycin, vinblastine, and dacarbazine, but dose reductions may be required in cases of prolonged neutropenia. Growth factors, which are generally avoided in this population, may be required. Autologous stem cell transplant has also been shown to be safe and effective for patients with HIV who have recurrent or relapsing Hodgkin lymphoma.

Supportive Care

In general, steroids should be avoided because of the risk of opportunistic infections, and a high index of suspicion, together with early testing for opportunistic infection, is appropriate. Live vaccines should be avoided if the CD4+ count is under 200 cells/ μ L, but patients over age 50 may receive the new recombinant zoster vaccine.

Coordinated Care

All patients with cancer should be screened for HIV. "Point of care testing [for HIV] is really in our domain" as oncologists, said Suneja, and together with an HIV specialist, the oncologist should undertake more frequent CD4+ T-cell count and viral load testing.

Drug-drug interactions should be reviewed by both specialists and a pharmacist. Of greatest concern are pharmacologic boosters like ritonavir and cobicistat, as well as protease inhibitors. Overlapping toxicities may be present; both cancer drugs and HIV therapies may cause neuropathy and neutropenia, for example. If there is the potential for drug-drug interactions or overlapping toxicities, the oncologist may substitute ART, choose a different cancer therapy, or temporarily discontinue ART if cancer treatment is curative or palliative in nature.

In the future, said Suneja, the NCCN plans to expand the number of cancers that it addresses in its guidelines, adapt guidelines for low-resource settings, generate an evidence base for the management of HIV-associated cancers, and increase clinical trial accrual. ♦

REFERENCE

CDC. *Pneumocystis pneumonia*—Los Angeles. *MMWR Morb Mortal Wkly Rep*. 1981;30(21):250-252.

Commissioner Gottlieb Updates Community Oncologists on the FDA's Mission to Improve Access

FROM THE DAY that he took office, Scott Gottlieb, MD, FDA commissioner, has been on a mission to develop policies and implement changes that can tackle the challenges facing the agency and healthcare in general. During his first year at the helm the FDA has taken several issues head-on.



GOTTLIEB

At the 2018 Community Oncology Conference hosted by the Community Oncology Alliance (COA) on April 12-13 in National Harbor, Maryland, Gottlieb gave an overview of current and future plans of the regulatory agency, particularly within the molecular diagnostic testing space and liquid biopsies.

In December 2017, the FDA approved the first comprehensive companion diagnostic test¹ for solid tumors that uses next-generation sequencing (NGS) technology to examine all classes of genomic alterations in the 324 genes known to cause cancer growth—Foundation Medicine's FoundationOne CDx test.

The rapidly falling cost of NGS, Gottlieb said, will allow whole-genome sequencing and aid precision-guided treatments. NGS, he added, is a glaring example of the innovative advances and strides in cancer research.

"FDA recognizes the importance of this, and we want to serve as a bridge to allow this innovation to come into the market," while simultaneously ensuring patient safety, he said.

In March, CMS announced² that it has finalized a national coverage determination that covers diagnostic laboratory tests that use NGS for patients with advanced cancer.

"We want cancer patients to have enhanced access and expanded coverage when it comes to innovative diagnostics that can help them in new and better ways," said CMS Administrator Seema Verma when making the announcement. "That is why we are establishing clear pathways to coverage, while at the same time supporting laboratories that currently furnish tests to the people we serve."

FDA wants to be "as nimble and sophisticated as the science that drives these technologies, so clinicians and patient can have access to them as soon as possible," Gottlieb said. This will allow NGS technology to guide clinical trial participation and allow personalized treatment options for cancer.

Gottlieb discussed 3 FDA announcements that can expand the routine use of NGS. The first addresses the design, development, and analytical validation³ of NGS-based diagnostics; the second provides guidance on the use of public human genetic variant databases⁴ to confirm clinical validity of the tests; and the third makes it easier for drug and diagnostic developers to file their documents with the FDA by providing a streamlined submission process⁵ for risk determination.

"The streamlined submission process will allow an easier common filing for the drug and its companion diagnostic and avoid 2 separate applications," Gottlieb said. This could ease some of the administrative burden on pharmaceutical manufacturers, as well as the regulators reviewing these documents, and create a more cohesive process.

Gottlieb noted that the guidelines can reduce screening time and cost. From the patient's perspective, NGS can help avoid multiple tissue biopsies. "NGS will also improve the process of matching patients to participate in suitable clinical trials," he said, considering the ease of the screening process and the large number of patients' genetic variations that the physicians would get a glimpse into.

Gottlieb emphasized, however, that although the recipe for oncology innovation includes researchers, clinicians, regulators, policy makers, and advocates, "public confidence in the institutions that support innovation is vital."

He then turned his attention to the high cost of care, especially in oncology. "Cost of care is one of the bigger challenges in oncology, and cancer patients are disproportionately shouldering these costs," Gottlieb said, via co-pays and deductibles. "While the FDA cannot regulate drug prices and it is not our

primary role, Congress has provided us the ability to reduce anticompetitive behavior to allow access to products such as biosimilars."

The other issues that influence cost are the drug development timelines and development costs, he added. Indirect financial costs of time and risk are inherent to clinical trials, which in turn affects drug costs. NGS, Gottlieb believes, can come into focus here. "Many trials fail, often in late stages, not just because of science but trial conductance. We need better clinical trial designs," he said.

Emphasizing the value of targeted and personalized treatments, Gottlieb said that biomarker-directed oncology trials are more likely to succeed.

Following a question by an oncologist from the audience on his prediction for the biosimilar drug market, Gottlieb said, "We are in very early stages of biosimilar development. We have challenges with physician adoption, especially for curative treatments, but not for treating chronic diseases like rheumatoid arthritis." However, he pointed out that physicians had similar concerns with generics when the Hatch-Waxman Act was instituted in 1984.

In March, Gottlieb told the audience at the 2018 National Health Policy Conference of America's Health Insurance Plans that misaligned incentives in the biosimilars market—a product of contracting practices as well as consolidation across the drug supply chain—could be a barrier to patient access to biosimilar medicines.⁶

"Market penetration for biosimilars is extremely hard, especially because of the rebate structure for branded drugs," Gottlieb pointed out to the COA audience. "This is a huge impediment for their market entry." ♦

REFERENCES

1. Rosenberg J. First-of-a-kind companion test for cancer gene profiling gets FDA approval. *The American Journal of Managed Care* website. ajmc.com/newsroom/firstofakind-companion-test-for-cancer-gene-profiling-gets-fda-approval. Published December 4, 2017. Accessed April 12, 2018.
2. Rosenberg J. CMS finalizes coverage for next generation sequencing tests. *The American Journal of Managed Care* website. ajmc.com/newsroom/cms-finalizes-coverage-for-next-generation-sequencing-tests. Published March 16, 2018. Accessed April 12, 2018.
3. Considerations for design, development, and analytical validation of next generation sequencing-based In vitro diagnostics intended to aid in the diagnosis of suspected germline diseases; guidance for stakeholders and Food and Drug Administration staff. *Fed Regist*. 2018;83(72):16106-16108.
4. Use of public human genetic variant databases to support clinical validity for genetic and genomic-based in vitro diagnostics; guidance for stakeholders and Food and Drug Administration staff; availability. *Fed Regist*. 2018;83(72):16110-16112.
5. Investigational in vitro diagnostics in oncology trials: streamlined submission process for study risk determination. FDA website. fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM604441.pdf. Published April 2018. Accessed April 12, 2018.
6. Inserro A. FDA's Gottlieb blames rebates, reimbursement issues for holding back biosimilar market. *The American Journal of Managed Care* website. ajmc.com/newsroom/fdas-gottlieb-blames-rebates-reimbursement-issues-for-holding-back-biosimilar-market. Published March 7, 2018. Accessed April 12, 2018.

Gene Therapy in Community Practices—Administering CAR T Therapies

ALTHOUGH IMMUNE-BASED treatments have gained significant strides in cancer care, chimeric antigen receptor (CAR) T cells have also started to make their mark. With 2 treatments approved, so far, for liquid cancers, the extent of remission has surprised the field.

However, the treatments are not easy to administer, and the adverse events (AEs) can prove extremely challenging—for the caregivers, patients, and families. So, how are community practices coping with administering CAR T treatments? At the 2018 Community Oncology Conference hosted by the Community Oncology Alliance, Houston Holmes, MD, MBA, FACP, Texas Oncology, shared his experience with administering CAR T cells in a community cancer center-based setting.

Holmes started the discussion with an overview of the recently published

CONFERENCE COVERAGE: COMMUNITY ONCOLOGY ALLIANCE

study for the first treatment that was approved in August 2017: Novartis' tisagenlecleucel (Kymriah).

The first case report with these CD19-specific CAR T cells was published in 2013,¹ Holmes said, and described the results of CAR T administration in 2 children with relapsed and refractory pre-B-cell acute lymphoblastic leukemia (ALL). Although T-cells proliferated and persisted in the cerebrospinal fluid for 6 months, significant grade 3 or 4 AEs were noted in the patients, including cytokine release syndrome (CRS)⁴ and B-cell aplasia.

Holmes said that 1 of the patients remained in complete remission (CR) at 11 months, but the second child had a relapse about 2 months following treatment, likely due to the absence of CD19-expressing blast cells.



HOLMES

Holmes then presented long-term results from the same trial that were recently published,² following a 25-center global phase study in pediatric and young adult patients with B-cell ALL. The results were very encouraging, according to Holmes, with an 81% overall remission rate at 3 months, following a single infusion of tisagenlecleucel. The CAR T cells persisted in these patients and the authors reported an overall survival of 76% (95% CI, 63% to 86%) at 12 months.

Holmes pointed out that the median duration of persistence of tisagenlecleucel in these patients was 168 days in the blood (range, 20 to 617 days).

There is a reason, however, that CAR T-cell therapy was designated the breakthrough of the year by the American Society of Clinical Oncology,⁵ Holmes said.

However, 77% of patients experienced CRS and about 50% were treated with tocilizumab,⁶ he said. Neurologic events were manageable as well, and occurred in 40% of patients.

"The patients did fine initially, but then crashed," Holmes said, "with fever, high cytokine levels, and high white blood cell count."

Toxicities are very common with this adoptive cell therapy, he said, "which can be very distressing for patients and their families." Supportive care, he said, is a typical management strategy for these AEs.

From a community clinic's perspective, administering these treatments to patients or participation in clinical trials to test these treatments, is feasible, Holmes said. "However, practices will need facilities that have the capacity for apheresis. Additionally, the program requires a team effort, with participation of the pharmacy, toxicity management, nursing services, social work, and consultant support," including critical care, neurology, cardiology, and an emergency department. Additionally, the clinic will need to establish a risk evaluation and mitigation strategy.

"All of this can certainly be achieved in the community setting," Holmes assured the caregivers representing community practices who were in attendance.

Holmes then brought up the elephant in the room: the cost of this treatment. There's been significant debate over whether the treatments are cost effective at \$373,000 (Kite Pharma's Yescarta) and \$475,000 (Novartis' Kymriah).⁷

"All major payers have approved these treatment," Holmes said. Payers such as Optum, Aetna, and Cigna, are accessing Transplant Network agreements for this treatment, he said. "Our experience has been that you have to deal with payers on a case-by-case basis," he added.

The Institute for Clinical and Economic Review (ICER) released a report⁸ based on their analysis of these treatments earlier this year. According to ICER, the cost of both treatments aligns with their clinical value. ♦

REFERENCES

- Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T-cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368(16):1509-1518. doi: 10.1056/NEJMoa1215134.
- Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448. doi: 10.1056/NEJMoa1709866.
- Dangi-Garimella S. 5 significant developments with CAR-T therapy. *The American Journal of Managed Care* website. ajmc.com/newsroom/5-significant-developments-with-car-t-therapy. Published September 1, 2017. Accessed April 13, 2018.
- Dangi-Garimella S. Q&A with Dr Jae Park on the promise of CAR-T cells in cancer care. *The American Journal of Managed Care* website. ajmc.com/journals/evidence-based-oncology/2017/february-2017/q-

a-with-dr-jae-park-on-the-promise-of-car-t-cells-in-cancer-care. Published February 16, 2017. Accessed April 13, 2018.

- ASCO. Advance of the year. American Society of Clinical Oncology website. asco.org/research-progress/reports-studies/clinical-cancer-advances-2018/advance-year. Accessed April 13, 2018.
- Davio K. Oncologist shares lessons learned from CAR T-cell therapy in ALL. *The American Journal of Managed Care* website. ajmc.com/conferences/nccn-2018/oncologist-shares-lessons-learned-from-car-tcell-therapy-in-all. Published March 27, 2018. Accessed April 13, 2018.
- Dangi-Garimella S. Kite Pharma's CAR T-cell treatment approved, cheaper than tisagenlecleucel. *The American Journal of Managed Care* website. ajmc.com/newsroom/kite-pharmas-car-t-cell-treatment-approved-cheaper-than-tisagenlecleucel. Published on October 19, 2017. Accessed April 13, 2018.
- Rosenberg J. ICER report: costs of approved CAR T-cell therapies aligned with clinical benefit. *The American Journal of Managed Care* website. ajmc.com/newsroom/icer-report-costs-of-approved-car-tcell-therapies-aligned-with-clinical-benefit. Published February 21, 2018. Accessed April 13, 2018.

Avalere Consultants Untangle the MIPS Conundrum for Oncologists

THE TRIALS AND tribulations of enrolling in reimbursement programs—particularly the quality reporting, technology requirements, and measures—have been a significant cause for concern for physicians and practices. This has proven true for CMS' Merit-based Incentive Payment System (MIPS), as well as the Advanced Alternative Payment Models (A-APMs).

MIPS experts Richard Kane and Caroline Pearson, both from Avalere Health, provided oncologists gathered at the 2018 Community Oncology Conference an overview of these programs and advice on navigating both MIPS and the cancer-specific Oncology Care Model (OCM).¹ The meeting, hosted by the Community Oncology Alliance (COA), was held April 12-13 in National Harbor, Maryland.



PEARSON

"We need a number of strategies to bend the cost curve," Pearson said. "Ultimately, we want value in the form of higher-quality, lower-cost care." It is challenging, however, to identify and measure value before we see it, which is really hard and complicated. "We also have to set up the right payment incentives to push people to adopt this path. And then, as a provider, they need a strategy to implement these changes," she added.

Pearson explained that while instigating these changes can be difficult, a stepwise approach can help. The first step is the initial decision to move away from the fee-for-service care model and toward value-based payments. The next step in this migration toward increased risk is shared savings, episodic bundles, partial capitation, and finally, full capitation, she said.

"Taking this specific approach, Congress passed MACRA² [Medicare and CHIP Reauthorization Act] and permanently provided a fix for SGR [sustainable growth rate]," Pearson said. This further encouraged the shift to value-based payments.

According to Pearson, the SGR fix is the first accomplishment of MACRA. The act also stabilized physician Medicare payments with a 0.5% payment update in each of the 4 years prior to MIPS kicking in. "MACRA also encouraged physician participation in advanced APMs," she said, with a A-APM annual bonus payment of 5%.

Pearson says she believes that a majority of providers will participate in MIPS, while A-APMs participation will grow over time. "CMS predicts that 75% of clinicians will participate in MIPS and 25% will be a part of an A-APM in 2018," she said.

So, what can CMS do to aid this migration? "Sharing data with physicians and practices and providing timely feedback is important," according to Pearson. Only APMs with 2-sided risk qualify as A-APMs. Importantly, OCM participants have the option to switch between 1- and 2-sided risk.

"MIPS is involuntary while OCM is not," Kane clarified. While the downside risk is key, how much risk are physicians expected to absorb, he asked. »

CONFERENCE COVERAGE: COMMUNITY ONCOLOGY ALLIANCE

With MIPS, there is a 2-year lag between reporting and when clinicians receive their incentive payment—meaning, 2017 reporting will affect a practice's 2019 payments.



KANE

Kane said that practices have the option to pick 6 measures³ to report on; there can also person-alyze their reporting based on specialty and subspecialty. “Additionally, practices also have the option to report as a group.”

In 2017, for example, 45 oncology measures were finalized, 11 of which are new for MIPS. An oncology specialty set⁴ has also been identified, Kane said.

“CMS plans to add improvement scoring to the cost performance methodology for 2018 performance year,” Kane told the audience, “which rewards clinicians for improving their cost category scores over time.”

The formula subtracts the number of cost measures with significant decline in performance from the number of cost measures with significant improvement in performance. The value obtained is then divided by the total number of cost measures to arrive at the improvement score.

The Physician-focused Payment Model Technical Advisory Committee is expected to comment on Physician-focused Payment Model proposals submitted by stakeholders and identifying if the proposals meet certain criteria, Kane told the audience. These criteria, he added, include: scope, promotion of quality and cost, value over volume, practitioner flexibility, patient choice and safety, among others.

CMS has introduced a new risk-adjustment approach using the OCM prediction model that can promote the use of novel therapies. This includes:

- Prediction Model, which calibrates using the national set of baseline episodes for the period between July 2012 and June 2015.
- Experience Adjuster, which controls for unmeasured selection at the practice level.
- Adjustment for Novel Therapies, which controls for the use of novel treatments.

In terms of improving A-APM options for oncology, Kane explained that the Centers for Medicare & Medicaid Innovation has made several changes within OCM, and the next iteration, OCM 2.0, is also under development.

It is important to consider that earlier this year the Medicare Payment Advisory Commission recommended replacing MIPS⁵ with a Voluntary Value Program (VVP), where clinicians would find 2% of their payment deducted if they chose not to enroll in an advanced alternative payment model or not be evaluated on certain population-based measures. Travis Broome, vice president for policy, Aledade, says such a move could push physicians to take up more risk-based payment models.

The proposal has gained some followers, such as Gail Wilensky, PhD, senior fellow, Project HOPE, who proposed that CMS should launch a pilot⁶ to test VVP. ♦

REFERENCES

1. Joszt L. Reacting to the results of the first performance period of OCM. *The American Journal of Managed Care* website. ajmc.com/conferences/ncoda-spring-forum-2018/reacting-to-the-results-of-the-first-performance-period-of-ocm. Published March 4, 2018. Accessed April 12, 2018.
2. Jain S, Vyavahare M, Lewis J. MACRA continues to catalyze movement towards value. *The American Journal of Managed Care* website. ajmc.com/contributor/the-health-management-academy/2018/01/macra-continues-to-catalyze-movement-towards-value. Published January 17, 2018. Access April 13, 2018.
3. CMS. Quality measures. CMS website. qpp.cms.gov/mips/quality-measures. Accessed April 12, 2018.
4. American Academy of Allergy, Asthma and Immunology. Table E: 2018 finalized MIPS specialty measure set. AAAAI website. Aaaaai.org/Aaaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/2017-MIPS-Specialty-Measures-Sets.pdf. Published 2018. Accessed April 13, 2018.
5. Dangi-Garimella S. MedPAC votes a resounding “No” to MIPS, recommends voluntary value program. *The American Journal of Managed Care* website. ajmc.com/newsroom/medpac-votes-a-resounding-no-to-mips-recommends-voluntary-value-program. Published January 12, 2018. Accessed April 12, 2018.
6. Inzerro A. Let CMS pilot MedPAC's idea to reform MIPS, economist suggests. *The American Journal of Managed Care* website. ajmc.com/newsroom/let-cms-pilot-medpacs-idea-to-reform-mips-economist-suggests. Published February 28, 2018. Accessed April 12, 2018.

Panelists Discuss Key Issues in Community Oncology Affecting Patients and Practices

A PANEL OF providers discussed key advocacy issues that affect patients and practices and could improve access to care and costs during the 2018 Community Oncology Conference, hosted by the Community Oncology Alliance, April 12-13, in National Harbor, Maryland.

Debra Patt, MD, MPH, MBA, vice president of Texas Oncology, kicked off the session with an overview of some of the most important policy issues and trends affecting patients and specialists in the oncology space.

One of the top issues that is affecting care and exacerbating other challenges is the aging US population, she explained. As the population ages, more people are likely to develop cancer. So, even though there are more cancer diagnoses, this isn't because oncologists are doing a bad job, said Patt. “We're doing a really good job,” because more people are surviving their cancer and then living longer.

As the population ages, this presents challenges with cost, because more people who have cancer are enrolling in Medicare. The program must now pay for more expensive and innovative drugs to treat cancer. Patt highlighted that data show that there are projected to be 80 million Medicare beneficiaries in 2030, compared with 47 million in 2010.

She also highlighted the need for cancer drug pricing reforms, as the cost of cancer drugs continues to increase at a higher rate than US gross domestic product growth. “It's an amazing time to be a cancer specialist,” she said, because of the innovations happening in treatment that have moved oncology from acute care to chronic care. But that innovation has translated to higher costs. “What we know is that that cost of care today is unsustainable.”

These higher costs, plus the combination of having more patients, means that the time is “ripe for drug pricing policy innovation.” Patt explained that she is expecting recommendations in the area to come from HHS, the Office of Management and Budget, legislation, and even an executive order with ongoing discussions about value-based pricing, indication-based pricing, and more.

The challenge in oncology is that some policies restrict how many days' worth of opioids a provider can prescribe, which presents an unfair situation for patients with cancer and chronic pain who may have to go to their doctor more often.

Patt discussed the 340B program, which was created for hospitals treating a high share of poor patients, so they could purchase drugs at a discount to provide charity care. The problem is the lack of transparency around the program, such as how many poor people are being helped or what hospitals do with the money they save, such as if they use the money for executive compensation or if they use it to provide more services.

“340B was developed with very good intentions of helping patients who don't have the means or patients who have a lot of co-pays and they can't get treatment because of the cost of the treatment,” added Sibel Blau, MD, medical director at Northwest Medical Specialties.

However, the problem Blau highlighted was that in many cases, the hospital wants the community oncologist to send the patient to the hospital for full care, so the hospital can get the discounts in the 340B program. This can cause challenges for the patients who then have to travel far and often when they need treatment. “Patients don't realize they can get the care next door or 5 minutes away from home and the reason is [340B],” she said.

The lack of control and transparency in the 340B program means there are a lot of hospitals getting 340B pricing, it's not only going to care for the poor or uninsured, but also going to patients with payers who don't need the discounts, added Lucio Gordan, MD, medical oncologist and hematologist at Florida Cancer Specialists and Research Institute. This makes hospitals have more money and they start buying up small practices and specialty groups. As a result, the smaller practices “are choked” because referrals are all going to the hospital, which is an expensive setting to get care.

“The cost of oncology care and the cost of the setting, is easily 200%, sometimes 300% higher compared to an old-fashioned community oncology outpatient setting,” Gordan said. ♦

Coverage by Jaime Rosenberg and Laura Joszt

FDA Grants Priority Review for Pembrolizumab, Chemotherapy Combination in NSCLC

THE FDA GRANTED priority review to Merck's supplemental biologics license application (BLA) for pembrolizumab (Keytruda) in combination with pemetrexed (Alimta) and platinum chemotherapy as first-line treatment for patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), the company announced April 16, 2018.

The Prescription Drug User Fee Act action date has been set for September 23, 2018. The FDA's acceptance of the application is based on overall survival (OS) and progression-free survival (PFS) data from the phase 3 KEYNOTE-189 trial. The trial is the confirmatory trial for KEYNOTE-021, a phase 2 study that led to pembrolizumab being the first FDA-approved anti-PD-1 therapy in combination with chemotherapy for the first-line treatment of patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression.

In the double-blind, phase 3 KEYNOTE-189 trial,¹ 616 patients with NSCLC without *EGFR* or *ALK* mutations who had no previous treatment were randomized 2:1 to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to 35 cycles plus pemetrexed maintenance therapy.

After a median follow-up of 10.5 months, the estimated rate of OS at 12 months was 69.2% in the pembrolizumab cohort compared with 49.4% in the placebo cohort. Median PFS in the pembrolizumab cohort (8.8 months) was nearly double that of the placebo cohort (4.9 months).

"Keytruda is the first immunotherapy to significantly extend [the] survival of patients with NSCLC in combination with chemotherapy as a first-line treatment, including in patients whose tumors are either PD-L1 negative or are untested," said Roger M. Perlmutter, MD, president, Merck Research Laboratories, in a statement.²

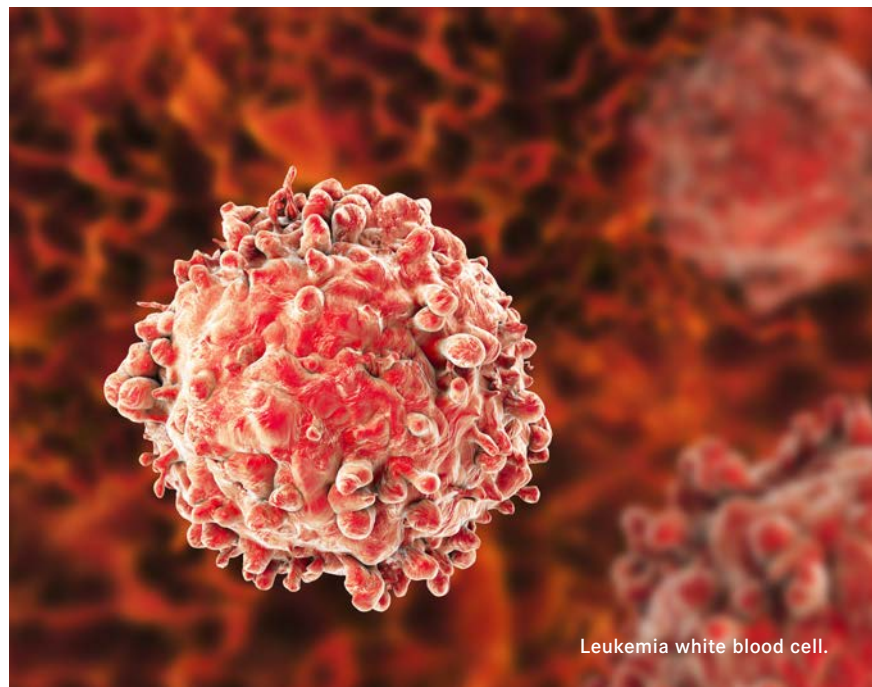
If approved by the FDA, this would represent the third indication for pembrolizumab in metastatic NSCLC in the United States based on OS data.

In early April, pembrolizumab monotherapy as first-line treatment in locally advanced or metastatic NSCLC met its primary endpoint of overall survival in the phase 3 KEYNOTE-042 trial compared with platinum-based chemotherapy.³

Outside of NSCLC, the anti-PD-1 therapy has indications for melanoma, head and neck cancer, classical Hodgkin lymphoma, urothelial carcinoma, and gastric cancer. In March, the FDA accepted a new supplemental BLA and granted a priority review to pembrolizumab as treatment for advanced cervical cancer, which marked the first filing acceptance and priority review granted for an anti-PD-1 therapy in cervical cancer.⁴ ♦

REFERENCES

1. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer [published online April 16, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1801005.
2. FDA grants priority review to Merck's sBLA for Keytruda (pembrolizumab) in combination with pemetrexed (Alimta) and platinum chemotherapy based on results from phase 3 KEYNOTE-189 trial as first-line treatment of metastatic nonsquamous NSCLC [press release]. Kenilworth, NJ: BusinessWire; April 30, 2018. [businesswire.com/news/home/20180430005480/en/FDA-Grants-Priority-Review-Merck%E2%80%99s-sBLA-KEY-TRUDA%C2%AE](https://www.businesswire.com/news/home/20180430005480/en/FDA-Grants-Priority-Review-Merck%E2%80%99s-sBLA-KEY-TRUDA%C2%AE). Accessed May 1, 2018.
3. Keytruda (pembrolizumab) monotherapy met primary endpoint in phase 3 KEYNOTE-042 study, significantly improving OS as first-line therapy in locally advanced or metastatic NSCLC patients expressing PD-L1 in at least 1 percent of tumor cells [press release]. Kenilworth, NJ: Merck; April 9, 2018. [mrknewsroom.com/news-release/oncology-newsroom/keytruda-pembrolizumab-monotherapy-met-primary-endpoint-phase-3-keynote](https://www.mrknewsroom.com/news-release/oncology-newsroom/keytruda-pembrolizumab-monotherapy-met-primary-endpoint-phase-3-keynote). Accessed May 1, 2018.
4. Rosenberg J. Pembrolizumab granted priority review for treatment of cervical cancer. *The American Journal of Managed Care*® website. ajmc.com/newsroom/pembrolizumab-granted-priority-review-for-treatment-of-cervical-cancer. Published March 13, 2018. Accessed April 16, 2018.



Leukemia white blood cell.

Researchers Identify New Gene That Predisposes People to ALL

RESEARCHERS HAVE IDENTIFIED a fourth gene that may predispose individuals to develop acute lymphoblastic leukemia (ALL), according to findings of a study published in *Cancer Cell*.¹ *IKZF1* joins 3 other genes—*TP53*, *ETV6*, and *PAX5*—which have been identified as predisposing carriers to develop B-cell ALL.

In addition to *IKZF1* indicating individuals who have an increased susceptibility to ALL, variants in the gene can influence patient response to treatment.

"This finding adds to the growing body of evidence that, while germline variations still account for a small percentage of pediatric ALL cases overall, more children than previously recognized inherit a predisposition to develop ALL," Charles Mullighan, MBBS, MD, a member of the St. Jude Department of Pathology, said in a statement.²

A decade ago, Mullighan and colleagues first reported that *IKZF1* was often mutated in leukemic cells, which indicated that the individual would have poor treatment outcomes.

Although not everyone carrying a germline *IKZF1* variant will develop ALL, the findings mean families can be informed about the potential risk to develop leukemia, added co-author Kim Nichols, MD, director of the St. Jude Cancer Predisposition Division.

The history of research into *IKZF1* includes 3 generations of a German family with a germline variation of the gene and a family history of B-cell ALL. Researchers found that 2 of the 5 family members with the variant developed ALL as children and died.

"In *IKZF1* and the other ALL predisposition genes, cells may require an additional cooperating mutation to develop into leukemia," Mullighan said. "While familial ALL is rare, these cases can point to genes and novel biology to examine in a larger patient population." ♦

REFERENCES

1. Churchman ML, Qian M, Kronnie G, et al. Germline genetic *IKZF1* variation and predisposition to childhood acute lymphoblastic leukemia [published online April 19, 2018]. *Cancer Cell*. doi: 10.1158/2159-8290.CD-RW2018-073.
2. Discovery adds to evidence that some children are predisposed to develop leukemia [press release]. Memphis, TN: St. Jude Children's Research Hospital; April 19, 2018. [stjude.org/media-resources/news-releases/2018-medicine-science-news/discovery-adds-to-evidence-that-some-children-are-predisposed-to-develop-leukemia.html](https://www.stjude.org/media-resources/news-releases/2018-medicine-science-news/discovery-adds-to-evidence-that-some-children-are-predisposed-to-develop-leukemia.html). Accessed May 1, 2018.

The advertisement features a scenic background of a river flowing through a lush green valley with mountains in the distance. Two people in a red canoe are navigating a section of the river with white water rapids. A hand from the right side of the frame is drawing a smooth, winding path on the grassy bank with a blue pencil. The pencil has the 'Jakafi' logo on it. In the top left corner, there is a box containing the 'Jakafi' logo and the text 'ruxolitinib (tablets)'. The main text is in a large, bold, purple font with a hand-drawn texture.

Jakafi
ruxolitinib (tablets)

In patients with polycythemia vera uncontrolled with hydroxyurea

**PROVIDE THE PATH THAT MAY
LEAD TO MORE CONTROL**

INTERVENE WITH JAKAFI

Indications and Usage

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia ($ANC < 0.5 \times 10^9/L$) was generally reversible by withholding Jakafi until recovery

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

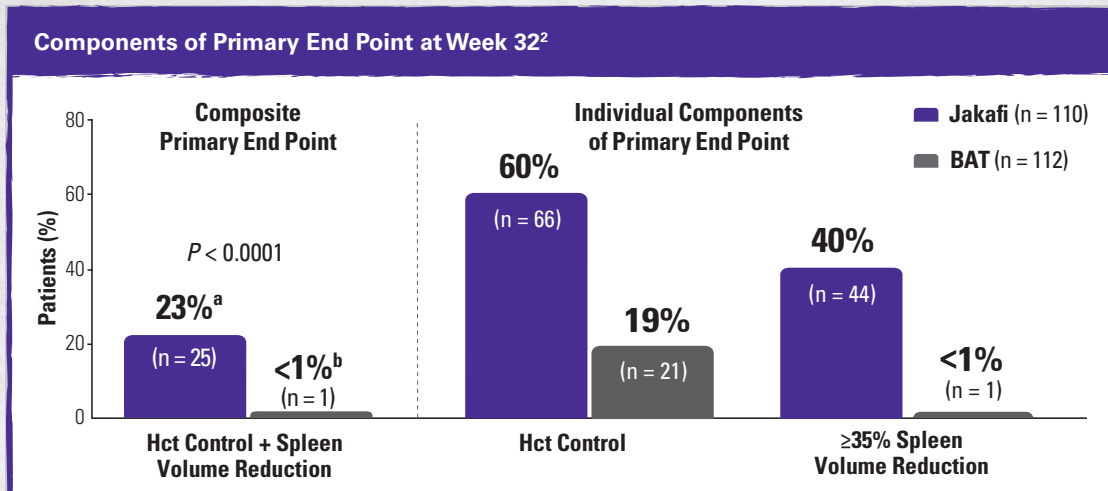


Jakafi is a registered trademark of Incyte.
© 2017, Incyte Corporation. All rights reserved. RUX-2216 12/17

Significantly more patients receiving Jakafi achieved the composite primary* and key secondary end points^{2,3†}

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

National Comprehensive Cancer Network® (NCCN®) recommends ruxolitinib as a treatment option for patients with polycythemia vera who have had an inadequate response to or are intolerant of cytoreductive therapy¹



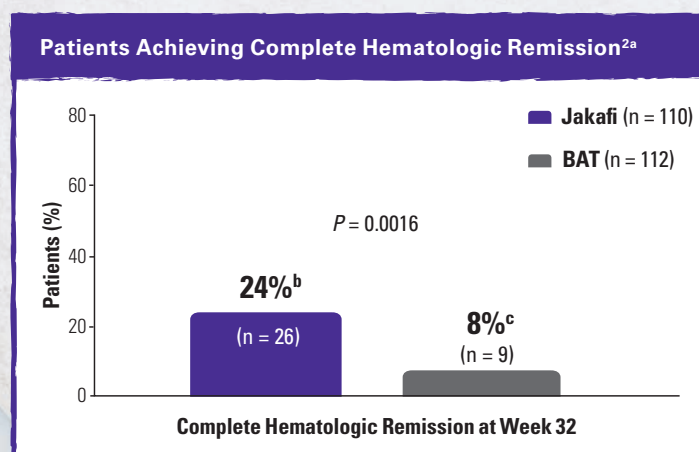
BAT, best available therapy; CI, confidence interval; Hct, hematocrit.

^a 95% CI, 15%-32%

^b 95% CI, 0%-5%

* The composite primary end point was defined as Hct control without phlebotomy eligibility and a ≥35% spleen volume reduction as measured by CT or MRI. To achieve the Hct control end point, patients could not become eligible for phlebotomy between weeks 8 and 32. Phlebotomy eligibility was defined as Hct >45% that is ≥3 percentage points higher than baseline or Hct >48% (lower value).

† The RESPONSE (Randomized study of Efficacy and Safety in POLycythemia vera with JAK iNhibitor ruxolitinib verSus bEst available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with polycythemia vera. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. BAT included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients enrolled in the study had been diagnosed with polycythemia vera for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy for Hct control, and exhibited splenomegaly. After week 32, patients were able to cross over to Jakafi treatment. A durability analysis was performed at week 80 in the original Jakafi arm.



Durable response at week 80²

- 19 of 25 patients (76%) who achieved a primary response at week 32 in the Jakafi arm maintained their response
- 51 of 66 patients (77%) who achieved Hct control at week 32 in the Jakafi arm maintained their response
- 43 of 44 patients (98%) who achieved a ≥35% spleen volume reduction at week 32 in the Jakafi arm maintained their response
- 15 of 26 patients (58%) who achieved complete hematologic remission at week 32 in the Jakafi arm maintained their response

BAT, best available therapy; CI, confidence interval.

^a Complete hematologic remission was defined as achieving hematocrit control (as specified in the primary end point), platelet count $\leq 400 \times 10^9/L$, and white blood cell count $\leq 10 \times 10^9/L$.^{2,3}

^b 95% CI, 16%-33% ^c 95% CI, 4%-15%

Durable count control

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache

- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose

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

To learn more about intervening with Jakafi, visit **Jakafi.com/HCP**.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V2.2018. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed September 7, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. 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. 2. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. 3. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.



BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS **Thrombocytopenia, Anemia and Neutropenia** Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see *Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see *Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10⁹/L) was generally reversible by withholding Jakafi until recovery [see *Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see *Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*].

Risk of Infection Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see *Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see *Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [see *Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [see *Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see *Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [see *Warnings and Precautions (5.4) in Full Prescribing Information*]. **Clinical Trials Experience in Myelofibrosis** 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 of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10⁹/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10⁹/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [see *Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [see *Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

Adverse Reactions	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^a (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Bruising ^b	23	<1	0	15	0	0
Dizziness ^c	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections ^d	9	0	0	5	<1	<1
Weight Gain ^e	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster ^f	2	0	0	<1	0	0

^a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
^b includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
^c includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
^d includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
^e includes weight increased, abnormal weight gain
^f includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10⁹/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10⁹/L to 200 X 10⁹/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10⁹/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study^a

Laboratory Parameter	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^b (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

^a Presented values are worst Grade values regardless of baseline
^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see *Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

Adverse Events	Jakafi (N=110)		Best Available Therapy (N=111)	
	All Grades ^a (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Headache	16	<1	19	<1
Abdominal Pain ^b	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness ^c	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea ^d	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema ^e	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster ^f	6	<1	0	0
Nausea	6	0	4	0

^a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

^b includes abdominal pain, abdominal pain lower, and abdominal pain upper

^c includes dizziness and vertigo

^d includes dyspnea and dyspnea exertional

^e includes edema and peripheral edema

^f includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment^a

Laboratory Parameter	Jakafi (N=110)			Best Available Therapy (N=111)		
	All Grades ^b (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

^a Presented values are worst Grade values regardless of baseline

^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS **Fluconazole** Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [see *Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [see *Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inhibitors** Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [see *Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [see *Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inducers** Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [see *Clinical Pharmacology (12.3) in Full Prescribing Information*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS **Pregnancy: Risk Summary** When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data: Animal Data** Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed infant, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data: Animal Data** Lactating rats were administered a single dose of [¹⁴C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose. The safety profile in children was similar to that seen in adults. **Geriatric Use** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and moderate (CLcr 30 mL/min to 59 mL/min as estimated using Cockcroft-Gault) or severe renal impairment (CLcr 15mL/min to 29 mL/min) with a platelet count between 50 X 10⁹/L and 150 X 10⁹/L [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and moderate (CLcr 30 to 59 mL/min) or severe renal impairment (CLcr 15 to 29 mL/min) [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for all patients with ESRD on dialysis [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. **Hepatic Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and any degree of hepatic impairment (Child-Pugh Class A, B and C) and with a platelet count between 50 X 10⁹/L and 150 X 10⁹/L [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and hepatic impairment (Child-Pugh Class A, B and C) [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. **OVERDOSAGE** There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.



Jakafi is a registered trademark of Incyte. All rights reserved.
U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 8829013; 9079912
© 2011-2018 Incyte Corporation. All rights reserved.
Revised: December 2017 RUX-2429

New Test Could Make Multiple Myeloma Diagnosis as Easy as Drawing a Blood Sample

ONE DAY, MULTIPLE myeloma may be diagnosed without subjecting patients to a painful bone biopsy, according to research on a new blood test published in *Integrative Biology*.¹

For the last 10 years, researchers at Kansas University (KU) have been developing a blood-based test for a variety of cancer diagnoses, including multiple myeloma. The blood test uses a small plastic chip that delivers the same diagnostic information through a simple blood draw.

“We’ll be able to eliminate the need for bone-marrow biopsies and allow the clinician to determine the best way to treat the disease using a blood draw,” Steven Soper, PhD, foundation distinguished professor of Chemistry and Mechanical Engineering at KU and a member of The University of Kansas Cancer Center, said in a statement.² “From this test, the clinician will be able to determine the stage of the disease, what type of drug will best treat the disease, and monitor for signs of recurrence if the disease goes into remission.”

“With our technology, we’ll be able to see if patients are developing cancers before they have overt symptoms and help improve survival.”

– Steven Soper, PhD

The new chip improves accuracy over previous chips developed to test for multiple myeloma, according to the researchers. Previous chips picked up regular blood cells instead of multiple myeloma cells. The chip test from KU identified circulating plasma cells in all patients with smoldering and symptomatic multiple myeloma, 78% of patients with monoclonal gammopathy of undetermined significance (a precursor to multiple myeloma), and none of the control patients.

The chip is also cheaper than previous versions and can be produced for a couple of dollars per unit, according to Soper, who led the research.

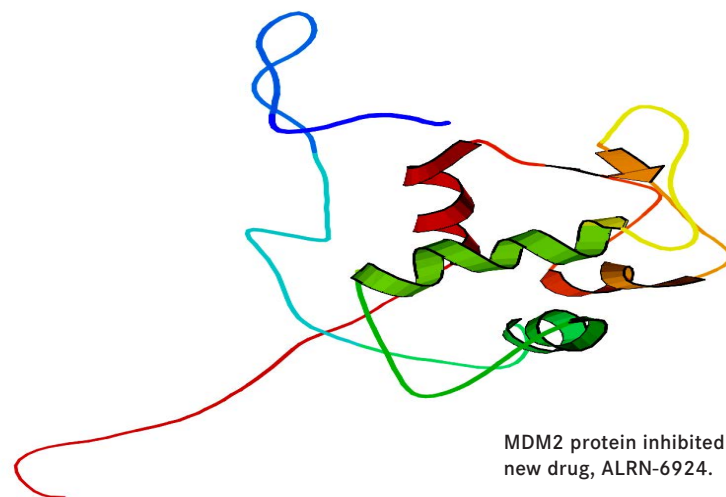
The goal, he said, is that screening for cancer will one day be routine and widespread so there can be a diagnosis long before symptoms present themselves. He added that integrating the test into care can be as easy as screening blood drawn during an annual physical for cancer.

The new test for multiple myeloma will be brought to market by BioFluidica. The technology is already being tested at Children’s Mercy Hospital in Kansas City on pediatric patients with acute leukemia, Soper explained. The test is being used to identify tumor cells in blood to see signs of disease recurrence.

“We’ve demonstrated the utility of this technology in a variety of cancer diseases,” Soper said. “Here, we’re homing in on multiple myeloma, but we’ve developed tests for 2 forms of leukemia and for pancreatic cancer, prostate cancer, ovarian cancer, colorectal cancer, and breast cancer. With our technology, we’ll be able to see if patients are developing cancers before they have overt symptoms and help improve survival.” ♦

REFERENCES

1. Kamande JW, Lindell MAM, Witek MA, Voorhees PM, Soper SA. Isolation of circulating plasma cells from blood of patients diagnosed with clonal plasma cell disorders using cell selection microfluidics. *Integr Bio (Camb)*. 2018;10(2):82-91. doi: 10.1039/c7ib00183e.
2. Chip-based blood test for multiple myeloma could make bone biopsies a relic of the past [press release]. Lawrence, KS; The University of Kansas; April 16, 2018. news.ku.edu/2018/04/16/chip-based-blood-test-multiple-myeloma-could-help-make-bone-biopsies-relic. Accessed May 1, 2018.



Novel Drug Shows Promise in Acute Myeloid Leukemia by Suppressing 2 Proteins

THE FIRST IN a new class of anticancer agents has shown promise against acute myeloid leukemia (AML), according to findings published in *Science Translational Medicine*.¹ The findings led to a phase 1/2 clinical trial for patients with advanced AML and advanced myelodysplastic syndrome.

The research, from investigators at Albert Einstein College of Medicine, describes how an experimental drug, ALRN-6924, targets p53, a protein that is inactivated in AML. The drug inhibits the proteins MDMX and MDM2, both of which inactivate p53 when they are overexpressed. When p53 is activated, it suppresses tumors.

In preclinical studies, ALRN-6924 tripled the median AML survival rate in mice transplanted with human leukemia cells from 50 days to approximately 150 days.

“This is a very striking response,” study leader Ulrich Steidl, MD, PhD, professor of cell biology and of medicine and the Diane and Arthur B. Belfer Faculty Scholar in Cancer Research at Einstein and associate chair for translational research in oncology at Montefiore Health System, said in a statement.² “Most experimental drugs for leukemia achieve an increase in survival of only a few days in these preclinical models. Even more importantly, ALRN-6924 effectively cured about 40% of the treated mice, meaning they were disease free more than 1 year after treatment—essentially a lifetime for a mouse.”

AML is an often-lethal cancer, with only 27% of people who are diagnosed surviving for 5 or more years. Furthermore, in the past half century, the outcomes for AML have not significantly improved, according to a press release from Albert Einstein College of Medicine.

The research found that not only did ALRN-6924 block interaction of both MDMX and MDM2 with p53 in more mature AML cells, but the effect was also seen in the immature stem cells that produce AML cells.

“This is important because AML is driven by stem cells—and if you don’t target stem cells, the disease will come back very quickly,” Steidl said.

He added that some other cancers driven by overexpression of MDMX and MDM2 and inactivation of p53, such as some forms of breast cancer and lung cancer, could be treated with ALR-6924. ♦

REFERENCES

1. Carvajal LA, Ben Neriah D, Senecal A, et al. Dual inhibition of MDMX and MDM2 as a therapeutic strategy in leukemia [published online April 11, 2018]. *Sci Transl Med*. doi: 10.1126/scitranslmed.aao3003.
2. Novel drug shows promise against acute myeloid leukemia [press release]. Bronx, NY: Einstein Medical Center; April 11, 2018. einstein.yu.edu/news/releases/1292/novel-drug-shows-promise-against-acute-myeloid-leukemia/. Accessed May 1, 2018.

THE REGULATORY PROCESS

Perspective: FDA/CMS Parallel Review Advances Coverage for Cancer Comprehensive Genomic Profiling

Lakshman Ramamurthy, PhD; Kristi Maxwell, MS, CGC;
Bethany Sawchyn, PharmD; and Rachel Anhorn, PharmD

CONTINUED FROM COVER

A key rationale for using CGP is the well-documented problem of low molecular testing rates and slow adoption rates for new biomarkers.^{3,4} Patients who receive incomplete or partial testing per guidelines may miss the opportunity to receive potentially life-extending therapies that, for some patients, have been shown to improve quality of life compared with cytotoxic chemotherapy. Alternatively, even if single-assay tests are performed, there is a high likelihood of having insufficient tissue or there being a need for repeated invasive biopsies.⁵ One study looking at diagnosis patterns in non-small cell lung cancer found that only 8% of patients received testing for all guideline-recommended biomarkers prior to therapy.⁴ Not receiving targeted therapy resulted in poorer outcomes. This is a significant area of opportunity for quality improvement in patients with advanced cancers. Unfortunately, the few established quality measures related to biomarker testing seem to be written in the reverse order, measuring if a certain test was used for patients who had received a certain drug.⁶ The more relevant measure might be to assess if a patient with cancer about to receive anti-oncologic therapy had received complete testing.

A CGP approach with FoundationOne CDx offers a potential solution for slow testing adoption rates and tissue exhaustion, and a 1-stop diagnostic to best leverage the rapidly changing treatment landscape. By using a platform that can accommodate additional biomarkers and companion diagnostics, FoundationOne CDx is well suited to keep pace with precision oncology. Testing patients with a CGP approach improves quality of care and offers the opportunity for patients to receive an evidence-based therapy or enroll into a clinical trial, which can be life extending but is often biomarker driven. FoundationOne CDx provides a comprehensive profile of 324 genes and is suitable for use in all solid tumors.⁷ It encompasses guideline-recommended genes for testing in solid tumors and has FDA approval as a companion diagnostic for 17 targeted therapies in 5 solid tumor types. In addition, FoundationOne CDx assesses complex genomic signatures to help inform immunotherapy decisions. A comprehensive genomic profile is essential for quantifying these genomic signatures.^{8,9} FoundationOne CDx is an efficient way of navigating all of these established and emerging biomarkers, potentially limiting the amount of tissue and time needed to assess for multiple clinically relevant alterations compared with sequential single-gene testing.

Foundation Medicine, Inc, was founded on the premise that no mechanism existed whereby clinicians, in the day-to-day practice of clinical oncology, could systematically obtain tumor information and efficiently interpret the specific molecular alterations associated with each patient's disease.¹⁰ This mission was

a driving force in its decision to participate in the parallel review process after being approached by the FDA and CMS.

FDA's Risk-Based Regulation of Diagnostics

Laboratory developed tests (LDTs) traditionally have not been required to receive approval by the FDA prior to being used. Additionally, the FDA process for medical devices (including LDTs) is somewhat less well defined and slightly more complex compared with the well-established regulatory path for small molecules and biologic therapies. The 1976 Medical Device Amendment provided a comprehensive regulatory framework for medical devices and established a risk-based regulatory classification system, as described in **Figure 1**.¹¹ Diagnostics are medical devices and are classified based on the risk posed to the patient using the device. The lowest risk devices are deemed Class I and are mostly exempt from any requirements prior to marketing within the United States. Examples of Class I devices include arm slings, latex examination gloves, and most hearing aids.

Premarket notification or 510(k)

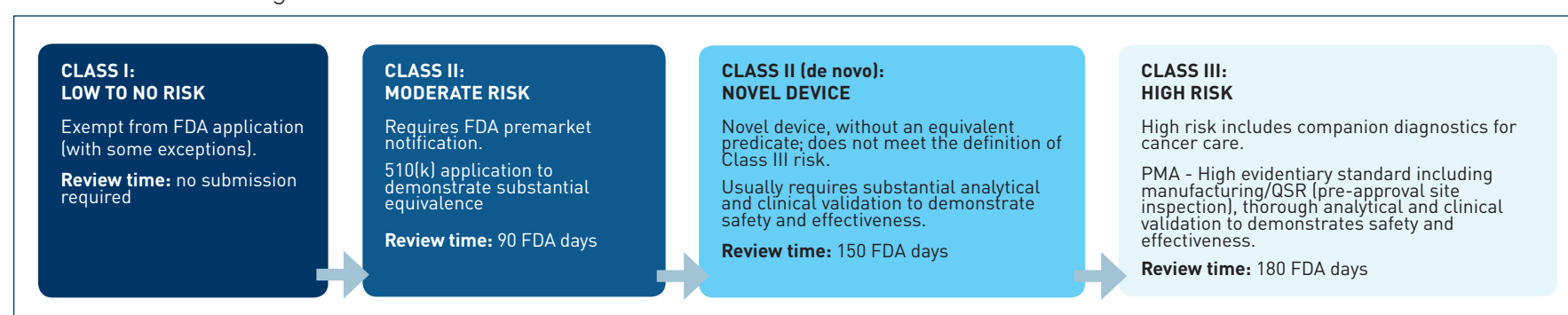
Most medical devices and diagnostics fall in the Class II category, and manufacturers of such devices are required to notify the FDA prior to marketing those devices via a 510(k) submission (premarket notification [PMN]).¹² The 510(k) application allows the manufacturer to demonstrate that its device is "substantially equivalent" in terms of its intended use, safety, and effectiveness to an already legally marketed "predicate" medical device in the United States.

Premarket approval

Class III is reserved for devices deemed high risk and subject to a premarket approval (PMA) procedure, like that for new drugs. By statute, the PMA process is reserved for medical devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."¹³ For this reason, almost all companion diagnostics that may direct treatment are also categorized as Class III and require FDA approval, based on clinical experience, before a product can be marketed.

Pre-market approval is the most involved and expensive process that a medical device manufacturer typically pursues. This type of approval is based on a determination by the FDA that the applicant has submitted sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). For example, **Figure 2** shows the types of »

FIGURE 1. Risk-based Regulation of Medical Devices¹¹



PMA indicates pre-market approval; QSR, quality system regulation.

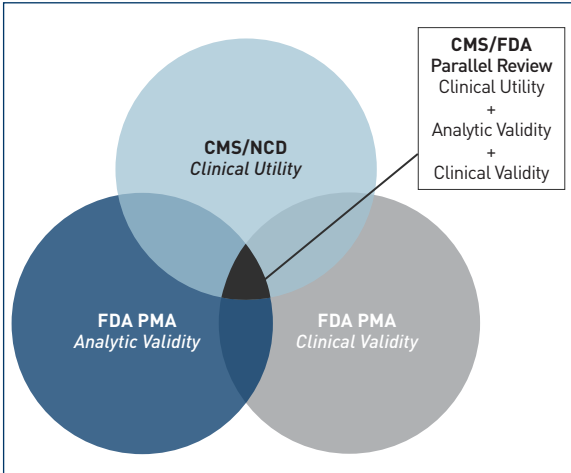
THE REGULATORY PROCESS

FIGURE 2. FoundationOne CDx Performance Studies for Premarket Approval

#	Study Name	F1CDx
1	LoB	x
2	LoD	x
3	Minimal tumor content	x
4	Specificity, endogenous	x
5	Specificity, exogenous	x
6	Specificity, in-silico	x
7	Interfering substances	x
8	Repeatability	x
9	Specimen handling reproducibility	x
10	Correlation/Concordance	x
11	Carry-over/cross-contamination	x
12	Precision/reproducibility	x
13	Reagent lot-to-lot reproducibility	x
14	Instrument-to-instrument reproducibility	x
15	Reagent lot interchangeability	x
16	Reagent stability	x
17	DNA stability	x
18	FFPET slide specimen stability	x
19	DNA extraction	x
20	Guard banding/robustness	x
21	Tissue comparability	x
22	Clinical reproducibility	n/a

F1CDx indicates FoundationOne CDx; FFPET, Formalin-Fixed Paraffin-Embedded Tissue; LoB, limit of blank; LoD, limit of detection; n/a, not applicable.

FIGURE 3. Areas of Focus During CMS/FDA Parallel Review



NCD indicates National Coverage Determination; PMA, premarket approval.

evidence submitted by Foundation Medicine for FoundationOne CDx.

Path to Market for LDTs

Rigorous FDA evaluations, as shown in Figure 2, are in stark contrast to the path to market for LDTs, although many valuable diagnostic assays have come to market via the LDT pathway. To date, the FDA has exercised a policy of enforcement discretion wherein LDTs have not been required to seek authorization in advance of being clinically offered as a test. LDTs are regulated by CMS' Clinical Laboratory Improvement

Amendments (CLIA), which is administered through various accreditation bodies, including the College of American Pathologists. Additionally, various state agencies, including the New York State Department of Health, have their own requirements for laboratories accepting patient samples originating in their states. Although CLIA establishes quality standards for laboratories to ensure the accuracy, reliability, and timeliness of patients' test results, they do not cover how to perform a pre-market review of analytic validation or require clinical validity data. This contrasts with the FDA review process for Class III PMAs where both analytic and clinical validity are evaluated. Moreover, whereas medical devices and diagnostics must register with the FDA and are also required to submit adverse events, recalls, and user complaints, LDTs have no such requirement. This can lead to lack of awareness of potential safety signals with a given LDT.

Medicare Coverage Determination

To be covered by CMS, medical products must fall into one of the statutorily defined "benefit categories" and be "reasonable and necessary" for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. To meet the "reasonable and necessary" standard, a product or service must improve health outcomes, be safe and effective, and not be deemed experimental or investigational. The reasonable and necessary provisions are not defined explicitly in regulation and remain at the discretion of Medicare. For Medicare, FDA-approved devices with therapeutic indications are presumed to meet this definition unless directly addressed through a Local Coverage Determination (LCD) or National Coverage Determination (NCD). Public payers are often subject to requirements to develop their coverage policies in an open and transparent manner. For example, LCDs and NCDs must undergo opportunities for public comment and are open to more political scrutiny given the nature of publicly funded programs.¹⁴

FDA/CMS Parallel Review Process

The FDA and CMS have clearly different objectives: safety and effectiveness of a device and whether the device is reasonable and necessary, respectively. Therefore, neither agency is usually influenced by the other's findings or decisions, nor has there been coordination between the individual review processes. To support medical device innovation, the FDA and CMS entered a memorandum of understanding, which led to a pilot FDA/CMS parallel review process.¹⁵ The purpose of this program was mainly to minimize the time between regulatory authorization and reimbursement, an important barrier to patient access for the latest medical device innovation.¹⁶ Creating accelerated approval processes or breakthrough device designations would be insufficient if there was no comparable innovation in reimbursement policies. This is particularly unique to the medical device/diagnostic space in contrast to the oncology therapeutic space where

FDA approval of a drug or biologic is sufficient for reimbursement and therefore access by the patient. Medical device/diagnostics must pursue reimbursement separately via an LCD or NCD following FDA review.¹⁷ The pilot project has since been made permanent.¹⁸

Careful evaluation of the National Coverage Analysis process and the resulting NCD can provide valuable insight. CMS assessed CGP technology through the parallel review process using the ACCE (analytical validity, clinical validity, clinical utility, and ethical, legal and social implications of genetic testing) model for assessment. For analytic validity and clinical validity, FDA approval of FoundationOne CDx signifies assurance of safety and effectiveness and that there is an acceptable evidence base for analytic and clinical validity requirements for coverage.^{19,20} A key area of focus for CMS in the parallel review was to evaluate clinical utility.^{20,21} When these processes are undertaken in parallel, the product's complete clinical value can be assessed (Figure 3).

Because the analytic validity, clinical validity, and clinical utility evidence reviewed by the FDA and CMS are not limited to patients 65 years and older, this same evidence should be considered by commercial insurers. Cancer is not a disease affecting only the Medicare population.

Through the parallel review process for FoundationOne CDx, CMS identified and reviewed over 250 studies to assess the clinical utility of NGS testing in advanced cancer, demonstrating the breadth of available evidence. The clinical outcome measures CMS considered included overall survival, progression-free survival, partial response, complete response, stable disease, time to progression, overall response rate, and time to treatment failure. Systematic evidence reviews and meta-analyses of clinical trial data provide a strong level of evidence, and observational and other study designs provide additional supportive evidence across a broad population of patients with cancer.^{20,22} Meta-analyses of data from therapeutic clinical trials, including randomized controlled trials, which have traditionally been the gold standard in evidence generation; data from nonrandomized studies utilizing CGP; and real-world evidence support the use of a genomically guided treatment approach to improve outcomes.²²⁻²⁷ From this evidence review, CMS concluded that there is sufficient clinical utility demonstrating that FDA-approved and FDA-cleared laboratory in vitro companion diagnostic tests using NGS improve health outcomes for patients with

THE REGULATORY PROCESS

TABLE. CMS National Coverage Criteria for NGS²⁰

Performed in a CLIA-certified laboratory
Ordered by a treating physician
Patient meets all of the following criteria: <ol style="list-style-type: none">Has either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancerHas not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physicianHas decided to seek further cancer treatment (eg, therapeutic chemotherapy)
The diagnostic laboratory test using NGS meets the following criteria: <ol style="list-style-type: none">FDA approval or clearance as a companion in vitro diagnosticAn FDA approved or cleared indication for use in that patient's cancerResults provided to the treating physician for management of the patient using a report template to specify treatment options

CLIA indicates Clinical Laboratory Improvement Amendment; NGS, next-generation sequencing.

advanced cancer when used by the treating physician and patient to guide selection of proven treatments.²⁰ In addition, in the final NCD, CMS encouraged the community of stakeholders to continue to develop and publish evidence related to the meaningful endpoints assessed in the coverage analysis. Foundation Medicine is committed to publishing evidence as it is generated, as evidenced by more than 300 Foundation Medicine–authored publications.

Paving The Way in Advanced Cancer: FoundationOne CDx

The parallel review process has served as an incentive for 2 LDTs to pursue regulatory approval: Exact Sciences' Cologuard for colorectal cancer screening and, more recently, FoundationOne CDx.^{20,28} These have been characterized as "single-site PMAs" where both diagnostic tests are offered from a single laboratory. The NCD for NGS-based diagnostics provides confirmed national coverage for FDA-approved or -cleared diagnostics, while LDTs without FDA approval or clearance may still be reimbursed at the discretion of the local Medicare Administrative Contractors.

The parallel review process culminated in FDA approval of FoundationOne CDx and a CMS NCD that provided Medicare beneficiaries with advanced

cancer broad access to CGP as a path to precision oncology treatment, as outlined by the coverage criteria in Table.²⁰

Translating Parallel Review to Commercial Payers

Although CMS coverage of NGS tests in advanced cancer does not automatically translate into commercial coverage, as reported in a recent survey of some major commercial payers,²⁹ it would seem prudent for commercial payers to seize this moment and re-evaluate the role of CGP in providing important and tangible benefits for the sickest cancer patients regardless of age or insurer. The parallel review process provides the opportunity to recognize and integrate the outcomes of the rigorous FDA regulatory and CMS coverage pathways in order to further pave the path forward for higher quality oncology care.

Commercial payers may be challenged to rethink the approach to coverage determination for non-Medicare Advantage members. With some exceptions, commercial policies have historically described CGP tests as investigational or experimental. These policies often cite lack of clinical utility as a reason for noncoverage; however, there are several considerations for determining clinical utility for genomic panel tests in oncology that differ from single gene testing, including:

- Supporting data are often scattered across multiple publications encompassing a diverse range of tumor types, because the clinical utility of CGP varies based on tumor type, stage, and line of therapy.
- Not all genomic alterations are directly correlated with a specific therapy; genomic alterations also often impact decision making due to their role in a critical signaling pathway or as a prognostic indicator.
- Randomized clinical trials for CGP testing have ethical and design limitations.

To further validate this, a CGP approach has been integrated into many large innovative clinical trials, such as the American Society of Clinical Oncology's TAPUR and Genentech's MyPathways; into numerous clinical guidelines; and is used routinely across academic centers and advanced community practices. The evidence base supporting the clinical utility of this approach stems from data across multiple types

of studies conducted in the oncology setting using biomarker-driven therapies. Collectively, these studies demonstrate that:

- A clinically validated NGS CGP test facilitates the accurate identification of patients with genomic alterations across tumor types.
- The presence or absence of these alterations helps inform treatment decisions.
- Health outcomes are improved overall when patients are treated with genomically matched FDA-approved drugs or biologics or genomically matched investigational agents.

Thus, genomic testing has a significant role in fulfilling the promise of precision medicine in oncology to improve outcomes for patients, and the NCD is a landmark event for patients with advanced cancer.

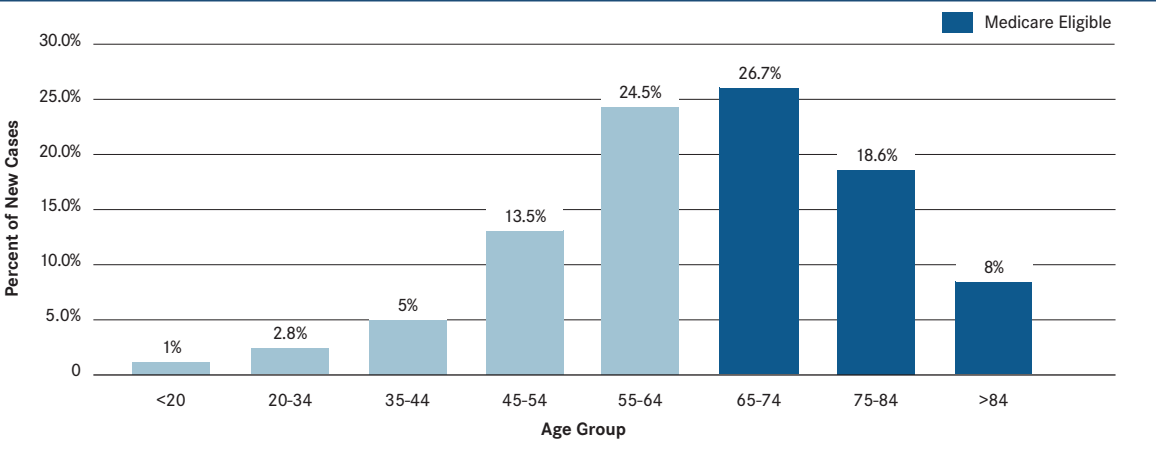
When it comes to broad commercial coverage, private payers are often faced with the challenge of addressing or creating a significant disparity in oncology care between patients with Medicare and other commercially covered patients with advanced cancers. Because the analytic validity, clinical validity, and clinical utility evidence reviewed by the FDA and CMS are not limited to patients ≥65 years, this same evidence base should be considered by commercial insurers. Cancer is not a disease affecting only the Medicare population. US epidemiology data (Figure 4³⁰) estimate the median age at cancer diagnosis to be 66 years, yet 46.8% of cancer diagnoses and 30.7% of cancer deaths occur before age 65.³⁰ In addition, the proportion of cancer cases that are reported as advanced stage (have spread locally or distant) for the Medicare and non-Medicare population are nearly equal (45.3% for <65 years vs and 45% for ≥65 years). Coverage for commercial lives is imperative so that patients with advanced cancer are provided the greatest opportunity to receive genomically matched or biomarker-driven therapies regardless of age or insurer.

Future of the Parallel Review Process in Precision Oncology

Now that CMS has released the NCD that addresses all NGS-based oncology assays used in advanced cancer, and with the subsequent announcements by multiple CGP diagnostics providers, it is expected that more laboratory tests will undergo the FDA approval process via the PMA pathway.³¹ Although commercial payers are only directly affected by a new NCD if they offer Medicare Advantage plans, the data supporting the NCD will offer the chance for payers to consider the same information used by CMS to ultimately determine for themselves that outcomes are improved by CGP utilization. If CGP is only accessible to the Medicare population, there is a risk of creating additional disparity in the US healthcare ecosystem. Given the numerous new biomarkers, novel biomarker-driven treatments, tumor-agnostic biomarkers (ie, microsatellite instability), and genomic signatures that require a large panel test, there is no doubt that CGP is not only here to stay but will become mainstream.

In many cases, testing is treated passively by payers (eg, by only asking if a patient was tested if a »

FIGURE 4. Percent of New Cancer (Any Site) Cases by Age Group³⁰



THE REGULATORY PROCESS

biomarker-driven therapy is requested). However, CGP offers an opportunity for payers to proactively require that all appropriate patients undergo guideline-driven testing to improve quality of care and decrease waste by assuring the right patients receive the right treatment at the right time. Payers who embrace CGP could be afforded the opportunity to not only improve quality of care but also to better manage and predict cancer drug spend. It would not be hard to imagine a payer taking it one step further and requiring CGP for certain patients, which undoubtedly would increase the utilization of biomarker-driven treatments. The predictable increase in use of biomarker-driven treatments, for both on-label and off-label use, could allow for improved value-based agreements based on the volume of patients receiving CGP thus offsetting possible cost increases for payers while improving quality of care for patients.

Because FoundationOne CDx completed the parallel review process, the path to CMS coverage has been paved for future NGS tests. The broad nature of the NCD means other NGS test providers will only need to pursue companion diagnostic FDA approval or clearance status to obtain coverage from CMS. As outlined in the CMS NCD, the FDA assesses analytic validity and clinical validity as part of the approval process. FDA approval or clearance, therefore, assures market access to high-quality CGP assays. While the CMS NCD ensures access to these approved assays to qualifying Medicare beneficiaries with advanced cancer, the CGP access created by this parallel review will undoubtedly lead to more patients with advanced cancers receiving life-extending precision medicine based therapies. It is fully expected that the understanding of the clinical utility of CGP will continue to evolve, the evidence will continue to grow, and the parallel review process will provide a sound starting place for reasonable assessment of clinical utility for other technologies in this unique space. Lastly, commercial payers will have the opportunity to move from passive to active management of biomarker-driven therapies in a way they have not in the past. Ultimately these decisions will catalyze the paradigm shift for the treatment of advanced cancers as a disease of the genome at all levels of patient care, from the lab to the provider to the payer. If value is defined in part by the therapy's efficacy, it is hard to see how we can achieve value in oncology without CGP.

AUTHOR INFORMATION

All authors are affiliated with Foundation Medicine, Inc, Cambridge, Massachusetts. Lakshman Ramamurthy, PhD, is the global regulatory lead; Kristi Maxwell, MS, CGC, is a certified genetic counselor; Bethany Sawchyn, PharmD, is associate director for Payer Policy and Health Outcomes; and Rachel Anhorn, PharmD, is the director, Payer Policy and Health Outcomes.

FUNDING SOURCE. None.

CORRESPONDING AUTHOR

Lakshman Ramamurthy
Foundation Medicine, Inc
150 Second Street
Cambridge, MA 20141
lramamurthy@foundationmedicine.com

REFERENCES

1. CDER drug and biologic approvals for calendar year 2017. FDA website. [fda.gov/downloads/Drugs/DevelopmentApprovalProcess/](https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/)

2. HowDrugsareDevelopedandApproved/DrugandBiologicApproval-Reports/NDAandBLAApplApprovalReports/UCM595045.pdf. Published December 31, 2017. Accessed April 1, 2018.
3. Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine [published online March 29, 2018]. *Nat Rev Clin Oncol*. doi: 10.1038/s41571-018-0002-6.
4. Chawla A, Peeples M, Li N, Anhorn R, Ryan J, Signorovitch J. Real-world utilization of molecular diagnostic testing and matched drug therapies in the treatment of metastatic cancers [published online January 19, 2018]. *J Med Econ*. doi: 10.1080/13696998.2017.1423488.
5. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: Gaps and opportunities. *Clin Lung Cancer*. 2017;18(6):651-659. doi: 10.1016/j.clcc.2017.04.004.
6. Rozenblum AB, Ilouze M, Dudnik E, et al. Clinical impact of hybrid capture-based next-generation sequencing on changes in treatment decisions in lung cancer. *J Thorac Oncol*. 2017;12(2):258-268. doi: 10.1016/j.jtho.2016.10.021.
7. American Society of Clinical Oncology. ASCO QOPI 2018 reporting tracks. ASCO website. [practice.asco.org/sites/default/files/drupal-files/QOPI-2018-Reporting-Tracks-Public-Posting.pdf](https://www.practice.asco.org/sites/default/files/drupal-files/QOPI-2018-Reporting-Tracks-Public-Posting.pdf). Published January 17, 2018. Accessed April 2, 2018.
8. FoundationOne CDx [technical information]. Cambridge, MA: Foundation Medicine; 2018. assets.ctfassets.net/vhrib-v12lmne/6Rt6csmCPuaguqumgi2iY8/e3a9b0456ed71a55d-2e4480374695d95/FoundationOne_CDx.pdf. Accessed April 2, 2018.
9. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(1):34. doi: 10.1186/s13073-017-0424-2.
10. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598-2608. doi: 10.1158/1535-7163.MCT-17-0386.
11. Foundation Medicine created by cancer genomics pioneers to help bring personalized cancer medicine to routine clinical practice [press release]. Cambridge, MA: Foundation Medicine; April 15, 2010. [files.shareholder.com/downloads/AMDA-23Y63R/6169620470x0x685138/0ADCF584-A81B-47AB-9C98-EE00360D00B0/685138.pdf](https://www.files.shareholder.com/downloads/AMDA-23Y63R/6169620470x0x685138/0ADCF584-A81B-47AB-9C98-EE00360D00B0/685138.pdf). Accessed April 1, 2018.
12. Classify your medical device. FDA website. [fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/). Published March 27, 2018. Updated March 27, 2018. Accessed April 1, 2018.
13. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. *N Engl J Med*. 2012;366(9):848-855. doi: 10.1056/NEJMhle1113918.
14. Premarket approval (PMA). FDA website. [fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket-submissions/premarketapprovalpma/#when](https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket-submissions/premarketapprovalpma/#when). Published March 27, 2018. Updated March 27, 2018. Accessed April 1, 2018.
15. Medicare coverage determination process. CMS website. [cms.gov/Medicare/Coverage/DeterminationProcess/index.html](https://www.cms.gov/Medicare/Coverage/DeterminationProcess/index.html). Published March 6, 2018. Accessed April 1, 2018.
16. HHS. Pilot program for parallel review of medical products. *Fed Regist*. 2011;76(196):62808-62810. [gpo.gov/fdsys/pkg/FR-2011-10-11/pdf/2011-25907.pdf](https://www.gpo.gov/fdsys/pkg/FR-2011-10-11/pdf/2011-25907.pdf). Published October 11, 2011. Accessed April 1, 2018.
17. Health policy brief: aligning FDA and CMS review. *Health Affairs*. August 28, 2015. [healthaffairs.org/doi/10.1377/hblog20150828.050220/full/](https://www.healthaffairs.org/doi/10.1377/hblog20150828.050220/full/). Accessed April 1, 2018.
18. Basu S, Hassenplug JC. Patient access to medical devices: a comparison of U.S. and European review processes. *N Engl J Med*. 2012;367(6):485-488. doi: 10.1056/NEJMp1204170.
19. HHS. Program for parallel review of medical devices. *Fed Regist*.

20. 2016;81(205):73113-73115. [gpo.gov/fdsys/pkg/FR-2016-10-24/pdf/2016-25659.pdf](https://www.gpo.gov/fdsys/pkg/FR-2016-10-24/pdf/2016-25659.pdf). Published October 24, 2016. Accessed April 1, 2018.
21. Food and Drug Administration, Department of Health and Human Services, 21 CFR §860.7 (2017).
22. Decision memo for next generation sequencing (NGS) for Medicare beneficiaries with advanced cancer (CAG-00450N). CMS website. [cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=AAAAAAAAACAA&](https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=AAAAAAAAACAA&). Published March 16, 2018. Accessed March 21, 2018.
23. HHS. CMS' process for making a national coverage determination. *Fed Regist*. 2013;78(152):48164-48169. [cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/FR08072013.pdf](https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/FR08072013.pdf). Published August 7, 2013. Accessed March 21, 2018.
24. Jardim DL, Schwaederle M, Wei C, et al. Impact of a biomarker-based strategy on oncology drug development: a meta-analysis of clinical trials leading to FDA approval [erratum in *J Natl Cancer Inst*. 2016;108(2). *J Natl Cancer Inst*. 2015;107(11). doi: 10.1093/jnci/djv423.
25. Schwaederle M, Zhao M, Lee JJ, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. *J Clin Oncol*. 2015;33(32):3817-3825. doi: 10.1200/JCO.2015.61.5997.
26. Schwaederle M, Zhao M, Lee JJ, et al. Association of biomarker-based treatment strategies with response rates and progression-free survival in refractory malignant neoplasms: a meta-analysis. *JAMA Oncol*. 2016;2(11):1452-1459. doi:10.1001/jamaoncol.2016.2129.
27. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006. doi: 10.1001/jama.2014.3741.
28. Wheler JJ, Janku F, Naing A, et al. Cancer therapy directed by comprehensive genomic profiling: a single center study. *Cancer Res*. 2016;76(13):3690-3701. doi: 10.1158/0008-5472.CAN-15-3043.
29. Haslem DS, Van Norman SB, Fulde G, et al. A retrospective analysis of precision medicine outcomes in patients with advanced cancer reveals improved progression-free survival without increased health care costs. *J Oncol Pract*. 2017;13(2):e108-e119. doi: 10.1200/JOP.2016.011486.
30. Decision memo for screening for colorectal cancer- stool DNA testing (CAG-00440N). CMS website. [cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=277](https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=277). Published October 9, 2014. Accessed April 2, 2018.
31. Ray T. Commercial payors unlikely to follow CMS policy on NGS cancer panels in short term, survey suggests. GenomeWeb website. [genomeweb.com/reimbursement/commercial-payors-unlikely-follow-cms-policy-ngs-cancer-panels-short-term-survey#](https://www.genomeweb.com/reimbursement/commercial-payors-unlikely-follow-cms-policy-ngs-cancer-panels-short-term-survey#). WsuwmPmnG1t. Published and Accessed April 9, 2018.
32. Surveillance, Epidemiology, and End Results Program. SEER*Stat Databases: November 2016 Submission: incidence - SEER 18 Regs research data + Hurricane Katrina impacted Louisiana cases, Nov 2016 Sub (2000-2014). NCI/SEER website. seer.cancer.gov/data-software/documentation/seerstat/nov2016/.
33. Ray T. Lab industry says CMS draft national coverage decision for NGS cancer tests bad for patients. GenomeWeb website. [genomeweb.com/reimbursement/lab-industry-says-cms-draft-national-coverage-decision-ngs-cancer-tests-bad-patients#](https://www.genomeweb.com/reimbursement/lab-industry-says-cms-draft-national-coverage-decision-ngs-cancer-tests-bad-patients#). WsBNjdP-wb-Y. Published December 22, 2017. Accessed April 3, 2018.

HEALTHCARE Analytics News

St. Jude Puts Huge Cancer Genomic Dataset in the Cloud: ajmc.com/link/2904

TECHNOLOGY VIEWPOINT

A Retrospective on the Oncology Care Model

Ryan Holleran; Arif Gilani; Abigail Orlando; and Brenton Fargnoli, MD

CONTINUED FROM COVER

increasingly complex, practices try to mutually optimize quality and cost, and risk-sharing decisions (or obligations) loom. There's no doubt the model has accelerated the transition from volume to value, particularly in more agile community practices, and its innovation will continue to serve as the foundation of newly proposed models. These include the Making Accountable Sustainable Oncology Networks model,³ which has been submitted to the Physician-Focused Payment Model Technical Advisory Committee.⁴

Although oncologists may feel they're straddling 2 divergent payment systems, only 1 is here to stay. HHS Secretary Alex Azar recently pointed out, in remarks to US hospitals, that the value-based transformation of our healthcare system is one of his department's top priorities.⁵ Given this, let's look at what's been working, what hasn't, and what could improve in the near term for the OCM specifically and value-based care more broadly.

What's Working

To kick off the retro process, let's start with reflecting on the successes of the OCM thus far, namely greater collaboration with CMS, investment in foundational infrastructure, and the implementation of care processes that can be consistently measured and adapted.

While the program continues to evolve with each consecutive reporting period, CMS has worked to cultivate collaborative partnerships, both with oncology practices and electronic health record (EHR) developers. As oncologist Barbara McAneny, MD, president-elect of the American Medical Association, said at the Association of Community Cancer Centers Annual Meeting in March,⁶ CMS' constant communication and willingness to incorporate feedback from practices is fostering a more collaborative relationship with oncologists. Through their monthly EHR vendor calls or regular "Support Lunch Hours" sessions with practices, CMS has built and maintained an entire apparatus to seek program feedback and consider program adjustments. This willingness to not only seek, but also implement, feedback has materialized most recently with the adaptation of quality measure criteria (eg, the removal of the OCM-7 measure) and the adjustment of patient-level clinical data submission requirements. This partnership among practices, EHR developers, and CMS will be imperative for the development of required technology infrastructure, to make performance more predictable, and ultimately assuage practice concerns about risk sharing.

Further, although the scope seemed insurmountable when the 160-page OCM Final Rule document was released, practices have made substantial progress within all 3 areas of foundational transformation, discussed in an earlier issue in *Evidence-Based Oncology*TM: program administration, care process development, and performance measurement.⁷ In many cases, given the OCM's rigorous quality and infrastructure requirements, practices have created new roles that focus on the program's administration. For example, according to Toni Perry, director of quality and regulatory affairs at Tennessee Oncology, "To ensure success in accurately reporting quality metrics, Tennessee Oncology's Quality and Regulatory Department added 4-5 full-time data abstractor positions, specifically devoted to validating, mining, and reporting quality data."

The Monthly Enhanced Oncology Services (MEOS) payments have also enabled practices to expand both administrative and clinical resources to their broader population. "As a practice, we have increased our investment in organizational staff resources in areas such as patient advocates and navigators in order to implement the OCM principles to both OCM and non-OCM patients," Perry said.

Within Flatiron's network of over 50 OCM practices, we observed that many began administering their OCM program like a clinical trial: Patients must be screened for eligibility, they must be closely monitored, and detailed clinical data must be captured and reported on a regular basis. To support this implementation, Flatiron leveraged its clinical trial technology to develop a screening tool that allows practices to identify, track, and manage OCM patient episodes. From this, all reporting and EHR-linked identification flows (Figure 1).

With the ability to more precisely identify patients and manage episodes, practices and EHRs have made significant investments in optimizing and codifying

FIGURE 1. The Look of the Flatiron Interface

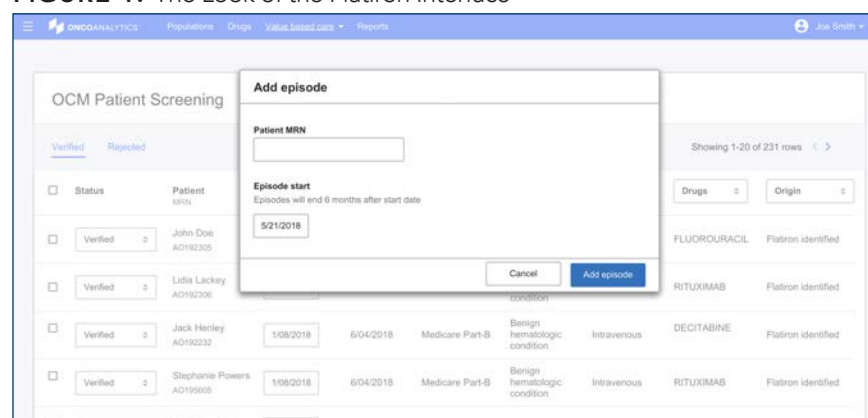
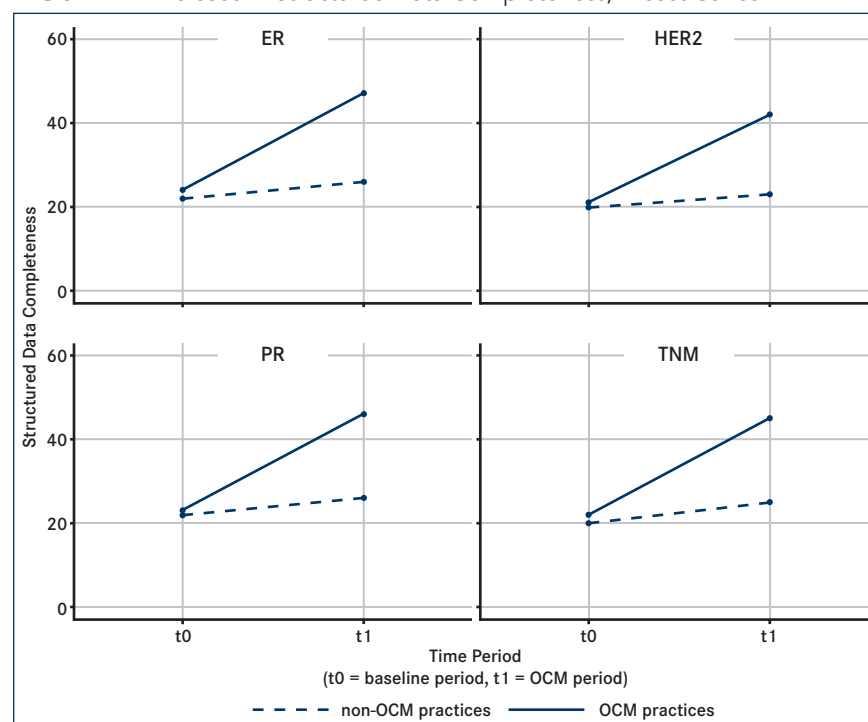


FIGURE 2. Increase in Structured Data Completeness, Breast Cancer



ER indicates estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; TNM, tumor, node, metastasis.

necessary processes for quality measurement and care planning. These workflows range from the familiar, like capturing pain, to the new and complex, like ensuring each provider referral loop is closed. EHR developers have deployed technology to make these processes as measurable, actionable, and frictionless as possible. For example, Flatiron's OCM practices are able to quantify and track screening for pain and depression directly from clinical workflows. Similarly, practices have been able to standardize and streamline delivery of the required care plan to their patients. Flatiron's care plan is autocompleted from existing data in the EHR, allowing physicians to focus more on patient engagement. Since the start of the program, Flatiron practices have delivered over 68,000 unique patient care plans.

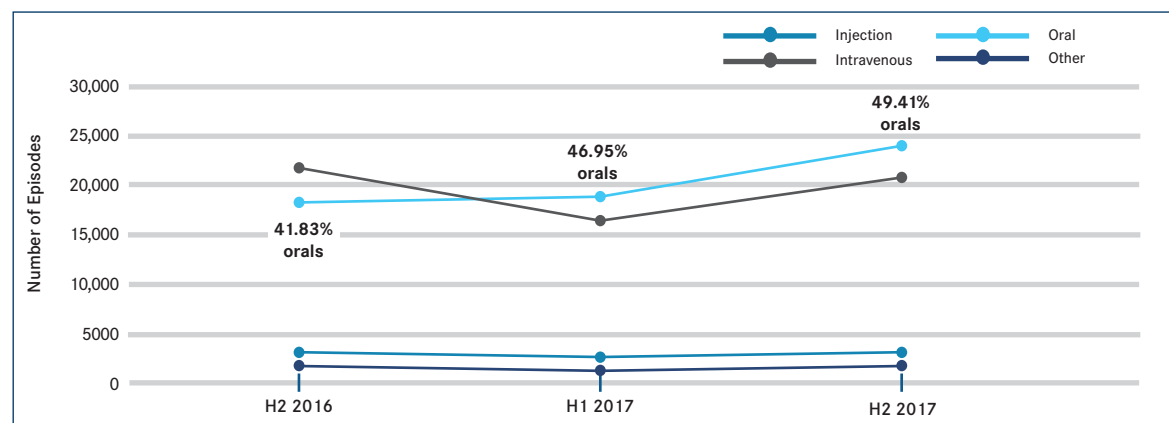
Redesigning products and workflows to enable practices to more effectively implement the OCM has the added benefit of encouraging data capture with maximum ease of use and reporting efficiency. This is evident in our network; for breast cancer alone, structured data completeness doubled less than 2 years from the start of the OCM program compared with a marginal increase in structured data completeness for non-OCM Flatiron practices (Figure 2).

What Needs Work

Although there's been progress integrating foundational components of the OCM, the nuances of the model's logic requirements and administrative »

TECHNOLOGY VIEWPOINT

FIGURE 3. Flatiron Network Episode Initiation



Orals indicates oral therapy; H2 2016, July to December 2016; H1 2017, January to June 2017; H2 2017, July to December 2017.

burdens have tempered the pace of transformation, hindering a full pivot to cost-reduction initiatives.

To date, practices have focused on the program elements that are well defined though not easily achieved: identifying patients, billing and collecting MEOS, and reporting registry data. These requirements have created management duties that previously did not exist, and have significantly increased administrative burdens. In particular, practices struggle with the OCM patient identification and clinical data submission components; they have trouble tracking patients on oral oncolytics, a task compounded by inconsistent access to prescription fill data outside the purview of the clinic. This pain point will continue to be burdensome with the increasing adoption of oral therapies.

From July 2016 to July 2017, the percent of Flatiron network OCM episodes initiated by an oral therapy increased by about 10% to over 24,000 episodes (Figure 3). Besides patient identification, CMS has outlined significant requirements for data completeness. To avoid penalties, practices have invested significant resources in abstraction and data backfill, an operational burden that is now necessary but costly.

A recent *JAMA* study revealed that “administrative costs of care (activities relating to planning, regulating, and managing health systems and services) accounted for 8% in the [United States] versus a range of 1% to 3% in the other countries.”⁸ This is evident across Flatiron’s OCM network: Over 2 million data elements were reported for almost 41,000 OCM patients to the OCM registry during the last submission period. Based on an analysis of the timing of data entry, we estimate that over 36% of breast cancer staging data were entered into the EHR via data abstraction and backfill. While executing these processes is imperative to enable the focus on more esoteric objectives of the model, these administrative components have taken over a year to fully implement for sites and have distracted practices from understanding how to approach the components that more directly affect patient care. The reality is that while collecting, reporting, and measuring high-fidelity data is arduous, much like the adoption of an EHR, they are fundamental enablers of administering value-based models. With the significant administrative investments in the program focused on tackling the OCM on ramp, the vast majority of practices have not yet demonstrated savings below their target spend.

Future Implications

The focal shift away from the administrative execution of the model toward higher-value activities, including gaining a deeper understanding of the financial model and exploring practice-specific opportunities to reduce costs, will be key to the OCM’s durability and ongoing practice success. This shift requires administrative and physician engagement to align on care coordination opportunities, enable productive conversations with the local healthcare ecosystem, and tailor care to each patient’s goals. Anne Marie Rainey, the compliance and quality control officer at Clearview Cancer Institute in Huntsville, Alabama, agrees. “Everyone at the practice—from the concierge to the physician board—needs to be aware of the program and future implications. Through the use of data-driven tools, detailed clinical reporting, and individual education we are beginning to notice a shift in physician engagement. We’re now investing in more clinical staff and supportive care services to better address the needs of our patient population and provide higher quality, patient-centered care.”

The OCM, among other quality programs, has shown that point-of-care technology is where and how clinicians experience alternative payment models (APMs) and can be an effective means to engage physicians. They’re where policy is translated into technology that is used to manage patients in value-based models. As such, EHRs must be held accountable for doing their part to reduce the administrative and bureaucratic friction that clinicians experience so they can better spend their time optimizing patient outcomes. During the first year of the model, our clinical team received significant feedback on the cumbersome nature of diagnosing conditions and staging patients in the EHR. Shortly after, the team employed a physician-centric approach when conducting user research with doctors and redesigned the interface to ensure these workflows were intuitive, user friendly, and encouraged structured data capture for programs like the OCM. Now it takes less time to diagnose a patient’s disease, clinicians see consolidated clinical information, and content is more easily updatable for when standards or reporting requirements inevitably change.

However, developing more physician-centric products to enhance usability isn’t enough. Point-of-care data products that leverage the scale of cancer networks must be developed with the data that’s being so meticulously captured for these models. For every

patient with cancer who walks into a clinic, a cohort of the most similar patients in a network, and their treatments and outcomes, could be generated. These types of predictive cohorts could enable physicians to make more personalized treatment decisions by learning from the experience of every patient with cancer. Outcomes of similar patients with cancer could become the evidence required to make a more value-based decision or the stories physicians use to have difficult end-of-life discussions with their patients.

The onus will continue to be on EHR developers to gain an empathetic understanding of users and build intuitive products they need to succeed in this new paradigm. Meanwhile, policymakers must see healthcare technology providers not merely as secondary constituents or APM facilitators, but rather as key stakeholders who must be engaged early and often throughout model design and implementation.

In examining the OCM through the lens which engineering and product teams use to reflect on their performance, the retro, it becomes clear just how much value-based care itself is a team effort. It starts with the care team and goes far beyond, relying upon novel partnerships between payer and provider, government and health information technology, and hospital and clinic. As we enter the second, and more trying, half of the OCM, we’ll soon know if this experiment is a collective win: if patients with cancer across the country have access to higher-quality, more affordable care. ♦

AUTHOR INFORMATION.

All authors are affiliated with Flatiron Health, a healthcare technology and services company focused on accelerating cancer research and improving care based in New York, New York. Ryan Holleran is a manager of product marketing and strategy; Arif Gilani is a manager of product operations; Abigail Orlando is a data insights engineer; and Brenton Fagnoli, MD, is the medical director of value-based care and director of product marketing and strategy.

REFERENCES

1. Oncology Care Model. CMS website. innovation.cms.gov/initiatives/Oncology-Care. Updated April 5, 2018. Accessed April 11, 2018.
2. Kline R, Adelson K, Kirshner JJ, et al. The Oncology Care Model: perspectives from the Centers for Medicare Medicaid Services and participating oncology practices in academia and the community. *Am Soc Clin Oncol Educ Book*. 2017;37:460-466. doi: 10.14694/EDBK_174909.
3. McAceny B. MASON - Making Accountable Sustainable Oncology Networks. Assistant Secretary for Planning and Evaluation/HHS website. aspe.hhs.gov/system/files/pdf/255906/ProposalOBS.pdf. Accessed April 13, 2018.
4. Physician-Focused Payment Model Technical Advisory Committee (PTAC). ASPE/HHS website. aspe.hhs.gov/ptac-physician-focused-payment-model-technical-advisory-committee. Updated March 10, 2017. Accessed April 13, 2018.
5. Azar A. Remarks on value-based transformation to the Federation of American Hospitals. HHS website. hhs.gov/about/leadership/secretary/speeches/2018-speeches/remarks-on-value-based-transformation-to-the-federation-of-american-hospitals.html. Published March 5, 2018. Accessed April 13, 2018.
6. Dangi-Garimella S. The price of innovation when improving cancer care delivery. *The American Journal of Managed Care* website. ajmc.com/conferences/acc-2018/the-price-of-innovation-when-improving-cancer-care-delivery?p=2. March 15, 2018. Accessed April 13, 2018.
7. Fagnoli B, Holleran R, Kolodziej M. Why oncologists need technology to succeed in alternative payment models. *Am J Manag Care*. 2017;23(SP5):SP196-SP198.
8. Papanicolaos I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. *JAMA*. 2018;319(10):1024-1039. doi:10.1001/jama.2018.1150.

PROVIDER PERSPECTIVE

The Impact of New CMS Rules for Telehealth on Cancer Genetic Counseling

Heather Zierhut, PhD, MS, CGC, and Adam Buchanan, MS, MPH, LGC

CONTINUED FROM COVER

HR 1892, the budget agreement signed into law in February 2018,¹⁰ is being hailed for removing some of these limitations and improving access to care for Medicare recipients. The law contains provisions from the Creating High-Quality Results and Outcomes Necessary to Improve Chronic Care Act of 2017¹¹ and other telehealth bills that seek to expand Medicare coverage of telehealth services. Previously unrecognized uses of telehealth under Medicare Part B will now be appropriate benefits, assuming they are clinically relevant and meet established requirements (section 303). In addition, accountable care organizations can access a variety of telehealth services with fewer restrictions (section 304). The bill also allows beneficiaries to choose whether they want to use telehealth options.

The potential for expanded coverage of telehealth is welcome news for several medical specialties, particularly those that offer limited access in rural areas. One such field is genetic counseling. Genetic counselors help people understand and adapt to the medical, psychological, and familial implications of hereditary cancer.¹² They also help identify patients who may benefit from genetic testing and direct them to the most appropriate test(s). The process of genetic counseling is particularly well suited for telehealth as it is primarily conducted via consultations that involve a communication process that can occur by phone or video. Cancer genetic counselors have seen a rapid expansion of telehealth services (telegenetics) in recent years. Although patient access to cancer genetic counseling varies widely across the United States, the demand for genetic counseling is increasing, as cancer patients' germline mutation status increasingly has implications for cancer treatment decisions.¹³⁻¹⁷ For instance, individuals with germline pathogenic variants in *BRCA1/2* genes and a growing list of cancer types (eg, ovarian, prostate) are eligible for treatment with poly ADP ribose polymerase (PARP) inhibitors.¹⁸ Accordingly, cancer genetic counselors have reported increased referral volume due to the FDA approval of PARP inhibitors in the settings of treatment-resistant ovarian cancer.¹⁸ Additionally, the immunotherapy pembrolizumab has now been approved by the FDA to treat tumors that exhibit mismatch repair deficiency, a hallmark of Lynch syndrome, and have progressed on prior treatment.¹⁹ Further, a broadening list of cancer presentations are being recognized as being associated with higher likelihood of germline etiology, including metastatic prostate cancer.^{20,21}

In keeping with the growing number of indications for referral to cancer genetic counseling, professional organizations are now requiring that cancer centers provide access to cancer genetics expertise. For example, in 2012 the American College of Surgeons began requiring that, to receive accreditation, cancer treatment centers provide patients with access to a qualified genetics professional.²² Some health insurance companies now require that a genetics expert be involved in the ordering of certain cancer genetic tests (eg, *BRCA1/2* genes) for the testing to be covered.²³ Private telegenetics companies have formed to help meet the growing number of recommendations and requirements for genetic counseling services.

Early research on patient outcomes in cancer telegenetics shows that it is acceptable to patients and can decrease costs to

health systems and patients. A randomized comparison of clinic-to-clinic telegenetics with in-person cancer genetic counseling found that telegenetics was substantially less expensive for the institution and was associated with comparable patient satisfaction.²⁴ This service delivery model has also been compared with telephone genetic counseling, showing comparable patient satisfaction. One difference that was perceived by genetic counselors was that patients pay better attention to a videoconferencing consult than to a phone consult.²⁵ Patients have reported high satisfaction with cancer telegenetics²⁴⁻³¹ due to reduced travel burden³¹ and greater convenience.^{29,31} Telegenetics has been associated with positive psychosocial outcomes, including improvements in cancer genetics knowledge and in anxiety, depression, and cancer worry.^{24,25} A model of telegenetics that connects genetic counselors to patients' home computers or devices has also shown promising psychosocial outcomes and favorable patient satisfaction³² while being deemed acceptable by genetic counselors.³³ What's more, a recent study of cancer genetic counselors showed high acceptance and usage of telegenetics, with two-thirds of respondents having conducted telegenetics consults.³⁴ This is a striking increase in the use of telegenetics from 5 years ago, when the results of 2 studies of cancer genetic counselors showed that fewer than 15% had conducted a telegenetics consult.^{35,36}

"Early research on patient outcomes in cancer telegenetics shows that it is acceptable to patients and can decrease costs to health systems and patients."

—Heather Zierhut, PhD, MS, CGC & Adam Buchanan, MS, MPH, LGC

However, in spite of the new budgetary provisions for telehealth reimbursement, professional recommendations, and high acceptance of telegenetics services, significant barriers to broad implementation of cancer telegenetics persist. First and foremost, genetic counselors are not CMS-recognized practitioners. Therefore, the changes under HR 1892 will have very limited impact for Medicare beneficiaries seeking genetic counseling. Efforts are underway to introduce a bill to address this, but until it passes, genetic counselors cannot seek reimbursement from Medicare for their services. For third-party payers, companies can use the Current Procedural Terminology code modifier 95 to identify telemedicine services. However, not all payers will reimburse for genetic counseling services. The second barrier that must be overcome to provide national coverage to cancer patients relates to genetic counseling licensure. Genetic counselors must obtain licenses for every state currently issuing licensure in which their patients reside. This »



ZIERHUT

Heather Zierhut, PhD, MS, CGC, is the assistant professor and the associate director of the Graduate Program of Study in Genetic Counseling at the University of Minnesota – Twin Cities.



BUCHANAN

Adam Buchanan, MS, MPH, LGC, is assistant professor and genetic counselor in the Geisinger Genomic Medicine Institute in Danville, PA.

PROVIDER PERSPECTIVE

leads to increased provider time and cost to ensure that genetic counselors are able to practice legally for all of their patients throughout a network. Additionally, reports on the effectiveness of cancer telegenetics frequently note technical glitches as barriers to delivery of care.^{24,25,31,32} Lastly, continuity of care is a concern for genetic counselors who play a key role in coordinating patients' care within and among institutions.^{37,38} Because genetic counseling providers may be employed by other health systems and companies rather than by a patient's main healthcare facility, the lack of a point person within that main healthcare facility could leave patients without referrals, follow-up care, and long-term medical management. In cancer care, this is especially important when guidelines recommend changes in medical management based upon genetic testing results (eg, increased frequency of screening using mammography and breast magnetic resonance imaging in *BRCA1/BRCA2* carriers and colonoscopy in patients with Lynch syndrome^{39,40}).

Delivering telehealth services will be an efficient and scalable means to providing quality healthcare and education to all patients, despite the barriers stated above. Overcoming these barriers is particularly important as genetic counselors are increasingly needed to assist in the care of patients who are at increased risk to develop cancer. As the etiology of cancer is better understood and the use of genetic-based therapies expands, genetic counselors will remain an integral part of care and are particularly suited to meet these mounting needs. Advances in access and in reimbursement to genetic counselors will aid in the deployment of telegenetic services nationally. Ultimately, it is hoped that this will result in increased patient care, satisfaction, and outcomes. ♦

AUTHOR INFORMATION

Heather Zierhut, PhD, MS, CGC, is the assistant professor and the associate director of the Graduate Program of Study in Genetic Counseling at the University of Minnesota – Twin Cities. Dr Zierhut has expertise in clinical, research, and public health genetic counseling. She has served as chair of the National Society of Genetic Counselors Access and Service Delivery, where she developed a passion for increasing efficiency and access to genetic counseling. She serves as senior advisor for GeneMatters to provide expertise on the integration and implementation of innovative, evidence-based genetic counseling services and testing into new and growing markets.

Adam Buchanan, MS, MPH, LGC, is assistant professor and genetic counselor in the Geisinger Genomic Medicine Institute in Danville, PA. Previously, he was a research associate at Duke Cancer Institute. He is an National Institute of Health-funded investigator with research interests in outcomes of genomic screening programs, service delivery models for genetics services, clinical decision support based on family health history, and assessing cancer risk management behaviors. His clinical expertise includes intimate knowledge of recommended risk management for hereditary cancer syndromes. He is co-leading Geisinger's MyCode genomic screening program for medically actionable genomic results, and he is helping to develop a health services research portfolio on patient-participant, family, and system outcomes of this program.

FINANCIAL DISCLOSURE

Dr Zierhut serves as chair of the advisory board for GeneMatters, LLC, a genetic counseling company that delivers services via Web- and telephone-based platforms.

REFERENCES

1. Mayo Clinic. Telehealth: technology meets health care. Mayo Clinic website. mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/telehealth/art-20044878. Published August 16, 2017. Accessed March 26, 2018.

2. Liu S, Feng W, Chhatbar PY, Liu Y, Ji X, Ovbiagele B. Mobile health as

a viable strategy to enhance stroke risk factor control: a systematic review and meta-analysis. *J Neurol Sci*. 2017;378:140-145. doi: 10.1016/j.jns.2017.04.050.

3. Lin MH, Yuan WL, Huang TC, Zhang HF, Mai JT, Wang JF. Clinical effectiveness of telemedicine for chronic heart failure: a systematic review and meta-analysis. *J Invest Med*. 2017;65(5):899-911. doi: 10.1136/jim-2016-000199.

4. Brearly TW, Shura RD, Martindale SL, et al. Neuropsychological test administration by videoconference: a systematic review and meta-analysis. *Neuropsychol Rev*. 2017;27(2):174-186. doi: 10.1007/s11065-017-9349-1.

5. Antonioti NM, Drude KP, Rowe N. Private payer telehealth reimbursement in the United States. *Telemed J E Health*. 2014;20(6):539-543. doi: 10.1089/tmj.2013.0256.

6. Wicklund E. ATA sees telemedicine momentum in new report cards. mHealthIntelligence website. mhealthintelligence.com/news/ata-sees-telemedicine-momentum-in-new-report-cards. Published February 10, 2017. Accessed March 26, 2018.

7. Neufeld JD, Doarn CR, Aly R. State policies influence Medicare telemedicine utilization. *Telemed J E Health*. 2016;22(1):70-74. doi: 10.1089/tmj.2015.0044.

8. Weinstein RS, Lopez AM, Joseph BA, et al. Telemedicine, telehealth, and mobile health applications that work: opportunities and barriers. *Am J Med*. 2014;127(3):183-187. doi: 10.1016/j.amjmed.2013.09.032.

9. Scott Kruse C, Karem P, Shifflett K, Vegi L, Ravi K, Brooks M. Evaluating barriers to adopting telemedicine worldwide: a systematic review. *J Telemed Telecare*. 2018;24(1):4-12. doi: 10.1177/1357633X16674087.

10. Bipartisan Budget Act of 2018, HR 1892, 115th Congress, 2nd Sess (2018).

11. Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act of 2017, S 870, 115th Congress (2017).

12. Resta R, Biesecker BB, Bennett RL, et al. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. 2006;15(2):77-83.

13. Hammers E. *Innovations in Service Delivery in the Age of Genomics: Workshop Summary*. Washington, DC: National Academy of Sciences; 2009.

14. Hawkins AK, Hayden MR. A grand challenge: providing benefits of clinical genetics to those in need. *Genet Med*. 2011;13(3):197-200. doi: 10.1097/GIM.0b013e31820c056e.

15. Battista RN, Blancquaert I, Laberge AM, van Schendel N, Leduc N. Genetics in health care: an overview of current and emerging models. *Public Health Genomics*. 2012;15(1):34-45. doi: 10.1159/000328846.

16. Olopade OI, Fackenthal JD, Dunston G, Tainsky MA, Collins F, Whitfield-Broome C. Breast cancer genetics in African Americans. *Cancer*. 2003;97(1 Suppl):236-245.

17. Knapke S, Haidle JL, Nagy R, Pirzadeh-Miller S. The current state of cancer genetic counseling access and availability. *Genet Med*. 2016;18(4):410-412. doi: 10.1038/gim.2015.98.

18. Buchtel KM, Vogel Postula KJ, Weiss S, Williams C, Pineda M, Weissman SM. FDA approval of PARP inhibitors and the impact on genetic counseling and genetic testing practices. *J Genet Couns*. 2018;27(1):131-139. doi: 10.1007/s10897-017-0130-7.

19. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. FDA website. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm. Updated May 30, 2017. Accessed March 26, 2018.

20. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453. doi: 10.1056/NEJMoa1603144.

21. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer, version 2.2018. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published March 8, 2018. Accessed March 26, 2018.

22. Commission on Cancer. Cancer program standards 2012: ensuring patient-centered care, v.1.2.1. American College of Surgeons website. facts.org/~media/files/quality%20programs/cancer/coc/programstandards2012.ashx. Published 2012. Accessed January 5, 2018.

23. Genetic testing and counseling program. Cigna website. cigna.com/healthcare-professionals/resources-for-health-care-professionals/genetic-testing-and-counseling-program. Accessed April 3, 2018.

24. Buchanan AH, Datta SK, Skinner CS, et al. Randomized trial of telegenetics vs. in-person cancer genetic counseling: cost, patient satisfaction and attendance. *J Genet Couns*. 2015;24(6):961-970. doi: 10.1007/s10897-015-9836-6.

25. Voils CI, Venne VL, Weidenbacher H, Sperber N, Datta S. Comparison of telephone and televideo modes for delivery of genetic counseling: a randomized trial. *J Genet Couns*. 2018;27(2):339-348. doi: 10.1007/s10897-017-0189-1.

26. Hilgart JS, Hayward JA, Coles B, Iredale R. Telegenetics: a systematic review of telemedicine in genetics services. *Genet Med*. 2012;14(9):765-776. doi: 10.1038/gim.2012.40.

27. Coelho JJ, Arnold A, Nayler J, Tischkowitz M, MacKay J. An assessment of the efficacy of cancer genetic counselling using real-time videoconferencing technology (telemedicine) compared to face-to-face consultations. *Eur J Cancer*. 2005;41(15):2257-2261.

28. d'Agincourt-Canning L, McGillivray B, Panabaker K, et al. Evaluation of genetic counseling for hereditary cancer by videoconference in British Columbia. *BCMJ*. 2008;50(10):554-559.

29. Zilliacus EM, Meiser B, Lobb EA, Kirk J, Warwick L, Tucker K. Women's experience of telehealth cancer genetic counseling. *J Genet Couns*. 2010;19(5):463-472. doi: 10.1007/s10897-010-9301-5.

30. Zilliacus EM, Meiser B, Lobb EA, et al. Are videoconferenced consultations as effective as face-to-face consultations for hereditary breast and ovarian cancer genetic counseling? *Genet Med*. 2011;13(11):933-941. doi: 10.1097/GIM.0b013e3182217a19.

31. Bradbury A, Patrick-Miller L, Harris D, et al. Utilizing remote real-time videoconferencing to expand access to cancer genetic services in community practices: a multicenter feasibility study. *J Med Internet Res*. 2016;18(2):e23. doi: 10.2196/jmir.4564.

32. Otten E, Birnie E, Ranchor AV, van Langen IM. Telegenetics use in presymptomatic genetic counselling: patient evaluations on satisfaction and quality of care. *Eur J Hum Genet*. 2016;24(4):513-520. doi: 10.1038/ejhg.2015.164.

33. Otten E, Birnie E, Ranchor AV, van Langen IM. Online genetic counseling from the providers' perspective: counselors' evaluations and a time and cost analysis. *Eur J Hum Genet*. 2016;24(9):1255-1261. doi: 10.1038/ejhg.2015.283.

34. Zierhut HA, MacFarlane IM, Ahmed Z, Davies J. Genetic counselors' experiences and interest in telegenetics and remote counseling. *J Genet Couns*. 2018;27(2):329-338. doi: 10.1007/s10897-017-0200-x.

35. Cohen SA, Marvin ML, Riley BD, Vig HS, Rousseau JA, Gustafson SL. Identification of genetic counseling service delivery models in practice: a report from the NSGC Service Delivery Model Task Force. *J Genet Couns*. 2013;22(4):411-421.

36. Trepanier AM, Allain DC. Models of service delivery for cancer genetic risk assessment and counseling. *J Genet Couns*. 2014;23(2):239-253. doi: 10.1007/s10897-013-9588-0.

37. Zierhut HA, Shannon KM, Cragun DL, Cohen SA. Elucidating genetic counseling outcomes from the perspective of genetic counselors. *J Genet Couns*. 2016;25(5):993-1001. doi: 10.1007/s10897-015-9930-9.

38. Pestoff R, Ingvaldstad C, Skirton H. Genetic counsellors in Sweden: their role and added value in the clinical setting. *Eur J Hum Genet*. 2016;24(3):350-355. doi: 10.1038/ejhg.2015.110.

39. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian version 1.2018. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Published October 3, 2017. Accessed January 5, 2018.

40. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal version 3.2017. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Published October 10, 2017. Accessed January 5, 2018.

HOW IMPACTFUL WILL WEARABLE TECHNOLOGY BE IN TREATMENT PROTOCOLS?


HRA[®]
DATA DRIVEN
INTELLIGENCE

A **MJ** MICHAEL J. HENNESSY COMPANY

HRA[®] is bridging the gap between drug and medical device manufacturers, payers, physicians, and patients to gauge their interactions with wearable healthcare technology, and to determine how wearables will impact the future of healthcare. We invite you to read our topline findings that shed light on the patients' perspective in this edition!

**CONTACT US TO LEARN MORE ABOUT
THIS LANDMARK SYNDICATED STUDY.**

 **inquiries@hraresearch.com**

 **609.716.7777**



SUPPORT FROM EVERY ANGLE.



PATIENTS FACE ENOUGH CHALLENGES. WE GET THAT.

That's why we created Amgen Assist 360™—so patients and their caregivers have a single place to go to find the support, tools, and resources they need.*



AMGEN REIMBURSEMENT COUNSELORS

Call an Amgen Reimbursement Counselor anytime or schedule a visit with a Field Reimbursement Specialist right at your office.



BENEFIT VERIFICATION

Our secure system makes it easy to electronically submit, store, and retrieve benefit verifications for all your patients currently on an Amgen product.



AMGEN NURSE AMBASSADORS†

Amgen Nurse Ambassadors offer your patients a single point of contact to help them find important resources,* which could include referrals to independent charitable organizations that may provide counseling and community resources.

*Resources include referrals to independent nonprofit patient assistance programs. Eligibility for resources provided by independent nonprofit patient assistance programs is based on the nonprofits' criteria. Amgen has no control over these programs and provides referrals as a courtesy only.

†Amgen Nurse Ambassadors are only available to patients that are prescribed certain products. Nurse Ambassadors are there to support, not replace, your treatment plan and do not provide medical advice or case management services. Patients should always consult their healthcare provider regarding medical decisions or treatment concerns.

ENROLL YOUR ELIGIBLE PATIENTS TODAY.

VISIT AMGENASSIST360.COM/ENROLL
OR CALL 888-4ASSIST (888-427-7478).

MONDAY-FRIDAY, 9 AM TO 8 PM ET



AMGEN ASSIST 360 is a trademarks of Amgen Inc.
©2018 Amgen Inc. All rights reserved. USA-OCF-061889 02-18