SPECIAL ISSUE: **ASCO MEETING RECAP**

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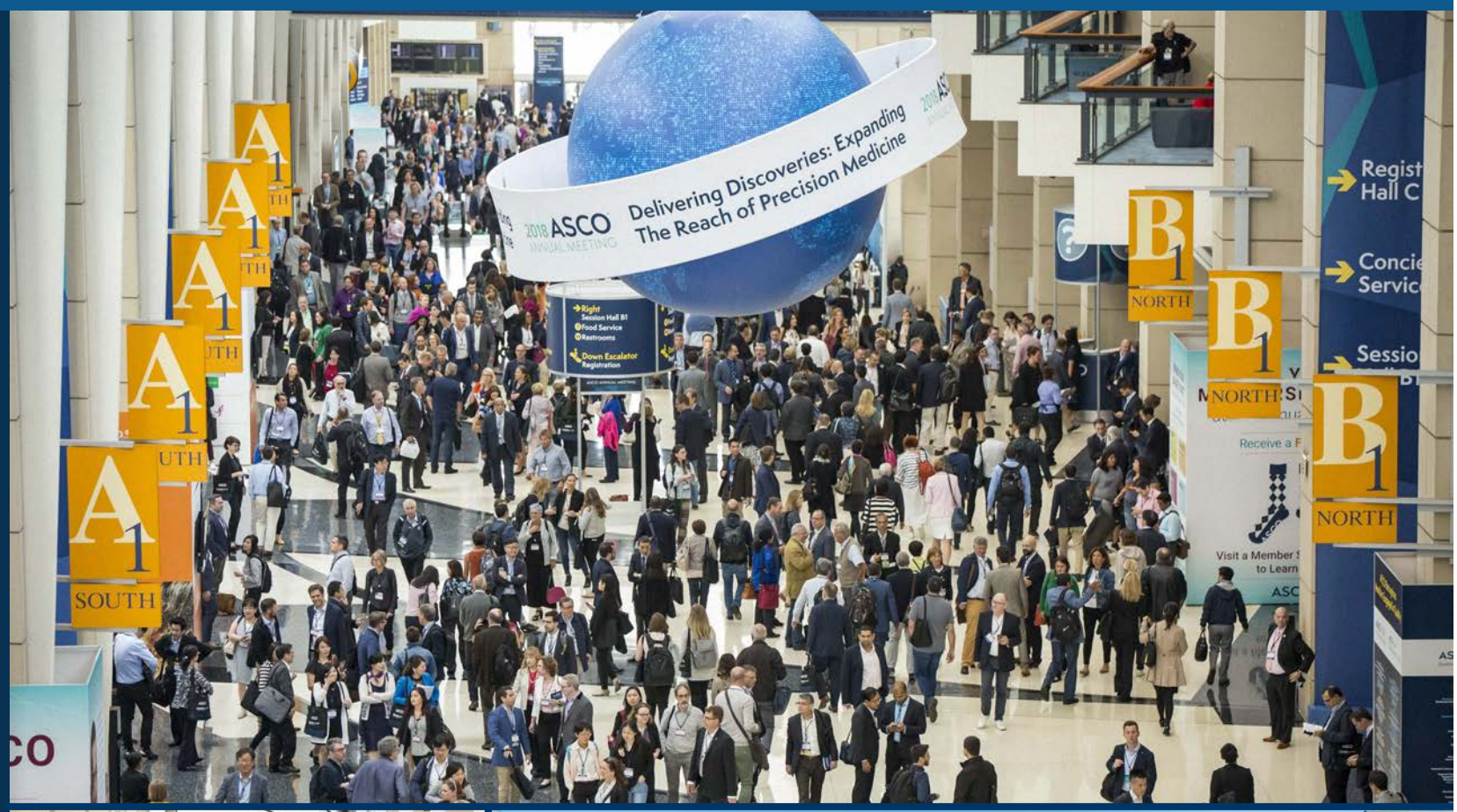
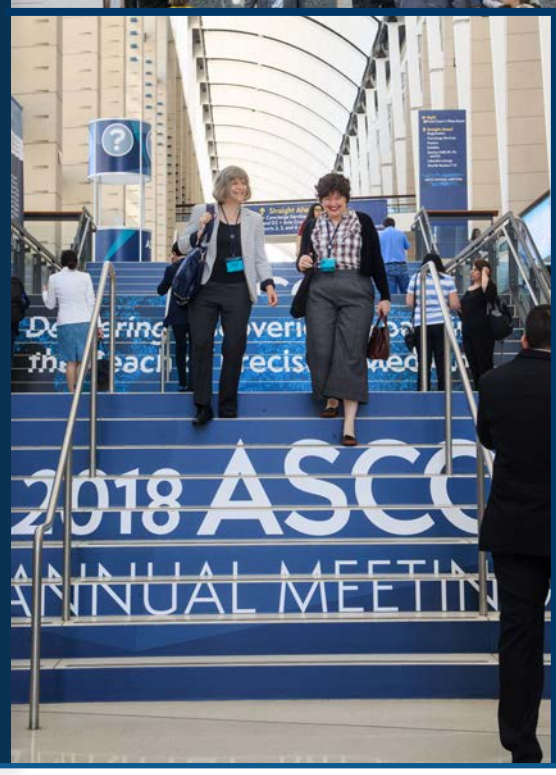
AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING | JUNE 1-5, 2018 | McCORMICK PLACE, CHICAGO, ILLINOIS

HIGHLIGHTS FROM THE MEETING

- Cemiplimab produces response in nearly half of patients with advanced CSCC, **SP352**.
- TAILORx shows most women with common early-stage breast cancer can avoid chemotherapy, **SP354**.
- Progress with immunotherapy in glioblastoma, **SP362**.
- ZUMA-1: Response to axi-cel treatment at 3 months predicts remission at 12 months, **SP367**.
- Too few heavy smokers are screened for lung cancer, **SP372**.
- Discussing the cost burden of cancer with patients, **SP375**.





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YES CAR T IS HERE

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

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

// PROVEN EFFICACY

51%

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

NR

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

// CYTOKINE RELEASE SYNDROME

13% Grade ≥3 incidence

94% Overall incidence

// NEUROLOGIC TOXICITIES

31% Grade ≥3 incidence

87% Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time†

99%

Manufacturing success of CAR T cells engineered and expanded ex vivo

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

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

†The median time from leukapheresis to product delivery.

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

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

Important Safety Information continued on adjacent page.

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

IMPORTANT SAFETY INFORMATION (continued)

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

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

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

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

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

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

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

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

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

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

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

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

Kite
A GILEAD Company
Santa Monica, CA

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

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

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

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

2.3 Management of Severe Adverse Reactions

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

Table 1. CRS Grading and Management Guidance

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

Table 1. CRS Grading and Management Guidance (continued)

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

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

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

Table 2. Neurologic Toxicity Grading and Management Guidance

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

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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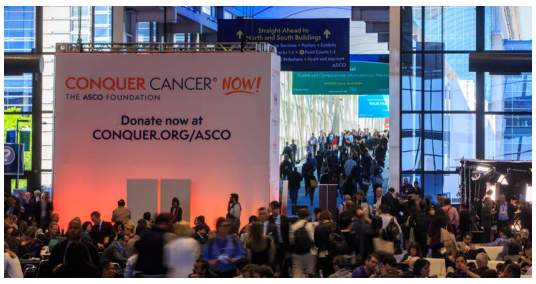
SPECIAL ISSUE / ASCO Recap
JULY 2018
VOLUME 24, ISSUE 9

Experts panelists during a session at the annual meeting of the American Society of Clinical Oncology.



More than 39,000 healthcare professionals attended the annual meeting in Chicago, Illinois.

McCormick Place is the home of the annual meeting of the American Society of Clinical Oncology.

CLINICAL FINDINGS

CAR T-CELL THERAPY UPDATE

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PREVENTION & MANAGED CARE UPDATES

CLINICAL UPDATES

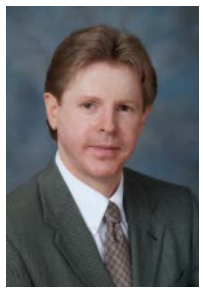
EDITORIAL MISSION

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

CLINICAL FINDINGS

Nearly Half of Patients With Metastatic CSCC Respond to Fast-Tracked Cemiplimab

Mary Caffrey



MIGDEN

Michael R. Midgen, MD, of The University of Texas MD Anderson Cancer Center.

AFTER TAKING THE programmed death-1 inhibitor cemiplimab for an average of close to 8 months, nearly half of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) responded to treatment in a phase 2 study. A median duration of response had not been reached, however, according to results presented June 4, 2018, at the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois.

The results were simultaneously published in the *New England Journal of Medicine*.[1] The journal featured both reports of the expansion cohort from phase 1, which saw a response from 13 of 26 patients (50%; 95% CI, 30%-70%) as well as results from phase 2, which reported responses from 28 of 59 patients.

"The study of cemiplimab for the treatment of advanced cutaneous squamous cell carcimona was underpinned by the recognition that a high mutation burden may render these tumors sensitive to effector T cells in the context of immune checkpoint blockade," the authors write.

The study of 54 men and 5 women, with an average age of 71 years (range, 38-93 years), involved a 3-mg/kg dose given intravenously every 2 weeks. Tumor measurements were performed every 8 weeks. Overall response rate (ORR) was the primary endpoint, and duration of response was the key secondary endpoint.

The FDA has already granted priority review status to cemiplimab, which is being developed by Regeneron and Sanofi. A decision on the biologics license application is expected by October 28, 2018.[2]

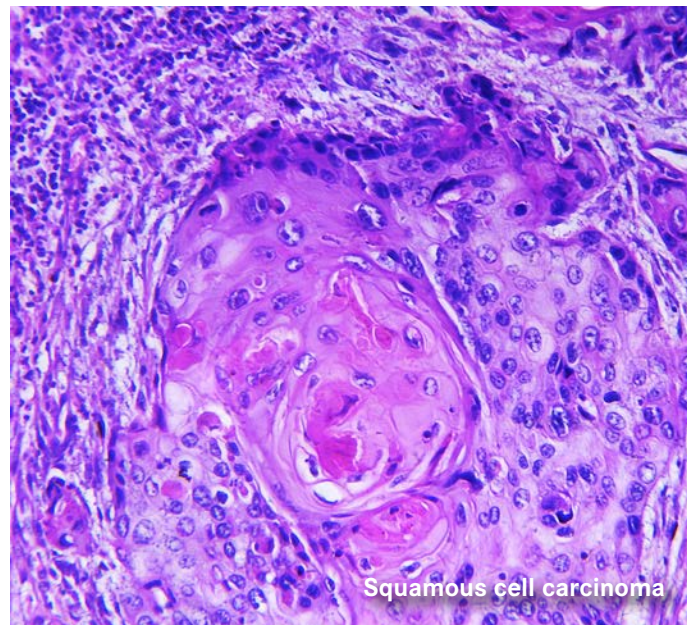
"The strong results seen with cemiplimab are noteworthy given that advanced [cutaneous squamous cell carcinoma] is a very serious condition that currently has no approved treatments once surgery is no longer an option."

—Michael R. Migden, MD,
The University of Texas MD Anderson Cancer Center

CSCC, or skin cancer, is very common in the United States, and most often it is treatable. But in 5% of the cases, it becomes metastatic, and there is no standard of care for this form of the disease. Thus, cemiplimab would fill a significant unmet need for patients with mCSCC. At ASCO 2017, Regeneron presented promising phase 1 results that resulted in the FDA's earlier designation of cemiplimab as a breakthrough therapy in this indication.[3] Results presented this year include data through October 27, 2017.[4]

At the time of data cutoff, patients had been followed for an average of 7.9 months (range, 1.1-15.6 months). ORR, as measured by an independent review team examining patient scans, was 47% (95% CI, 34%-61%). The rate of durable disease control was 61% (95% CI, 47%-74%), with 4 complete responses and 24 partial responses. The average time to initial response was 1.9 months.[1] Of the 28 patients who had a response, the duration of response exceeded 6 months for 57%, and 82% still had a response and were taking cemiplimab at the time of the data cutoff.

The most common adverse events (AEs) were diarrhea (27%), fatigue (24%), and nausea (17%). The paper reported 25 AEs of grade 3 or higher, including 17 that were serious and 3 that led to discontinuation of treatment; 3 were associated with an outcome of death. The study's authors said the side effects observed were typical among patients treated with checkpoint inhibitors.[3]



Squamous cell carcinoma

"The strong results seen with cemiplimab are noteworthy given that advanced CSCC is a very serious condition that currently has no approved treatments once surgery is no longer an option," Michael R. Migden, MD, co-lead author and associate professor in the Departments of Dermatology and Head and Neck Surgery at The University of Texas MD Anderson Cancer Center, said in a statement. "Advanced CSCC tumors were shown to be responsive to cemiplimab in both metastatic and locally advanced patients, with the results being clinically meaningful and consistent between the phase 1 and phase 2 trials."[5] ◆

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KEYNOTE-042 Confirms First-Line Pembrolizumab Superior to Chemotherapy in PD-L1–Low Advanced NSCLC

Surabhi Dangi-Garimella, PhD

A LATE-BREAKING ABSTRACT presented on June 3 at the 2018 American Society of Clinical Oncology Annual Meeting confirmed that pembrolizumab significantly improved the primary end point of overall survival (OS) over platinum-based chemotherapy in treatment-naïve advanced/metastatic non–small-cell lung cancer (NSCLC). The effect, the authors from the KEYNOTE-042 study found, was agnostic of PD-L1 expression, meaning the monoclonal antibody was effective for tumors expressing PD-L1 at ≥50%, ≥20%, and ≥1%.[1]

However, the secondary outcome of progression-free survival (PFS) was not met at data cut-off on February 26, 2018.

Previously, pembrolizumab monotherapy has shown significant improvement in OS over docetaxel as second-line treatment in metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥1%. Additionally, patients whose NSCLC had a PD-L1 TPS of ≥50% saw significant improvements in both PFS and OS with first-line pembrolizumab, compared with platinum-based chemotherapy (KEYNOTE-024).[2]

Results from the KEYNOTE-189 study, published earlier this year, emphasized the advantage of combining chemotherapy with pembrolizumab: The researchers showed that the combination approach as first-line treatment in patients with metastatic NSCLC, who had no *EGFR* or *ALK* alterations, was significantly better than chemotherapy alone and was agnostic of PD-L1 expression.[3]

"Our trial, KEYNOTE-042, is evaluating pembrolizumab monotherapy against platinum-based chemotherapy for metastatic NSCLC with low expression of PD-L1," said lead author Gilberto Lopes, MD, MBA, Sylvester Comprehensive Cancer Center, University of Miami Health System. The trial was designed to develop a more effective and tolerable first-line treatment for metastatic NSCLC, he said.

> **"Our data confirm and potentially extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1–expressing tumors."**
>
> —Gilberto Lopes, MD, MBA,
> Sylvester Comprehensive Cancer Center, University of Miami Health System

Eligibility criteria included locally advanced or metastatic tumors with PD-L1 TPS ≥1%, without *EGFR* or *ALK* alterations. The ECOG status had to be 0 or 1; patients had to be free of untreated or unstable CNS metastases.

Treatment-eligible patients were randomized 1:1 to ≤35 cycles of pembrolizumab 200 mg every 3 weeks or investigator's choice of ≤6 cycles of paclitaxel + carboplatin or pemetrexed + carboplatin with optional pemetrexed maintenance (nonsquamous only). Primary end points were OS in patients with TPS ≥50%, ≥20%, and ≥1%. Secondary end points were PFS and objective response rate for all 3 TPS, and safety in patients with TPS ≥1%.

At 12.8 months median follow-up, 13.7% of patients were still on pembrolizumab and 4.9% were receiving pemetrexed maintenance treatment.

In the TPS ≥50% subset, median OS at 24 months was 20 months (range, 15.4-24.9) in the pembrolizumab-treated patients (event rate: 44.7%) and 12.2 months (range, 10.4-14.2) in those treated with chemotherapy (event rate: 30.1%). Similarly, in the TPS ≥20% subset, median OS at 24 months was 17.7 months (range, 15.3-22.1) in the pembrolizumab-treated patients (event rate: 40.5%) and 13.0 months (range, 11.6-15.3) in those treated with chemotherapy (event rate: 29.6%). Among patients whose tumors expressed a low level of PD-L1 (TPS ≥1%), median OS at 24 months was 16.7 months (range, 13.9-19.7) in the pembrolizumab-treated arm (event rate: 39.3%) and 12.1 months (range, 11.3-13.3) in those treated with chemotherapy (event rate: 28.0%).

Lopes shared the PFS data in the TPS ≥20% cohort. Median PFS at 12 months was 6.2 months (range, 5.1-7.8) in the pembrolizumab-treated arm (event rate: 32.4%) and 6.6 months (range, 6.2-7.3) in those treated with chemotherapy (event rate: 28.8%).

Grade 3-5 drug-related adverse events (AEs) were less frequent with pembrolizumab, Lopes said (17.8% vs 41.0% for chemotherapy). However, the rates of discontinuation (about 9.0%) and treatment-related deaths (about 2.0%) were similar between the 2 groups. Immune-related AEs (irAEs) are significant concerns that accompany the use of immune checkpoint inhibitors such as pembrolizumab.[4] Lopes shared that about 27.8% of patients treated with pembrolizumab experienced irAEs, and 1 patient died as a result. Only 7% of patients in the chemotherapy arm had irAEs.

"KEYNOTE-042 is the first study with a primary end point of overall survival to demonstrate superiority of pembrolizumab over platinum-based chemotherapy in patients with previously untreated advanced/metastatic NSCLC without sensitizing *EGFR* or *ALK* alterations and a PD-L1 TPS ≥1%," the authors concluded.

"Our data confirm and potentially extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1–expressing tumors," said Lopes. He shared that based on the advice of their external drug monitoring committee, the trial continues to evaluate PFS in this trial population.

Leena Gandhi, MD, currently the director of thoracic medical oncology and an associate professor of medicine at the New York University School of Medicine, who will soon be joining Eli Lilly and Company,[5] was the discussant for this abstract.

Comparing the performance of nivolumab, the other PD-1 inhibitor, with pembrolizumab, Gandhi questioned whether the crossover allowed in the CheckMate-026 study may have resulted in the failure of nivolumab as first-line treatment in advanced/metastatic NSCLC. "Overall, the studies are more similar than they are different," she said. However, CheckMate-026 allowed 60.4% of patients in the chemotherapy arm to cross over to the nivolumab arm, whereas only 19.8% in KEYNOTE-042 who received chemotherapy were subsequently treated with pembrolizumab.

She identified several caveats with the KEYNOTE-042 results:

- The benefit is driven by high PD-L1 expressors
- PD-L1 expression has high clinical utility and should be used, but it could be complemented by following tumor mutation burden expression in the tumor samples
- She advised researchers to analyze the tumor microenvironment ◆

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Phase 3 TAILORx Results Confirm Chemotherapy Unnecessary in 70% of Women With Early-Stage Breast Cancer

Surabhi Dangi-Garimella, PhD

TRIAL ASSIGNING INDIVIDUALIZED Options for Treatment (Rx), or TAILORx, successfully confirmed the benefit of endocrine therapy (ET) alone in patients with early-stage breast cancer who have an Oncotype DX Breast Recurrence Score (RS) of 11 to 25.

The long-awaited results of the TAILORx study, the largest-ever breast cancer treatment trial, sponsored by the National Cancer Institute and led by the ECOG-ACRIN Cancer Research Group, were presented at the 2018 American Society of Clinical Oncology Annual Meeting by Joseph A. Sparano, MD, professor of medicine and obstetrics, gynecology, and women's health at the Albert Einstein College of Medicine; associate chairman for clinical research in the Department of Oncology at Montefiore Medical Center; and associate director for clinical research at the Albert Einstein Cancer Center, all in New York City.

The Oncotype DX RS ranges from 0 to 100 and can predict chemotherapy benefit when the score is high, meaning higher than either 26. A score lower than 10 means the risk of distant recurrence is low, and the women will not benefit from chemotherapy. "The gray area has been the mid-range RS score of 11 to 25—this target population accounts for about 50% of women in the United States," Sparano said.

The TAILORx trial was designed to help personalize treatment for women aged 18 to 75 years with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative, axillary node (AN)-negative breast cancer whose tumors were 1.1 cm to 5.0 cm in size and who had a mid-range RS. The trial, which enrolled 10,273 women, aimed to clarify whether hormone therapy alone or together with chemotherapy is better for women with an RS of 11 to 25. The trial also was designed to confirm that a low RS of 0 to 10 is associated with a low rate of distant recurrence when patients receive endocrine therapy alone.

A majority (6711; 69%) of the 9719 eligible women had a midrange RS of 11 to 25 and were randomized to either the chemoendocrine treatment (CET) arm or the ET arm. Women with an RS of 10 or lower (1619; 17%) were in the ET arm and those with a RS of 26 or higher (1389; 14%) were in the CET arm. The primary endpoint was invasive disease-free survival (iDFS), and the trial was designed to show noninferiority for ET alone.

Key secondary end points included freedom from recurrence of breast cancer at a distant site, freedom from recurrence of breast cancer at a distant or local–regional site, and overall survival (OS).

At a median follow-up of 90 months (7.6 years), there were 836 iDFS events at final analysis. ET was noninferior to CET for iDFS (hazard ratio [HR], 1.08; 95% CI, 0.94-1.24; $P = .26$) in the intention-to-treat (ITT) population. ET was also noninferior for distant recurrence-free interval (DRFI; HR, 1.03; $P = .80$), recurrence-free interval (RFI; HR 1.12; $P = .28$), and OS (HR, 0.97; $P = .80$).

Nine-year rates were similar for iDFS (83.3% vs 84.3%), DRFI (94.5% vs 95.0%), RFI (92.2% vs 92.9%), and OS (93.9% vs 93.8%) for the RS 11-to-25 arm. The overall recurrence rate was 5%. The study found 3% distant recurrence with ET alone in the RS 0-to-10 arm and 13% distant recurrence with CET in the RS 26-to-100 arm.

The study observed a potential chemotherapy benefit in younger women (≤50 years) with an RS of 16 to 25, while RS of 0 to 15 had good prognosis with endocrine therapy. "Chemotherapy should be used with caution in this [RS 11-to-25] subgroup with a shared decision-making process for deciding the treatment path," Sparano concluded.

Sparano concluded that in women with hormone receptor–positive, HER2-negative, AN-negative breast cancer who had a RS of 11 to 25, adjuvant ET was not inferior to CET in the ITT analysis. However, recurrence was high in the RS 26-to-100 arm despite adjuvant CET.

"The results of our trial suggest that the 21-gene assay may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy, especially those who are older than 50 years of age and have a recurrence score of 25 or lower, as well as women 50 years of age or younger with a recurrence score of 15 or lower," Sparano and colleagues wrote in the accompanying paper, published in the *New England Journal of Medicine*. ◆

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CLINICAL FINDINGS

Cetuximab With Chemoradiation Worse Than Chemoradiation Alone in Older Patients With HNSCC

Surabhi Dangi-Garimella, PhD

TREATMENT WITH CETUXIMAB (CX), concurrent with chemoradiation (CRT), in older patients diagnosed with head and neck squamous cell carcinoma (HNSCC) has similar toxicity as CRT alone, but the overall survival (OS) is inferior. These are the results of a retrospective analysis that was presented at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.[1]

Cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor, was approved in 2006[2] for the treatment of metastatic colorectal cancer; local or advanced HNSCC, in combination with CRT; and metastatic HNSCC.

The antibody has been increasingly used in older patients with HNSCC as a radiosensitizer for CRT. "However, overall survival after definitive CRT-CX, compared with definitive CRT, has not been adequately evaluated outside of younger more highly selected clinical-trial populations with locally advanced HNSCC," said Dan Paul Zandberg, MD, Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland, who presented the results of the study.

For their study, the authors used the Surveillance Epidemiology and End Results (SEER) cancer registry programs data that were linked with the Medicare database to evaluate OS in patients with HNSCC diagnosed between 2005 and 2011.

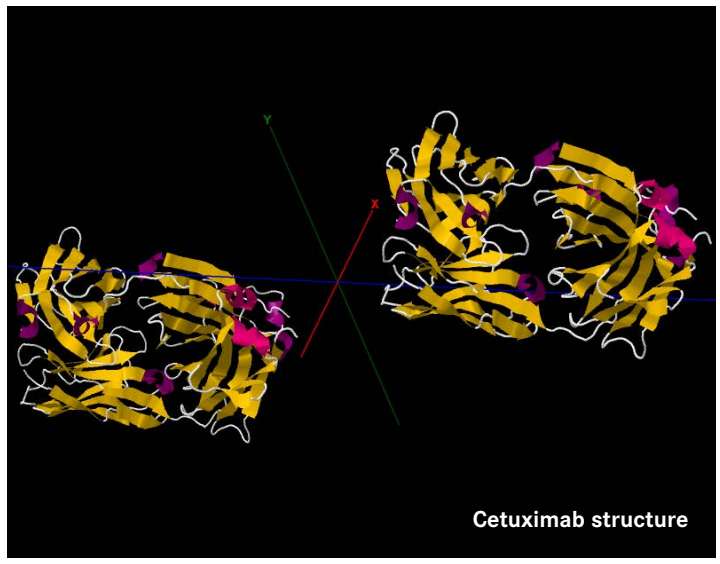
Inclusion criteria included individuals who had continuous Medicare Part A and B coverage. Patients on a health maintenance organization plan during the 12 months prior to receiving their diagnosis were excluded. Additionally, inclusion in the study required access to complete claims for at least a year after diagnosis and primary treatment should have been radiation treatment (RT) alone or CRT.

"Analysis of real-world data and the large patient numbers are strengths of our retrospective study."

—Dan Paul Zandberg, MD,
Marlene and Stewart Greenbaum Comprehensive Cancer Center,
University of Maryland

Enforcement of the inclusion/exclusion criteria identified 2135 beneficiaries, a majority of whom were male (73.5%), with a median age of 73 years (range, 66-104 years). Primary subsites of disease in these patients were oropharynx (OP, 61%), hypopharynx (HP, 15%), nasopharynx (5%), and larynx (19%). Eighty-two percent of patients received platinum-based chemotherapy, of which 52% received cisplatin.

The authors found that OS in the CRT-CX–treated patients was worse than those who received CRT (P <.005) and similar to RT (P = .21): The 5-year OS was 46% for CRT, 35% for CRT-CX, and 32% for RT. The median survival was 4.5 years (range, 3.8-4.9 years), 2.5 years (range, 2.2-3.0 years), and 2.2 years (range, 2.0-3.0 years) in the CRT, CRT-CX, and RT populations, respectively. The risk of death was greater with CRT-CX compared with CRT (HR, 1.41 [range, 1.24-1.61]; P = .0001), after stratifying by stage and primary site and adjusting for gender, race, age, income, Charlson comorbidity index, marital status, hospital type, and year of diagnosis.



ZANDBERG

Dan Paul Zandberg, MD, of the Marlene and Stewart Greenbaum Comprehensive Cancer Center, University of Maryland.

In the context of the primary site, a similar trend was observed. The 5-year OS in patients with OP disease was highest with CRT-treated patients (54%; median OS, 5.59 years) compared with CRT-CX (39%; median OS, 2.95 years) and RT (34%; median OS, 2.24 years). In patients with HP disease, the 5-year OS was 34%, 22%, and 26% in the CRT, CRT-CX, and RT groups, respectively.

However, CRT led to a significantly higher rate of hearing loss within the first 3 months of treatment compared with CRT-CX (9.3% vs 4.1%; P <.001); dysphagia, gastrostomy tube placement, pneumonia, and weight loss occurred at similar rates between the 2 treatment groups over the first 12 months after diagnosis.

"Analysis of real-world data and the large patient numbers are the strengths of our retrospective study," Zandberg said. He acknowledged, however, that their research group was unable to obtain data on performance status, overall frailty, and severity of comorbidities in the patient population.

Zandberg concluded that definitive treatment with CRT-CX was associated with inferior OS compared with CRT even after adjustment for established prognostic factors, and with similar toxicity, in the SEER-Medicare patient population. "Our data suggest that noncetuximab-based CRT should be used for eligible older HNSCC patients," he said.

Cisplatin remains the standard of care for concurrent therapy with RT, with CX as an option in patients who cannot tolerate cisplatin. ◆

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CLINICAL FINDINGS

Immune Checkpoint Inhibitors Improve Outcomes in Mismatch Repair Deficient CRC, but Can Induce Immune-Related Adverse Effects

Surabhi Dangi-Garimella, PhD

OVERMAN

Michael J. Overman, MD, of The University of Texas MD Anderson Cancer Center.

TREATMENT OF COLORECTAL cancer (CRC)—the third leading cause of cancer-related death in the United States—remains challenging. But according to leading oncologists in the field, who were speaking at a session at the 2018 American Society of Clinical Oncology Annual Meeting, screening patients diagnosed with CRC for deficient mismatch repair (dMMR) could help create a roadmap for precision treatment.

Michael J. Overman, MD, of The University of Texas MD Anderson Cancer Center in Houston, chaired the session and was the first presenter. During his presentation, Optimal Approach to Colorectal Cancer With Deficient Mismatch Repair, he said that microsatellite instability (MSI) and dMMR testing should be universal for patients with CRC, especially individuals who have a family history of CRC.

In terms of new treatment options, he noted that immune checkpoint inhibitors, namely the programmed death-1 (PD-1) inhibitors, nivolumab and pembrolizumab, now have added indications in the treatment of CRC:

- Nivolumab: MSI high (MSI-H) or dMMR metastatic CRC (mCRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan
- Pembrolizumab: adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

The National Comprehensive Cancer Network, Overman said, recommends nivolumab or pembrolizumab as a treatment option for patients with metastatic dMMR CRC as second- or third-line therapy.

The rationale here is based on studies showing that high tumor mutational burden (TMB) can increase sensitivity to immune checkpoint inhibitors and has been shown to be more significantly associated with response to PD-1 and programmed death ligand-1 (PD-L1) blockade immunotherapy.

Frameshift mutations in CRC can result in new neoantigen targets, including proteins involved in differentiation (eg, melanocyte differentiation antigens), overexpressed proteins (eg, human epidermal growth factor receptor 2), and viral proteins (eg, human papillomavirus). MSI-H tumors have a very high mutation rate; when that is combined with frameshift mutations, in which a single alteration leads to multiple amino acids, the results are mutations that have significant qualitative and quantitative mutation rates.

"In the clinic, we typically see patients present with a very high rate of mutation," Overman said.

He noted, however, that there remain significant discrepancies between the testing methodologies used to detect dMMR. Mosaic testing, Overman said, is much more sensitive and more specific than polymerase chain reaction.

Overman's group conducted studies comparing nivolumab and ipilimumab in patients diagnosed with dMMR/MSI-H CRC who had received at least 2 prior lines of treatment. They investigated whether addition of the cytotoxic T-lymphocyte-associated protein 4 inhibitor, ipilimumab, could further enhance outcomes compared with nivolumab alone. The study results, published in the *Journal of Clinical Oncology*,[1] found that the investigator-assessed objective response rate (ORR) was 55% (95% CI, 45.2%-63.8%) and the disease control rate for ≥12 weeks was 80% for patients treated with the combination. At data cut-off, the median duration of response was not reached and most responses were ongoing. Progression-free survival (PFS) rates were 76% (9 months) and 71% (12 months), and overall survival (OS) rates were 87% (9 months) and 85% (12 months).

Overman also drew attention to the results from KEYNOTE-164, which evaluated pembrolizumab in patients with MSI-H CRC who had received at least 2 prior lines of treatment. When data were acquired in October 2017, after a median of 12.6 months of follow-up, the ORR was 32% (95% CI, 21%-45%), with 2 complete responses and 18 partial responses. Median PFS was 4.1 months, and the 12-month PFS rate was 41%. The 12-month OS rate was 76%.[2]

"Questions remain, however, around the durability of nivolumab's effect in dMMR CRC," Overman said.

Several phase 3 trials are ongoing, he said, to test these immune checkpoint inhibitors in patients with MSI-H/dMMR CRC.

- NRG-G1004/SWOG-1610 is evaluating how well the combination of chemotherapy, bevacizumab, and/or atezolizumab will work in advanced MSI-H/dMMR CRC[3]
- KEYNOTE-177 is evaluating the combination of pembrolizumab with mFOLFOX/bevacizumab in advanced MSI-H/CRC[4]
- Alliance 021502 is evaluating combination chemotherapy and atezolizumab in patients with stage II dMMR CRC.[5]

"Pembrolizumab is now standard of care for dMMR non-CRC patients" Overman said, and he sees a way forward for success with immune checkpoint inhibitors in combination with chemotherapy, in CRC as well.

Immune-Related Adverse Events

Another speaker during the session, Marc S. Ernstoff, MD, of Roswell Park Comprehensive Cancer Center in Buffalo, New York, gave an overview of the management of immune-related adverse events (irAEs) in mCRC.

When Ernstoff surveyed oncologists asking if they were comfortable with managing irAEs, the results indicated that discomfort is common, he shared. A total of 32% of providers are very uncomfortable with managing irAEs, he said, while 5% are somewhat uncomfortable, 19% somewhat comfortable, and 33% very comfortable.

Ernstoff noted that immune toxicities in CRC may not necessarily be related to the specific antibody being administered. It's important to understand, he said, that the effects are not immediate; rather, one might be dealing with latent toxicity, and such toxicities can affect any organ.

The most common of these toxicities are pruritis, rash, and diarrhea, and they were more often observed when nivolumab was combined with ipilimumab, compared with when nivolumab was administered alone. The incidence of irAEs was also high when ipilimumab was administered alone.[6]

The recognition of irAEs is vital, Ernstoff emphasized. Some of the more unusual symptoms can include the development of diabetes, nephritis, myositis, myocarditis, and uveitis.

"A high percentage of low-grade (<3) irAEs are common, even with single agents," he said, with 10%-25% remaining unresolved

for at least 12 months. Ernstoff explained that a majority of patients may require steroid treatment for symptom resolution, especially if they are on combination immune checkpoint inhibitors.

Dealing with long-term irAEs is the biggest challenge of cancer survivorship in patients receiving these checkpoint inhibitors, he said.

It is vital to recognize the grade of the AEs: For low-grade AEs, symptom management can usually suffice, whereas for high-grade AEs, immunosuppression using glucocorticoids or infliximab/mycophenalate is recommended. Chronic immune suppression would require steroid treatment, anti-integrins, or anti–tumor necrosis factor agents.

Is mitigation an option? This remains unknown for the time being, Ernstoff said, adding that an individual's genetic predisposition could be investigated. Another strategy could be boosting the microbiome, using, for instance, probiotic agents. A further tactic would be identifying members of high-risk populations, including those patients with existing autoimmune disease or those who have had an organ transplant.

"Overall, immune checkpoint inhibition of the PD1/PD-L1 axis has been well tolerated and is safer than conventional chemotherapy," Ernstoff said. He emphasized the importance of oncologists educating themselves and their immediate teams, as well as their communities, about the toxicity profile of these agents, especially because "irAEs can masquerade as other common symptoms." ◆

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Cemiplimab, in GOG 3016, Looks to Break New Ground for Immunotherapy in Cervical Cancer

Mary Caffrey

SEVERAL STUDIES INVOLVING immunotherapy to treat cervical cancer have reached phase 2. But a phase 3 trial is under way with cemiplimab, after researchers at Regeneron saw a positive signal in a phase 1 study and opted to move immediately to a randomized clinical trial. GOG 3016, which is now recruiting participants at 53 locations in the United States and internationally, activated in late 2017 to study patients with recurrent and metastatic cervical carcinoma.[1]

"These observations suggested to us that cemiplimab has the potential to improve survival in women with advanced cervical cancer who have exhausted the potential for clinical benefit with currently availabe treatments, and that a phase 3 trial was the way to go."

—Matthew Fury, MD, Regeneron

While patients with cervical cancer may experience modest survival benefits with initial treatment (with or without bevacizumab), those who have a recurrence after being treated with platinum-based chemotherapy have a median survival of just 7 months, according to the research update offered June 4, 2018, at the annual meeting of the American Society of Clinical Oncology, held in Chicago, Illinois.[2]

But the nature of cervical cancer meant that immunotherapy could be a treatment choice.

"For women with metastatic cervical cancer who have progressed on first-line therapy, there really has been nothing out there for them," Matthew Fury, MD, senior director of clinical sciences in oncology for Regeneron, said in an email to *The American Journal of Managed Care®*. "Because almost all cervical cancers are HPV [human papilloma virus]-associated, the presence of a viral antigen in these tumors creates the potential for robust anti-tumor immune responses and prolonged survival."

GOG 3016, a randomized (1:1), open-label trial, seeks to enroll 436 patients who have previously been treated with platinum-based chemotherapy. They will receive either cemiplimab, a human monoclonal anti–programmed death cell-1 therapy, or the investigator's choice of several forms of chemotherapy:

- antifolate: pemetrexed
- topoisomerase 1 inhibitor: topotecan or irinotecan
- nucleoside analogue: gemcitabine
- vinca alkaloid: vinorelbine[1]

Fury said GOG 3016 results from the phase 1 study of cemiplimab showed durable responses in 2 of the 3 cervical cancer patients who were enrolled in the dose-escalation portion of the study. "We thought that this was a potentially important efficacy signal in a patient population with unmet need," Fury said, and the results dovetailed with those being seen with immune checkpoint inhibitors in other virally associated cancers, like oropharynx cancer and Merkel cell carcinoma.

"These observations suggested to us that cemiplimab has the potential to improve survival in women with advanced cervical cancer who have exhausted the potential for clinical benefit with currently available treatments, and that a phase 3 trial was the way to go," Fury said.

Similarly, Regeneron moved quickly on an early impressive signal in a patient with advanced cutaneous squamous cell carcinoma, he said. ◆

FURY

Matthew Fury, MD, is senior director of Clinical Sciences in Oncology, Regeneron.

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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

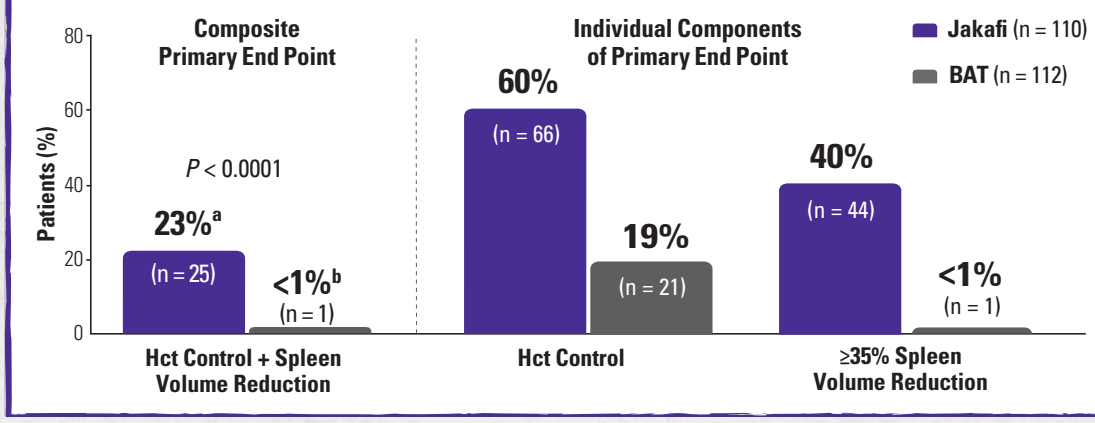
Incyte

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 therapy[1]

Components of Primary End Point at Week 32[2]



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

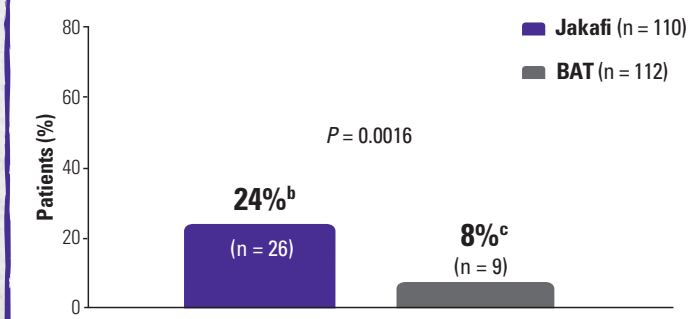
[a] 95% CI, 15%-32%

[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.

Patients Achieving Complete Hematologic Remission[2a]



Durable response at week 80[2]

- 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 ≤400 × 10^9/L, and white blood cell count ≤10 × 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 V.2.2018. © 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.

Jakafi®
ruxolitinib (tablets)

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 10^9/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 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/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

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**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 10^9/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 10^9/L to 200 X 10^9/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 10^9/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]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**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

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**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]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**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 [^{14}C]-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/m^2 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 10^9/L and 150 X 10^9/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 10^9/L and 150 X 10^9/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.

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CLINICAL FINDINGS

Identifying Rational Immunotherapy Combinations for Glioblastoma: A Progress Report

Surabhi Dangi-Garimella, PhD

FOR IMMUNOTHERAPY TO work in glioblastoma multiforme (GBM), which has an estimated 5-year survival rate of 33% in the United States, combination treatments are the way forward, according to global experts who appeared at a session of the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.

Chairing the session was Amy B. Heimberger, MD, professor, Department of Neurosurgery, The University of Texas MD Anderson Cancer Center. During her presentation, Heimberger offered a flavor of the potential strategies that clinicians can pursue for antitumor immune induction in glioblastoma.

"What are key steps necessary for an optimal antitumor immune therapeutic response in brain tumors?" she asked, considering that glioblastomas are highly immunosuppressive.

How do we overcome lack of T-cell infiltration in the tumor? She shared the results of a successful single-patient strategy in a patient with recurrent multifocal glioblastoma who received chimeric antigen receptor (CAR) T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2). Multiple intracranial infusions of the IL13Rα2 CAR T cells in the resected tumor cavity, as well as in the ventricular system, resulted in a regression of intracranial and spinal tumors in that patient—a response that was sustained for 7.5 months.[1]

The CAR domain has several limitations, Heimberger pointed out: the lack of tumor-specific antigens, antigen escape, and in vivo persistence and generation of a product in a timely fashion.

"All these limitations need to be addressed to view the efficacy of CAR T cells in GBM," she said.

Her laboratory has developed a small molecule inhibitor against STAT3, which is another key driver of GBMs. The researchers developed a small-molecule inhibitor called WP1066, which, they found, can block M2 macrophages. The drug has minimal toxicity, but it is lipophilic, meaning it is difficult for the drug to dissolve in the blood stream. The team had to be innovative in its approach, so the researchers spray-dried the drug with methylcellulose. A phase 1 trial of WP1066 is ongoing in patients with GBM refractory to treatment.

Another approach to treating GBM is via viral vaccines, and Michael Platten, MD, Mannheim University Hospital, German Cancer Research Center, provided the audience with an overview of where the field stands. His team has developed a novel method to detect the immunological presentation of the mutated antigen in tumor tissue of patients with brain tumors.

"We don't know what the relevance of whole tumor vaccines is," Platten said, and explained that several unknowns remain, including:

- How do you select appropriate target antigens?
- What are the appropriate biomarkers?
- How do you bring the vaccine in context with immunotherapeutics and checkpoint blockade agents?

There are 3 categories of antigens in GBMs, he noted:

- Tumor-associated antigens are shared antigens that have both low immunogenicity and potential for side effects
- Viral antigens are usually not endogenous; they are heterogenous if exogenously expressed
- Tumor antigen are specific but do not elicit a strong immune response.

A recent paper published by Liau et al evaluated the impact of adding an autologous tumor lysate-pulsed dendritic cell vaccine to standard therapy in new GBM. The randomized phase 3 trial results demonstrated a median overall survival of 34.7 months from surgery, with a 3-year survival rate of 46.4%.[2]

Platten said that there is growing understanding in the field for neoepitope vaccines; these are unique to tumor cells and most arise from single nucleotide variables. Most neoepitopes are private, meaning they are found within a single family or small population, with the majority being class II epitopes. Gliomas have about 30 to 100 nonsynonymous mutations per megabase. Shared neoepitopes include EGFRvIII and IDH1R132H receptors.

"Clonality remains a question with shared epitope vaccines," he said, adding that the natural clonal evolution of GBM results in the acquisition and loss of subclonal neoepitopes.

Platten believes the following treatments can complement vaccines in GBM treatment:

- Immunosuppressive agents for the tumor microenvironment
- Radiation therapy and oncolytic viruses
- Immune checkpoint blockade agents
- Small molecule targets

Immune response monitoring remains a significant issue in GBM treatment. "We need better tools to capture patient response to treatment," said Platten.

Gavin P. Dunn, MD, PhD, Washington University School of Medicine in St. Louis, was up next. He provided an update on checkpoint inhibitors and combination strategy with targeted immunotherapies in GBM. Current checkpoint inhibitors do not have any indication for GBM.

Although there are some responders to immunotherapies, presenting with long-term control and partial remission after pseudoprogression, the question is, how do you identify these responders? "While there are anatomic site-specific considerations, the checkpoint pathway does remain the canonical pathway for targeting T-cell immune responses," Dunn said.

Study findings have shown a trend of increased sensitivity to checkpoint blockade with increasing mutational burden for different cancer types, he said. "Therefore, mutation burden is the engine for generating candidate neoantigens."

Whereas some studies' results have shown that the incidence of hypermutated genotype in primary GBMs is low, research from Dunn's lab shows that hypermutated patients with GBM do respond to PD-1 inhibitors—in this case, pembrolizumab (Keytruda).[3]

However, researchers need to be aware of the failure nodes of immune function, which can lead to lack of response to checkpoint blockade in GBM:

- Lack of efficient antigen presentation
- Impaired homing mechanisms
- STAT reactivation at the tumor site
- Checkpoint inhibition blockade inhibition or T-cell exhaustion

Dunn noted that there are 4 ongoing trials that are evaluating rational combination treatments for recurrent GBM, including the CAPTIVE trial,[4] and another evaluating a LAG3 inhibitor or urelumab[5] in combination with nivolumab.

Dunn agreed with previous speakers that combination therapy may be the way forward for the successful treatment of GBMs. ◆

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CLINICAL FINDINGS

Persephone Trial: Cutting Trastuzumab Duration by Half Safer, Efficacious in HER2-Positive Breast Cancer

Surabhi Dangi-Garimella, PhD

MORE THAN 4000 women with HER2-positive early-stage breast cancer who were treated with trastuzumab (Herceptin) for 6 months had a similar rate of disease-free survival (DFS) as women who received the drug for twice the length of time. Meanwhile, nearly double the number of women who were treated with trastuzumab for a year dropped out of the trial due to cardiac problems compared with the shorter duration. These results from the Persephone trial were presented during the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, held in Chicago, Illinois.[1]

The 12-month adjuvant treatment with trastuzumab, added to chemotherapy, is adopted from the drug's registration trials and is the current standard of care. However, the addition of trastuzumab led to significantly high rates of cardiotoxic effects, resulting in several follow-up studies evaluating the high risk of cardiac problems that the drug induces.[2,3]

The Persephone trial worked on the hypothesis that a shorter treatment duration could reduce toxicities and cost while providing similar efficacy. Hailed as the largest reduced-duration noninferiority international trial, Persephone recruited HER2-positive patients diagnosed with early-stage breast cancer who were then stratified based on their estrogen receptor (ER) status, chemotherapy type, and timing of chemotherapy and trastuzumab. The trial's primary endpoint was DFS from the time of diagnosis. The noninferiority query of the 6-month treatment was defined as "no worse than 3%" below the 80% 4-year DFS assumed for the 12-month arm.

Of the 4089 patients randomized to receive the treatment in 152 sites in the United Kingdom between 2007 and 2015:

69% were ER positive

- 41% received anthracycline-based chemotherapy
- 49% received anthracycline- and taxane-based chemotherapy
- 10% received taxane-based chemotherapy
- 85% received adjuvant chemotherapy
- Sequential trastuzumab was administered in 54% of patients

At a median follow-up period of 5 years, the researchers found near-identical results between the 2 treatment arms: DFS was 89.4% among women in the 6-month arm and 89.8% in the 12-month arm (HR, 1.29).

Significant reductions in cardiac events was observed in the 6-month treated group compared with the 12-month treated group: Only 4% of women treated with trastuzumab for 6 months experienced heart-related issues and stopped treatment. On the other hand, 8% of women in the 12-month group had to stop their cancer care because of cardiotoxicity (P <.0001).

Speaking during a press cast hosted by ASCO prior to the meeting, the study's lead author, Helena Earl, MD, professor of clinical cancer medicine, University of Cambridge, United Kingdom, said that the results from the Persephone trial confirmed the noninferiority of 6-month adjuvant treatment with trastuzumab compared with the 12-month treatment. "The 6-month treatment also reduced cardiac toxicity and costs the patient and the health system less," she added.

Ongoing research in this patient population is evaluating quality-of-life and patient-reported outcomes in this study population. The study authors are also conducting health economic assessments of the reduced treatment duration with the drug. ◆

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Opdivo Plus Chemo Boosts Progression-Free Survival 26% Over Chemo Alone in Late-Stage NSCLC

Mary Caffrey

COMBINATION TREATMENTS INVOLVING checkpoint inhibitors continue to gain attention, including those involving more than 1 immunotherapy and that comprise immunotherapy and chemotherapy. Researchers continue to seek biomarkers that will allow them to match treatment combinations with patients who will most benefit.

Bristol-Myers Squibb results presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois, followed up on results ASCO released earlier in 2018 from the phase 3 Checkmate 227 trial in non–small cell lung cancer (NSCLC). The earlier results, involving the nivolumab (Opdivo) and ipilimumab (Yervoy) combination, showed that this combination reduced progression risk by 42% for patients with a high tumor mutation burden.[1]

The Checkmate 227 results presented June 4, 2018, involved patients in the trial arm who were treated with nivolumab and chemotherapy. The abstract included 550 chemotherapy-naïve patients with stage IV or recurrent NSCLC; they had no known *EGFR*/*ALK* mutations and had <1% PD-L1 expression. The results compared 177 patients in the nivolumab-plus-chemotherapy arm compared with 186 who were treated with chemotherapy only.[2]

Those in the nivolumab/chemotherapy arm had improved progression-free survival (PFS) over the chemotherapy arm (HR, 0.74; CI 95%, 0.58-0.94). The minimum follow-up was 11.2 months, and patients were treated for up to 2 years. Most subgroups saw PFS with the nivolumab/chemotherapy combination, but the benefit was more pronounced among nonsquamous (HR = 0.68) than among squamous (HR = 0.92) histologies.

The rates of adverse events that caused patients to stop taking therapy were about the same in both the nivolumab/chemotherapy arm (13%) and the chemotherapy arm (14%). ◆

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Robotic Surgery Complements Chemotherapy, Safer Than Radiation, in Oral Cancer

Surabhi Dangi-Garimella, PhD

SIEGEL

Robert S. Siegel, MD, of the George Washington University School of Medicine and Health Sciences.

TRANSORAL ROBOTIC-ASSISTED surgery (TORS), following chemotherapy and neck resections, is an effective model for the definitive treatment for oropharyngeal squamous cell carcinoma (OPSCC) while avoiding the adverse effects of radiation. These results were presented at the 2018 American Society of Clinical Oncology Annual Meeting, June 1 to 5, in Chicago, Illinois.

According to the National Cancer Institute, incidence of oropharyngeal cancer has been on the rise in the United States, and the growing number of human papillomavirus (HPV) infections might be responsible. With over 50,000 cases estimated in 2018, oropharyngeal cancer is expected to lead to more than 10,000 deaths this year.

"The standard of care for OPSCC includes chemoradiation or surgery with adjuvant radiation," said Robert S. Siegel, MD, George Washington University School of Medicine and Health Sciences, and a senior investigator for the study. He explained that while the treatments are successful 80% to 90% of the time in curing oropharyngeal cancer and 90% of the time in HPV oropharyngeal cancer, radiation treatment can be harsh and can significantly affect morbidity. Long-term effects of radiation treatment can include gum and dental disease, change in taste, difficulty with swallowing, and others.

"We therefore assessed the efficacy of a 2-drug induction regimen, followed by TORS and neck dissection for locally advanced OPSCC," Siegel said.

Siegel said that with this treatment, the risk of distal disease is diminished and surgery is easier. "Additionally, TORS is more effective than older surgical techniques, with less tissue damage and quicker recovery," he added.

> **"Of the 20 patients who started the trial, at a mean follow-up of 22 months, 18 patients are alive and disease-free."**
>
> —Robert S. Siegel, MD, George Washington University School of Medicine and Health Sciences

The single-arm phase 2 study recruited treatment-naïve stage III or IVA patients with a diagnosis of OPSCC who had an Eastern Cooperative Oncology Group score <2. The treatment plan included induction chemotherapy with cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 every 21 days for 3 cycles. Tumor shrinkage was examined after each cycle. If the primary tumor was ≥80% smaller, patients were scheduled for TORS and neck dissection(s). At postoperation visits, flexible laryngoscopy, blood tests, and imaging with positron emission tomography/computed tomography and/or magnetic resonance imaging were done.

The study outcomes that were evaluated included short- and long-term toxicities, progression-free survival, overall survival, and quality of life (QOL).

Of the 20 patients who met the inclusion criteria and were treated, 19 were male, 17 were Caucasian, and 19 were HPV-positive; median age at diagnosis was 57 years. Thirteen patients had a tumor in their tonsil and 7 at the base of their tongue. Three patients were stage III, and 17 were stage IVA.

Chemotherapy treatment

© SUDOK1/FOTOLIA

The study found that tumor size was reduced by 53.4% after the first induction cycle, 80% after the second, and 90.5% after the third. Therefore, all patients were eligible for surgery, Siegel said. Pathologic complete response (CR) of the primary site occurred in 15 of the 20 patients, and CR among lymph node neck dissections occurred in 13 patients. CR was noted in 12 of 20 patients.

The pre- versus posttreatment QOL scores did not change much: Fourteen patients had very good to excellent QOL at baseline, while 15 patients had good to excellent QOL following treatment.

"At a mean follow-up of 22 months, 18 patients are alive and disease-free," Siegel said. Three patients who had a recurrence an average of 2.2 months after surgery were treated with salvage chemoradiation therapy, he said. Two of three patients who had metastatic disease died, and all 3 had positive lymph node disease at surgery.

Siegel concluded by stating that induction chemotherapy with TORS and neck dissection can be an alternative for standard chemoradiation in patients who are HPV-positive. He recommends chemoradiation as an option for patients whose tumors do not shrink by 8% or more after induction chemotherapy and who have at least 1 lymph node positive for disease following surgery. ◆

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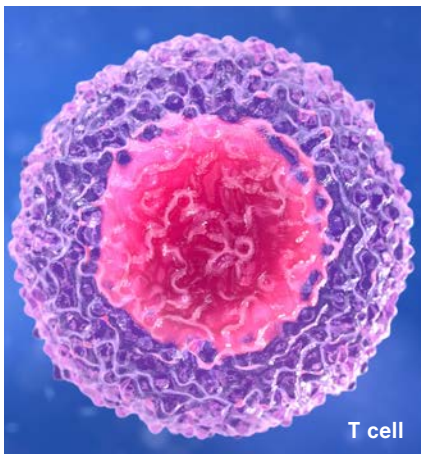
Nelarabine With Chemotherapy Boosted Outcomes in Pediatric and YA Patients With T-Cell Cancers

Surabhi Dangi-Garimella, PhD

A PHASE 3 STUDY, started in 2007 by the Children's Oncology Group (COG), among children and young adults diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic leukemia (T-LL), has found a 90% survival rate at 4 years after the start of treatment. Among these patients, 84% were declared cancer free at the 4-year mark in their treatment trajectory. Results were presented at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.

The COG AALL0434 study enrolled 1895 patients aged 1 to 30 years between January 2007 and July 2014 to test nelarabine (Arranon), an antineoplastic agent directed against T cells, in combination with chemotherapy. The trial had 4 arms, and all patients received COG-augmented Berlin-Frankfurt-Munster (BFM) or augmented BFM chemotherapy. Additionally, they were randomized to receive escalating-dose methotrexate (MTX) without leucovorin rescue plus pegaspargase (Oncaspar) (CMTX) or high-dose MTX (HDMTX) plus leucovorin rescue. Patients with moderate or high risk (based on genetics or prior radiation exposure) were randomized to receive, or not receive, six 5-day courses of nelarabine 650 mg/m^2/day complemented with chemotherapy and cranial radiation.


T cell

"T-cell ALL is a disease that requires the use of a very intense and complex chemotherapy regimen. Historically, about 80% of people live at least 4 years after being treated for their disease, but we felt we could and must do better," lead author Kimberly Dunsmore, MD, professor, Virginia Tech Carilion School of Medicine, said in a press release. "Our trial shows that we could further increase survival rates by about 10%, which is very encouraging."

For all patients, the overall disease-free survival (DFS) rate was 84.3% +/- 1.1% at 4 years and the overall survival rate was 90.2% +/- 0.9%. The 4-year DFS rate for patients with T-ALL randomized to nelarabine (n = 323) versus no nelarabine (n = 336) was 88.9% +/- 2.2% versus 83.3% +/- 2.5%, (P = .0332).

Among patients with T-ALL randomized to CMTX, the 4-year DFS for nelarabine (n = 147) versus no nelarabine (n = 151) was 92.2% +/- 2.8% versus 89.8% +/- 3.0% (P = .3825). For patients randomized to HDMTX, the 4-year DFS was 86.2% +/- 3.2% with nelarabine (n = 176) versus 78.0% +/- 3.7% without nelarabine (n = 185; P = .024).

There was no advantage of nelarabine treatment for high-risk patients with T-LL. The 4-year DFS rates were 85.0% +/- 5.6% for nelarabine (n = 60) and 89.0% +/- 4.7% for patients who did not receive nelarabine (n = 58; P = .2788).

Overall toxicity and neurotoxicity were acceptable and not significantly different between all 4 arms, the authors concluded.

Future studies are directed to evaluate using nelarabine along with chemotherapy without cranial radiation to avoid the late adverse effects associated with radiating the brain, including cognitive changes, learning disabilities, neuroendocrine changes, and the development of secondary cancers. ◆

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Promising Early-Phase Results With bb2121 CAR T Treatment in Relapsed Refractory Multiple Myeloma

Surabhi Dangi-Garimella, PhD

RAJE

Noopur S. Raje, MD, of the Center for Multiple Myeloma, Massachusetts General Hospital.

INNOVATION AROUND DEVELOPING safe and effective chimeric antigen receptor (CAR) T cells to treat cancer continues, and at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois, Noopur S. Raje, MD, director, Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, presented results from the phase 1 multicenter study with a second-generation CAR T-cell therapy called bb2121.

The therapy, which uses biomarker-directed targeting of T cells to recognize and kill malignant myeloma cells in patients diagnosed with multiple myeloma, was tested for safety and efficacy in a dose-escalation phase of the CRB-401 trial. Raje reported updated safety and efficacy results in 43 patients enrolled in this ongoing study. The modified T cells were devised to target the B-cell maturation antigen (BCMA). Raje confirmed that based on preclinical results, bb2121 is not inhibited by high levels of soluble BCMA in serum by myeloma cells.

Patients with relapsed/refractory multiple myeloma who were selected for the dose-escalation treatment had received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or were double refractory. BCMA expression on plasma cells was 50% or higher. Patients in the dose-expansion phase were required to have been treated with daratumumab, and they were refractory to their last line of therapy; BCMA expression was not required. A single infusion of bb2121 was administered to the patients following a 3-day lymphodepletion procedure with fludarabine (30 mg/m^2)/cytarabine (300 mg/m^2) given daily for 3 days.[1]

Safety concerns with CAR T-cell administration have lingered—cytokine release syndrome (CRS) and neurotoxicity CAR T cell–related encephalopathy syndrome are frequently documented in this patient population.[2] For instance, one CAR T-cell therapy that was being developed to treat acute lymphocytic leukemia registered 5 fatalities following patients' cerebral edema, and development had to be terminated.[3] ROCKET was initially halted following an FDA directive, and the company made changes to its preconditioning regimen (leukapheresis), eliminating fludarabine from the preconditioning process. This, however, did not prove an effective solution and the trial was shelved.

When the abstract about bb2121 was submitted in October 2017 for presentation at this year's ASCO annual meeting, 21 patients at that point had received bb2121 in the 4 dose-escalation cohorts, and the median follow-up was 35 weeks. The majority of patients were male and the median age was 58 years. All 21 patients had received a prior autologous stem cell transplant (ASCT) and a median 7 prior lines of treatments (range, 3-14).

As of October, the authors had observed no dose-limiting toxicities and no grade 3 or higher neurotoxicities. However, grade 1-2 CRS was reported in 15 patients (71%), 2 of whom had grade ≥3 CRS that resolved in 24 hours.

Surprisingly, 2 patients died, even though they had achieved a complete response (CR) and their disease had not progressed. Of the remaining 19 evaluable patients, the overall response rate in the dose escalation cohorts, who received at least 150×10^6 CAR T cells, was 94%: 10 of 18 patients (56%) patients had CR or unconfirmed CR; 9 of 10 evaluable patients were minimal residual disease–negative.

At a median follow-up of 40 weeks (in October), in the 150×10^6 or greater dose-escalation cohorts, median response duration and progression-free survival (PFS) had not been reached. PFS rates at 6 and 9 months were 81% and 71%, respectively. In the expansion phase, patients were administered 150 to 300×10^6 CAR T cells.

At ASCO, Raje also presented results of 22 patients who were in the dose-expansion cohort—10 had <50% BCMA expression and 12 had ≥50% BCMA expression. The majority of patients in this cohort were male, as well, and the patients' median age was 65 years. Nineteen of these patients had received prior ASCT and had received a median 8 lines of treatment (range, 3-23).

In the updated results presented at the meeting, Raje showed that 27 of the total 43 patients experienced CRS, of which 2 incidences were grade 3 or higher. Only 9 patients needed treatment with tocilizumab for their CRS. Fourteen patients experienced neurotoxicity, 35 had neutropenia, 26 had thrombocytopenia, and 24 had anemia. There were no grade 4 CRS events.

The overall response rate (ORR) was 33.3% in the low-dose patients (50x10^6), 57.1% in patients who received the 150x10^6 dose, and 95.5% in those who received an even higher dose. ORR was not significantly different between low–BCMA-expressing patients (100%) versus high–BCMA-expressing patients (91%).

Finally, Raje discussed the significant improvement in PFS in patients receiving a high dose of bb2121. Median PFS in 18 patients in the dose-escalation phase was 11.8 months, while it was 17.7 months in 16 subjects who were negative for minimal residual disease.

A lingering question with the approved CAR T-cell treatments—tisagenlecleucel (Kymriah; Novartis) and axicabtagene ciloleucel (Yescarta; Kite Pharma/Gilead)—surrounds their costs. The treatment cycle of tisagenlecleucel costs $475,000 for B-cell acute lymphoblastic leukemia, while axicabtagene ciloleucel costs $373,000. While these numbers may seem steep, the Institute for Clinical and Economic Review released a report earlier this year on their price analysis; the Institute concluded that the prices align with the clinical value that both treatments present.[4]

Novartis, meanwhile, has negotiated a value-based contract with CMS for tisagenlecleucel. ◆

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ZUMA-1: Response to Axi-cel at 3 Months Prognostic for Remission in B-cell Lymphoma

Surabhi Dangi-Garimella, PhD

A LONG-TERM FOLLOW-UP of patients with B-cell lymphoma treated with axicabtagene ciloleucel (axi-cel), a chimeric antigen receptor (CAR) T-cell therapy, was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. Results indicate that a response at 3 months may be prognostic for long-term remission in those patients.

An autologous anti-CD19 CAR T-cell therapy developed by Kite Pharma, axi-cel was granted priority review following interim results showing that 82% of patients had met the primary end point of an objective response rate at 8.7 months of follow-up. Subsequently, the drug was approved within 5 months by the FDA for the treatment of adult patients with relapsed/refractory large B-cell lymphoma whose disease has progressed on at least 2 lines of systemic therapy.[1]

"Patients who are in response at 3 months are 80% likely to maintain their response to the treatment at 12 months."

—Frederick Locke, MD, Moffitt Cancer Center and Research Institute

At ASCO, Frederick Locke, MD, program co-leader in immunology at the Moffitt Cancer Center and Research Institute in Tampa, Florida, presented the longer-term update. Patients (n = 101) with refractory large B-cell lymphoma received 2×10^6 CAR T cells/kg after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine.[2] The best objective response rates (ORRs) were analyzed by both the local investigators and by an independent review committee (IRC).[3]

Results collected at a median follow-up of 15.4 months showed that while the best ORR was 82% at primary analysis (median follow-up of 8.7 months) it remained consistent in the longer term, with follow-up by local doctors (median 15.4 months). The complete response (CR) rates increased from 54% to 58%. Of the 34 patients who had a partial response (PR) at 3 months, 18 (44%) converted to a CR by the long-term follow-up cut off.

The researchers report observing a high concordance (77%-79%) for ORRs between local investigators and the IRC at all times assessed.

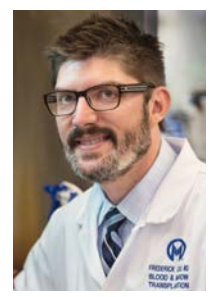
Locke emphasized that patients who responded at 3 months had an 80% likelihood of a durable response at 12 months. Analysis of progression-free survival (PFS) by local investigators found that most of the 60 patients with disease control (stable disease or better) at 3 months had prolonged disease control a year out and a PFS of 78% at the benchmarked 6, 9, and 12 months.

Among patients who had a CR, 88% had a CR at 6 months, 83% at 9 months, and 79% at 12 months.

Adverse events, primarily cytokine release syndrome (CRS) and neurologic events, were observed at a similar rate across all response groups, Locke said. CRS was observed in all 9 patients with PR, but all instances were low grade (<3); 39 CR patients experienced CRS, of which 5 instances were grade 3 or higher. In total, 7 PR patients experienced neurologic events, 3 of which were grade 3 or higher; 28 CR patients had neurologic adverse events, of which 15 were grade 3 or higher.

The authors concluded that based on the ORR and increasing CR rates during the long-term follow-up, patients can achieve CR even 1 year out following infusion of the axi-cel CAR T-cell treatment, which suggests that responses deepen over time.

"Patients who are in response at 3 months are 80% likely to maintain their response to the treatment at 12 months," Locke said. He emphasized that a PR or CR at 3 months following the infusion can serve as a prognostic marker for long-term remission in patients with B-cell lymphoma who are administered axi-cel. ◆



LOCKE

Frederick Locke, MD, of the Moffitt Cancer Center and Research Institute.

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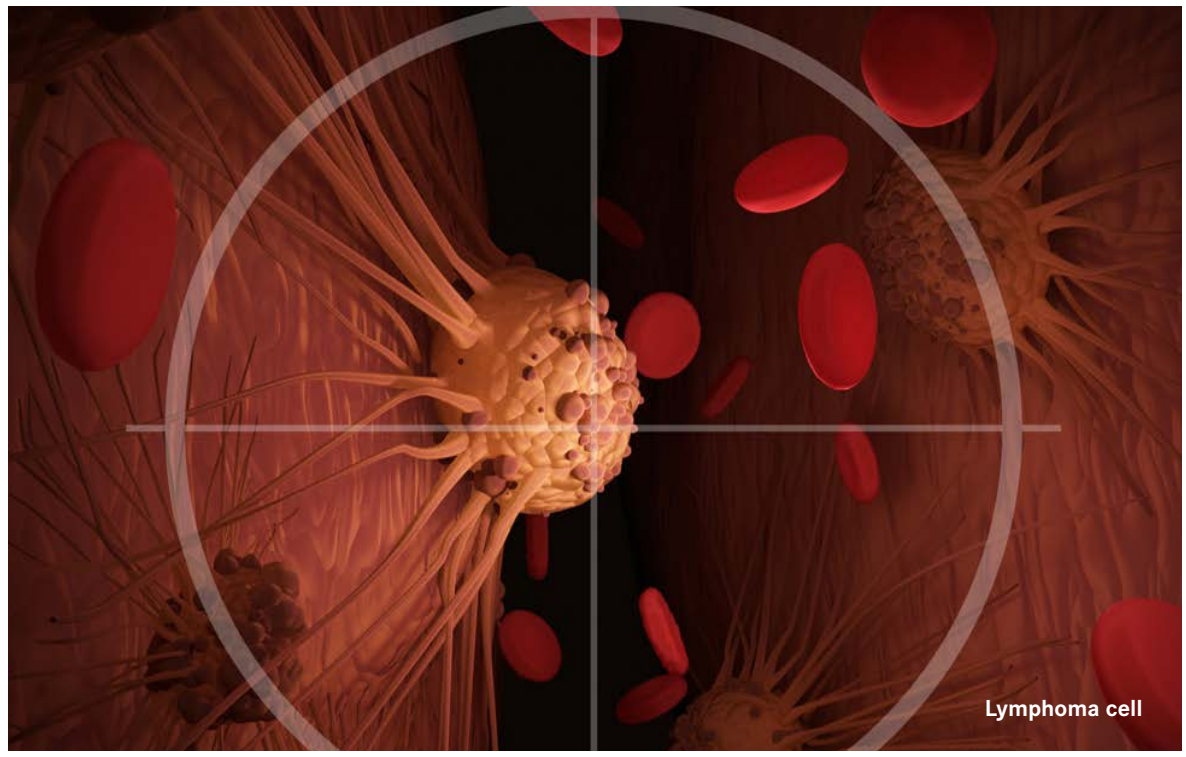

Lymphoma cell

TREATING MYELOMA CAN SEEM LIKE A MARATHON

WOULD YOU TAKE OFF YOUR SHOE WHEN RUNNING A MARATHON?

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

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

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

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

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

Important Safety Information

Warnings and Precautions

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

Adverse Reactions

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

Special Populations

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

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

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

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Please see accompanying Brief Summary.

Takeda ONCOLOGY

 Printed in USA 4/18 MAT-US-IXA-18-00238

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

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

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

1 INDICATION

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 CLINICAL TRIALS EXPERIENCE

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

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

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

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

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

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

*Represents a pooling of preferred terms

(Continued on next page)

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

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

Herpes Zoster

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

Eye Disorders

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy:

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

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

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

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

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

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

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

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

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

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

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

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

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

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

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

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

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

CARE STRATEGIES

Despite USPSTF Recommendations, Lung Screening Rates Low Among Heavy Smokers

Surabhi Dangi-Garimella, PhD

JOHNSON

Bruce E. Johnson, MD, FASCO, of the American Society of Clinical Oncology.

A RETROSPECTIVE ANALYSIS1 conducted by researchers at the University of Louisville, Kentucky, has found that less than 2% of more than 7.5 million eligible smokers were screened for lung cancer in 2016 despite recommendations by the United States Preventive Services Task Force (USPSTF). These results were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois.

"This study makes a strong case that our country needs an effective public service campaign about encouraging lung cancer screening. Public service campaigns from the 1990s encouraged women to get mammograms, saving many lives in subsequent years. We need something similar to encourage current and former heavy smokers to get screened for lung cancer," said ASCO President Bruce E. Johnson, MD, FASCO, in a press release that described the findings from the study.

A leading cause of cancer-related mortality, lung cancer is expected to be responsible for over 154,000 deaths in the United States in 2018, according to estimates by the American Cancer Society (ACS).[2] This disease remains the most common cancer diagnosed in men and women.

In 2013, USPSTF rendered a B-grade recommendation[3] for an annual lung cancer screening with low-dose computed tomography (LDCT) among adults aged 55 to 80 years who have a 30 pack-year history of smoking (defined as heavy smokers) and if they continue to smoke or did within the past 15 years (eligible smokers). The B recommendation means USPSTF expects a moderate to substantial net benefit from the LDCT screening service.

With their current study, the authors analyzed the impact of the USPSTF recommendation on screening rates using data from the Lung Cancer Screening Registry, which was acquired from the American College of Radiology in 2016. This registry spanned 1796 accredited radiographic screening sites. The data were compared with National Health Interview Survey estimates of eligible smokers who could be screened based on the USPSTF recommendations.

The geographic grid covered the Northeast, South, Midwest, and West, and the screening rate was derived by dividing the number of LDCT scans by the number of eligible smokers. Although the South had the most accredited screening sites (n = 663) and the highest number of eligible smokers, the screening rate in the region was the second lowest in the country (1.6%), with the West documenting the lowest screening rate (1%) and the fewest accredited screening sites (n = 232).

The overall national rate for screening among the potentially 7,612,965 eligible smokers was just under 2%: Only 141,260 individuals received LDCT screening.

Smoking cessation tools were offered to a significant portion (85%) of current smokers, and the authors report that the percentage of current and former smokers who were offered these tools was not influenced by the geographic location.

These results are not a surprise. A study[4] commissioned by ACS and published in *JAMA Oncology* in early 2017 found that lung cancer screening rates remained low, and unchanged, following the USPSTF recommendations.

Several questions remain unanswered, according to lead study author Danh Pham, MD, a medical oncologist at the James Graham Brown Cancer Center, University of Louisville, who presented the results during a press cast organized by ASCO. "Are physicians not referring enough or do patients resist screening?" Pham asked. He added that there is stigma associated with this screening test, which could also be responsible for the low rates of screening.

Further initiatives are needed, including awareness programs and mandating lung cancer screening as a national quality measure, the authors conclude in their abstract. "Effective screening can prevent nearly 12,000 premature annual lung cancer deaths," Pham said during the press cast.

Pointing out that Medicare approved payment for LDCT screening only in 2015,[5] Johnson said that the outcome being measured by this study has not yet reached a steady state. A long-term follow-up might provide a more realistic picture of where screening rates stand. ◆

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Clinical Trials: Sharing the Road With Real-World Evidence

Jaime Rosenberg

IN THE ERA OF real-world data and evidence, and their growing roles in oncology, panelists discussed collecting and using these data in combination with clinical trials to inform evidence-based care during a session at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.

Although clinical trials remain the gold standard for the context in which they were designed and developed—evaluating efficacy in tightly controlled and highly annotated samples—there are some drawbacks to using clinical trial data alone, explained Kathryn Reeder-Hayes, MD, MBA, MSc, assistant professor, University of North Carolina at Chapel Hill.

"In this context, assuming they meet their accrual goals, there [are] almost never too little data for the job in terms of the level of detail and the completeness of the data," she said. She also noted that clinical trials are a familiar and comfortable form of evidence generation for multiple key stakeholders who are involved in the development of novel therapies for oncology.

"In [some] contexts, clinical trials may in fact waste time and resources, both in terms of our economic sources and our patients' time. Real-world evidence, I would argue, may be less expensive and more appropriate for some questions as they relate to post hoc analyses and diffusion into broad populations."

—Kathryn Reeder-Hayes, MD, MBA, MSc, University of North Carolina, Chapel Hill

However, clinical trials can also be prohibitively expensive and may not be the best fit for every question relevant to clinical practice, Reeder-Hayes warned. In particular, they are not optimally suited for questions of application of the innovational treatments being studied within the trial to broad and diverse populations. Neither are they well adapted to answer post hoc questions about differences in efficacy across subgroups or treatment application to populations outside the clinical trials, often because the sample is either too small, too homogenous, or both, for the data to be able to answer these questions.

"In those contexts, clinical trials may in fact waste time and resources, both in terms of our economic sources and our patients' time," said Reeder-Hayes. "In those contexts, real-world evidence, I would argue, may be less expensive and more appropriate for some questions as they relate to post hoc analyses and diffusion into broad populations."

According to Reeder-Hayes, real-world evidence can be beneficial in several places:

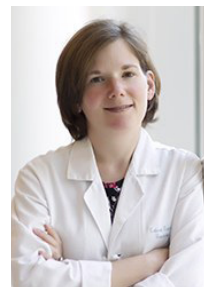
- After a randomized clinical trial is conducted, to test the dissemination of the findings and if they are being adopted, in which patients they're being adopted, and which patient populations are being left behind.
- Alongside randomized clinical trials, to extend findings to broader populations and answer secondary questions about differences among subgroups.
- Before anticipating trials, to inform the important problems and questions, quantify effect sizes, and identify the right population.

She concluded by cautioning that big data studies require expertise in handling and analyzing observational data with its unique challenges related to potential bias and the need for complex data management strategies. Similar to clinical trials, these studies are best performed by experienced cross-disciplinary teams and are most useful when they answer the questions important to physicians and patients.

Sean Khozin, MD, MPH, director, Information Exchange and Data Transformation (INFORMED), followed Reeder-Hayes with an introduction to the FDA's recently launched INFORMED program.

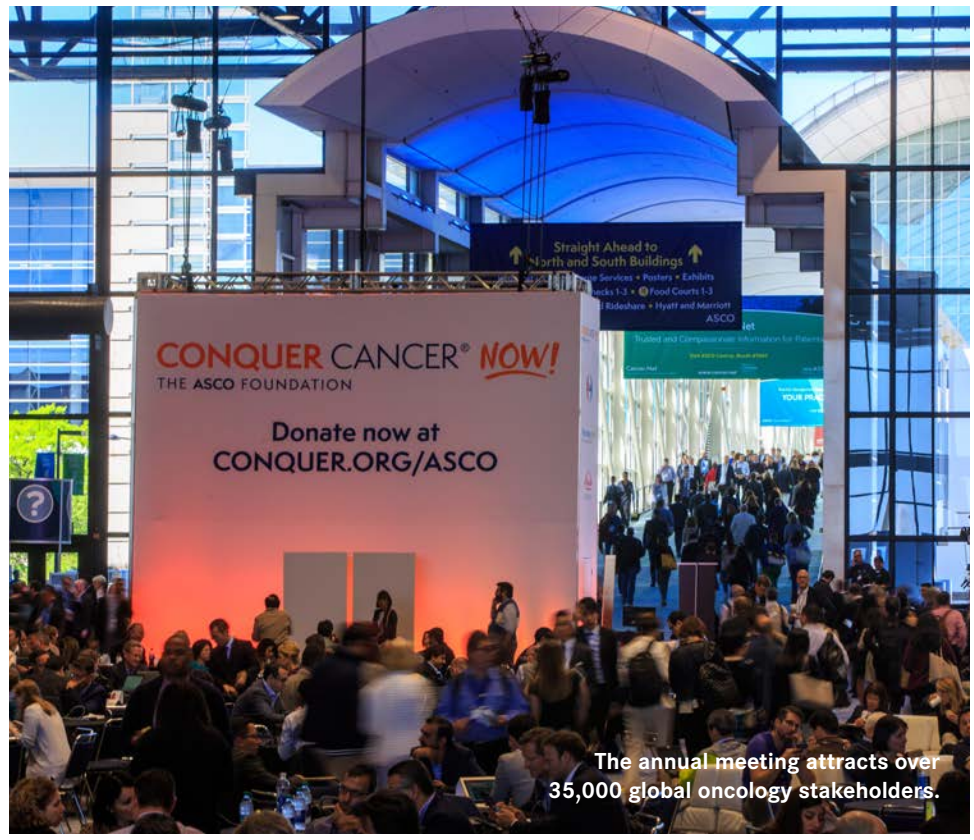
"Big data [have] many difference dimensions," said Khozin. To explore and address these dimensions, the FDA launched the INFORMED program in April as an incubator for collaborative oncology science research. The program pairs engineers and data scientists with medical reviewers and regulatory scientists to conduct regulatory research using a variety of data inputs, including: clinical trials, electronic health records, biometric monitoring devices, and applications.

From these inputs, results come in the form of publications, abstracts, and, more recently, codes and algorithms that can be incorporated into decision support tools, explained Khozin. Outputs also include policy positions and guidance documents that can disseminate findings to the community and inform development programs, he added. ◆



REEDER-HAYES

Kathryn Reeder-Hayes, MD, MBA, MSc, of the University of North Carolina, Chapel Hill.



The annual meeting attracts over 35,000 global oncology stakeholders.

Remote Monitoring Can Reduce Radiation-Related Symptoms in Head and Neck Cancer

Surabhi Dangi-Garimella, PhD

PETERSON

Susan K. Peterson, PhD, MPH, of The University of Texas MD Anderson Cancer Center.

USE OF THE MOBILE and sensor technology CYCORE (CYberinfrastructure for COmparative Effectiveness Research) to remotely monitor symptoms in patients with head and neck cancer (HNC) undergoing radiation therapy found these patients had fewer symptoms overall and specific to HNC.

The study,[1] presented at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois, was included in a press cast that was broadcast ahead of the meeting.

According to the National Cancer Institute, over 51,500 individuals[2] will be get an HNC diagnosis in 2018, accounting for over 3% of new cancer diagnoses for the year. Although the 5-year survival rate of this cancer hovers close to 65%, a little over 10,000 patients are estimated to die from the disease this year in the United States. HNC patients have high risk of symptom burden and risk of dehydration.

Chemotherapy, surgery, and radiation therapy are the forms of treatment available for patients with HNC, but the treatment plan is determined based on disease stage, potential side effects, and the patient's overall health and preferences. Patients who receive radiation therapy may experience significant treatment-related burden,[3] including pain, difficulty swallowing, swelling and scarring at the site of treatment, and loss of appetite, all of which can lead to dehydration. Other side effects include dry mouth, bone pain, nausea, fatigue, mouth sores, and hearing loss.

Researchers from 4 institutions, who designed and implemented the current trial, used CYCORE to compare remote patient monitoring with usual patient care among 357 patients. A majority of the patients were male, and there were 169 patients in the CYCORE arm and 188 in the usual care arm of weekly doctor visits. Patients in the CYCORE arm were provided with blood pressure cuffs and weight scales that were Bluetooth-enabled and given mobile tablets with proprietary Wi-Fi. Sensor readouts were transmitted to firewall-protected computers through a secure mobile app to ensure data protection.

> **"Our study generated evidence on how newer technologies can be integrated into cancer care relatively easily and improve patient outcomes without interfering too much in a person's daily life."**
>
> —Susan K. Peterson, PhD, MPH
> The University of Texas MD Anderson Cancer Center

The real-time readouts were reviewed on a daily basis by physicians, which allowed for an early intervention if needed. Patients in both groups had a weekly in-person visit with their physician.

Patients filled out the 28-item MD Anderson Symptom Inventory (MDASI) survey[4] prior to initiation of radiation treatment, at the end of therapy, and 6 to 8 weeks after radiation ended. A scale of 0 to 10 was used to rate symptom severity, with lower scores indicating better outcomes.

The study found that while there was no difference in self-reported health severity scores between the 2 groups at the start of the trial, MDASI scores of the CYCORE group were lower for severity of general (2.92 vs. 3.4; $P = .003$) and HNC-specific symptoms (4.21 vs 4.83; $P = .009$) at the completion of the radiation treatment. Similarly, MDASI scores were lower for the CYCORE group at 6 to 8 weeks after completing radiation, for general (1.69 vs 1.96; $P = .003$) and HNC-specific symptoms (1.78 vs. 2.11; $P = .009$).

Remote monitoring led to lower overall rates of symptoms.

"Our study generated evidence on how newer technologies can be integrated into cancer care relatively easily and improve patient outcomes without interfering too much in a person's daily life," said lead study author Susan K. Peterson, PhD, MPH, professor, Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, in a press release. "This study was done during a rather intense period in the patients' care for head and neck cancer. The system helped their physicians to provide valuable support that ultimately resulted in lower symptom severity."

An important observation was the high rate of adherence in a majority of patients, despite the intensity of treatment. "Using mobile tech for remote monitoring of patients during critical periods of outpatient treatment can provide timely info for clinical decision making and can improve [quality of life] and health outcomes," the authors concluded. ◆

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Discussing the Cost Burden of Cancer With Patients

Jaime Rosenberg

PATIENTS WITH CANCER often have medical bills and other health costs significantly higher than those of others. Now, with cancer drugs becoming increasingly effective and more tolerable for patients, patients take these drugs for longer periods of time, leading to increased financial burden, said oncologist and health services researcher Ryan Nipp, MD, MPH, during a session at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois. Nipp is with Massachusetts General Hospital Cancer Center in Boston.

In addition to out-of-pocket costs, such as co-payments, deductibles, and prescriptions, patients with cancer often experience issues indirectly related to finances during cancer treatment, he said, including:

Employment issues such as missing work, being on disability, or "job lock," when patients feel they cannot change jobs because it would interrupt health coverage.

Lifestyle factors including interruptions to their children's education, or being unable to pay the mortgage or basic living expenses.

Concurrent issues such as psychological distress, fear of the unknown, and symptom burden.

Patients with cancer experience financial burdens related to the disease and its treatment across all insurance types at higher rates than those with other chronic conditions and those with no chronic conditions, explained Nipp; 43% of privately insured patients with cancer spend more than 20% of their income on health-related costs, compared with 29.8% of such patients with another chronic condition and 16.4% of those with no chronic condition. For those with public insurance, 24% of patients with cancer spend more than 20% of their income on health-related spending, compared with 18.7% and 5.8% of the other groups, respectively.

"Increasingly, efforts are needed to foster appropriate patient–clinician communication about the cost of cancer care," said Nipp. Such "discussions…have the potential to improve care delivery and outcomes for patients by fostering informed decision making."

However, numerous barriers face both clinicians and patients, he explained. For clinicians, barriers include lack of knowledge about costs incurred by patients, potentially time-consuming discussions, concerns that providing information about cost may encourage patients to forgo care, and concerns that cost discussions may jeopardize the patient–clinician relationship.

Patients, for their part, may feel unsure of the appropriateness of discussing costs with their clinician team, and may feel embarrassed or self-conscious to raise the issue; they also may have a desire to respect their clinician's time, are not sure their clinicians would have a solution for the concern, or may prioritize other concerns during a time-limited visit.

Ellen Miller Sonet, MBA, JD, chief strategy and policy officer, Cancer*Care,* followed up Nipp by asking the audience, "Have you ever made a major purchase without knowing the price, be it a car, camera, or computer? Because that's what cancer patients do. They agree to a cancer treatment plan, and they don't know what it will cost them."

Until there are some policy solutions, it's the problem of the patient/physician relationship, she said. She outlined different solutions that can be implemented to alleviate the burden facing these patients.

First, clinicians should determine who within their office will address the issues with patients. "I think that, very often, the physician thinks the nurse is doing it, the nurse thinks the office manager is doing it, and sometimes nobody's doing it," she said.

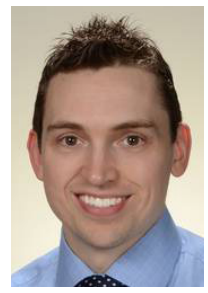
Other strategies highlighted by Sonet included ensuring that patients know the major costs prior to treatment, considering lower-priced options and alternate dosing schedules, asking patients to discuss if treatment is too great a financial burden, and referring them to financial and psychosocial counseling.

She also outlined available resources available to patients, such as co-pay and patient assistance funds, hospital charity care, patient advocacy organizations, voluntary and faith-based resources within communities, and financial planning and insurance navigation.

Cancer*Care* offers "A Helping Hand," an online resource guide about financial assistance. There is a searchable database where patients can input a diagnosis and zip code and be presented with different resources available to them.

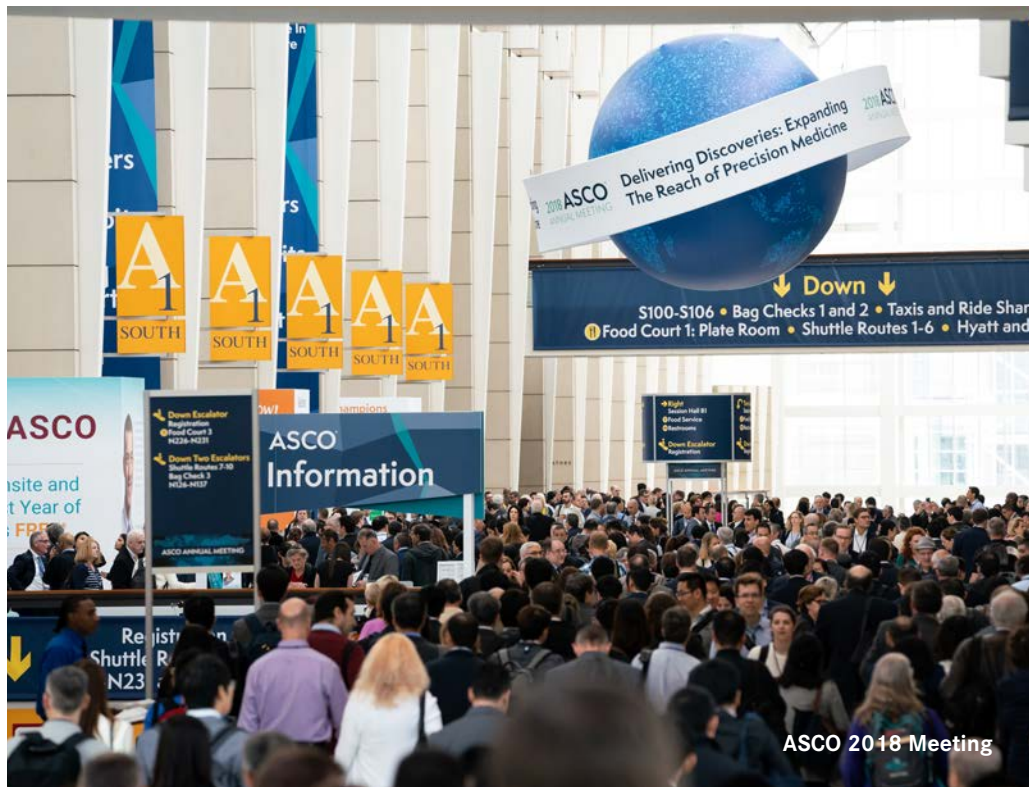
She also encouraged the use of patient portals for education and links. A patient will feel comfort knowing that if they're up in the middle of the night worrying about something, they can go online to the website and learn about what's troubling them, she explained.

"Patients' learning styles may vary. Some people are visual learners, and some patients like to hear information. They will forget most of what their clinician tells them, because they're anxious, and they're upset, and they don't really understand a lot of the information that's being communicated," Sonet said. "So, recognize that lots of different media can be very helpful." ◆



NIPP

Ryan Nipp, MD, MPH, of the Massachusetts General Hospital Cancer Center.



ASCO 2018 Meeting

Researchers Report Findings on Three Biosimilar Trastuzumab Products

Kelly Davio

DURING THE 2018 American Society of Clinical Oncology's (ASCO) Annual Meeting, researchers presented findings on 3 biosimilar trastuzumab products: Samsung Bioepis' SB3, Agmen's ABP 980, and Biocad's Herticad.

One-year safety and survival data for SB3 support biosimilarity

SB3, which is approved in the European Union as Ontruzant and is under review by the FDA, was the subject of a report on safety and survival data from patients with HER2-positive early or locally advanced breast cancer. In a clinical trial,[1] patients received either SB3 or the reference trastuzumab and had follow-up of at least 12 treatment-free months after 12 cycles of neoadjuvant-adjuvant therapy.

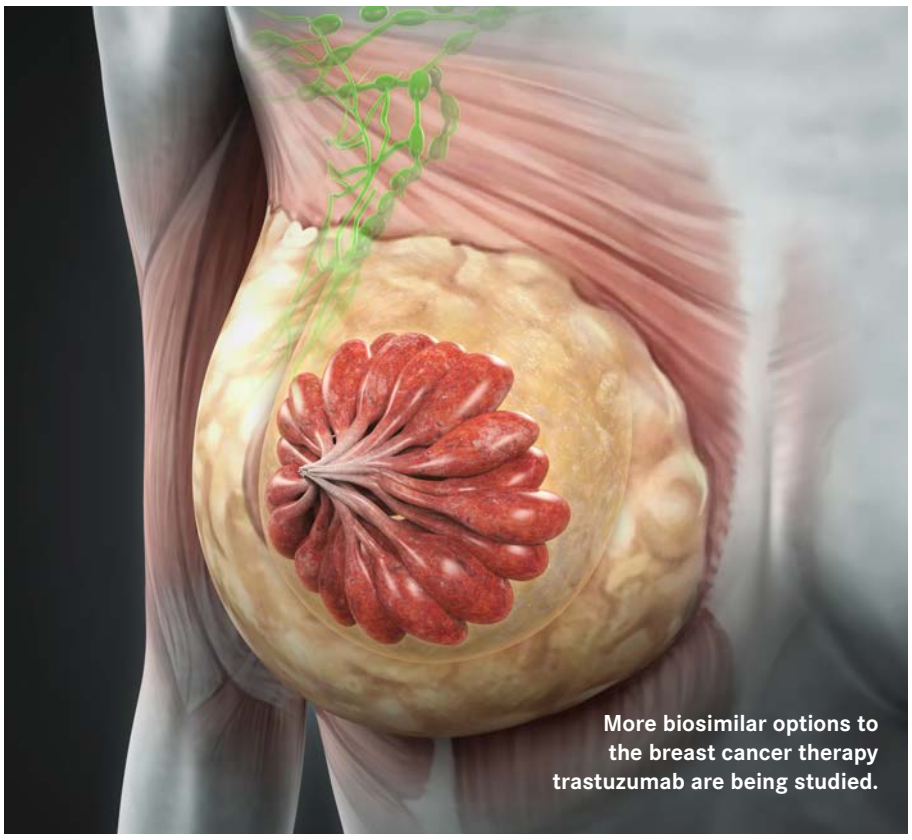
In total, 367 patients were randomized to receive 8 cycles of either SB3 (n = 186) or the reference trastuzumab (n = 181) in the neoadjuvant setting with chemotherapy. Patients then underwent surgery and another 10 cycles of SB3 or the reference trastuzumab.

Patients were followed up every 6 months to observe the incidence of symptomatic congestive heart failure, asymptomatic significant left ventricular ejection fraction (LVEF) decrease, cardiac events, event-free survival (EFS), and overall survival (OS). The median follow-up from initiation of the study was 30.1 months for the SB3 arm and 30.2 months for the reference arm.

During the 1-year follow-up, the incidence of asymptomatic significant LVEF decrease was similar in the SB3 (n = 1) and reference groups (n = 2), and no significant cardiac conditions or cardiac-related death were reported.

Eight patients in the SB3 group and 14 in the reference group experienced disease recurrence, progression, or death. In the SB3 arm, there was 1 patient death, and in the reference arm, there were 3 patient deaths. At 24 months, EFS rates (SB3, 96.7%; reference, 94.3%) and OS rates were comparable between groups (100.0% and 99.4%, respectively).

These results, say the authors, further support the biosimilarity of SB3 with its reference.



More biosimilar options to the breast cancer therapy trastuzumab are being studied.

Central evaluations from LILAC further support clinical equivalence of ABP 980 and reference trastuzumab

One day after Amgen revealed that the FDA had issued a complete response letter for its ABP 980 (which was authorized for marketing in Europe under the name Kanjinti in May 2018), researchers reported results of a pathologic complete response (pCR) analysis based on a central laboratory evaluation of tumor samples collected in the phase 3, randomized, multicenter, double-blind, active-controlled LILAC study that compared ABP 980 to reference trastuzumab in patients with HER2-positive early breast cancer.[2] Results from a local laboratory evaluation were previously reported.

In the LILAC study, 725 patients were randomized to receive either the biosimilar (n = 696) or the reference trastuzumab (n = 338) plus paclitaxel after run-in chemotherapy. The coprimary endpoints were risk difference (RD) and risk ratio (RR) of pCR adjusted for baseline covariates in breast tissue and axillary lymph nodes. Clinical similarity of the trastuzumab products was supported if the 2-sided 90% CIs were within the equivalence margin for RD (–13% to 13%) and RR (0.759-1.318). Each sample was evaluated by 2 independent central pathologists.

The researchers report that, based on central review, pCR was achieved in 47.8% of patients receiving ABP 980 and 41.8% of those receiving the reference product. The RD was 5.8% (90% CI, –0.5 to 12.0%), and the RR was 1.14 (90% CI, 0.993-1.312). Both the RD and RR fell within the prespecified equivalence margins.

The researchers say that the results of the central evaluations further support the clinical equivalence of the biosimilar and its reference and the feasibility of including central laboratory review of pCR rates in a large, multicenter, multinational studies.

Biocad's Herticad reduced the cost of trastuzumab therapy by 75%

Biocad's Herticad, which is approved for use in Russia, has been available since 2016, and new research reports on the effectiveness, safety, and economics of using the biosimilar in clinical practice.[3]

Researchers conducted a study that included 55 women with stage II or stage III HER2-positve breast cancer who were treated at Russia's National Research Cancer Center from March 2016 to December 2017. All patients received neoadjuvant chemotherapy together with the biosimilar trastuzumab, after which the patients had surgery with an assessment of pCR.

The rate of pCR was 55.6% in the breast and 45.8% in the breast and lymph nodes, and was similar in patients with primary-operable and locally advanced disease. There were no reports of treatment-associated cardiac dysfunction in any of the patients, nor were there any infusion-related reactions.

The cost to provide neoadjuvant therapy with trastuzumab decreased 75% during the study period by using the biosimilar, and the researchers report that the biosimilar provides an economically reasonable option that is both safe and effective. ◆

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Along the MBC journey*– explore Verzenio[1]

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

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

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

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

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

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

Select Important Safety Information

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

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

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

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

Lilly

For women with HR+, HER2− MBC

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

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

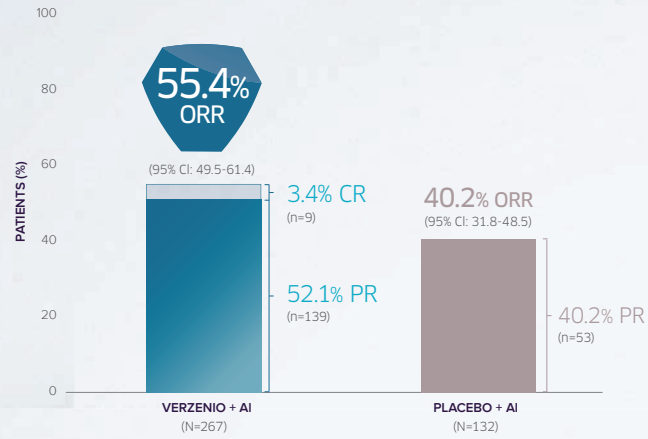
ITT[1]

28.2 months mPFS

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

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

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



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

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

Exploratory subgroup analyses

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

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

Liver metastases[13]

15.0 months

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

Treatment-free interval <36 months[14]

29.5 months

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

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

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

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

Select Important Safety Information (cont'd)

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

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

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

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

For women with HR+, HER2− MBC

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

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

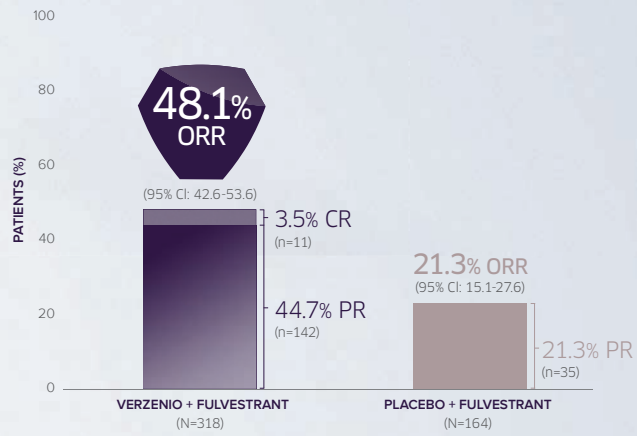
ITT[1]

16.4 months mPFS

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

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

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



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

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

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

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

Primary resistance[16]

15.3 months

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

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

Visceral disease[16]

14.7 months

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

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

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

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

Select Important Safety Information (cont'd)

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

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

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

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

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

For heavily pretreated women with HR+, HER2− MBC

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

ORR[1]

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

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

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

Median duration of response (mDoR)[1†]

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

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

Select Important Safety Information (cont'd)

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

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

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

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

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

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

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

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

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

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

CATEGORY 1*

Abemaciclib (Verzenio) + fulvestrant[19†]

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

Abemaciclib (Verzenio) + an AI[19†]

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

CATEGORY 2A‡

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

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

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[19]
†If there is disease progression while on CDK4 & 6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4 & 6–containing regimen.
‡Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[19]
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Select Important Safety Information (cont'd)

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

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

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

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

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

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

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Lilly

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

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

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

INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Diarrhea

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

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

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

Neutropenia

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

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

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

Hepatotoxicity

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

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

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

Venous Thromboembolism

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

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

Clinical Studies Experience

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Creatinine Increased

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

MONARCH 2: VERZENIO in Combination with Fulvestrant

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

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

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

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

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

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

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

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

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

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

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

[c] Includes neutropenia, neutrophil count decreased.

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

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

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

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

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

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

Creatinine Increased

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

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

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

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

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

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

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

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

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

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

[a] Includes asthenia, fatigue.

[b] Includes neutropenia, neutrophil count decreased.

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

[d] Includes platelet count decreased, thrombocytopenia.

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

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

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

Creatinine Increased

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

DRUG INTERACTIONS

Effect of Other Drugs on VERZENIO

Strong CYP3A Inhibitors

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

Ketoconazole

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

Other Strong CYP3A Inhibitors

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

Strong CYP3A Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*see* Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Infertility

Males

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

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

Rx only.

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

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Utilization Management in Oncology: Current Strategies and a Path Forward

Jaime Rosenberg

ALTHOUGH UTILIZATION MANAGEMENT is generally a pain point for everyone, it's a necessary evil in the United States, where we spend 18% of our gross domestic product on healthcare, explained Debra Patt, MD, MPH, MBA, vice president, Policy and Strategy, Texas Oncology, and medical director, Analytics, McKesson Specialty Health, during a session at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.

"We have real problems in our house of medicine, and they're worse in oncology than they are in other places because we've been ripe with innovation, and a lot of that is tied to very expensive drugs," she added.

There is a myriad of strategies used to control the cost of oncology drugs, including: prior authorization (PA), step therapy, drug quantity supply limitations, member cost sharing, closed specialty pharmacy networks, formulary tiering, and adjusted drug reimbursement to lower expenditures.

Patt highlighted step therapy, which is particularly common among commercial insurers. In 2014, nearly 75% of large employers reported offering employee plans that use step therapy. While it makes sense to lower costd by utilizing lower-cost therapies prior to higher-cost therapies, there's a concern in oncology that preferring some drugs over others in a step-therapy strategy can have a negative impact on patients by not getting the optimal drug first, she explained. In response to these concerns, many states have passed laws against step therapy and fail-first therapy, stating that commercial insurers in those states cannot participate in such programs.

"We have real problems in our house of medicine, and they are worse in oncology than they are in other places, because we've been ripe with innovation, and a lot of that is tied to very expensive drugs."

—Debra Patt, MD, MPH, MBA

Patt then discussed the use of PA, its importance, and its consequences. "When I started in oncology practice 12 years ago, I would write a chemotherapy [prescription], and if we had the drug, the patient could be treated the same day; and if we didn't have the drug, the patient could be treated the next day," she said. "Now, I set the expectation to all my patients that there is just no way, in the absence of [an] emergency, that they're going to get their drug within a week."

Patt recognized that when PAs are denied, it is likely because the therapy is considered experimental, not compliant with guidelines, or there is a lack of adequate supporting evidence. In these cases, PA serves as a deterrent for having less than guideline-based care. However, she noted that there is a lack of transparency on what will lead to a successful authorization, and it's often a significant administrative burden.

In regard to patient cost sharing, she noted that when patients have a higher stake in, or have to pay more for, their healthcare, they utilize it more efficiently, and that holds true with therapies as well.

A seamless system for cancer care.

PATT

Debra Patt, MD, MPH, MBA, of Texas Oncology and McKesson Specialty Health.

The last utilization management strategy she highlighted were formularies. "In general, we don't think they are a great strategy to get patients their optimal treatment," said Patt. "However, I think there probably are some scenarios where they're very useful." She gave the example of a state Medicaid program that has a certain budget, where formulary drugs can be utilized to allow Medicaid to stay within the budget.

Patt ended her session by discussing a path forward. "As we think about utilization management in general, I do think there is a better solution," she said. "In general, I think that because oncology decision making is sophisticated, the decision tree by which you make decisions has to be populated by many data elements. It's not a blunt instrument, it's a much more sophisticated tool."

She urged for collaboration and investing in information solutions to provide the right information for approval early on. Instead of having an administrator call to go through the process of PA, using a support system embedded in the electronic health record can automatically move toward PA.

"When I'm in clinic and I see a patient with stage II breast cancer and I enter in all [of] their information, I come up with a set of choices of therapy through the decision support system embedded in my health record that gives me appropriate pathways," Patt explained. She argued that the same should happen when going through PA. "We can use the information system in and of itself to communicate that information and make our machines work for us. ◆

Managing Cancer-Related Pain in the Era of the Opioid Crisis

Jaime Rosenberg

DEL FABBRO

Egidio Del Fabbro, MD, of Virginia Commonwealth University Massey Cancer Center

AS THE OPIOID epidemic persists in the United States, there are growing questions and concerns over how to manage cancer-related pain and aberrant opioid use. During a session at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois, Egidio Del Fabbro, MD, Virginia Commonwealth University Massey Cancer Center, discussed several management strategies that can be used to address these concerns.

The overuse of opioids can lead to intense and severe consequences, including opioid-induced neurotoxicity, poor quality of life, addiction, overdose, and death, Del Fabbro explained. "Ongoing vigilance is necessary, even with the patient that is successfully treated and successfully managed."

Minimum steps to manage patients on opioids include:

- Make a differential diagnosis: Identify tumor-related causes of pain and patient-related factors influencing pain perception and expression
- Take a history of risk factors for chemical coping: tobacco use, depression, history of substance abuse, personality disorder
- Have an opioid agreement that includes outlining of patient obligations: receive opioids from a single provider and no early refills
- Provide psychological support, motivational interviews, and increased vigilance and structure for those at high risk for opioid misuse
- Keep documentation of all prescriptions, office visits, agreements, and instructions.

"You need a lot of documentation when you see these patients: documentation of the treatment agreements, documentation of a prescription monitoring program, and that it's being checked," Del Fabbro explained. "Many states now regard this as mandatory or ask that this be mandatory."

If a patient displays aberrant behavior or isn't adhering to prescriptions, they need to be seen more frequently and the intervals between visits must be shorter. Adopt an interdisciplinary approach and refer the patient to a specialist team that frequently encounters these more complex patients and has more resources, he said Del Fabbro.

Who exactly should be referred? According to Del Fabbro, those taking high doses, having complex pain, taking complex opioid regimens, or exhibiting aberrant behavior. For physicians treating patients with cancer by prescribing opioids, he highlighted 4 management strategies.

Education

"You have to start at the beginning and explain that opioids should only be used for pain," said Del Fabbro. "It may seem obvious, but I had a health practitioner tell me that he was using opioids at night for his insomnia."

Physicians also need to discuss the risks and adverse effects, as well as emphasize function as an outcome. It's important that the patient know they will still experience pain but that they will be more functional. Education is also important because many patients don't store or dispose of the opioids in an appropriate manner. Simple measures, such as a pamphlet, may be useful in combination with a personalized approach.

Harm Reduction

Ways to optimize harm reduction include using long-acting opioids and avoiding a rapid-acting opioid or prescribing excessive quantities. Physicians should also limit the number of days' supply in both the outpatient and inpatient settings.

"My concern is that naloxone might be another pitfall, where we think there's an easy fix with one prescription for the opioid epidemic. Much the same as we landed in this mess by assuming that opioids alone would be able to manage pain successfully."

—Egidio Del Fabbro, MD, Virginia Commonwealth University Massey Cancer Center

"We seldom prescribe naloxone for our patients," said Del Fabbro. "My concern is that naloxone might be another pitfall, where we think there's an easy fix with one prescription for the opioid epidemic. Much the same as we landed in this mess by assuming that opioids alone would be able to manage pain successfully." He added that it should be indicated for those at very high risk or who have had an overdose in the past.

Del Fabbro also noted the use of opioid rotation, where a physician can switch a patient's high dosage of an opioid to a lower dose by switching the opioid. Because of incomplete cross-tolerance, the patient can achieve better pain control at a lower dose.

Managing Psychological and Spiritual Distress

To manage distress, motivational interviewing has shown to be effective. The idea is to first express empathy for the patient, especially those struggling with substance use disorder. When encountering resistance, arguing with patients won't help, as it will likely increase resistance.

The physician should ask patients their goals and explain that drug misuse will not help facilitate those goals, as well as push for self-efficacy. If this does not work, the physician should bring in a specialized interdisciplinary team to work with these patients.

Risk Mitigation

Del Fabbro emphasized the importance of documentation: the pill counts, the education provided, and the plan that has been explained to the patient. He also reinforced the need for routine documentation of the prescription monitoring program and urine drug screenings.

"Adapted universal precautions, I think, unfortunately need to be expanded even further for these patients who have an opioid misuse problem or even the potential," he said. "I think here, again, it's going to be necessary to refer either to a supportive care clinical or to a pain service." ◆

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Produced by Samantha DiGrande and Jaime Rosenberg

Ambassador Nancy G. Brinker, founder and chair of Global Strategy, Susan G. Komen

When you started Susan G. Komen, there was a lot of stigma surrounding the subject of breast cancer. How did you bring the conversation about breast cancer into the open?

Well, we really brought it out into the open because it was there, it was growing. People just didn't have the place to talk about it or share their feelings or share their insights or survival or their treatment—or their lack of survival. It was really waiting to happen. Because I had lost my only sister to the disease in 1980 and she asked me, I promised her that I would help cure breast cancer.

So, it's been a long ride, a long time. It's been almost 40 years of my life—she was diagnosed in 1978—and I realized that we had to do something, and it was going to require a movement. It wasn't just going to be a one-[time] fundraiser, it was a movement. And of course, this pre-dated computers and cellphones and fax machines and everything else. We really only had telephones and each other to work with.

So, we named it Susan G. Komen in her honor, her memory, and set about working for many, many years. We've managed to bring up the awareness, the sharing, and we've created a large community—a worldwide community—focused on breast cancer.

What do you see as the future of the Susan G. Komen Foundation?

What I think is that the organization, every organization goes through major changes and rebuilding and new ideas and innovation. It's time for major innovation.

We have such strength in our affiliate communities, who are really people on the ground that have learned so much. It's not so much what we do, it's how we do it that's going to be very important.

People are very sensitive to high overheads, they're very sensitive to anything spent. They want to see money that they give go directly to a mission. So we're going to try very hard to make sure that we have collaborations with other people already doing the same thing, that we do things in a way—as we've always tried to do—as cost-effective as possible. Events become very expensive to do, so we have to figure out other ways [to use] technology to raise money and make sure that we connect with people.

[We also need to] get people of wealth in the country to understand that it's as important to fund a program as it is a building. In fact, sometimes the program goes farther to train people, to bring people in the system. So those are the sorts of things we'll work on.

John Schorge, MD, associate editor of *The Green Journal* and gynecologic oncologist at Tufts Medical Center

What has your research shown about different methods to prevent ovarian cancer?

[My] presentation [was] about ovary cancer and the current updates. It is the case that ovary cancer happens in about 1 [in] 70 women in their lifetime. [There are] people that are at higher genetic risk for that, but really, it's been a disappointing number of decades trying to identify a screening test. So

part of the presentation is just kind of presenting the data [that are] out there, showing that it's not all that helpful.

There are some methods of preventing ovarian cancer, such as removal of the ovary. It's [known as] prophylactic surgery, [and it's meant] to reduce the risk. However, that comes with menopausal, early menopause, and other health consequences. What has been more recently shown is that many of these "ovarian cancers" actually start in the tube, and the tube has no function other than allowing pregnancy.

So, what has tilted in the last couple of years—and the ACOG [American College of Obstetrics and Gynecology] practice bulletins sort of magnify—[is] the recommendation to remove the tube at the time of GYN surgery or instead of tubal ligation. We think that that is one of the more effective ways, and easy ways, of decreasing ovarian cancer in the United States.

What were the findings of your study that investigated the delivery of neoadjuvant chemotherapy to women with advanced ovarian cancer?

One of the conundrums, and controversies, in the field is people [who] present with ovarian cancer. Two-thirds of the time it's fairly advanced. Whether to start with surgery first or chemotherapy first has been the dilemma.

Historically, people have started with surgery first, and yet over the last decade or so, there's been a lot more evidence that starting with chemotherapy—such as neoadjuvant chemotherapy, which means chemo first—seems to work out just as well in the long run in many cases.

Part of our work was looking at that trend and then determining that [to be] an interval operation, which means halfway through the chemotherapy. If you're able to do a minimally invasive operation, like a standard laparoscopy, people have similar outcomes to open surgery and a lot fewer side effects and a lot less complication risk.

In your retrospective analysis, how were palliative care services utilized in ovarian cancer and was the utilization in line with national guidelines?

Yes, we did look at palliative care practices specifically for ovarian cancer. It is a relevant topic in that field in that even though most ovarian cancer patients will go into remission, 80% to 90% will relapse. And when a woman has relapsed, it is at some point a palliative care discussion.

Yet, the logistics of care in the country means that many people never hear the word "hospice." If they do, it's at the very end—like the last days or hours of their life—and yet there's a tremendous amount of expense that goes into the last 6 or 12 months on a fairly predictable end result, specifically for ovarian cancer.

So, what we were trying to do is just identify where the deficiencies were so that more attention could be brought to that and I think that more people would be thinking about that earlier.

What sort of disparities did your research uncover about the receipt of care for high-grade endometrial cancer?

High-grade endometrial cancer is sort of the atypical version of endometrial cancer. Endometrial cancer has doubled in incidence in the United States in the last 20 years. The reason for that is the obesity epidemic, by and large, but most of those people are cured. It's the people with the high-grade, or so-called type 2, endometrial cancers [who] require something other than surgery and have a much higher relapse rate.

So, even though it's 5% of people being diagnosed, it accounts for more than

half of people that die from endometrial cancer. It seems to be shifted in the minority and nonclassic populations.

For example, black women are more at risk for fibroids. They're also more at risk for some of these type 2 or high-grade endometrial cancers. So, it's looking at the different health disparities, and you would think that if there [are] 100 people with the same diagnosis that they would be treated the same way, [patients with] one of these more aggressive types of tumors. But that's not the case. And so, there are certain ethnic groups or race groups that tend to be undertreated for some reason or another.

Sometimes it's related to their insurance status, sometimes it's related to different philosophy, but that's what we were trying to drill down into.

Jamie Bakkum-Gamez, MD, associate professor of obstetrics and gynecology and gynecologic oncologist at Mayo Clinic

Why is genetic counseling so important after a patient is diagnosed with ovarian cancer?

Thank you for asking this question. I think this is really, really important. A lot of patients and providers don't realize that ovarian cancer has a huge genetic component as far as the causes of it. About 20% of women who are diagnosed with an ovarian cancer actually have a gene mutation that caused it. When I say "gene mutation," I mean something that they inherited, something that they could potentially pass on to their children or be sharing with a sibling.

Ovarian cancer is one of the most lethal cancers that a woman can be diagnosed with. In fact, 75% of the time it's diagnosed at an advanced stage. We don't have a screening test for it, so picking it up early is really by luck or by chance. In women who are diagnosed with advanced stage, the likelihood of them being alive at 5 years is around 60%. Again, that is because this is a highly lethal disease.

Women who are diagnosed with an ovarian cancer should be seen by a genetic counselor. Basically, what will happen when they're seen by a genetic counselor is that the genetic counselor will go through their family history, personal history, and look for other signs that may indicate a genetic mutation that caused the cancer.

So, [because] ovarian cancer tends to travel with breast cancer, it's important for women to know that a strong family history of breast and/or ovarian cancer should prompt genetic counseling. The National Comprehensive Cancer Network [NCCN] basically has guidelines for when women should be referred for genetic counseling. A personal diagnosis of ovarian cancer is all you need to be recommended for genetic counseling.

The Society of Gynecologic Oncology also has a statement supporting the fact that women should be referred for genetic counseling if they have this diagnosis. At Mayo Clinic, in 2015, we looked at our genetic counseling referral rates for women with [an] ovarian cancer diagnosis. It was a quality improvement project, actually, and we defined what our current rate was, and it was 20%. Which really, we weren't compliant, then, essentially with NCCN guidelines. And so, we implemented a bundled approach that included patient education, order sets. and referral guideline implementation into the electronic medical record for each woman diagnosed with ovarian cancer.

Patient education [was] not just through check lists of risks factors but also education in the form of a short video that they watched in the hospital after their surgery. What we were able to do is we were able to increase our rates of referral from our pre- or historic, referral rate, which by the time we implemented the project, we actually moved the needle a little bit already. We were at 40% referral. But with our quality improvement project, we actually went up to 77% referral rate.

So, we're continuing to try to refine that because, ideally, we do want to chase 100% because all of these women really should be seen for genetic counseling and offered genetic testing.

What sort of novel approaches did you research to assist in the early detection of endometrial cancer?

One of the projects that I've been working on from the research side of things, since I came on staff at Mayo Clinic, is the development of an early detection test for endometrial cancer.

In gynecology, we've had huge success when it comes to screening for cervical cancer with the Pap test and Pap + HPV [human papillomavirus], but we do not have a screening test for endometrial cancer. Endometrial cancer is now the most common gynecologic malignancy that we care for in the United States. One in 50 women will develop an endometrial cancer, and when they come in to see me, oftentimes the question that I get asked is, "My Pap smear was normal. How could I have cancer and have a normal Pap smear?"

Well, the Pap smear is not a test that is designed to pick up endometrial cancer. In fact, the sensitivity of a Pap test to pick up abnormal cells that indicate endometrial cancer up inside the uterus is only about 30%. But we know that there are molecular markers that are shed from cancers into other biospecimens, whether it's peripheral blood or other downstream biospecimens.

So, the biospecimen that we have been focusing our research on is that of the vaginal pool. The vaginal pool is defined as everything that comes from up in the female reproductive tract and flows down into the vagina. This could be fluid and material that comes from the fallopian tubes, maybe even the ovaries. [There are] actually some data out there that suggest that mutations that arise in ovarian cancer can actually be detected in samples from the vagina and cervix, so we know that there is some downstream targeting of that. Also, fluid from the endometrium cavity, the cervix and the vagina. So, all of that is what's in the vaginal pool.

What we've been doing is trying to design an early detection test using a tampon as the tool for collecting that biospecimen. In that biospecimen, we look for molecular markers such as methylation or mutations. Similar to the most recent paradigm shift in colorectal cancer screening, which is that of the stool-based test called Cologuard, we aim to develop a multipanel/multimarker test that will pick up endometrial cancer or endometrial cancer precursors. [This would] allow women to have the diagnosis earlier, ideally, and allow better access to care, because this would be a test or a specimen that could be collected from the comfort of our patient's own bathroom.

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

What role does precision medicine currently play in the community setting?

I just got done giving a talk with Lora Jane Black, [RN, MPH, OCN, CCRP, Sanford Research], and Edward S. Kim, [MD, Levine Cancer Institute, Atrium Health], about community oncology and precision medicine. As anywhere, most patients are treated in the community and understanding precision medicine is important.

There are some unique barriers, including geographic access, infrastructure, and things like that. But every physician needs to know about precision medicine, as it's becoming both standard of care as well as [an] emerging target that we can try to work on and [is] being discussed widely at ASCO. So, this is important information for every oncologist, but it's increasingly becoming important in the community setting.

Does this role differ from that in an academic medical center?

Many of the issues are the same, whether you're at an academic medical center or at the community sites. Some community sites may have people

[who] treat multiple tumor types and aren't specializing in 1 area, where the information is exploding in every area of cancer. There may be a greater need for a systemized, centralized way to approach all [of] this molecular information versus if you're only doing 1 cancer. If you're only doing brain cancers, you may know the mutations that are most important and the information more than someone who's treating every type of cancer available. That's why we have been talking about how do you set up a whole system to track that.

But even in the university settings, that's still a need. One of the limitations is actually genetic counselors. There's not enough to go around, and that's one of the huge areas of need, including doing telemedicine or having clinical trials that bring in genetic counseling for around the whole country.

What are some novel therapies being used in the treatment of hematologic malignancies?

So, there are many examples of this. *BCR-ABL* is the prototypic example of precision medicine used for chronic myeloid leukemia [CML] with tyrosine kinase inhibitors, or TKIs. Acute myeloid leukemia [AML], which had not seen a lot of new therapies for decades, now has targeted therapies versus *Flt3*, versus *IDH2*, and we're developing therapies for acute lymphoblastic leukemia [ALL], including Philadelphia-positive, just like CML.

And then in multiple myeloma, there have been limited reports of BRAF inhibition in myeloma. T(11;14) appears to be a marker for BCL-2 inhibition with venetoclax [Venclexta].

What biomarkers have you identified for deciding on a treatment approach for hematologic malignancies?

The biomarkers for treatment can either be prognostic, which we have a lot of biomarkers, or they can be predictive, which actually tells us that a drug is more likely to work in that area. My colleague has studied t(11;14) as a predictive biomarker in myeloma for effective venetoclax, and then we talked about BCR-ABL for Philadelphia-positive ALL for CML, and there are other emerging ones, so IDH2, *Flt3* in AML.

Increasingly, people are trying to find other markers, which may be targets, and it's somewhat theoretical sometimes, so FGFR in various hematologic malignancies. There's JAK2 inhibition, but other JAK-related pathways, so there's a lot of emerging information. Some of these are in standard of practice. Some are almost becoming standard. And then others are still in the research category of trying to discover and implement new targeted therapies.

Victoria Villaflor, MD, associate professor of medicine (hematology and oncology), Northwestern University

What challenges are associated with trying to pursue precision medicine?

There are multiple challenges. We'll start with the clinician. So, when the physician comes in to see the patient, [there're] so much data [that are] out there, and depending on the environment the physician is seeing the patient in, [that] also dictates some of this. A physician [who] has to know every single tumor type [is not] going to be able to keep up with the massive data and the studies and everything that's coming out for every single tumor type. So, keeping up with the data, integrating it, being able to actually teach the patient about it, and implement[ing] it is one of the great challenges that is out there.

Other challenges are who should we be testing with this, what test should we be doing, and keeping the physician up-to-date with that. [On] the patient's end of things, the willingness to do some of the precision techniques, because they do take time, and also their expectations may be somewhat unrealistic. Things that you have to worry about [are] that the patient says, "Oh great, I have this mutation. I should be responding to X therapy," or perhaps, "My tumor proportion score of PD-L1 is 80. I should have a great response to one of the checkpoint inhibitors," and in fact, they don't.

Studies have shown, with most of these agents, response rates are somewhere in about [the] 50th percentile, maybe 54th percentile. A couple actually go up into the 60 to 70th percentile. But not everybody who should respond is responding, so the expectations can be unrealistic on both the clinicians and the patient standpoint.

As far as testing, that's a whole other ball of wax. You know, we start out with, how do we identify the patients [who] should be getting testing and how do we identify, of those patients, who should be getting treatment and who shouldn't. One of the early examples of this is the Oncotype DX, which is used in breast cancer to determine patients, who have undergone surgery with estrogen-receptor positivity, who should be getting adjuvant chemotherapy. Well, that's only 1 example. How do we pick out other patients who should be being treated and who shouldn't be being treated?

Another example would be: How do we pick out who is going to respond. What test should we be doing? Should they be immunohistochemistry? Should they be fluorescence in situ hybridization–type testing? Should it be something along the lines of next-generation sequencing? Nobody really knows the answer to that, and there are standardization issues. Other issues that occur are: What toxicity tests should we be doing?

Other things could include who should be being tested for germline mutations. We usually [decide on] that if a patient comes in and has many of their family members affected by cancer. But those are the only patients that, right now, we're recommending have germline testing. Are there are other families that we are missing? Other germline mutations we really don't know about yet?

So, I think, overall, it's a very complicated situation, and really determining which patients should get what tests and as to what patients should get what tests is complicated.

Now, when we get to treatment, what are the actual treatments we should be having? Some of it has been well worked out. A lot of it hasn't been. The other thing is, we need to have well-developed molecular marker-driven clinical studies for patients to be enrolled in.

The other things are the master protocols and getting patients to participate in that. And then what about those that are nonresponders? What do we do about them? How do we figure out what the heck is going on with them? So, overall, it's a very complicated and complex problem.

How have novel therapies changed the cancer treatment landscape?

The premise of precision medicine, first and foremost, is to match the right patient with the right treatment at the right time. Immune therapies, or checkpoint inhibitors, have been very successful in a subset of patient with multiple different types of malignancies and has changed their trajectory tremendously.

For example, melanoma has had a very high success rate with the immunologic therapies. As we all know, it's where we started out in. President Jimmy Carter had actually gotten an experimental checkpoint inhibitor for his melanoma, which had traveled to his brain. He has been disease free for a number of years, potentially even cured, which doesn't happen often. But it can happen with these therapies.

Additionally, there are [patients with] lung cancer who have also benefitted tremendously form these therapies. Case-in-point: [There] are patients who have had [a] greater than 50% tumor proportion score of PD-L1. These particular patients tend to have a very strong and lasting response to these drugs. However, it's only about half of these patients who have these parameters.

I think [there are] a lot of questions that still remain unanswered with them. I think they're great therapies, they're here to stay, and they do benefit some of our patients. But my questions still remain: What is the proper sequencing of many of these agents? What should we be doubling them up with? Should we be doubling them up with anything? And why are there patients who, in all rightfulness, should be responding to them and are not? Is it because of their innate immune systems? Is it because of other underlying comorbidities? Is it due to other problems within the microenvironment of these tumors? Even their microbiome, that remains pretty unclear at this time, and I think there's a lot of work to be done.

#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 OS[2]

*Based 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 deletion[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and 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.

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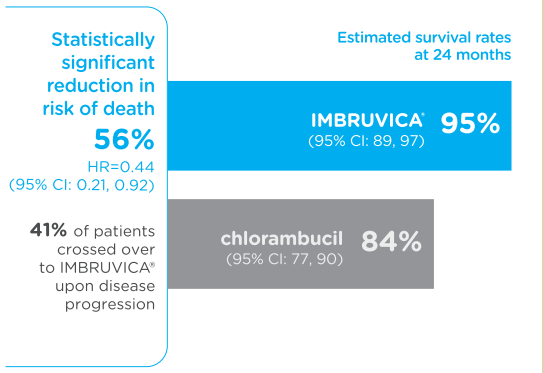
RESONATE™-2 FRONTLINE DATA

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 excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

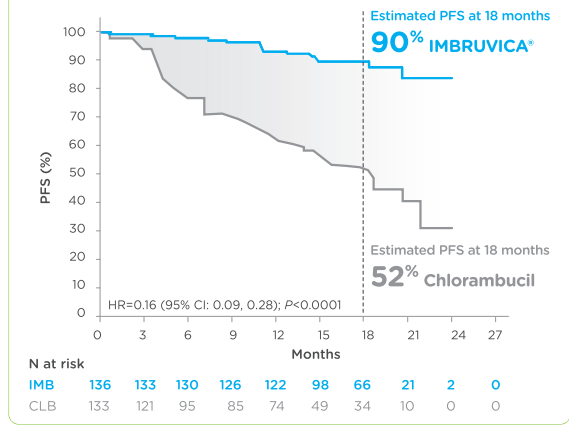


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

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.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

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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.

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

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients 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 Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The 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 Nausea Dyspepsia Stomatitis* Abdominal pain Constipation Abdominal pain upper Vomiting	43 25 19 17 16 14 13 11	5 0 0 2 2 0 0 2
General disorders and administrative site conditions	Fatigue Peripheral edema Pyrexia	44 24 17	6 2 2
Skin and subcutaneous tissue disorders	Bruising * Rash* Pruritus	41 29 14	0 5 0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain* Arthralgia Muscle spasms	40 24 19	3 2 3
Infections and infestations	Upper respiratory tract infection Sinusitis* Bronchitis Pneumonia*	21 19 11 11	0 0 0 10
Metabolism and nutrition disorders	Decreased appetite Hyperuricemia Hypoalbuminemia Hypokalemia	16 16 14 13	2 0 0 0
Vascular disorders	Hemorrhage* Hypertension*	30 14	0 5
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	22 21	2 2
Nervous system disorders	Dizziness Headache	19 13	0 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 Pyrexia Edema peripheral	57 17 12	12 5 0
Skin and subcutaneous tissue disorders	Bruising* Rash*	40 12	0 0
Gastrointestinal disorders	Diarrhea Stomatitis* Nausea Constipation	36 29 26 12	10 2 0 0
Musculoskeletal and connective tissue disorders	Muscle spasms Musculoskeletal pain*	29 14	2 5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia* Upper respiratory tract infection Sepsis*	21 19 10	10 0 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 Dyspnea	14 12	0 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), onychoclasis
- 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].*

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PRC-03818

James Lin Chen, MD, Ohio State University, and chair of ASCO CancerLinQ Oncology Informatics Task Force

How has precision medicine changed the information needs for oncologists and tumor boards?

So, I talked about 5 "rights" of precision medicine today: the right diagnosis, the right test that needed to be made to make a diagnosis, the right targets, the right treatment, and the right monitoring. That all goes along with this. But along these rights for the right treatment for precision medicine are the data sets that underlie it. So, you need prognostic biomarkers, diagnostic biomarkers, monitoring biomarkers.

You also need guidelines in terms of what are the appropriate tests to run in the first place. Precision medicine has really opened up the world of biomarkers to oncologists, and that is, I think, one of the big paradigm shifts.

How does health information technology play a role in obtaining the information needed to make an informed decision for a patient?

In order for precision oncology to be fruitful and to be effective, we need interoperability and we need to be able to share patient data, because the more data that we have that we can aggregate together, the better the better the quality of the predictions we can make. So, predicting for a very small set of patients is going to be prone to error, but if we have a very large set of patients, we're going to be able to make better predictions for who might respond to therapy.

So, in the era of electronic health records, I don't think we're quite there yet, but there's a lot of work that needs to be done from a harmonization standpoint, from an interoperability standpoint, as well as [simple] data standardization. One of the issues that came up today during the talk was that we don't have a common nomenclature on how to capture genes or gene alterations. These standards are being developed and they're starting to be implemented. But they're starting to be implemented. We're not quite there yet from an interoperability point of view.

How has the shift to precision medicine changed the way oncologists think about cancer treatment?

We still need to see the patient, diagnose the patient, figure out what's targetable, and find treatments for the patients. So, that part is still the same and that will probably not change. What has really changed is that precision medicine adds a layer of data to each of those steps, and each of those steps now require a lot more data synthesis. So, in effect, what we have is a data problem. [It's] less about a clinical problem. But how do you manage all this data to help treat your patient?

What is the difference between personalized medicine and precision medicine?

There is a shift from personalized medicine to precision medicine, because if you really think about it, we're really trying to customize medications for a group of patients with a similar feature. For example, if we think about *BRCA1* or *BRCA2* alterations, we think about PARP inhibitors. We're not talking about a particular patient's cancer with that alteration. We're talking about a group of patients who all have that particular gene loss or gene alteration.

I like to think of this as: If you were to try to start a clothing store, for example, if you tried to customize clothing for every single person who came into the store, that's not really feasible or possible with what we have today. Instead, what we're trying to do is find what are the most common alterations, what are the most targetable ones, and create treatments or therapies that really do fit these groups of people.

So, when we talk about precision medicine, we're moving to trying to treat similar groups of patients.

Peter Paul Yu, MD, FASCO, FACP, physician-in-chief, Hartford HealthCare Cancer Center

How have health technologies helped enhance high-quality cancer care and improve outcomes for patients?

So, the great challenge we've always faced is how do we keep pace with the new technologies that are coming down the pipe? Because we're getting so good at developing new technologies, whether it's informatics or it's precision medicine or new drug therapies or diagnostics. Our ability to create these new tools is much faster than our ability to figure out what to do with it, because when you want to measure outcomes improvement, it requires acquisition of the technology, which has certain expense to it. It requires learning how to use it properly, adapting it to its use, and then measuring the outcomes.

There may be many intermediary steps between the technology and actually the outcomes measures, so it's a real difficult question to answer: How have these improved our outcomes? It's really that lack of ability to measure adequately that's slowing us down more than anything else at this time.

Having said that, I think we are seeing real progress with the use of information technology. I think, without question, if you ask most physicians would they rather go back to paper charts, the answer would probably be "no." If you asked patients, would you like to go back to the age where you could not get a patient portal? Find out your lab tests? I mean you always want more, but would you want to go back to the point where you had nothing? People would say, "No, that's not a good idea either."

So, I think that we are frustrated with how slow it goes, but that tends to make us not realize how far we've gone and where we used to be just a short while ago.

How is next-generation sequencing changing the landscape for cancer care?

Next-generation sequencings tests are just starting to change the landscape for [patients with] cancer. We've had quite a bit of FDA and CMS regulations just in the first half of this year, which have begun to lay down the road map for how the FDA will look at laboratory diagnostic tests based on genomics and how [the agency] will go about ascertaining the quality of [those tests] and how CMS is starting to think about how they will decide when they will pay for these tests. So, the fact that we have the 2 major regulatory agencies in the United States starting to set policy is a big step forward.

However, the payment policy issued by the National Coverage Decision by CMS a couple of months ago [March 16, 2018] is extremely narrow. It essentially, as I interpret it, limits it to when there is a specific genomic biomarker match to a specific drug that's been FDA approved. In that circumstance, combined with a patient with advanced cancer, there will be payment for it. But it's still a very, very limited role.

The alternative is that we rely on traditional biomarker testing, which is either a series of sequential tests that consume a lot of sample—and very often you may run out of sample before you've done all your testing—or some limited panel, which is increasingly being looked at as both an inefficient and expensive way of doing genomic testing.

So, I think that it's good news that the FDA and CMS are recognizing that requiring a specific companion diagnostic test for every single drug that is precision medicine-based is no longer the way to go. But we're not quite there yet.

Reporting by Jaime Rosenberg, Mary Caffrey, Kelly Davio, and Christine Potkul

Scalp Cooling System for Chemotherapy-Induced Alopecia Approved for Multiple Solid Tumors

THE FDA HAS GREENLIGHTED an expanded indication for Paxman's cooling cap system in the United States. The medical device company, based in the United Kingdom, announced that the Paxman Scalp Cooling System is now indicated to reduce the likelihood of chemotherapy-induced alopecia in patients with solid tumors, such as ovarian, breast, colorectal, bowel, and prostate cancer.[1]

The system was approved in August 2017 to reduce and prevent hair loss associated with chemotherapy treatment in women with breast cancer.[2] Made from lightweight silicone, the cooling cap is soft and flexible, molding to different head shapes and sizes. Liquid coolant passes through the cap, removing heat from the patient's scalp to ensure it remains at a constant temperature, minimizing hair loss.

According to Paxman, the expanded indication will substantially increase the number of new patients per year who can benefit from the system, from an estimated 250,000 patients with breast cancer to over 1 million with breast cancer or other solid tumors.

Made from lightweight silicone, the cooling cap is soft and flexible, molding to different head shapes and sizes. Liquid coolant passes through the cap, removing heat from the patient's scape to ensure it remains at a constant temperature.

"Scalp cooling has been a real game changer for so many of our patients with breast cancer, minimizing the risk of one of the most dreaded [adverse] effects of chemotherapy," Steven Jay Isakoff, MD, PhD, a medical oncologist at Massachusetts General Hospital in Boston, said in a statement.[1] "Thanks to the recent expanded FDA indication for the Paxman Scalp Cooling System, so many more patients with solid tumors in the US can now consider this option as a safe and effective way to keep their hair during chemotherapy."

Since the system's original clearance, 225 have been installed, and another 65 await delivery and installation.

Highlighting the importance of the affordability of scalp cooling, Richard Paxman, chief executive officer of Paxman, told *The American Journal of Managed Care®* in an email: "We are working hard with health plans and payers to ensure that in the future, this will be covered. However, at present, the majority of patients are paying out of pocket.

"We are seeing positive feedback from a number of commercial payers," he added.

Currently, the cap kit costs patients $500; cycles 1 through 4 are $200 each; cycles 5 and 6, $150 each; and cycles 7 through 12, $100 each. However, the pricing per patient is capped at $2200.

No payer coverage exists for the system yet, but the nonprofit HairToStay helps subsidize the cost for eligible patients: The system is discounted by 25%, and HairToStay covers 60% of the remaining cost.

"HairToStay has had the privilege of subsidizing a growing number of Paxman scalp cooling users for nearly a year now," said Bethany Hornthal, founder of HairToStay, in a statement. "This expanded clearance will increase this wonderful option for patients, and we expect to see a significant increase in demand for scalp cooling and subsidies."[1] ◆

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NCI-Designated Cancer Centers Endorse Goal of Eliminating HPV-Related Cancers

RECOGNIZING A RISE IN the rate of cancers caused by the human papillomavirus (HPV) as a significant public health problem, the nation's top cancer centers have endorsed the goal of eliminating HPV-related cancers.[1]

The joint statement from the 70 National Cancer Institute (NCI)–designated cancer centers underscores the importance of increased HPV vaccination and evidence-based screening, with the goal of eliminating cancers caused by the virus. Completion of the recommended 3 doses of the cancer-preventing HPV vaccine remains low across the nation. According to the CDC, 49.5% of girls and 37.5% of boys ages 13 to 17 completed the series in 2016.[2]

"All 70 cancer centers, representing the nation's leaders in cancer care and research, perceive low vaccination rates as a public health threat and call upon physicians, patients, and young adults to take advantage of this opportunity to prevent several types of cancer in men and women," according to a statement from MD Anderson Cancer Center in Houston, Texas.[3]

In particular, people living with HIV are at an increased risk of developing cancers caused by HPV due to a weakened immune system and a decreased ability to fight viral infections. Because of the higher risk of cervical cancer—often caused by HPV—among women with HIV, it is recommended they be screened regularly for the disease.[4] The CDC also recommends HPV vaccination for both women and men with HIV infection up to age 26.

In alignment with the Healthy People 2020 Initiative, the statement called for:

- Vaccination of more than 80% of males and females ages 13 to 15 by 2020
- Screening of 93% of age-eligible females for cervical cancer by 2020
- Prompt follow-up and proper treatment of females who screen positive for high-grade cervical precancerous lesions[1,3]

It is also encouraged that men and women up to age 26 complete the recommended vaccine series; healthcare providers make clear and strong recommendations for HPV vaccination and cervical screening; and healthcare community members educate parents, guardians, community members, and colleagues about the goal of eliminating HPV-related cancers.

The statement estimates that higher rates of vaccination and evidence-based cancer screening can prevent 12,000 cervical cancers and nearly 40,000 other HPV-related cancers. "Increased HPV vaccination rates combined with appropriate cervical cancer screening measures could soon eliminate cervical cancer, with other HPV-related cancers in males and females to follow," reads the statement.

In addition to the 70 cancer centers, the American Cancer Society, American Association for Cancer Research, American Society for Clinical Oncology, Prevent Cancer Foundation, American Society for Preventive Oncology, and Association of American Cancer Institutes endorsed the statement.

This is the third national call to action from the NCI-designated cancer centers, with the first statement published in 2016. ◆

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Cancer Increases Risk of Developing Type 2 Diabetes, Study Finds

HAVING CANCER BOOSTS A person's chances of later developing type 2 diabetes (T2D), even when risk factors that existed before cancer are taken into account, according to a recent study in *JAMA Oncology*.

Authors of the study, which examined health records of 494,189 people in South Korea for an average of 7 years, said the findings should alert primary care physicians to routinely screen cancer survivors for T2D. The authors speculate that some cancer-fighting drugs increase the risk of developing T2D, including corticosteroids, which are used in many regimens but raise the risk of hyperglycemia. Some chemotherapy agents also elevate blood glucose, they said.

Investigators used data from the National Health Insurance Service–National Sample Cohort, a 2.2% representative sample of the population. Under the country's single-payer healthcare system, Koreans receive a free health screening every 1 to 2 years, when cardiovascular and diabetes risks are assessed.

By tracking diagnostic codes for patients who had been treated for cancer, investigators found a link between having the disease and being at increased risk of T2D, even after controlling for preexisting conditions. During the study period, 15,130 participants developed cancer. Those who did were more likely to be women, drink alcohol every day, have a higher body mass index, and have additional comorbidities. Of this group, the number of incident cases of diabetes seen at follow-up was 834, compared with 25,776 who developed diabetes but not cancer. The overall sex- and age-adjusted hazard ratio (HR) for diabetes associated with cancer was 1.36 (95% CI, 1.26-1.45).

"Increased survival due to advances in cancer diagnosis and treatment is driving the emphasis toward chronic disease and long-term outcomes."

—study authors

Cancer survivors were most at risk of developing T2D within the first 2 years after diagnosis, but their risk level remained elevated throughout the follow-up period. Risk levels varied by cancer type:

Patients with pancreatic cancer had 5 times the risk of developing T2D (HR, 5.15; 95% CI, 3.32-7.99).

Those with kidney cancer had twice the risk (HR, 2.06; 95% CI, 1.34-3.16), and those with liver cancer had close to twice the risk (HR, 1.95; 95% CI, 1.50-2.54).

Elevated risk was also seen among patients with some of the most common forms of cancer, such as lung (HR, 1.74; 95% CI, 1.34-2.24) and breast (HR, 1.60, 95% CI, 1.27-2.01).

Those with blood cancers had a significantly elevated risk (HR, 1.61; 95% CI, 1.07-2.43). Elevated risk was also seen among those who had gallbladder, thyroid, or stomach cancer.

Besides facing the risk of T2D posed by some of the cancer treatments, patients often lose weight and muscle, the authors noted, and many experience a loss of appetite, a condition called cancer cachexia that is associated with increased insulin resistance. Being hospitalized can trigger bouts of stress hyperglycemia.

"Clinical studies in cancer traditionally focus on cancer progression, cancer-related mortality, and treatment-related complications but often neglect long-term consequences of cancer and its treatment," the authors wrote. "Increased survival due to advances in cancer diagnosis and treatment, however, is driving the emphasis toward chronic disease and long-term outcomes." ◆

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Vigorous Exercise May Reduce Mortality in Adult Survivors of Childhood Cancer

IT IS WELL UNDERSTOOD THAT, in the general population, regular exercise is associated with a longer life. But less is known about whether exercise similarly benefits adult survivors of childhood cancer, who may already have an a shortened life expectancymeas because of late effects of treatment, including subsequent malignant neoplasms and cardiovascular disease (CVD). A study published in *JAMA Oncology* sought to evaluate whether vigorous exercise can change mortality in this population.

The authors suggest counseling all cancer survivors to increase rigorous exercise to at least once a week may be a realistic and achieveable goal for a significant number of survivors.

The retrospective cohort study of adult survivors who participated in the Childhood Cancer Survivorship Study (CCSS) followed 15,450 patients who received diagnoses and were treated at 27 locations in the United States and Canada between January 1970 and December 1999.

At baseline and follow-up, enrollees were asked to report how many days in the prior week they had engaged in vigorous exercise (sufficient to result in heavy breathing, sweating, or increased heart rate). The investigators converted self-reported exercise into an average of metabolic equivalent tasks (METs) in hours per week. MET-hours per week were then categorized into 4 groups: 0, 3 to 6, 9 to 12, and 15 to 21.

The investigators found that vigorous exercise exposure greater than 0 MET-hours per week was associated with a significant reduction in the incidence of all-cause, relapse-related, and health-related mortality. At year 15, the group with 0 MET-hours per week had an incidence of all-cause mortality of 11% (95% CI, 10.6%-12.8%). By comparison, the other groups had the following incidence of all-cause mortality:

- 3 to 6 MET-hours per week: 8.6% (95% CI, 7.4%-9.7%)
- 9 to 12 MET-hours per week: 7.4% (95% CI, 6.2%-8.6%)
- 12 to 21 MET-hours per week: 8.0% (95% CI, 6.5%-9.5%)

Compared with the no-exercise group, the adjusted risk ratio (RR) was 0.81 (95% CI, 0.68-0.97) for the group with 3 to 6 MET-hours; 0.82 (95% CI, 0.68-1.00), 9 to 12 MET-hours; and 0.79 (95% CI, 0.62-1.00), 15 to 21 MET-hours. Exercise exposure of 15 to 18 MET-hours per week, which could be divided into sessions of 60 minutes per day, 5 days per week, appeared to be optimal.

Additionally, survivors who increased their exercise over time continued to reduce their risk of mortality; increased exercise exposure over 8 years was associated with an adjusted 40% reduction in the rate of all-cause mortality, compared with maintaining a low level of exercise (RR, 0.60; 95% CI, 0.44-0.82).

The authors say that their findings significantly extend the current evidence base and provide epidemiological evidence to support endorsing exercise for cancer survivors, though they warn that, because observational studies are susceptible to reverse-causation bias, the results must be interpreted with caution. At a minimum, they suggest, the study supports counseling all cancer survivors, as appropriate, to increase participation in vigorous exercise at least once a week, which may be a realistic and achievable goal for a significant proportion of survivors. ◆

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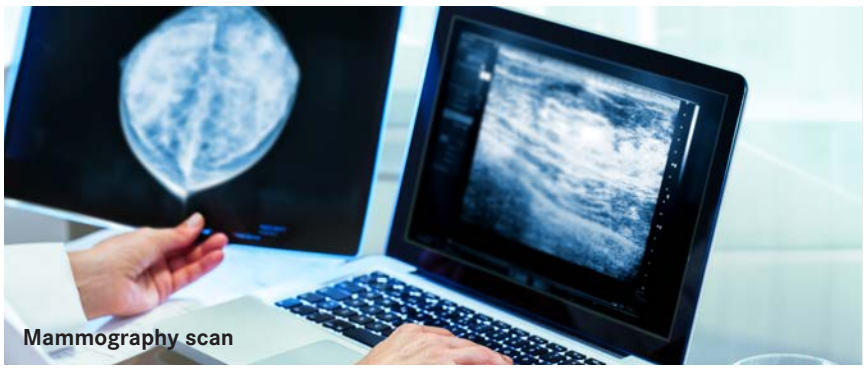
Reporting by Samantha DiGrande


Mammography scan

Link Found Between Mammographies, Other Screenings in Medicare Enrollees

WOMEN WHO UNDERGO MAMMOGRAPHY screenings are more inclined to follow up with other preventive measures, according to new study results. US Medicare claims data gathered between 2010 and 2014 have found that women enrolled in Medicare were more likely to follow preventive guidelines and use those services following a mammography screening. The additional preventive screenings that were evaluated include bone mass measurement, Papanicolaou testing, and influenza vaccination.

For their study, published in *Radiology*,[1] investigators at New York University (NYU) School of Medicine used a sample of women aged 65 years or older. The 555,705 women were sorted into 2 groups: 185,675 (33.4%) patients who received mammogram screenings and 370,080 (66.6%) who did not. The screened group was further divided between false and positive results and then subdivided among false-positive and true-positive patients.

The data were collected via multivariate logistic regression models and inverse probability of treatment weighting to evaluate the relationship between screening status and other preventive tests. Standards from the American College of Radiology were used to categorize results, because these factors play a critical role in the patient experience and willingness to participate in other preventive tests, according to the investigators.

The group of women who initially underwent mammography screenings, having either positive or negative results, had a greater chance of participating in a bone mass measurement (odds ratio [OR], 1.70; 95% CI, 1.63-1.78), Papanicolaou test (OR, 1.49; 95% CI, 1.40-1.58), and influenza vaccination (OR, 1.45; 95% CI, 1.37-1.53) compared with the control group. The study found that women with false-positive screenings showed no difference in their likelihood of undergoing further preventive testing. Also, at screening, false-positive and true-positive findings were found to be the same.

"Screening has the potential to identify early disease that can be curable," said Stella Kang, MD, MSc, assistant professor in the departments of Radiology and Population Health at NYU School of Medicine, in a statement. "It's encouraging to see that women undergoing mammography may have increased awareness to other preventive screening measures."[2] The current study sheds light on the idea of bundling preventive services for women.

The lack of data on the link between mammography screenings and other preventive tests motivated them to do this study, the investigators said. Further research must be done to reveal the association's impact on policy and clinical practices. ◆

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MS Drug Could Reduce Adverse Events Associated With Cancer Treatment

FINGOLIMOD (GILENYA), AN FDA-APPROVED orally administered drug to treat multiple sclerosis, could reduce painful adverse effects (AEs) of multiple myeloma treatments, according to findings recently published in the *Journal of Experimental Medicine*.[1]

Chemotherapy-induced peripheral neuropathy (CIPN), a common and painful AE of many anticancer drugs, can persist for years, reducing quality of life for cancer survivors. Bortezomib (Velcade), which is used to treat multiple myeloma and mantle cell lymphoma, causes CIPN in over 40% of patients, but why this occurs was not previously known.

Investigators from Saint Louis University School of Medicine in Missouri have discovered that bortezomib causes the dysregulation of sphingolipid metabolism in the spinal cord and increases the levels of sphingosine 1-phosphate and dihydrosphingosine 1-phosphate. Higher levels of these molecules can activate S1PR1, a cell surface receptor protein, on specialized nervous system support cells called astrocytes. This results in neuroinflammation and enhanced release of the excitatory neurotransmitter glutamate.

In a preclinical model, rats treated with bortezomib had higher accumulations of sphingosine 1-phosphate and dihydrosphingosine 1-phosphate at the time they started to show signs of neuropathic pain. By blocking the production of these molecules with the fingolimod inhibitor, researchers prevented the animals from developing CIPN and even reversed its effects.

Notably, fingolimod did not inhibit bortezomib's ability to kill myeloma cells. In fact, fingolimod was previously reported to inhibit tumor growth and enhance the effects of bortezomib in vitro and in tumor-bearing animals.[2]

"Our studies provide a compelling case for the consideration of repurposing [fingolimod] as an adjuvant to bortezomib for the prevention and treatment of chemotherapy-related neurotoxicity to address an immense unmet medical need," concluded the study authors. "As [fingolimod] also shows promising anticancer potential and is FDA approved, rapid clinical translation of our findings is anticipated." ◆

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New Immunotherapy Increases Survival Time for Patients With Brain Cancer

TOCAGEN, A CANCER-SELECTIVE gene therapy company, is developing vocimagene amiretrorepvec (Toca 511) and extended-release 5-fluorocytosine (Toca FC), an immunotherapy for patients with recurrent brain cancer. Known as the Toca regimen, the investigational products are being evaluated in a phase 2/3 randomized, multicenter, open-label trial.[1]

The trial is being conducted at 68 sites across the United States, Canada, Israel, and South Korea in patients undergoing planned resection for recurrent glioblastoma or anaplastic astrocytoma. Enrollment is scheduled to be completed by the end of 2018.

After completion of the successful phase 1 study, the Toca regimen showed a favorable safety profile, extended patient survival compared with other therapies, and provided complete tumor shrinkage.[2]

In phase 2/3, patients will be randomized 1:1 to receive either the Toca

regimen or standard of care treatment of single-agent chemotherapy (lomustine or temozolomide) or bevacizumab. The Toca regimen will involve 2 parts. In the first step, patients will receive Toca 511, a replicating virus that selectively infects cancer cells during surgery. The second step requires patients to receive cycles of Toca FC, a potent anticancer pill that kills cancerous cells and activates immune cells selectively to fight off cancerous ones, leaving healthy cells unharmed.[3]

"Toca 5 uses a virus to stimulate a patient's own immune system and attack recurring high-grade gliomas—glioblastoma and anaplastic astrocytoma," said Yaron Moshel, MD, PhD, a neurosurgeon with Atlantic NeuroSurgical Specialists and codirector of the Gerald J. Glasser Brain Tumor Center, the principal investigator for the local arm of the study in a statement.[4]

With the current standard of care treatment, newly diagnosed patients have a median survival 14 to 16 months. After recurrence, this falls to 7 to 9 months, on average.[1] Conversely, phase 1 results of the Toca regimen showed a median longevity of 14.4 months for patients with a recurrence.

"Patients with complete tumor shrinkage are still alive almost 3 years after starting the Toca regimen. These results are encouraging—for patients, their loved ones, and the medical community—and we look forward to sharing further findings from phase 3 within the next 18 months," Moshel said in statement.[2] ◆

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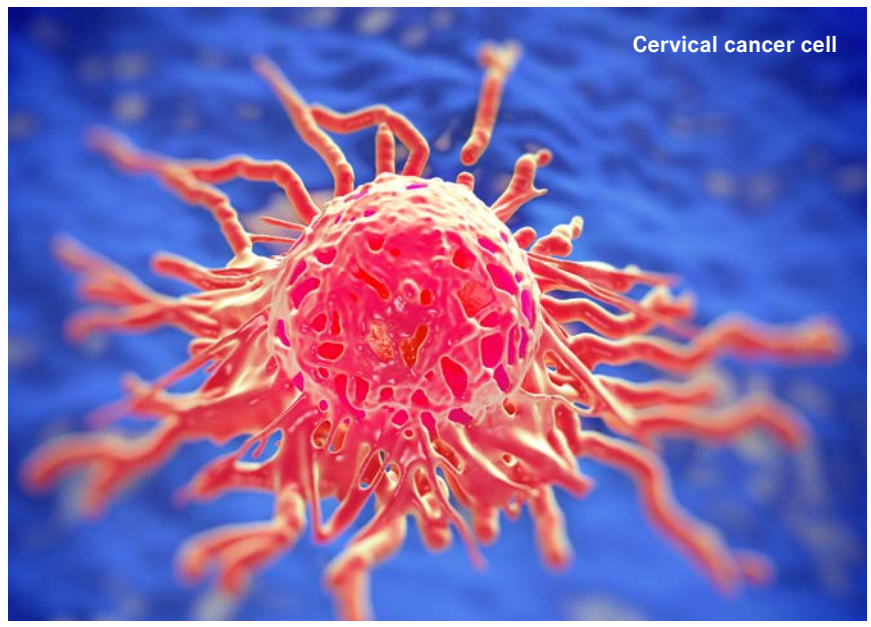
Pembrolizumab Indications Expand to Include Cervical Cancer

THE INDICATIONS OF PEMBROLIZUMAB (Keytruda) now include recurrent or metastatic cervical cancer with disease progression on or after chemotherapy for patients whose tumors express PD-L1, the FDA announced on June 12.[1]

The agency approved this expanded indication following a priority review based on tumor response rate and durability of response. Pembrolizumab's indications include an earlier approval as a first-line treatment in patients with metastatic non–small cell lung cancer, as well as unresectable or metastatic melanoma.

"Keytruda is now the first anti-PD-1 therapy approved for the treatment of advanced cervical cancer, providing an important new second-line option for certain patients with this disease," Roy Baynes, MD, senior vice president, head of global clinical development, and chief medical officer at Merck Research Laboratories, said in a prepared statement.[1] "This approval also marks the first indication for Keytruda in a gynecologic cancer and reflects our ongoing commitment to bring forward innovative treatment options across a broad range of cancers, including cancers that disproportionately affect women."

The approval was based on results from the KEYNOTE-158 trial, in which 98 patients with recurrent or metastatic cervical cancer were enrolled in a multicenter, nonrandomized, open-label, multicohort trial. Participants were treated with 200 mg of pembrolizumab delivered intravenously every 3 weeks until they showed either unsafe levels of toxicity or documented disease progression. Patients without disease progression could be treated for up to



24 months, and a tumor status assessment was completed every 9 weeks for the first 12 months and every 12 weeks thereafter.

Within the trial, 77 patients had tumors that expressed PD-L1, with a combined positive score of 1 or greater. The objective response rate was 14.3% (95% CI, 7.4%-24.1%), with a complete response rate of 2.6% and partial response rate of 11.7%. Among 11 patients who responded, median diagnostic odds ratio was not yet reached (range, 4.1-18.6+ months), and 91% of patients had a response duration of 6 months or longer.

Overall, the most common adverse events (AEs) reported, occurring in at least 20% of patients, were fatigue, musculoskeletal pain, diarrhea, pain and abdominal pain, and decreased appetite. In addition, 8% of patients discontinued treatment due to AEs. Serious AEs occurred in 39% of patients, the most serious of which were anemia, fistula, hemorrhage, and infections.[2]

"Even with the many advances observed across gynecologic cancers, new treatment options have been lacking for previously treated patients with advanced cervical cancer. The approval of Keytruda in this indication is important news—and as an oncologist, [I am excited] to see a much-needed option made available to these patients," Bradley Monk, MD, an oncologist at Arizona Oncology and medical director of US Oncology Research's gynecology program, said in a statement.[1]

The FDA also announced on June 13 that it had granted pembrolizumab accelerated approval for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL) or patients who have relapsed after 2 or more lines of prior therapy. The approval was based on data from 53 patients with relapsed or refractory PMBCL who participated in KEYNOTE-170, a multicenter, open-label, single-arm trial. Pembrolizumab also received orphan product and breakthrough therapy designations for this indication; however, "continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials," according to a statement from the FDA.[3] ◆

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RA Drug May Reduce Toxicity Caused By CAR T Treatment

ALTHOUGH THE DEVELOPMENT OF CHIMERIC antigen receptor (CAR) T-cell therapy changed the landscape of cancer treatment and was named Advance of the Year by the American Society of Clinical Oncology for 2018,[1] the treatment can cause challenging, difficult-to-treat adverse effects, such as cytokine release syndrome (CRS).

Symptoms caused by CRS vary, including rash, fever, and neurotoxicity. Last year, the FDA expanded the treatment indications of tocilizumab (Actemra) from its original designation for rheumatoid arthritis (RA) to include CRS in patients undergoing CAR T treatment. Tocilizumab works by blocking interleukin 6 (IL-6), an inflammatory cytokine. Though oncologists have used this inhibitor with some success in patients receiving CAR T treatment, it doesn't always provide relief from symptoms.[2]

Recently, 2 studies published in *Nature Medicine* reported on another rheumatoid arthritis drug that could help treat CRS.

Symptoms of cytokine release syndrome (CRS) vary, but can include rash, fever, and neurotoxicity. Last year, the FDA expanded indications of tocilizumab from its original designation for rheumatoid arthritis to include CRS in patients receiving CAR T-cell treatment.

The first study[3] investigated the effect of anakinra (Kineret) on patients if administered prior to CAR T therapy. Unlike tocilizumab, anakinra targets interleukin 1 (IL-1) and is able to cross the blood-brain barrier, potentially limiting the toxic adverse effects of CRS. During the study, investigators noticed that IL-1 cytokines were present well before IL-6, and IL-1 actually induced IL-6 production. When the mice being studied were given anakinra, they had significantly improved overall survival, and investigators discovered that targeted intervention against IL-1 may help successfully treat toxicity caused by CAR T-cell treatment.

The second study[4] also investigated the role of IL-1 in connection with CRS. The investigators found that IL-1, IL-6, and nitric oxide produced by recipient macrophages can counteract CRS. The mouse models used also included treatment with anakinra, which was found to be more effective than simply targeting IL-6.

The next step in determining the safety and efficacy of this approach in treating CRS is to study it in human clinical trials. Investigators hypothesized that these results could lead to a CAR T treatment that has an IL-1 inhibitor built into the genetically modified immune cells. ◆

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Genetic Analysis of Thyroid Cancer Suggests Personalized Treatment Possible

UNIVERSITY OF COLORADO CANCER Center investigators have completed the largest study of thyroid cancer genetics to date, the results of which were published in *Clinical Cancer Research.* [1]

The study included data from 583 patient samples of advanced differentiated and 196 anaplastic thyroid cancers (ATC) generated from targeted next-generation sequencing (NGS) cancer-associated gene panels MSK-IMPACT and FoundationOne CDx. Investigators aimed to identify genetic alterations with potential diagnostic, prognostic, and therapeutic significance.[1]

FoundationOne CDx, the first comprehensive companion diagnostic test for solid tumors, made history in December 2017, when it was under parallel review and subsequent approval by both the FDA and CMS. The test helps identify which patients may benefit from on-label targeted therapies. Both FoundationOne CDx and MSK-IMPACT are commonly used for cancer genotyping in clinical practice. By combining data generated by both panels, investigators compiled the largest collection of genetic alterations in advanced thyroid cancer to date.

In their analysis of data from the NGS tests, the study authors found that in several samples of advanced differentiated thyroid cancer and ATC, DNA repair mechanisms were broken and led to a subset of thyroid cancers with a high mutational burden.

The investigators also found specific genetic mutations associated with anaplastic cancers, including amplifications of the *KDR, KIT*, and *PDGFRA* genes. These receptor tyrosine kinases enable cancer cells to reproduce faster and are targeted by lenvatinib, which is FDA approved to treat kidney cancer. Investigators administered this drug to a cohort of participants within the study and found that the cell line that amplified *KDR, KIT,* and *PDGFRA* responded well, suggesting that treatment with lenvatinib could show promising results.

As a clinician, I learn from this study that every patient with advanced thyroid cancer that we consider for systemic therapy should be genotyped—knowledge of genetic background may affect how we treat that patient.

—Nikita Pozdeyev, MD, PhD
Division of Endocrinology, Metabolism, and Diabetes
University of Chicago School of Medicine

Finally, the study identified several genetic alterations that may be vital for developing personalized therapies for thyroid cancer. The amplifications of *CD274, PDCD1LG2, JAK2,* and DNA mismatch repair (MMR) deficiencies have been associated with a positive response to immune checkpoint inhibitors such as pembrolizumab and nivolumab.

"As a clinician, I learn from this study that every patient with advanced thyroid cancer that we consider for systemic therapy should be genotyped—knowledge of genetic background may affect how we treat that patient," the lead study author, Nikita Pozdeyev, MD, PhD, an assistant professor of medicine in the Division of Endocrinology, Metabolism, and Diabetes at the University of Colorado School of Medicine, said in a statement. "There are many drugs targeting many genetic changes that are approved for other cancers, which we would not usually think to use in thyroid cancer. Some of the findings in this paper will potentially change that."[2] ◆

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