ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | FALL 2020

A BEACON OF HOPE

NCODA SHINES THROUGH THE FOG OF COVID-19

NCODA

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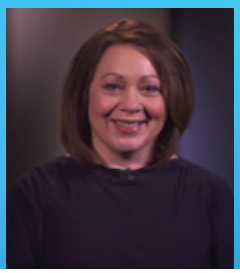

A Practice Manager's Perspective on Quality Initiatives for Patients With Myeloproliferative Neoplasms (MPNs)

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Flemington, NJ

This article, sponsored by Incyte Corporation, is based on a paid interview with Kellie J. Mozingo, RN, which was conducted on October 30, 2019.

> ***"In our experience, quality initiatives inspire staff engagement and help improve the performance of our care teams. The success we have carries over and encourages them to recommend quality initiatives for patients with other types of cancer."***

Quality initiatives for patients with MPNs are important to practice managers

Oncology practice managers have a responsibility to ensure that all of the business, human, and capital resources at our disposal are being managed wisely. This naturally motivates us to seek out ways to improve practice processes while optimizing care for our patients.

Quality initiatives are a great way to help streamline care for patients with MPNs and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1] provide a foundation for implementing quality initiatives for the management of these patients.

Determining which quality initiative to implement

There are many competing priorities within a hematology/oncology practice, so making decisions on which quality initiatives to focus on can be difficult. Therefore, we choose initiatives that have the potential to deliver the biggest positive impact to our patients.

Data we extracted from our electronic health record (EHR) system showed that patients with polycythemia vera (PV) who received a high number of phlebotomies in the last 12 months to help maintain hematocrit below 45% also had frequent symptom complaints. This suggested to us that there might be an opportunity to improve outcomes for patients with PV by improving the processes by which their care is delivered. In our review, we discovered that while phlebotomy may have helped our patients with PV feel better in the short term, their physicians were not familiar with changes in their symptom burden over time and were unaware how often phlebotomies were being administered.

Strategies for implementing quality initiatives for patients with MPNs

Determining which strategy to adopt when implementing a quality initiative may be based primarily on the problem areas identified in an EHR search. Quality initiatives might include, for example, a strategy to ensure risk stratification is performed for all patients with MPNs.[1] Other strategies might include managing cardiovascular risk factors, monitoring patients for new thrombosis and bleeding, monitoring and maintaining blood counts within target ranges, as well as assessing and managing splenomegaly and MPN-related symptoms in all patients. Being over the age of 60 or having had a previous thrombotic event are risk factors to consider when determining the appropriate treatment path for patients with PV.[1,2]

Quality Initiatives for Patients With MPNs May Include Strategies to Ensure:

- **Risk stratification** is performed for all patients with MPNs
- **Cardiovascular risk factors** are managed and patients are monitored for **new thrombosis and bleeding**—especially in patients with PV and essential thrombocythemia (ET)
- **Blood counts** are monitored and maintained within target ranges
- **Splenomegaly** is assessed and managed (occurs most frequently in patients with myelofibrosis [MF])
- **MPN-related symptoms** are assessed and managed in all patients
- **Dosing** is optimized to achieve therapeutic goals for all patients

Our EHR search suggested the need for more rigorous symptom assessment at each visit. The short version of the Myeloproliferative Neoplasm-Symptom Assessment Form (MPN-SAF), known as the MPN-SAF Total Symptom Score (MPN-SAF TSS) or MPN-10, which has 10 questions that query the most representative and pertinent MPN-related symptoms, including fatigue, vascular symptoms, constitutional symptoms, and spleen-related symptoms.[3,4] The MPN-10 is recommended by the NCCN Guidelines® for the assessment of symptom burden at baseline and monitoring symptom status during the course of treatment and is often used in clinical practice.[1] However, we got our information technology department to create a specialized template for us that can be easily populated in a disease-specific manner. Our template is embedded and the data can be easily accessed and tracked over time. It is particularly important to query patients with PV about their symptoms because the signs of progression in PV can be subtle and occur over a longer time frame than among patients with other types of cancer.

Recommendations for the Assessment of Symptom Burden From the NCCN Guidelines[1]:

- Assessment of symptoms at baseline and monitoring symptom status (stable, improved, or worsening) during the course of treatment is recommended for all patients
- The MPN-10 symptom assessment form is recommended for the assessment of symptom burden at baseline and monitoring symptom status during the course of treatment
- Symptom response requires a clinically meaningful reduction in the total symptom score on a patient by patient basis
- Changes in symptom status could be a sign of disease progression. Therefore, a change in symptom status should prompt evaluation of treatment efficacy and/or disease status

Monitoring symptoms can help a physician or any member of the patient's care team recognize disease progression, or when a patient with PV may be transitioning to MF or leukemia. Splenomegaly is a potential indication for starting or changing cytoreductive therapy in patients with PV,[1] and our physicians evaluate spleen size to determine if a treatment plan is working.

During routine patient follow up, it's also important to be vigilant for the clinical characteristics of advanced PV—a hematocrit ≥45% plus either a white blood cell count >11 x 10^9/L or burdensome disease-related symptoms despite treatment with the maximum tolerated dose of hydroxyurea and phlebotomy—which may suggest ineffective disease control.[4-7]

Recommendations for implementing a quality initiative

The first thing I would recommend to other practice managers who are interested in implementing a quality initiative would be to identify and empower leaders in every department who are either caring for patients directly or helping to navigate their care. We found the key to successful implementation was to get buy-in from physicians and the leaders of patient care teams, which includes physician assistants, pharmacists, nurses, care coordinators, and administrative staff. Our patient care teams meet within the first week of implementation and then every 3 to 4 weeks thereafter to monitor patient progress. Pharmacists on our patient care teams play a unique role by performing patient assessments and ordering laboratory tests, among other activities.[8-10]

It's also important to tailor your EHR system so that patients with the same type of MPN diagnosis are asked the same questions, which along with lab values, are consistently documented. Once the EHR is set up to capture patient data, the care teams need to take the time to proactively and regularly monitor patient status.

Lastly, take time to celebrate successes. I fondly recall one particular case during our implementation of a PV quality initiative. This patient had ongoing symptoms and was coming into the office frequently for symptom relief. As a result of the quality initiative, we were able to better evaluate his symptoms and assess the management approach. The patient felt and looked better, and no longer needed regular phlebotomies. He went out more and no longer considered himself to be a recluse.

Tips for Successful MPN Quality Initiatives:

- Identify and empower leaders for implementation
- Tailor your EHR system to accommodate disease-specific information
- Put practice-wide interventions in place to help physicians optimize patient outcomes
- Monitor patient progress regularly
- Celebrate success stories

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed November 21, 2019. 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.** Marchioli R, Finazzi G, Landolfi R, et al. *J Clin Oncol*. 2005;23(10):2224-2232. **3.** Scherber R, Dueck AC, Johansson P, et al. *Blood*. 2011;118(2):401-408. **4.** Emanuel RM, Dueck AC, Geyer HL, et al. *J Clin Oncol*. 2012;30(33):4098-4103. **5.** Marchioli R, Finazzi G, Specchia G, et al. *N Engl J Med*. 2013;368(1):22-33. **6.** Barbui T, Masciulli A, Marfisi MR, et al. *Blood*. 2015;126(4):560-561. **7.** Barosi G, Birgegard G, Finazzi G, et al. *Br J Haematol*. 2010;148(6):961-963. **8.** Nubla J, Dave N, Reff M. *Am J Manag Care*. 2017;23(12 Spec No.):SP500-SP501. **9.** Holle LM, Michaud LB. *J Oncol Pract*. 2014;10(3):e142-145. **10.** Hematology/Oncology Pharmacy Association. Scope of Hematology/Oncology Pharmacy Practice. www.hoparx.org/images/hopa/resource-library/professional-tools/HOPA13_ScopeofPracticeBk.pdf. Accessed November 21, 2019.

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NCODA Cost Avoidance and Waste Tracker

The NCODA Cost Avoidance and Waste Tracker is an online tool created to help practices document the great work they are doing saving money for patients, payers and employers and showcasing the waste produced by outside vendors.

How it works:

Cost Avoidance: Whenever you perform an intervention for a patient that helps prevent an unnecessary Rx from being given to a patient, *record the savings.*

Waste: Whenever a patient brings in medication that was not used at all, *record the information*.

How to use the data:

Share the information with your administration, payers, employers, etc., to showcase the benefits of your practice over mail-order services.

HELP US CREATE CHANGE AND ACCOUNTABILITY FOR HEALTHCARE SPENDING NATIONWIDE!

Cost Avoidance & Waste Reported *To Date* by NCODA Members

Cost Avoidance

$5,679,751

Waste

$7,214,851

To learn more about the tracker tool, please visit www.ncoda.org/CAWT

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NCODA's focus is to advance the value of dispensing practices for oncology physicians. We will provide leadership, expertise, quality standards and sharing of best practices with all members. We will deliver positive outcomes through collaboration with all stakeholders involved in the care of oncology patients.

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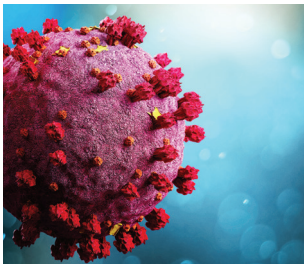

A BEACON AMID THE CHAOS

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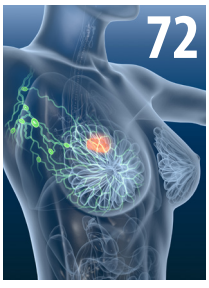

Oncolytics Today

PUBLISHED BY THE
NATIONAL COMMUNITY ONCOLOGY
DISPENSING ASSOCIATION, INC.

FALL 2020 | VOLUME 2, NO. 2

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Oncolytics Today™ (ISSN 2643-2544) is published by the National Community Oncology Dispensing Association, Inc., and is issued semiannually in print and online.

IN DARKEST DAYS OF THE PANDEMIC, NCODA OFFERS A RAY OF SUNSHINE

Before writing this message for the Fall 2020 issue of *Oncolytics Today*, I went back and read the version I wrote this past Spring. Back then, with NCODA growing and new programs being developed and rolled out, it was all blue sky.

All that is still true, but now the dark cloud of the COVID-19 pandemic hangs over us all. The world has become a darker place, with uncertainty around every corner, and no timeline for when things will go back to "normal."

Jim Schwartz

The reality is that there are very large gaps in our understanding of this deadly new virus. Our inability to find any real effective treatment and the time needed to develop effective vaccines has caused many of us to feel uncertain about both the present and the future.

But let's go back to our blue-sky world, which actually still exists in many ways.

Healthcare providers throughout the world are putting aside their fears of the COVID-19 virus, using proper PPE and continuing to care for patients and their families.

And while cancer patients with compromised immune systems are more susceptible to any infectious agent, oncology providers are taking maximum precautions to protect them as they continue treatment regimens that will contain the progression of their diseases.

In times like these, we should focus on the care of those in need of our help rather than worrying about what may or may not happen.

By overcoming this hurdle, healthcare providers — especially those involved in treating cancer along with those on the frontline treating COVID-positive patients — are, indeed, today's heroes.

But then so are support staff, who manage the flow of both patients and critical supplies, especially the now-vital PPE.

And then again, so are our pharmaceutical partners, who have continued their strong support for oncology practices. But now they've altered their method of doing business, accepting the fact that personnel allowed into cancer clinics must be kept to a minimum to decrease the risk to patients and staff.

By working together and putting the needs of others before our own, we will get through this uncertain time and move into a new "normal" way of life.

Through all of this chaos, NCODA has continued to grow.

Our membership now includes more than 2,500 members representing more than 55,000 healthcare providers.

NCODA's website registers thousands of daily visits for our highly effective Oral Chemotherapy Education (OCE) sheets (thanks to our collaboration with the Association of Community Cancer Centers, the Hematology/Oncology Pharmacy Association and the Oncology Nursing Association).

NCODA continues to provide Treatment Support Kits (TSKs) for generic oral oncolytic drugs that no longer have manufacturer kits. TSKs educate patients on the nature of the drug they are taking and provide samples of supportive care drug(s) they may need.

Current generic TSKs available for purchase include abiraterone, capecitabine and temozolomide.

NCODA's Patient Quality Interventions (PQI) documents and PQI in Action articles are being used throughout the oncology community to help healthcare providers manage the treatments and side effects of the drugs they are using.

On the business side of oral oncolytics, there will soon be a document on the NCODA website detailing the nature of Direct and Indirect Renumeration (DIR) fees, with suggestions on how to minimize the financial damage they cause to oncology practices and their patients.

By turning our attention to the good work that continues through this dangerous time, some of our fear and uncertainty can only fall away.

After all, hope is the belief in things not seen, and the certainty of what we wish for. The fact is that we all still persevere in our fight against cancer, and that is a ray of sunshine, even amid the darkest days of the pandemic.

James R Schwartz

James R. Schwartz, RPh

NCODA President, 2019-2020

EXPANDING PHARMACIST PRACTICE WITH A CPA IN ORAL ONCOLYTICS

By Amanda L. Wright, PharmD

The Medically Integrated Dispensing (MID) pharmacy at St. Luke's Cancer Institute (SLCI), formerly Mountain States Tumor Institute, has been an integral part of patient care through the use of oral oncolytics since the success of a resident project in 2010.

Over the last decade, the MID has rapidly grown to serve more than 500 patients treated at the health system's five oncology clinics. Many improvements have been implemented during this time, including the transition to an electronic medical record (EMR).

Amanda Wright

With the transition in 2016 from paper prescriptions to electronic orders in the EPIC EMR, medical oncologists began reaching out to pharmacists for assistance in entering the appropriate treatment plans or adjusting prescriptions for dose changes. Each time an adjustment or renewal was required, a new prescription would be entered and sent electronically to the provider for signature within EPIC.

During the first few months of this transition, the rate-limiting step was identified as waiting for provider signatures for prescription changes or renewals. Not only was pharmacist workflow affected, due to interruptions in the filling process and re-reviewing patient charts for signed prescriptions, but on occasion there were treatment delays as well.

Challenges with timely turnaround of prescriptions led to a resident project focused on the implementation of a collaborative practice agreement (CPA) for oral oncolytics in the MID.

The most common prescription requests were for the following: renewal requests for refills as well as Celgene renewals each cycle, dose rounding to the nearest tablet size, dose adjustments for renal or hepatic function, and requests for labs/tests as part of treatment. These categories became the focus for pharmacist responsibilities for the CPA.

The CPA and the outline for a pilot project were presented to the medical oncologists at the health system's Oncology Pharmacy and Therapeutics (P&T) committee. As a result of the positive relationship between pharmacists and medical oncologists at SLCI, and the added success of an antiemetic CPA, the pilot project for the oral oncolytic CPA was approved.

Four of the 15 medical oncologists served as the pilot group, with the remaining providers acting as the control group. Oral oncolytic prescription changes and renewals in the pilot group were signed by the oncology pharmacists on behalf of the providers per the CPA, while the control group required provider signatures and verification.

After three months of data collection, results showed a turnaround time of 365 minutes for 54 prescriptions in the pilot group. The control group had a total turnaround time of 399,999 minutes for 87 prescriptions. This was found to be a significant difference in the prescription turnaround time with the CPA, an average of seven minutes, in comparison to the control group, an average of 3,311 minutes.

The results from the pilot project were presented to the Oncology P&T Committee and resulted in sitewide approval of the CPA at SLCI. Three more months of data collection showed the impact of sitewide implementation.

The post-CPA implementation phase showed a total turnaround time of 1,190 minutes for 197 prescriptions, an average of six minutes per prescription change.

These results reinforced the impact that implementation of the CPA had on pharmacist workflow and time.

The opportunity for pharmacists to adjust and sign prescriptions in real time has positively impacted patient care at SLCI.

Workflow for both providers and pharmacists has improved with fewer interruptions throughout the day. Providers expressed satisfaction with interventions made by the pharmacists during the pilot and after sitewide implementation of the CPA.

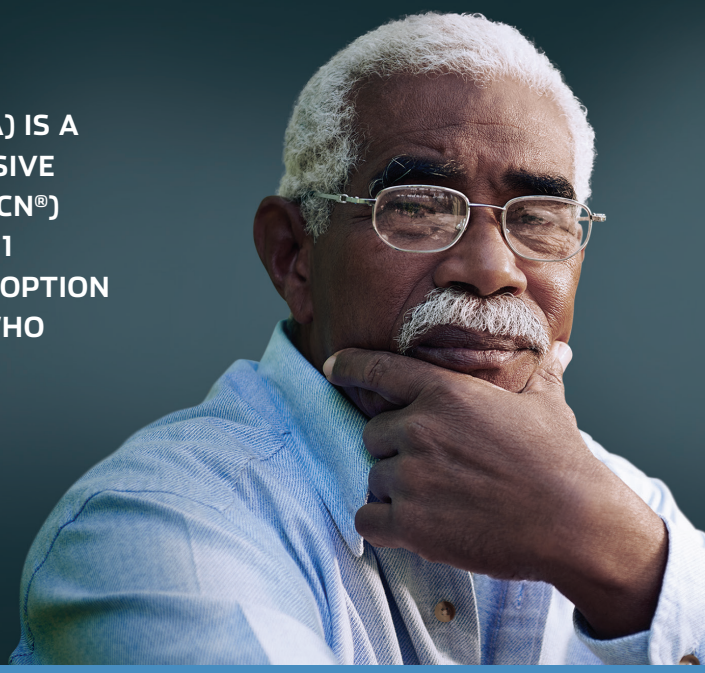
Job satisfaction for pharmacists also has improved as they are able to work at the top of their license with expanded clinical responsibilities. A similar CPA can be implemented in other oral oncolytic MIPs, allowing pharmacists to provide better patient care and expand their pharmacy practice.

▲ **Amanda L. Wright**, PharmD, is a clinical oncology pharmacist at St. Luke's Cancer Institute in Boise, Idaho. **Stephanie Matta**, PharmD, BCOP, and **Julia Kerr**, PharmD, also assisted with this project.

FOR MORE INFORMATION
Scan the QR code to access the full article.

JEVTANA® (cabazitaxel) injection

CABAZITAXEL (JEVTANA) IS A NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) DESIGNATED CATEGORY 1 SECOND-LINE THERAPY OPTION FOR mCRPC PATIENTS WHO PREVIOUSLY RECEIVED DOCETAXEL†



TROPIC[1] Study (n=755)

Validated JEVTANA as a treatment in mCRPC after docetaxel

A randomized, open-label, international, multicenter study of JEVTANA 25mg/m^2 (n=378) vs mitoxantrone 12 mg/m^2 (n=377) in patients with mCRPC previously treated with a docetaxel-containing regimen.

Primary endpoint: overall survival

PROSELICA[1] Study (n=1200)

Established JEVTANA 20mg/m^2 as the recommended dose

25 mg/m^2 can be used in select patients at HCP discretion

A noninferioriy, randomized, open-label, multicenter study of JEVTANA 20 mg/m^2 (n=598) vs 25 mg/m^2 (n=602) in patients with mCRPC previously treated with a docetaxel-containing regimen.

Primary endpoint: overall survival

JEVTANA is the only microtubule inhibitor approved in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen.

IMPORTANT SAFETY INFORMATION

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm^3. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features.

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive premedication. JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

CONTRAINDICATIONS

JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500/mm^3, patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80, and patients with severe hepatic impairment (total bilirubin >3x upper limit of normal (ULN)).

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression (BMS): BMS manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Caution is recommended in patients with hemoglobin <10 g/dl.

Increased Toxicities in Elderly Patients: Patients ≥65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely.

Hypersensitivity Reactions: Severe hypersensitivity reactions can occur. Premedicate all patients with antihistamines, corticosteroids and H2 antagonists prior to JEVTANA. Observe patients closely, especially during the first and second infusions. Discontinue JEVTANA immediately if severe hypersensitivity occurs and treat as indicated.

Gastrointestinal (GI) Adverse Reactions: Nausea, vomiting, and severe diarrhea may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials and mortality related to diarrhea has been reported. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Rehydrate and treat with antiemetics and anti-diarrheals as needed. If experiencing grade ≥3 diarrhea, dosage should be modified.

GI hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding. Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

Renal Failure: Cases, including those with fatal outcomes, have been reported. Identify cause and manage aggressively.

What's next...
what's possible.

Discover the possibilities for your metastatic castration-resistant prostate cancer (mCRPC) patients when prescribed JEVTANA early post docetaxel

Prescribed to over 40,000 men*

The efficacy and safety of JEVTANA were evaluated in the TROPIC and PROSELICA trials. Most recently, results from the CARD study were published in the *New England Journal of Medicine* and presented at the 2020 ASCO GU symposium. Data from the TROPIC and PROSELICA studies are included in the US Prescribing Information.

*Estimate based on US sales & use data. 01/2010-10/2019

CARD[2] Study (n=255)

The first comparative, prospective, phase 4 trial evaluating JEVTANA versus abiraterone or enzalutamide

A randomized, open-label, multicenter study of JEVTANA 25 mg/m^2 vs an androgen receptor (AR)-targeted agent (abiraterone or enzalutamide) in patients with mCRPC who had previously received docetaxel and had disease progression within 12 months on an alternative AR-targeted agent.

Primary endpoint: radiographic progression free survival

SEE CARD RESULTS AT:
JEVTANApro.com/results

Urinary Disorders including Cystitis: Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

Respiratory Disorders: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection. Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

Use in Patients with Hepatic Impairment: JEVTANA dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN) and moderate (total bilirubin >1.5 to ≤3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients. Administer JEVTANA 20 mg/m^2 for mild hepatic impairment. Administer JEVTANA 15 mg/m^2 for moderate hepatic impairment. Monitor closely.

Embryo-Fetal Toxicity: JEVTANA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

ADVERSE REACTIONS (ARs)

The most common all grades adverse reactions and laboratory abnormalities (≥10%) with JEVTANA 20 mg/m^2 or 25 mg/m^2 are neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

DRUG INTERACTIONS

Avoid coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk.
- **Lactation:** The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of JEVTANA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
- **Females and Males of Reproductive Potential:** Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of JEVTANA.

Please see Brief Summary of full Prescribing Information, including Boxed WARNING on following pages.

† Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed March 11, 2020. 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.

1. JEVTANA Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC **2.** De Wit R, de Bono J, Sternberg CN, et al; for the CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019. doi: 10.1056/NEJMoa1911206.

 MAT-US-2017716 08/2020

SANOFI GENZYME

JEVTANA® **Rx Only**
(cabazitaxel) injection, for intravenous use

Brief Summary of Prescribing Information

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm^3. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features *[see Contraindications (4) and Warnings and Precautions (5.1, 5.2)]*.

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive premedication. JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

JEVTANA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of JEVTANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m^2 administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment.

A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider *[see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Clinical Studies (14) in the full prescribing information]*.

Premedicate at least 30 minutes prior to each dose of JEVTANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity *[see Warnings and Precautions (5.3)]*:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed *[see Warnings and Precautions (5.3)]*.

JEVTANA injection single-dose vial requires **two** dilutions prior to administration *[see Dosage and Administration (2.5)]*.

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue JEVTANA dosing for adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA

Toxicity	Dosage Modification
Prolonged grade ≥3 neutropenia (greater than 1 week) despite appropriate medication including granulocyte-colony stimulating factor (G-CSF)	Delay treatment until neutrophil count is >1,500 cells/mm^3, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.
Grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.
Grade ≥3 peripheral neuropathy	Discontinue JEVTANA.

Patients at a 20 mg/m^2 dose who require dose reduction should decrease dosage of JEVTANA to 15 mg/m^2 *[see Adverse Reactions (6.1)]*.

Patients at a 25 mg/m^2 dose who require dose reduction should decrease dosage of JEVTANA to 20 mg/m^2. One additional dose reduction to 15 mg/m^2 may be considered *[see Adverse Reactions (6.1)]*.

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to ≤1.5 × Upper Limit of Normal (ULN) or AST >1.5 × ULN): Administer JEVTANA at a dose of 20 mg/m^2.
- Moderate hepatic impairment (total bilirubin >1.5 to ≤3 × ULN and AST = any): Administer JEVTANA at a dose of 15 mg/m^2 based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin >3 × ULN): JEVTANA is contraindicated in patients with severe hepatic impairment *[see Warning and Precautions (5.8) and Clinical Pharmacology (12.3) in the full prescribing information]*.

2.4 Dose Modifications for Use with Strong CYP3A Inhibitors

Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with these drugs. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full prescribing information]*.

2.5 Preparation and Administration

JEVTANA is a cytotoxic anticancer drug. Follow applicable special handling and disposal procedures *[see References (15) in the full prescribing information]*. If JEVTANA first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water.

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of JEVTANA infusion solution.

JEVTANA should not be mixed with any other drugs.

Preparation

Read this **entire** section carefully before mixing and diluting. JEVTANA requires **two** dilutions prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to overdose *[see Overdosage (10)]*.

Note: Both the JEVTANA injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire contents** of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL JEVTANA.

Inspect the JEVTANA injection and supplied diluent vials. The JEVTANA injection is a clear yellow to brownish-yellow viscous solution.

Step 1 – first dilution

Each vial of JEVTANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the **entire contents** of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEVTANA.

When transferring the diluent, direct the needle onto the inside wall of JEVTANA vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted JEVTANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

Step 2 – second (final) dilution

Withdraw the recommended dose from the JEVTANA solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of JEVTANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Fully prepared JEVTANA infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

Discard any unused portion.

Administration

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the JEVTANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

Use an in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) during administration.

The final JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

4 CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- neutrophil counts of ≤1,500/mm^3 *[see Warnings and Precautions (5.1)]*
- history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Warnings and Precautions (5.3)]*
- severe hepatic impairment (total bilirubin >3 × ULN) *[see Warnings and Precautions (5.8)]*

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

JEVTANA is contraindicated in patients with neutrophils ≤1,500/mm^3 *[see Contraindications (4)]*. Closely monitor patients with hemoglobin <10 g/dL.

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

In a randomized trial (TROPIC) in previously treated patients with metastatic castration-resistant prostate cancer, five patients (1.3%) died from infection (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%). Grade 3–4 neutropenia has been observed in 82% of patients treated with JEVTANA in the randomized trial.

In a randomized trial (PROSELICA) comparing two doses of JEVTANA in previously treated metastatic castration-resistant prostate cancer, 8 patients (1%) on the 20 mg/m^2 arm and 15 patients (3%) on the 25 mg/m^2 arm died from infection; of these, 4 deaths on the 20 mg/m^2 arm and 8 deaths on the 25 mg/m^2 arm occurred within the first 30 days of treatment.

Fewer patients receiving JEVTANA 20 mg/m^2 were reported to have infectious adverse reactions. Grade 1–4 infections were experienced by 160 patients (28%) on the 20 mg/m^2 arm and 227 patients (38%) on the 25 mg/m^2 arm. Grade 3–4 infections were experienced by 57 patients (10%) on the 20 mg/m^2 arm and 120 patients (20%) on the 25 mg/m^2 arm. Noninferiority for overall survival was demonstrated between these two arms *[see Clinical Studies (14) in the full prescribing information]*.

Based on guidelines for the use of G-CSF and the adverse reactions profile of JEVTANA, primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features (older patients, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. The effectiveness of primary prophylaxis with G-CSF in patients receiving JEVTANA has not been studied. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients at increased risk for neutropenia complications.

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed *[see Dosage and Administration (2.2)]*.

5.2 Increased Toxicities in Elderly Patients

In a randomized trial (TROPIC), 2% of patients (3/131) <65 years of age and 6% (15/240) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. Patients ≥65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia. The incidence of the following grade 3–4 adverse reactions were higher in patients ≥65 years of age compared to younger patients; neutropenia (87% vs 74%), and febrile neutropenia (8% vs 6%).

In a randomized clinical trial (PROSELICA) comparing two doses of JEVTANA, deaths due to infection within 30 days of starting JEVTANA occurred in 0.7% (4/580) patients on the 20 mg/m^2 arm and 1.3% (8/595) patients on the 25 mg/m^2 arm; all of these patients were >60 years of age.

In PROSELICA, on the 20 mg/m^2 arm, 3% (5/178) of patients <65 years of age and 2% (9/402) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. On the 25 mg/m^2 arm, 2% (3/175) patients <65 years of age and 5% (20/420) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose *[see Adverse Reactions (6) and Use in Specific Populations (8.5)]*.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm.

Premedicate all patients prior to the initiation of the infusion of JEVTANA *[see Dosage and Administration (2.1)]*. Observe patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. JEVTANA is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.

5.4 Gastrointestinal Adverse Reactions

Nausea, vomiting and severe diarrhea, at times, may occur. Deaths related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Antiemetic prophylaxis is recommended. Treat patients with rehydration, antidiarrheal or antiemetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥3 diarrhea *[see Dosage and Administration (2.2)]*.

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with JEVTANA *[see Adverse Reactions (6.2)]*. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants, and patients with a prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.

Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

The incidence of gastrointestinal adverse reactions is greater in the patients who have received prior radiation. In PROSELICA, diarrhea was reported in 41% (297/732) of patients who had received prior radiation and in 27% (118/443) of patients without prior radiation. Of the patients who had previously received radiation, more patients on the 25 mg/m^2 arm reported diarrhea, compared to patients on the 20 mg/m^2 arm.

5.5 Renal Failure

In the randomized clinical trial (TROPIC), renal failure of any grade occurred in 4% of the patients being treated with JEVTANA, including four cases with fatal outcome. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy *[see Adverse Reactions (6.1)]*. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.6 Urinary Disorders Including Cystitis

Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation *[see Adverse Reactions (6.2)]*. In PROSELICA, cystitis and radiation cystitis were reported in 1.2% and 1.5% of patients who received prior radiation, respectively. Hematuria was reported in 19.4% of patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

5.7 Respiratory Disorders

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome *[see Adverse Reactions (6.2)]*. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection.

Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

5.8 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) *[see Contraindications (4)]*. Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) and moderate (total bilirubin >1.5 to ≤3.0 × ULN and any AST) hepatic impairment, based on tolerability data in these patients *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*. Administration of JEVTANA to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

5.9 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies and its mechanism of action, JEVTANA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose (approximately 0.06 times the C_{max} in patients at the recommended human dose). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*
- Increased Toxicities in Elderly Patients *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Renal Failure *[see Warnings and Precautions (5.5)]*
- Urinary Disorders Including Cystitis *[see Warnings and Precautions (5.6)]*
- Respiratory Disorders *[see Warnings and Precautions (5.7)]*
- Use in Patients with Hepatic Impairment *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

TROPIC Trial (JEVTANA + prednisone compared to mitoxantrone)

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROPIC trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in

JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common (≥5%) grade 3–4 adverse reactions in patients who received JEVTANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received JEVTANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEVTANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVTANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2: Incidence of Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone in TROPIC

	JEVTANA 25 mg/m² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m² every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1–4 n (%)	Grade 3–4 n (%)	Grade 1–4 n (%)	Grade 3–4 n (%)
Any Adverse Reaction				
Blood and Lymphatic System Disorders				
Neutropenia†	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile Neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia†	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia†	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia†	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac Disorders				
Arrhythmia‡	18 (5%)	4 (1%)	6 (2%)	1 (<1%)
Gastrointestinal Disorders				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (<1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (<1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (<1%)
Abdominal Pain§	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia¶	36 (10%)	0	9 (2%)	0
General Disorders and Administration Site Conditions				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (<1%)
Peripheral Edema	34 (9%)	2 (<1%)	34 (9%)	2 (<1%)
Mucosal Inflammation	22 (6%)	1 (<1%)	10 (3%)	1 (<1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections and Infestations				
Urinary Tract Infection#	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Investigations				
Weight Decreased	32 (9%)	0	28 (8%)	1 (<1%)
Metabolism and Nutrition Disorders				
Anorexia	59 (16%)	3 (<1%)	39 (11%)	3 (<1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (<1%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle Spasms	27 (7%)	0	10 (3%)	0
Nervous System Disorders				
Peripheral Neuropathy Þ	50 (13%)	3 (<1%)	12 (3%)	3 (<1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (<1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and Urinary Tract Disorders				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (<1%)
Dysuria	25 (7%)	0	5 (1%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (<1%)
Cough	40 (11%)	0	22 (6%)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular Disorders				
Hypotension	20 (5%)	2 (<1 %)	9 (2%)	1 (<1%)
Median Duration of Treatment	6 cycles		4 cycles	

*Graded using NCI CTCAE version 3.
†Based on laboratory values, JEVTANA: n=369, mitoxantrone: n=370.
‡Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
§Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
¶Includes gastroesophageal reflux disease and reflux gastritis.
#Includes urinary tract infection enterococcal and urinary tract infection fungal.
ÞIncludes peripheral motor neuropathy and peripheral sensory neuropathy.

PROSELICA Trial (comparison of two doses of JEVTANA)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA), 1175 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were treated with either JEVTANA 25 mg/m² (n=595) or the 20 mg/m² (n=580) dose.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m² and 32 (5.4%) patients in the 25 mg/m² arm. The most common fatal adverse reactions in JEVTANA-treated patients were related to infections, and these occurred more commonly on the 25 mg/m² arm (n=15) than on the 20 mg/m² arm (n=8). Other fatal adverse reactions in JEVTANA-treated patients included cerebral hemorrhage, respiratory failure, paralytic ileus, diarrhea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, diverticular perforation, and cardiorenal syndrome.

Grade 1–4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, nausea, diarrhea, asthenia, and hematuria. Grade 3–4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, and febrile neutropenia.

Treatment discontinuations due to adverse drug reactions occurred in 17% of patients in the 20 mg/m² group and 20% of patients in the 25 mg/m² group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m² group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m² group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m² group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m², 19 patients (3%) had a dose reduced from 20 to 15 mg/m² and 1 patient (0.2%) had a dose reduced from

15 to 12 mg/m^2. In the 20 mg/m^2 group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m^2, and 9 patients (2%) had a dose reduced from 15 to 12 mg/m^2.

Table 3: Incidence of Adverse Reactions* in ≥5% of Patients Receiving JEVTANA 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone in PROSELICA

	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=595	
Primary System Organ Class Preferred Term	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**
Blood and Lymphatic System Disorders				
Febrile Neutropenia	12 (2%)	12 (2%)	55 (9%)	55 (9%)
Neutropenia†	18 (3%)	14 (2%)	65 (11%)	57 (10%)
Infections and Infestations				
Urinary tract infection‡	43 (7%)	12 (2%)	66 (11%)	14 (2%)
Neutropenic infection§	15 (3%)	13 (2%)	42 (7%)	36 (6%)
Metabolism and Nutrition Disorders				
Decreased appetite	76 (13%)	4 (0.7%)	110 (19%)	7 (1%)
Nervous System Disorders				
Dysgeusia	41 (7%)	0	63 (11%)	0
Peripheral sensory neuropathy	38 (7%)	0	63 (11%)	4 (0.7%)
Dizziness	24 (4%)	0	32 (5%)	0
Headache	29 (5%)	1 (0.2%)	24 (4%)	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	30 (5%)	5 (0.9%)	46 (8%)	4 (0.7%)
Cough	34 (6%)	0	35 (6%)	0
Gastrointestinal Disorders				
Diarrhea	178 (31%)	8 (1%)	237 (40%)	24 (4%)
Nausea	142 (25%)	4 (0.7%)	191 (32%)	7 (1%)
Vomiting	84 (15%)	7 (1.2%)	108 (18 %)	8 (1%)
Constipation	102 (18%)	2 (0.3%)	107 (18%)	4 (0.7%)
Abdominal pain	34 (6%)	3 (0.5%)	52 (9%)	7 (1%)
Stomatitis	27 (5%)	0	30 (5%)	2 (0.3%)
Skin and Subcutaneous Tissue Disorders				
Alopecia	15 (3%)	0	36 (6.1%)	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	64 (11%)	5 (0.9%)	83 (14%)	7 (1%)
Bone pain	46 (8%)	10 (2%)	50 (8%)	13 (2 %)
Arthralgia	49 (8%)	3 (0.5%)	41 (7%)	5 (0.8%)
Pain in extremity	30 (5%)	1 (0.2%)	41 (7%)	3 (0.5%)
Renal and Urinary Disorders				
Hematuria	82 (14%)	11 (2%)	124 (21%)	25 (4%)
Dysuria	31 (5%)	2 (0.3%)	24 (4%)	0
General Disorders and Administration Site Conditions				
Fatigue	143 (25%)	15 (3%)	161 (27%)	22 (4%)
Asthenia	89 (15%)	11 (2%)	117 (20%)	12 (2%)
Edema peripheral	39 (7%)	1 (0.2%)	53 (9%)	1 (0.2%)
Pyrexia	27 (5%)	1 (0.2%)	38 (6 %)	1 (0.2%)

Table 3: Incidence of Adverse Reactions* in ≥5% of Patients Receiving JEVTANA 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone in PROSELICA (continued)

	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=595	
Primary System Organ Class Preferred Term	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**
Investigations				
Weight decreased	24 (4%)	1 (0.2%)	44 (7%)	0
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	2 (0.3%)	0	32 (5%)	0

*Grade from NCI CTCAE version 4.03.
†Based on adverse event reporting.
‡Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.
§Includes neutropenic sepsis.

Table 4: Incidence of Hematologic Laboratory Abnormalities in Patients Receiving JEVTANA 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone in Study PROSELICA

	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=577		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=590	
Laboratory Abnormality	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**	**Grade 1–4 n (%)**	**Grade 3–4 n (%)**
Neutropenia	384 (67%)	241 (42%)	522 (89%)	432 (73%)
Anemia	576 (99.8%)	57 (10%)	588 (99.7%)	81 (14%)
Leukopenia	461 (80%)	167 (29%)	560 (95%)	351 (60%)
Thrombocytopenia	202 (35%)	15 (3%)	251 (43%)	25 (4%)

Hematuria
In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.
In study PROSELICA, hematuria of all grades was observed in 18% of patients overall.
Hepatic Laboratory Abnormalities
The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.
Gastrointestinal: Gastritis, intestinal obstruction.
Respiratory: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome.
Renal and urinary disorders: Radiation recall hemorrhagic cystitis.

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Cabazitaxel is primarily metabolized through CYP3A *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the

drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose *[see Data]*.

Data

Animal data

In an early embryonic developmental toxicity study in rats, cabazitaxel was administered intravenously for 15 days prior to mating through Day 6 of pregnancy, which resulted in an increase in pre-implantation loss at 0.2 mg/kg/day and an increase in early resorptions at ≥0.1 mg/kg/day (approximately 0.06 and 0.02 times the C_{max} in patients at the recommended human dose, respectively).

In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased postimplantation loss, embryolethality, and fetal deaths when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the C_{max} in patients at the recommended human dose). Decreased mean fetal birthweight associated with delays in skeletal ossification was observed at doses ≥0.08 mg/kg. Cabazitaxel crossed the placenta barrier within 24 hours of a single intravenous administration of 0.08 mg/kg to pregnant rats at gestational day 17. A dose of 0.08 mg/kg in rats resulted in a C_{max} approximately 0.02 times that observed in patients at the recommended human dose. Administration of cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

8.2 Lactation

Risk Summary

The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of cabazitaxel in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats *[see Data]*.

Data

Animal data

In a milk excretion study, radioactivity related to cabazitaxel was detected in the stomachs of nursing pups within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the C_{max} in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of JEVTANA *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal toxicology studies, JEVTANA may impair human fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

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

JEVTANA was evaluated in 39 pediatric patients (ages 3 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m^2 intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid pre-medication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearances by body surface area were comparable to those in adults.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥65 years of age and younger patients. Elderly patients (≥65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients *[see Warnings and Precautions (5.2)]*. The incidence of grade 3–4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. The following grade 1–4 adverse reactions were reported at rates ≥5% higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (97% vs 89%), asthenia (24% vs 15%), pyrexia (15% vs 8%), dizziness (10% vs 5%), urinary tract infection (10% vs 3%), and dehydration (7% vs 2%), respectively.

In the PROSELICA study, the grade 1–4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were diarrhea (43% vs 33%), fatigue (30% vs 19%), asthenia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 3%).

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients <65 years (n=100) and older (n=70).

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance CL_{CR} <15 mL/min/1.73 m^2), should be monitored carefully during treatment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) should have JEVTANA dose of 20 mg/m^2. Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3.0 × ULN and AST = any) was 15 mg/m^2, however, the efficacy at this dose level was unknown. JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) *[see Contraindications (4)]*.

10 OVERDOSAGE

There is no known antidote for JEVTANA overdose. Overdose has resulted from improper preparation *[see Dosage and Administration (2.5)]*. Read the entire section *Dosage and Administration (2)* carefully before mixing or diluting. Complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcome.

In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

CAB-BPLR-SL-MAR20 Revised: March 2020

LINDA FRISK

IRONWOOD CANCER AND RESEARCH CENTERS

Linda Frisk, PharmD, has been a member of the NCODA Executive Council since 2017. Frisk is pharmacy manager for Ironwood Cancer and Research Centers of Phoenix, Arizona.

How did you become involved with NCODA and what prompted you to join its Executive Council?

I was in the process of implementing several Medically Integrated Dispensing (MID) pharmacy sites in Arizona. Since most of my career was spent as a hospital pharmacist and I was currently managing the IV business in an oncology clinic setting, I needed help setting up a quality oral program.

NCODA was just getting started and I was lucky enough to become involved. It has been an exceptional experience to participate in and watch the growth of NCODA. The website is full of very useful information and we can communicate with each other to share information. And now we have quality standards in partnership with the American Society of Clinical Oncology (ASCO) that are patient-centered and guide us to best practices.

Being part of the Executive Council has introduced me to many of the thought leaders in oral dispensing. I have been able to sit in on many NCODA presentations that have increased my knowledge of oral targeted drugs as well as prepared me for audits and other financial issues.

Tell us a little about your expertise and what you bring to the table in helping shape NCODA's strategies.

I was the first pharmacist in Arizona to become a pharmacy manager of a physician owned oncology clinic. We started with six physicians and grew to 60-plus before I left 17.5 years later. During that time, 12 MID sites were implemented in the practice. The experience taught me a lot along the way, allowing me to contribute this understanding to the strategies that NCODA was building.

My current position as pharmacy manager for Ironwood Cancer and Research Centers has added a new depth of MID processes. We have one central MID location and courier to nine other Ironwood clinics. Timely communication with providers and nurses at other sites is critical, especially when oral agents are combined with IV therapies. Clear documentation in electronic medical records (EMR) is required. NCODA has incorporated communication strategies in their quality standards based on discussions with the Executive Council members.

The current payer environment presents challenges both from the perspective of patient care and the business health of the dispensing practice. What changes would you like to see to help improve the quality of patient care?

I do not understand how payers can simply disallow an oral targeted therapy when it is prescribed for its FDA indication. We recently had a patient with a chronic hepatic condition who could not receive a thrombopoietin receptor agonist specifically indicated for adult patients with chronic liver disease because it was not included in the payer's formulary. Then I found out that we could not have dispensed it, anyway, because this particular manufacturer only allows a very small group of mail-order pharmacies to dispense their drug. Both of these challenges need to be improved to benefit our patients.

How can NCODA members (nurses, physicians, pharmacists, technicians, administrators, pharmaceutical partners, etc.) who share your expertise best focus their efforts to improve delivery of oral oncolytics and ultimately improve the level of patient care?

The NCODA website has extensive information on how to improve the patient experience. The Oral Chemotherapy Education (OCE) sheets are an NCODA-led initiative in collaboration with the Association of Community Cancer Centers (ACCC), Hematology/Oncology Pharmacy Association (HOPA) and Oncology Nursing Society (ONS). These OCE sheets provide precise, easy to understand patient education. NCODA's Positive Quality Interventions (PQIs) add increased information on targeted agents and handling of specific adverse reactions.

For sites that want to become accredited, policies are already available to download thanks to the credentialing committee. NCODA's Treatment Support Kits are very helpful in alleviating patient side effects from oral anti-cancer medications.

NCODA faces many daunting challenges in trying to bring forth its message of the efficacy of Medically Integrated Dispensing to a diverse audience that includes providers, payers, legislators and manufacturers. How do we keep that message on target, and how do we measure success?

NCODA's growth to more than 2,500 members has provided a forum for sharing ideas and information. Monthly meetings for all members provide highlights of different practices, drug and disease presentations, and information on various current topics.

Members can all contribute to the Cost Avoidance and Waste Tracker tool to drive home the value of the MID pharmacy model, and this data can also be used with payers to help **Go Beyond the First Fill**.

NCODA's Patient Satisfaction Survey (available in multiple languages) is available to download to help each site measure their MID's success and identify what they can do better for their patients. NCODA has already achieved much success but it takes all of us working together and sharing our stories to continue to spread the value of the MID pharmacy model.

Scan here to learn more about Going Beyond the First Fill.

BIRTH OF AN ORAL ONCOLYTIC

THE QUEST FOR A NEW CANCER DRUG IS NOT FOR THE FAINT OF HEART

By Brett Williams, PhD

With 10 new FDA approvals in the second half of 2019 alone, the toolbox of oral oncolytics is continuously expanding.

These new approvals present patients and providers alike with new therapeutic options, but also bring the challenges of appropriately dispensing these agents and monitoring patient outcomes.

While many oncology providers are aware of the challenges and opportunities that come with each new chemotherapeutic, the tribulations of the discovery and development of these drugs may not be as familiar. Knowledge of the drug discovery process can bring providers and patients a valuable perspective on chemotherapeutics and their properties.

Put simply, drug discovery is not for the risk averse. The journey from concept through the clinic is long (10-15 years), fraught with high cost ($1-3 billion) and low probability of success (12%).[1] Despite the odds, a number of molecules do successfully navigate the maze, earn FDA approval and make it to the patient's bedside.

REWARD EVEN IN FAILURE

For those that do not earn approval, there is still reward even in failure. While both costly and disheartening, the research behind a failed drug candidate still adds to the greater body of knowledge on disease biology and informs future drug discovery efforts.[2]

The birth of an oral oncolytic begins with an intimate knowledge of cancer biology. Physicians, biologists, statistical geneticists and other scientists perform cutting-edge research to find new tactics to destroy malignancies. Their work ultimately culminates in a validated drug target. This is an enzyme or biological process – e.g. kinase, GPCR, ion channel, etc., that when modulated, results in cancer cell death.

PHOTO BY ANDREW CLARK

Brett Williams, Senior Scientist at Tango Therapeutics in Cambridge, Massachusetts, gave a presentation on how oral oncolytics are created during the 2019 NCODA Fall Summit in Orlando, Florida.

Once the biological target is known, chemists and biochemists begin the search for small molecules that preferentially interact with the biological target.

Biochemists first develop robust and scalable assays to test the binding affinity or activity of small molecules. Then, libraries of up to several million compounds are tested for activity in a carefully engineered high-throughput screen (HTS).

SEARCHING FOR 'HITS'

Small molecules that are active in the HTS are called "hits." These hits need to be tested in orthogonal assays to confirm their observed activity in the HTS. Chemical inhibition of off-target biological processes can lead to dose-limiting toxicity, so selectivity of the hits is important and may be assessed early on in a drug discovery program.

Once the hit activity is confirmed, a medicinal chemistry campaign begins. The overall goal of the medicinal chemistry team is to turn these hits into a drug, which requires the interconnected efforts of many scientists including medicinal chemists, biochemists, biologists and pharmacologists.

THE HIT-TO-LEAD PHASE

The first phase of a medicinal chemistry campaign is called "hit-to-lead." Hits require optimization before they can be considered "drug-like." In the hit-to-lead phase, chemists synthesize analogs of the "hits," creating a series of compounds that are assessed in biological assays for their physicochemical properties (e.g., solubility) to determine

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ORAL ONCOLYTIC

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if the chemical matter has the potential to become a drug. If so, then the "hit" series will be labeled a "lead" series and move one step closer to the clinic; hence the name, hit-to-lead.

Once the team has turned hits into leads, a new phase begins – lead optimization (lead op). In lead op, attention turns from increasing potency and selectivity to crafting the chemical matter into a drug.

This process involves optimizing the *in vivo* exposure of the drug (determined in animal pharmacokinetic studies) and assessment of safety with *in vitro* safety assays. Some standard safety assays are cytochrome P450 inhibition or activation (a source of drug-drug interactions), inhibition of hERG (human Ether-a-go-go-Related Gene) activity, which can cause QT prolongation, and activity against a panel of targets and pathways that are known to cause adverse clinical events.

PRECLINICAL TOXICOLOGY STUDIES

The final hurdle for compounds to pass before they enter clinical trials are preclinical toxicology studies. This is an *in vivo* safety assessment in at least two animal species. In these studies, high doses of a small molecule (drug candidate) are given to the animals for an extended period of time (from days to months), and a toxicologist examines the major toxic effects of the small molecule to determine a therapeutic index (efficacious dose/toxic dose).

If the toxicology report and therapeutic index are satisfactory, the small molecule is designated a development candidate (DC) and is ready for clinical trials.

When a development candidate enters the clinic, the baton is passed from the drug discovery team to the clinical team that designs and monitors the evaluation of its safety and efficacy in humans.

THE POINT OF NO RETURN

Extensive work persists throughout the preparation and duration of clinical trials, but it is important to note that the chemical structure cannot be changed once the compound enters the clinic.

The discovery of an oral oncolytic can be filled with scientific, practical and logistical challenges at nearly every phase. Teams of people in many different functions are required to confront and dismantle these hurdles in order to gain FDA approval.

The odds are low, and the timelines are long, but the battles are still hard-fought for the chance to provide new therapies for the oncology community.

PHOTO BY BRETT WILLIAMS

Gabby Cooper, a co-op student from Northeastern University, prepares to set up a chemical reaction at minus 78 degrees Celsius. Cooper set up more than 100 reactions in her pursuit to produce an important compound. The reaction she is setting up here was the key reaction in making a particular compound.

THE STEPS IN DEVELOPING AN ORAL ONCOLYTIC

I. TARGET ID

Biology and statistical genetic research indentifies a target.

II. DRUG DISCOVERY

Chemist/biochemists find chemical matter, than optimizes it into a drug candidate.

III. PRE-CLINICAL DEVELOPMENT

Drug candidate is tested in two animal species for safety.

IV. CLINICAL DEVELOPMENT

Phase I: Assess drug safety in humans, identify maximum tolerated dose (MTD).

Phase II-III: Test for efficacy.

V. APPROVAL

Phase IV: Drug is distributed to patients in need. Safety and efficacy are monitored in patients.

▲ **Brett Williams**, PhD, is Senior Scientist at Tango Therapeutics in Cambridge, Massachusetts.

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NURSING DOCUMENTATION: EFFECTIVE COMMUNICATION AND PATIENT SAFETY

By Mary K. Anderson, BSN, RN, OCN, & Elizabeth Bettencourt, MSN, RN, OCN

Documentation of patient care is a fundamental and critical skill used by nurses to communicate the current status of patients' individual needs and responses to care.

Nurses are responsible for providing safe, quality care and documentation is the means of recording it.[1]

Interdisciplinary communication through concise and complete documentation is essential for patient safety in the oral oncolytic space.[2]

In 2013, the American Society of Clinical Oncology and Oncology Nursing Society updated the Chemotherapy Administration Safety Standards to include the safe administration and management of oral chemotherapy.

These guidelines, most recently updated in 2016, outline the criteria necessary for the documentation of oral chemotherapy management.[3]

The NCODA nursing committee is comprised of 50 oncology nurses dedicated to promoting patient safety and providing resources for optimal management and support of patients taking oral oncolytics.

The committee's most recent initiative involved developing, reviewing and approving a documentation template to assist the user with documentation and communication

Mary Anderson

Elizabeth Bettencourt

of the patient's oral oncolytic.

This tool provides the essential elements recommended in the ASCO/ONS guidelines necessary for quality documentation and communication of essential information with the health care team.

The tool also provides interviewing questions to be used to elicit accurate information from patients about current symptoms, possible toxicities, and adherence to the treatment plan.

A toxicity grading scale, based on the Common Terminology Criteria for Adverse Events (CTCAE)[4] is provided, which includes common AEs experienced by patients taking oral oncolytics such as constipation, diarrhea, fatigue, rash and shortness of breath. This tool enables the user to quickly grade toxicities and coordinate continued management with the provider.

NCODA members may access this resource to use as a template when developing, evaluating or improving their current oral oncolytic program.

▲ **Mary Anderson**, BSN, RN, OCN, is the Oral Oncolytic Nurse Navigator for Norton Cancer Institute in Louisville, Kentucky. **Elizabeth Bettencourt**, MSN, RN, OCN, is the Oral Oncolytic Nurse Navigator for Palo Alto Medical Foundation in Sunnyvale, California.

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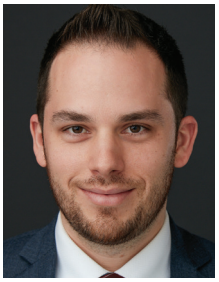
FOR MORE INFORMATION
Scan the QR code to access this resource.

BIOSIMILARS: SAFE, LOWER-COST OPTION TO BIOLOGIC REGIMENS

By Jorge J. García, PharmD, MS, MHA, MBA, FACHE

Over the last several decades, biologics have revolutionized the treatment of serious medical conditions in the U.S. However, the costs associated with these therapies have also increased exponentially over time.

Biosimilars were first introduced in the U.S. in 2015, with the core value proposition of offering the same high-quality biologic products in a biosimilar form, and at a fraction of the cost.



Jorge García

The simplest forms of biologic drugs entered the U.S. market in the 1970s and primarily consisted of blood products and vaccines.

THE BIOLOGICS REVOLUTION

The rise of cloning and gene expression technology enabled biosynthesis of genetically modified organisms, which allowed the production of increasingly complex biologic molecules. This included Genentech's recombinant human insulin in 1982, the first FDA-approved monoclonal antibody and the entry of recombinant monoclonal antibodies in cancer treatment in 1997.[1]

Since then, biologics have revolutionized the treatment of serious medical conditions in the U.S.[2] However, the high cost associated with biologic therapies along with increasing biologic utilization over the years have led to sharp increases in the overall healthcare cost curve.

THE RISE OF BIOLOGICS

Factors increasing biologics utilization include, but are not limited to:

- Population growth
- Increasing number of biologics available
- Improved biologics side effect profile
- Earlier initiation of therapy
- Longer tolerability
- Allowing concomitant lines of therapy
- Improved efficacy
- Improved survival rate & longer duration of therapy
- Improved cure rate
- Biologic utilization for secondary and/or unrelated diseases

As a drug category, biologics show an increasing cost rate relative to overall drug cost. Overall drug cost remains a top public concern in the U.S.

A similar phenomenon took place in the U.S. in the 1980s as drug cost associated with branded, chemically synthesized products reached record highs leading to the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Hatch-Waxman Amendment, which established an approval pathway for generic drugs.

The act enabled an avenue for generic drug competition, becoming one of the most impactful cost savings interventions in the U.S. healthcare system to date.

However, the Hatch-Waxman Amendment did not provide the appropriate regulatory framework to support approval of biosimilars due to marked differences in the development among generics and biosimilars.[1,3]

Generic drugs are developed by following multistep chemical synthesis yielding exact molecular copies of the brand compound. The generic drugs approval process is based on pharmaceutical equivalence and human bioequivalence.

THE RISE OF BIOSIMILARS

Biosimilars are biologic agents that are not chemically identical, but are highly similar to an approved reference biologic, notwithstanding minor differences in clinically inactive components and with no meaningful differences in efficacy, safety and purity.[1]

The Public Health Service Act was amended in 2009 to include the Biologic Price Competition and Innovation (BPCI) Act, also referred to as the 351(k) approval pathway, which created an avenue for an abbreviated licensure pathway for biologics demonstrating biosimilarity or interchangeability to FDA-licensed biologics.[4,3]

It is of important distinction to note that the goal of the 351(k) pathway is not to reestablish primary safety and efficacy of biologic compound – as that has already been established by the innovator company – but rather to demonstrate product is highly similar and/or interchangeable to the reference biologic. This FDA-abbreviated approval pathway is a mainstay for the ability to bring biosimilars to the market at a lower cost.[5]

REVERSE-ENGINEERING

Biosimilars are manufactured following reverse-engineering, in other words, by starting with the final therapeutic protein of interest and working the synthesis steps backwards.[6]

Biosimilars, like other biologics, come from living systems (e.g., bacteria and yeast) and for that reason, it is essentially impossible to consistently produce

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Biologics and Biosimilars

BIOLOGIC

Brand name for a discovered therapy

BIOSIMILAR

Brand that provides essentially the same treatment as Biologic after 20-year patent expires

SIMILARITIES BETWEEN THE TWO

- ✓ Proteins grown, isolated and purified from living cells
- ✓ Complex and expensive to make
- ✓ Grown under strict conditions (temperature, pH, food)
- ✓ Cells programmed to make specific proteins

RESULTS

- ✓ Same protein
- ✓ Work the same way
- X Similar effect but small differences due to variations in growth conditions

WHAT THEY'RE USED TO TREAT

- ✓ Inflammatory arthritis (including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis)
- ✓ Inflammatory bowel disease
- ✓ Anemia (related to cancer treatment)
- ✓ Psoriasis
- ✓ Breast cancer

SOURCE: BIOSIMILARS COUNCIL

BIOSIMILARS

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an identical copy of biologic drugs. Even batches of the same reference product that are produced with the use of the same cell line may be dissimilar.

During product development, different steps in the manufacturing process can lead to molecular differences in clinically inactive components of the drug. Examples include post-translational protein modifications (alterations to the C or N terminals) and glycosylation; a process by which sugar residues are attached to the amino acid chain bearing amino or hydroxyl groups.

These resulting variations are demonstrated to not be clinically meaningful in terms of efficacy and safety during the development and approval process. However, in every case, biosimilars are required to have the same therapeutic amino acid sequence as the reference product.[7]

The ultimate goal of the biosimilar development and approval process is to demonstrate biosimilarity and/or interchangeability; not to reestablish primary efficacy and safety already proven by the innovator company.

Unlike the development pathway for reference biologics, biosimilar development programs focus a great deal of the time conducting analytical studies to understand the physical characteristics of the biosimilar molecule relative to that of the reference product.[4]

THE APPROVAL PROCESS

Once there is sufficient evidence supporting analytical test findings, preclinical and clinical studies are conducted. These include pharmacodynamics (PD), pharmacokinetics (PK) and immunogenicity studies.[2] PD, PK and immunogenicity studies can yield sufficient evidence to support biosimilarity and product approval; however, if the FDA considers there is remaining uncertainly, the agency may require additional clinical studies seeking further confirmatory evidence.[4,8]

Molecular variability or "drift" is expected in both reference biologics and biosimilars and this drift is not necessarily due to error. Because biologics come from living systems, and not from a controlled chemical synthesis as is the case of generics, product variability is inevitable.[4,7,8]

All biologics are highly sensitive to many factors, including changes in manufacturer and production scale. The FDA requires manufacturers to have a product comparability quality plan for each biologic product in order to monitor product drift over the life of the biologic. This monitoring plan calls for routine continuous batch analyses, which establish comparisons based on product historical data to assess degree of variability.

Biosimilar approval requires submission of analytical comparability that is much more extensive and in-depth compared to original producers after production process changes post regulatory approval.[1,2]

BIOSIMILAR INDICATION EXTRAPOLATION

Biosimilar approval studies are designed to demonstrate biosimilarity in the indication with the most sensitive patient population. Through the process of extrapolation, biosimilars can be licensed for one or more additional indications of the reference biologic without the need for repeat clinical trials in each indication; however, such designation isn't automatic and is based on assessment of scientific justification for each indication.

Scientific justification may include,

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BIOSIMILARS

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but is not limited to, assessment of mechanism of action, biodistribution, expected toxicities and immunogenicity, all relative to the different indications.[7] Therefore, extrapolation may avoid unnecessary clinical studies in all indications of the reference biologic, also helping reduce the burden on patients.[9]

Furthermore, extrapolation helps reduce sponsors' development cost, and is critical to ensure biosimilars can be marketed at the lowest viable price.[2] These gains in product development efficiency may also translate into more resource allocation to other areas such as research and development to help produce new innovative drugs.

The FDA approvals to date lean toward complete or near-complete extrapolation; however, from a non-clinical perspective, it is important to recognize that active reference product patents many times hinder the biosimilars' ability to achieve complete label indications.[3] As of September 2019, no approved biosimilar has been denied an indication due to safety or efficacy concerns.

Lastly, there is now over a decade of real-world evidence showing a good biosimilar track record, including utilization of these agents in extrapolated indications. This makes extrapolation fundamentally vital to allow biosimilars to come to the market at the lowest viable cost.[2,10]

INTERCHANGEABILITY

To date, the FDA has not deemed any biosimilar interchangeable.[8] If interchangeability is established for a biosimilar in the future, pharmacy substitution would still be subject to individual state pharmacist drug substitution requirements.[7]

However, regulatory bodies at the institutional setting level, such as the health system's Pharmacy and Therapeutics (P&T) Committee, can establish internal interchangeability protocols to enable independent pharmacy product substitution.[8]

To a degree, payers at the national level are treating biosimilars as interchangeable, as many have benefits design and coverage policies that call for either the reference or biosimilar as a preferred therapy option.

In 2019, the FDA finalized its Biosimilar Interchangeability Guidelines, detailing study design and full requirements for manufacturers that pursue biosimilar interchangeability status. However, given existing avenues to establish internal institutional substitution protocols and given the current high level of payer autonomy on therapy preference at the national level, it is not known if biosimilar sponsors would be willing to invest additional resources to achieve FDA interchangeability designation.[11]

POST-MARKETING SURVEILLANCE

Pharmacovigilance is critical for all drugs to further establish their efficacy and safety profiles. With biosimilars emerging in the U.S., it is critical to continuously assess the efficacy and safety properties of these products.

Pharmacovigilance reporting is generally challenging due to the fragmented nature of healthcare in the United States. Pharmacovigilance reporting in the biosimilar setting introduces new challenges in terms of nomenclature and effect attribution.

With biosimilar and new biologics nomenclature calling for a four-letter, meaningless suffix, biosimilar reports can potentially be erroneously attributed to the reference product if the suffix is not included in the report.

In addition, reports in patients using the reference and the biosimilar interchangeably can be difficult to attribute to the reference or biosimilar due to overlapping product half-life.[8]

With the first biosimilar being introduced in the U.S. market in 2015, today we benefit from an exponentially increasing amount of clinical evidence that signals a strong track record for biosimilar as a broad drug category in the U.S. and abroad.[4]

This includes no evidence of biosimilar market removal due to efficacy or safety concerns. Moreover, with more patients utilizing biosimilars specifically in the extrapolation and product interchanged setting, we continue to grow the body of real-world evidence that helps us better understand the long term effects and outcomes in this setting.[11,10]

BARRIERS TO MARKET ENTRY

Biosimilars have faced strong barriers to market entry globally, but especially in the U.S. Barriers are encountered both through and during the development and approval process as well as post-marketing. Examples prior to marketing include patent litigation, prolonging biosimilar availability for months to years, and lack of originator company cooperation providing reference product samples necessary for biosimilar development.[6,12]

However, the strongest headwinds often times take place post biosimilar product marketing, and these include many such as provider reluctance, insufficient education, lack of payer coverage, reimbursement, operational implementation

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DEMONSTRATING BIOSIMILARITY

Examples of Analytical Methods

- Mass spectrometry
- Peptide mapping
- Protein concentration
- Proliferative bioassay
- Fluorescence
- Edman sequencing
- Analytical ultracentrifugation

Examples of Attributes

- Amino acid sequence
- Potency
- Strength
- Receptor binding
- Molar mass
- Oxidation
- Deamidation
- Secondary and tertiary structures

BIOSIMILARS

CONTINUED FROM PREVIOUS PAGE

and other issues. According to survey data, biosimilars' lack of payer coverage and reimbursement is among the top three barriers to implementation.

Biosimilars are intended to be market disruptors, with the goal of increasing competition — among reference and other biosimilars — thereby lowering cost. In an attempt to stop or slow down this market evolution, many originator companies have focused their counter strategies on competitive rebating practices that can maintain or elevate payer formulary positioning of their products. These arrangements many times take place just prior to the launch of a biosimilar.

As a result, payer policies may call for utilization of the reference product — at a premium cost to patients and providers — thereby blocking access to lower cost biosimilar(s).[6,3] Payer formulary positioning isn't new; however, the practice introduces added scrutiny in the biosimilar setting as it can boldly violate the principle of "cost-effectiveness" and the general provider commitment to exercise judgement to provide the most effective therapy relative to cost, and other factors.

In addition, Medicare, Medicaid and commercial payers have all taken a different approach to biosimilar reimbursement, making it very challenging for practices to understand the financial implications of a biosimilar adoption prior to implementation.

Similarly, during post-implementation, many practices lack the ability to dissect claims to accurately assess biosimilar payment. This hinders pharmacy leaders' and other institutional proponents' ability to make a comprehensive financial case for biosimilar adoption.

Today, there are pronounced inconsistencies with regard to payer reference and biosimilar coverage, making it necessary for practices to carry a wide variety of products. This has introduced great logistical challenges for practices from a safety and a product inventory standpoint, but also from a reimbursement standpoint.

Healthcare professionals have a duty to evaluate the safety and efficacy of biosimilars, and enable biosimilar utilization where there is evidence supporting biosimilarity.

In order to ensure appropriate reimbursement, practices have to tailor each dispensation to the plan's coverage policy. This requires a great deal of coordination at the level of each dispensation between the prescribing provider, the authorization team, pharmacy, nursing and others. Any failure points in this routine and laborious process can lead to reimbursement denial.[13]

Payer landscape evolution is needed to support a more stable and long-term sustainable biosimilar pharmacoeconomic model. Such a model needs to support trickle down economics that provide a benefit to all involved stakeholders, including patients and the providers.

The generic market has achieved this, and remains a long-term sustainable model for all stakeholders involved, and in many respects, can help us pave the path to a more just biosimilar economic model.[8,10]

Biosimilars provide a very strong value proposition to help mitigate the increasing cost of healthcare. However, to reap that economic benefit, biosimilars must be used. Healthcare professionals have a duty to evaluate the safety and efficacy of biosimilars, and enable biosimilar utilization where there is evidence supporting biosimilarity.

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TREATMENT SUPPORT KITS PROVIDE PROVEN VALUE TO PATIENTS, PROVIDERS AND PRACTICES

NCODA's Treatment Support Kits (TSKs) provide a tremendous, proven value to not only cancer patients undergoing oral chemotherapy, but also to the providers and practices caring for them.

The kits, which include supportive medications for potential side effects coupled with easy-to-understand instructions and user-friendly adherence tools, help reinforce both patient education and compliance.

"They're especially great when the nurses are providing education," said Donnell Hale, BSN, RN, OCN, Manager of Nursing Services at Texas Oncology, an early adopter of TSKs.

"In the exam room, we walk through each item with the patient," Hale said. "As we go through the symptoms they're going to have, the patient is referencing the items in the treatment kit: thermometer, creams, loperamide."

"This is important because it can be overwhelming when patients first get their diagnosis. TSKs are a great way to be sure they are absorbing the information. They know what to use when a side effect happens, and when to call us if it isn't being controlled."

Support kits were once part and parcel with the introduction of new oncolytics. But as generic formulations began entering the market, the kits became less of priority for the manufacturers.

That gap has now become a major challenge for many practices, noted Jim Schwartz, RPh,Texas Oncology's Executive Director of Pharmacy Operations.

"When a drug goes generic, it's a benefit to the patient," Schwartz explained. "Allegedly the co-pay should be less, but it leaves a big clinical and educational gap because they don't have that starter kit. Yet we rely on those kits for all oral oncolytic drugs, generic or not."

Enter NCODA, an FDA-approved kit manufacturer, which launched its first TSK in 2019 for capecitabine.

Patient response has been overwhelmingly positive. During beta testing of NCODA's capecitabine TSK, 90% or more of the patients surveyed found the kits to be high quality, with useful products and education. More importantly, 90% of those surveyed use the kit products on a weekly basis.

Yet the value doesn't end with the patient. TSKs also provide savings in both time and financials for providers and their practices.

"The financial benefit is there, especially when you compare the cost of the kit to the cost of treating the side effects, whether hand-foot syndrome or dehydration due to massive diarrhea," Schwartz said.

President and Chairman of Texas Oncology Roy Paulson, MD, agreed. "The cost of the kit is trivial compared to the value," he said.

NCODA CAPECITABINE TREATMENT SUPPORT KIT AT A GLANCE

This TSK includes:

- A comprehensive treatment booklet including a welcome letter, contents overview, an Oral Chemotherapy Education (OCE) sheet on capecitabine;
- A customized treatment calendar;
- Twelve 2 mg caplets of loperamide;
- A digital thermometer;
- A large pill container designed for twice-daily regimens; and
- Flexitol skin and lip care products: 4.4 oz. of Very Dry Skin Cream (12.5% urea), 2 oz. of Heel Balm (25% urea) and 0.35 oz. of Lip Balm (steroid-free).

Each kit bears the logo of the respective practice on its bag.

The capecitabine TSK is $22.95 per kit (includes free shipping).

Upcoming Treatment Support Kits:

- Abiraterone acetate and temozolomide TSKs are now available for pre-order. Cost is $13.25 per kit (includes free shipping).

For more information, visit www.ncoda.org/treatment-support-kits

TREATMENT UPDATES FOR ADVANCED GASTROINTESTINAL STROMAL TUMOR

By Kayla Randle, PharmD, BCOP

Gastrointestinal stromal tumors (GISTs) are the most common soft tissue sarcomas of the gastrointestinal (GI) tract with an estimated 4,000 to 6,000 GIST cases diagnosed in the U.S. each year.

GISTs can occur in any location along the GI tract, but are most commonly diagnosed in the stomach and proximal small intestine.[1,2] An estimated 10-25% of GIST patients will present with unresectable or metastatic disease, and up to 40% of patients with initially resectable GIST will experience recurrence with metastases.[3,4]

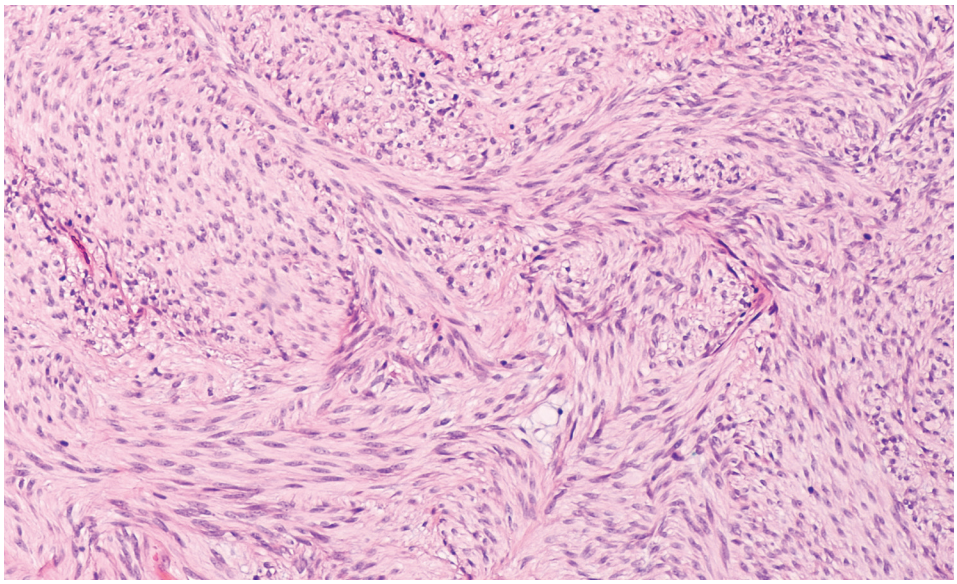
Kayla Randle

Overexpression of the KIT receptor tyrosine kinase, or mutation in the c-Kit protooncogene, drives tumor growth in 70-80% of GIST cases. Mutation of platelet-derived growth factor receptor alpha (PDGFRA) has also been linked to GIST proliferation in roughly 5-10% of cases.[5]

The advent of tyrosine kinase inhibitors (TKIs) specifically targeting KIT and PDGFRA revolutionized the treatment of GIST.[6,7] Mutations of KIT and PDGFRA are known to cause primary and secondary treatment resistance, and National Comprehensive Cancer Network (NCCN) guidelines strongly recommend genetic testing for KIT and PDGFRA mutations if TKIs are part of the treatment plan for patients with GIST.[8]

FIRST-LINE TREATMENTS

Imatinib, which inhibits both KIT and PDGFRA, is the NCCN recommended first-line treatment for unresectable or metastatic GIST.[8] Primary resistance to imatinib occurs in approximately 15% of GIST patients.



A microscopic image of a gastrointestinal stromal tumor (GIST).

The PDGFRA exon 18 D842V mutation, which is the activating mutation in over 60% of PDGFRA-related GIST cases, is known to cause primary imatinib-resistant disease.[9]

Another 80% of patients will experience disease progression following an initial response to imatinib therapy.[10]

Sunitinib, approved for imatinib-resistant GIST, and regorafenib, approved for disease that has failed imatinib and sunitinib, represent the NCCN recommended second and third-line treatment options for unresectable or metastatic GIST.[8]

While these agents may delay disease progression between one to five months, on average, development of treatment resistance is inevitable and likely driven by secondary gene mutations.[7] For example, the KIT exon 17 D816V mutation is estimated to account for up to 50% of GIST with acquired imatinib-resistance, and it has also been linked to the development of sunitinib resistance in previously responsive disease.[9]

In Spring 2020, two novel TKIs for the treatment of advanced GIST were approved. Both drugs target KIT and PDGFRA, including mutant variants that have been linked to resistant disease.

AVAPRITINIB

In January 2020, avapritinib was FDA approved for first-line treatment of unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V. Aside from D842V, avapritinib also targets different mutant forms of KIT including the exon 17 D816V mutation.

Results from the phase I NAVIGATOR trial lead to avapritinib's approval. Forty-three patients with PDGFRA exon 18 mutant GIST, including 38 patients with the D842V mutation, received oral avapritinib once daily.

Initially, avapritinib was administered

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GIST

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at a dose of 400 mg daily, however, the dose was later decreased to 300 mg daily due to a high rate of central nervous system toxicities.

Overall response rate (ORR) was 84% with 7% of patients achieving complete response (CR) and 77% exhibiting a partial response (PR). In patients with the D842V mutation specifically, ORR was 89% (8% CR, 82% PR). Sixty-one percent of patients overall, and 59% of patients with the D842V mutation, experienced a duration of disease response lasting longer than six months.

The most common adverse events included edema, nausea, vomiting, diarrhea, fatigue and cognitive impairment, including memory impairment, amnesia, mental status changes, encephalopathy, dementia and abnormal thinking.

Common laboratory abnormalities included anemia, leukopenia and increased bilirubin. The prescribing information for avapritinib includes a warning for central nervous system effects including cognitive impairment, dizziness, hallucinations and disorders of sleep, mood and speech. GIST patients to be treated with avapritinib would need confirmation of PDGFRA mutation status via an appropriate assay.[11]

RIPRETINIB

Ripretinib was approved by the FDA in March 2020 as a fourth-line treatment of advanced GIST in adults who have received at least three prior TKI-based therapies, including imatinib. Ripretinib binds to both KIT and PDGFRA in their wild type and various primary and secondary mutant forms.

Approval was based on results from the phase III INVICTUS trial which compared ripretinib 150 mg or matching placebo administered once daily. The trial included 129 patients, 85 in the ripretinib group and 44 in the placebo group, with unresectable, locally advanced or metastatic GIST who had previously been treated with at least imatinib, sunitinib and regorafenib.

The treatment of unresectable and metastatic GIST relies on targeting KIT and PDGFRA via TKI-based therapy. Avapritinib and ripretinib represent two new treatment options for patients with advanced GIST.

A statistically significant improvement in progression-free survival (PFS), the trial's primary endpoint, was shown in the ripretinib group with an 85% reduction in progressive disease compared to placebo (HR 0.15; 95% CI: 0.09, 0.25; P < 0.0001). Median PFS was 6.3 months versus one month in the ripretinib versus the placebo arms, respectively. Reported median overall survival was 15.1 months in the ripretinib group versus 6.6 months in the placebo group, though the study was not powered to detect statistical significance of this endpoint (HR 0.36; 95% CI: 0.21, 0.62).

The most common adverse events seen in patients receiving ripretinib included alopecia, fatigue, nausea, abdominal pain and myalgia.[12]

MOVING FORWARD

The treatment of unresectable and metastatic GIST relies on targeting KIT and PDGFRA via TKI-based therapy. Avapritinib and ripretinib represent two new treatment options for patients with advanced GIST.

Pharmacists can play a key role in treatment optimization with either of these agents via appropriate patient selection, based on mutational status and/or place in therapy, medication counseling, adherence monitoring and symptom management.

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When treating non-metastatic castration-resistant prostate cancer (nmCRPC),

METASTASIS-FREE SURVIVAL IS JUST THE HALF OF IT

NUBEQA®—Focus on both survival* and tolerability[1-3]

40 MONTHS

More than double the median MFS with NUBEQA + ADT† vs 18 months with ADT alone‡

(HR: 0.41; 95% CI: 0.34-0.50; *P*<0.0001) †95% CI: 34.3-NR. ‡95% CI: 15.5-22.3.

PROVEN TOLERABILITY

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%)§

SAME RATE OF PERMANENT DISCONTINUATION

9% of men permanently discontinued due to adverse reactions whether on NUBEQA + ADT or ADT alone

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT.

The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%). The most frequent reasons for dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). The most frequent reasons for dose reductions included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

NUBEQA®—proven to extend MFS, now supported by statistically significant OS[1,3]

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone[3]

***Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.** At first analysis, OS data were not mature (57% of the required number of events). At final analysis, OS was statistically significant; HR: 0.69 (95% CI: 0.53-0.88), median not reached. *P*=0.003.[1,3]

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, ^{99m}Tc bone scan by BICR, unacceptable toxicity, or withdrawal.[1,2]

§All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

Final analysis data now available

Visit NUBEQAhcp.com

INDICATION

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity: Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

Clinically significant adverse reactions occurring in ≥ 2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo).

Drug Interactions

Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NR=not reached; GnRH=gonadotropin-releasing hormone; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging; AST=aspartate aminotransferase.

NUBEQA® (darolutamide) 300 mg tablets

Please see the following page for brief summary of full Prescribing Information.

NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology (12.1)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

Table 1: Adverse Reactions in ARAMIS

Adverse Reaction[2]	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades ≥ 3 %	All Grades %	Grade ≥ 3 %
Fatigue[1]	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash	3	0.1	1	0

[1] Includes fatigue and asthenia

[2] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

Laboratory Abnormality	NUBEQA (N=954)[1]		Placebo (N=554)[1]	
	All Grades[2] %	Grade 3-4[2] %	All Grades[2] %	Grade 3-4[2] %
Neutrophil count decreased	20	4	9	0.6
AST increased	23	0.5	14	0.2
Bilirubin increased	16	0.1	7	0

[1] The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

[2] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure *[see Clinical Pharmacology (12.3)]* which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed *[see Dosage and Administration (2.2)]*.

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy *[see Clinical Pharmacology (12.1)]*. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m^2) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function *[see Clinical Pharmacology (12.3)]*.

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose *[see Dosage and Administration (2.1)]*.

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy *[see Use in Specific Populations (8.1)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

Infertility

Advise male patients that NUBEQA may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland
Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

6711000BS1

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. **2.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246. **3.** Fizazi K, Shore ND, Tammela T, et al. Overall survival results of the phase III ARAMIS study of darolutamide added to androgen deprivation therapy for non-metastatic castration-resistant prostate cancer. Presented at: 2020 ASCO Annual Meeting; May 29-31, 2020.

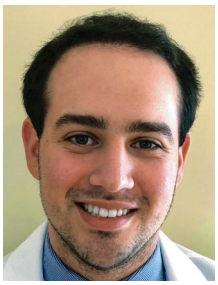
NCODA APPE PROVIDED A SAFE, UNIQUE LEARNING EXPERIENCE

By Connor Longo, PharmD

To be honest, up until recently I didn't know all that much about NCODA, or even Medically Integrated Dispensing (MID).

But the COVID-19 pandemic helped change all that.

Originally, as part of the curriculum at the University of Rhode Island College of Pharmacy, I was scheduled to take part in a standard health systems Advanced Pharmacy Practice Experience (APPE).



Connor Longo

But with the coronavirus pandemic ramping up around the start date of the APPE, the health system organization and school made a joint decision to provide a safer experience through a remote rotation.

The NCODA APPE turned out to be the perfect solution to this dilemma; the program offered a unique experience from a safe distance.

When asked if I had ever heard of NCODA before or knew what MID was, all I remember was that I had heard of the organization through my professor at URI.

My first task was to search the internet and the NCODA website to formulate an informative 30-second elevator pitch on both NCODA and MID. Completing this task really helped me understand NCODA's Mission.

Afterwards, I kept busy learning about different NCODA initiatives, such as the Oral Chemotherapy Education (OCE) sheets.

The OCE committee strives to make the experience of undergoing chemotherapy easier for the patients by providing free and accessible OCE medication sheets for patients, family members or anyone else interested in learning about oral chemotherapy agents.

These sheets contain relevant medication information in easy-to-understand sections. I listened in on the group's meeting and later prepared a drug comparison chart on two brands of the same oral chemotherapy agent for committee members.

Another project I helped NCODA members and other pharmacy students with was the NCODA IV Education (IVE) initiative.

Similar to OCE sheets, IVE sheets will provide easy-to-understand literature for patients undergoing treatment with various IV medications.

I also had the opportunity to make a presentation to the NCODA Oncology Pharmacy Technician Association (OPTA) on the new FDA drug approval for isatuximab-irfc, and on how its approval might change what pharmacists and technicians see in their workplace.

While working on my assigned projects, I also spent time attending online webinars designed to keep NCODA members informed and educated.

These included the NCODA National Monthly Webinar and the joint NCODA-ASCO Quality Standards webinar.

These webinars are integral pieces to NCODA as they spread important news and updates that reach NCODA members internationally.

The NCODA virtual learning experiences provided opportunities to learn about new medication approvals and guideline updates, as well as how NCODA practices adapt to changes in the oncology world.

Throughout the COVID-19 pandemic, NCODA developed resources to keep the public updated and informed by hosting a webinar series from March through June entitled "Supporting Patients and Practices Through the COVID-19 Pandemic."

These webinars were led by healthcare, pharmaceutical, and GPO industry leaders. Each webinar provided insight on how to navigate the pandemic while still providing the best patient care.

Along with my direct NCODA experience, I also worked with Britny Rogala, PharmD, BCPS, BCOP, (The University of Rhode Island College of Pharmacy) and her Institutional Oncology APPE students.

Each week we dove into oncology-related clinical topic discussions that furthered our knowledge and experiences on different cancer-related issues.

As I reflect on my APPE experience, I want to thank NCODA for providing me with a comprehensive educational experience.

With the help of my professors, the University of Rhode Island and NCODA, I was able to complete a satisfying remote APPE experience from a safe location.

▲ **Connor Longo**, PharmD, is a 2020 graduate from The University of Rhode Island College of Pharmacy. He completed his Advanced Pharmacy Practice Experience (APPE) with NCODA during his Spring semester 2020.

PHSP: KEEPING PACE WITH THE COMPLEXITIES OF PATIENT CARE

By Felicia Britt, PharmD, BCPS

Felicia Britt, PharmD, BCPS, is the PGY2 Health-System Pharmacy Administration and Leadership Resident at Massachusetts General Hospital in Boston, Massachusetts.

Research and development of new medications has become more and more costly over the last few years resulting in highly specialized therapies. These new medications are typically focused toward treating high-acuity or complex disease states such as autoimmune disorders, cancer, neurology disorders, cystic fibrosis and cardiac abnormalities.

As these therapies become more complex, so does the care of the patient. Partners Healthcare Specialty Pharmacy (PHSP) provides high-quality care to patients as part of integrated care at Massachusetts General Hospital, Newton-Wellesley Hospital and other Partners-affiliated hospitals and clinics.

Founded in December 2017 and now accredited by the Utilization Review Accreditation Commission (URAC), PHSP services the surrounding clinics and academic medical centers in the greater New England area that are part of Partners' network of hospitals and clinics. PHSP started with autoimmune disorders and now has access to medications to treat a wide variety of disease states such as seizures, cancer, and soon, cystic fibrosis.

THE MULTI-STEP ORDERING PROCESS

The model of PHSP is to capture 100% of patients at eligible Partners Healthcare clinics through an innovative design within the Electronic Health Record (EHR), referred to as the Multi-Step Ordering Process (MSOP).

MSOP automatically captures any prescriptions for medications that are serviced by PHSP. Once received into the electronic system, PHSP will complete an eligibility check to determine if the patient is eligible to fill at PHSP based on his/her payer. A pharmacy representative will determine if a prior authorization (PA) is needed based on the payer and reach out to the patient to determine his/her interest in filling with PHSP.

Financial assistance in the forms of grants, copay assistance cards and manufacturer assistance programs are offered at the time of patient contact for those patients who meet eligibility but are unable to afford their medications.

If a prescription is not eligible, a PHSP representative will triage the prescription to the appropriate pharmacy and inform the clinic and patient. For patients who are serviced by PHSP, a clinical pharmacist follows the patient beginning with medication initiation. Each patient receives phone calls at the time of prescription refill to assess adherence and medication therapy, and is screened for potential side effects.

The clinical encounters are documented in a patient monitoring software system that provides anyone at PHSP with immediate access in the event of an emergent patient question. Any clinical changes, recommendations, and documentation are also entered directly into the EHR for the primary team to evaluate and close the loop on communication with prescription refills.

CUTTING-EDGE INNOVATION

PHSP remains on the cutting-edge of innovation as it continues to expand beyond the clinic services in the Partners network.

Based on feedback from patient satisfaction surveys and in an effort to remain environmentally friendly, PHSP uses biodegradable packing materials in almost every package it ships.

For refrigerated items, an innovative foam made from corn and completely biodegradable – designed to replace bubble packing and Styrofoam – reduces the carbon footprint of every refrigerated product.

MSOP allows pharmacists to remain focused on patient care and does not rely on clinical pharmacists to be the sole driver of prescription volume, unlike other specialty pharmacy models. Clinical

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PHSP

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pharmacists are able to spend 100% of their time focused on patient care, provider education and clinical review, allowing them to practice at the top of their license.

MSOP can be easily customized by tagging new drugs and providers, thus, sending all prescriptions to PHSP. This type of capture allows the pharmacy staff to focus on providing PA work to all prescriptions, regardless of the patient's eligibility to fill with PHSP, meaning no patient treated at eligible Partners clinics are left without an initial clinical and PA review.

This is not only better for patient care as pharmacists at PHSP have direct access to the EHR to check for appropriate dosing on initial prescriptions, but it also increases efficiency of turnaround time if the prescription is sent to an outside mail-order pharmacy.

Pharmacy staff in the oncology division with PHSP completed more than 1,100 PAs with an average prescription capture rate of nearly 50%. The volume of PAs and capture rate percentage rate continues to grow as PHSP expands to more clinics within the Partners Healthcare enterprise.

PHSP clinical staff are currently working with providers in the oncology division to decrease turn around time for oral oncolytic agents for patients with specific genetic mutations.

Given the clinical benefit of starting oral targeted therapies as soon as possible, PHSP is working with pathologists, physicians and inpatient pharmacists at one of its flagship academic medical centers, Massachusetts General Hospital, to triage potential patients, provide clinical review and decrease turnaround time of these agents.

MONITORING PATIENT SATISFACTION

PHSP monitors patient satisfaction in the form of surveys mailed to patients. In 2019, 95% of patients stated they were "somewhat satisfied" or "very satisfied" with PHSP in the following areas: filling initial specialty medications; refilling specialty medications; timeliness of receiving prescriptions; pharmacy customer service; pharmacist's ability to answer questions and the likelihood of recommending PHSP to others. PHSP also sets monthly goals of telephone abandonment rates and time to answer the telephone that are stricter than national guidelines and accreditation standards.

PHSP continues to set high standards for specialty pharmacy best practices and innovation. The added features of MSOP, biodegradable packaging and proactive clinical review with pathologists and physicians is unparalleled and will continue to set the stage for future clinic expansion, increased pharmacy presence for teaching, clinical review and provider education.

▲ **Felicia Britt**, PharmD, BCPS, is the PGY2 Health-System Pharmacy Administration and Leadership Resident at Massachusetts General Hospital in Boston, Massachusetts.

ORAL ONCOLOGY DRUG APPROVALS BY THE FDA FOR Q1, Q2 & Q3 2020

By Derek Gyori, PharmD, BCOP, & Kirollos Hanna, PharmD, BCPS, BCOP

During Q1, Q2 and Q3 (through Aug. 14) of 2020, the Food & Drug Administration (FDA) approved 20 oral oncology agents. On the following six pages is a table reviewing important information regarding the newly approved medications and new indications for already approved medications. **For abbreviations and references, see Page 37.**

Further information can be found on the FDA website, in the medication-specific prescribing information or clinical trials.

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Avapritinib (Ayvakit)	1/9/2020	Unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation including D842V mutations: 300 mg orally once daily	To view the full new drug update on Avapritinib (Ayvakit), please visit Pages 60-61 of the Spring 2020 issue of *Oncolytics Today*.		
Tazemetostat (Tazverik)[1,2]	1/23/2020	Metastatic or Locally Advanced Epithelioid Sarcoma: 800 mg by mouth twice daily	N=62 ORR: 15% (95% CI: 7-26%) CR: 1.6% PR: 13% 67% responded for > 6 months	>20%: Pain, fatigue, nausea, decreased appetite, vomiting, constipation	Take with or without food Available as 200 mg tablet
Neratinib (Nerlynx)[1,3]	2/25/2020	*In combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting: 240 mg (6 tablets) given orally once daily with food on days 1-21 of a 21-day cycle plus capecitabine (750 mg/m2 given orally twice daily) on days 1-14 of a 21-day cycle until disease progression or unacceptable toxicities	Median PFS: 5.6 months (95% CI: 4.9 - 6.9) for patients who received neratinib with capecitabine and 5.5 months (95% CI: 4.3 - 5.6) for those receiving lapatinib with capecitabine (HR 0.76; 95% CI: 0.63 - 0.93; p=0.0059) The PFS rate at 12 months was 29% (95% CI: 23 - 35) vs 15% (95% CI: 10 - 20) Median OS: 21 months (95% CI: 17.7 - 23.8) for patients receiving neratinib with capecitabine compared to 18.7 months (95% CI: 15.5 - 21.2) for those receiving lapatinib plus capecitabine (HR 0.88; 95% CI: 0.72 - 1.07; p=0.2086). ORR: 32.8% (95% CI: 27.1 - 38.9) vs. 26.7% (95% CI: 21.5 - 32.4), respectively. Median response duration was 8.5 (95% CI: 5.6 - 11.2) vs 5.6 months (95% CI: 4.2 - 6.4)	>5%: Diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment and muscle spasms	Take with food Available as 40 mg tablet

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Encorafenib (Braftovi)[1,4]	4/8/2020	*Metastatic Colorectal Cancer with BRAF V600E mutation: 300 mg by mouth once daily given in combination with cetuximab	Control group was Irinotecan or FOLFIRI plus cetuximab Median OS: 8.4 (95% CI: 7.5-11) vs 5.4 (95% CI: 4.8-6.6) months Median PFS: 4.2 (95% CI: 3.7-5.4) vs 1.5 (95% CI: 1.4-5.4) months ORR: 20% (95% CI:13- 29%) and 2% (95% CI:0- 7%), Median DoR: 6.1 months (95% CI: 4.1 - 8.3) months and not reached for control group (95% CI: 2.6 - NR)	>25%: Fatigue, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia and rash Hemorrhage, QTc prolongation, malignancy, and ocular toxicity have been reported	Take with or without food Moderate emetic potential Available as 75 mg capsule
Selumetinib (Koselugo)[1,5]	4/10/2020	Pediatric patients, 2 years of age and older, with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN): 25 mg/m2 orally twice a day on an empty stomach until disease progression or unacceptable toxicity	ORR: 66% (n=33; 95% CI: 51 - 79) All patients had a PR and 82% of responders had sustained responses lasting at least 12 months ORR by IRC: 44% (95% CI: 30 - 59)	≥40%: Vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, fever, acne, stomatitis, headache, paronychia and pruritus	Take without food Available as 10 and 25 mg tablet
Tucatinib (Tukysa)[1,6]	4/17/2020	Advanced unresectable or metastatic HER2+ breast cancer: 300 mg taken orally twice a day	Tucatinib plus trastuzumab and capecitabine (tucatinib arm, n=410) or placebo plus trastuzumab and capecitabine (control arm, n=202) PFS: 7.8 months (95% CI: 7.5 - 9.6) vs. 5.6 months (95% CI: 4.2 - 7.1); (HR 0.54; 95% CI: 0.42 - 0.71; p<0.00001) OS: 21.9 months (95% CI: 18.3 - 31.0) vs. 17.4 months (95% CI: 13.6 - 19.9); (HR: 0.66; 95% CI: 0.50 - 0.87; p=0.00480) ORR: 40.6% (95% CI: 35.3, 46.0) vs. 22.8% (95% CI: 16.7, 29.8); (p=0.00008)	≥ 20%: Diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia and rash	Take with or without food Used in combination with trastuzumab and capecitabine Available as 50 and 150 mg tablets

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Pemigatinib (Pemazyre)[1,7]	4/20/2020	Adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test: 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy in 21-day cycles	ORR: 36% (95% CI: 27 - 45%), including 3 complete responses Median DoR: 9.1 months with responses lasting ≥ 6 months in 24 of the 38 (63%) responding patients and ≥ 12 months in 7 (18%) patients	≥20%: Hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain and dry skin	Take with or without food Available as 4.5, 9, 13.5 mg tablet
Ibrutinib (Imbruvica)[1,8]	4/21/2020	*Initial treatment of adult patients with CLL or SLL with rituximab: 420 mg orally once daily	Ibrutinib with rituximab versus FCR PFS: not reached in either arm at 72 month follow-up (HR 0.34; 95% CI: 0.22 - 0.52; p<0.0001)	≥30%: Thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising and nausea	Take with a full glass of water Rituximab initiated on Cycle 2 Ibrutinib available as 140 mg, 280 mg, and 420 mg tablet and 70 mg and 140 mg capsule
Niraparib (Zejula)[1,9]	4/29/2020	*Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy: 300 mg taken orally once daily	Median PFS in the homologous recombination deficient population: 21.9 months (19.3 - NE) for patients receiving niraparib compared with 10.4 months (8.1 - 12.1) for those receiving placebo (HR 0.43; 95% CI: 0.31 - 0.59; p<0.0001) Median PFS in the overall population: 13.8 months (11.5 - 14.9) for patients receiving niraparib compared with 8.2 months (7.3 - 8.5) for those receiving placebo (HR 0.62; 95% CI: 0.50 - 0.76; p<0.0001)	≥10%: Thrombocytopenia, anemia, nausea, fatigue, neutropenia, constipation, musculoskeletal pain, leukopenia, headache, insomnia, vomiting, dyspnea, decreased appetite, dizziness, cough, hypertension, AST/ALT elevation and acute kidney injury	Take with or without food Available as 100 mg tablet
Capmatinib (Tabrecta)[1,10]	5/6/2020	Metastatic NSCLC with mesenchymal - epithelial transition (MET) exon 14 skipping mutation: 400 mg orally twice daily	28 treatment naive patients ORR: 68% (95% CI: 48 - 84) DoR: 12.6 months (95% CI: 5.5 - 25.3) 69 previously treated patients ORR: 41% (95% CI: 29 - 53) DoR: 9.7 months (95% CI: 5.5 - 13.0)	≥ 20%: Peripheral edema, nausea, fatigue, vomiting, dyspnea and decreased appetite May also cause interstitial lung disease, hepatotoxicity, photosensitivity and embryo-fetal toxicity	Take with or without food Available as 150 mg and 200 mg tablets

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Selpercatinib (Retevmo)[1,11]	5/8/2020	Adult patients with metastatic RET fusion-positive NSCLC; Adult and pediatric patients ≥12 years of age with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy; Adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate): 120 mg for patients <50 kg, and 160 mg for those ≥50	**RET-fusion-positive NSCLC** ORR (previously treated): 64% (95% CI: 54% - 73%); 81% of responding patients had responses lasting 6 months or longer ORR (no prior systemic therapy): 85% (95% CI: 70% - 94%); 58% of responding patients had responses lasting 6 months or longer **RET-mutant MTC** ORR (previously treated): 69% (95% CI: 55% - 81%); 76% of responding patients had responses lasting 6 months or longer ORR (untreated): 73% (95% CI: 62% - 82%); 61% of responding patients had responses lasting 6 months or longer **RET fusion-positive thyroid cancer** ORR (previously treated): 79% (95% CI: 54% - 94%); 87% of responding patients had responses lasting 6 months or longer ORR (untreated): All 8 patients responded (95% CI: 63% - 100%) and 75% had responses lasting 6 months or longer	≥25%: Increased aspartate aminotransferase, increased alanine aminotransferase, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium and constipation	Selpercatinib is taken orally twice daily with or without food; or with food when co-administered with a proton pump inhibitor Available as 40 and 80 mg tablet
Olaparib (Lynparza)[1,12]	5/8/2020	*Ovarian cancer, advanced (homologous recombination deficient-positive), first-line maintenance therapy: 300 mg taken orally twice daily	2:1 ratio to receive bevacizumab plus olaparib (n=537) or bevacizumab plus placebo (n=269) Median PFS: 37.2 months in the olaparib group vs. 17.7 months in the placebo group (HR 0.33; 95% CI: 0.25 -0.45) Median OS: Not mature	≥10%: Nausea, fatigue (including asthenia), anemia, lymphopenia, vomiting, diarrhea, neutropenia, leukopenia, urinary tract infection and headache	Used in combination with bevacizumab Available as 100 or 150 mg tablet Approved with the Myriad myChoice® CDx as a companion diagnostic for olaparib

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Pomalidomide (Pomalyst)[1,13]	5/14/19	*Adult patients with AIDS-related Kaposi sarcoma after failure of highly active antiretroviral therapy and Kaposi sarcoma in adult patients who are HIV-negative: 5 mg once daily taken orally with or without food on days 1 through 21 of each 28-day cycle until disease progression or unacceptable toxicity	ORR (HIV-positive): 67% (95% CI: 41 - 87) Median DoR (HIV-positive): 12.5 months (95% CI: 6.5 - 24.9). ORR (HIV-negative): 80% (95% CI: 44 - 98) Median DoR (HIV-negative): 10.5 months (95% CI: 3.9 - 24.2)	≥30%: Decreased absolute neutrophil count or white blood cells, elevated creatinine or glucose, rash, constipation, fatigue, decreased hemoglobin, platelets, phosphate, albumin, or calcium, increased ALT, nausea and diarrhea	Take with or without food Available as 1, 2, 3, 4 mg tablet
Rucaparib (Rubraca)[1,14]	5/15/2020	*Deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy: 600 mg orally twice daily	n=62 ORR: 44% (95% CI: 31 - 57) Median DoR: NE (95% CI: 6.4 - NE); range for the DOR was 1.7-24+ months. 56% of patients with a confirmed ORR had a DoR of 6 months or greater	≥20%: Fatigue, nausea, anemia, increased ALT/AST, decreased appetite, rash, constipation, thrombocytopenia, vomiting and diarrhea	Take with or without food Should also receive a gonadotrophin-releasing hormone analog concurrently or have had a bilateral orchiectomy Available as 200, 250, and 300 mg tablet
Ripretinib (Qinlock)[1,15]	5/15/2020	GIST after with 3 or more kinase inhibitors, including imatinib: 150 mg orally once daily with or without food	PFS: 6.3 months (95% CI: 4.6 - 6.9) for ripretinib compared with 1.0 month (95% CI: 0.9 - 1.7) for placebo ORR: 9% (95% CI: 4.2 - 18) in the ripretinib arm compared with 0% (95% CI: 0 - 8) in the placebo arm Median OS: ripretinib arm was 15.1 months (95% CI: 12.3 - 15.1) compared with 6.6 months (95% CI: 4.1 - 11.6) in the placebo arm	≥20%: Alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia and vomiting	Take with or without food Available as 50 mg tablet

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Olaparib (Lynparza)[1,12]	5/19/2020	*Deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone: 300 mg taken orally twice daily	Compared to abiraterone or enzalutamide in a 2:1 ratio Median rPFS: 7.4 vs 3.6 months (HR 0.34; 95% CI: 0.25 - 0.47; p<0.0001) ORR: 33% vs 2% (p<0.0001) Median OS: 19.1 vs. 14.7 months (HR 0.69; 95% CI: 0.50 - 0.97, p=0.0175)	>10%: Anemia, nausea, fatigue (including asthenia), decreased appetite, diarrhea, vomiting, thrombocytopenia, cough and dyspnea Venous Thromboembolic events occurred more in the olaparib arm	Take with or without food Available as 100 or 150 mg tablet Approved with the FoudationOne CDx for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test
Brigatinib (Alunbrig)[1,16]	5/22/2020	*Advanced anaplastic lymphoma kinase (ALK)-positive NSCLC who had not previously received an ALK-targeted therapy: 90 mg orally once daily for the first 7 days; then increase to 180 mg orally once daily	Compared crizotinib 250 mg twice daily PFS: 24 months (95% CI: 18.5 - NE) compared with 11 months (95% CI: 9.2 - 12.9) for those treated with crizotinib (HR 0.49; 95% CI: 0.35 - 0.68; p<.0001) ORR: 74% (95% CI: 66 - 81) and 62% (95% CI: 53 - 70)	>25%: Diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting and dyspnea	Take with or without food Available as 30 mg, 90 mg, and 180 mg tablets Approved with the Vysis ALK Break Apart FISH Probe Kit as a companion diagnostic for brigatinib
Selinexor (Xpovio)[1,17]	6/18/2020	*R/R DLBCL after at least 2 lines of systemic therapy:60 mg taken orally on days 1 and 3 of each week with antiemetic prophylaxis	ORR: 29% (95% CI: 22 - 38) CR: 13% 38% had response durations of at least 6 months and 15% had response durations of at least 12 months	≥20%: Fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting and pyrexia	Take with or without food Available as 20 mg tablet

Tazemetostat (Tazverik)[1,2]	6/18/2020	*R/R Follicular Lymphoma, EZH2-mutation positive or salvage therapy: 800 mg by mouth twice daily	n= 42 EZH2 mutant patients ORR: 69% (95% CI: 53 - 82%) with 12% CR and 57% PR Median DoR:0.9 months (95% CI: 7.2 - NE) n=53 salvage therapy patients (EZH2 wild type) ORR: 34% (95% CI: 22 - 48%) with 4% CR and 30% PR Median DoR: 13 months (95% CI: 5.6 - NE)	>20%: Fatigue, upper respiratory tract infection, musculoskeletal pain, nausea and abdominal pain Second primary malignancy can occur Serious adverse drug reactions occurred in 30% of patients, mostly due to infection	Take with or without food Available as 200 mg tablet
Decitabine & cedazuridine (Inqovi) [1,18]	7/7/2020	Adult patients with myelodysplastic syndromes (MDS): 1 tablet (35 mg decitabine and 100 mg cedazuridine) taken orally on an empty stomach once daily on days 1 through 5 of each 28-day cycle	Clinical trials provided comparison of exposure and safety in the first two cycles between oral Inqovi and IV decitabine and description of disease response with Inqovi Comparison of disease response between the Inqovi and IV decitabine was not possible because all patients received Inqovi starting from Cycle 3. 5-day cumulative decitabine AUC following 5 consecutive once daily doses of Inqovi compared to that of intravenous decitabine was 99% (90% CI: 93-106%)	≥20%: Fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia and transaminase increased	Dose reductions: 1st – 1 tablet orally once daily on Days 1 through 4; 2nd – 1 tablet orally once daily on Days 1 through 3; 3rd – 1 tablet orally once daily on Days 1, 3 and 5

***New Indication for approved medication**

Abbreviations: ORR – Objective Response Rate, CI – Confidence Interval, CR – Complete Response, PR – Partial Response, HER-2 – Human Epidermal Growth Factor Receptor 2, PFS – Progression Free Survival, OS – Overall Survival, HR – Hazard Ratio, DoR – Duration of Response, FCR – Fludarabine, Cyclophosphamide, Rituximab, NSCLC – Non-Small Cell Lung Cancer, mCRPC – Metastatic Castration Resistant Prostate Cancer, GIST – Gastrointestinal Stromal Tumor, DLBCL – Diffuse Large B Cell Lymphoma

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DRIVEN TO FULFILL THE PROMISE OF BIOSIMILARS—THE PFIZER WAY

The Pfizer Promise is simple:

To help you provide patients with more treatment options while delivering the largest portfolio of potentially cost-saving biosimilars.[1-3]

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Pfizer has the largest portfolio of oncology biosimilars on the market, including both cancer therapies and supportive care products, to give patients more treatment options.[2,3]

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Pfizer oncology biosimilars are all produced to meet the same high-quality standards as its biologics—using the same robust protocols for monitoring quality throughout every stage of the manufacturing process.[4]

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Pfizer leverages more than 30 years of state-of-the-art manufacturing and supply-chain experience in biologics to reliably deliver biosimilars to patients.[4]

To learn more about Pfizer's oncology biosimilars, visit us online at PfizerBiosimilars.com

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A BEACON OF HOPE

NCODA SHINES THROUGH THE FOG OF COVID-19

As COVID-19 enshrouded the world in a fog of confusion and uncertainty in Spring 2020, NCODA burst forth as a beacon for healthcare professionals to share treatment information, best practices and support during the developing pandemic.

Six days after the U.S. proclaimed a National Emergency on March 13, NCODA launched "Supporting Patients and Practices Through the COVID-19 Pandemic," a weekly webinar series for oncology professionals featuring healthcare experts discussing a wide range of topics related to both the novel coronavirus and cancer care.

The nine-week series explored COVID-19 from a variety of perspectives, including that of physicians, pharmacists, practice administrators, industry leaders and elected officials. More than 2,000 oncology healthcare professionals attended the live webinars, which can now be found at **www.ncoda.org/covid-19-provider-patient-resources**.

COVID-19 AND CANCER

From the beginning, the webinars focused on two key topics: COVID-19 and its effect on cancer care. And with reports changing by the day, just getting a handle on the emerging coronavirus was no easy task.

Jeffrey Topal, MD, an infectious disease specialist at Yale New Haven Health, provided an overview on COVID-19 during the March 25 webinar and identified why cancer patients are particularly at potential risk.

"It significantly impacts cancer care because this population needs frequent follow-ups, is at higher risk of possible complications … (and) often requires increased use of healthcare

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resources which have become quite scarce in some parts of the United States," Topal said.

At the time, he noted, it was likely things would get worse before they got better. "We are still on the upside of the epidemic curve; it has not plateaued," Topal said.

On the other hand, experts like Jeffrey Bratberg, a clinical professor at the University of Rhode Island College of Pharmacy, noted during the April 15 webinar that relatively few cancer patients had been seen among those being treated for COVID-19 infection.

"While people who are immunosuppressed are at greater risk, the most common comorbidities being seen are hypertension, obesity and diabetes which are all interrelated but also disproportionally seen among vulnerable marginalized populations that divide on racial and ethnic lines," Bratberg, PharmD, FAPhA, said. "We've seen a significant preponderance of folks who are Hispanic or African American who are hospitalized in ICUs in critical condition who are ventilated, and, in some cases, among the deaths. But immunosuppressed people were not really in those numbers."

Part of that success is no doubt due in part to screening, scheduling and sanitizing steps taken by oncology practices to protect their patients. Oral oncolytics are likely another reason.

"The oncology world is living in a golden era," Topal noted. "Oral oncolytics can deliver high-level care in an outpatient setting. Fifteen years ago, this would have been quite different."

Another breakthrough is having new support options to treat neutropenia, even in the clinical setting.

At St. Elizabeth Healthcare in Northern Kentucky, for instance, providers are intentionally reducing patient visits and exposure by administering rituximab prior to patient discharge, according to clinical coordinator Alicia Gesenhues, PharmD, BCOP.

"Similarly, if patients required myeloid growth factor, we typically discharged them and sent them back to the treatment site the following day for a peg-filgastrim injection," Gesenhues said. "To decrease that visit we are now placing Neulasta on the patient's body immediately prior to discharge. It injects at home 27 hours later so they don't have to come back to us."

The webinars also offered insight into promising COVID-19 treatments like:

• The broad-spectrum antiviral remdesivir (almost two months before

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THE MEN AND WOMEN WHO BROUGHT YOU

Sam Abdelghany
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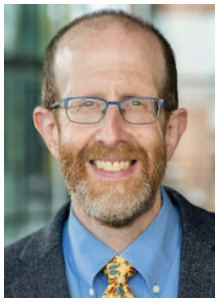
Chris Barnes
Executive Director, Alabama Oncology

Holly Books
BSN, RN, OCN, Executive Director of Operational Excellence, Texas Oncology

Jeffrey Bratberg
PharmD, FAPhA, Clinical Professor, Univ. of Rhode Island College of Pharmacy



Howard Forman
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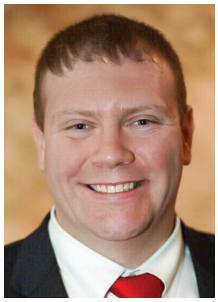

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Kashyap Patel
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Jim Schwartz
RPh, Executive Director of Pharmacy Operations, Texas Oncology, 2019-2020 President, NCODA

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THE NCODA COVID-19 WEBINAR SERIES

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RPh,
U.S. Representative,
Georgia First
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Randy Erickson
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Stephen Ziter
Webinar Moderator
Assistant Director – Patient
Centered Initiatives,
NCODA

FOR MORE INFORMATION

Scan here to view the NCODA COVID-19 webinar recordings.

COVID-19

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it was touted on mainstream media as a "miracle drug");

• The controversial immunosuppressive hydroxychloroquine (noting that it would likely be ineffective in late-stage infections in a hospital environment); and

• The RA immunosuppressive tocilizumab (which shows promise dampening cytokine storm syndrome brought on by COVID-19).

EFFECT ON PRACTICES

The coronavirus has profoundly affected oncology centers in a number of ways as practices work to protect both patients and staff.

Remote staffing of non-essential employees has become the norm, while those remaining on-site must now follow strict personal protective equipment (PPE) guidelines and regular screening.

On the patient side, rescheduling or postponing appointments for non-urgent patients is now in play, as well as a shift to virtual appointments via telemedicine.

Moving non-essential staff off-site was a first priority at many practices:

At 5,000-plus employee Florida Cancer Specialists & Research Institute, for instance, 70 percent of the group's 800-member revenue cycle team and 85 percent of the outpatient pharmacy team are now working from home, according to Lucio Gordan, MD, President and Managing Physician.

At Seattle Cancer Care Alliance, staffing was stratified so the bulk of the group's 30 clinical pharmacists work could switch back and forth from remote to in-clinic work based on workflow, said Eve Segal, PharmD, BCOP, Lead Clinical Oncology Pharmacist, Seattle Cancer Care Alliance.

At Utah Cancer Specialists, which has 17 oncologists and more than 250 employees at 11 clinics in a largely rural setting with relatively few COVID-19 cases, only 5-10% of the workforce is at home, according to Chief Executive Officer Randy Erickson, BSN, RN, OCN.

Obtaining PPEs and other supply chain issues proved to be a particular challenge at many sites.

At Oncology Hematology Care in Cincinnati, Ohio, medical oncologist/hematologist David Waterhouse, MD, MPH, voiced a common refrain during the March 25 webinar: "I'm given a surgical mask, not an N95 mask but a plain old surgical mask, which I have to make sure lasts a week," he said. "I keep it in a brown paper bag at night."

At Carolina Blood and Cancer Care Associates, in Rock Hill, South Carolina, CEO Kashyap Patel, MD, noted at the April 8 webinar his group was still struggling to acquire N95 masks.

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"We've had to make reusable masks from cloth and then clean them in boiling water to reuse them," Patel said.

At Texas Oncology, Jim Schwartz, RPh, Executive Director of Pharmacy Operations, and 2019-2020 President of NCODA was able to purchase 30,000 "KN95" masks. "That means they're authorized for use in South Korea," Schwartz said, a country that has been proactive in managing the pandemic.

Yet while things have been tough all over this Spring, few places have had it tougher than New York.

Early on in the crisis, New York City became ground zero for the pandemic in the United States, if not the world. Because of this, one practice hit particularly hard was New York Oncology Hematology (NYOH) in Albany, New York.

"As of last week we had more cases than the entire nation of France," Executive Director Sabrina Mosseau, BS, RN, OCN, noted during the April 1 webinar.

Things became even more difficult when NYOH was forced to temporarily close its primary clinic at Albany Medical Center after a huge influx of COVID-19 patients were moved there from New York City and 46 providers later tested positive.

Public confusion, political infighting and social media rumors only added to the problem.

"Our patients are scared," Mosseau said. "Cancer care has enough conflicting education out there without layering on social media and legends about gargling with hot water and drinking tea or holding your breath really long to figure out whether or not you have coronavirus."

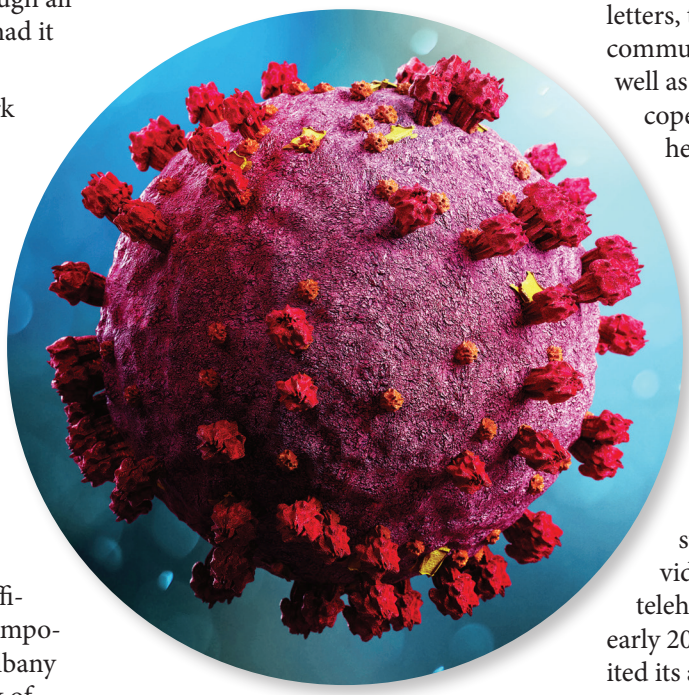
EFFECT ON STAFF

From a business standpoint, COVID-19's effect on practices has been profound.

Florida Cancer Specialists saw a 35 percent reduction in patient returns within three weeks, Gordan noted on the April 1 webinar. "New patients are down 20% and infusions by 13% or 14%," he said.

At NYOH, the practice has seen a 30 percent drop in visits week over week starting March 7.

"We've already begun taking our one-year appointments and moving them further out, taking our six-month appointments and moving them further out and that in and of itself causes stress with our patients," Mosseau said. "Oddly enough, we are holding stable and strong in the world of imaging, our infusion rooms and our MID, and also just starting to tick back into radiation."



Utah Cancer Specialists has seen a 25 percent drop in new patient volumes, and similar numbers in first-hour chemotherapy administration.

The drop in business often had a chilling effect on staff. Some practices closed sites due to staff furloughs. Others had to contend with school closures, loss of daycare and spousal unemployment, as well as the risk of infection for those remaining in the workplace.

And while options like the Payroll Protection Program helped soften the blow, many practices worked diligently to ensure staff would have jobs to return to once the pandemic ends.

At hard-hit NYOH, Mosseau noted "our personnel are not OK."

"These folks are going on week three of the schools being closed, spouses out of work, losing jobs," Mosseau said. "There's lots of economic stress."

Most practices have utilized newsletters, town hall meetings and constant communication to help reassure staff as well as keep them informed and help cope with the current chaos of daily healthcare.

At Carolina Blood & Cancer Care Association, Patel said the practice didn't compromise salaries but instead "paid staff a comfortable wage for their reduced hours and assured them the jobs were safe."

TELEHEALTH

One bright spot in the current crisis has been the sudden surge of telehealth through both video and audio platforms. While telehealth has been around since the early 2000s, government restrictions limited its application largely to rural areas.

All that changed on March 6 when the Coronavirus Preparedness and Response Supplemental Appropriations Act loosened restrictions, followed by a March 17 decision by the Centers for Medicare & Medicaid Services (CMS) that outlined telehealth payments and reimbursements.

Texas Oncology rapidly adopted the option.

"We have more than 500 physicians and currently 400 of them are using telemedicine," Schwartz said. "Not only are they doing evaluations and checkups, but patients can call in. They are put in a virtual waiting room where the doctor can go in

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and talk to them. It's working really well for both the patients and the physicians."

For Holly Books, Texas Oncology's Executive Director of Operational Excellence, the change has been eye-opening.

"Honestly, I never ever thought you could round in the hospital via telehealth, but here we are," said Books, BSN, RN, OCN. "Our doctors are utilizing it frequently to keep patients at home, while the APPs are able to do program visits like genetics, treatment reviews and advanced care planning with this platform."

Telemedicine is also gaining traction at smaller practices.

St. Elizabeth Healthcare, which operates five facilities in Northern Kentucky, has seen enormous growth in telemedicine.

"We went from a goal of 700 video visits per year to more than 35,000 last week," said Douglas Flora, MD, LSSBB, St. Elizabeth's Executive Medical Director of Oncology. "And this is a community hospital in the middle of the Midwest, not a gigantic digital enterprise. I think it's pretty clear to all of us that the digital health train has left the station and cancer patients and cancer physicians are now on board."

More importantly, telehealth also has proved popular with patients.

"The patients who enjoy the telehealth platform really take to it," said Segal of Seattle Cancer Care Alliance. "We are able to treat patients who are at the other end of the state and they don't have to drive hours and hours to have these appointments."

Yet the shift to telehealth is not without obstacles. Staff need to be trained on equipment and software, interactions must be documented, procedures must be explained to patients and their consent obtained.

"While 80% of patients have a smart device, that doesn't mean 80% know how to use it," explained Waterhouse, of Oncology Hematology Care in Cincinnati, Ohio. "It can be cumbersome. Right now, we have a lot of cancellations. After the crisis, it will be more difficult to execute."

THE COMING SURGE

When the COVID-19 crisis is finally brought under control, one question remains for oncologists: What happens next?

Due to healthcare closures, the next wave of cancer patients is still undiagnosed, and that wave won't break until the coronavirus is in the rear-view mirror.

"Our pivot now is, how do we accommodate this massive influx of patients that's expected with possibly some stage migration based on delayed colonoscopy, delayed mammography," said Flora of St. Elizabeth Healthcare. "We went from doing 420 CT scans per month to 17 (for April). Those patients have to present, hopefully soon, and I hope their care hasn't suffered because of these necessary breaks in treatment."

Mosseau summed it up like this: "No screening is being done. There are no mammography centers, no elective processes are being done so no colonoscopies, no bronchoscopies, no endoscopies, no prostate exams, zero. They're shut down, but understand that cancer is still out there … (and) cancer untreated is a 100 percent mortality."

PATIENT CARE AND COOPERATION

The coronavirus pandemic has placed unprecedented pressure on the entire healthcare industry. Yet in the midst of their daily struggle, the healthcare professionals who spoke during the NCODA COVID-19 webinars remained adamant on two major themes: 1. The absolute commitment to patient care, and 2. The absolute need for mutual support across the industry during the crisis.

Dan Duran, Senior Vice President of Provider Solutions at Cardinal Health Specialty Solutions, provided examples of how practices, manufacturers, Group Purchasing Organizations, trade associations and government are all working together to help get through the crisis.

"We're seeing a level of collaboration never seen before, both internally and externally," Duran said.

However, this kind cooperation can't take place without open communication, and that's where NCODA comes in, bringing together healthcare's brightest minds in a safe and secure environment at a time when a deadly pandemic is fracturing our world.

"It's extremely isolating to work in an environment of social and physical distancing," noted Casey Foster, Senior Manager of Site of Care Dispensing for Cardinal Health Specialty Solutions. "Yet NCODA (promotes) working collaboratively towards a common goal of taking care of patients. It's really an amazing thing that you guys are doing right now hosting these webinars and bringing all these people together to talk about the experiences we're seeing on a day-to-day basis."

SUBCUTANEOUS CHEMOTHERAPY: TO CONVERT OR NOT TO CONVERT?

By Mollie Beck, PharmD, BCOP, Doug Flora, MD, & Alicia Gesenhues, PharmD, BCOP

Alternative methods of administration that aid in eliminating or reducing lengthy infusion times are paramount for oncology patients and hospital systems. In addition to oral oncolytics, subcutaneous biologic antineoplastic agents are attractive options, as there is a growing body of evidence supporting therapeutic substitution for their intravenous counterparts.

Three FDA approved subcutaneous products currently available include **Darzalex Faspro** (daratumumab and hyaluronidase-fihj), **Herceptin Hylecta** (trastuzumab and hyaluronidase-oysk), and **Rituxan Hycela** (rituximab and hyaluronidase).

Drug	Darzalex Faspro (daratumumab and hyaluronidase-fihj)[8]	Herceptin Hylecta (trastuzumab and hyaluronidase-oysk)[9]	Rituxan Hycela (rituximab and hyaluronidase)[10]
Dose	1,800 mg daratumumab + 30,000 units hyaluronidase	600 mg trastuzumab + 10,000 units hyaluronidase	INDICATION DEPENDENT Diffuse large B-cell lymphoma: 1,400 mg rituximab + 23,400 units hyaluronidase Follicular lymphoma: 1,400 mg rituximab + 23,400 units hyaluronidase Chronic lymphocytic leukemia: 1,600 mg rituximab + 26,800 units hyaluronidase
Frequency	Same as intravenous product	Same as intravenous product	Same as intravenous product
Volume	15 mL	5 mL	11.7 mL = 1,400 mg rituximab 13.4 mL = 1,600 mg rituximab
Administration	Abdomen Over 3 – 5 minutes *A second injection site may be chosen on the opposite side of the abdomen if the patient experiences pain, not relieved by slowing the delivery rate	Thigh Over 2 – 5 minutes *Second site option not mentioned in package labeling	Abdomen 5 minutes = 1,400 mg rituximab / 23,400 units hyaluronidase 7 minutes = 1,600 mg rituximab / 26,800 units hyaluronidase *A second abdominal injection site may be chosen if the administration is interrupted

DARZALEX FASPRO

Subcutaneous daratumumab (Darzalex Faspro [daratumumab and hyaluronidase-fihj]) was approved by the FDA in May 2020 upon release of data from the ongoing, phase III, non-inferiority COLUMBA trial.[1]

Eligible patients included those with a diagnosis of refractory or relapsed (received at least three lines of previous therapy including a proteasome inhibitor and an immunomodulatory drug) or double refractory (failed a proteasome inhibitor and an immunomodulatory drug but had a response to at least one previous treatment regimen) multiple myeloma. Patients were randomized to subcutaneous (SQ) (n=263) or intravenous (IV) (n=259) daratumumab and doses matched package labeling. Groups were well matched except the SQ group had more patients with Eastern Oncology Cooperative Group (ECOG) scores of one or higher as well as more patients with high-risk cytogenetics.

Ultimately, non-inferiority was achieved for both primary endpoints, mean maximum C_{trough} and overall response.[1] Bodyweight was specifically analyzed and there were no meaningful differences reported for the mean maximum C_{trough} levels in the subgroups (≤ 65 kg, 65 – 85 kg, and ≥ 85 kg), which was further substantiated with similar response rates across the same subgroups.

Progression-free survival (PFS) was similar between the SQ and IV groups (5.6 months versus 6.1 months, p=0.93). Overall survival data is not yet mature. Investigators evaluated patient satisfaction using a modified Cancer Therapy

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SUBCUTANEOUS

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Satisfaction Questionnaire (CTSQ). Mean scores for "Satisfaction with therapy" was consistently higher in the SQ group versus the IV group.

Lastly and importantly, infusion reactions were significantly lower for the SQ versus IV group (13% versus 34%, p<0.0001).[1] This finding was independent of bodyweight.

The COLUMBA trial reported the average time to reaction in the SQ group was 3.4 hours (IQR 1.5 – 4.4), which is an important patient education concept and may warrant extended observation post-administration. All patients received pre-medications (antipyretic, H1 antagonist, steroid and leukotriene antagonist optional) as well as post-dose steroids. Low-grade injection site reactions occurred in 7% of patients who received the SQ product and did not lead to any treatment discontinuations.

Mollie Beck

Doug Flora

Alicia Gesenhues

CONSIDERATIONS

▲ Potential, significant time savings for patients, pharmacy (verification, preparation) and nursing (administration)

▲ Pre-medications and post-medications recommended

▲ Patient education for delayed reaction recommended

▲ Consider observation time post-dose

▲ Non-inferior overall response

▲ Non-inferior mean maximum C_{trough}

▲ Monitor indications for use

HERCEPTIN HYLECTA

Subcutaneous trastuzumab (Herceptin Hylecta [trastuzumab and hyaluronidase-oysk]) was approved by the FDA in February 2019 upon release of data from two trials, HannaH[2,3] and SafeHER.[4]

The HannaH2 phase III trial, compared SQ versus IV trastuzumab in patients with newly diagnosed HER2+, early, non-metastatic breast cancer. Patients received SQ (n=297) or IV (n=299) trastuzumab, concurrent with chemotherapy in the neoadjuvant setting, followed by monotherapy in the adjuvant setting for one year.

In the primary analysis, non-inferiority was achieved for both primary endpoints, mean maximum C_{trough} (cycle 8, pre-surgery) and pathological complete response. Yet, the C_{trough} was approximately 30% higher in the SQ group at cycle 8. Investigators later indicate that despite the increased C_{trough}, the overall exposure based on the area under the curve (AUC) calculation was similar, due to the lower Cmax in the SQ group. This is likely due to the removal of a loading dose.

Additionally, adverse events (AEs) were overall similar in number, yet serious AEs were reported 20% more often in the SQ group. Cardiac AEs were overall uncommon and similar between both groups. Upon deeper analysis, serious AE descriptions were comparable indicating a possible reporting bias. In the final analysis of HannaH, six-year event-free survival, overall survival (OS), and serious AEs were comparable.[3]

The SafeHER phase III trial was similar to the HannaH trial, except for non-randomization, larger patient population (N > 2500), method of SQ administration (Cohort A: vial versus Cohort B: handheld syringe), adjuvant setting and a primary objective of safety and tolerability.[4]

Patients could receive trastuzumab SQ monotherapy or in combination with investigator's choice chemotherapy (concurrent or sequential). Ultimately, the rate of AEs varied in accordance with the timing of chemotherapy, which is to be expected. About 20% in each cohort of SQ administration experienced low-grade injection site reactions.

Overall, subcutaneous biologic antineoplastic medications offer many benefits, including a reduction in patient treatment time, pharmacy and nursing resources, in addition to data-supported, patient preference.

The PrefHER trail further demonstrates a patient preference for SQ formulations.[5] This randomized, two-cohort crossover study interviewed patients (N=236) who received SQ trastuzumab or IV trastuzumab for four cycles then switched to the opposite product for four cycles.

Of the responses, 216 (91.5%) patients preferred the SQ formulation due to time savings, less pain/discomfort, convenience, ease of administration, problems with IV, less stress/anxiety and other. The 16 (6.7%) patients who preferred IV indicated fewer reactions, environment/staff, perceived efficacy, ecological considerations and other. Additionally, of the 103 healthcare professionals interviewed, 73.8% were more satisfied with the SQ, 1.9% preferred IV and the remaining 24.3% of respondents indicated no preference.

CONSIDERATIONS

▲ Potential, moderate time savings for patients, pharmacy (verification, preparation) and nursing (administration)

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SUBCUTANEOUS

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▲ No loading dose recommended

▲ Non-inferior, long-term efficacy and safety data

▲ Non-inferior pharmacokinetic parameters

▲ Uncertain pharmacy/patient cost savings if compared to FDA approved biosimilar

▲ Monitor indication for use (especially HER2+ non-breast cancer, currently not approved)

RITUXAN HYCELA

Subcutaneous rituximab (Rituxan Hycela [rituximab and hyaluronidase]) was the first SQ antineoplastic approved by the FDA in June 2017.

The SAWYER study, a phase 1b, randomized, non-inferiority trial investigated SQ (n=88) versus IV (n=88) rituximab as first line in patients being treated for CD20+ chronic lymphocytic leukemia (in combination with fludarabine and cyclophosphamide).[6]

The primary endpoint of pharmacokinetic non-inferiority was met, demonstrating no meaningful difference between SQ rituximab 1,600 mg and IV rituximab 500 mg/m2.

AEs were similar between groups. Local cutaneous reactions occurred in 42% of the SQ population (versus 2% in the IV cohort), which were mainly grade 1 and 2. Time to B-cell depletion was similar between both groups.

The SABRINA studied similarly validated pharmacokinetic noninferiority for SQ rituximab 1,400 mg and IV rituximab 375 mg/m2 in patients with CD20+ follicular lymphoma (in addition to chemotherapy).

Overall response rates were comparable between groups. Although complete response rates were numerically higher in the SQ group, the study was not designed to demonstrate superiority.[7]

CONSIDERATIONS

▲ Potential, significant time savings for patients, pharmacy (verification, preparation) and nursing (administration)

▲ Patient MUST tolerate IV prior to switching to SQ

▲ Pre-medications recommended (antipyretic and antihistamine +/- steroid)

▲ Non-inferior pharmacokinetic parameters

▲ Uncertain pharmacy/patient cost savings if compared to FDA approved biosimilar

▲ Monitor indication for use (especially for non-oncology indications)

Overall, subcutaneous biologic antineoplastic medications offer many benefits, including a reduction in patient treatment time, pharmacy and nursing resources; in addition to data-supported, patient preference.

With all three current SQ approvals, efficacy and safety appear non-inferior to the IV formulations.

Institutions may consider conversion, yet should remain mindful of product-specific indications and billing codes, as well as proactivity with patient and staff education. As the transition to value-based care continues, critical examination of IV to SQ conversion is recommended.

With all three current SQ approvals, efficacy and safety appear non-inferior to the IV formulations. Institutions may consider conversion, yet should remain mindful of product-specific indications and billing codes, as well as proactivity with patient and staff education.

▲ **Mollie Beck**, PharmD, BCOP, is a Clinical Pharmacist Specialist, Inpatient Oncology at St. Elizabeth Healthcare. **Douglas Flora**, MD, is the Executive Medical Director of Oncology at St. Elizabeth Healthcare. **Alicia Gesenhues**, PharmD, BCOP, is the Oncology Pharmacy Clinical Coordinator and Oncology PGY2 Residency Program Director at St. Elizabeth Healthcare.

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ONCOLOGY CARE MODEL: MAKING THE MOVE FROM VOLUME TO VALUE

By William R. Mitchell, MD

The business of oncology is evolving from a volume-based model of fee-for-service to a value-based model of cost avoidance and shared savings.

The recent submission of the Oncology Care Model (OCM) version 2.0 to the Centers for Medicare & Medicaid Services (CMS) has private and commercial insurers actively exploring value-based models to minimize costs, and maximize quality and outcomes for their members.

Why is this important? In the fiscal year 2020, the total cost of cancer care in United States is projected to be at least $160 billion. The majority of this cost will not be related to direct care and active treatment of cancer patients; at least 65% of the total will be attributed to hospitalizations, emergency room visits, readmissions and financial toxicity.[1]

Within a value-based model of care, the medically integrated dispensing (MID) pharmacy offers an opportunity to minimize such costs, maximize shared cost savings and improve quality for oncology patients with high satisfaction in return.

TOXICITY

Toxicity is first and foremost among unnecessary healthcare costs. It can take on many forms, including financial toxicity, in which the patient cannot afford the medication, and physical toxicity, in which the patient experiences the biologic side effects of the medication.

Acute toxicity that progresses to involve emergency rooms and hospitals is the largest driver of healthcare costs for oncology patients.[2] Such visits can result from staff sending the patient to the emergency room, or patients who take the initiative upon themselves to go there. In either case, this represents a lost opportunity to minimize healthcare costs.

The healthcare team at Southern Oncology Specialists in Charlotte, North Carolina, includes (from left) Allison Knox, PA-C, Jack Burton, MD, Swetha Gujja, MD, and William R. Mitchell, MD.

Symptoms of toxicity and subsequent emergency room visits rest within four categories:

- **Gastrointestinal** – nausea, vomiting, dehydration, electrolyte abnormalities;
- **Pain-disease** related;
- **Hematologic** – anemia and neutropenia; and
- **Infectious** – pneumonia and sepsis.

Southern Oncology Specialists and its fully integrated pharmacy has the ability to help patients avoid hospitalization and ER visits by providing onsite IV hydration, simple analgesia, supportive medications, electrolyte replacement and

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It's important to recognize that toxicity begins at the time a new oncolytic prescription is written. The pharmacist must be the "hub of the wheel" for success. The role of the pharmacist must not only be to dispense medications, but to identify, notify and troubleshoot issues prior to any event worsening.

ONCOLOGY CARE MODEL

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antibiotics. Based on my experience, patients do not want to go to the hospital, and would prefer to go home, resulting in higher patient satisfaction.

THE FIRST FILL

It's important to recognize that toxicity begins at the time a new oncolytic prescription is written. The pharmacist must be the "hub of the wheel" for success. The role of the pharmacist must not only be to dispense medications, but to identify, notify and trouble-shoot issues prior to any event worsening.

Once the prescription is written, the first toxic event that can occur is financial in nature. Approximately 10% of any oral oncolytic prescriptions written cannot be filled due to finances.[3]

The pharmacist should involve a process that utilizes insurance approval and prior authorizations. The pharmacist should assist in completing all necessary paperwork. This will inform the pharmacist of whether or not the prescription can be filled within the MID pharmacy.

Filling the prescription within the medically integrated pharmacy will improve the utilization of co-pay assistance programs and enrollment into local and national foundations. This will ultimately help reduce the financial burden to the patient.

Free drug programs should be considered when all else fails in an effort to get the medication to the patient.

The ability to fill a second prescription rests with the patient to successfully complete the first prescription. Irrespective of any practice differences, this goal should be the same.

ADHERENCE AND SATISFACTION

Adherence is important for improved outcomes. Communication improves adherence. It requires that the pharmacy ensure the patient understands the medication and any potential side effects, the patient notifies the practice once toxicity begins, and follows up with proper documentation if the medication is not creating any toxicity.

With the help of the pharmacy, a practice can establish supportive processes to minimize, improve and reverse any toxic event.

Patient satisfaction is self-explanatory. If there is good communication, immediate intervention, minimization of financial toxicity and medication is delivered in an efficient manner, then the patient will be pleased with the service given and the quality improves.

INTEGRATION CONSIDERATIONS

The goal of any private practice with pharmacy integration should include the following:

Access: Increased and improved access for patients to receive oral oncolytics;

Adherence: Increased or improved adherence of patients to their oral oncolytics to maximize efficacy/response to therapy;

Cost/Risk: Mechanisms in place to minimize cost/risk to the patients and practice to reduce the likelihood of financial toxicity;

Logistics: Processes and pathways in place to quickly identify, intervene and prevent toxicity associated with oral oncolytics; and

Satisfaction: The ability to capture, measure and maximize patient satisfaction for those receiving oral oncolytics.

If you do not have an MID pharmacy within your practice, now is the time. Changes within healthcare and payment alternatives from conventional volume-based fee-for-service are becoming obsolete and unsustainable. For practices to remain solvent and survive, they most evolve to a value-based model.

TIME TO CHANGE IS NOW

If you do not have an MID pharmacy within your practice, now is the time. Changes within healthcare and payment alternatives from conventional volume-based fee-for-service are becoming obsolete and unsustainable. For practices to remain solvent and survive, they most evolve to a value-based model.

NCODA can provide essential resources to assist in this process, including their recently published *Patient-Centered Standards for Medically Integrated Dispensing* (in collaboration with ASCO), Positive Quality Intervention documents, Oral Chemotherapy Education sheets, Treatment Support Kits, financial assistance and patient monitoring/tracking tools.

Together we can improve the delivery of healthcare, reduce costs, improve outcomes and, most importantly, be there in direct care of our patients for their success.

▲ **William R. Mitchell**, MD, is founder of Southern Oncology Specialists in Charlotte, North Carolina.

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		500 mg/25 mL single-use vial		500-mg vial = 50 units

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REGION 10 LEADER TARYN NEWSOME LOVES HELPING CUT PATIENT COPAYS

Taryn Newsome, CPhT, is NCODA's Regional Leader for Region 10 – North Carolina, South Carolina, Virginia and West Virginia.

Newsome began her career as a medical assistant in San Diego, California, before moving to Richmond, Virginia. Newsome says becoming a pharmacy technician was never on her radar. She enjoyed her job and was taking classes to become a nurse when she was promoted to work as a pharmacy technician at Virginia Cancer Institute, where she continues to practice today.

After learning about NCODA from her pharmacist, Newsome decided to do her own research and quickly discovered NCODA's Oncology Pharmacy Technician Association (OPTA) and was overjoyed. Newsome said she wanted to help the voice of oncology pharmacy technicians and was soon on the leadership team. She is now one of the OPTA co-chairs. Prior to joining NCODA, she did not know of any leadership opportunities for pharmacy technicians.

Newsome says she loves waking up each morning to work as a pharmacy technician; her relationships with her coworkers and patients motivate her each day. She says she particularly enjoys helping reduce copays for patients; she loves providing affordable and effective care to her patients.

She said her parents were her biggest role models growing up, always ensuring she developed good values. Now, Newsome tries to be the same type of role model with her two energetic sons. She bonds with them each day by playing video games.

After a long and stressful day, she enjoys a glass of wine on the patio as well as spending time with family and friends. In her free time, Newsome says she enjoys getting wrapped up in a page-turning book or taking her sons to the movie theater.

MEET NCODA'S REGION 10 REGIONAL LEADER

Taryn Newsome, CPhT | *Virginia Cancer Institute*

Newsome looks forward to continue nurturing Region 10, OPTA & NCODA initiatives in her future years as an oncology leader.

Newsome describes herself as passionate, happy and empathetic. Her colleagues say you will see her smiling through the day, no matter what stressors she may face.

At previous NCODA meetings, Newsome said she took a backseat compared to her role now. Then she took the time to learn, connect and observe. Now, she looks forward to her first face-to-face meetings with NCODA Regional Leaders and OPTA leadership teams to put faces to names and relationships she has been growing over the years.

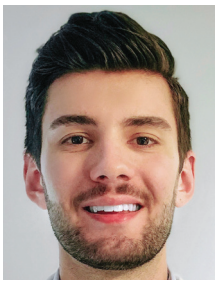
Newsome looks forward to continue nurturing Region 10, OPTA and NCODA initiatives in her future years as an oncology leader.

NCODA DIGITAL PLATFORMS ALLOW PHARMACY STUDENTS TO STAY ENGAGED DESPITE THE CHALLENGES OF COVID-19

By Jason Darmanin, PharmD Candidate (2021)

The COVID-19 pandemic has forced many people to make drastic lifestyle adjustments, and students in the healthcare field are no exception.

Not only has there been a complete switch to online courses and education for us, but internship and employment conditions have rapidly changed as well. Many employers are now requesting their students to take on additional shifts at both community and inpatient institutions, this in addition to an already jam-packed academic schedule. Still, other students have opted to graduate early to accommodate the high demand for much-needed medical personnel.



Jason Darmanin

Rapidly adjusting to a completely different learning style and increased workload was difficult for many of us; everything seemed to unravel at once and it quickly became hard to keep up.

Fortunately, as a student member of an NCODA Professional Student Organization (PSO) chapter, this change in lifestyle was a little easier for me. NCODA's digital platforms and resources helped keep me engaged in both learning and in the community. Our PSO has added a bit of normalcy to the academic lives of myself and my fellow classmates.

PSO chapter members have access to all NCODA resources, including initiatives like Oral Chemotherapy Education (OCE) sheets and the Financial Assistance tool for patients. Students also have the opportunity to attend NCODA's Spring Forum and Fall Summit international meetings, where we can gain valuable insights on the latest oral oncolytics, network with oncology and industry professionals and submit poster presentations on our own research.

But it's the PSOs that really sets NCODA apart for students. The initiative provides monthly calls, personal and professional development opportunities, Student Educational Talks (SETs) webinars, Oncology Leadership Series (OLS) and postgraduate opportunity Question & Answer sessions and webinars.

During the monthly PSO calls, NCODA collaborates with students from colleges and universities internationally to help advance NCODA's mission to improve patient care. Students can exchange ideas about activities their PSO chapter is partaking in, such as community outreach efforts. The calls also are available to students at schools who are working towards developing their own NCODA PSO chapters.

Currently there are 18 NCODA PSO chapters across 23 campuses, with dozens more in the pipeline, and all these schools are able to communicate monthly to stay up to date with NCODA news and events.

NCODA's webinars also provide an opportunity for Personal Professional Development (PPD), which are now a requirement at many schools. They provide an opportunity to document how students have developed into leadership roles.

NCODA also provides Student Educational Talks (SETs), allowing students to learn from oncology experts in the field, encompassing a wide variety of specialties. It's an incredible opportunity; most pharmacy schools don't teach oncology curriculum until the final year or final semester, not long before students go on their rotations and make final career path decisions.

Another NCODA student resource is the Oncology Leadership Series (OLS). These webinars give students a glimpse into the lives of prominent oncology and industry leaders. Students learn key details on different career path options and how to be the best leader for their future team and patients.

NCODA also offers Question & Answer sessions for students interested in fellowship or residency training programs. These sessions give students details on the day-to-day responsibilities of current residents and fellows, and they provide key guidance on how to better prepare for post-graduate endeavors.

NCODA's oncology journal club workshops allow students to digitally converse with oncology professionals about scientific papers and research journals. Participating students are provided with an introduction and deeper insights into the latest clinical oncology trials.

Finally, NCODA's COVID-19 debriefings have proven beneficial at a time when information and facts are changing a mile a minute. With so much misinformation spreading on social media, it is reassuring for students to know that they can access briefings from the experts to keep up to date on the latest information.

While the COVID-19 pandemic has forced many students in the healthcare field to make drastic lifestyle adjustments, being a student member of an NCODA PSO chapter has enabled myself and my fellow classmates to continue to pursue our academic and career goals.

▲ **Jason Darmanin** is a PharmD candidate (2021) at The University of Rhode Island College of Pharmacy in Kingston, Rhode Island. Jason also serves as the National President of the NCODA Professional Student Organization.

PROFESSIONAL STUDENT ORGANIZATION

EMPOWERING YOUR EDUCATION

NCODA is collaborating with universities and colleges worldwide to offer pharmacy students membership into a professional organization that is centered on advancing NCODA's Mission of improving patient care.

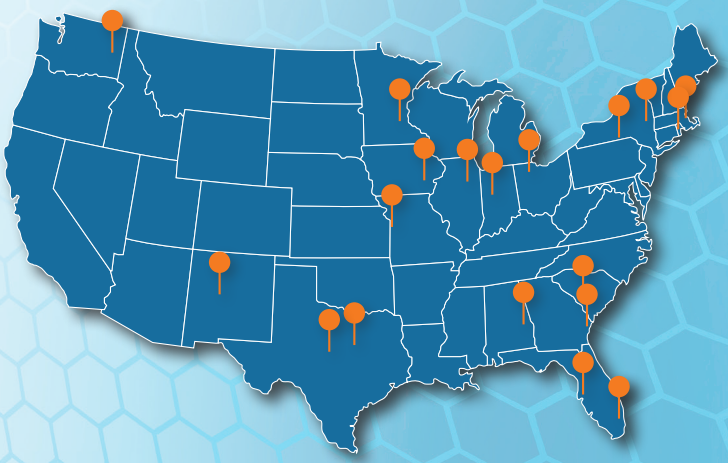
The NCODA Professional Student Organization was established for students interested in oncology pharmacy, association management & industry leadership.

BENEFITS

- Opportunities to attend NCODA international meetings & present research
- Increased networking opportunities with clinical & industry professionals
- Participation in community service events through NCODA-led initiatives & partnerships
- Opportunities to help create new educational materials that will aid cancer patients worldwide

ESTABLISHED CHAPTERS

- Albany College of Pharmacy and Health Sciences (Albany, NY)
- Auburn University Harrison School of Pharmacy (Auburn, AL)
- Binghamton University School of Pharmacy and Pharmaceutical Sciences (Johnson City, NY)
- Lake Erie College of Osteopathic Medicine (Bradenton, FL)
- Massachusetts College of Pharmacy and Health Sciences (Boston, MA)
- Midwestern University Chicago College of Pharmacy (Downers Grove, IL)
- Nova Southeastern University College of Pharmacy (Davie, FL)
- Purdue University College of Pharmacy (West Lafayette, IN)
- South University School of Pharmacy (Columbia, SC & Savannah, GA)
- Texas Tech University Health Sciences Center School of Pharmacy (TX)
- The University of Rhode Island College of Pharmacy (Kingston, RI)
- The University of Toledo College of Pharmacy (Toledo, OH)
- University of Iowa (Iowa City, IA)
- University of Minnesota College of Pharmacy (Minneapolis, MN)
- University of Missouri-Kansas City (Kansas City, MO)
- University of New Mexico College of Pharmacy (Albuquerque, NM)
- University of North Texas Health Science Center (Fort Worth, TX)
- Washington State University College of Pharmacy (Spokane, WA)



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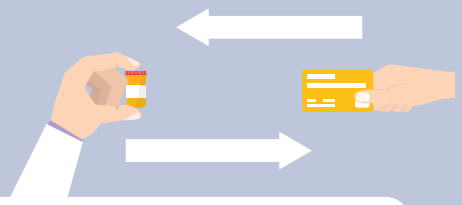
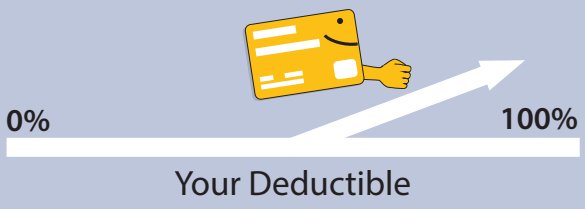
COPAY ACCUMULATORS: WHAT TO KNOW

WHAT'S THE DIFFERENCE?

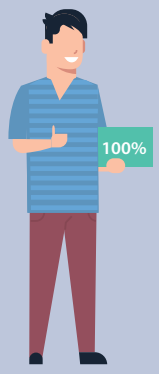
WITHOUT ACCUMULATOR PROGRAMS



Patients with certain types of insurance can use manufacturer coupon cards to cover copays



The patient's manufacturer coupon card helps to meet their deductible requirement



Once the deductible has been met, insurance will begin providing maximum coverage

RECEIPT

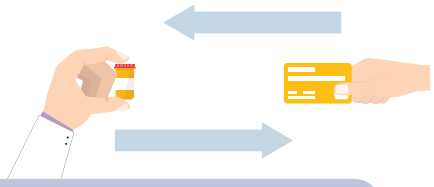
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

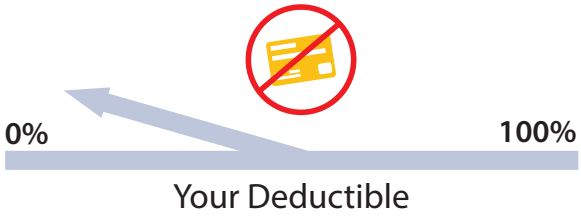
$0.00
Remaining Deductible After Coupon*

*$2,000.00 = $5.00 paid by patient
$1,995.00 coupon

WITH ACCUMULATOR PROGRAMS



Patients can still use their coupon cards but ...



With the accumulator program, the amount paid by your coupon card would no longer count towards helping to meet your deductible

You as the patient will still need to pay all the money left over to reach your deductible!

RECEIPT

Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

$1,995.00
Remaining Deductible After Coupon*

*Only $5.00 counts toward the patient's deductible and health insurers keep the $1,995.00 coupon!

VS.

An example of what happens at the pharmacy counter

NCODA

Looking for more information?
Email contact@ncoda.org to get connected
Scan to visit, or check out www.NCODA.org

OPTA'S MONTHLY WEBINARS AT A GLANCE

Pharmacy technicians who are members of NCODA's Oncology Pharmacy Technician Association (OPTA) are eligible to attend webinars held the first Wednesday of each month (typically at 3 p.m. Eastern Time).

OPTA webinars are designed to allow oncology pharmacy technicians to engage with one another, join upcoming projects and learn about new opportunities.

Oncology Pharmacy Technician Association
Dispensing Positive Outcomes

Each month's webinar is moderated by a member of the OPTA leadership team, and follows a similar agenda: a review of the group's mission, association updates, new medication reviews, a Technician in Focus, and either a peer presentation or hot topic.

In July, for instance, the webinar was moderated by OPTA leader Sara Eisenhart. Stephen Ziter, NCODA Assistant Director of Patient Centered Initiatives, presented updates from the recent OPTA survey, which provided insight on content to be presented on future webinars.

OPTA Cochair Becki Tinder announced the new regional liaisons who will be assisting NCODA's Regional Leaders. Allison Monsell, a PharmD candidate from Shenandoah University's Bernard J. Dunn School of Pharmacy, provided a presentation on the new medication ZEPZELCA (lurbinectedin), which is indicated as a second-line treatment for metastatic non-small cell lung cancer with disease progression on or after platinum-based therapy. It is packaged as a single-dose powder vial, and the dosing is 3.2 mg/m2 for 21 days, infused over one hour, until disease progression or unacceptable toxicity.

The most common side effects included in patient monitoring are thrombocytopenia, neutropenia, grade 3 hepatotoxicity, fatigue and nausea. Supportive medications recommended are dexamethasone and ondansetron.

ZEPZELCA's access and reimbursement program is called JazzCares. For more information, refer to Monsell's presentation on the OPTA Basecamp page, or go to www.zepzelcapro.com.

Brandi Gudwien, CPhT, was the Technician in Focus in July. Her practice, Alabama Oncology, is located in Birmingham, Alabama. The practice has a medically integrated dispensing (MID) pharmacy, Alabama Rx, that dispenses for all eight clinics. Alabama Oncology has 18 medical oncologists, two gynecologic oncologists and a surgical oncologist. Alabama Rx has one pharmacist and three patient advocates/pharmacy technicians on staff.

The hot topic for July was "Protecting Your Pharmacy," an open discussion session to define how policies and procedures should be formed to ensure the safety of your pharmacy. Some technicians said their policy is centered around physical location, accreditation standards and what they have found worked in previous personal experience.

Out of OPTA's 220 members, 85% are certified (CPhT). Most members have two to five years of practice experience in the community/in-office setting. Thirty percent handle both IV and oral chemotherapy, while 21% and 49% are IV or oral only, respectively.

Scan here for more info about OPTA or to complete the online membership application.

DAN DURAN

CARDINAL HEALTH SPECIALTY SOLUTIONS

Dan Duran, is Senior Vice President of Provider Solutions with Cardinal Health Specialty Solutions, a multinational healthcare services company with headquarters in Dublin, Ohio, and Dublin, Ireland. The company specializes in the distribution of pharmaceuticals and medical products, serving more than 100,000 locations. It also manufactures medical and surgical products, including gloves, surgical apparel and fluid management products.

Cardinal Health has been a strong supporter of NCODA. Share with us areas where Cardinal and NCODA have collaborated in the past, as well as any initiatives that we may be working on in the future.

Cardinal Health is proud to be a platinum sponsor of NCODA. We believe that NCODA offers networking, connection and community for Medically Integrated Dispensing (MID) practices, which is important for their success.

With the challenges these practices face in the industry today, the ability to come together as a group and access education and resources offered by NCODA, such as webinars and the annual conference events, is vital to their continued success. And, supporting organizations like NCODA enables the oncology community to work together to improve cancer care, which ultimately benefits the patients we all serve.

NCODA offers added value to practices by bringing together stakeholders who play important roles across the patient journey– from doctors to pharmacists, and pharmacy technicians to business partners. Bringing together a diverse group enables more insightful conversations, which is one of the many reasons we support NCODA.

In what ways has NCODA brought value to your organization? Are any of the NCODA initiatives particularly useful from your perspective?

In our conversations with practices, we have repeatedly heard that the ***Beyond the First Fill*** program is incredibly helpful.

Additionally, practices have noted that connections they have made through NCODA have been particularly helpful when working through contract issues and getting access to networks. By leveraging their networks, practices are able to reach out to others who have been in similar situations for advice and guidance on new and different approaches.

Cardinal Health also has championed initiatives such as The Cost Avoidance and Waste Tracker and compliance tools, which we believe enable practices to optimize and grow their business. We also encourage the pharmacy technicians we work with to become a part of the Oncology Pharmacy Technician Association (OPTA). This subgroup of NCODA offers discussion forums and a centralized website to network and connect with other pharmacy technicians from around the country.

Is there anything specifically that NCODA can do in the future to continue to support Cardinal Health and its respective member practices?

Moving forward, NCODA should continue to provide resources for practices to optimize their ability to serve patients and operate successfully.

Specifically, as our communities work to address the COVID-19 global pandemic and work on recovery, NCODA can play an important role in sharing best practices and mobilizing its membership to work collectively to address the challenges community oncology practices are facing. We believe this is an inflection point and a moment where NCODA can lead the way.

From the GPO perspective, what are the greatest challenges you see in the short- and long-term future? What would a possible solution look like and how could it be accomplished?

In a challenging market, Cardinal Health and VitalSource GPO are focused on helping practices stay viable and build a roadmap for success in the future.

Some of the most common challenges we encounter when we work with practices who have Medically Integrated Dispensaries are cash flow, access to payers and reimbursement.

Through our Site of Care Dispensing program, we consult with these practices and offer guidance on how to overcome these obstacles and navigate the complexities so they can gain network access. We also offer tools and expertise to help practices maximize their reimbursement and have visibility into their cash flow.

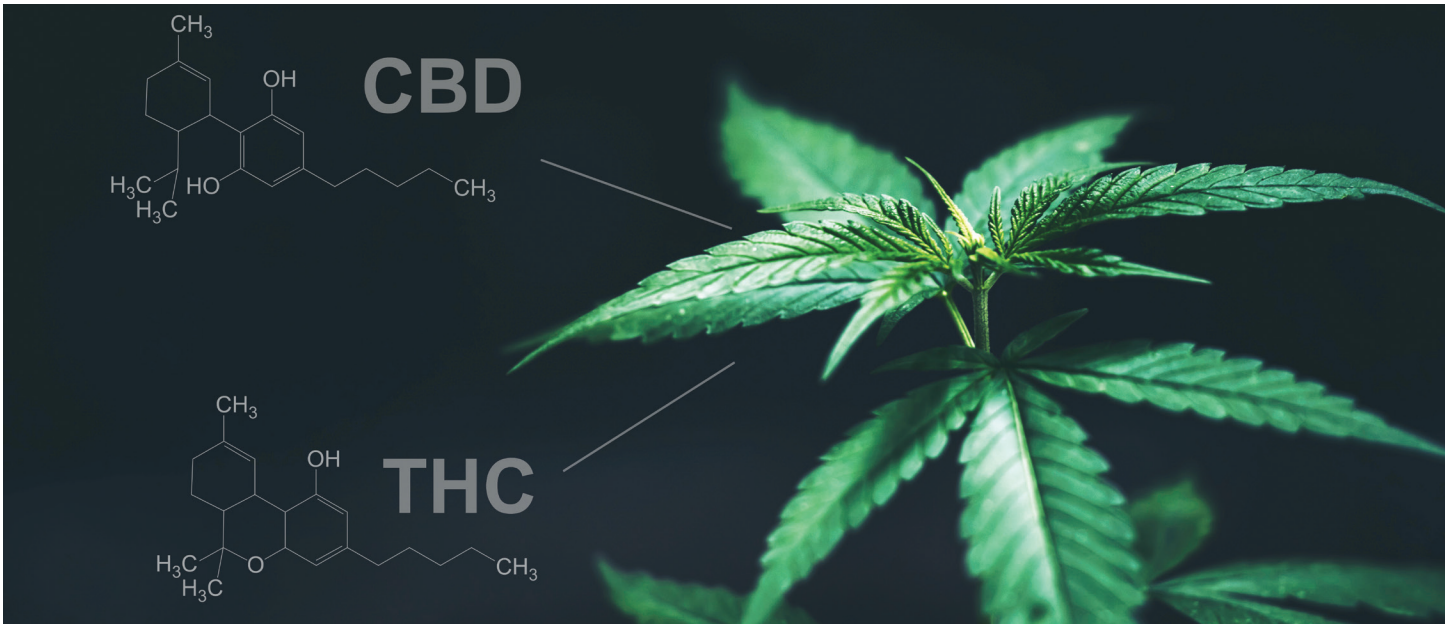
During our 16-week implementation process, we create a detailed action plan that walks the practice through how to set up a dispensary and keep it running smoothly.

We also consult with practices on establishing a retail pharmacy or converting an existing dispensary to a retail pharmacy.

In addition to helping practices with their MIDs, we offer expert insights, responsive tools and committed support to enable oncology practices to deliver high-quality, cost-effective care.

Through our technology solutions, practices can access deep insights to deliver more for their patients find new opportunities to add value and make more informed decisions to enhance their financial, operational and clinical performance. Our team of practice consultants has extensive experience in ACHC and URAC accreditation, as well as technology integration.

Overall, we are committed to helping community oncology practices remain a vital asset to their patients and community.



CANNABIS AND CANCER

A PRIMER FOR CLINICIANS

By Paul J. Daeninck, MD, MSc, FRCPC, & Janice M. Vaughn Knox, MD, MBA

While cannabis has been used as medicine since nearly the dawn of civilized history, its potential in the field of cancer treatment is a relatively recent discovery.[1]

Cannabis has been found in the tombs of Chinese emperors, Indian mystics and Egyptian royalty, a nod to its sacred status in ancient culture.

The earliest recording of cannabis as medicine is found in the ancient Chinese pharmacopeia, the "Shennong Bencao Jing," which dates back to 2737 BC.[2] Cannabis found its way to the American colonies as early as the 1600s and hemp-based products became widely used for clothing, rope and paper as well as medicine. By the 1850s, cannabis had been added to the American pharmacopeia.

Yet throughout history there has been pushback against the use of cannabis for medicinal, spiritual or political reasons.

The early 1900s saw significant limitations and outright prohibition of cannabis use by many U.S. states. The 1937 Marijuana Tax Stamp Act delivered a devastating blow to the use of cannabis as medicine. Physicians, pharmacists, and processors faced a mountain of required governmental paperwork and monetary penalties (users were required to purchase a federally issued marijuana stamp) that proved onerous, effectively reducing the willingness to prescribe or produce cannabis for medicinal use.

The final blow came when the plant was dropped from the American pharmacopeia and subsequently added to Schedule I of the Controlled Substance Act in 1970.[3]

FIRST FDA APPROVALS

However, resourceful chemists created synthetic isomers of tetrahydrocannabinol (THC), thought to be the most active component of cannabis and, after human clinical trials, nabilone and dronabinol were approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting (CINV) in 1985. Dronabinol indications were updated in 1992 when the FDA added treatment of "anorexia associated with weight loss in patients with AIDS."[4]

In spite of the prohibition of cannabis in many Western countries, Israeli researchers continued to study the plant. Dr. Raphael Mechoulam, a forward-thinking organic chemist, synthesized and described the 21-carbon structure of cannabidiol (CBD) in 1963, followed by the structures of Δ-9-THC and cannabigerol (CBG) in 1964.

Twenty-four years would

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CANNABIS

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pass before Mechoulam's work would lead to a key discovery by researchers Allyn Howlett and William Devane in St. Louis. They radioactively tagged dronabinol to map out and pinpoint the exact locations of a previously unrecognized neuroreceptor system, widely pervasive and appearing to outnumber other neuroreceptor systems (including the opiate receptors).

This first neuromodulatory receptor, labeled CB1, was primarily isolated to structures in the brain and CNS. A second receptor, CB2, identified in 1992, was found to be immunomodulating in function, and isolated primarily in the immune system and the peripheral nervous system.

Both receptors located on the presynaptic membrane, which eventually led to discovery of their function.[5] In broad simplification, the CB1 receptor mediates psychoactivity, while CB2 regulates immune response.[6]

RESEARCH CONTINUES

In 1992, Dr. Mechoulams's team isolated the first "endo"-cannabinoid ligand, anandamide (Sanskrit for "bliss"), also known as N-arachidonoylethanolamine (AEA). This was followed by the isolation of a second endocannabinoid, 2-arachydonyl glycerol (2-AG) in 1995.

Both are endogenous lipid ligands produced on-demand in postsynaptic membranes and act in a retrograde fashion, traveling across the synaptic junction to trigger the cannabinoid receptors on the presynaptic membrane, working in a feedback fashion to control the release of other neurotransmitters and thus modulating their activity.[7]

Researchers also identified the enzymes responsible for synthesizing (DAGL and NAPE) and degrading (FAAH and MAGL) the endocannabinoids. These major components, cannabinoid receptors, endocannabinoid ligands, and synthesizing and degrading enzymes, are now collectively known as the endocannabinoid system or ECS.[8]

Janice M. Vaughn Knox, MD, MBA

Paul J. Daeninck, MD, MSc, FRCPC

Clinical evidence of benefits for cancer-related symptoms in patients using cannabinoids has been mounting since the 1980s, but most publications report small trials of short duration.[9] Large-scale, randomized controlled trials, long held to be gold standard for drug interventions, are few and far between. This is the result of the continuing Schedule I status of cannabis in the USA and other jurisdictions, as well as the general lack of standardized cannabis-derived products.[10]

More recently, meta-analysis and systematic reviews have defined the level of evidence and the potential role of cannabinoids in cancer care. Moderate levels of evidence support use as adjuvant agents in CINV as well as cancer pain.[9,11] This has been supported in guidelines from the NCCN and ASCO for CINV, pain in cancer survivors and palliative care.[12,13]

Clinical evidence of benefits for cancer-related symptoms in patients using cannabinoids has been mounting since the 1980s, but most publications report small trials of short duration. Large-scale, randomized controlled trials, long held to be gold standard for drug interventions, are few and far between.

Evidence for use in cachexia and as an appetite stimulant is less robust, with no studies showing additional benefit when compared to megestrol acetate.[9]

Use in anxiety and depression related to malignancy is not well-supported nor recommended at this juncture.[9,10]

Pharmaceutical cannabinoids or cannabis extracts (THC or THC combined with CBD) have the strongest supportive evidence, with very few studies showing benefit for inhaled cannabis and virtually none for any other format of administration.[14]

CANNABOIDS AND CANCER

Are cannabinoids a treatment for cancer? Research employing cell culture and animal models has progressed rapidly since the initial Journal of National Cancer Institute report in 1975.[1] The list of different malignancies sensitive to cannabinoids (mostly THC, but some THC/CBD combination products) in pre-clinical and animal studies is growing, and the mechanisms have been well documented.[15,16]

Support for use in malignancies includes increased expression of CB1/CB2-receptors by aggressive cancers (such as ovarian or breast cancer), GPR-55 expression in multiple cancers (silencing of which reduces malignant potential) and identification of CB1/CB2 up-regulation in malignant gliomas.[15,16] However, clinical trial evidence in humans is sorely lacking.

There are a few case reports and case series documenting a reduction in size or prolongation of survival in patients using cannabis or extracts.[10,17] However, these n-of-1 reports are complicated by lack of consistency in product and dosing.

Two small clinical trials have been reported: the first showed the use of a THC extract to be safe in nine patients diagnosed with gliomas, but did not show any survival benefit.[18]

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CANNABIS

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The second study also in patients with gliomas (only reported in poster form to date), demonstrated an increase in response rate and prolongation of one-year survival in patients using temozolomide and a balanced THC/CBD combination product when compared to patients taking temozolomide and placebo.[19]

Other clinical trials are ongoing, hopefully with results reporting within the next few years.[20]

NOT A SUBSTITUTE FOR CHEMOTHERAPY

We also know that some patients may forego standard chemotherapy for cannabinoids in the belief that these "natural" products will be effective against their malignancies. There have been no reports of spontaneous remissions or cures using cannabinoids as single agents. These patients end up either resorting to chemotherapy with some benefit, or unfortunately, succumb to their disease after refusing to stop their cannabis products.[10]

Clinicians should also be aware of the possible adverse events that patients could encounter using THC or THC/CBD-containing products for cancer-related symptoms. These include dizziness, dry mouth, mood disturbances, psychosis, paranoia, anxiety, impaired cognitive function, confusion, hallucinations, impaired reaction time, increased heart rate, decreased blood pressure, risk of arrhythmias and diarrhea.[21,22]

Drug interactions due to the induction or inhibition of CYP 450 isoenzyme activity have been documented to occur with warfarin, valproic acid, clobazam and theophylline.[23,24] It is best for clinicians to review all medications patients are taking and educate them on possible adverse effects before starting a course of medicinal cannabinoids.

Cannabis and cannabinoids have an established role in supportive care for cancer patients. These compounds are also gaining more public acceptance as more jurisdictions move forward with medical and more recently, recreational legalization. As we discover more about these highly useful compounds and how they interact with our ECS, we will be able to help more patients to effectively target their cancer and cancer-related conditions.

▲ **Paul J. Daeninck**, MD, MSc, FRCPC, is an attending medical oncologist and palliative medicine consultant with CancerCare Manitoba, and an Assistant Professor with the University of Manitoba, Winnipeg, Canada. **Janice M. Vaughn Knox**, MD, MBA, is the co-founder of American Cannabinoid Clinics, Advent Academy, and CEO of Doctors Knox, Inc., in Portland, Oregon.

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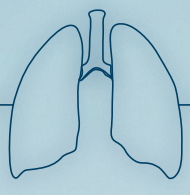


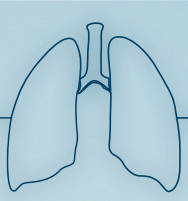
NOW APPROVED

OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

+

YERVOY® (ipilimumab)
Injection for intravenous use 5 mg/mL

Please scan the QR code above for more information on a new indication for OPDIVO + YERVOY



NOW APPROVED

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Checkmate 227

For patients with 1L mNSCLC (PD-L1 ≥1%)

OPDIVO®, in combination with YERVOY®, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Primary analysis (PD-L1 ≥1%): median OS was 17.1 months (95% CI: 15.0–20.1) with OPDIVO + YERVOY vs 14.9 months (95% CI: 12.7–16.7) with chemo (HR=0.79; 95% CI: 0.67–0.94; *P*=0.0066).[1]

Checkmate 9LA

For patients with 1L r/m NSCLC, regardless of PD-L1 expression

OPDIVO, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

Primary analysis: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY and chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo (HR=0.69; 96.71% CI: 0.55–0.87; *P*=0.0006).[1]

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous use.[1,2]

1L=first-line; ALK=anaplastic lymphoma kinase; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; mNSCLC=metastatic non-small cell lung cancer; OS=overall survival; PD-L1=programmed death-ligand 1; r/m=recurrent or metastatic.

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions

- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

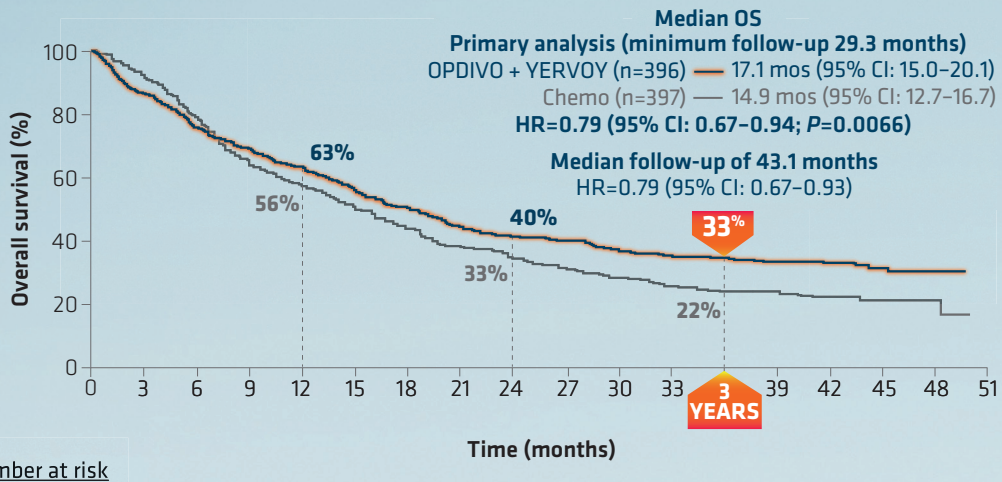
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of full Prescribing Information for OPDIVO and YERVOY on the following pages.

Bristol Myers Squibb™

For patients with mNSCLC (PD-L1 ≥1%)

OPDIVO® (nivolumab) + YERVOY® (ipilimumab) offers dual I-O durability and long-term survival: 33% of patients alive at 3 years[1,3*]

Checkmate 227 **OS for PD-L1 ≥1% (extended follow-up analysis)[1,3,4]**



Number at risk

OPDIVO + YERVOY	396	341	295	264	244	212	190	165	153	145	132	124	121	97	67	27	5	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	62	32	13	4	0

Median follow-up of 43.1 months.[3]

- The median PFS was 5.1 months (95% CI: 4.1–6.3) with OPDIVO + YERVOY and 5.6 months (95% CI: 4.6–5.8) with chemo alone; HR=0.82; 95% CI: 0.69–0.97[1]
- 29% of patients enrolled had SQ disease; 71% had NSQ disease[1]

Study design: Checkmate 227 was a randomized, open-label phase 3 trial in patients with metastatic or recurrent NSCLC. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1, and no prior systemic anticancer therapy. Patients with known *EGFR* mutations or *ALK* translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. In Part 1a (n=793), patients with PD-L1 ≥1% were randomized to OPDIVO 3 mg/kg q2w + YERVOY 1 mg/kg q6w (n=396) or platinum-doublet chemotherapy* (n=397). The primary endpoint in Part 1a was OS in patients with PD-L1 ≥1%. Pre-specified descriptive efficacy outcome measures included PFS, ORR, and DOR.[1,5]

*Vs chemo. In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.[1,4,5]

CR=complete response; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IHC=immunohistochemistry; I-O=immuno-oncology; mDOR=median DOR; mo=month; NSQ=non-squamous; ORR=overall response rate; PFS=progression-free survival; PR=partial response; q2w=every 2 weeks; q3w=every 3 weeks; q6w=every 6 weeks; SQ=squamous.

Summary of Warnings and Precautions

- OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials. YERVOY is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogenic hematopoietic stem cell transplant after YERVOY, embryo-fetal toxicity and risks associated when administered in combination with OPDIVO.

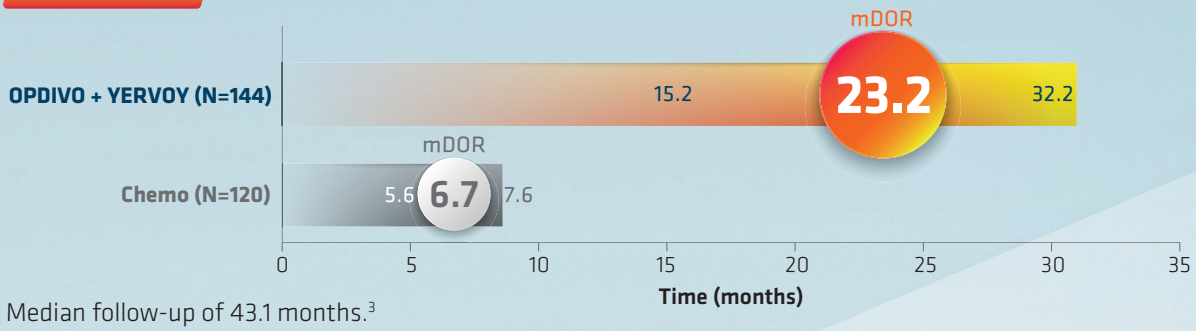
Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of full Prescribing Information for OPDIVO and YERVOY on the following pages.

For patients with mNSCLC (PD-L1 ≥1%)

mDOR of 23.2 months among OPDIVO + YERVOY responders[1]

- ORR was 36% (142/396, 95% CI: 31–41), 5.8% CR, 30.1% PR with OPDIVO + YERVOY and 30% (119/397, 95% CI: 26–35), 1.8% CR, 28.2% PR with chemo[1,4,5]

Checkmate 227 **mDOR and range (extended follow-up analysis)[3]**



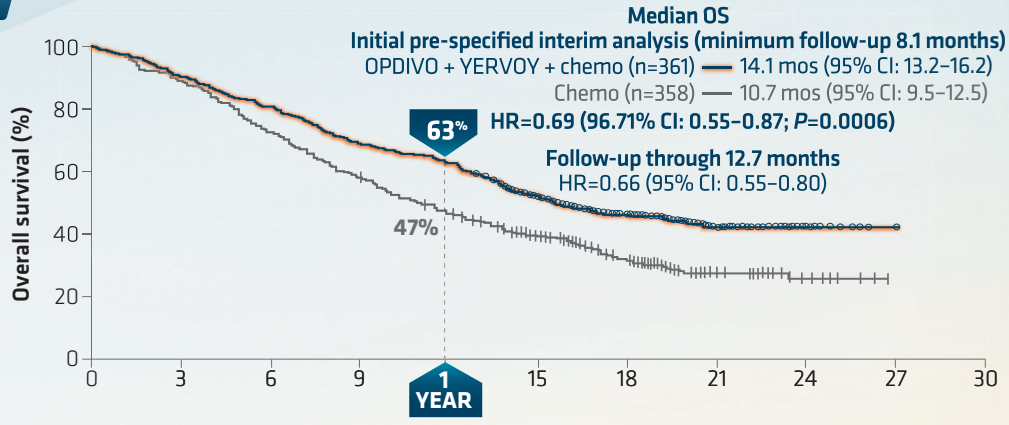
Median follow-up of 43.1 months.[3]

- In Checkmate 227 Part 1a, PFS, ORR, and DOR were pre-specified descriptive analyses. The primary efficacy outcome measure was OS[1,5]

For patients with r/m NSCLC, regardless of PD-L1 expression

OPDIVO + YERVOY with limited chemo† achieved superior OS[1‡]

Checkmate 9LA **Overall survival[1,6]**



Number at risk

OPDIVO + YERVOY + chemo	361	326	292	250	227	153	86	33	10	1	0
Chemo	358	319	260	208	166	116	67	26	11	0	0

Minimum follow-up of 12.7 months.[6]

- Efficacy results from pre-specified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) with an 8.1-month minimum follow-up[1,6]
  - Median PFS: 6.8 months (95% CI: 5.6–7.7) with OPDIVO + YERVOY with chemo vs 5.0 months (95% CI: 4.3–5.6) with chemo alone; HR=0.70 (97.48% CI: 0.57–0.86); *P*=0.0001
  - ORR: 38% (95% CI: 33–43) with OPDIVO + YERVOY with chemo and 25% (95% CI: 21–30) with chemo
- Median OS at the 12.7-month follow-up analysis: 15.6 months (95% CI: 13.9–20.0) with OPDIVO + YERVOY with chemo and 10.9 months (95% CI: 9.5–12.5) with chemo[1,6]

Study design: Checkmate 9LA was a randomized (1:1), open-label phase 3 study of OPDIVO 360 mg q3w in combination with YERVOY 1 mg/kg q6w and 2 cycles of histology-based chemotherapy‡ versus 4 cycles of platinum-doublet chemotherapy‡ as a first-line treatment in patients with metastatic or recurrent NSCLC regardless of histology or PD-L1 status. Treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. The primary endpoint was OS.
Additional efficacy outcome measures included PFS, ORR, and DOR.[1]

†Two cycles of platinum-doublet chemo.[1]
‡Vs chemo. In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance therapy; SQ: paclitaxel + carboplatin.[1]

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur at any time after starting or discontinuing YERVOY® (ipilimumab). Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue YERVOY depending on severity. In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less followed by corticosteroid taper for at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroid therapy. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Pneumonitis

- OPDIVO® (nivolumab) can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In NSCLC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with OPDIVO 360 mg every 3 weeks in combination with YERVOY 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with OPDIVO in combination with YERVOY only.

Immune-Mediated Colitis

- OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis.
- Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Immune-Mediated Hepatitis

- OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4.

Immune-Mediated Endocrinopathies

- OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Withhold for Grades 2, 3, or 4 endocrinopathies if not clinically stable. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction

- OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine.

Immune-Mediated Skin and Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous exfoliative rashes. Withhold YERVOY until specialist assessment for Grade 2 and permanently discontinue for Grade 3 or 4 exfoliative or bullous dermatologic conditions.

Immune-Mediated Encephalitis

- OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis.

Other Immune-Mediated Adverse Reactions

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Dose modifications for YERVOY for adverse reactions that require management different from these general guidelines are summarized as follows. Withhold for Grade 2 and permanently discontinue YERVOY for Grade 3 or 4 neurological toxicities. Withhold for Grade 2 and permanently discontinue YERVOY for

Grade 3 or 4 myocarditis. Permanently discontinue YERVOY for Grade 2, 3, or 4 ophthalmologic adverse reactions that do not improve to Grade 1 within 2 weeks while receiving topical therapy OR that require systemic therapy. Across clinical trials of OPDIVO in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome. In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, nerve paresis, angiopathy, temporal arteritis, pancreatitis (1.3%), arthritis, polymyositis, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis, blepharitis, episcleritis, orbital myositis, and scleritis. Some cases of ocular IMARs have been associated with retinal detachment.

- If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. Severe infusion-related reactions can also occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions and interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1 or CTLA-4 receptor blockade and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody or YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

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

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

- In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation

- It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO or YERVOY, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

Serious Adverse Reactions

- In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions

- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

Please see accompanying brief summary of Full Prescribing Information for OPDIVO and YERVOY on the following pages.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **3.** Ramalingam SS, Ciuleanu TE, Pluzanski A, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: three-year update from CheckMate 227 part 1. Oral presentation at ASCO 2020. Abstract 9500. **4.** Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med.* 2019;381(21):2020-2031. **5.** Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med.* 2019;381(21):2020-2031 [supplementary appendix]. **6.** Reck M, Ciuleanu TE, Dols MC et al. Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA. Oral presentation at ASCO 2020. Abstract 9501.

Bristol Myers Squibb™

7356US2001819-02-01 07/20

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Please also see Brief Summary for YERVOY® (ipilimumab) following OPDIVO® (nivolumab).

OPDIVO® (nivolumab) injection, for intravenous use

℞ ONLY

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

INDICATIONS AND USAGE

- OPDIVO (nivolumab), in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test *[see Dosage and Administration]*, with no EGFR or ALK genomic tumor aberrations.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.3) in full Prescribing Information]*. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology. Fatal cases have been reported.

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 5% of patients and withholding of OPDIVO with ipilimumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of OPDIVO with ipilimumab.

The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with OPDIVO in combination with ipilimumab only.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of OPDIVO *[see Dosage and Administration (2.3) in full Prescribing Information]*.

When administered in combination with ipilimumab, withhold OPDIVO and ipilimumab for moderate colitis (Grade 2). Permanently discontinue OPDIVO and ipilimumab for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations.

For patients without hepatocellular carcinoma (HCC): withhold OPDIVO for moderate (Grade 2) immune-mediated hepatitis and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Endocrinopathies

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Adrenal Insufficiency

OPDIVO can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Hypothyroidism and Hyperthyroidism

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

Type 1 Diabetes Mellitus

OPDIVO can cause Type 1 diabetes mellitus. Monitor for hyperglycemia. Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue OPDIVO for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Immune-Mediated Skin Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.3) in full Prescribing Information]*.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO (nivolumab) for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash.

Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients who received OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients who received OPDIVO or OPDIVO in combination with ipilimumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Embryo-Fetal Toxicity

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

Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling *[see Warnings and Precautions]:* Immune-Mediated Pneumonitis, Immune-Mediated Colitis, Immune-Mediated Hepatitis, Immune-Mediated Endocrinopathies, Immune-Mediated Nephritis and Renal Dysfunction, Immune-Mediated Skin Adverse Reactions, Immune-Mediated Encephalitis, Other Immune-Mediated Adverse Reactions, Infusion-Related Reactions.

Clinical Trials Experience

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

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks (n=576) in patients enrolled in CHECKMATE-227; and OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361).

First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.3) in full Prescribing Information]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. OPDIVO and ipilimumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction. The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus. Tables 1 and 2 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 1: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7

(Continued)

Table 1: Adverse Reactions in ≥10% of Patients Receiving OPDIVO (nivolumab) and Ipilimumab - CHECKMATE-227 *(Continued)*

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.
[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.
[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.
[d] Includes pruritus and pruritus generalized.
[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[h] Includes dyspnea and dyspnea exertional.
[i] Includes cough and productive cough.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were: *Skin and Subcutaneous Tissue:* urticaria, alopecia, erythema multiforme, vitiligo; *Gastrointestinal:* stomatitis, pancreatitis, gastritis; *Musculoskeletal and Connective Tissue:* arthritis, polymyalgia rheumatica, rhabdomyolysis; *Nervous System:* peripheral neuropathy, autoimmune encephalitis; *Blood and Lymphatic System:* eosinophilia; *Eye Disorders:* blurred vision, uveitis; *Cardiac:* atrial fibrillation, myocarditis.

Table 2: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

Laboratory Abnormality	OPDIVO and Ipilimumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.3) in full Prescribing Information]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 3 and 4 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 3: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0

(Continued)

Table 3: Adverse Reactions in >10% of Patients Receiving OPDIVO (nivolumab) and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA *(Continued)*

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.
[a] Includes fatigue and asthenia
[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis
[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain
[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria
[f] Includes pruritus and generalized pruritus
[g] Includes cough, productive cough, and upper-airway cough syndrome
[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea
[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine
[j] Includes dizziness, vertigo and positional vertigo

Table 4: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Immunogenicity

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

Of the patients with metastatic or recurrent NSCLC who were treated with OPDIVO and ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 36.7% (180/491) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks. The incidence of neutralizing antibodies against nivolumab was 1.4% (7/491) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks.

Of the patients with NSCLC who were treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy, and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 34% (104/308); the incidence of neutralizing antibodies against nivolumab was 2.6% (8/308).

There was no evidence of increased incidence of infusion-related reactions with anti-nivolumab antibody development.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OPDIVO. 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. *Eye:* Vogt-Koyanagi-Harada (VKH) syndrome; *Complications of OPDIVO Treatment After Allogeneic HSCT:* Treatment refractory, severe acute and chronic GVHD.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to

the developing fetus. The effects of OPDIVO (nivolumab) are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk.

Advise pregnant women of the potential risk to a fetus.The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

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

Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations–Pregnancy]*.

Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations–Pregnancy]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose.

Pediatric Use

The safety and effectiveness of OPDIVO and YERVOY (ipilimumab) have not been established in pediatric patients less than 18 years old with NSCLC *[see Indications and Usage]*.

Geriatric Use

Of the 576 patients randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received OPDIVO with ipilimumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.3) in full Prescribing Information]*.

Of the 361 patients randomized to OPDIVO (nivolumab) 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including: Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*; Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*; Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*; Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions]*; Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*; Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*. Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

Revised: June 2020

YERVOY® (ipilimumab) injection, for intravenous use

℞ ONLY

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

INDICATIONS AND USAGE

- YERVOY (ipilimumab), in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, *[see Dosage and Administration]*, with no EGFR or ALK genomic tumor aberrations.
- YERVOY, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.6) in full Prescribing Information]*. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting YERVOY. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of YERVOY.

Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.8) in full Prescribing Information]*. In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroid therapy. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Diarrhea or Colitis

YERVOY can cause immune-mediated diarrhea/colitis, which may be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated diarrhea/colitis. In cases of corticosteroid-refractory diarrhea/colitis, consider repeating infectious workup to exclude alternative etiologies. If other causes are excluded, consider addition of an alternative immunosuppressive agent to the corticosteroid therapy or replacement of the corticosteroid therapy in corticosteroid-refractory immune-mediated colitis.

Immune-Mediated Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.8) in full Prescribing Information]*.

Immune-Mediated Endocrinopathies

Hypophysitis:

YERVOY can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue YERVOY (ipilimumab) depending on severity *[see Dosage and Administration (2.8) in full Prescribing Information]*.

Immune-Mediated Pneumonitis

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of YERVOY with nivolumab in 5% of patients and withholding of YERVOY with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of YERVOY with nivolumab.

The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with YERVOY in combination with nivolumab only.

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome

Infusion-Related Reactions

Severe infusion-related reactions can occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.8) in full Prescribing Information]*

Complications of Allogenic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly *[see Adverse Reactions]*. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations]*.

Risks Associated When Administered in Combination with Nivolumab

When YERVOY is administered in combination with nivolumab, refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions]*.
- Infusion-related reactions *[see Warnings and Precautions]*.

Clinical Trials Experience

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

The data described in the Warnings and Precautions section reflect exposure to YERVOY (ipilimumab) 1 mg/kg administered with nivolumab 3 mg/kg in CHECKMATE-227 and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.6) in full Prescribing Information]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received YERVOY 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received YERVOY and nivolumab for >6 months and 23% of patients received YERVOY and nivolumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. YERVOY and nivolumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction. The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 1 and 2 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 1: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.
[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.
[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.
[d] Includes pruritus and pruritus generalized.
[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[h] Includes dyspnea and dyspnea exertional.
[i] Includes cough and productive cough.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were: *Skin and Subcutaneous Tissue:* urticaria, alopecia, erythema multiforme, vitiligo; *Gastrointestinal:* stomatitis, pancreatitis, gastritis; *Musculoskeletal and Connective Tissue:* arthritis, polymyalgia rheumatica, rhabdomyolysis; *Nervous System:* peripheral neuropathy, autoimmune encephalitis; *Blood and Lymphatic System:* eosinophilia; *Eye Disorders:* blurred vision, uveitis; *Cardiac:* atrial fibrillation, myocarditis.

Table 2: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY (ipilimumab) and Nivolumab (CHECKMATE-227)

Laboratory Abnormality	YERVOY and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

The safety of YERVOY in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.6) in full Prescribing Information]*. Patients received either YERVOY 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in YERVOY in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received YERVOY and nivolumab for >6 months and 13% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with YERVOY in combination with nivolumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with YERVOY in combination with nivolumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 3 and 4 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 3: Adverse Reactions in >10% of Patients Receiving YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.
[a] Includes fatigue and asthenia
[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis
[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain
[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria
[f] Includes pruritus and generalized pruritus
[g] Includes cough, productive cough, and upper-airway cough syndrome
[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea
[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine
[j] Includes dizziness, vertigo and positional vertigo

Table 4: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on YERVOY (ipilimumab) and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidences of antibodies to other studies or to other products may be misleading.

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of YERVOY. 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.

Immune System: graft-versus-host disease

Skin and Subcutaneous Tissue Disorders: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]*, YERVOY can cause fetal harm when administered to a pregnant woman. There is insufficient human data for YERVOY exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *[see Data]*. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-593-7869.

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

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the human exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/–), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/– heterozygous offspring. Mated CTLA-4+/– heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4–/–). The CTLA-4–/– homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Lactation

Risk Summary

There are no data on the presence of YERVOY (ipilimumab) in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with YERVOY and for 3 months following the last dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating YERVOY *[see Use in Specific Populations–Pregnancy]*.

Contraception

YERVOY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations–Pregnancy]*. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months following the last dose.

Pediatric Use

The safety and effectiveness of OPDIVO (nivolumab) and YERVOY have not been established in pediatric patients less than 18 years old with NSCLC.

Geriatric Use

Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks with in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.6) in full Prescribing Information]*.

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received YERVOY with nivolumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Advise patients that YERVOY can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions]:*

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

Advise patients who are receiving YERVOY of the potential risk of an infusion-related reaction *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.
- Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations]*.
- Advise patients who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-844-593-7869 *[see Use in Specific Populations]*.

Lactation

- Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

Revised: June 2020

7356US2002699-01-01 06/20

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MICHAEL YBARRA

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Michael Ybarra, MD, FACEP, FAPCR, has been a member of the NCODA Executive Advisory Board since 2015.

His dual roles as a board-certified emergency physician and Vice President and Chief of Medical Affairs at Pharmaceutical Research and Manufacturers of America (PhRMA) have given him a unique perspective on today's healthcare industry.

Tell us a little about your professional career, clinically and with PhRMA.

In my capacity at PhRMA, I lead stakeholder outreach on federal and international health policy issues and PhRMA's internal and external medical affairs engagement. I also have the great joy of working as an emergency room physician at MedStar Georgetown University Hospital in Washington, DC.

How has the COVID-19 pandemic affected your work roles?

When I work clinically, I'm struck by the high prevalence of underlying health conditions in individuals impacted by COVID-19.

While people of all ages and health status have been impacted by COVID-19, we know that older individuals and people with comorbidities like cancer, chronic lung disease and cardiovascular disease are at higher risk of complications.

Unfortunately, disparities for patients infected with COVID-19 are real and the pandemic is particularly challenging for patients with cancer.

I'm lucky to have two incredible jobs that allow me to address this crisis.

As vice president at PhRMA, I work to advance policies that support access to medicines, as well as with companies developing COVID-19 treatments and vaccines.

As an emergency room physician, I have spent many hours over the last six months learning about COVID-19 and reading about the evolving evidence and best practices on prevention, diagnosis and treatment.

What is the biopharmaceutical industry doing to combat the novel coronavirus?

In my role at PhRMA, I work with our members and groups advocating on behalf of patients, physicians, pharmacists and businesses to understand how the pandemic is impacting patient care.

Right now, the industry is working around the clock to develop vaccines and treatments for COVID-19 — progress is being made faster than ever before. This means that companies are working together in unprecedented ways to develop new diagnostics to test for the virus, finding potential candidates to treat it and scaling facilities to produce treatments and vaccines once they are approved.

At the end of the day, NCODA is primarily focused on improving patient care. What are some of the key concerns that oral oncolytic patients face during the pandemic, and what can be done to relieve their burden?

Patients are facing a number of issues related to the pandemic, including safety for those who are immunosuppressed, as well as receiving continuous access to care. However, much is being done to quickly address these problems.

For example, Congress recently passed legislation that allows patients to receive 90-day refills for certain prescription drugs, helping to ensure they have continuous access to life-saving medicines.

Additionally, the biopharmaceutical industry is working diligently to ensure a safe, stable and secure pharmaceutical supply chain.

For years, we have carefully built robust global supply chains to ensure patients in the United States and around the world have uninterrupted access to medicines. These efforts have allowed us to avoid major disruptions due to the COVID-19 pandemic because of the flexibility a diverse supply chain offers.

Many of my clinical colleagues have also faced issues with access to personal protective equipment and medical supplies in their hospitals.

The biopharmaceutical industry is working closely with frontline health care workers and has donated hundreds of thousands of masks, critical medicines and monetary support to health systems in need.

To address the increased demand on physicians, many biopharmaceutical companies are also allowing employees to work on a volunteer-basis on the frontlines of the crisis.

How are NCODA and your organization collaborating to improve patient care?

NCODA and PhRMA are continuing to work together to understand the challenges facing oral oncolytic patients during this time. The virus has made it more difficult to receive care, so together we are identifying solutions and working tirelessly to achieve them.

A key pillar of this is education about how the virus is impacting patient access to care, as well as pharmaceutical research and development. In March, I presented at the 2020 NCODA Spring E-Forum to educate and inform patients and physicians on the biopharmaceutical industry's efforts to combat the virus and improve care for cancer patients, as well as how we are working with physicians to identify and address issues brought to light during the pandemic, such as antimicrobial resistance.

This pandemic has inspired countless collaborations between PhRMA, its member companies and other organizations as we all work toward a common goal: defeating coronavirus. Together, we will find the cures and treatments we need to get back to normal.

NEW TREATMENTS FOR EARLY-STAGE AND METASTATIC BREAST CANCER

By Jennifer Hutchinson, PharmD

Breast cancer continues to be the most commonly diagnosed malignancy for women in the United States, and accounts for 30% of all new cancer diagnoses in women. For 2020, the American Cancer Society predicts that 279,100 new diagnoses and 42,690 deaths will be attributed to the disease.[1]

Jennifer Hutchinson

However, the paradigm surrounding breast cancer is ever-evolving, and survival is significantly prolonging, especially in the metastatic setting. This review summarizes recent guideline updates in breast cancer management for both early-stage breast cancer (ESBC) and metastatic breast cancer (MBC) and covers treatment for the three major subtypes: hormone-receptor positive (HR+), human epidermal growth-factor receptor 2 positive (HER2+) and triple negative breast cancer (TNBC).

ESBC: HR+

One major shift in treatment of HR+ ESBC is the implementation of the results from the TAILORx trial, a prospective, randomized trial in HR+, HER2- lymph node negative women with breast cancer.[2] The trial utilized the 21-gene recurrence-score assay (OncotypeDX) to determine prognostic information in HR+ ESBC patients and addressed whether the addition of chemotherapy was beneficial in reducing the risk of distant recurrence for women with intermediate scores of 11-25.

In the trial, women who were low risk (score ≤10) received endocrine therapy alone. High-risk women (score ≥26) received adjuvant chemoendocrine therapy. And for intermediate risk, women were randomized to either endocrine monotherapy or chemoendocrine therapy. TAILORx concluded there was no added benefit with the addition of chemotherapy to endocrine therapy in women who scored intermediately, with similar invasive disease-free survival (IDFS) and OS between both groups.

The exception to this was in a subgroup analysis of intermediate scores, which demonstrated a significant benefit of chemoendocrine therapy in women 50 years or younger. Based on these results, the NCCN guidelines have updated to state that consideration should also be given to chemoendocrine therapy in node-negative women ≤50 years with intermediate OncotypeDX scores.[3]

Looking forward, the RxPONDER study, which is estimated to be completed in 2022, will further explore the utility of the OncotypeDX scores in the node-positive population of women.[4]

ESBC: HER2+

In the HER2+ ESBC setting, the ExteNET trial assessed the efficacy and safety of adjuvant neratinib, an oral tyrosine kinase inhibitor (TKI) targeting HER1, HER2, and HER4, after >1 year of adjuvant trastuzumab. In this randomized, double-blind phase III trial, women with node positive HER2+ ESBC received neratinib 240 mg daily or placebo for extended adjuvant therapy up to one year.[5]

The primary endpoint of IDFS rates at two years were 93.9% for neratinib and 91.6% for placebo. Additionally, a prespecified subgroup of women with HR+ disease had greater IDFS with neratinib compared to those with HR- disease, indicating neratinib's preferential use in HR+, HER2+, node-positive disease.

Diarrhea was the main adverse event reported in the ExteNET trial, with 95% all-grade diarrhea, and 40% grade 3. It presented most commonly during the first month, lasted a median of five days, and led to discontinuation in 17% of patients. Given the significance of this adverse effect, patients should be educated regarding diarrhea prophylaxis when initiating neratinib. An around-the-clock loperamide taper should begin at the first dose of neratinib. Budesonide and colestipol should also be considered for loperamide-refractory diarrhea.

Another recent development for this subtype is the KATHERINE trial, a phase III study in HER2+ ESBC patients with residual invasive disease after neoadjuvant taxane therapy and trastuzumab.[6] Patients were randomized to receive either trastuzumab or the HER2-targeted antibody drug conjugate (ADC) comprised of trastuzumab and the microtubule inhibitor emtansine. Ado-trastuzumab emtansine (T-DM1) was given as 3.6 mg/kg IV q3 weeks for 14 cycles.

More patients had IDFS with T-DM1 compared to trastuzumab and the risk of recurrence was 50% lower with the ADC. The safety data was also consistent with the known safety profile of T-DM1, with more adverse events (including serious and grade ≥3 adverse events) reported with T-DM1 compared to trastuzumab (98.8% vs. 93.3%), particularly in relation to thrombocytopenia and elevated liver function tests. However, more patients also discontinued T-DM1 due to adverse events compared to trastuzumab (18% vs. 2.1%).

ESBC: TNBC

TNBC has also seen substantial developments recently with the CREATE-X trial, a randomized phase III trial that evaluated the efficacy and safety of adjuvant capecitabine monotherapy in HER2- ESBC patients with residual invasive disease after receipt of neoadjuvant chemotherapy with an anthracycline and/or taxane.[7] Patients received capecitabine 1,250 mg/m2 BID for 14 days of a 21-day cycle for 6-8 cycles, or

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standard of care treatment, after neoadjuvant chemotherapy.

The primary endpoint of DFS was significantly greater in the capecitabine group than in the control, particularly in the TNBC population (69.8% vs. 56.1%).

In terms of safety, common adverse events included hand-foot syndrome, diarrhea, stomatitis, liver enzyme elevations, neutropenia and thrombocytopenia. It is also important to note the dosing of capecitabine used in the CREATE-X trial, which was higher than the typical 1,000 mg/m2 BID dosing used in the metastatic setting.

One theory for why patients in the CREATE-X trial were able to tolerate a 25% higher dose is based on the pharmacogenetics of capecitabine. According to the drug's manufacturer, Asian patients had a 24% lower AUC of capecitabine.[8] The patient population in the CREATE-X trial were Japanese and Korean, and likely were able to tolerate the higher dose for that reason. Because of this, some providers opt to prophylactically dose-reduce to 1,000 mg/m2 BID.

MBC: HR+

The population that has perhaps seen the most rapid development is in the metastatic setting. For patients with HR+, HER2- PIK-3CA-mutated MBC, the SOLAR-1 trial has shown promising results.[9] In this phase III trial, patients who had previously received endocrine therapy were given alpelisib (a PI3Ka-specific inhibitor) at 300 mg PO daily or placebo in addition to fulvestrant after confirmation of a PIK3CA mutation via an FDA-approved diagnostic test.

The primary endpoint of PFS at 20-month follow-up was 11.0 months in the alpelisib group vs. 5.7 months in the placebo group.

The most frequent adverse events for alpelisib were hyperglycemia, rash and diarrhea. In patients starting alpelisib, it is particularly important to closely monitor their plasma blood glucose weekly for the first two weeks of therapy, and then monthly thereafter, in addition to routine hemoglobin A1C monitoring. Patients should also be educated on following a low-sugar diet while on alpelisib to reduce the risk of hyperglycemia and in some instances, antidiabetic agents such as metformin may need to be initiated. Some institutions have also adopted the addition of prophylactic cetirizine for the first month to reduce the risk of rash associated with alpelisib as well as prophylactic metformin, however these recommendations are currently not reflected in the drug's prescribing information.

MBC: HER2+

Findings from the DESTINY-Breast01 trial for HER2+ MBC led to the accelerated FDA approval of fam-trastuzumab deruxtecan-nxki (T-DXd) in December 2019.[10] In this two-part, single-arm phase II study, patients who had previously received T-DM1 were given one of three different doses of T-DXd (an ADC comprised of trastuzumab and the topoisomerase I inhibitor deruxtecan). After establishing 5.4 mg/kg IV q3 weeks as the appropriate dose, T-DXd was then assessed for efficacy and safety.

The primary endpoint of ORR was 60.9%, with a median PFS of 16.4 months and a median response duration of 14.8 months in patients with heavily pretreated metastatic breast cancer.

Safety-wise, low-grade gastrointestinal (nausea, diarrhea and vomiting) and hematologic toxicities (decreased neutrophil and lymphocyte counts) were the most common adverse events. There was also a substantial risk (13.6%) of interstitial lung disease (ILD), which led to death in some patients. It is important to educate patients on monitoring for signs and symptoms of ILD, and to utilize glucocorticoids for the management as soon as ILD is suspected. Additionally, unlike with trastuzumab, clinically significant cardiotoxicity was not an observed side effect of T-DXd.

Future phase III trials with T-DXd are currently underway, including a head-to-head comparison of T-DM1 to T-DXd and the use of T-DXd in patients with low HER2 expression.

Neratinib has also had significant success in the metastatic setting, as demonstrated in the 2019 ASCO Annual Meeting abstract for the NALA trial, which led to the accelerated approval of neratinib plus capecitabine for HER2+ MBC patients.[11] This randomized, phase III trial assessed neratinib 240 mg PO daily with capecitabine 750 mg/m2 PO BID on days 1-14 of a 21-day cycle (N+C) compared to lapatinib 1,250 mg PO daily with capecitabine 1,000 mg/m2 PO BID on days 1-14 of a 21-day cycle (L+C) in patients who had at least two prior lines of HER2-directed therapy.

The primary endpoint of PFS for 12-month rates were significantly greater in the N+C arm compared to L+C, almost doubling the PFS from 14.8% to 28.8%. OS rates at 12 months also favored N+C (72.5% vs. 66.7%).

TEAEs (treatment emergent adverse events) were similar between both groups, and more patients discontinued therapy due to TEAEs with L+C – likely due to the higher dose of capecitabine in that arm. Neratinib did have higher rates of grade 3 diarrhea, however discontinuation due to diarrhea was also similar between N+C and L+C. As with neratinib use in the early stage setting, antidiarrheal prophylaxis with loperamide (and colestipol or budesonide) should also be considered.

The addition of the recently FDA-approved oral HER2-targeted TKI tucatinib to capecitabine and trastuzumab resulted in greater PFS and OS compared to placebo, as demonstrated in the HER2CLIMB trial.[12] This phase III, randomized, double-blind trial evaluated heavily-pretreated HER2+ MBC patients who had previously received trastuzumab, pertuzumab and T-DXd. Notably, 47.5% of the population also included patients with stable or progressing brain metastases – a population not commonly included in MBC trials.

Patients were randomized to receive tucatinib 300 mg PO BID or placebo, plus trastuzumab 6 mg/kg IV q21 days (with an initial loading dose of 8 mg/kg) and capecitabine 1,000 mg/m2 PO BID on days 1-14 of a 21-day cycle.

The one-year PFS of the tucatinib arm was 33.1% compared to 12.3% for placebo and the two-year OS was 44.9% vs. 26.6% for tucatinib vs. placebo, respectively. Additionally, within the group of patients with brain metastases, PFS was also significantly greater for the tucatinib arm, at 24.9% vs. 0% for placebo.

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Common adverse events for the tucatinib arm included diarrhea, hand-foot syndrome, nausea/vomiting and elevated LFTs, with greater reports of diarrhea and increased LFTs for tucatinib. Notably, the majority of tucatinib-associated diarrhea was grade 1 or 2, and prophylactic antidiarrheal agents were not required per protocol. LFT elevations were also commonly low-grade and transient. The HER2CLIMB trial and subsequent approval of tucatinib marks a significant advancement for heavily pretreated HER2+ MBC patients — particularly those with brain metastases.

MBC: TNBC

The IMpassion130 trial has demonstrated an advancement in the realm of metastatic TNBC, particularly in patients with programmed death ligand 1 (PD-L1) positive tumors.[13] This randomized, phase III trial allocated patients with treatment-naïve metastatic TNBC to receive placebo or atezolizumab, a monoclonal antibody that selectively targets and inhibits PD-L1, at 840 mg IV on days 1 and 15 every 28 days plus nab-paclitaxel 100mg/m2 IV on days 1, 8, and 15 of every 28-day cycle, continued until progression or unacceptable toxicity.

The two primary endpoints included PFS and OS, for both intention-to-treat (ITT) and PD-L1-positive subgroup populations. The trial concluded that atezolizumab/nab-paclitaxel (atezo/nab-P) significantly prolonged PFS in both the ITT and PD-L1 populations, with a median PFS of 7.2 months vs. 5.5 months in the ITT population and 7.5 months vs. 5.0 months in the PD-L1+ subgroup, for atezo/nab-P vs. placebo/nab-P, respectively. Additionally, among PD-L1+ patients, the median OS was also greater with atezo/nab-P, establishing this regimen as a new standard of care for PD-L1+ tumors.

Adverse events were more common in the atezo/nab-P arm, with the most common grade 3-4 events including neutropenia, peripheral neuropathy, fatigue and anemia. Immune-related adverse events were also seen with the addition of atezolizumab, including hepatitis, hypo- and hyperthyroidism, pneumonitis and colitis – with immune-related hepatitis being the most common grade 3-4 toxicity.

Finally, for the most recent FDA approval in MBC management, sacituzumab govitecan-hziy (saci-govi), demonstrated durable objective responses in heavily pretreated metastatic TNBC patients.[14] The IMMU-132-01 trial led to the accelerated approval of saci-govi, an ADC comprised of a monoclonal antibody that targets the human trophoblast cell-surface antigen 2 (Trop-2) and the active metabolite of irinotecan (SN-38). It is a phase I/II single-arm, multicenter trial that examined saci-govi 10 mg/kg IV on days 1 and 8 of a 21-day cycle in metastatic TNBC patients who had received at least two prior lines of therapy for metastatic disease.

The ORR was 33.3%, with a median duration of response of 7.7 months, of which 55.6% maintained a response for six or more months.

Common adverse effects included neutropenia, diarrhea, and nausea/vomiting, of which neutropenia also had significant grade 3-4 toxicities (43%). Prophylactic antidiarrheal agents (including anticholinergics) should also be considered, given the pharmacology of the ADC. Of note, since part of the ADC includes the active metabolite of irinotecan, it is important to monitor for patients who may be UGT1A1 inhibitors and inducers, which may alter the toxicity or efficacy of the drug.

Further data for saci-govi is pending results from the phase III ASCENT trial, estimated to be completed in July 2020.[15]

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RARE DISEASE, CHANCE MEETING CREATE A FRIENDSHIP FOR LIFE

Adversity builds character which beget human connections.

Kirollos Hanna, PharmD, BCPS, BCOP, can vouch for it. Though they rarely see each other, this oncology pharmacist and soccer-loving Iowa student Isabelle Hall bonded by persevering against the same rare disease.

"We'll have this friendship for the rest of our lives," said Hanna, an Assistant Professor of Pharmacy at the Mayo Clinic College of Medicine in Minnesota.

Flash back to the summer of 2017.

Hanna, a member of the NCODA Executive Council, was on service at the Mayo Clinic in Rochester. It was a normal day, until he was presented with an inpatient with aplastic anemia (AA).

Student Isabelle Hall and Kirollos Hanna, PharmD, BCPS, BCOP, (inset), met while Hall was being treated for aplastic anemia — an exceedingly rare and deadly disease that Hanna also has survived — at the Mayo Clinic.

A GRIM DIAGNOSIS

So rare is this bone marrow disorder, marked by a deficiency of blood cells, that few physicians see a case in their lifetimes. Symptoms include fatigue, unexplained bruising and persistent infections. AA affects all ages, regardless of race or sex, and severe cases can lead to death within a year.

Hanna knew the grim facts. Four years earlier, he received the same diagnosis while a third-year pharmacy student at Florida A&M University. After feeling exhausted for weeks, he went home to Tennessee for a checkup and routine bloodwork.

His physician called a few hours later and asked him to go to a Nashville hospital. "The doctor told me I have six months to live unless I had treatment," Hanna recalled.

According to the National Organization for Rare Disorders, most cases of acquired aplastic anemia are unrelated to identifiable causes. Some researchers believe the immune system mistakenly destroys stem cells, sabotaging the production of new blood cells and platelets essential for life.

Standard treatment – similar to regimens for serious blood cancers – features intensive chemotherapy, a bone marrow transplant from a donor, and immunosuppressive therapy. A tiny fraction of individuals – from 1.5 to 7 Americans per million people – develop the disease each year.

The pragmatic Hanna, then 22, did what had to be done. He researched his condition, investigated therapy regimens, and began chemo.

Though he was braced for it, losing his hair was still a shock. "I rubbed my scalp in the shower one day and all my hair came off," he said.

A bone marrow transplant followed — his younger sister served as donor — and his recovery began. Hanna scheduled his three-month-plus treatment over a summer break and graduated with his class.

A ONE IN A MILLION MEETING

Now, years later, another college student was facing the same ordeal at the hospital where he worked. Hall, 19, was a freshman at the University of Missouri-Columbia.

"I knocked on her door," Hanna remembered. "I said, 'Hi, my name is Kirollos. I'm in pharmacy services. I just wanted to share with you that

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SUCCESS STORY

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I had aplastic anemia. Would you like to hear my story?'"

Hall was sitting and talking with her father in her room. She lit up. "I loved it," she said of his introduction.

Hall, captain of her high school soccer team, was a superb athlete conditioned by summer jobs that involved painting, landscaping and roofing back home in Pella, Iowa.

She was fine when she left for college. She returned home with a nagging cold over Thanksgiving break. Bruises appeared on her arms and legs.

"My doctor prescribed a generic cold medicine," she said.

A LIFE-SAVING TREATMENT

By Christmas, Hall was sleeping 12 hours a day. She took a leave of absence from Mizzou and began visiting specialists. She was finally diagnosed in March at the Mayo Clinic and scheduled to begin a 100-day treatment cycle that summer, much as Hanna had done in 2013. In her case, she received life-saving marrow from a donor on the Be the Match registry.

"I was shocked at how my life switched … from never being at a doctor's office to living there at Mayo," she said.

On the positive side, her stay marked the launch of a unique friendship that has transcended illness and recovery. Hanna briefed Hall on what to expect during her treatment and empathized when she suffered the side effects of chemo, too.

"I had mouth sores," Hall said ruefully. "I couldn't eat for a month and a half." When she was discharged, the pair pledged to keep in touch and continue to exchange news and updates to this day.

If they clicked as survivors, shared values reinforced their mutual respect. Both Hanna and Hall harnessed a "move forward" mindset and persevered in seeking out the best care. Both also relied on their faith and families for support.

Each prizes care continuity as well. Hall, now 22, returns to the Mayo Clinic every three months for lab work and a five-hour infusion to boost her immune system. "Other visits, I can do at the University of Missouri," she said.

Likewise, Hanna, 30, returns annually to the Nashville hospital and medically integrated team where he was first diagnosed. "My providers know everything about my history," he said.

'THINGS HAPPEN FOR A REASON'

Neither understands how or why they developed AA, yet both agree they were meant to learn and grow from their experience. As Kirollos put it, "I'm a big believer in things happening for a reason."

From his perspective, his brush with the rare disease has made him a passionate advocate of patient care. As for Hall, she has spearheaded two Be the Match drives, plans to earn a graduate degree in dietetics at Mizzou, then transition into the role of physician assistant.

"Having a care provider who'd been through the same experiences as me helped me so much emotionally," she said. "I can relate to patients. That's what's made a difference for me."

A LIGHT AMID THE FOG: NCODA FINDS NEW STRATEGIES TO COPE WITH CHAOS

Michael Reff

This is a pivotal moment in healthcare. Once the fog finally clears, nothing will be quite the same. It's our mission and our duty to see that patient care is kept in the forefront of the post-COVID-19 world.

The theme of the Fall 2020 Edition of *Oncolytics Today* is about shining through the fog of chaos and confusion brought on by the COVID-19 pandemic.

Like the physicians, nurses, pharmacists, technicians, administrators and countless other oncology healthcare professionals that comprise our membership, we at NCODA also have been forced to deal with sudden, dramatic and ongoing changes brought on by the onset of the novel coronavirus this spring.

First and foremost was our call to shift the 2020 Spring Forum to a Virtual E-Meeting on March 10, just days before the onsite meeting originally scheduled for March 18-20 in Dallas.

Our top priority in making the decision was the health and safety of our patients, members, staff, exhibitors and faculty. Our 2020 Spring Forum team took on the monumental effort of putting together a new program — a task that usually takes months — in less than a week.

The resulting Virtual E-Meeting on March 19 was a huge and, more importantly, safe success featuring 10 hours of expert presentations.

At the same time, the team also was charged with cancelling hundreds of flight and hotel registrations. I'd like to take this opportunity to thank them for their hard work, as well as our corporate partners for standing by us.

Yet this was only the beginning of NCODA's digital strategy to help the oncology healthcare community cope with the onset of COVID-19. Beginning that same day, NCODA launched its weekly webinar series "Supporting Patients and Practices Through the COVID-19 Pandemic."

Nine webinars featuring experts in infectious disease, pharmaceuticals, governance, policy-making and industry were presented, along with frontline reports from NCODA practice executives, physicians, pharmacists and other oncology experts coping with the crisis.

Among the many great presentations, Dr. Doug Flora's comments about how to lead in the fog of war really hit home. Flora compared the daily chaos being wrought by COVID-19 to the movement of starling flocks, also known as "murmurations."

"All these birds need to know is move to the center, follow your neighbor and don't collide," explained Flora, Executive Medical Director of Oncology at St. Elizabeth Healthcare. "As a leader we need to try and do the same thing for our providers and team members by saying, 'We'll give you rules of engagement, but we trust that you know your business best.' Instead of micromanaging every detail, give some simple rules just like these starlings have."

That's a strategy we at NCODA take to heart. We're here to bring the oncology healthcare community together to collaborate on treatments, research and best practices.

Make no mistake. We are in the middle of a war, a war against COVID-19. And while it's hard to say we are anywhere near the beginning of the end, I'm hopeful that with the ideas, resources and commitment of all of our NCODA members, we are near the end of the beginning.

This is a pivotal moment in healthcare. Once the fog finally clears, nothing will be quite the same. It's our mission and our duty to see that patient care is kept in the forefront of the post-COVID-19 world.

Thank you for your commitment in this most difficult of times.

Michael J. Reff, RPh, MBA
Executive Director and Founder of NCODA

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Arlie, marrow transplant recipient (left), with Ryan, her donor.

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